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Catalytic Oxidative Coupling of Phenols and Related Compounds

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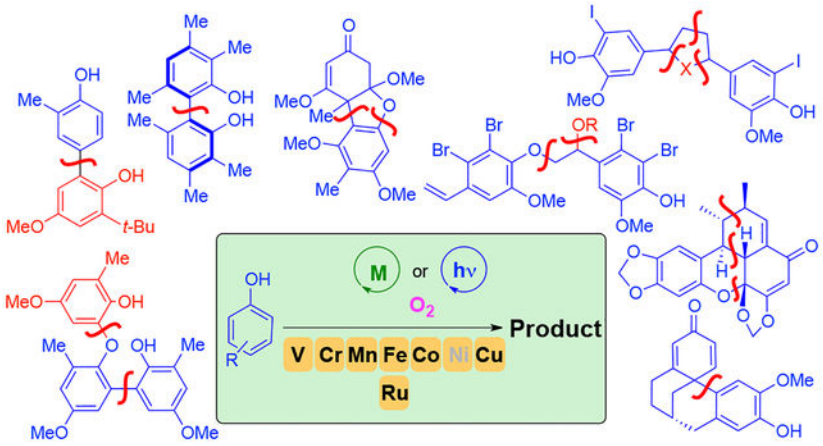
Abstract

Phenols and their derivatives are the elementary building blocks for several classes of complex molecules that play essential roles in biological systems. Nature has devised methods to selectively couple phenolic compounds, and many efforts have been undertaken by chemists to mimic such coupling processes. A range of mechanisms can be involved and with well-studied catalysts, reaction outcomes in phenol-phenol oxidative coupling reactions can be predicted with a good level of fidelity. However, reactions with catalysts that have not been studied or that do not behave similarly to known catalysts can be hard to predict and control. This Perspective provides an overview of catalytic methods for the oxidative coupling of phenols, focusing on the last 10 years, and summarizes current challenges.

Graphical Abstract



Keywords

oxidative coupling; dehydrogenative coupling; phenol coupling; cross-coupling; biphenols

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1 INTRODUCTION

Nature is replete with examples of natural products built from electron-rich aromatic units including phenols, indoles, and alkenyl phenols. When considering how these structures might be constructed using chemical methods, several different approaches can be imagined. An example with the natural product honokiol (Scheme 1)[1] is instructive. In a redox neutral (or reductive) approach,[2,3] the positions where bonds will be formed are prefunctionalized with reactive groups such as halides, pseudohalides, boron species, or metals which allows Suzuki, Negishi, Kumada, Ullmann, etc. couplings to be deployed. These groups then direct both the site of functionalization as well as the sequence of the coupling often allowing for complete control of regiochemistry as well as cross-coupling vs homo-coupling. A downside of this approach is that the prefunctionalization reduces atom economy. Furthermore, many of these reactions are sensitive to air or water, adding limitations to the reaction conditions. Oxidative coupling reactions provide an alternate approach that overcomes some of these limitations by using the unfunctionalized substrates (Scheme 1).[4] Nature likely utilizes a similar set of transformations and the challenge for the synthetic chemist is to develop control of chemoselectivity as well as selectivity for homo-coupling vs cross-coupling.

This Perspective provides an overview of our contributions to catalytic phenol oxidative homo-couplings and cross-couplings focusing on substrates with one arene ring. The couplings of 2-naphthols and higher order analogs (e.g., phenanthrols) are not covered since they are more well-developed. In these systems, the additional conjugation affords high control of selectivity due to radical localization.[5] The reactions of exocyclic conjugated alkenes are included. The review finishes with a brief survey of the couplings of phenols with non-phenolic substrates. The focus is on reactions since 2014 as there are good reviews of the material prior to this time.[6] There is also an excellent synopsis on iron[7] catalyzed phenol couplings and on phenol directed C-H functionalization[8] in 2019.

2 DISCUSSION

2.1 Challenges in Oxidative Phenolic coupling

Oxidative coupling reactions also have potential downsides. Overoxidation of the product may occurs since some of the reactions require the use of strong oxidant. For any given phenol, there may be multiple sites where reaction can occur, including both carbon and oxygen centers. Depending on substitution, the biphenol product may possess a chiral axis in which case enantiocontrol is also germane. The coupling of two different phenols adds more complexity in that hetero-coupling vs homo-couplings needs to be controlled. Finally, intramolecular reactions are subject to geometrical control as the phenols typically must approach parallel or nearly parallel to allow alignment of orbitals[9,10,11] for an oxidative coupling between carbons of the aromatic ring to occur which is a very different geometry relative to a metal-catalyzed reductive elimination process seen in redox neutral couplings. Below, we explore in more detail some of these major challenges in phenol-phenol oxidative coupling reactions and then review our recent progress to solve these issues.

2.1.1 Reactivity and Overoxidation—Oxidative phenol coupling requires substrates with accessible redox couples. For these reasons, almost all substrates for these reactions are

electron-rich phenols. The prevalence of this motif in natural products highlights that even enzymatic catalysts have difficulty in overcoming this limitation. Thus, methods that can utilize electron-deficient phenols are particularly notable.[12,13]

In an oxidative phenol coupling reaction, the products can also be substrates for further oxidation processes since they often have similar structural profiles relative to the starting materials (e.g., free OH, reactive sites, etc. – see Scheme 1). This scenario is particularly problematic if there are unsubstituted *ortho/para* positions in the product where further reaction can occur and if the product is more oxidizable that then initial starting material. For example, the reaction in Scheme 2a generates a product with a lower oxidation potential (1.07 V) than the tyrosine substrate (1.13 V).[14] As a consequence the product can both quench the catalyst by engaging in a reversible electron transfer and can also undergo further oxidation, both of which lower the yield. Another example is found is Scheme 2b. On the other hand, the reverse scenario holds for the reaction in Scheme 2c; now, the product is resistant to oxidation under the same conditions that act on the starting material leading to higher overall yields.[14]

2.1.2 Achieving Site-Selectivity—In the coupling of phenols, singular outcomes may occur depending on the substrates used. For example, there is only one C–C coupling outcome for the tyrosine derivatives illustrated in Scheme 2a. However, it is far more common that multiple different outcomes could occur. For example, Scheme 2b shows a homo-coupling resulting from bond formation between the C6-positions (an *ortho-ortho* coupling). Alternate outcomes that do not occur in this particular process include bond formation between the C4-positions (*para-para* coupling) or between C6 and C4 (*ortho-para*), C4–O coupling, C6–O coupling, or trimerization (or other higher order couplings). For more substrates with few or no substituents, the number of outcomes can increase exponentially, and selectivity may be difficult to achieve if different sites have similar reactivity profiles and/or a catalyst is unable to differentiate sites. An example can be seen in the oxidative coupling reactions of alkenyl-phenols, for which no generalized site selective synthetic method has been reported. As shown in Scheme 3, reactions at different sites on the alkenyl-phenols can lead to completely different products arising from one C–C bond formation (ortho-ortho), two C–O bond formations (β-O followed by α-O), or one C–O and one C–C bond formation (β-ortho followed by α-O).[15]

2.1.3 Enantioselective coupling—While there has been much progress in achieving catalytic enantioselective oxidative coupling of naphthols and polycyclic phenols through Cu, Ru, V, and Fe catalysts in the past 30 years,[16,17,18,19,20] oxidative asymmetric phenol coupling reactions remain underdeveloped. Compared to naphthol oxidative coupling reactions, phenol oxidative coupling reactions are much harder to initiate and control due to the higher oxidation potentials for phenols and multiple resonance forms that contribute to the reactivity of oxidized phenol intermediates. There are also fewer cases where the biphenol products possess a chiral axis. For those that do, achieving regio- and enantio-selective asymmetric phenol coupling reactions may be challenging (Scheme 4).[21] Hetero-couplings that generate C_1-symmetric adducts are even more difficult; not only must the

stereoselectivity be controlled, but homo-coupling vs hetero-coupling and regioselectivity need to be controlled.

2.1.4 Achieving Selectivity for Cross-Coupling vs Homo-Coupling—As discussed above, multiple sites on oxidized phenol intermediates may be reactive, including both carbon and oxygen centers leading to *para-para, para-ortho* and C–O coupling. In many of the initial discoveries in oxidative phenol coupling with stoichiometric oxidations, the reaction is uncontrolled yielding multiple products.[22] The challenge here lies in the suppression of background free radical-radical reactions and promotion of catalyst-controlled site-selective oxidative phenol coupling reactions. The example shown in Scheme 5 highlights the complexity of the issue as all the compounds shown could arise from an oxidative process. While there is reason to be optimistic (metal coordination and controlled oxidation lead to one product in 85% isolated yield in this case – see section 2.3.3 for further discussion), there are still many reaction pairs where such control cannot be achieved.

2.1.5 Intramolecular coupling—Compared to intermolecular phenol oxidative coupling reactions, there has been even less development in intramolecular catalytic phenol coupling reactions. Only certain coupling types occur readily such as the spirodienone cyclization reactions (Scheme 6a) where good stoichiometric oxidants were identified over 60 years ago.[23] Even within this one subclass, most methods require phenol substrates with electron donating groups to improve the reactivity. Moreover, substrates in an oxidative intramolecular phenol coupling reactions must approach parallel or nearly parallel to allow alignment of orbitals[9–11] for bond formation between carbons of the aromatic ring. The strict geometrical requirements in these conformationally flexible systems can make intramolecular oxidative coupling reactions difficult. For example, attempts to synthesize myracinol by intramolecular oxidative coupling have failed (Scheme 6b).[24] As this cyclization is likely involved in the biosynthetic route to this material, the lack of success with nonenzymatic catalysts and reagents highlight current limitations. The current synthetic process to myracinol uses prefunctionalized phenol substrates instead where ring closure occurs via a redox-neutral Suzuki-Miyaura cross-coupling reaction.[25]

2.2 Mechanistic types

Within the different metal catalyzed oxidative coupling reactions, adducts can be formed via inner-sphere or outer-sphere reactions.[26] In an inner-sphere reaction, the substrate directly binds to the transition metal reaction center through ligand coordination or exchange. Subsequent redox chemistry then provides a reactive intermediate which can react in several ways including with a coordinated substrate, with a noncoordinated substrate, or with a coordinated substrate that resides on a second metal center. An advantage of inner-sphere processes is that reaction can occur while an intermediate remains bound affording stabilization, as in the case of metal-coordinated radicals, and the complex can also exert control over chemoselectivity and regioselectivity. In an outer-sphere reactions, the reagent does not bind to the transition metal center; rather redox transfer occurs through other proton and electron transfer processes.

Regardless of whether inner-sphere or outer-sphere processes occur, the oxidative couplings of phenols can be roughly divided into four categories (Scheme 7)[6] that differ mainly in when electrons are abstracted (oxidation) and protons lost. In the first category phenols are first oxidized to phenol radicals that recombine in a radical-radical reaction to form the coupled adduct after tautomerization. This type of reaction can be favored when metal-stabilized radicals are present, which does not require a high concentration of reactive free radicals. In these reactions, homo- and cross-coupling can occur at different sites of the phenol radical, depending on the catalyst environment and the amount of radical character at the different positions. In the second category, a phenol radical can react directly with a phenol. After loss of a hydrogen atom, the final adduct will form by tautomerization. Phenol radicals can also react with the phenolate anions. In this case, electron transfer followed by tautomerization affords the product. Finally, two-electron oxidation can generate a phenoxonium. In such a case, the nucleophilic phenol attacks the electrophilic phenoxonium, and the biphenol adduct is formed after tautomerization.

2.3 Intermolecular Phenol-Phenol Coupling

2.3.1 Catalytic Homo-Coupling the Same Sites—A number of bioactive natural products contain biphenol scaffolds, which are likely generated by Nature through oxidative coupling reactions. As such, many efforts have been invested to mimic such processes. An oxidized phenol can have multiple resonance structures (Scheme 8), each of which can lead to a different reaction outcome. In a phenol oxidative homo-coupling reaction, depending on the phenol substrate, *para-para*, *ortho-ortho* and *ortho-para* adducts are possible. The likelihood of each of these events occurring is controlled by both the substitution pattern of the phenol and by the catalyst/reagent utilized. Typically, reaction does not occur at substituted positions since aromaticity cannot be regained via loss of a proton; however, there are exceptions when there are other thermodynamic traps to overcome the energetic penalty associated with loss or aromaticity.[5,27]

Early work showed that catalytic coupling of two phenols was possible with a vanadium catalyst, but that rates were much slower than for the corresponding 2-naphthol perhaps due to greater steric hindrance about the oxygen of the *ortho*-substituted phenols (2-naphthol has no substituents *ortho* to the phenol) limiting binding to the vanadium center.[28] Prolonged reaction times did not improve outcomes but resulted in no further conversion or in formation of intractable materials. We have found that salen/salan metal complexes can resolve this issue and show good phenol site-selectivity in homo-coupling reactions.[5] Stabilization of the oxidized phenol intermediates by metal coordination during oxidative coupling reaction accounts for much of this control. As shown in Scheme 9a, *ortho-ortho* diphenol products were obtained with good yield when the other *ortho*- and *para*-positions are blocked. When both *ortho*-positions are blocked, *para-para* coupling occurs (Scheme 9b).[10] When both *ortho*- and *para*-positions are unsubstituted, more diverse outcomes can be observed. Calculations indicate that the most radical character of the phenol radical is found at the *para*-position. Together with the lesser steric hindrance at the *para*-position, these factors account for the *para-para* coupling outcome in Scheme 9c. The degree of radical localization can, however, be overcome by steric factors either through kinetic

(irreversible coupling) or thermodynamic (reversible coupling, irreversible rearomatization) control leading to the *ortho-ortho* coupling outcome in Scheme 9d.

From the cases discussed above, one might conclude that the catalyst plays only a minor role in controlling the site of homo-coupling. However, Scheme 9e and 9f show that different outcomes can occur for the same substrate depending on the catalyst; namely, *ortho-ortho* coupling with a copper salan catalyst and *para-para* coupling with a chromium salen catalyst. These cases support the participation of the catalyst during the C–C bond forming event, and possibly different mechanisms for the coupling (see Scheme 7).

Photocatalytic couplings also can differentiate positions during homo-coupling. With no metal catalyst being coordinated during the coupling, substrate control is more likely to dominate through a phenol radical-phenol mechanism (Scheme 7). As shown in Scheme 10a, *ortho-ortho* coupling occurs, most likely because the *para*-position is more hindered.[14] Notably, the oxidative couplings of mono-substituted phenols is difficult, and a particularly notorious case is the coupling of tyrosine derivatives. Nature can clearly accomplish this oxidative coupling as this motif appears in a number of natural products (e.g. mycocyclosin) or in their precursors (e.g. herqulines); however, total synthesis efforts have relied on Suzuki couplings.[29] Efforts to overcome this hurdle include the addition of *tert*-butyl substitution to the phenol ring to both activate ring for oxidation and to block reactive sites.[30] In efforts to solve this long-standing challenge, we hypothesized that a sufficiently oxidizing photocatalyst would allow activation of this high-oxidation potential substrate. Using high throughput experimentation, we ultimately discovered that $Ru(bpz)_3[PF_6]_2$ with oxygen as the terminal oxidant could accomplish this coupling in 40% yield with the balance of the yield being primarily starting material (Scheme 10b).[14] Reaction was halted at low conversion because this particular system gives rise to a product that possesses a lower oxidation potential that the starting material (see Scheme 2a above). Nature may overcome this limitation by size exclusion via enzymatic catalysis, and further work is needed to discover small molecule catalysts to circumvent this issue.

There are limited reports on metal catalyzed oxidative homo-couplings of phenols[31] with more work being directed to the cross couplings (see Section 2.3.3 below). A substantial amount of work using electrochemistry to affect such couplings has been reported.[32]

2.3.2 Homo-Coupling at Different Sites—Unsymmetrical coupling outcomes can also be envisaged from a single monomer if there is more than one type of reactive site. However, control of such an outcome is more difficult problem. Notably, a chromium catalyst was discovered that allowed such an unsymmetrical *ortho-para* coupling (Scheme 11a).[5] For the exact same substrate, different catalysts could afford *ortho-ortho* (Scheme 9e) or *para-para* coupling (Scheme 9f), again reinforcing the idea that catalysts can control the outcomes.

In another case, an *ortho-para* coupling was accomplished with a manganese catalyst where the *para*-position is substituted (Scheme 11b). In this case, the driving force of aromatization is absent for one ring. It appears that the driving force is an intramolecular conjugate addition that forms a new five-membered ring. Electrochemical reactions have

also been identified that lead to this motif.[33] This Pummerer ketone structure comprises the cores of several natural product families including the usnic acids,[34] galanthamine,[35] and morphinone alkaloids.[36]

Another unsymmetric homo-couplings was found in the case of hydroxycarbazole. Greater radical character is expected at the *ortho*- position vs *ortho'*-position due to the adjacent amine and oxygen groups. However homo-coupling gives rise to the unsymmetrical dimer as the more reactive *ortho*-position is also more hindered, which prevents two monomers from joining at this poitions. A compromise is thus achieved where one monomer undergoes bond formation at the most reactive site and the other undergoes bond formation at the less hindered site (Scheme 12). If the reaction is allowed to continue beyond dimerization by either using higher concentrations or longer reaction times, then an ordered assembly occurs. First, all the monomer reacts to form unsymmetrical dimer. For this unsymmetrical dimer, the available *ortho*-position is too hindered to accept the larger dimer substrate and reaction reverts to a symmetric coupling between two ortho'-centers to generate a tetramer (Scheme 12).[37] When the *ortho'* site is blocked by a substituent, only a symmetric *ortho-ortho* dimer is observed (see Section "Intermolecular Asymmetric Phenol-Phenol Coupling" below).

