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Oxidative Dehydrogenative Couplings of Alkenyl Phenols

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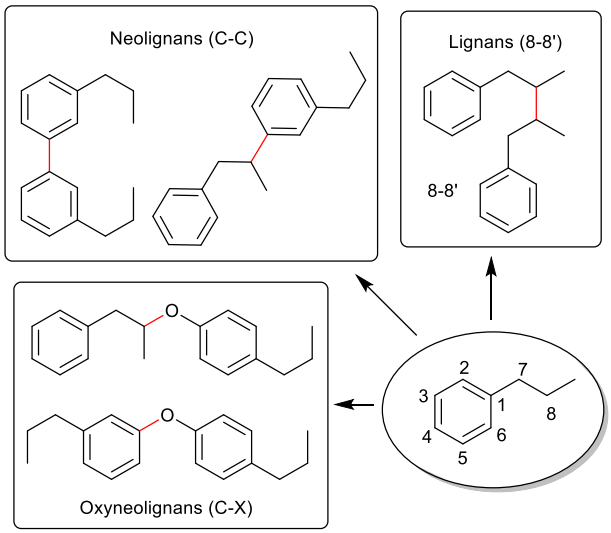
Alkenyl phenols are utilized by nature in the construction of one of the most important biopolymers, lignin. Using similar building blocks, an array of distinct structures can be formed by selective dimerization of the starting phenols to form lignans, neolignans, oxyneolignans, and norlignans. Given the multitude of possible outcomes, many methods have been reported to affect the desired bond formations and access these biologically relevant scaffolds. The most biomimetic of these methods, discussed here, involve the unprotected phenols undergoing oxidative bond formation that proceed via dehydrogenative coupling. This review aims to place the known literature in context, highlight the progress made toward synthesis of these important molecules, and recognize the gaps and limitations that still exist.

Introduction

Alkenyl phenols are a key building block to the biopolymer lignin. Besides cellulose, lignin is the most abundant biopolymer. It makes up approximately 30% of the content in wood and is produced primarily as a waste product in excess of 50 million tons every year, mainly from the paper pulping industry.[1-3]

Of more interest to the synthetic chemist, however, are lignan and neolignane small molecule structures. Lignans are defined as a dimer of a compound with an aryl n-propyl core. Any dimers in which a bond has formed at the 8-8' positions are considered lignans. Molecules resulting from any other bond linkage between monomers are considered neolignans. A neolignan resulting from a C–O bond formation is classed as an oxyneolignan. Furthermore, any lignan or neolignan which lost one or two carbons from its core is classified as a norlignan (Scheme 1).[4]



Scheme 1. Lignan scaffolds

Hundreds of lignans and neolignans have been isolated from natural sources.[5] These compounds have antiviral, anticancer, and many other medical properties.[6] A 2019 review described the value of these classes of compounds in the treatment of neurodegenerative diseases.[7]

All of these classes of molecules derive from the same basic starting material, the alkenyl phenol. Nature has found many ways to efficiently produce these structurally diverse compounds, however, as is often the case, synthetic chemists lag far behind. Much of the early literature in this area was aimed at synthesizing natural products of these types and nonnatural analogues for biological evaluation. Many of these end-goal driven syntheses involved separation and characterization of multiple oxidized products to obtain the single species of interest (Scheme 2 shows possible bond formations and reactive intermediates). Advancements have been made using biocatalytic and electrochemical methods as well as stoichiometric and catalytic metal oxidant. However, the

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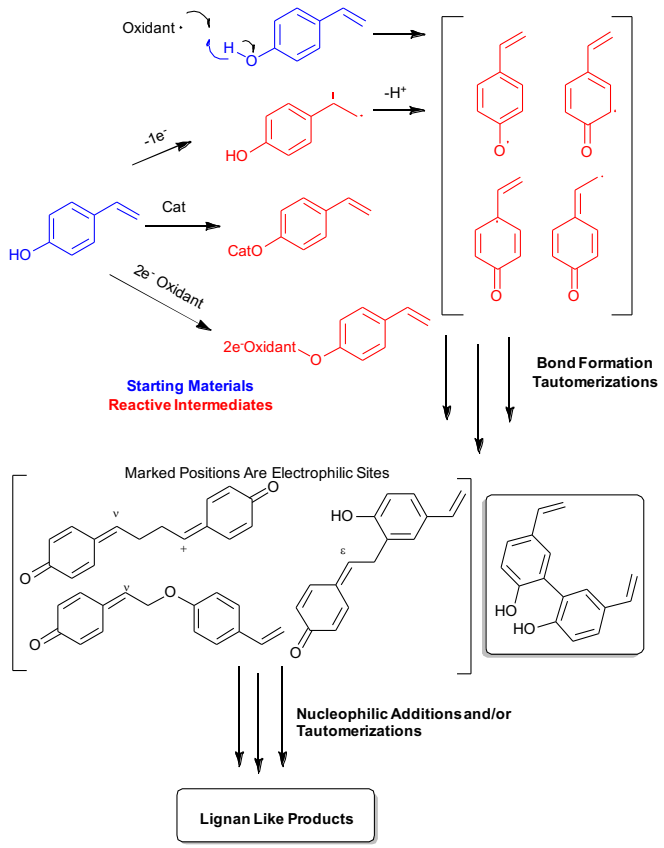
selectivity of these methods is often poorly understood, and results tend to be highly substrate specific.



Scheme 2. Variety of pathways by which lignan scaffolds can be made from *para*-alkenyl phenols

Laccase and horseradish peroxidase enzymes are broadly applicable and have been demonstrated to give the 5–5', 5–8', 4-O-8', and 8–8' linked dimers depending on the substrate (see Scheme 3 for map of product classes). Electrochemistry has similar utility as do iron, silver, and copper salts. Despite the variety of effective systems, very few have been modified to give any stereochemical selectivity despite the abundance of the chiral natural products. The existing methods utilize chiral auxiliaries or dirigent proteins rather than catalytic asymmetric induction.

The mechanism of many of these transformations is likewise poorly understood or poorly explored. The initial oxidation of the alkenyl phenol and subsequent coupling event may proceed via radical (Scheme 2) or polar paths. Due to the inherent reactivity of the styryl moiety, the methods developed for phenols do not directly extended to alkenyl phenols. The greater reactivity associated with alkenyl phenols creates an even greater challenge when designing selective methods and remains the reason this area of the field is underdeveloped.

This review describes the significant contributions to the synthesis of the manifold alkenyl phenol coupling products while highlighting the existing gaps and limitations in the current literature.

Review Scope

Each section of this review is dedicated to the methods for forming a specific alkenyl phenol dimer bond. Within each section relevant examples of natural products and known biological activity are given. The general mechanism for forming each skeleton is outlined before giving specific examples of the reported methods by which products may be synthesized. When possible, each method is contextualized with similar methods and the scope and limitations are discussed together to give a broader view of the known chemistry. The methods developed come from disparate parts of the literature and will be of interest to researchers engaged in biochemistry, biomimetic synthesis, catalysis, natural product synthesis, and even materials science. Singular reports are also discussed to ensure a thorough understanding of the current technology. Many of these reports are serendipitous discoveries that are not further explored but are nonetheless relevant to the discussion.

In the case of *para* alkenyl phenols, the reactive carbons are those at the 5- and 8-positions (Scheme 3). Thus, we can imagine two monomers coming together in three ways: 1) each at the 5- position, giving the 5–5' biaryl dimer, 2) each at the 8-position, giving the reactive di-*para*-quinone methide intermediate, or 3) one at the 5-position and one at the 8-position, giving an unsymmetrical quinone intermediate. The phenol oxygen can also act as a nucleophile to give the C–O linked 4-O–8' dimers or close the ring to generate the 2,3-dihydrobenzofuran products in the 5-8'–coupling route.

The reactive *para*-quinone intermediates can give an array of products either by intramolecular reactions or reactions with external nucleophiles. Some quinone products have been isolated supporting these reaction pathways. In the case of the 4-O–8' coupling the *para*-quinone methide reacts with a nucleophile to give the vicinally difunctionalized alkene. The di-*para* quinone resulting from the 8–8' coupling can similarly react with a nucleophile bearing two available electron pairs to give the tetrahydrofuran or pyrrolidine. Similarly, if the alkenes in the reactive intermediate from the 8-8' coupling bear pendant nucleophiles such as hydroxyl or carboxyl groups, the intramolecular cyclization reactions can give the tetrahydrofuran or lactone products.

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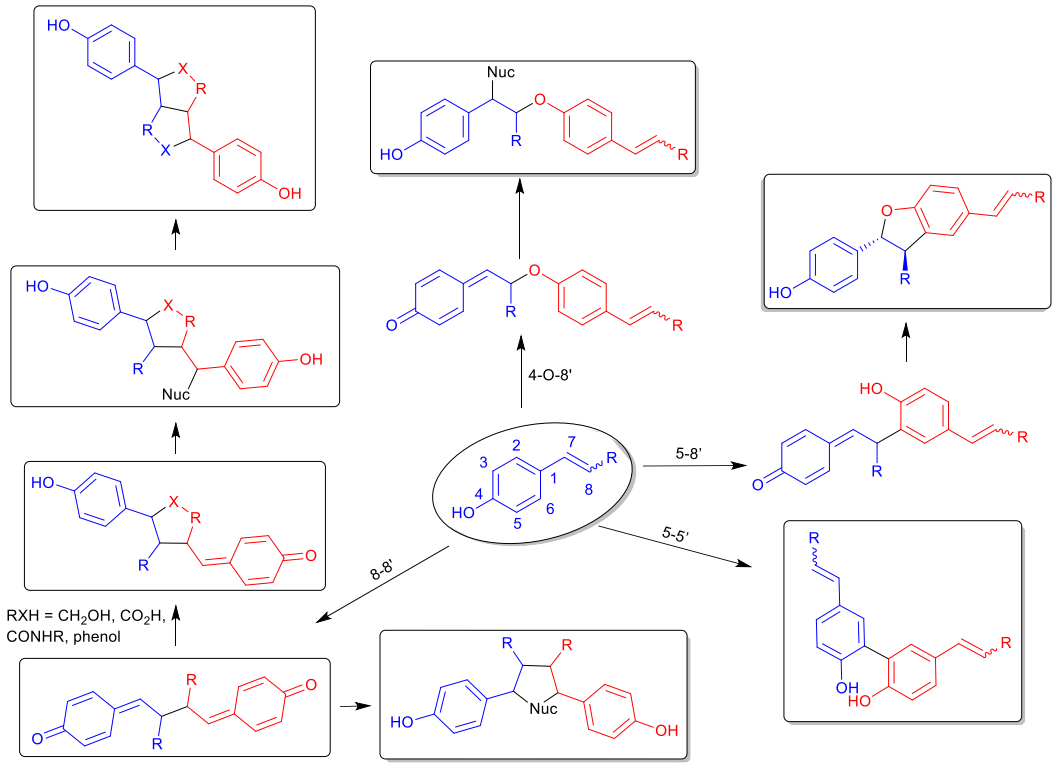
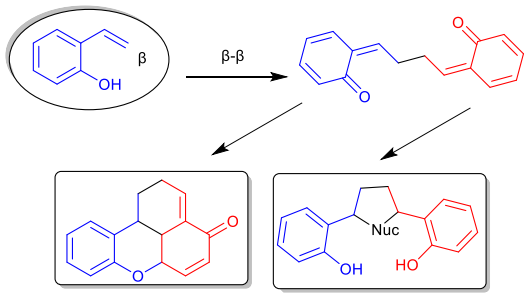


Scheme 3. Reactive intermediates and product types covered by this review deriving from *para*-alkenyl phenols

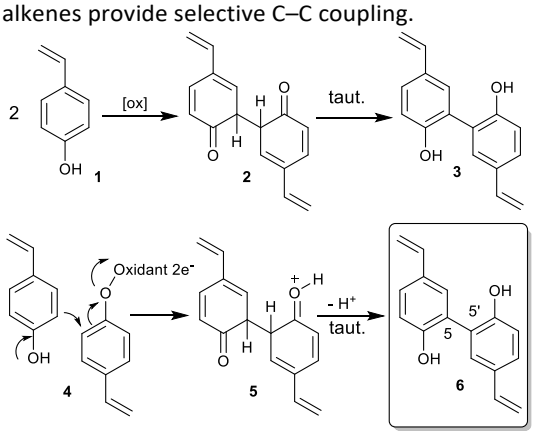
The coupling of *ortho*-alkenyl phenols is less well explored than that of *para*-alkenyl phenols. Here, only the C–C bond formation has been found (Scheme 4). As with the *para*-phenol substrates, there are also a number of natural products that can be synthesized from the coupling of *ortho*-alkenyl phenols and much of the work to-date has been in the pursuit of the benzoxanthenone, carpanone.



Scheme 4. Reactive intermediate and product types covered by this review deriving from *o*-alkenyl phenols

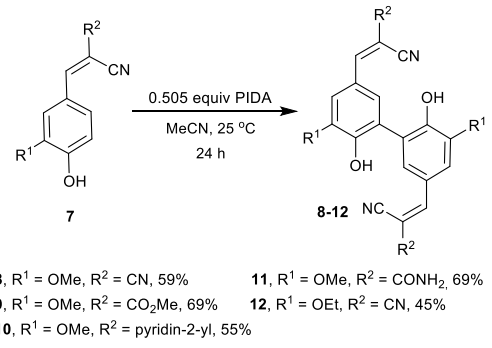
5–5’ Couplings

The coupling at between the *ortho* positions of both alkenyl phenols partners (5,5’-coupling) has seen few reports and no natural products are known. The mechanism proceeds as outlined in Scheme 5. After oxidative coupling at the 5,5’-poistions, intermediate **2** is obtained. A subsequent double tautomerization generates both aromatic rings generating **3**. Only alkenyl phenols that have disubstituted electron poor alkenes provide selective C–C coupling.