Very unusual unsymmetrical couplings have been observed with methoxy-substituted phenols when an electrochemical method is used (Scheme 13),[38] which is rationalized with a radical-phenol mechanism (Scheme 7). It is unclear if the resultant *para-meta* or *meta-meta* adducts arise from the methoxy groups exerting a greater effect to enhance nucleophilicity at the reacting positions than the hydroxyl groups (see intermediate arising from neutral phenol reacting with phenolic radical in Scheme 13) or if the electrophilic phenolic radical is more reactive at the *meta*-position. Hydrogen bonding of the methyl ethers with the HFIP solvent may also play a role as has been proposed in other Fe catalyzed couplings.[7]

2.3.3 Unsymmetrical Electrochemical Coupling of Phenols—Biphenol products can also arise from coupling of two different monomers. A case in point can be found in honokiol[1] (Scheme 1), which arises from an *ortho*-coupling of 4-allylphenol and *para*-coupling of 2-allyl phenol. In such a case, a catalyst must promote cross-coupling between the two substrates much faster than the corresponding homo-coupling reactions of each substrate to achieve an effective process.

To address this problem we screened our catalyst library[5] against different pairs of phenols and found that chromium-salen complex gave good cross-selectivity on a variety of phenol substrates containing alkyl, electron-donating, and weakly electron-withdrawing groups (Scheme 14a).[10] The cross-selectivity is controlled by several features (Scheme 14b). Only unhindered phenols can directly coordinate the catalyst. From this complex, the chromium oxo will deprotonate a second phenol molecule led to an ion pair assembly (radical anion mechanism, see Scheme 7); the more acidic phenol is deprotonated at this stage. When two possible ion pairs can form (e.g., if the two phenols have similar acidity), the more reactive ion pair is that in which there is SOMO occupancy on both phenol partners after intersystem crossing to the quartet. The reaction from such an assembly is lower in energy since it entails less electron reorganization. Within this ion pair, the site of reaction of the two substrates is controlled by both steric hindrance and the nucleophilicity of the reactive sites.

With the Cr-catalyzed method, honokiol was synthesized[39] and many cross-coupled honokiol analogs could be made, which enabled studies of their biological activity and identified compounds more potent than honokiol.[40]

Besides the cases described above, a number of other research groups have made important advances in catalytic oxidative phenol cross-couplings. Waldvogel and coworkers have a series of reports in this area using electrochemistry,[41,42] one example of which is shown in Scheme 15a. The reactions are proposed to proceed largely via radical-phenol mechanisms (Scheme 7). Pappo and coworkers have described iron catalyzed process that proceed through radical-anion (Scheme 15b)[43] or radical-radical[13] mechanisms as well as cobalt catalyzed system.[44] Reactions with an iodine(III) catalyst that proceed through a two electron pathway have also been reported (Scheme 7).[45]

Oxidative phenol cross-coupling reactions can also be accomplished via photocatalysis. Our experiments on photocatalytic homo-coupling of tyrosine showed promising results (Scheme 10b),[14] giving solid evidence for using photocatalysts in oxidative phenol coupling reactions. Mechanistic studies revealed that adduct forms via phenol radical-phenol type mechanism (see Scheme 7) suggesting that cross-coupling of different phenols should be feasible. Specifically, the excited state photocatalyst acts as an oxidant on the more oxidizable phenol and ultimately a phenol radical is generated. The biphenol adduct is then formed after the phenol radical reacts with a corresponding nucleophilic phenol coupling partner. Based on the findings, cross-coupling is then feasible when one phenol coupling partner is more oxidizable and the other is more nucleophilic. Using this method with a $MesAcr^{+}BF_4^{-}$ photocatalyst, a range of biphenol adducts could be formed good yield (Scheme 16)[14] and often with higher yields or selectivities that the metal catalyzed method described above. One limitation, however, is that the reaction does not proceed well in if the product is more oxidizable that then starting phenols (see Scheme 2). In such a case, the product quenches the photocatalyst which both inhibits the reaction and leads to byproducts through further oxidative processes. For the metal catalysts described in Scheme 14, this issues is less pervasive since substrate coordination is key. As the substrate phenol is less hindered than the product, it binds preferentially, which limits overoxidation. Thus, the two methods are complementary.

2.3.4 Intermolecular Asymmetric Phenol-Phenol Coupling—Compared to asymmetric *naphthol* oxidative coupling reactions,[16–20] there are fewer protocols for asymmetric *phenol* oxidative coupling reactions. To fill in this gap, we developed a monomeric[46] asymmetric vanadium catalyst to achieve enantioselective oxidative coupling of phenol substrates. During the development of this reaction, the use of Lewis acid or protic acid was determined to be key to obtaining higher reactivity and selectivity. To further improve the reaction reactivity, a more oxidizing catalyst was introduced by installing nitro groups on the catalyst (**V3**). This modification to catalyst led to higher reaction yield and *ortho-ortho* selectivity (Scheme 17a).[21] For hydroxycarbazoles, a C3-substituent enforces coupling at the C1-position (see section “Homo-Coupling at Different Sites” above) and the V catalyst gave excellent yield and enantioselectivity (Scheme 17b).

Studies on the reaction mechanism showed that the reaction proceeds via an inner-sphere controlled phenol radical-anion type mechanism (Scheme 7). During the reaction, the phenol substrate first coordinates to the vanadium complex by ligand exchange (Scheme 18). Then, acetic acid serves as a bridging ligand aggregating two vanadium-phenolate complexes from less hindered faces. After intersystem crossing (ISC) to the triplet, the C–C bond forms in an enantioselective manner. Upon a second inner-sphere electron transfer, tautomerization and dissociation gives the final *S* enantiomer of the product.[10]

This enantioselective coupling was deployed as the key step in the first total synthesis of chaetoglobin A, a natural product that inhibits the propagation of human breast cancer and cancer cell lines.[47] Additional efforts by the groups of Sasai and Takizawa have shown the general utility of vanadium catalysts in asymmetric resorcinol[48] and hydroxycarbazole couplings,[49] including the enantioselective synthesis of the sorazolon E2.[50]

There have also been advances in biocatalytic oxidative phenol coupling reactions.[51] Narayan and coworkers report P450 variants that are effective in enantioselective couplings of coumarins, a class of substrates that are difficult to couple oxidatively due to the electron withdrawing vinylogous ester embedded with in the ring.[52]

Performing asymmetric oxidative cross-coupling reactions of phenols without directing groups remain as a major challenge. Uchida and coworkers have developed an enantioselective oxidative coupling method for naphthol-phenol cross-couplings.[53] To overcome the differences in oxidizability of the substrates, an excess (2 equiv) of the phenol is employed. Even so, mixtures of homo-coupling and cross-coupling products are observed although the latter dominated (5.3–9.5:1, Scheme 19). For phenols with only one coupling site available, a single cross-coupled product was observed with good enantioselectivity (Scheme 19a). When more than one coupling site was available on the phenol, mixtures were observed and enantioselectivity levels were modest (Scheme 19b).

In 2021, Sasai and coworkers reported that vanadium catalysts were highly effective in cross-coupling naphthols with hydroxylcarbazole (Scheme 20).[54] This oxidative coupling through a monomeric vanadium catalyst afforded both good enantioselectivity and yield, establishing the feasibility of using vanadium catalysts in enantioselective oxidative hetero-coupling reactions.

2.4 Intramolecular Phenol-Phenol Coupling

There has been only limited development of small molecule catalytic methods to accomplish *intramolecular* oxidative phenol couplings. As outlined above (Section 2.1.5, Scheme 6), there are many cases where even stoichiometric oxidants fail to affect such intramolecular couplings. Presumably, the conformational constraint afforded by enzymatic catalysts[55] are difficult to induce with small molecule reagents or catalysts. One class of intramolecular couplings that has proven tractable, however, are couplings that afford phenol-dienone products, a class of natural products with many important bioactivities.[6] Even so, there has not been much development of catalytic processes since the discovery of spirodienone cyclization reactions with stoichiometric oxidant nearly 60 years ago. Rather, catalytic efforts focusing on the more easily controlled phenolic ethers[56] rather than phenols.

Screening of our catalyst library revealed that vanadium catalysts are particularly effective in intramolecular phenol oxidative coupling to construct phenol dienone structures. Reactivity was improved by using a monomeric catalyst with increased Lewis acidity and oxidizing ability. These features were optimized by introduction of a hexafluoropropoxide ligand and an electron-withdrawing nitro-substituent on the ligand. The *ortho-para coupling* products arising from dearomatization were obtained in good yields for range of compounds (Scheme 21).[57] In addition the method was used in the synthesis of several natural products including pulchelstyrene D (±)-spirolouveline, and a salutaridine analog.

2.5 C–O Coupling

Phenolic coupling products can also arise from bond formation between a carbon and oxygen (C–O coupling) rather than between two carbons (C–C coupling). The latter modality has been the focus of the above sections. The C–O coupling motif is found in numerous natural products including peptide derived compounds like vancomycin, teicoplanin, bouvardin, etc. as well as in non-peptidic natural products like pyrolaside B and riccardin C (Scheme 22)[55]. Development of protocols for selective C–O coupling are limited and are highly substrate dependent.[58]

Compounds like pyrolaside B pose a particularly difficult synthetic challenge as this trimeric compound arises from both C–C and C–O couplings of the same monomer. We have discovered that a copper catalytic system with oxygen can provide a high yielding ordered assembly of 2,4-substituted phenols in a manner similar to that found in pyrolaside B and related trimeric phenol natural products (Scheme 23).[59]

Investigation of the mechanism revealed how such an ordered assembly can occur and why other reaction manifolds (e.g., C–O polymerization) are not dominant (Scheme 24).[59] The first product observed in this process is a dimeric adduct from C–C bond formation. Notably, the oxidation potential of this C–C dimer is *lower* than that of the monomer. Thus, the next oxidation occurs on the dimer, which possesses no open *ortho*- or *para*-sites meaning that any C–C bond formation would be reversible since the driving rearomatization cannot occur. Thus, reaction must occur from the oxygen of the dimer; when combining with remaining monomer, a C–C/C–O coupled trimer results. This trimer is rapidly oxidized further by the catalyst resulting in another intramolecular C–O coupling to form an *ortho*-quinone spiroketal. Thus, three bond formation reactions (C–C/C–O/C–O) occur in a controlled manner.

Consistent with the above mechanism, we found it possible to construct unsymmetrical trimers be preforming a dimer and then exposing it to the reaction conditions with a different monomer (Scheme 25).

The *ortho*-quinone spiroketal can be selectivity reduced to the linear C–C/C–O trimers by means of palladium catalyzed hydrogenolysis (Scheme 26). This approach then allowed a highly efficient synthesis of pyrolaside B relative to those utilizing nonoxidative couplings.[59]

Similar C–O couplings are also possible in other oxidative couplings involving phenols. During investigation of an aniline-phenol C–C coupling, we discovered that C–O coupling could intervene. Specifically, when the phenolic oxygen is unhindered (no *ortho*-groups or only one small *ortho*-group), C–O coupling can dominate the outcome (Scheme 27).[60] In separate work from Waldvogel and coworkers, certain substrates were also found to undergo selective C–O coupling with aminonaphthalenes when electrochemical conditions were employed.[61]

A number of selective C–O couplings of phenols have been reported by Lumb and coworkers employing copper catalysts with oxygen as the terminal oxidant. Detailed mechanistic work is consistent with formation of a copper(II) semiquionone species which then reacts with further phenol and oxygen to form the *ortho*-quinone-phenol adduct (Scheme 28a).[62] This method has been used to synthesize natural products such as norathyriol. The approach also allows a further second coupling to add in a third substrate, typically an amine or amide, and even a fourth substrate, a phenol (Scheme 28b,c).[63] These methods allowed expeditious syntheses of the natural products (*S,S*)-tetramethylmagnolamine and (*S, S*)-thalicarpine.

Another example of a C–O coupling can be found in the couplings of phenols with arenes (trimethoxybenzene) where a C–O coupling and one or more C-C couplings occur.[64]

2.6 Exocyclic Intermolecular Phenol-Phenol Coupling

2.6.1 *para*-Alkenyl Phenols—When alkenyl groups are present at the *ortho*- or *para*-positions of phenol, reactions can also occur on the alkene portions due to delocalization of radical character. These substrates have been explored with stoichiometric oxidants with limited control of selectivity, but there were no reports of general or selective catalytic couplings. To fill in this gap, we investigated our oxidative catalyst library and discovered that a vanadium catalyst was highly effective with oxygen and that conditions could be controlled to afford selective formation of each of the two isomeric products, the *β-β* and *β-O* adducts.

Depending on the solvent, V-catalyst and nucleophile, the *β-O* coupling can lead to four different reaction outcomes.[65] Using a dimeric-vanadium catalyst along with 1,4-dioxane gave good selectivity for the *β-O* product (Scheme 29). After the oxidative *β-O* coupling the quinone methide intermediate could be trapped with either a water or an alcohol nucleophile. However, the yield drops significantly when the nucleophile must add to a tertiary carbon center.

Further investigation revealed that the catalyst loading, the solvent polarity, and the concentration of the substrates were the determining factors with respect to the reaction selectivity. For the *β-O* product, coordination of the oxidized phenol substrate via oxygen to the vanadium center accounts for *β-O* bond formation (blue pathway in Scheme 30). Thus, high catalyst concentrations, dimeric catalysts, and nonpolar solvents favor *β-O* bond coupling as they stabilize the vanadium-radical adduct.

When there is a lower catalyst concentration, monomeric catalyst, or more polar solvent, more of the free radical builds up leading to *β*-*β* coupling between either two radicals (red pathway in Scheme 30) or between a radical and neutral uncoordinated substrate. The presence of this radical is supported by TEMPO trapping studies (bottom right, Scheme 30). Such free radicals from electron rich *para*-alkenyl phenols are expected to be more stable, which also explains the greater success of such substrates in this reaction. The bisquinone methide intermediate from *β*-*β* coupling can be trapped with water to generate tetrahydrofuran adducts or with aniline to form a pyrrolidine (Scheme 31).

Reaction of coniferyl alcohol with a dirigent protein and an enzymatic catalyst, laccase, generates enantiopure pinoresinol via a *β*-*β* coupling followed by intramolecular cyclization.[66] The reaction of isoeugenol electrochemically gives rise to a different α-β coupling to form the lignin diisoeugenol.[67]

2.6.2 *ortho*-Alkenyl Phenols—*ortho*-Alkenyl phenols can undergo oxidative processes similar to the related *para*-alkenyl phenols in the preceding section. In these cases, the substrates were found to oxidize spontaneously when oxygen was employed as the terminal oxidant. A screen of other oxidants revealed that with silver chloride would turn over a vanadium catalyst while not directly oxidizing the substrate.

This combination of reagents causes *β*-*β* homo-coupling of the *ortho*-alkenyl phenols (Scheme 32).[68] However, this adduct is not stable and is poised for an intramolecular Diels-Alder reaction to generate the carpanone scaffold. All prior reports on this oxidative coupling generate the *endo* product after the Diels-Alder reaction, which corresponds to the carpanone natural product stereochemistry.[69] However, our vanadium catalyst gives the *exo* adduct as the major product. Apparently, the vanadium catalyst is coordinated during this second step. It likely acts as a Lewis acid exerting control over the diastereoselectivity of this second reaction as well as the enantioselectivity of the prior *β*-*β* coupling.

2.7 Nonphenolic Substrates in Cross-Couplings Phenols

The above sections have described the reactions of phenols and alkenyl phenols; however, other substrate classes are amenable to mechanistically related oxidative cross-coupling process including anilines, indoles, oxindoles, etc. There are many oxidative coupling possibilities between these different partners. Below, we survey some of the catalytic cross-couplings of phenols with these related substrates.

2.7.1 Phenols with Anilines—While there have been many successful methods for homo-coupling of aminonaphthalenes and a few reports for cross-coupling[61,70] of aminonaphthalenes with phenols, methods for the corresponding anilines are underdeveloped. As was the case for phenols vs naphthols, anilines are more difficult to oxidize selectively than aminonaphthalenes. Previous reports on aniline-phenol cross-coupling reaction required super-stoichiometric silver oxidant.[71] Examination of our chromium-salen catalyst[5] revealed that it can effectively couple *para*-substituted *N,N*-dimethylanilines with phenols (Scheme 33).[60] These reaction conditions also proved effective with other cases, including when the *N,N*-dimethyl group is substituted with the more challenging *N,N*-diethyl group[71] as well as the pyrrolidine, piperidine or morpholine

derivatives. However, pyrroles and indoles did not react nor did anilines and phenols with electron-withdrawing groups. Studies suggest that during the reaction the aniline is first to oxidized and then couples with the most nucleophilic carbon of the phenol.[60]

Examples of C–N coupling with an anline are also known (Scheme 34). In Scheme 34a,b the substrates first proceed through an oxidatve amination to form the *para* phenol-aniline coupled quinamine intermediate.[27] From there, depending on the sites available on the phenol substrates and the functional group at the *para*-site of the phenol, the reaction can proceed to form a benzoquinone aniline adduct (Scheme 34a). In a different case, when there is an open *ortho*-site on the phenol, the initial adduct can under a sigmatropic rearrangment to generate a phenol aniline *ortho-ortho* cross-coupled adduct. (Scheme 34b)

In the case of Scheme 34c, the phenol undergoes oxidative C–N coupling with an oxazole to form a cyclized intermediate. Subsequent hydrolysis of the ring generates the phenol-aniline adduct.[72] There are also reports of photocatalyic[73] and electrochemical C–N[74] couplings between phenols and anlines.

2.7.2 Phenols with β-Ketoesters—Phenols can undergo oxidative coupling with β-ketoesters to generate a C–C bond. When this coupling occurs in the *ortho*-postion of the phenol, a subsequent redox neutral cyclization involving the phenolic oxygen can occur. Li and coworkers formed benzofurans using this approach with an iron catalyst (Scheme 35a)[75] and proposed that the oxidized phenol radical reacts with a b-ketoester anion (see Scheme 7). In a later work from Pappo and coworkers, cyclic b-ketoesters were used (Scheme 35b).[76] This oxidative coupling approach permitted coumestrol to be made in two steps, a dramatic improvement over other approaches.[77]

In other cases, C–O couplings between a phenol and a β-ketoester can also be seen. (Scheme 36).[78] Under these conditions, the outcome of C–C vs C–O couping was found to depend on the nature of the substrate. In most cases involving electron rich phenols, the C–C coupled adduct is either the predominant or the sole adduct. However, C–O and C–C cross-coupled adducts can be seen when electron-poor phenols are used. Investigation into the mechanism showed that the stability of the phenoxyl radical intermedate is the determining factors to whether C–O or C–C adduct is formed. Electron-withdrawing groups placed *para* to the hydroxyl group can destablize the phenoxyl radical, and favor the C–C coupled aduct. Conversely, electron-withdrawing groups placed *ortho* to the hydroxyl group stablizes the phenol radical, giving rise to the C–O coupled adduct

2.7.3 Phenols with Malononitriles—The use of other readily oxidized enolic precursors was further examined with malononitrile. The nitrile groups both lower the acidity allowing facile deprotonation of the malonate and stabilizes a radical after oxidation of the anion. With these considerations in mind, the arylmalonontirles were explored with a range of oxidizing catalysts. In this case, $Cu(OTf)_2$ with $K_2S_2O_8$ as the terminal oxidant afforded excellent yields for malononitrile-phenol couplings (Scheme 37).[79] In addition, other heterocycles (indoles, carbazoles, and thiophenes)[80] could be used in place of the phenol coupling partner. Measurement of oxidation potentials revealed that the malononitrile was the most readily oxidized species. It appears that the neutral phenol adds thereby

mitigating competing phenol homo-coupling. The malononitrile radical formed during the oxidation can oxidatively dimerize, but this process is readily reversible due to the weak bond strength.

2.7.3 Phenols with Arenes—Arenes that are neither phenols or anilines can also couple to phenols (Scheme 38).[64,81] Electron-rich substrates are the most prevalent, especially phenolic ethers which share many features with phenols. However, there are distinct differences in that phenol ethers do not have an acidic OH hydrogen and cannot transit through intermediate derived from the phenolic anion or hydrogen atom abstraction of the O–H. When a phenol combines with a phenolic ether, oxidation of the phenol to phenolic radical can occur more readily followed by nucleophilic addition of the phenolic ether. Subsequent oxidation and proton loss generates the product. Electrochemical[82] and photocatalytic[83] methods are also effective in this reaction type.

2.7.4 Phenols with Alkenes—Several examples of oxidative C–O coupling with phenols and alkenyl phenols have been shown above. Alkenes can also engage phenols in C–O coupling processes to form a benzofuran adduct (Scheme 39).[84] In this process, the phenol reacts with a styrene through a radical neutral mechanism (See Scheme 7) to form the phenol alkene C–C bond. Subsequent oxidation and addition of the hydroxyl group to the electrophilic carbon of the alkene leads to a benzofuran adduct. Electrochemcial[85] and photocatalytic[86] versions of these reactions have also been reported.

2.7.5 Phenols with Hydrazides—Oxidative C–N coupling with non-aniline species is also feasible. For example, Lumb and coworkers reported the oxidative cross-coupling of a nucleophilic phenol and a nucleophilic hydrazine (Scheme 40).[87] The formation of the azophenol proceeds through a double dehydrogenative coupling mechanism, wherein two equivalents of H_2 are removed from the substrates. Mechanism studies revealed that the phenol is first oxidized to generate a quinone. Subsequent condensation with the hydrazine generates the final azophenol adduct.

2.7.6 Phenols with Oxindoles—We became interested the oxindole motif as it contains an aromatic enol similar to that found in phenols. Prior reports showed that these substrates are indeed effective in stoichiometric enolate couplings that employ an excess of base to generate an enolate and superstoichiometric oxidants such as copper(II) ethylhexanoate or ceric ammonium nitrate.[88] We envisioned a catalytic method with oxygen as the terminal oxidant. Screening our catalyst library rapidly led to a copper salan catalyst that was highly effective with a range of substrates (Scheme 41).[89] Mechanism studies support the formation of a copper enolate with the oxindole that undergoes facile oxidation to a captodative radical which can reversibly dimerize. Capture of this radical by the radical cation of the second substrate leads to irreversible formation of the product upon rearomatization of the second component. Thus, a range of different aromatic substrates could be coupled to the oxindole including indoles at the C3-position (black in Scheme 41). When the C3-position of the indole was substituted, the reaction was selective for the C2-position (green in Scheme 41). Pyrroles (red in Scheme 41) and other electron rich

aromatics (blue in Scheme 41) were also highly effective, and most of these latter cases did not proceed well with the previously reported methods.[88]

Oxindoles have also been reported as effective in coupling the *ortho* or *para*-positions of phenols by Pappo and coworkers with an iron catalyst.[90] Dimerization of the oxindole was also observed in this case supporting an oxindole radical. Further mechanism experiments supported a mixed radical anion mechanism (see Scheme 7) involving a ligated iron species. Depending on the substrate, an oxindole radical/phenolate coupling or an oxindole anion/phenol radical coupling can occur.[91]

Notably, couplings of oxindoles with indoles can be carried out by using a phosphoric acid catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[92] With a chiral phosphoric acid catalyst, an asymmetric coupling of oxindole and indole was achieved.

3 CONCLUDING REMARKS

As mentioned in the introduction, a phenol substrate can have multiple reactive sites and many of the early synthetic methods for oxidative coupling are non-selective. The development of chemoselective catalysts has allowed many of the selectivity issues to be addressed. Transition metal catalysts derived from the non-precious metals such as vanadium, chromium, manganese, iron, and copper have enabled selective phenol coupling reactions with good yield and selectivity. Electrochemical methods have also provided good results for many of these transformations and, more recently, photocatalytic methods have been shown to be effective.

While surprising at first, the cross-couplings between phenol and nonphenolic substrates can be easier to achieve as the two different substrates often have very distinct oxidation profiles. On the other hand, the cross-coupling of electronically similar phenols or alkenyl phenols is often challenging as there are few differentiating characteristics. When there are multiple reaction sites and/or C–O coupling can occur, then the challenges are compounded. The use of catalysts that can bind selectively to one phenolic partner can be powerful and much of the remaining control relies on substrate features including sterics that block addition to particular centers and electronic features that either localize spin density in the radical intermediate or that render a position more nucleophilic for addition to an electrophilic radical, radical cation, or cation. Thus, oxidative cross-coupling reactions on substrates with similar oxidation states and without directing groups remain as a major challenge

Another area where the control features are incompletely understood is intramolecular phenol oxidative coupling reactions. Many tethered phenolic substrates are resistant to cyclization with either stoichiometric reagents or oxidizing catalysts. Presumably, the natural products containing such motifs benefit from the conformational constraint offered by enzymatic catalysts. The development of small molecule catalysts that can reproduce these features is a current aspiration.

In the above sections, this Perspective has discussed some of the major challenges in devising oxidative phenol couplings and highlighted our recent discoveries. Even so, many reactions remain difficult or are not feasible pointing to areas for further investigation.

Further efforts to improve our mechanistic understanding are needed to allow the design of new catalytic systems to address the challenges outline above.

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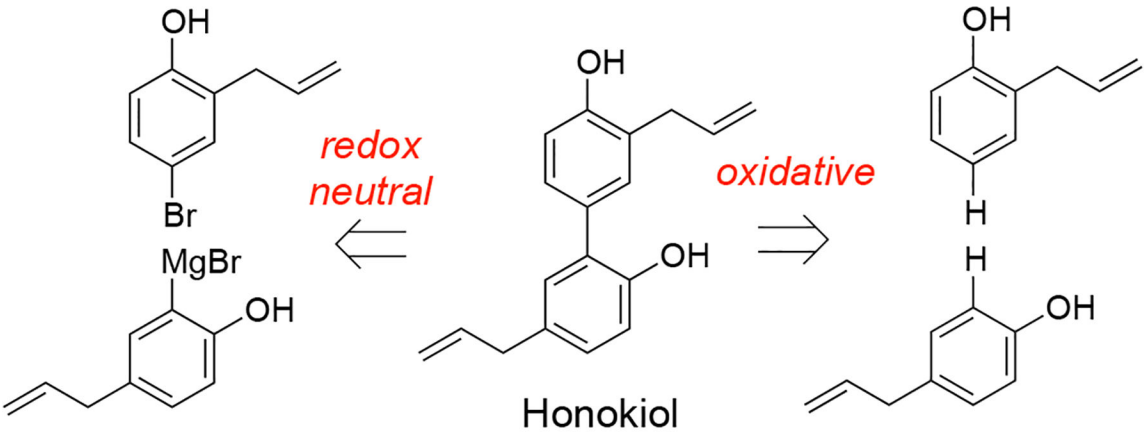
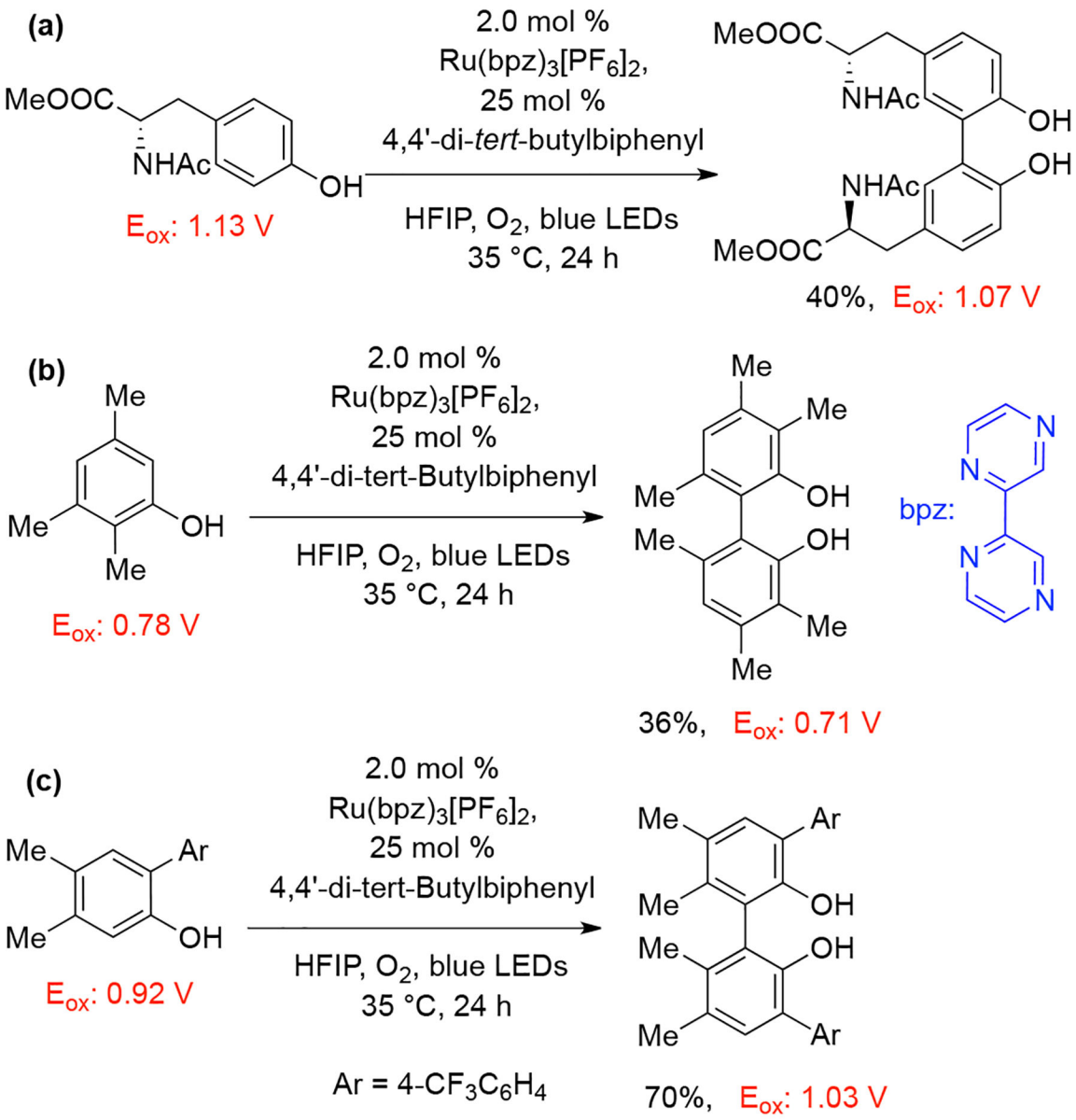
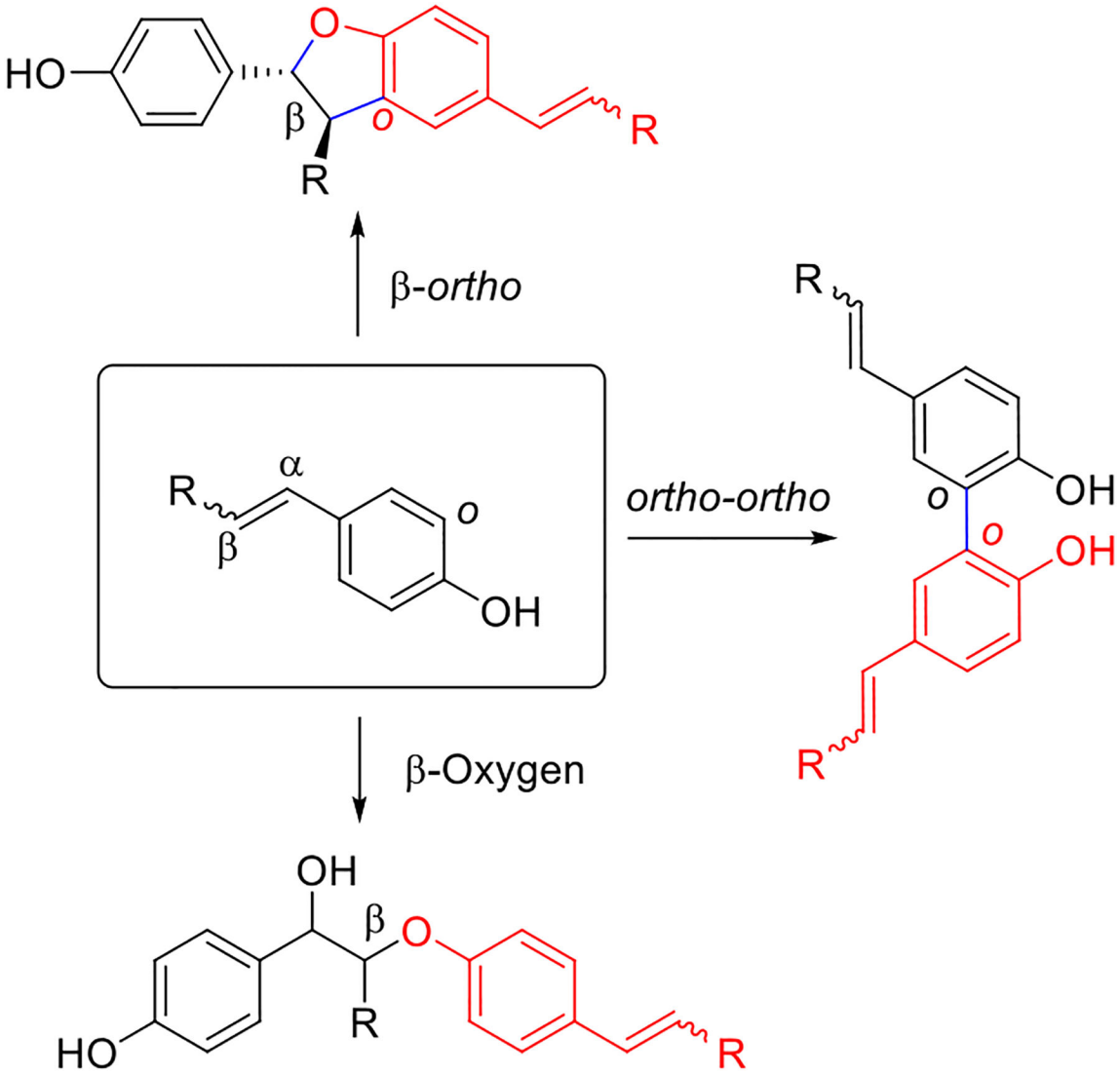


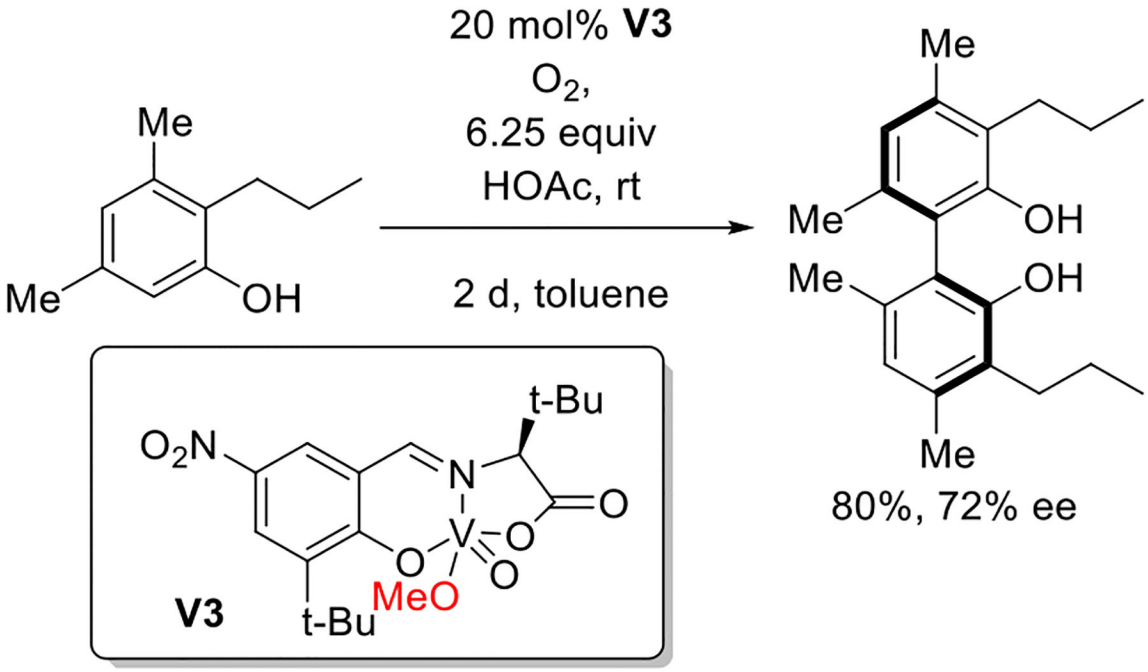
Scheme 1.
Retrosynthetic Analysis of Honokiol