Scheme 5. General mechanism for formation of the 5-5' dimer or *para*-alkenyl phenol

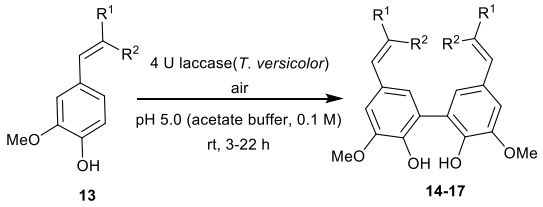
In 2000, a 5,5'-coupling was reported by Wells wherein phenyliodine(III) diacetate (PIDA) acts as an efficient oxidant to dimerize alkenyl phenols with two electron withdrawing groups on the alkene. Yields were modest, 49-69%, and the scope was limited (Scheme 6).[8] The mechanism of this C–C bond formation is not explored but likely involves one neutral substrate and one oxidized cationic substrate.



8, R^1 = OMe, R^2 = CN, 59% **11**, R^1 = OMe, R^2 = $CONH_2$, 69%
9, R^1 = OMe, R^2 = CO_2Me, 69% **12**, R^1 = OEt, R^2 = CN, 45%
10, R^1 = OMe, R^2 = pyridin-2-yl, 55%

Scheme 6. 5-5' Coupling of *para*-alkenyl phenols using a hypervalent iodine reagent

In 2012, Constantin and co-workers developed a much milder aerobic laccase catalysed dimerization reaction. Under these conditions, 79%-100% yields were seen (Scheme 7).[9] Again, scope is limited to electron poor alkenes. The coupling may proceed by generation of free phenoxyl radicals followed by a radical-radical coupling. The 5-8' coupling products with other substrates using the same system are formed without enantioselectivity, indicating poor interactions with the enzyme.



14, R^1 = R^2 = CO_2Et, 22 h, 79% **16**, R^1 = R^2 = COMe, 5 h, 93%
15, R^1 = R^2 = CN, 21 h, quant. **17**, R^1 = CO_2Et, R^2 = COMe 3 h, 86%

Scheme 7. Enzyme-mediated 5-5' coupling of *para*-alkenyl phenols

To date, there is no reported general method for the 5–5' dimerization and this remains an underexplored area within alkenyl phenol chemistry.

5–8' Couplings

Many common neolignan products can be thought of as the homo or cross dimers of 5–8' coupling (Chart 1). Licarin A is the most commonly synthesized natural product in this class. It is known for its relatively potent activity against *T. cruzi*, the causative agent of Chagas disease.[10] It was isolated from a multitude of plants including the bark of *Machilus tunbergii*.[11] *trans*-δ-Viniferin was isolated from grape cultures in *Vitis vinifera*.[12] Shengansu B was isolated from the roots of *Belamcanda chinensis*.[13]

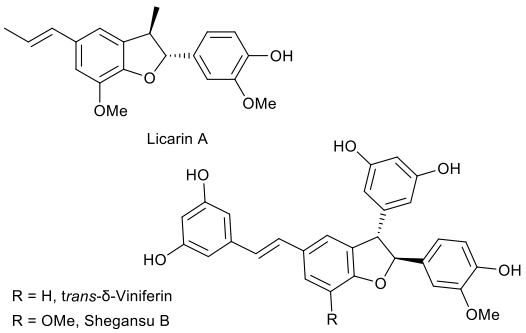
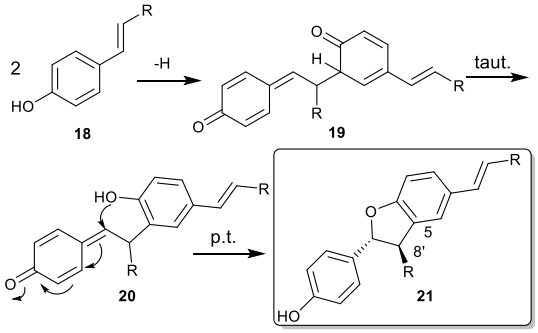


Chart 1. Natural products containing the 5-8' dimer linkage

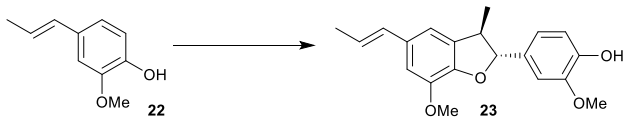
In the general mechanism of these couplings (Scheme 8), the oxidized alkenyl phenol monomers for a bond between the 5,8'-carbons to give a non-aromatic intermediate (**19**). The right-hand portion then deprotonates and rearomatizes providing a phenol oxygen that can act as a nucleophile (**20**). This addition results in the *trans* product even in achiral environments indicating a strong preference to avoid eclipsing interactions between the two R groups as cyclization ensues. Once the C–O cyclic bond is formed, aromaticity is re-established in left-hand portion to give the 2,3-dihydrobenzofuran product (**21**).



Scheme 8. General mechanism for the 5–8' coupling of *para*-alkenyl phenols

The synthesis of licarin A from oxidative dimerization of isoeugenol can afford the natural product in a single step. Multiple approaches are reported resulting in 30 - >95% yields. The current technology for the synthesis of licarin A is summarized in Table 1.

Table 1. Summary of methods reported for the synthesis of licarin A



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Entry	Catalyst	Oxidant/ Additives	Solvent	Temp	Time	Yield (%)
1	-	$FeCl_3$ (60 mol%)	$EtOH/H_2O$	rt	48 h	30[14]
2	-	Ag_2O (0.5 equiv)	Acetone/Toluene	70-75 °C	48 h	40[15]
3	-	CAN (1.5 equiv)	THF	0	0.5 h	81[16]
4	-	$PhI(OAc)_2$ (0.62 equiv)	CH_2Cl_2	rt	48 h	35-40[17, 18]
5	Boron-Doped Diamond Anode (1.06 V)	Electrode $LiClO_4$ Electrolyte	MeOH	rt	-	40[19]
6	2500 U Horse Radish Peroxidase	H_2O_2 (0.5 equiv)	pH 3 Buffer/MeOH	rt	70 min	98-99[20, 21]

Transition metal chemistry has also been reported in the literature to synthesize many neolignans. Simple iron salts like $FeCl_3$ can affect oxidation in 30% yield, but prolonged reaction seems to be necessary (Table 1, entry 1).[14] Silver oxide was likewise found to be an effective oxidant at higher temperatures (Table 1, entry 4).[15] The low selectivity of these low yielding methods likely points to a free radical intermediate which gives a statistical mixture of products depending on the reaction conditions. An exception is the single electron oxidation of isoeugenol by cerium ammonium nitrate (CAN). Through careful control of the number of equivalents and reaction time, licarin A could be isolated in 81% yield (Table 1, entry 3).[16]

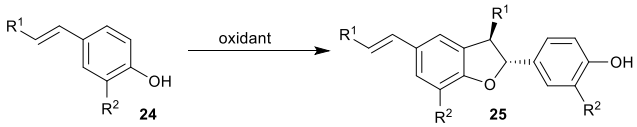
The hypervalent iodine reagent PIDA, seen above for 5–5' dimerization (see Scheme 6), is also effective in the 5–8' dimerization over two days with a different substrate to give 35-40% yield (Table 1, entry 4).[17, 18] PIDA acts as a two electron oxidant, leading to a cationic intermediate, while the other methods discussed above for synthesizing licarin A likely proceed by radical intermediates. Thus, both one and two electron oxidative pathways affect 5-8' dimerization. It is noteworthy that the PIDA oxidation, while modest yielding, gives only small amounts of polymer as by-product and does not give a mixture of oxidation products from which licarin A is separated, as many of the other reported methods which give comparable yields.

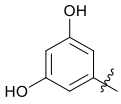
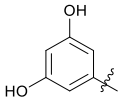
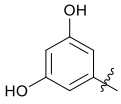
Licarin A was also electrochemically synthesized in a 2012 report via a boron-doped diamond anode at a controlled 1.06 V in 40% yield (Table 1, entry 5).[19]

Even with the success of the variety of chemical oxidations described, enzymatic chemistry remains the most effective method for synthesis of licarin A. Three separate groups have reported using horseradish peroxidase (HRP) to synthesize the neolignan in excellent yield. Environmentally benign hydrogen peroxide is utilized as the terminal oxidant, and reaction times are 2 h or less with yields greater than or equal to 95% (Table 1, entry 6).[20-22] Other reports demonstrate that selectivity and yield can be controlled through careful pH regulation.[23]

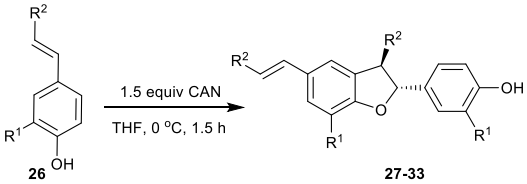
Of the methods described above, silver (I) salts are highly effective for a range of substrates, with yields usually hovering around 30% for a wide variety of substrates).[24-26] However, only esters and electron rich aryl groups are tolerated at R^1 (Table 2, entries 1-2). This result is consistent with the relatively low oxidation potential of silver (I) salts (0.6 V vs SCE). Iron salts have afforded a broad range of yields outside of synthesis of licarin A, but it appears that with electron rich substrates dimerization can be effected at synthetically useful levels (Table 2, entries 3-4).[27, 28]

Table 2. Transition metal oxidation reactions reported to give the 5–8' *para*-alkenyl phenol coupling



Entry	R^1	R^2	Oxidant (equiv)	Solvent	Temp	Time	Yield (%)
1	CO_2Me	OMe	Ag_2O (0.6)	Acetone/Benzene	rt	19 h	50
2		H	AgOAc (1)	MeOH	50 °C	1 h	97[24]
3		H	$FeCl_3$ (1)	Acetone	rt	20 h	97 (HPLC)[28]
4		OMe	$K_3Fe(CN)_6$ (1.18), NaOAc (4.4)	Acetone/Water	rt	15 d	52[27]

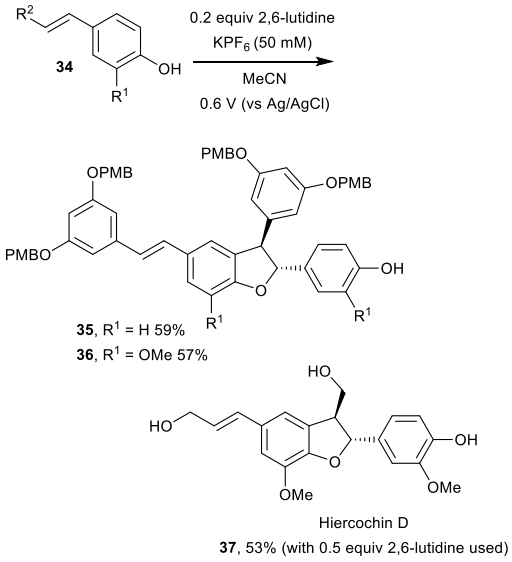
In terms of general scope, cerium ammonium nitrate is effective with good yields >80% (Scheme 9).[16] The ability to oxidize substrates including ketones at the 8-positions in high yield could be due to its relatively high oxidation potential of 0.96 V vs SCE. This is a full 360 mV more oxidizing that the commonly used silver salts which give lower yields for similar substrates. Careful monitoring is needed for these reactions because the equivalents of oxidant and the reaction time must be optimized to avoid overoxidation.



27, R^1 = H, R^2 = Me, 85%
28, R^1 = R^2 = H, 82%
29, R^1 = OMe, R^2 = H, 86%
30, R^1 = OMe, R^2 = $COCH_3$, 89%
31, R^1 = OMe, R^2 = Me, 81%
32, R^1 = H, R^2 = iPr, 84%
33, R^1 = H, R^2 = $COCH_3$, 88%

Scheme 9. CAN oxidation to give 5–8' coupled *para*-alkenyl phenols

Romero and co-workers in 2018 expanded the work on electrochemical synthesis of 5–8' coupling products (Scheme 10).[29] By using catalytic amounts of 2,6-lutidine they showed that the deprotonation of the phenol by the pyridine base reduced the oxidation potential of the substrate. The potential at which the reaction is run is similar to the oxidation potential of silver (I) salts, differing by less than 100 mV.

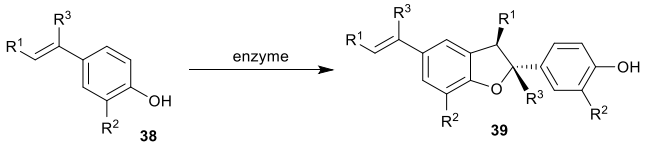


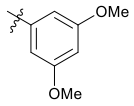
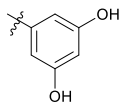
Scheme 10. Electrochemical oxidation of *para*-alkenyl phenols to give the 5–8' dimers

Enzymatic chemistry has, arguably, become the leading synthetically useful oxidative system for 5-8' coupling even outside of licarin A synthesis. It is unclear whether there is any intrinsic advantage to using either laccases or peroxidases (Table 3). Laccases are aerobic and thus require no external oxidant besides air. A corresponding disadvantage is poorer control over the precise number of oxidant equivalents over the course of the reaction. Both enzymes are able to oxidize electron rich systems and relatively electron poor systems containing ketones. When attempting to optimize the dimerization of resveratrol, it was found that pH had a very significant impact on the product distribution. Scanning pHs from 3.0-10.0 revealed that pH 8.0 gave the desired 5–8' dimer almost exclusively (Table 3, entry 4).[23] The authors hypothesize that protonation or deprotonation of histidine residues in the heme-containing cavity of the horse radish peroxidase

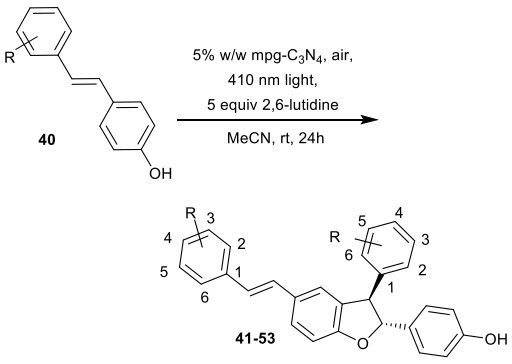
enzyme change the protein conformation and therefore binding mode of the substrate. Since that report in 2012 by the Pan group, no further investigations into the effect of pH on peroxidase promoted 5–8' dimerizations have been performed.