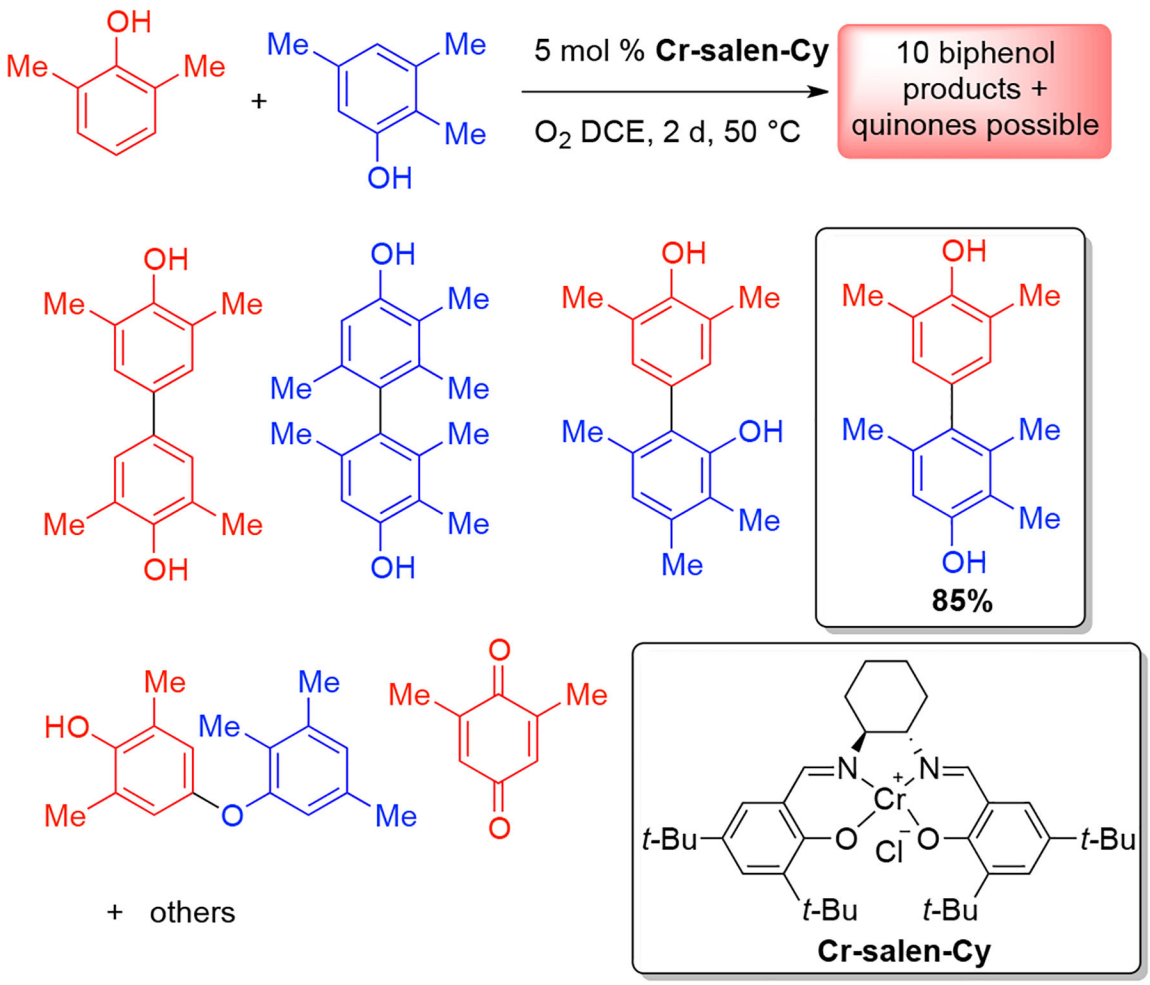
Scheme 2.
Effect of Oxidation Potentials on Reaction Outcomes



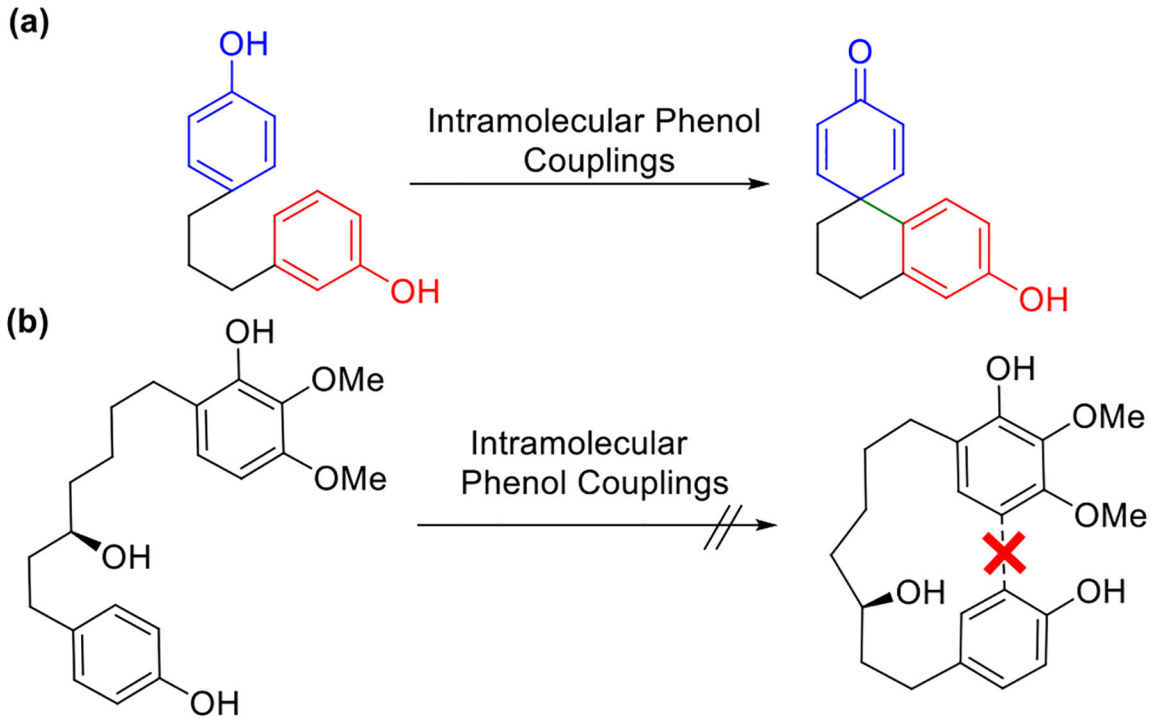
Scheme 3.
Phenol-Phenol Coupling Site-selectivity



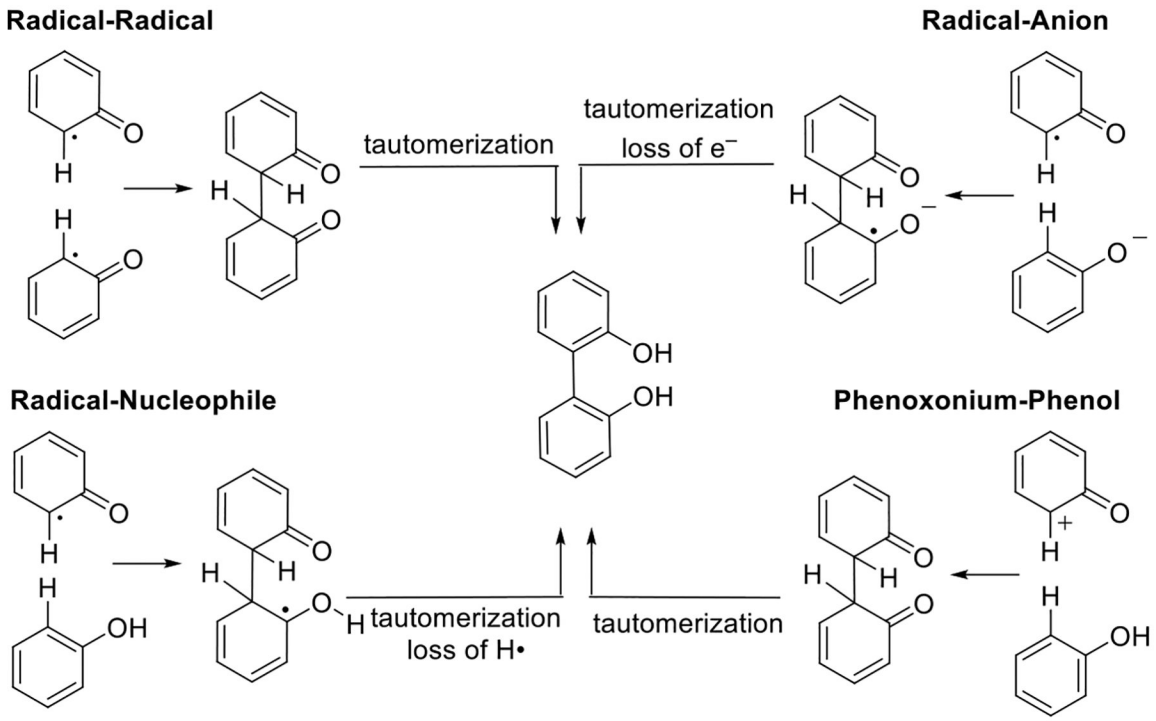
Scheme 4:
Enantioselective Phenol-Phenol Oxidative Coupling



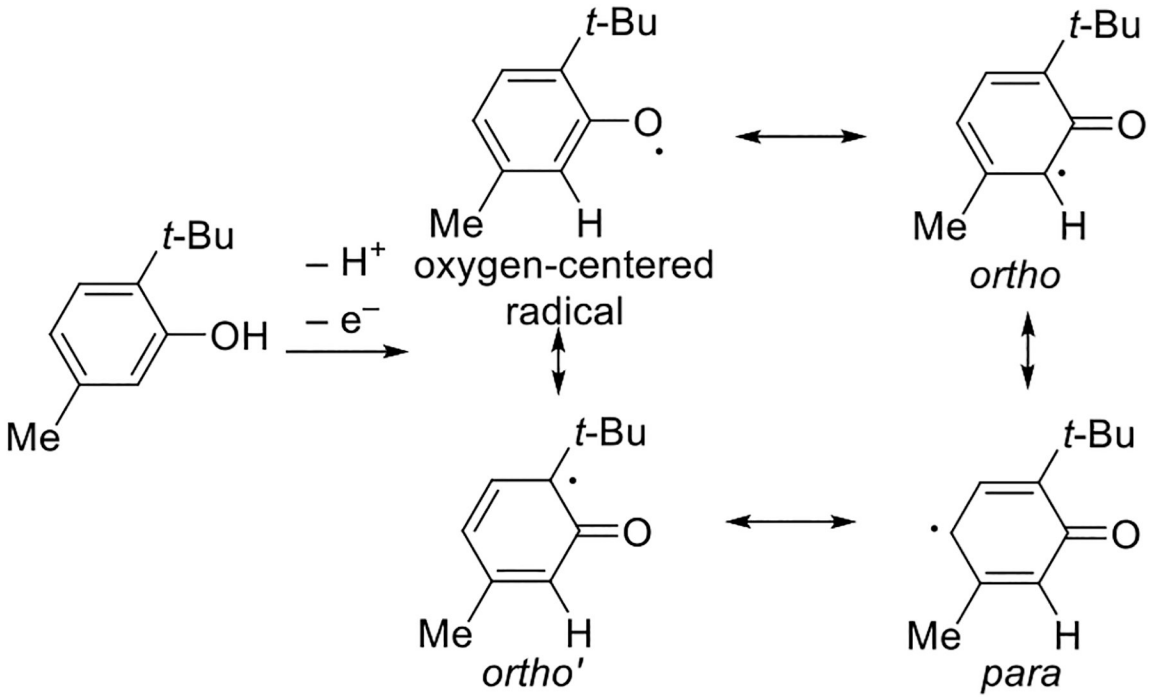
Scheme 5:
Oxidative Phenol Coupling and Possible Reaction Outcomes



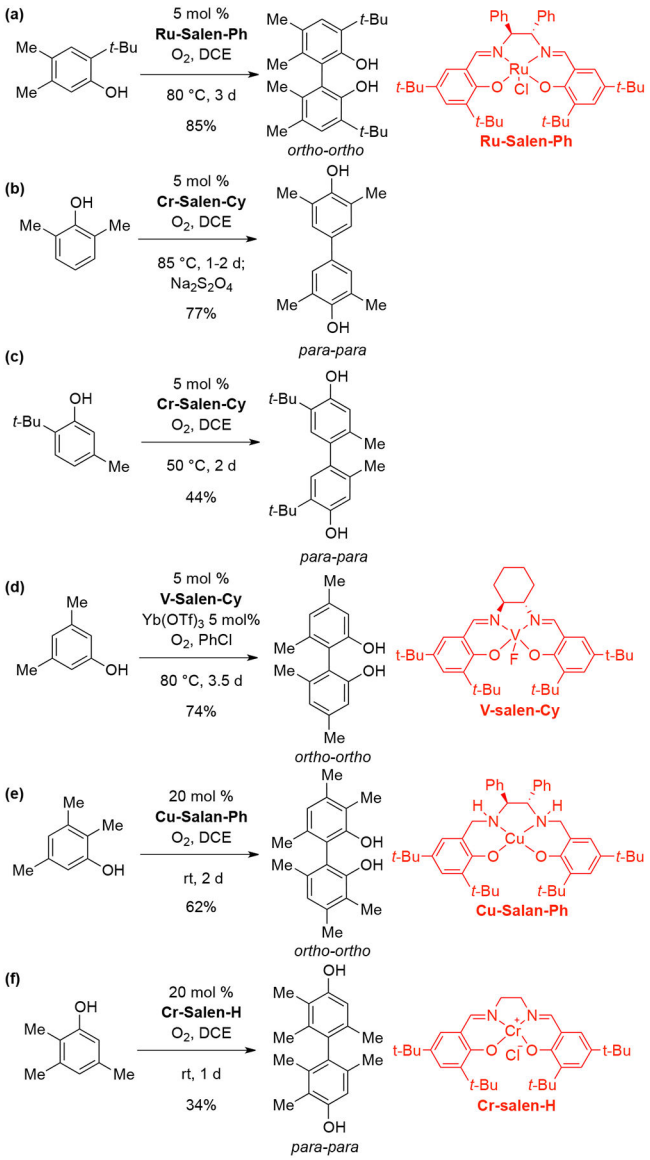
Scheme 6:
Intramolecular Phenol-Phenol Coupling and Myricanol Synthesis



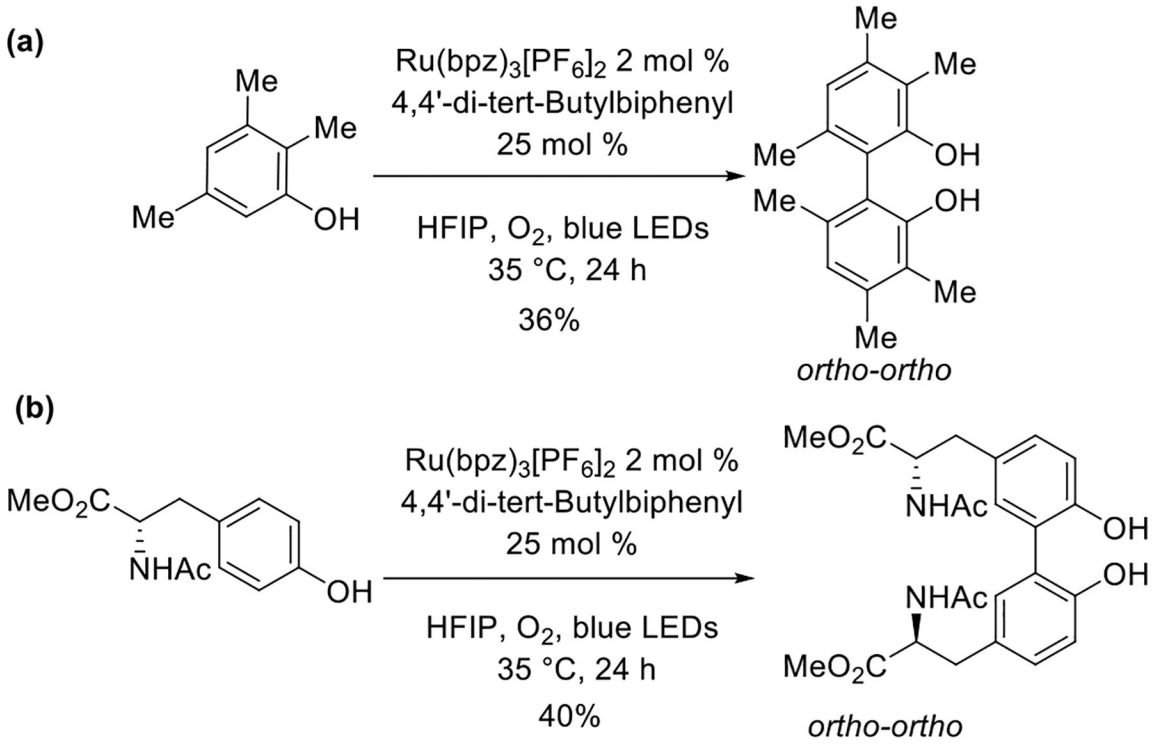
Scheme 7:
Mechanisms of Oxidative Phenol Coupling Reaction