Table 3. Enzyme methods reported for the 5–8' coupling of *para*-alkenyl phenols



Entry	R^1	R^2	R^3	Catalyst	Oxidant	Solvent	Temp	Time	Yield (%)
1	CO_2Me	OMe	H	HRP	H_2O_2 (0.5 equiv)	MeOH/pH 3 Buffer	37 °C	10 min	43[30]
2	CO_2Me	OMe	H	Crude Onion Peroxidase Extract	H_2O_2 (12 equiv)	pH 5 Buffer	rt	30 min	90[31]
3		H	H	Laccase (*T. Pubescens)*	Air	EtOAc/pH 4.5 Buffer	40 °C	5 d	59[32]
4		H	H	HRP	H_2O_2 (1.3 equiv)	Acetone/pH 8.0 Buffer	40 °C	30 min	93 (HPLC)[23]

To date, the method with the largest scope for 5–8' coupling of alkenyl phenols was developed by Song and co-workers in 2014 (Scheme 11). A mesoporous graphitic carbon nitride material acts as a photocatalyst with air as the terminal oxidant. The 2,6-lutidine base was again found to be necessary for good yields, as in the above report by Romero *et al.* Both electron deficient and electron rich aryl systems were tolerated at the 8-position. Yields are consistently moderate to good (40-88%) across 13 examples. It was proposed that the photocatalyst acts to reduce molecular oxygen to a super oxide species which can then abstract an H-atom from each of two substrates. Radical-radical coupling then ensues.[33]



mpg-C_3N_4 = mesoporous graphitic carbon nitride
41, R = 3,5-OH 86%; **42,** R = 3,5-OMe 85%; **43,** R = 3,5-OAc 51%
44, R = H 71%; **45,** R = 4-F 40%; **46,** R = 4-Cl 77%; **47,** R = 4-Br 71%
48, R = 4-CF_3 70%; **49,** R = 4-OH 88%; **50,** R = 4-OMe 77%
51, R = 3-OMe 78%; **52,** R = 2-OMe 73%; **53,** R = 3,4-OMe 84%

Scheme 11. Photocatalyzed oxidative coupling of *para*-styrenyl phenols to give the 5–8' dimer

A notable gap in the literature, is the lack of successful enantioselective oxidative couplings with achiral substrates to form enantioenriched neolignan 5–8' coupling products. Diastereoselective coupling strategies have been reported using chiral amide auxiliaries with 62-84% de and fair to good yields[34,35] While no enantioselective synthetic method for the 5–8' dimers absent an auxiliary has been reported, it is possible to employ biocatalysis to enrich the mixture. Lipases

cause selective alcoholysis one enantiomer to give modest enantiomeric excess of either stereoisomer depending on the enzyme selected.[36, 37]

In conclusion, a variety of methods have been employed to synthesize 5–8' alkenyl phenol dimers. Synthesis of licarin A and its analogues has been a particular driver in this field. Transition metal oxidation, electrochemical oxidation, photocatalysis, and biocatalysis are all effective methods for forming the 5–8' C–C bond. Limitations include the selectivity of these reactions being largely substrate driven, generally modest scope, and the absence of enantioselective methods.

4-O–8' Coupling

There are many examples of 4-O–8' linked dimers but the vast majority of these lignan products have the phenol oxygen methylated. This trend may arise from the protected products being more stabile. The discussion here is limited to the phenol products only.

Macilin C was isolated from *Macilus thunbergii*.[38] An unnamed example (Chart 2, bottom structure) was isolated from *Ribes fasciculatum* and shown to be effective as an inhibitor of the nuclear factor of activated T cells.[39]

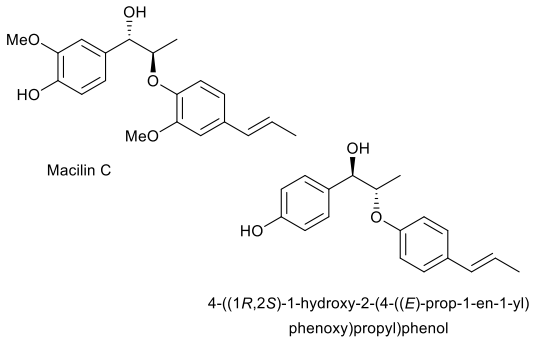
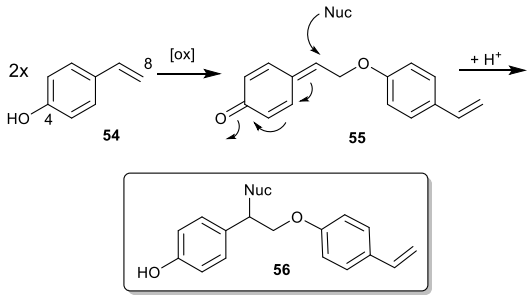


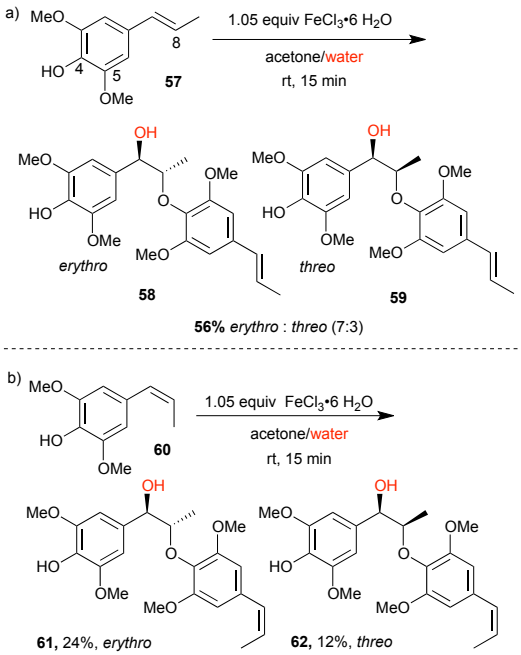
Chart 2. Natural products containing the 4-O–8' linkage

The mechanism to form these products involves an initial oxidative coupling between the phenol on C4 and C8' to generate **55** (Scheme 12). Addition of an external nucleophile to the *para*-quinone methide **55** provides the product **56**.



Scheme 12. General mechanism for the 4-O–8' coupling of *para*-alkenyl phenols

Oxidative coupling to give 4-O–8' coupled products in appreciable yields was first reported in 1973 when Wallis found that 2,6-dimethoxy-4-propenylphenol could be transformed via stoichiometric iron (III) chloride hexahydrate to give a mixture of dimers (Scheme 13).[40]



Scheme 13. Diastereoselective synthesis of 4-O–8' *para*-alkenyl phenol dimers using iron(III) chloride

In this case, the 5-position was blocked, preventing the formation of the 5–8' coupling product. Notably, the *cis* alkenyl phenol gave significantly lower yields than the *trans* isomer. The major product was as assigned as the *erytho* diastereomer, with a 2:1 ratio of diastereomers formed whether the *cis* or *trans* alkenyl phenol was used. Based on the mechanism discussed at the beginning of this section (Scheme 12), this result is consistent with a more favourable approach to the *para*-quinone methide from the side of the smaller methyl group as illustrated in the Newman conformations shown in Chart 3 (Q = quinone). In this case, water from the solvent acted as the nucleophile to trap the intermediate *para*-quinone methide, which provided the secondary alcohol product.

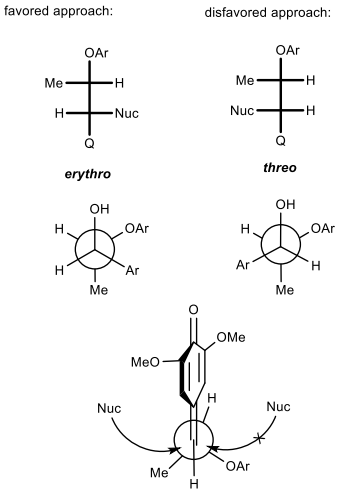
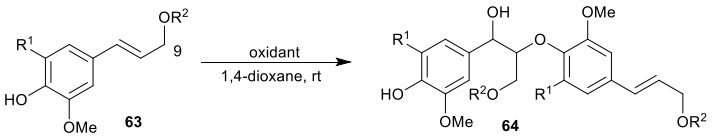
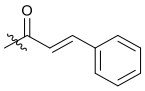


Chart 3. Model of diastereoselectivity for addition of a nucleophile to the reactive *para*-quinone methide intermediate (Q = quinone).

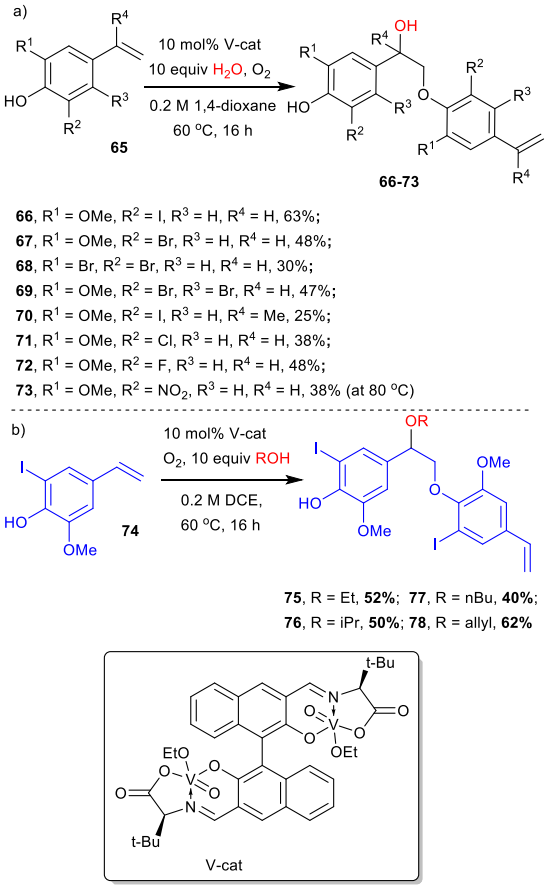
The Nakajima group found that Ag_2O works consistently well with electron-rich alkenyl phenols to affect C–O coupling (Table 4). In their first 2015 paper , they found that R^2 = COMe afforded substantially higher yields than with R^2 = H when 1.1 equiv of Ag_2O was used (entry 1 vs 3).[41] This outcome is positive to arise from coulombic repulsion between the two radicals in a radical-radical coupling. This repulsion would be reduced by the slightly electron withdrawing nature of an ester group vs a hydroxy group on C9. Later work with an excess of Ag_2O (3.25 equiv) eliminates this difference in reactivity (entry 2 vs 4).[42] The source of the trapping agent is presumably trace water in the highly hydroscopic solvent 1,4-dioxane.

Table 4. Ag(I) oxidation of *para*-alkenyl phenols to give the 4-O–8' coupled product



Entry	R^1	R^2	Oxidant (equiv)	Time	Yield (%)
1	OMe	H	Ag_2O (1.1)	1 h	32[41]
2	OMe	H	Ag_2O (3.25)	4.5 h	70[42]
3	OMe	COMe	Ag_2O (1.1)	20 min	48 *erythro*, 18 *threo* (66 total) [41]
4	OMe	COMe	Ag_2O (1.1)	4.5 h	71[42]
5	OMe		Ag_2O (3.25)	4.5 h	53[42]
6	H	H	Ag_2O (3.25)	4.5 h	70[42]
7	H	COMe	Ag_2O (3.25)	4.5 h	46[42]

In 2019, our group developed a method relying on a vanadium Schiff base catalyst to aerobically oxidize alkenyl phenols to the 4-O–8' dimers.[43] Notably, the successful substrates are all relatively electron poor in contrast to prior literature (Scheme 14a, 8 examples). Alcoholic nucleophiles could be employed without appreciable changes in yield (Scheme 14b, 4 examples).

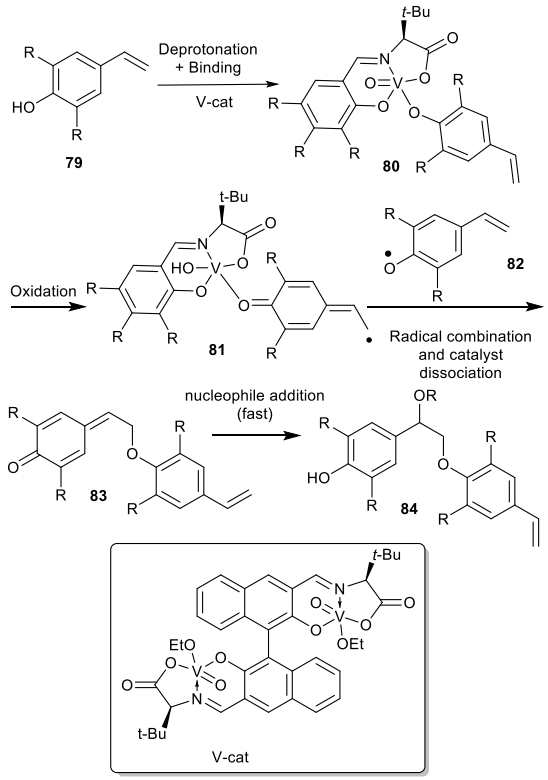


66, R^1 = OMe, R^2 = I, R^3 = H, R^4 = H, 63%;
67, R^1 = OMe, R^2 = Br, R^3 = H, R^4 = H, 48%;
68, R^1 = Br, R^2 = Br, R^3 = H, R^4 = H, 30%;
69, R^1 = OMe, R^2 = Br, R^3 = Br, R^4 = H, 47%;
70, R^1 = OMe, R^2 = I, R^3 = H, R^4 = Me, 25%;
71, R^1 = OMe, R^2 = Cl, R^3 = H, R^4 = H, 38%;
72, R^1 = OMe, R^2 = F, R^3 = H, R^4 = H, 48%;
73, R^1 = OMe, R^2 = NO_2, R^3 = H, R^4 = H, 38% (at 80 °C)

75, R = Et, **52%**; **77**, R = nBu, **40%**;
76, R = iPr, **50%**; **78**, R = allyl, **62%**

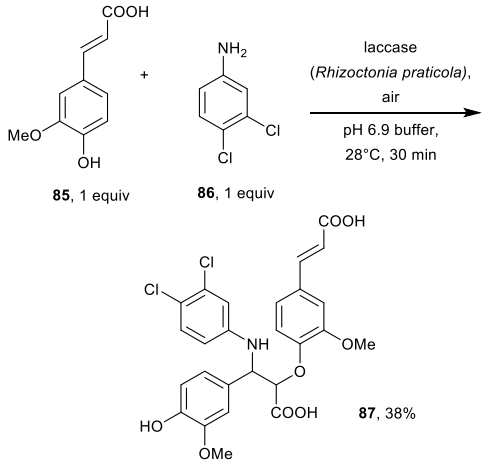
Scheme 14. Vanadium catalyzed coupling of *para*-alkenyl phenols to give the 4-O-8' dimer

The catalyst is a dimeric vanadium(V) Schiff-base catalyst (V-cat), the structure of which was hypothesized to assist in limiting the amount of unbound phenoxy radical, due to the presence of two catalytic V sites (Scheme 15). The 4–O–8' coupling is preferred over the radical-radical 8-8' coupling in non-polar solvents; such solvents should stabilize the phenol-catalyst complex and limit the amount unbound radical. These observations, along with NMR evidence of catalyst-phenol complexation in nonpolar solvents, lead us to the mechanistic hypothesis detailed in Scheme 15. After ligand exchange, coupling is proposed to take place between one substrate bound to the catalyst (**81**) and a second substrate as the free radical (**82**). At the time of publication, this report was the most thorough study of mechanism of an alkenyl phenol oxidation. It is our hope that this method may serve as a model for future reaction development to obtain other alkenyl phenol coupled products with high selectivity.



Scheme 15. Mechanism of vanadium catalyzed coupling of *para*-alkenyl phenols

The scope of nucleophiles for 4-O–8' dimerization reactions is not limited to hydroxyl containing compounds. The Bollag group in 1994 reported a laccase catalysed oxidation of ferulic acid where the quinone intermediate is intercepted by 3,4-dichloro aniline (Scheme 16). However, this study only provided a few exampes.[44]



Scheme 16. Enzyme catalysed oxidation of *para*-alkenyl phenol to give the 4-O–8' dimer, intercepted by an aniline nucleophile

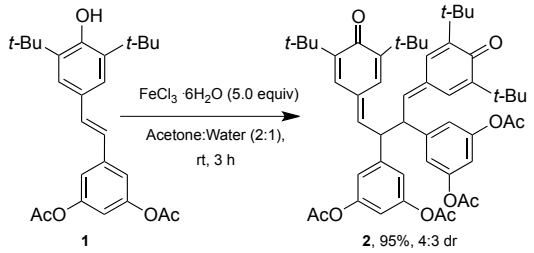
As with 5–8' coupling, many modes of forming the 4-O–8' C–O bond are known, but the reactivity is mostly substrate driven. The stereochemistry is not well controlled in these systems, with selectivity resulting largely from steric bias. Only the mechanism for the vanadium-catalysed coupling is well-explored.

8–8' Coupling

Di-*para*-quinone Methide

To the our knowledge, no examples of stable di-*para*-quinone methides natural products have been reported. This finding is unsurprising given the highly reactive nature of these compounds to nucleophiles. Biological media contains a plethora of nucleophiles, including water and amino acids, that would be sufficiently reactive to sequester any *para*-quinone methides formed. Mechanistically the formation of these products should proceed through a simple oxidative C–C coupling.

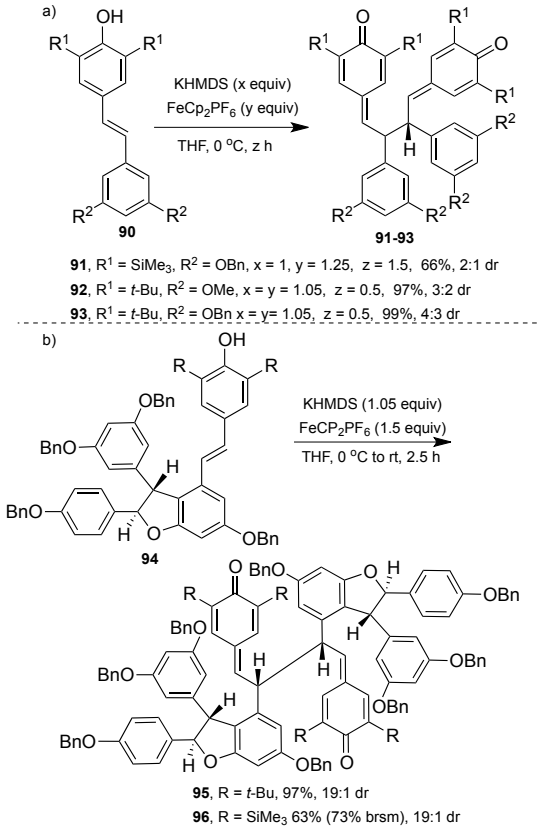
Stoichiometric iron salts have been found to be highly effective at generating these products. For example, substrate **88** with $FeCl_3$ gave the 88' homodimer **89** in almost quantitative yield with a relatively dilute 0.027 M acetone/water mixture (Scheme 18). One factor contributing to the success of this substrate **88** is the poor nucleophilicity of the aryl ring attached to C8. The authors of this work hypothesized that the dilute reaction conditions prevented the $FeCl_3$ from acting as a Lewis acid to promote the formation of intramolecular trapping products via nucleophilic aromatic substitution. The majority of other conditions reported in this work gave the corresponding water trapped tetrahydrofuran as the major product.[45]



Scheme 17. Highly efficient use of $FeCl_3$ to effect 8–8' coupling to give a di-*para*-quinone methide

In 2016, Matsuura and co-workers *en route* to pallidol and quadrangularin A optimized the dimerizations of **90** to give di-*para*-quinone methides **92, 93** in greater than 90% yield (Scheme 18a). The reaction of the monomer for substrate **92** was optimized, and it was shown that this substrate would auto-oxidize (60-80%) in CCl_4 under O_2 in the presence of stoichiometric amount of KOtBu base after 1 h indicating that this substrate is highly oxidizable. The deprotonation of the phenol reduces the oxidation potential of the substrate thus making it more susceptible to autooxidation by O_2. Photocatalysts were also surveyed with a variety of oxidants, but a stoichiometric iron salt with base most effective in generation the product [46] Because the NMR spectra of the diastereomeric dimers were highly similar the relative configurations could not be determined.

Keylor and co-workers further expanded the scope of this transformation and found that even the formation of lignan *tetramers* **95, 96** is possible using this system in excellent 19:1 dr (racemic) by using the previously formed 5-8' formed scaffold as assisting groups (Scheme 19b). The bond strength of the 8-8' C-C bond formed in **95** is extremely weak (17.0 ± 0.7 kcal/mol). Unsurprisingly, it was determined by EPR analysis that these dimers exist as an equilibrium between monomer radical and combined dimer.[47] After all of these dimerizations were performed, the respective groups showed that Lewis acids could promote the intramolecular cyclization of the pendant aryls on to the electrophilic *para*-quinone methides of products **91,92,93** to give pallidol-like products (see "Stilbenoid Dimers, Five Membered Rings" below).



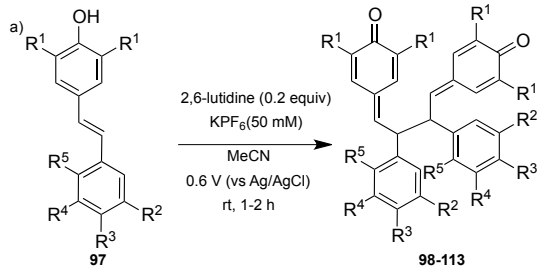
Scheme 18. Examples of a mildly oxidizing iron salt being used to generate di-*para*-quinone methides at cooled temperatures

Romero and co-workers showed in 2018 that 8–8' coupling could be performed electrochemically in good yields, >65% in all cases (Scheme 19a). A wide range of substrates, both electron-rich and electron-poor, gave good yields. However, aryl silyl protecting groups reduced the yield of the reaction significantly. Again, the structure of the major diastereomer is unknown. An advantage of this method is that column chromatography is not required at the end of the reaction, rather the products are acceptably pure after solvent evaporation.

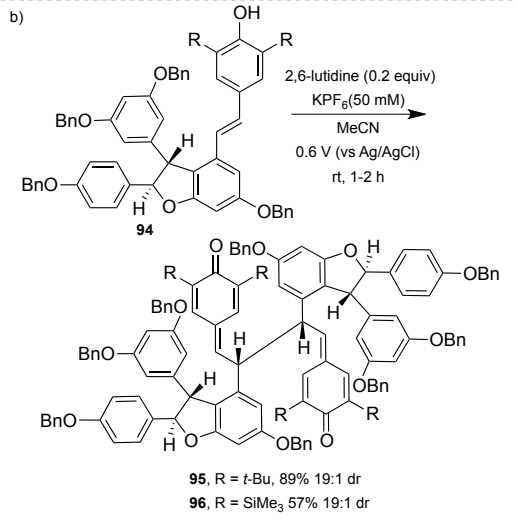
The same tetramers as those synthesized by Keylor and co-workers were also produced in moderate (>55%) yields via electrochemical means (Scheme 19b). The authors remark on the antioxidant activity of these dimers.[29]

Catalytic amounts of base were found to be beneficial and no reaction was reported to occur in the absence of base. In the absence of base additives, the oxidation potential of all the phenol substrates were above +0.8 V (vs Ag/AgCl). In the

presence of 2,6-lutidine, the oxidation potentials dropped below + 0.6 V (vs Ag/AgCl). This effect allowed lower potentials to be applied, minimizing overoxidation of the products.



98, R^1 = *t*-Bu, R^2 = OBn, R^3 = H, R^4 = OBn, R^5 = H, 99% 4:3 dr
99, R^1 = t-Bu, R^2 = OMe, R^3 = H, R^4 = OMe, R^5 = H, 99%, 3:2 dr
100, R^1 = *t*-Bu, R^2 = OPMB, R^3 = H, R^4 = OPMB, R^5 = H, 99% 5.4 dr
101, R^1 = *t*-Bu, R^2 = H, R^3 = H, R^4 = H, R^5 = H, 99% 4:3 dr
102, R^1 = $SiMe_3$, R^2 = OBn, R^3 = H, R^4 = OBn, R^5 = H, 65% 2:1 dr
103, R^1 = $SiEt_3$, R^2 = OBn, R^3 = H, R^4 = OBn, R^5 = H, 68% 2:1 dr
104, R^1 = *t*-Bu, R^2 = H, R^3 = H, R^4 = H, R^5 = NO_2, 93% 2:1 dr
105, R^1 = *t*-Bu, R^2 = H, R^3 = H, R^4 = H, R^5 = CF_3, 98% 5:1 dr
106, R^1 = *t*-Bu, R^2 = H, R^3 = H, R^4 = CF_3, R^5 = H, 97% 4:3 dr
107, R^1 = *t*-Bu, R^2 = H, R^3 = NO_2, R^4 = H, R^5 = H, 92% 1:1 dr
108, R^1 = *t*-Bu, R^2 = H, R^3 = CF_3, R^4 = H, R^5 = H, 94% 1:1 dr
109, R^1 = *t*-Bu, R^2 = OCH_2-, R^3 = O-, R^4 = H, R^5 = H, 99% 3:2 dr
110, R^1 = *t*-Bu, R^2 = OBn, R^3 = OBn, R^4 = H, R^5 = H, 94% 5:4 dr
111, R^1 = *t*-Bu, R^2 = H, R^3 = SMe, R^4 = H, R^5 = H, 93% 4:3 dr
112, R^1 = *t*-Bu, R^2 = H, R^3 = OBn, R^4 = H, R^5 = H, 95% 3:2 dr
113, R^1 = *t*-Bu, R^2 = H, R^3 = NHBoc, R^4 = H, R^5 = H, 96% 3:2 dr