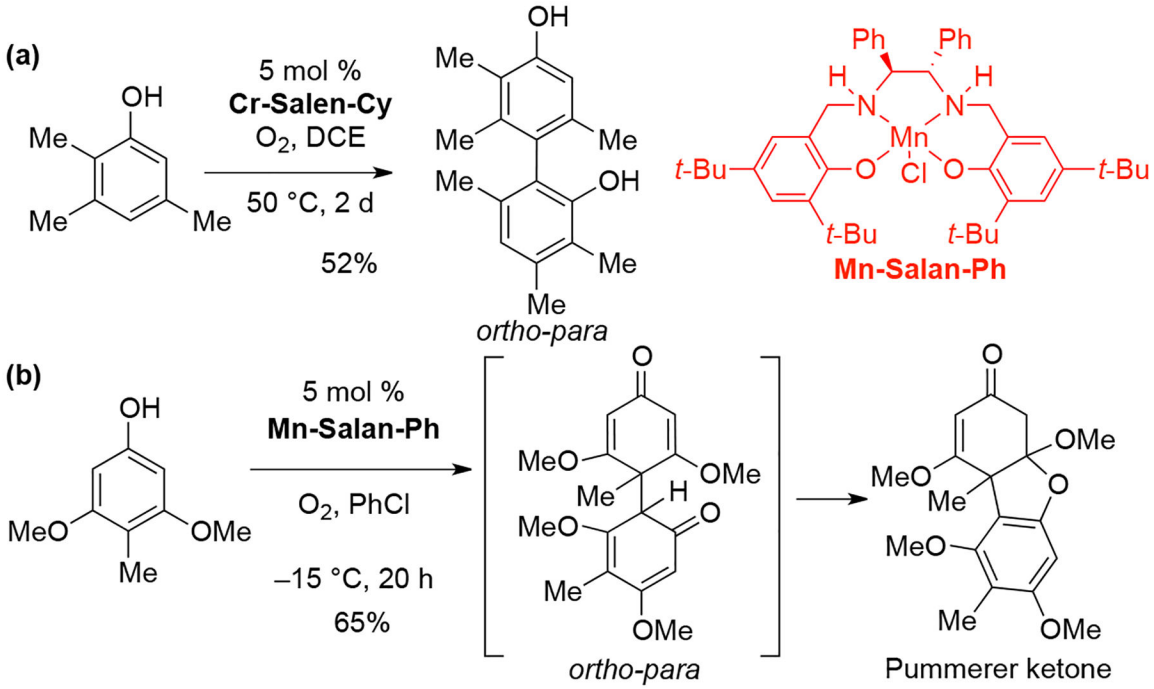
Scheme 8:
Resonance Forms of a Phenoxyl Radical



Scheme 9:
Selective Phenol Homo-Coupling Reactions.

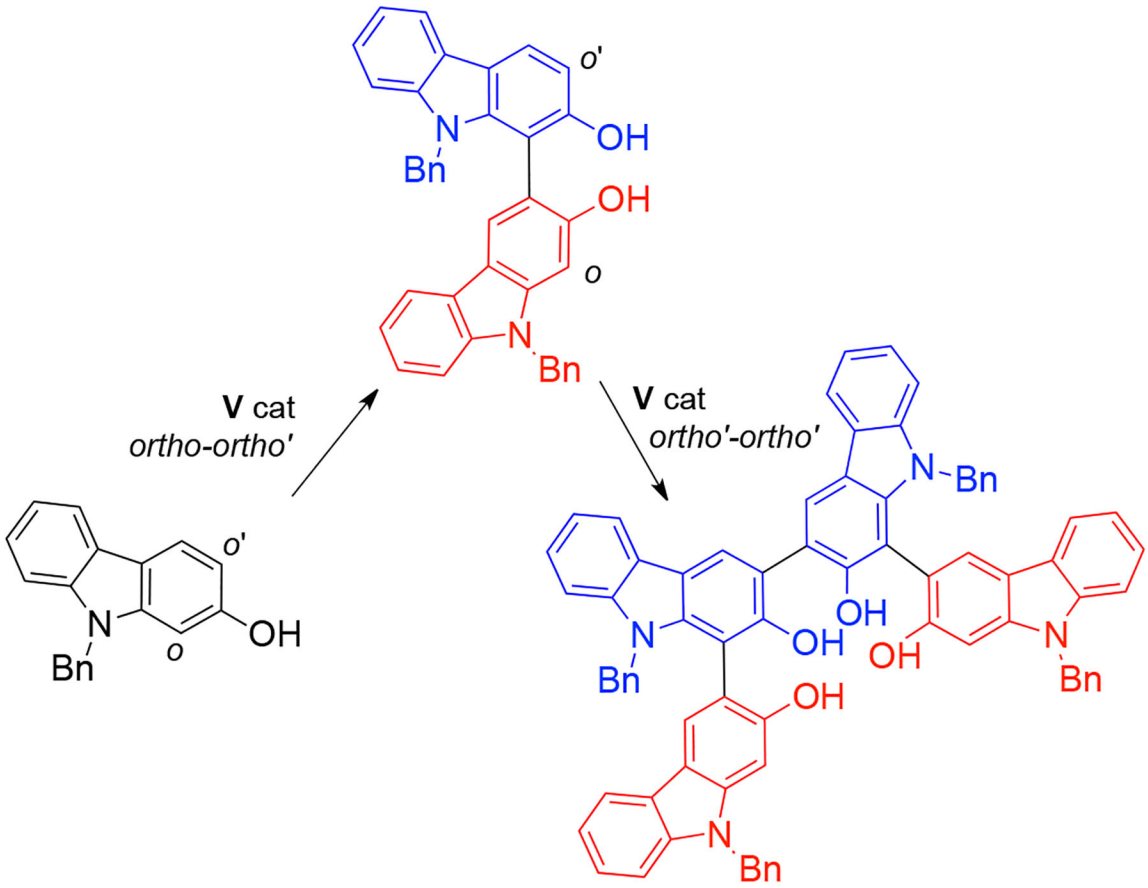


Scheme 10:
Photocatalytic Phenol Homo-Coupling Reactions

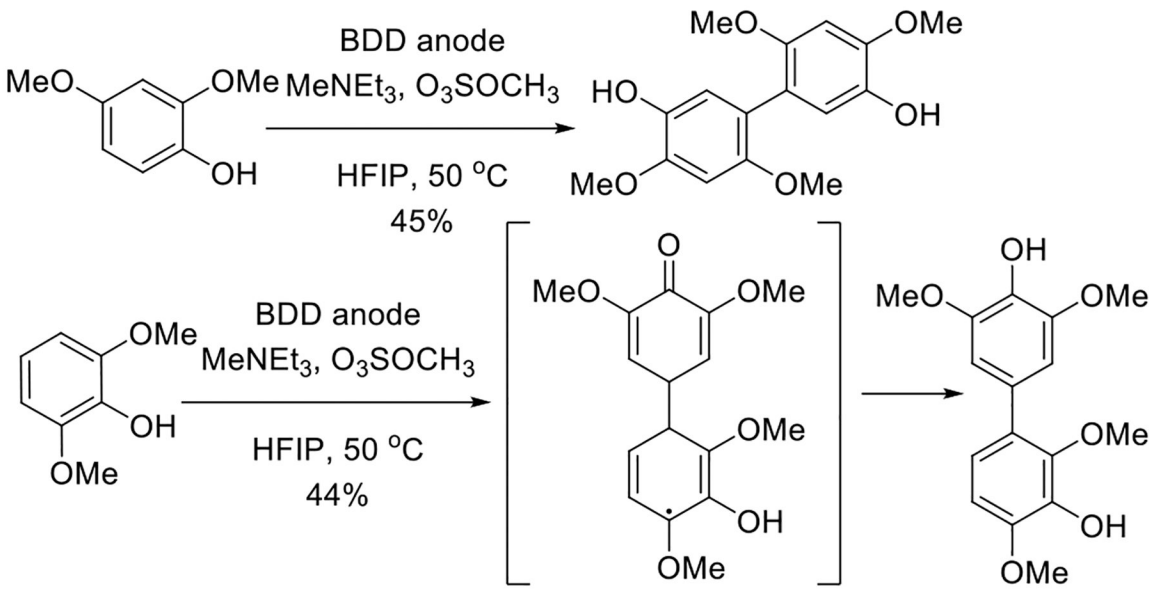


Scheme 11:

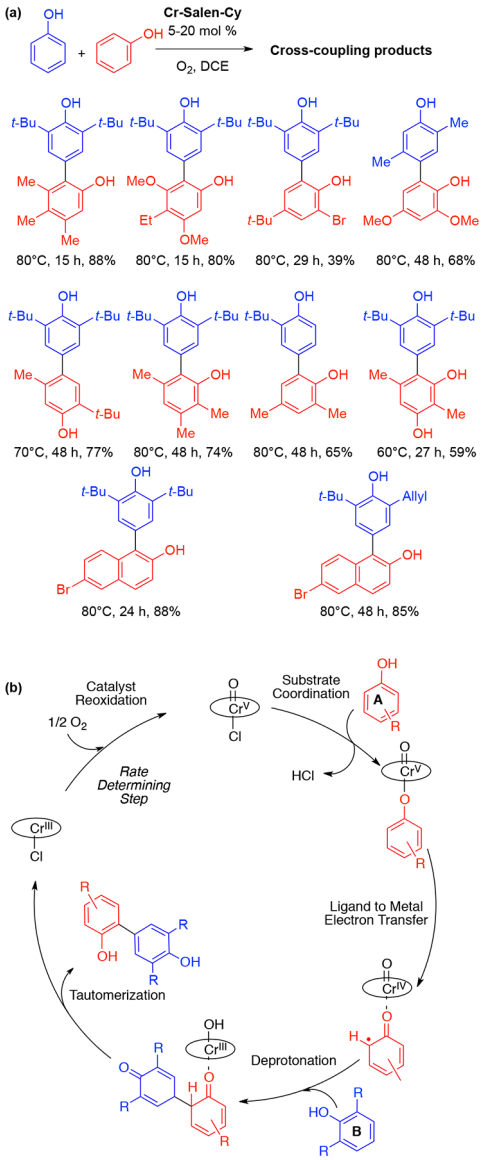
a) *ortho-para* Site Selective Oxidative Phenol Homo-Coupling b) *ortho-para* Site Selective Oxidative Phenol Homo-Coupling Leading to Pummerer Ketone Generation



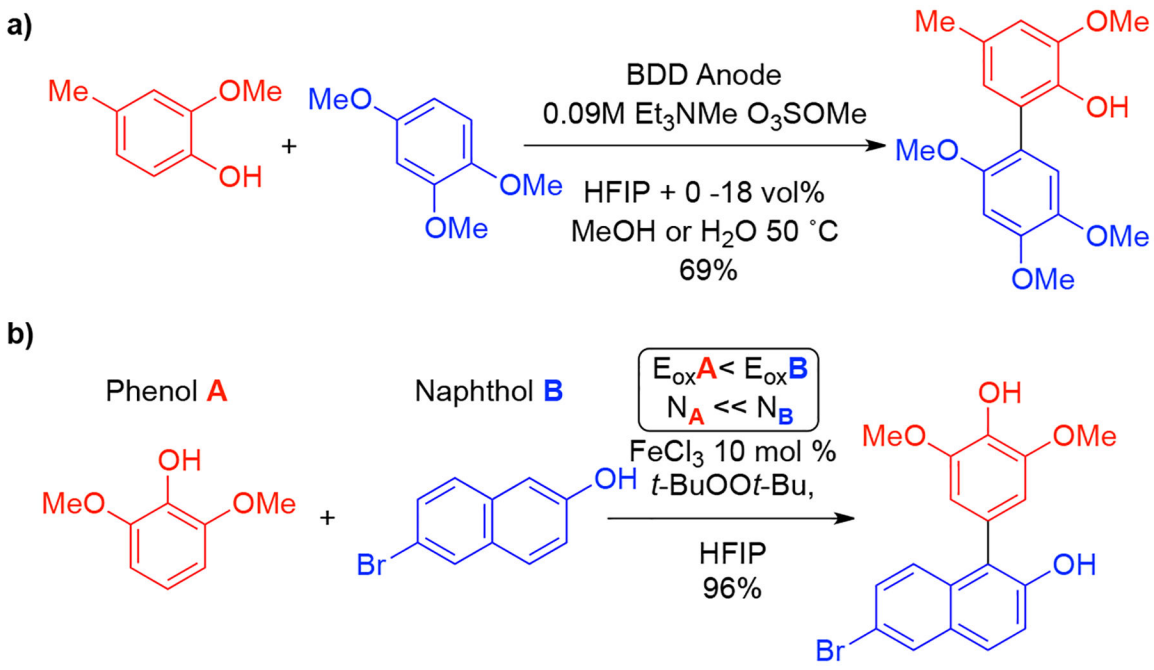
Scheme 12:
Hydroxycarbazole *ortho-ortho'* Dimerization and *ortho-ortho* Tetramerization



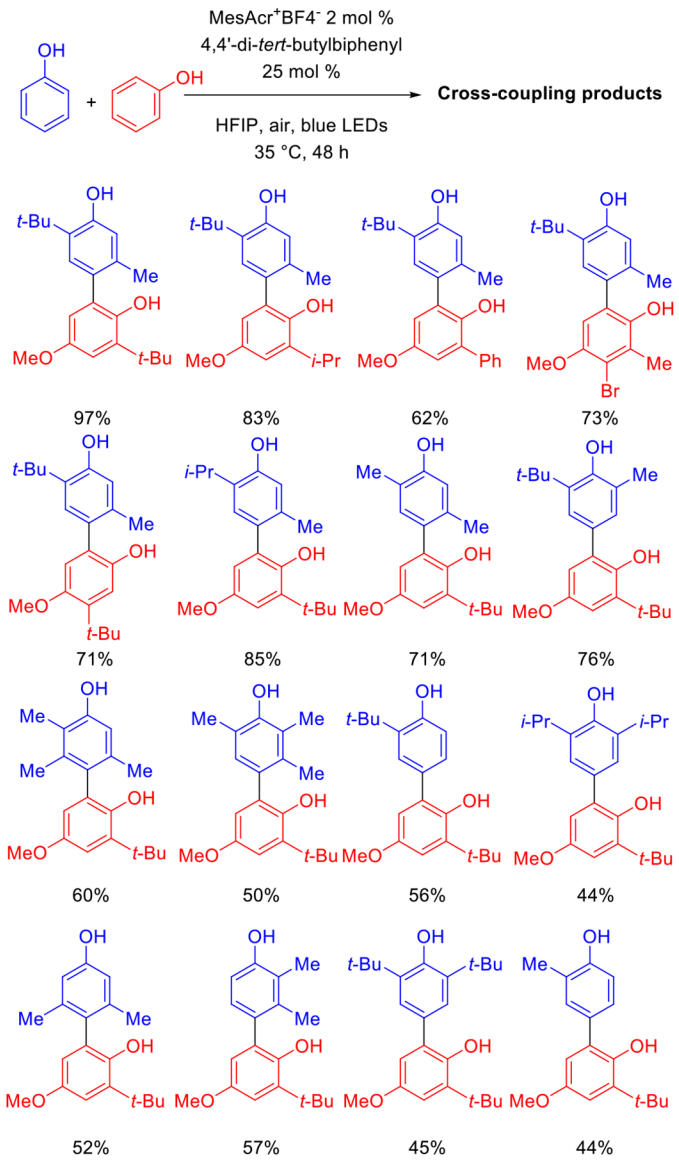
Scheme 13:
Electrochemical *meta-meta/meta-para* Oxidative Phenol Couplings



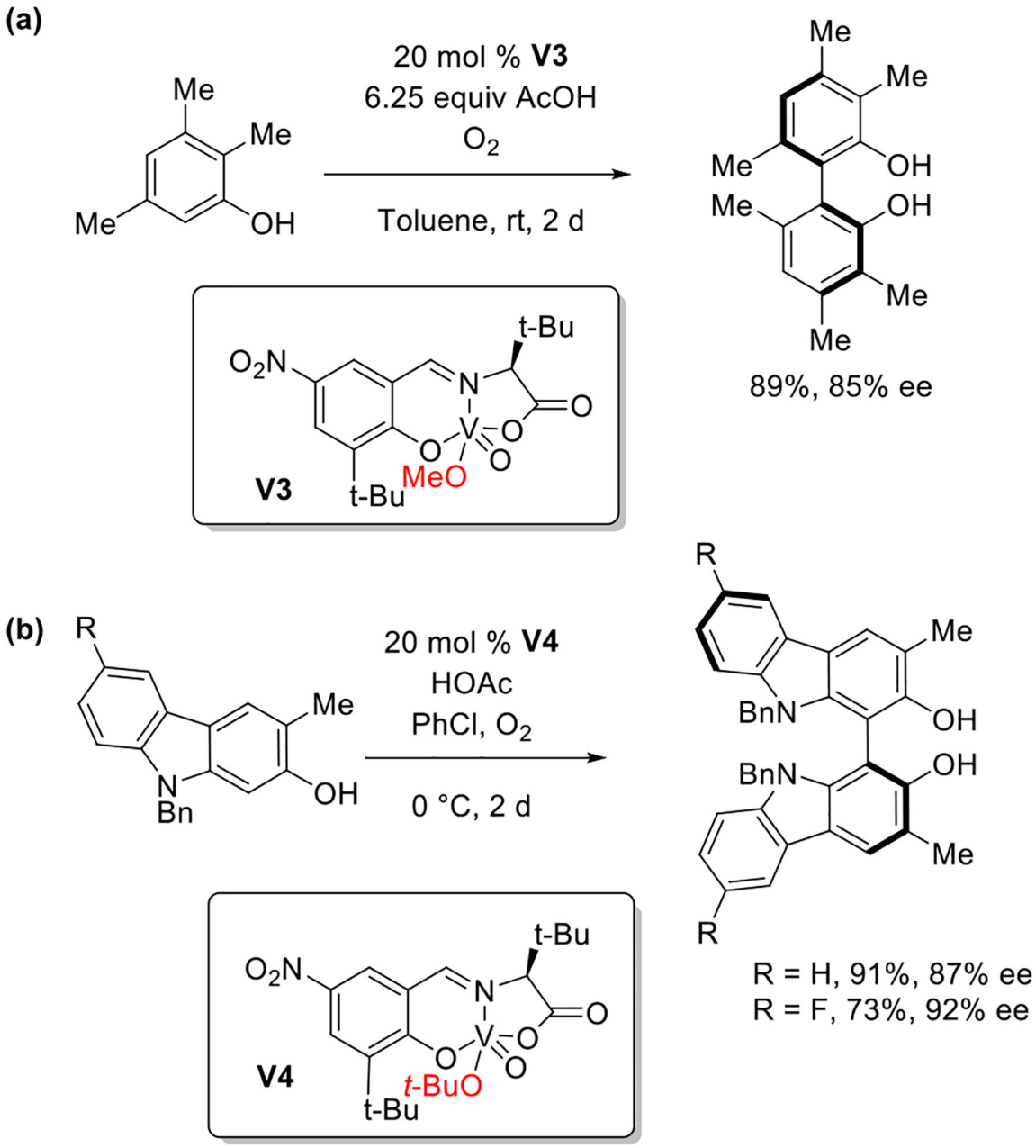
Scheme 14:
Chromium Catalyzed Phenol Cross-Coupling



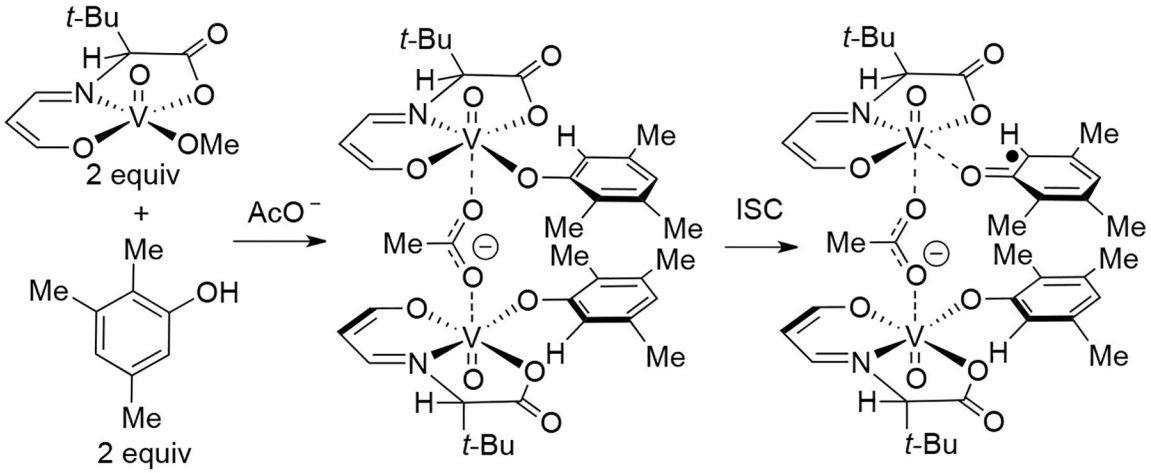
Scheme 15:
Electrochemical and Iron Catalyzed Phenol Cross-Coupling



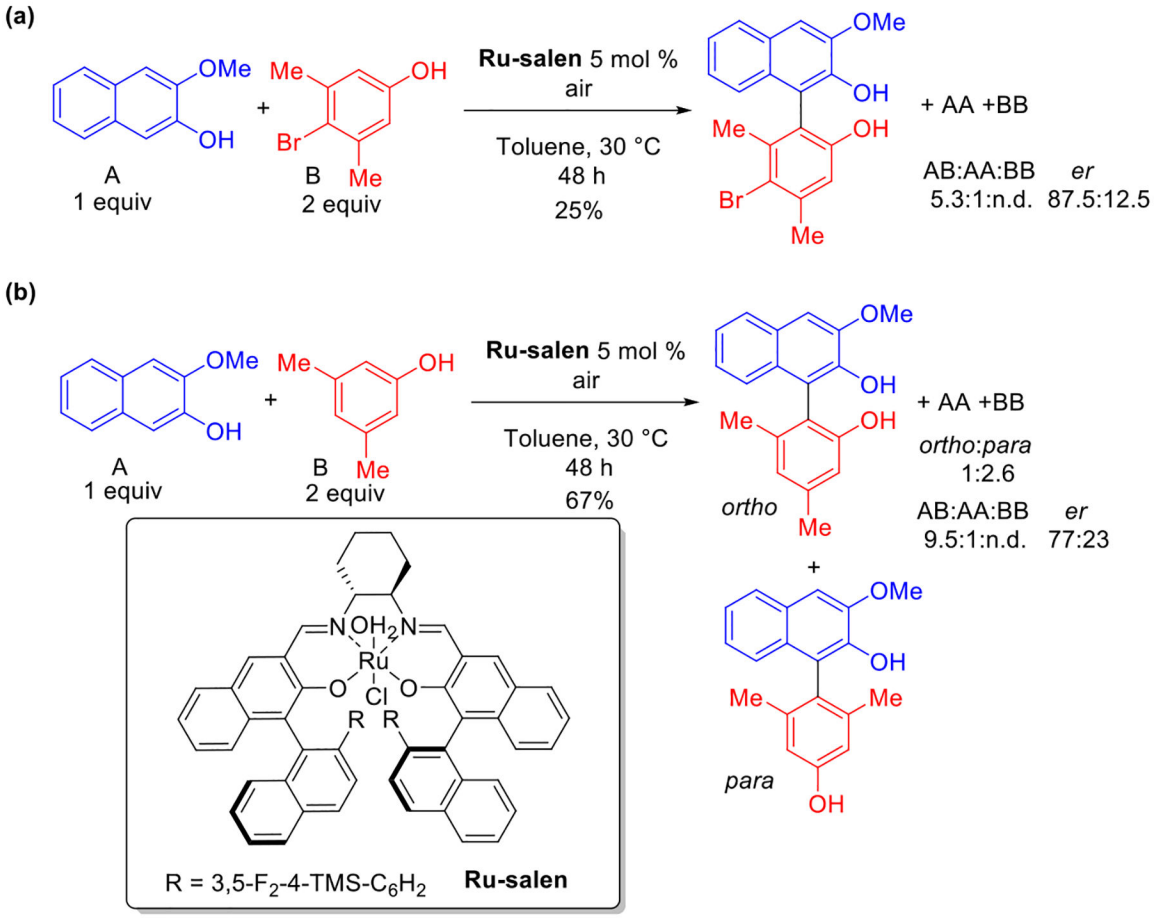
Scheme 16:
Photocatalytic Phenol Cross-Coupling



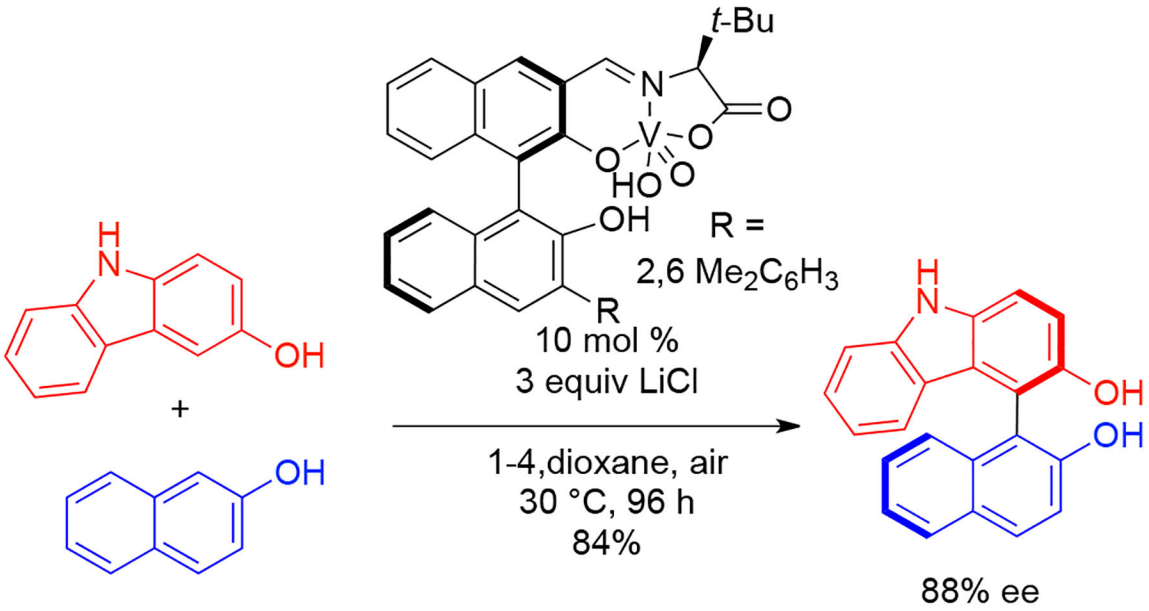
Scheme 17:
Enantioselective Phenol-Phenol Oxidative Coupling



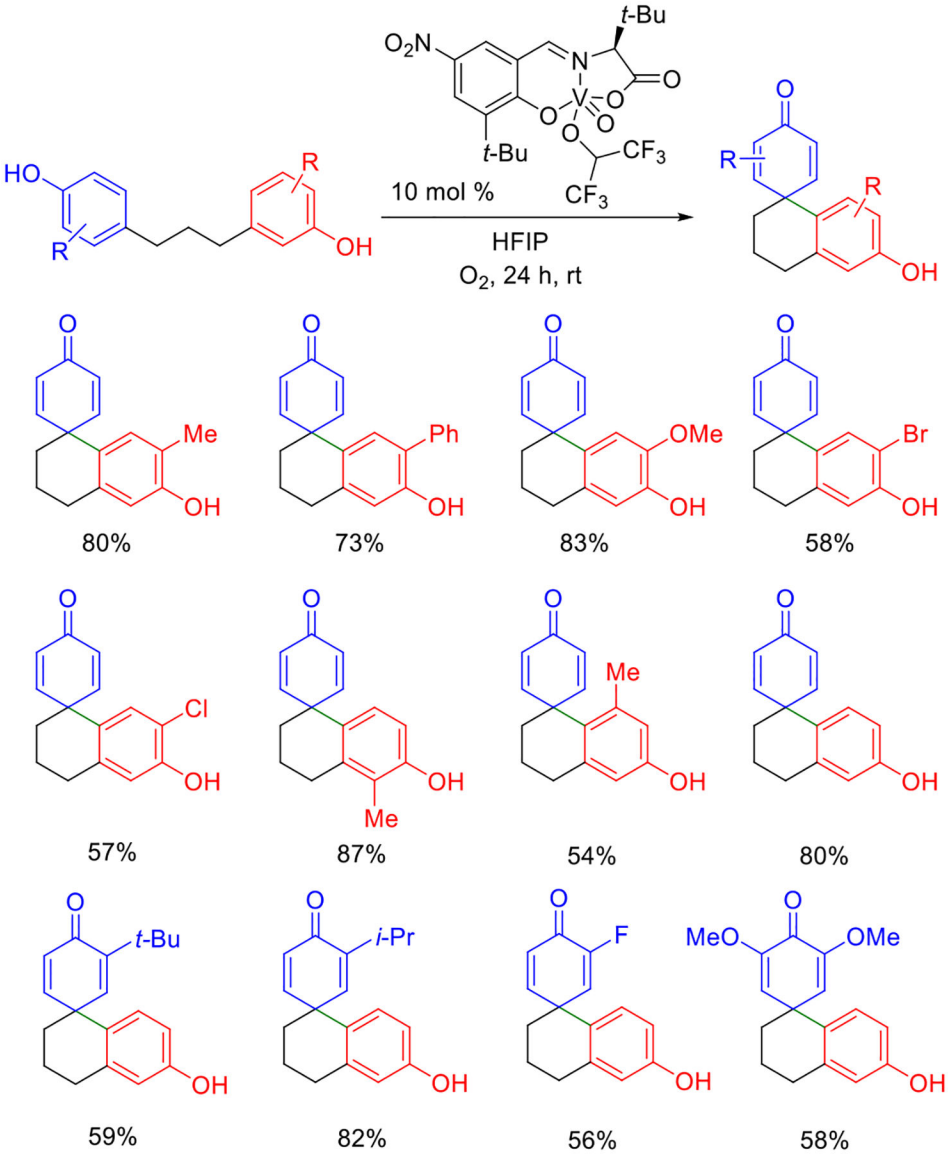
Scheme 18:
Enantioselective Phenol-Phenol Oxidative Coupling Mechanism



Scheme 19:
Ruthenium Catalyzed Enantioselective Cross-Coupling Reaction

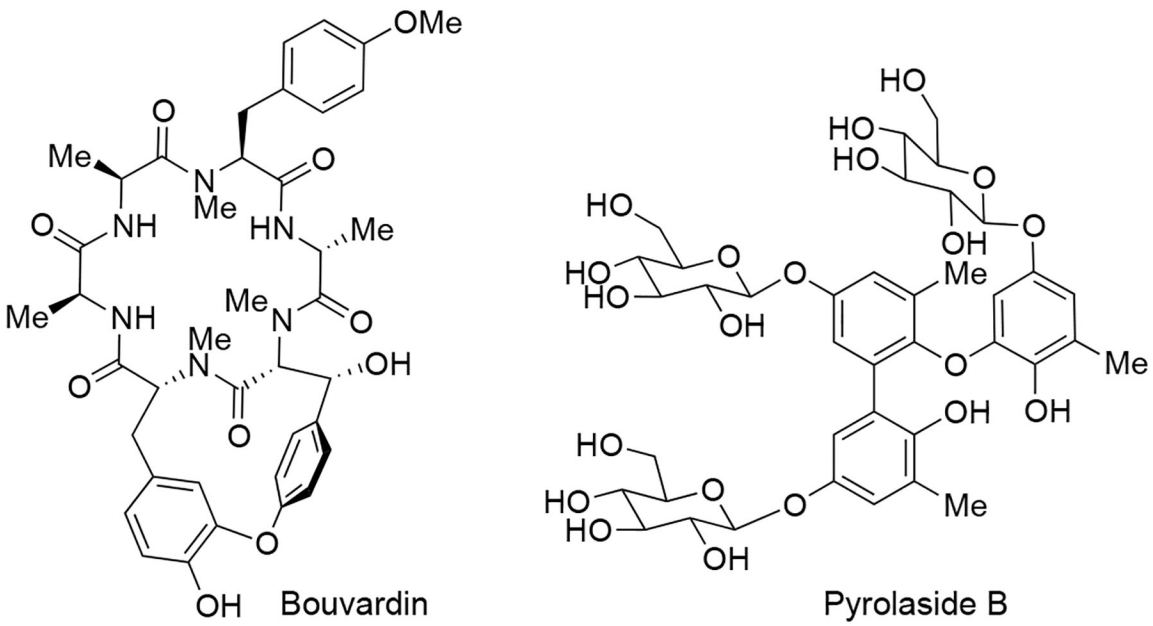


Scheme 20:
Vanadium Catalyzed Enantioselective Cross-Coupling Reaction

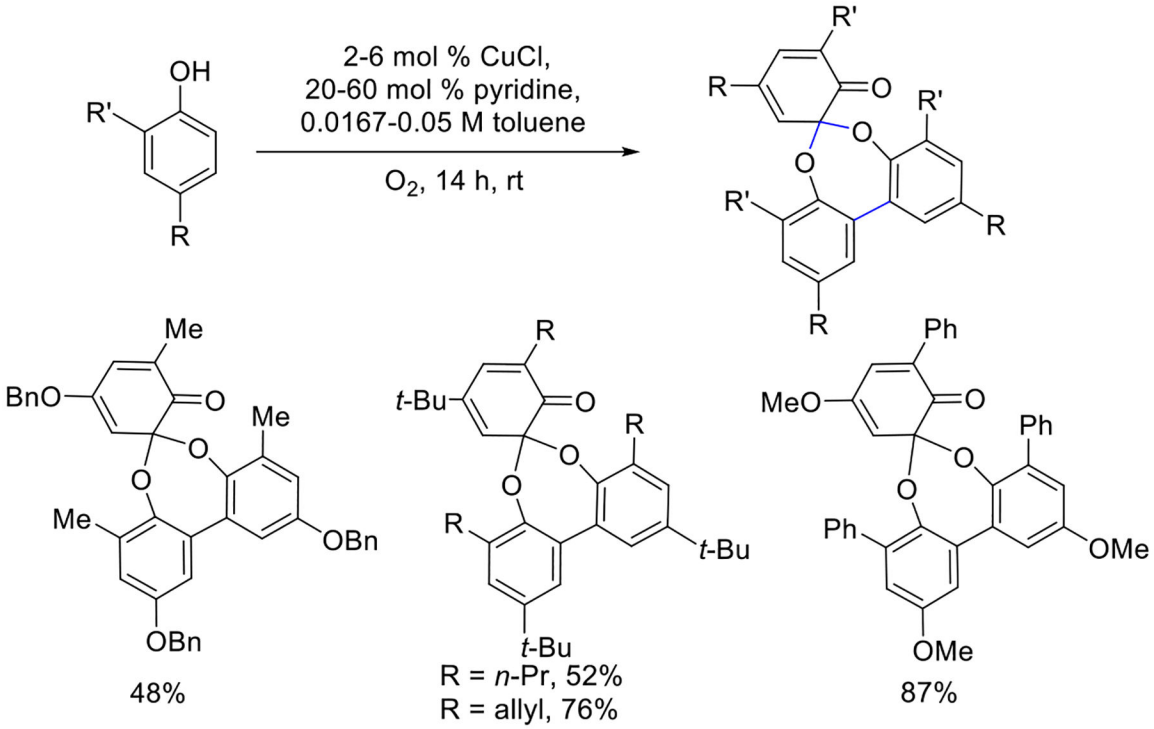


Scheme 21:

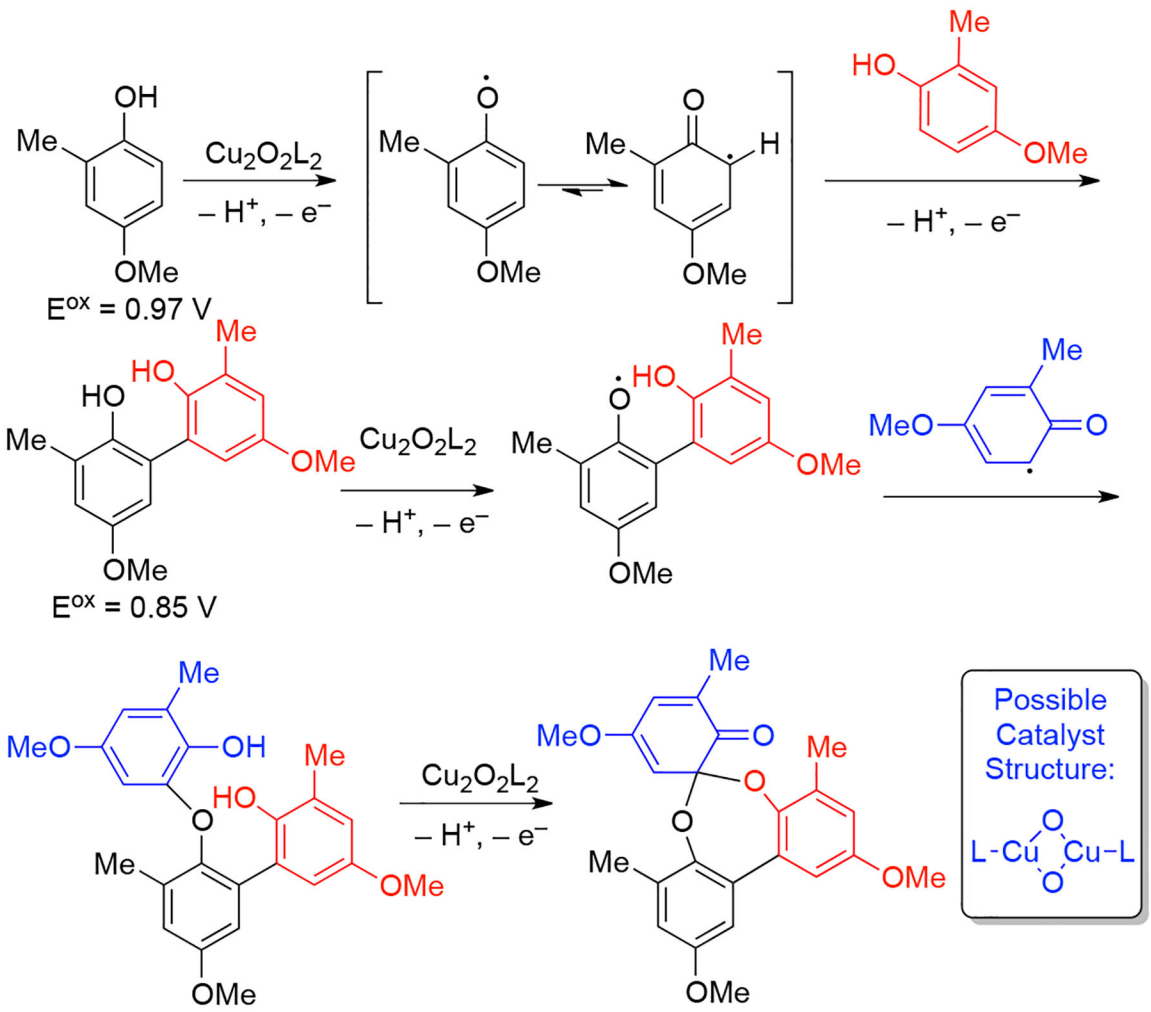
Scope of the Intramolecular Oxidative Phenol Coupling with a Vanadium Catalyst



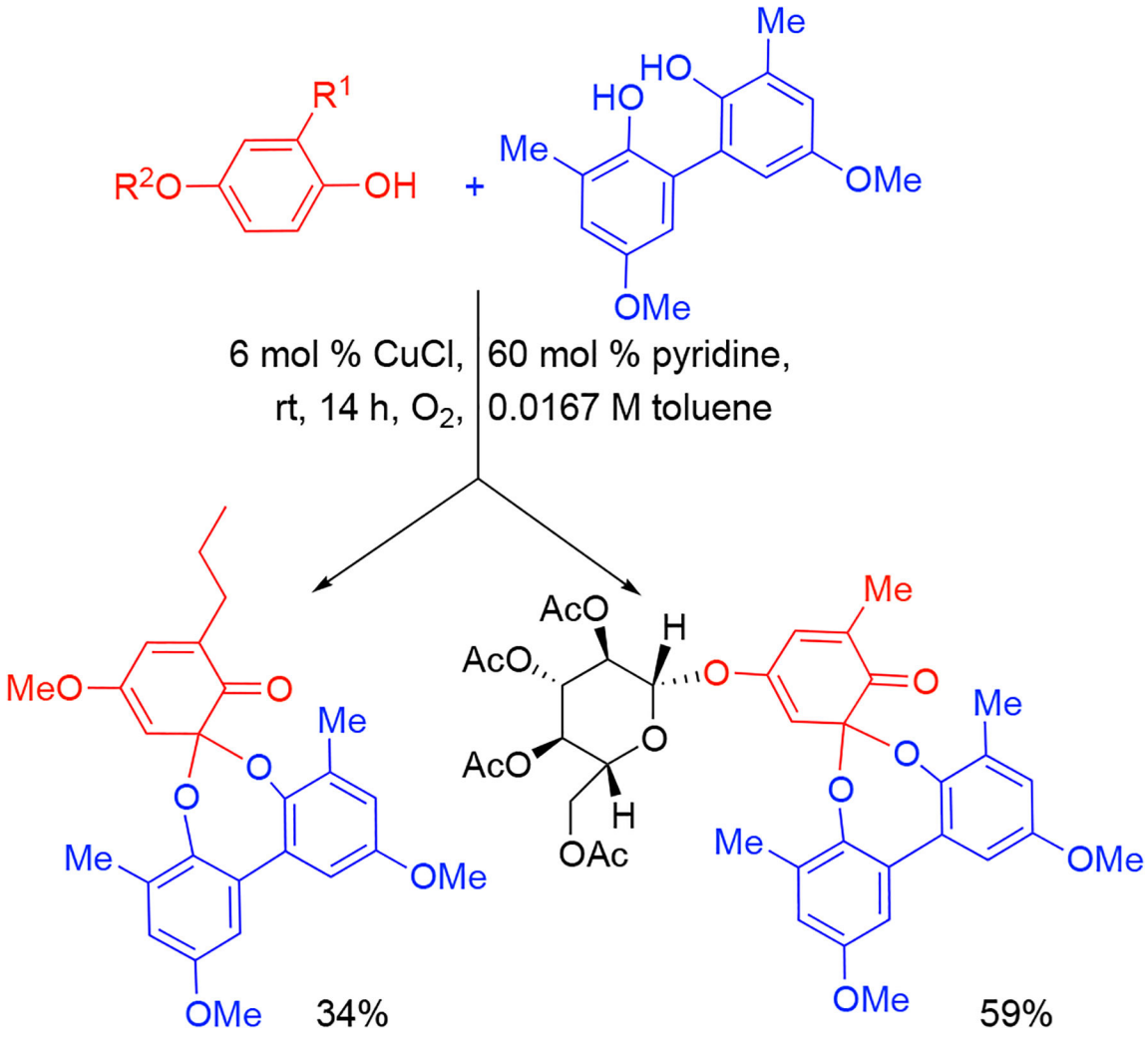
Scheme 22:
Natural Products with Phenol C–O Couplings



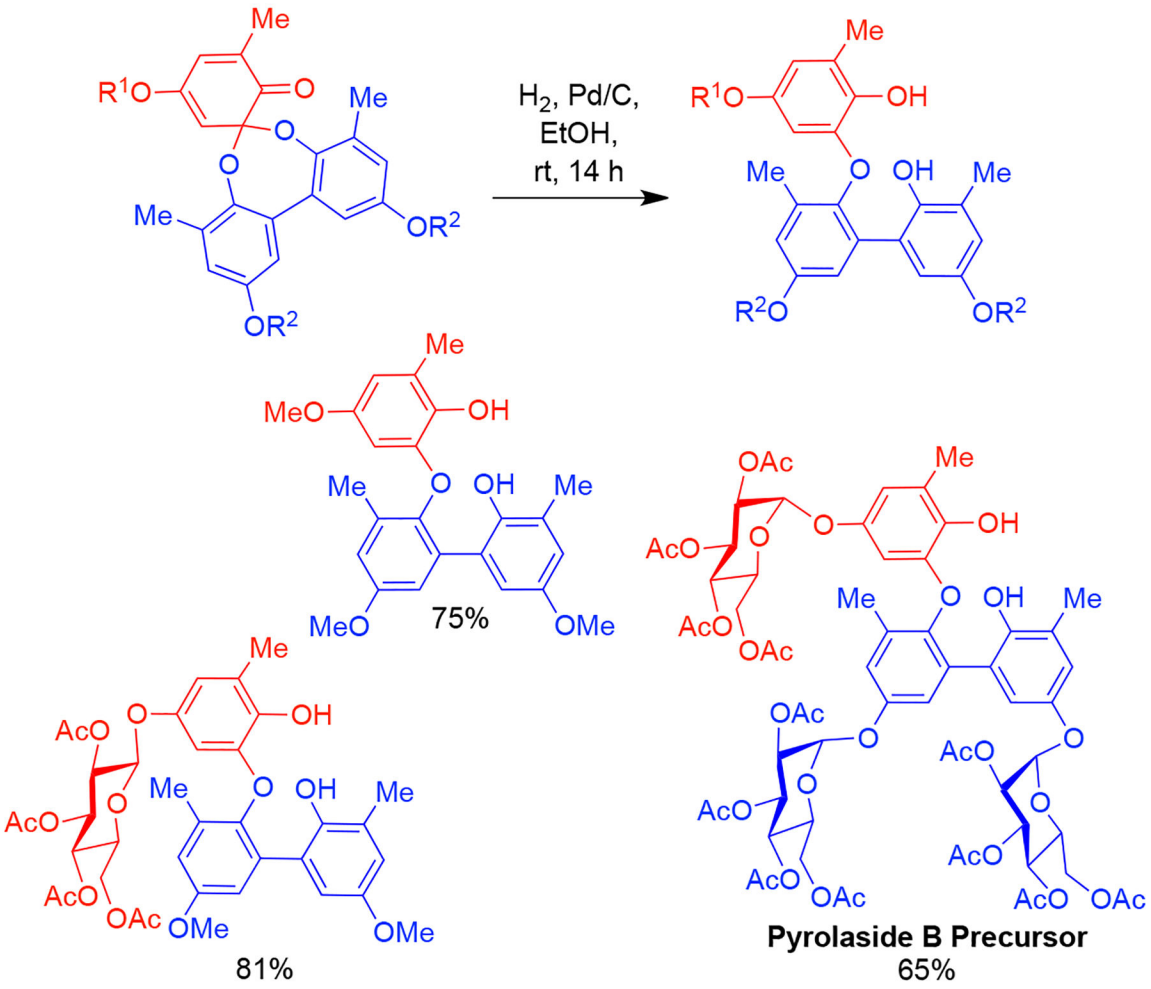
Scheme 23:
C–C/C–O/C–O Phenol Coupling with a Copper Catalyst



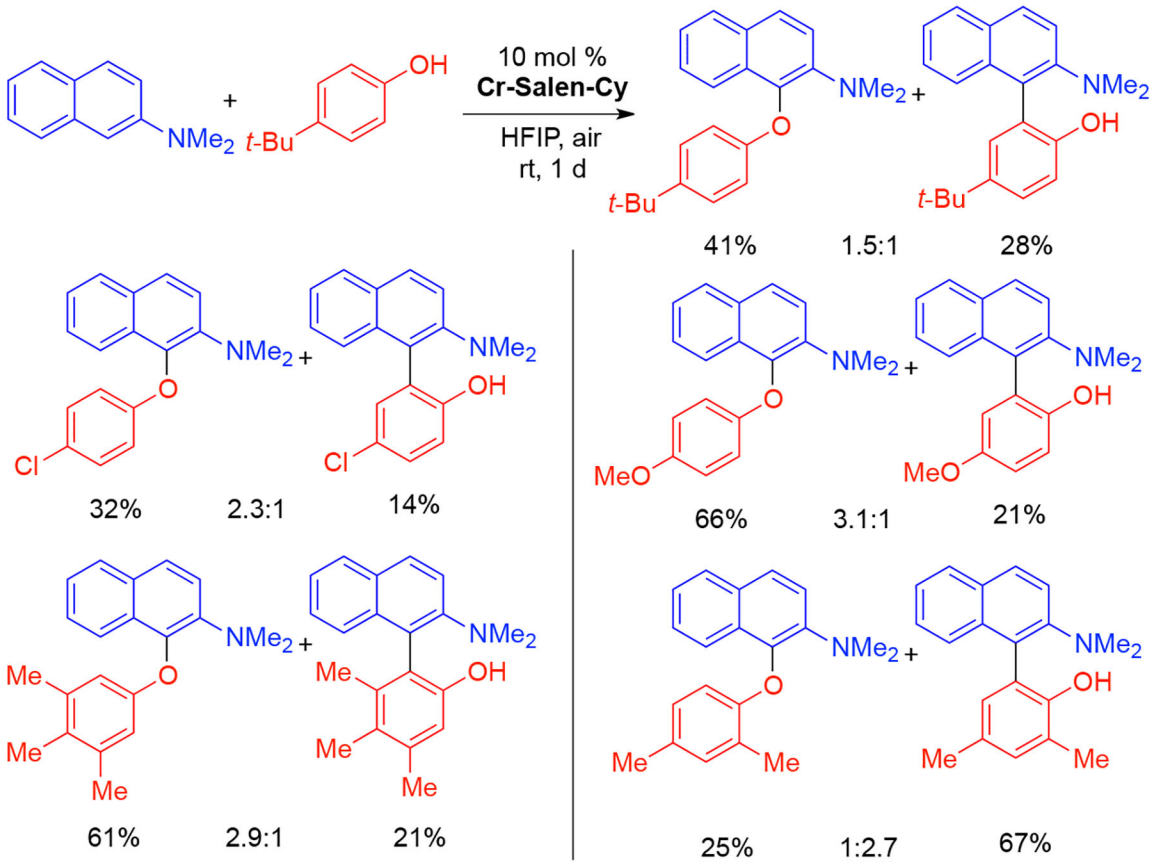
Scheme 24:
Mechanism of the C–C/C–O/C–O Phenol Coupling



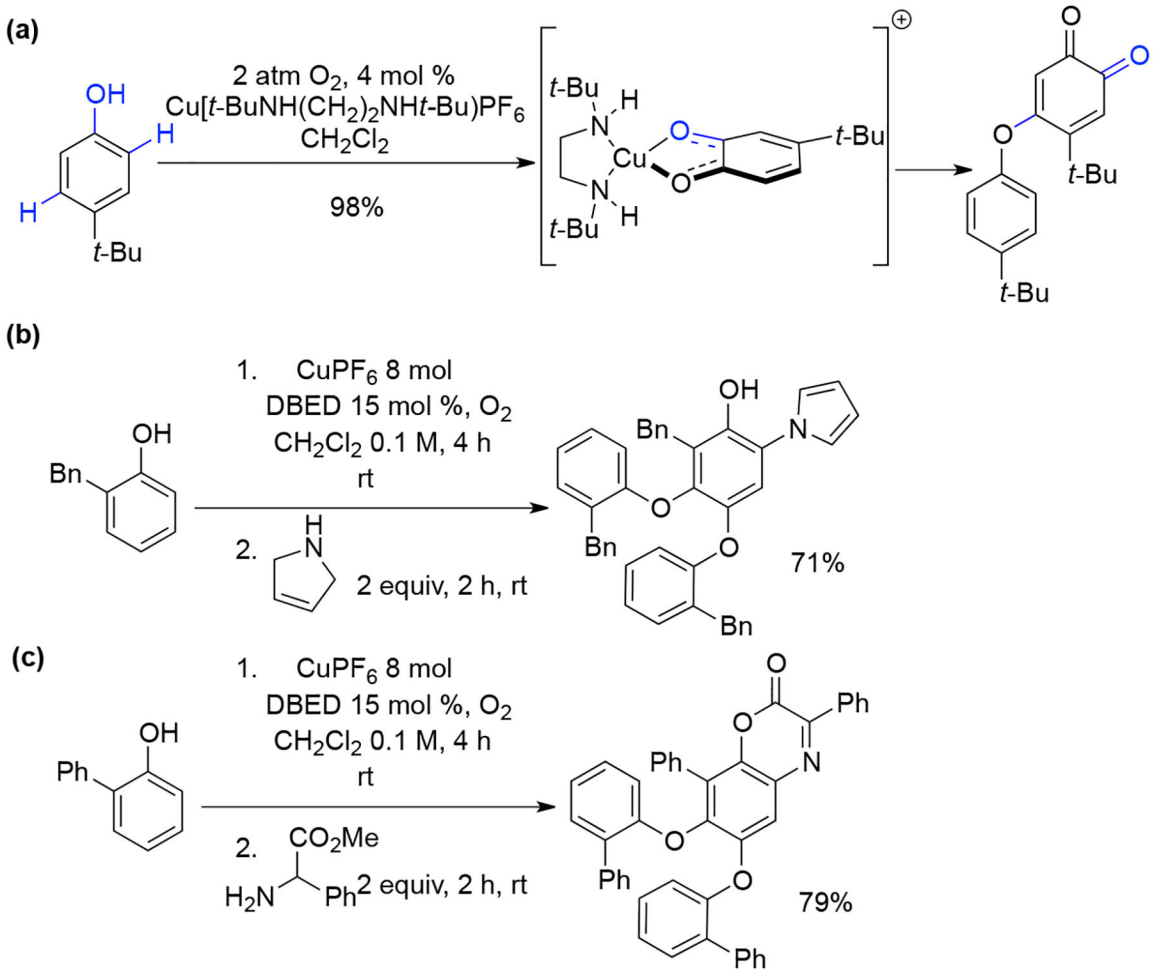
Scheme 25:
Unsymmetrical Trimerization via C–O Coupling