95, R = *t*-Bu, 89% 19:1 dr
96, R = $SiMe_3$ 57% 19:1 dr

Scheme 19. Scope of electrochemical di-*para*-quinone methide generation using a base to faciliate oxidation

Dilactones and Furofurans

Additional examples of products found in nature that could arise from 8–8' coupling of alkenyl phenols are shown in Chart 4. Pinoresinol is a lignan that is found in a multitude of plants and also in the caterpillar *Pieris rapae*, which acts as a feeding deterrent to ants.[48] Syringaresinol was isolated from *Holacantha emoryi*.[49] Dehydrodiferulic acid dilactone was found to have antioxidant, anti-inflammatory, and anti-*T. cruzi* activities.[50]

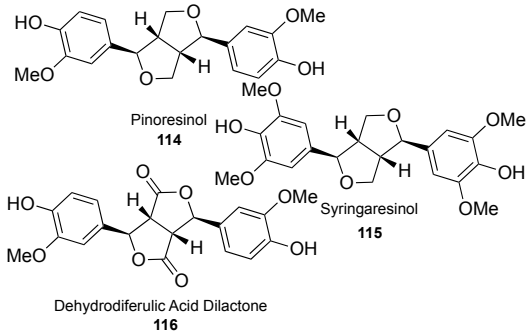
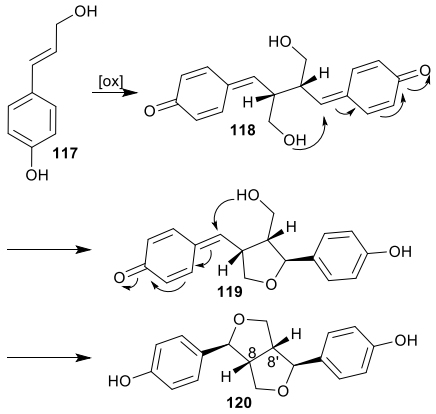


Chart 4. Examples of dilactone and furofuran natural products

The formation of dilactones and furofurans occurs first by the oxidative formation of the 8–8' C–C bond to give an intermediate like **118** (Scheme 20). Cyclization from an intramolecular oxygen nucleophile forms the first 5-member ring in **119**. A second intramolecular cyclization affords the product **120** with both aromatic rings regenerated.

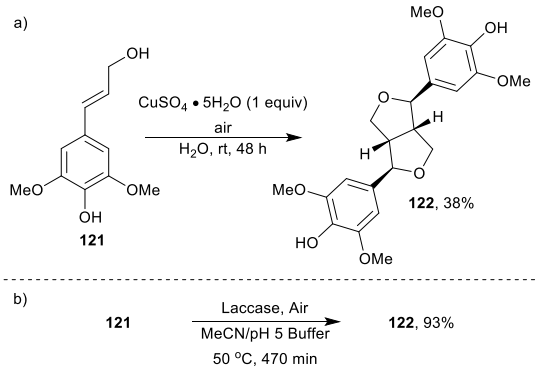


Scheme 20. General mechanism for the formation of dilactones and furofurans

Formation of furofurans is scant in the chemical literature. The pendant alcohol under oxidizing conditions is subject to competing reactions, such as oxidization to the aldehyde, and also coordinates metal ions. The dilactones enjoy greater precedent and substrates with *para*-coumaric acid core are surveyed in Table 5. $FeCl_3$ was the most general, and gave adequate (52-75%) yields of non, mono, and di-substituted alkenyl phenols with 0-2 substituents, with sinapinic acid giving the best yields (Table 5, entries 1-3).[50-52] A catalytic aerobic $CuSO_4$ system was also found to be effective with sinapinic acid to give dilactone in 83% yield (Table 5, entry 4).[53] Horseradish peroxidase was used to dimerize this same substrate in 77% yield with just 0.6 equiv of H_2O_2 in an acetone/water mixture (Table 5, entry 5).[54] Sinapinic acid was, likewise, successfully transformed via aerobic laccase oxidation to the desired dimer using a biphasic EtOAc/buffer system in excellent yield (Table 5, entry 6). [55-57] Broadly speaking, only sinapinic acid has been found to consistently show this type of reactivity.

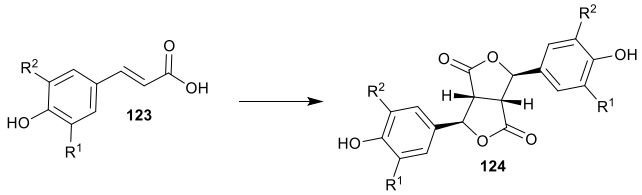
Two reports to the furofurans, however, have appeared. Using the sinapyl alcohol **121** with a stoichiometric copper salt the reaction gives the corresponding dimer syringaresinol (**122**) in 38% yield (Scheme 21a).[30] Using a

laccase system, this same transformation could be effected in 93% yield (Scheme 21b).[56, 57] Other substrates without the 5-position blocked have been reported, but the yields are typically only ~20% because of competing processes.[30, 58]



Scheme 21. Formation of furofurans

Table 5. Summary of all relevant reported syntheses of dilactone products via oxidative dimerization of alkenyl phenols

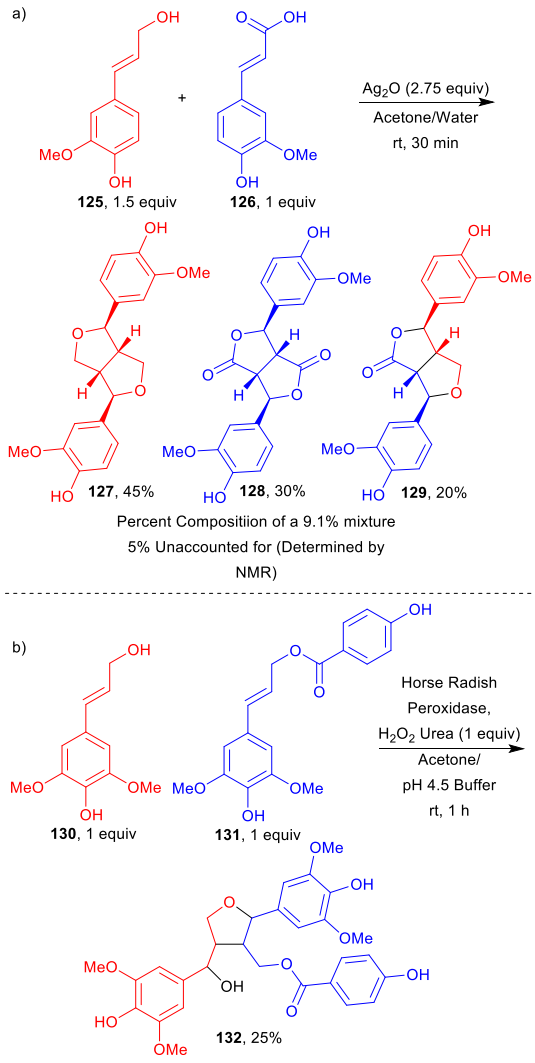


Entry	R^1	R^2	Catalyst/Additive	Oxidant	Solvent	Temp	Time (h)	Yield (%)
1	H	H		$FeCl_3$ (2.2 equiv)	EtOH	rt	1	52[51]
2	OMe	H		$FeCl_3$ (2.2 equiv)	EtOH	rt	1	56[51]
3	OMe	OMe		$FeCl_3$ (2.2 equiv)	EtOH	rt	1	75[51]
4	OMe	OMe	$CuSO_4 \cdot 5H_2O$ (20 mol%)	air	MeCN/Water	rt	7	83[53]
5	OMe	OMe	Horse Radish Peroxidase	$H_2O_2 \cdot$ Urea Complex (0.6 equiv)	Acetone/Water	rt	2.5	77[54]
6	OMe	OMe	Laccase	Air	EtOAc/pH 5.0 Buffer	rt	0.5	97[55]

Formation of pinoresinol (Chart 4) via a direct oxidative enantioselective dimerization has not been achieved. However, Davin and co-workers in 1992 found that enzymes from the stem of *Forsythia suspensa* afforded (+)-pinoresinol in ~60% ee from achiral coniferyl alcohol.[59] Similarly, Pickel and co-workers in 2009 discovered that two proteins in conjunction with laccase could afford enantioenriched pinoresinol. The (+)-enantiomer is obtained in 57% ee with laccase and FIDIR1 from *Forsythia intermedia* and the (–)-enantiomer is obtained in 78% ee with laccase and AtDIR6 from *Arabidopsis Thaliana*. These proteins are known as enantiocomplementary dirigent proteins (EDPs). In effect these proteins bind to substrate and allow for the asymmetric coupling to occur. [60] At this time, these reactions have not been reported on a preparative scale.

Cross Coupling

Examples of cross couplings are limited in the literature for 8–8′ coupling. The first report in 1992 showed that oxidation of a mixture of coupling partners **125, 126** with Ag_2O affords the cross coupling adduct as a minor product (Scheme 22a).[61] This outcome is interesting as the use of different stoichiometries of each starting material and two substrates with different electronic activation is expected to perturb the outcome. However, the formation of both homocoupling products to a greater extent that the cross-coupling product is most consistent with a radical-radical coupling where reaction of two monomers with similar SOMO levels is fastest.



Scheme 22. Only examples of 8–8' cross coupling reported

In a later report, horse radish peroxidase with a 1:1 stoichiometry of the two substrates produced cross product x-3 in 25% yield (Scheme 22b). A 1:2:1 mixture of the AA:AB:BB dimers was observed, but only the cross dimer isolated yield was provided. This study indicated that the alcohol protecting group had very little effect on the coupling because a statistical mixture of products was generated.[62]

2,5-Diaryltetraydrofurans

Examples of the many natural 8–8' linked tetrahydrofuran natural products can be seen in Chart 5. In 1997, Schöttner and coworkers identifed neoolivil from the roots of *Urtica dioica*.[63] Fragransin A_2, fragransin C_1, as well as verrucosin were all isolated from *Myristica fragrans* in 1987.[64] The grapevine pathogen *Botrytis cinereal* was found to produce the dimer restrytisol B.[65]

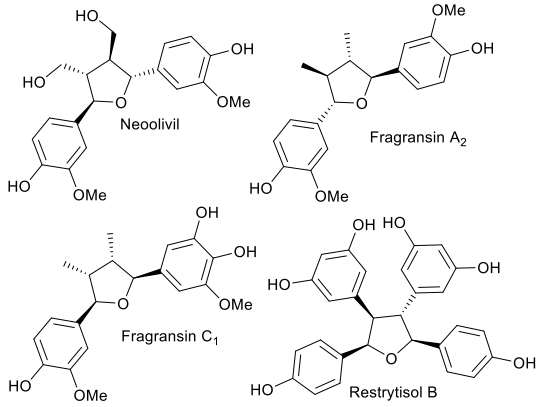
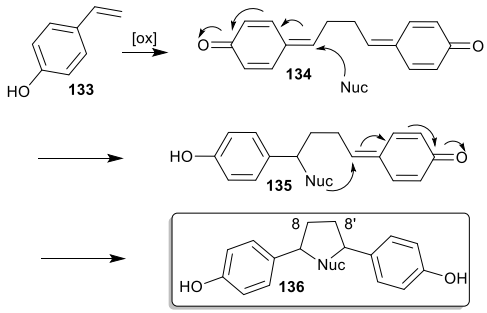


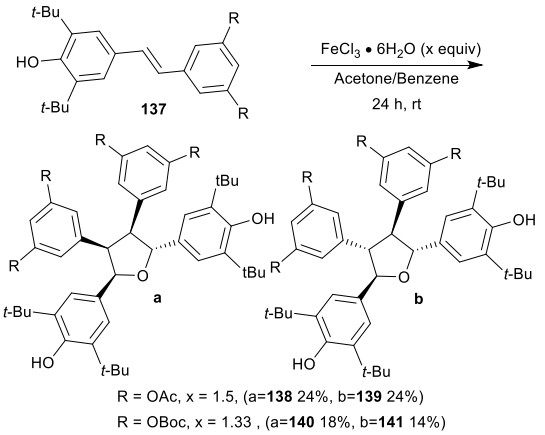
Chart 5. Examples of tetrahydrofuran lignan natural products

Mechanistically, these tetrahydrofurans arise from, first, oxidative 8–8' coupling (Scheme 23). The resultant di-*para*-quinone methide **134** is then subject to addition by a "bi-dentate" nucleophile in solution to give **135** and then **136**. The tetrahydrofurans are a result of addition of a water molecule, but as will be seen, aniline can also act as a suitable nucleophile to afford a five-membered cycle.



Scheme 23. General mechanism for the formation of 8–8' coupled alkenyl phenols trapped by "bidentate" nucleophiles

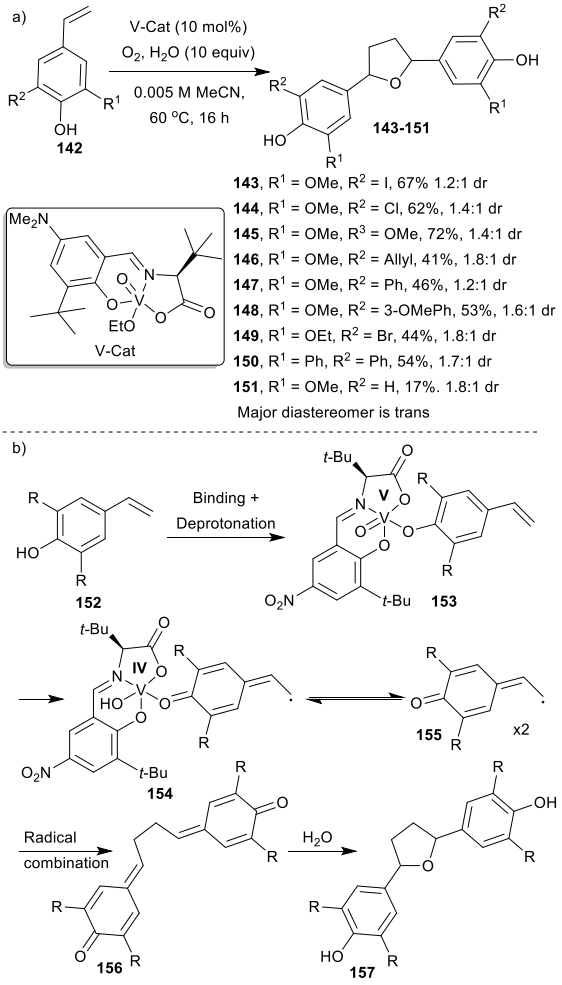
There are very few reports of successfully oxidizing alkenyl phenols to tetrahydrofuran products. In 2014, oxidative coupling of di-*ortho*-*tert*-butylated alkenyl phenols (substrates of **138, 140**) with stoichiometric $FeCl_3$ to form tetrahdyrofurans was reported (Scheme 24).[66] These substrates with flanking *tert*-butyl groups were much more effective as substrates relative to less substituted systems; presumably, the steric bulk suppresses other reactions such as those originating from the phenol (see O-4–C8' Coupling Section above). Only two of these substrates were reported and both of them resulted in a ~1:1 mixture of *cis/trans* diastereomers. These products were investigated *en route* to the natural products restrytisols B and tricuspidatol A; ultimately, the route did not prove successful because the *tert*-butyl groups could not be removed without accompanying decomposition.



Scheme 24. $FeCl_3$ promoted formation of tetrahydrofurans by the oxidation of alkenyl phenols

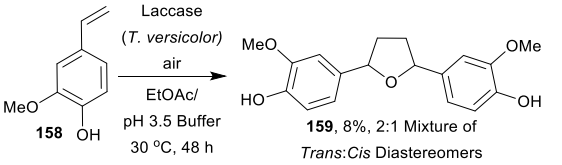
In 2019, our group developed a relatively general method to oxidatively couple alkenyl phenols to generate the tetrahydrofuran products (Scheme 25a). A vanadium(V) Schiff base complex was used as an aerobic catalyst in this system. Yields ranged from 17-72%; all products were mixtures of both *trans* and *cis* diastereomers, with the *trans* isomer predominating. Electron rich substrates tended to perform better.[43]

After a series of experiments, a mechanism was postulated in which **152** first deprotonates and bind to the vanadium catalyst to form **153** (Scheme 25b). This binding was supported by a rapid shift in the ^{51}V NMR spectrum upon treatment with the phenol substrate. Subsequent electron transfer to the metal gives an oxidized phenol that equilibrates between the bound and unbound form. The formation of more tetrahydrofuran upon dilution supports formation of the product from the unbound form **x**. Additionally, polar solvents promoted more 8–8' coupling, possibly because more polar solvents shift the equilibrium to unbound phenoxy radical **155**. The di-*para*-quinone methide intermediate **156** is then trapped with water to form tetrahydrofuran **157**.



Scheme 25. Vanadium catalysed selective formation of tetrahydrofurans through the aerobic oxidation of alkenyl phenols

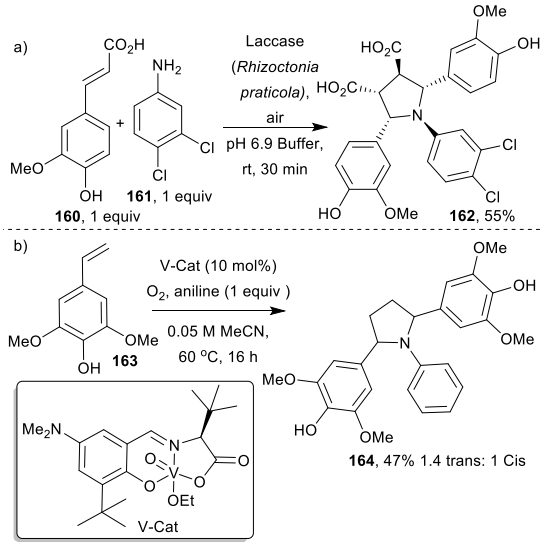
In an earlier 2011 report, Gavezzotti and co-workers described an 8% yield of 8-8' tetrahydrofuran product **159** via enzymatic coupling under aerobic conditions (Scheme 26). The reaction with laccases was slow, taking two days, and gave a 2:1 mixture of diastereomers. This product was one component of a mixture of three other isomers, in which the major isomer was the 5-8' coupled product in 13% yield. This reaction was the first example of an alkenyl phenol with not substituent at C8 undergoing coupling to give the tetrahydrofuran product.[36]



Scheme 26. Enzymatic oxidative coupling to form tetrahydrofurans from alkenyl phenols

A consequence of tetrahydrofuran formation via double nucleophilic addition to a di-*para*-quinone methide intermediate is that alternative "bi-dentate" nucleophiles should also be effective. In 1994, it was found that trans-ferulic acid **160** could be oxidized in 55% yield in the

presence of 3,4-dichloroaniline (**161**) to form a pyrrolidine product **162** (Scheme 27a). Notably, intermolecular trapping by one equivalent of aniline was faster than the intramolecular trapping by the carboxylic acid moieties. Furthermore, this result establishes that the nitrogen of the pyrrolidine product is relatively stable to laccase oxidation.[44] Our group then discovered that a vanadium(V) Schiff base catalyst oxidative coupling catalyst also permitted aniline trapping of a di-*para*-quinone intermediate generated *in situ* to give the pyrrolidine **164** (Scheme 27b) in 47% as a mixture of isomers (1.4:1 *trans:cis*).[43]



Scheme 27. All reports of forming pyrrolidines through trapping of di-*para*-quinone methide intermediates

Stilbenoid Dimers with Five Membered Rings

Stilbenoid dimers are a ubiquitous class of compounds found in nature (Chart 6). These molecules have also been the target many total synthesis efforts. The dimer gnemontanin C was found in *Gnetum montanum* in 2016 by Zhai and co-workers.[67] Quadrangularin A was isolated in 1999 from *Cissus quandrangularis* and synthesized in 2006 by Li and co-workers.[68] Gnetulin has been isolated from multiple species of the *Gnetum* genus and was synthesized in 2019 by the Yao group.[69] The natural product leachianol F was isolated from the roots of *Sophora leachiana* in 1995.[70] Gnetuhainin I was isolated in 2000 from *Gnetu hainanense* by the Lin group.[71] Pallidol was first isolated from *Cissus pallida* in 1986.[72] Gneafricanin F was found in 2002 in the stem lianas of *Gnetum africanum*.[73]

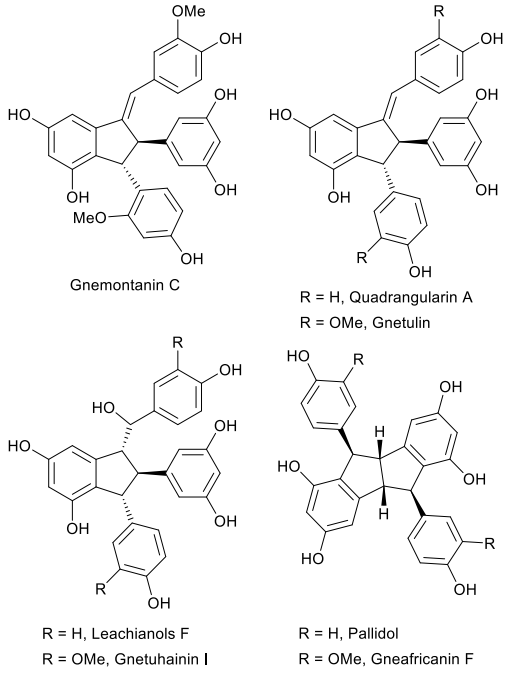
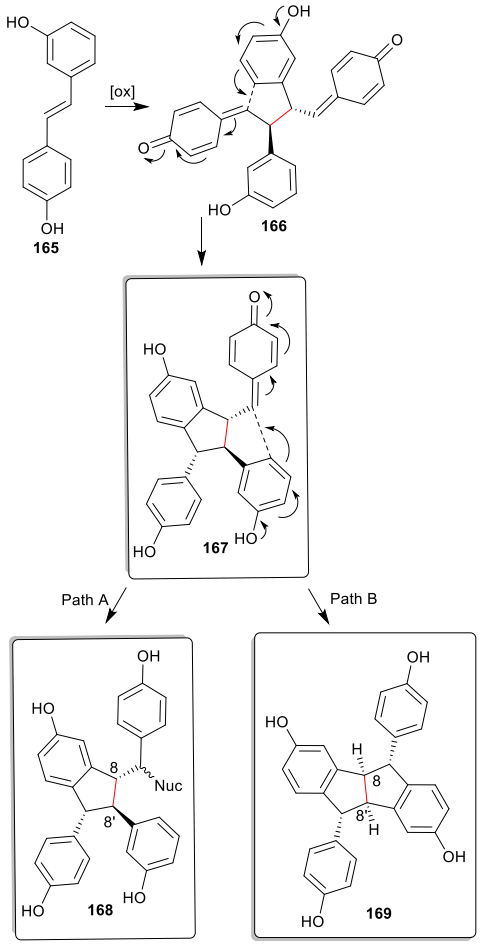


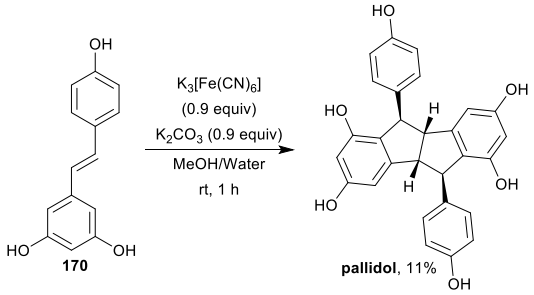
Chart 6. Examples of stilbenoid dimer natural products

The mechanism (Scheme 28) proceeds first by formation of the di-*para*-quinone methide **166** (see Scheme 27). Subsequent cyclization by intramolecular addition of one phenol to the *para*-quinone methide provides **167** with the cyclopentyl substituents residing *trans* to one another. From there, the remaining *para*-quinone methide can either be subject to addition by an intermolecular nucleophile to form **168** (path a), or by the intramolecular nucleophilic pendant aryl group to form **169** (path b). In the case where a relatively small intermolecular nucleophile adds in, a mixture of diastereomers of **168** will result. In the case where the intramolecular nucleophilic addition occurs to form **169**, the ring fusion hydrogens and the stereogenic aryl substituents are all *syn* orienting toward the convex face to mitigate steric interactions.



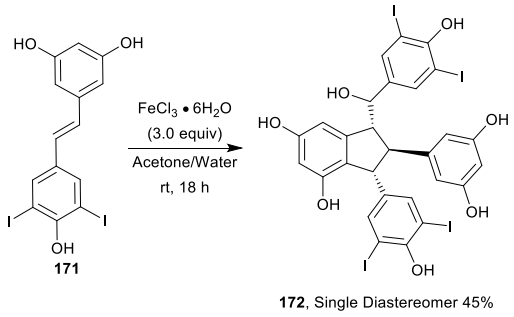
Scheme 28. General mechanism for the formation of stilbenoid dimer products from oxidation

Oxidation of the stilbene monomer resveratrol **170** with $K_3[Fe(CN)_6]$ for 1 h in the presence of weak base forms the natural product pallidol (Scheme 29). While the reaction provides only modest yield (11%), synthetically useful amounts of the product pallidol are formed in one step from a cascade process involving double intramolecular trapping of the di-*para*-quinone methide.[74]



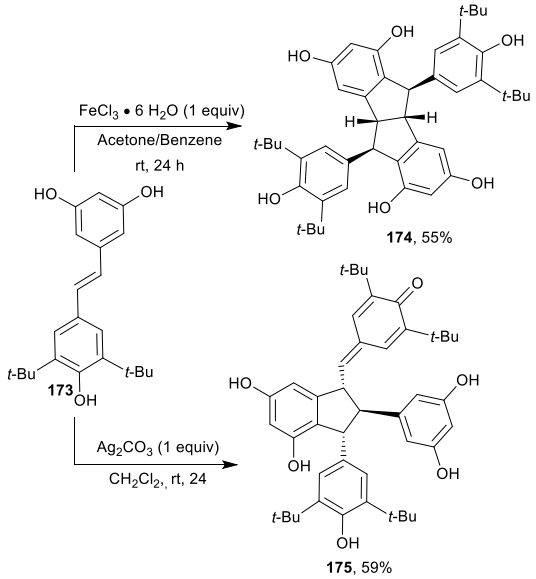
Scheme 29 Low yielding direct oxidative coupling to form pallidol

A bis-iodinated stilbene **171** with a different stoichiometric iron oxidant, $FeCl_3$ in an acetone water mixture, halts after one cyclization to give **172** (45%) with water trapping the second *para*-quinone methide (Scheme 30). Only a single diastereomer was generated and no other coupling products were reported. The role of the Lewis acidic $FeCl_3$ vs substrate control on the high diastereoselectivity is unclear.[75]



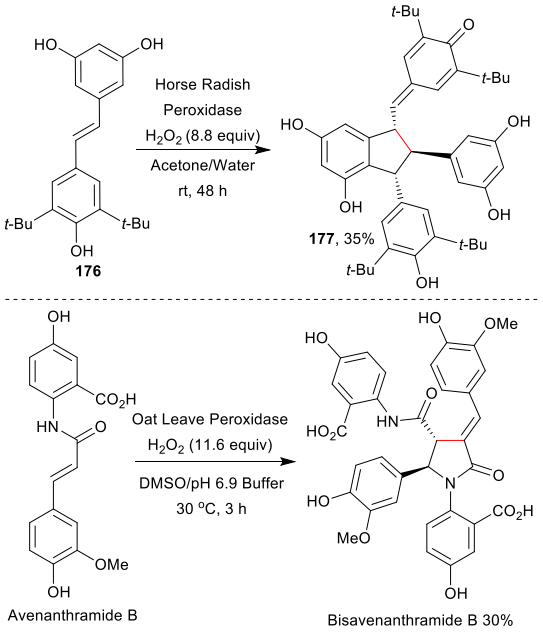
Scheme 30. Formation of a stilbenoid dimer promoted by $FeCl_3$

Depending on the substrate, the reaction outcome can vary depending on the identity of the transition metal oxidant (Scheme 31). In the presence of Lewis acidic $FeCl_3$, nucleophilic addition from the proximal resorcinol occurs to form the second five-membered ring in **174**. On the other hand, Ag_2CO_3 stopped after formation of the first five-membered ring and left the reactive *para*-quinone methide intact (Scheme 31, **175**). These outcomes highlight that Lewis acidity of the oxidizing metal species can modulate selectivity by effecting post-oxidative coupling steps.[76]



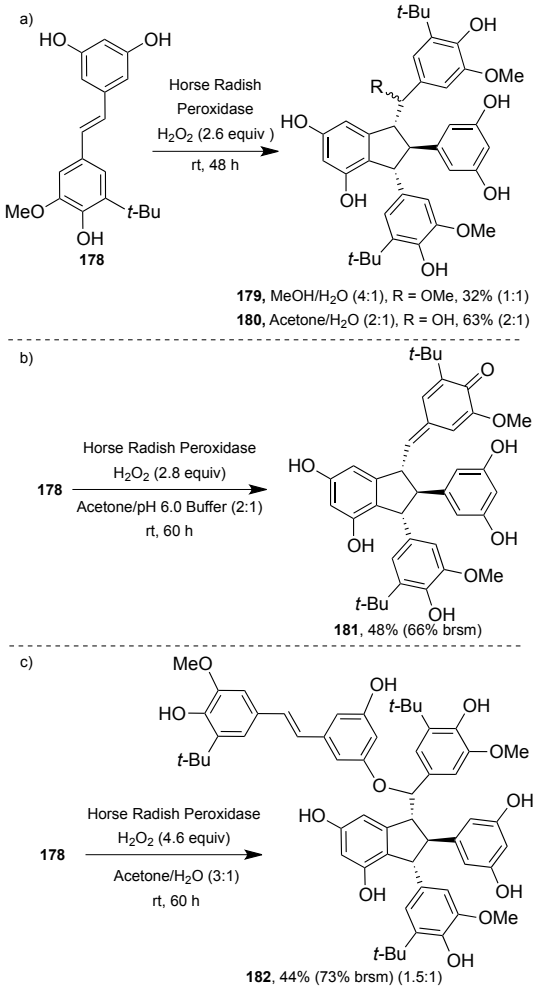
Scheme 31. Demonstration of the impact of oxidant choice on reaction outcome of a model stilbene

In the mid-2000s, use of a large excess (>8 equiv) of H_2O_2 oxidant with a peroxidase permitted isolation of the *para*-quinone methide after one intramolecular cyclization in acceptable yields (35%, Scheme 32). Notably, the *para*-quinone methide can be isolated from an aqueous system without trapping by water. This strategy was used *en route* to the synthesis of natural product quadrangularin A.[68] This strategy was also effective in converting avenathramide B to bisavenanthramide B.[77, 78]



Scheme 32. Enzymatic oxidations of electron rich alkenyl phenols to give five member cycles

In 2014, a study investigated the effect of solvent, oxidant equivalents, and time on the oxidation of a model stilbene **178** with horse radish peroxidase. Under all conditions, the major product was a five-membered carbocycle. With a methanol/water mixture, methanol traps the postcyclization *para*-quinone methide intermediate to form **179** in 32% yield (1:1 dr). In neutral water/acetone mixture, the major product (**180**) arises from trapping of water (Scheme 33a) in 63% yield (2:1 dr). However, when slightly acidic buffer is used instead of neutral water, the major product becomes a stable *para*-quinone methide **181** in 48% yield (Scheme 33b). Remarkably, increasing to greater than four equivalents of oxidant and minimizing the amount of water in the acetone/water solvent mixture allowed another monomer to act as the trapping agent to afford **182** in 44% yield and 1:1 dr (Scheme 33c). This work was performed as part of the synthesis of gnetulin.[79]



Scheme 33. Oxidation of an identical stilbene under various oxidative enzymatic conditions to give a diverse range of dimeric products

ortho-Alkenyl Phenols

Benzoxanthenones are an important class of tetracyclic lignans which are typically highly oxygenated (Chart 7). One example, carpanone, was first isolated in 1969 from the bark of the Carpano tree.[80] Polemannones A-C were isolated in 1986 from the species *Polemannia montana*.[81] The compound sauchinone cannot be synthesized directly via oxidative coupling, but has significant biological activity with anti-inflammatory,[82] immunosuppressive,[83] and hepatoprotective effects.[84] Compound CCL-19 was identified as a specific and relatively potent inhibitor of $VSVG^{ts}$-GFP trafficking by screening a library of 10,000 benzoxanthenones.[85]

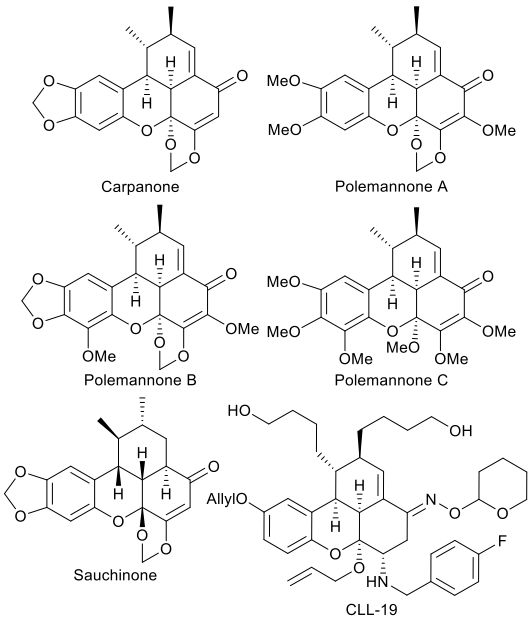
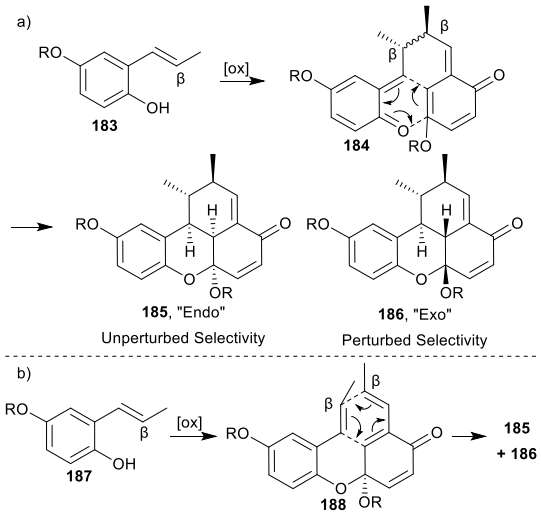


Chart 7. Examples of benzoxanthenone natural products and one example of an artificially synthesized pharmacologically relevant benzoxanthenone analogue

There are two commonly accepted mechanisms for the oxidative formation of benzoxanthenone dimers. With one electron oxidants, it is hypothesized that 8-8' coupling occurs via radical intermediates (see Scheme 34) to form a di-*ortho*-quinone methide **184** intermediate which can then undergo a Diels-Alder cyclization to **185, 186** (Scheme 34a). For the thermal reaction, the kinetic product is the *endo* diastereomer **185**. For carpanone, DFT calculations (B3LYP/6-31G) indicate that the *endo* diastereomer **185** is the thermodynamically more stable product by 9.1 kcal/mol compared to **186**.[86] With two electron oxidants such as PIDA, it is hypothesized that the C–O bond forms first to give **188**, and a subsequent Diels-Alder cyclization gives the same diastereomer **185, 186** (Scheme 34b).[85]



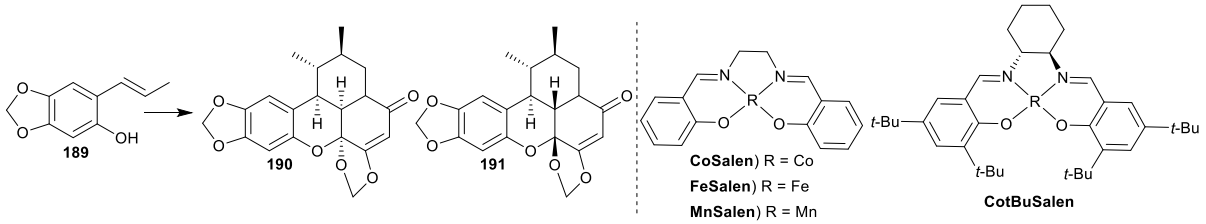
Scheme 34. The two generally accepted oxidative mechanistic schemes for the formation of benzoxanthenones from the oxidation of *ortho*-alkenyl phenols

Carpanone has been synthesized many times via different methods as researchers probed these mechanisms that rapidly construct complexity from simple substrate. Notably, carpanone forms spontaneously from its monomer in the presence of oxygen, which highlights the low oxidation potential of this substrate.[87] In 1971, Chapman reported the first synthesis of carpanone via two electron oxidation using stoichiometric $PdCl_2$ (Table 6, Entry 1). In this work, the authors propose a mechanism in which the two phenols displace the chlorides of palladium and form the initial carbon bond via 8-8' coupling through concerted reductive elimination process.[88]

Fe, Mn, or Co salen catalysts were highly effective in this process (Table 6, entries 2-6).[89] Use of a flow reactor with the CotBuSalen catalyst provided a further benefit (92% HPLC, Table 6, entry 6).[90] In another tactic, Ley and co-workers used a polystyrene-bound Co(salen) catalyst under aerobic conditions to produce carpanone in 80% yield (Table 6, entry 7).[91] This catalyst had the advantage that it could be easily removed, and potentially recycled from the reaction mixture by a simple filtration.

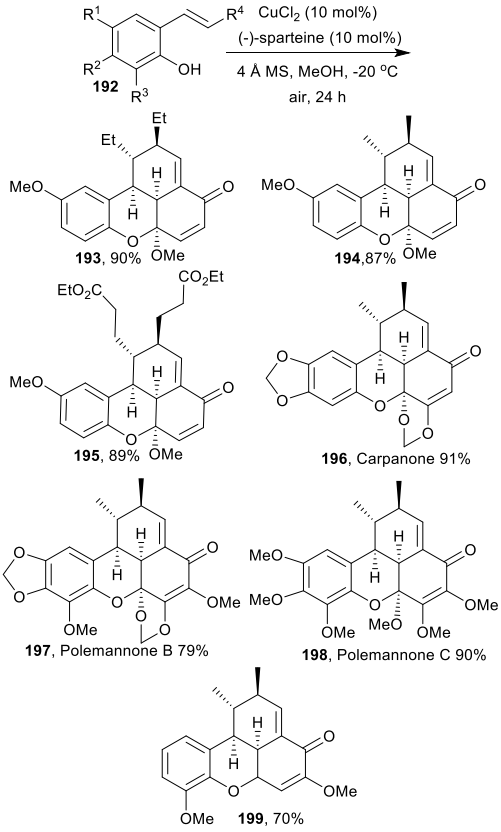
This reaction can also be performed in a moderate 48% yield with the one electron oxidant Ag_2O (Table 6, Entry 8).[92] The organocatalyst 4-MeO-TEMPO (4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy) and the enzyme laccase under aerobic conditions also give good yields (Table 6, entries 9,10).[93]

Table 6. A representative overview of many of the reported syntheses of carpanone



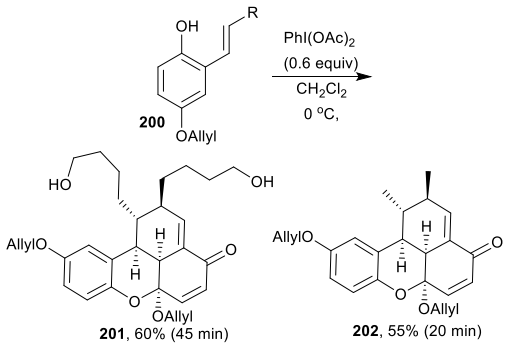
Entry	Catalyst	Oxidant	Solvent	Temp	Time	Yield (%)	dr (**190**:**191**)
1		$PdCl_2$ (0.5 equiv),	MeOH/Water	38 °C	2 h	46	1:0[88]
2	CoSalen (5 weight %)	O_2	CH_2Cl_2	rt	1.5 h	94	1:0[89]
3	FeSalen (5 weight %)	O_2	CH_2Cl_2	rt	1.5 h	78	1:0[89]
4	MnSalen (5 weight %)	O_2	CH_2Cl_2	rt	1.5 h	80	1:0[89]
5	CotBuSalen (2.6 mol %)	O_2	CH_2Cl_2	rt	4 h	79	9:1[93]
6	CotBuSalen (10 mol %)	O_2	DCE	40 °C	Flow Reactor	92	HPLC 1:0[90]
7	Polystyrene-CoSalen (10 mol % Co)	O_2	CH_2Cl_2	rt	3 h	80	HPLC 98% pure
8		Ag_2O (2 equiv)	CH_2Cl_2	rt	30 min	48	1:0[92]
9	4-MeO-TEMPO (27 mol%)	O_2	Benzene	70 °C	4 h	79	9:1[93]
10	Laccase (*T. versicolor*)	Air	Acetone/pH 5.0 Buffer	rt	2 h	68	9:1[93]

Catalytic copper systems have been found to be effective in diastereoselective oxidative coupling of alkenyl phenols. Yields are very good with a $CuCl_2$, (–)-sparteine, and air system (Scheme 35). The natural products carpanone, polemannone B, and polemannone C have all been made in high yields using this system (Scheme 35).[94] No enantiomeric excess was observed in any trial which is most consistent with outer sphere oxidation and free radical coupling.[95] Only very electron rich substrates without any reactive functional groups are compatible with this system.



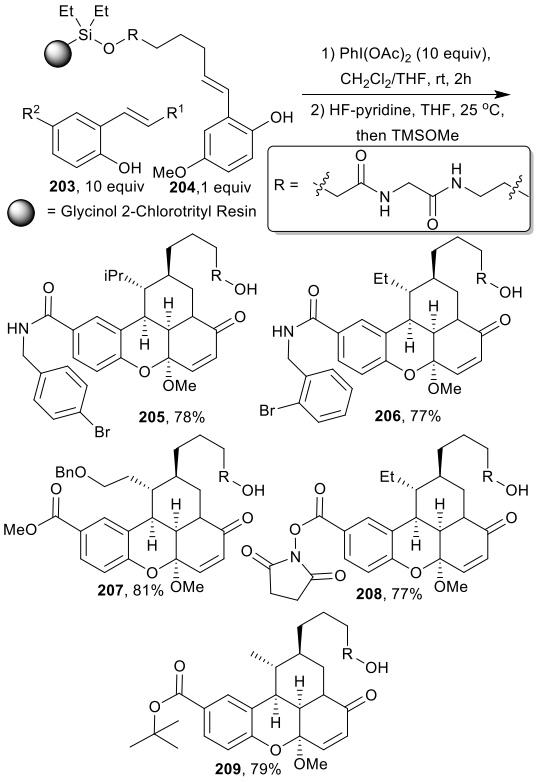
Scheme 35. Scope of aerobic copper catalysed benzoxanthenone formation

In 2006, the Shair group showed that PIDA was an effective oxidant to afford benzoxanthenone dimers **201, 202** in 60% and 55% yields respectively (Scheme 36). Unexpectedly, the pendant alcohols on **201** were compatible with the reaction conditions. The authors propose that this reaction takes place by the C–O coupling of the phenolic oxygen to the *para*-position of another phenol monomer. This coupling intermediate would then be primed for an inverse electron demand Diels-Alder reaction per Scheme 34a to give the product.[85]



Scheme 36. Efficacy of PIDA to effect dimerization of *ortho*-alkenyl phenols to benzoxanthenones

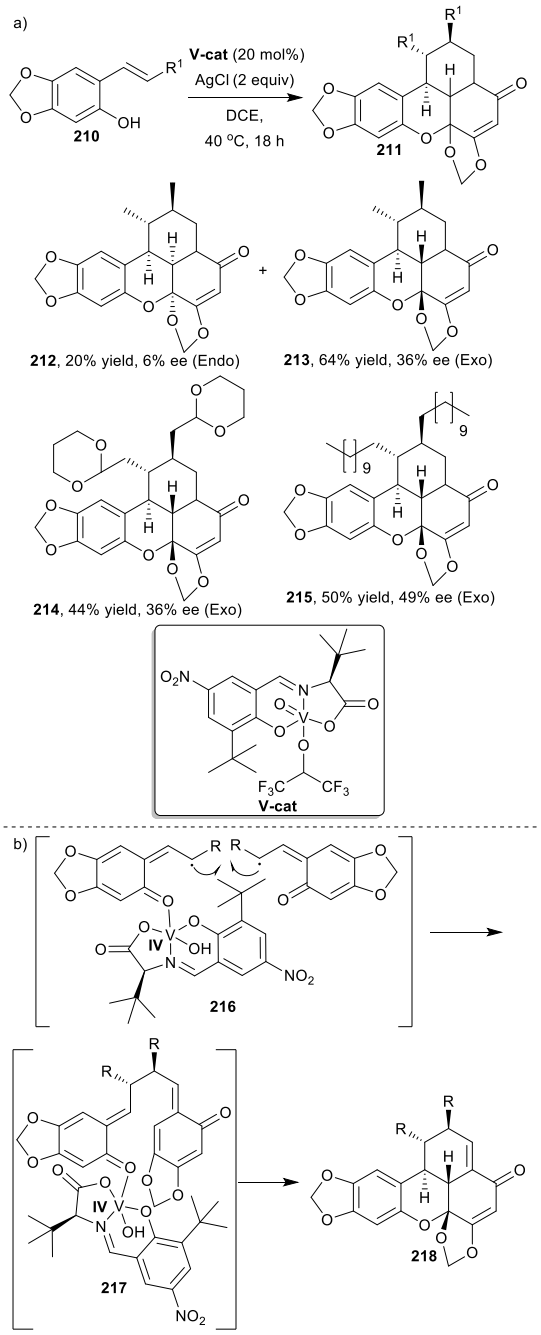
In order to afford cross coupling, Lindsley and co-workers tethered the more electron rich coupling partner to a glycinol-2-chlorotrityl resin solid support (Scheme 37).[96] With a large excess of PIDA, good yields (77-81%) of cross coupling products were observed. This approach mitigated homocoupling by sufficient separation of the monomers on the solid support and allowed for easy isolation of the heterodimer as the major product. One key limitation is the use of 10 equivalents on the unbound coupling partner. The authors also note that PIDA was the only oxidant that afforded any of the cross dimer.



Scheme 37. Cross coupling examples to form benzoxanthenones using solid supports

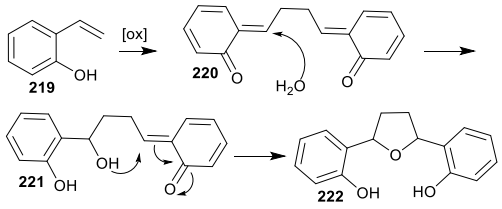
There is only one report of formation of the *exo* product of a benzoxanthenone diastereoselectively via an oxidative alkenyl phenol coupling strategy. With a monomeric vanadium(V) Schiff base catalyst and a silver oxidant, the *exo* diastereomer is the major product (Scheme 38a).[86] Silver salts were employed as the terminal oxidant because they caused no reaction in the absence of the catalyst. Most other oxidants, including air, would directly act on the substrate causing uncontrolled homocoupling from the free phenoxy radical which afford the *endo* diastereomer. Modest enantioselectivities (36-49% ee) and yields (44-64%) were seen across the three-molecule scope. This transformation was found to be poorly scalable because of the low solubility of the silver salts, making this a heterogeneous reaction.[86]

The proposed mechanism proceeds 8–8' coupling between a vanadium-bound phenoxy radical and an unbound radical (Scheme 38b, transition state **216**) where the catalyst induces enantioselectivity (Scheme 40b). The diastereoselectivity is thought to be perturbed by the continued presence of the catalyst in transition state **217** to generate the *exo* product **218**. The importance of catalyst binding to the selectivity was supported by a very strong trend between solvent polarity and the product ee. Non-polar solvents stabilize the vanadium coordination adduct vs a free phenol (see Scheme 26). The negligible enantioselectivity of the *endo* product **212** to support formation of the *endo* product via a free radical process absent interactions from the vanadium catalyst in the key bond forming steps.



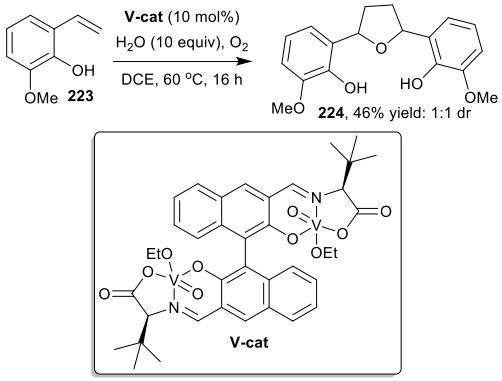
Scheme 38. Vanadium catalysed diastereoselective coupling to afford "Exo" benzoxanthenones

Since 8–8' coupling can occur for *ortho*-alkenyl phenols, it is logical that the di-*ortho*-quinone methide could be intercepted by an external nucleophile so long as the intramolecular reactions are slower (Scheme 39). With bidentate nucleophile such as water, formation of the tetrahydrofuran scaffold should be viable as with the *para*-alkenyl phenols (see 2,5-Diaryltetraydrofurans section above).



Scheme 39. Proposed mechanism for the oxidative formation of tetrahydrofurans from *ortho*-alkenyl phenols

Only one example of an *ortho*-alkenyl phenol undergoing oxidatively dimerized to a tetrahydrofuran has been reported.[43] With a dimeric vanadium catalyst under aerobic conditions product **224** was formed in 46% yield as a 1:1 *cis*:*trans* mixture (Scheme 40). Water was added to the reaction mixture to act as a trapping agent for the di-*ortho*-quinone methide intermediate that would form after the initial C–C coupling between the alkene termini.



Scheme 40. Tetrahydrofuran formation by oxidation of an *ortho*-alkenyl phenol

Conclusion

The couplings of alkenyl phenols can give a range of highly structurally diverse products, often rapidly building complexity. Only in select cases are the mechanisms that control the different reaction pathways well understood. Reviewing the features of the substrates employed to arrive at each coupling product as well as the types of oxidizing systems employed, can aid in understanding the broad trends in this field.

With respect to the 5–5' couplings, only substrates with electron rich groups on the aryl component and electron withdrawing groups on the alkene component proceed well. It is surprising to see that both PIDA and laccases are effective oxidants for this C–C coupling, because their mechanisms are fundamentally different (one electron oxidation to radical vs two electron oxidation to phenoxonium).

While the 5–8' couplings are much more widely studied, there are still significant substrate limitations even though many oxidizing systems have been shown to be effective. A multitude of diastereoselective couplings have also been performed using chiral auxiliaries, but the best result is 92:8 dr. The development of an enantioselective catalytic method is difficult due to weak or no catalyst-substrate interactions during the key coupling events, but would be useful to supplant the need for chiral auxiliaries and to improve atom economy.

C–O coupling, as in the 4-O–8' case, has been well-studied but possesses a fundamental limitation, in that electron rich substrates are not well tolerated. This coupling is further hampered by its generally poor yields, with the best reported yield being 71%. While synthetically useful, these poor yields point to either product instability or to challenges in selectivity that account for the narrower substrate scope.

The 8-8' couplings results in diverse products, but almost all instances of a successful 8-8' couplings have either an electron rich or electronically neutral aryl system. The nature of the groups on the alkene often significantly impact the resultant product, and in some cases, products require that the substrate have a nucleophilic component on the alkene.

Out of the many of potential 8–8' products, only a general method for formation of di-*para*-quinone methides has been developed, namely via electrochemical oxidation. The dilactone and furofuran product classes require pendant alcohol or carboxylic acid substittuion on the alkene of the substrate. Good yields of these cyclized products are only obtained when the 5-position of the substrate is blocked, to prevent 5-8' coupling. Some remarkable enzymatic work highlights the feasibility of enantioselective couplings to give these products.

Diaryltetrahydrofurans will also form under certain conditions via water addition to any di-*ortho*-quinone methide intermediate arising from 8-8' coupling. The maximum yield of 72% across the reports indicates the difficulty in selectively trapping of these highly reactive intermediates.

Formation of stilbenoid dimers containing five-membered rings features a broad substrate scope including both electron-poor to electron-rich monomers. Unfortunately, the methods are hindered by poor yields, likely due to the reactive nature of the intermediates and selectivity challenges after achieving the initial 8–8' coupling.

ortho-Alkenyl phenols are much less studied than *para*-alkenyl phenols. This may be due to the fact that far fewer of the corresponding coupling products are seen in nature.

The driving force over the last 50 years of alkenyl phenol research has been formation of structurally complex assemblies from simple starting materials by cascade formation of multiple bonds and stereocenters. This research has led to a many selective oxidation methods, cross coupling technologies, and enantio/diastereoselective couplings. Racemic couplings to form the natural *endo* diastereomers of the benzoxanthenones homodimers has almost been perfected. The cross coupling of the corresponding substrates is only highly effective when one monomer is tethered to a solid support to bias the reaction outcome. Likewise, only a modest 49% ee can be achieved for the *exo* diastereomers of these dimers. Much work

remains to be done to devise homogenous catalysts for cross-couplings and enantioselective processes.

The reactions of *ortho*-alkenyl phenols are rare with only one report of the formation of a tetrahydrofuran in modest yield. Further exploration of such variants is warranted to enable rapid access to greater structural diversity.

In conclusion, alkenyl phenols are one of the key molecular building blocks Nature uses to construct the ubiquitous polymer lignin, as well as the medicinally relevant lignan natural products. The understanding of the selectivity control elements in oxidative alkenyl phenol coupling is still in its early stages. This review provides on overview of the last 50 years in the field and defines areas where new discoveries are needed.

Conflicts of interest

There are no conflicts to declare.

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