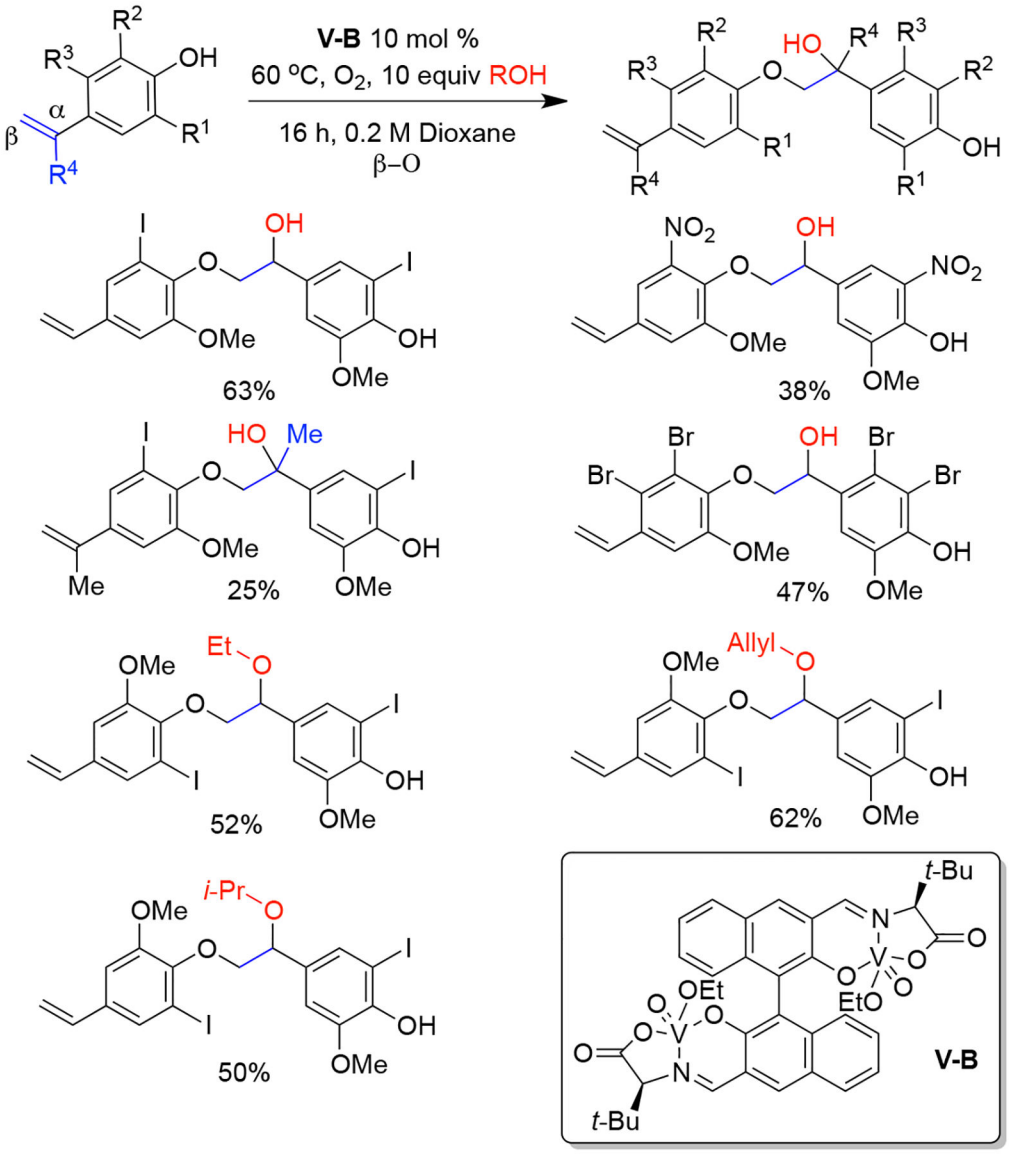
Scheme 26:
Linear Triphenols from the *ortho*-Quinone Spiroketals



Scheme 27:
Naphthylamine Phenol C–C vs C–O coupling

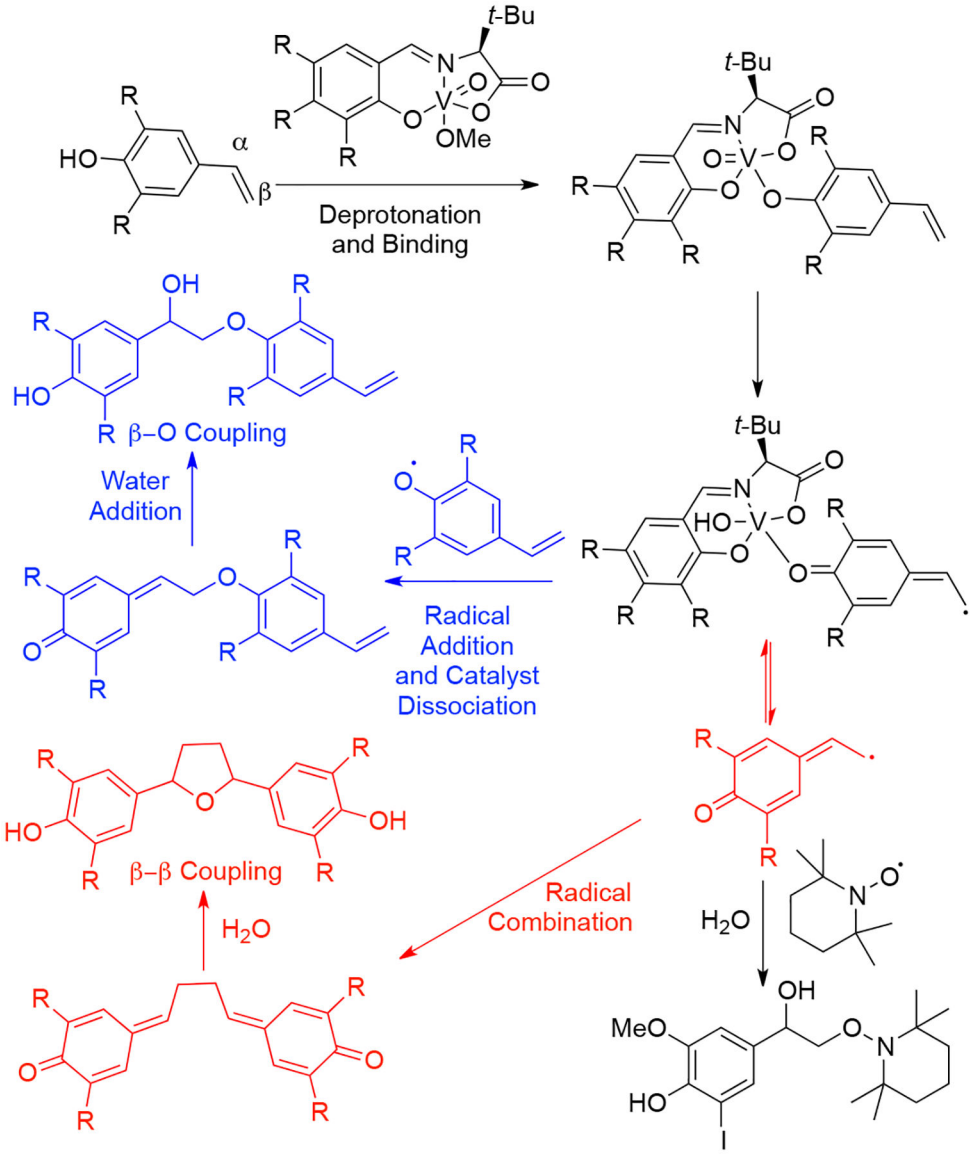


Scheme 28:
Copper Catalyzed Selective Phenol C–O Coupling



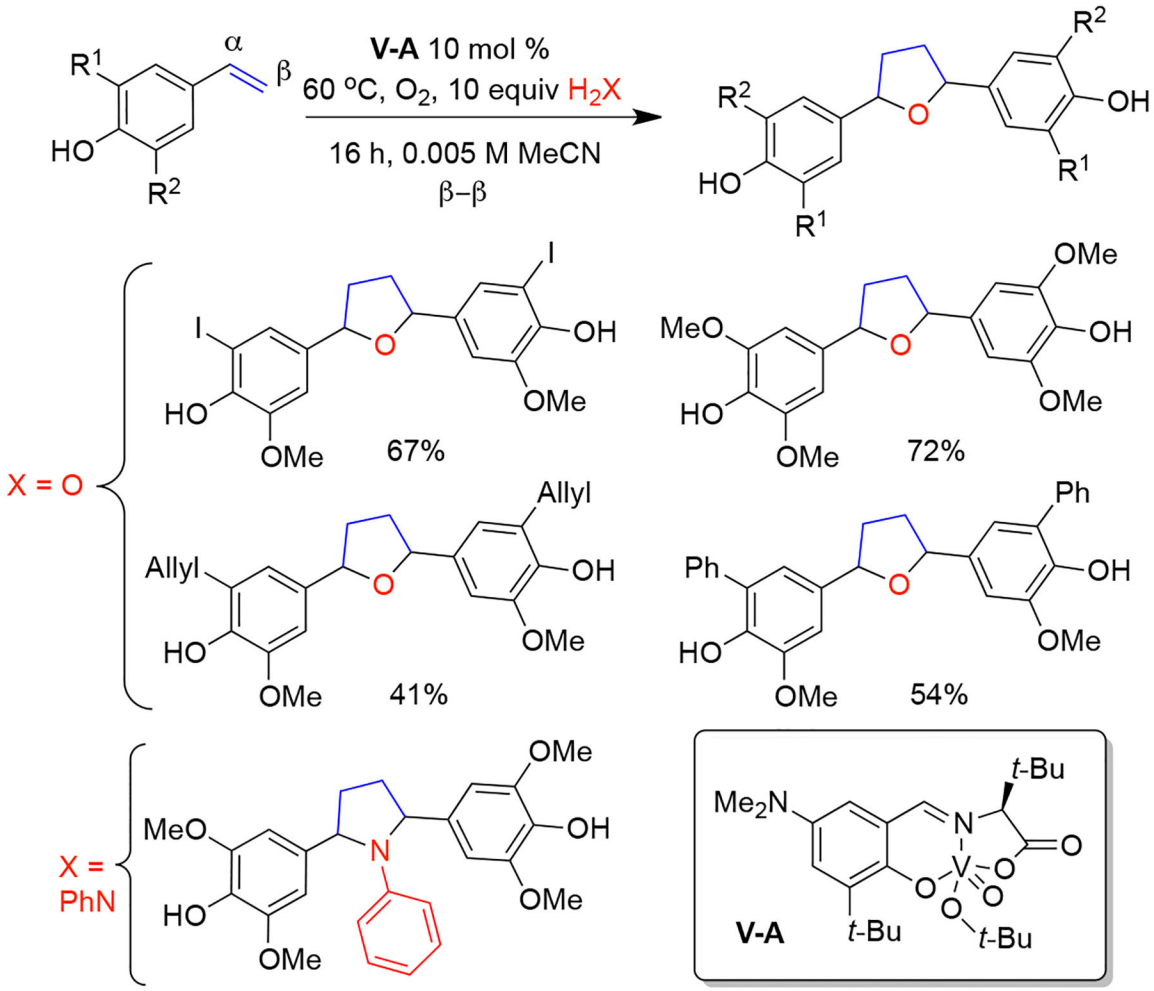
Scheme 29:

β-O Alkenylphenol Coupling with a Vanadium Catalyst

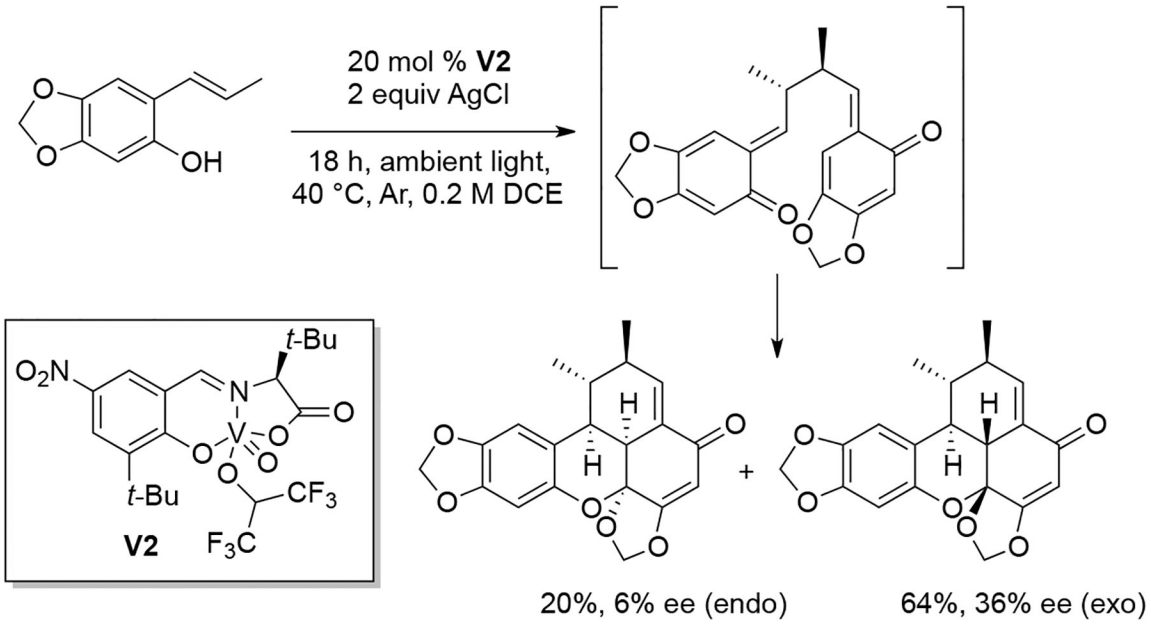


Scheme 30:

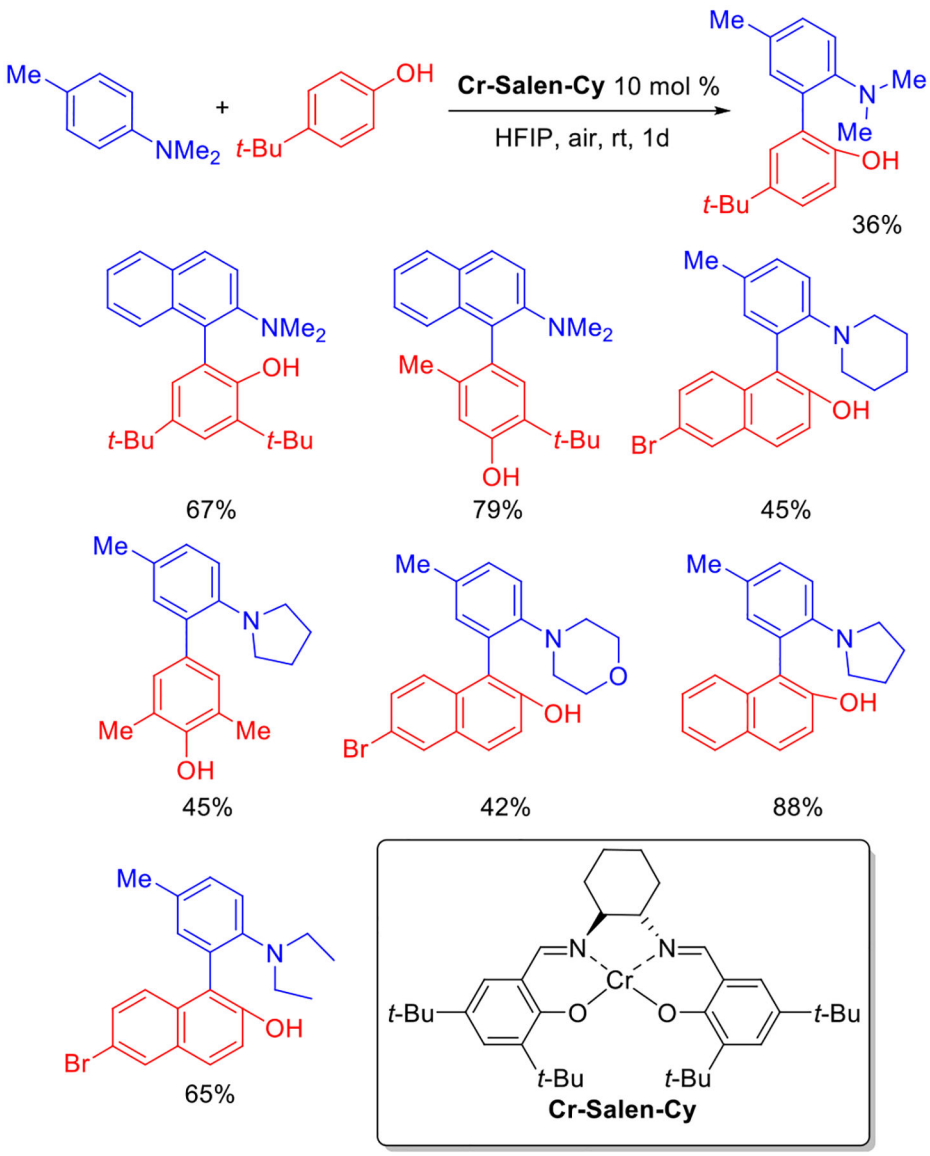
Mechanism of Vandium Catalyzed *β*-O vs *β*-*β* Alkenylphenol Coupling



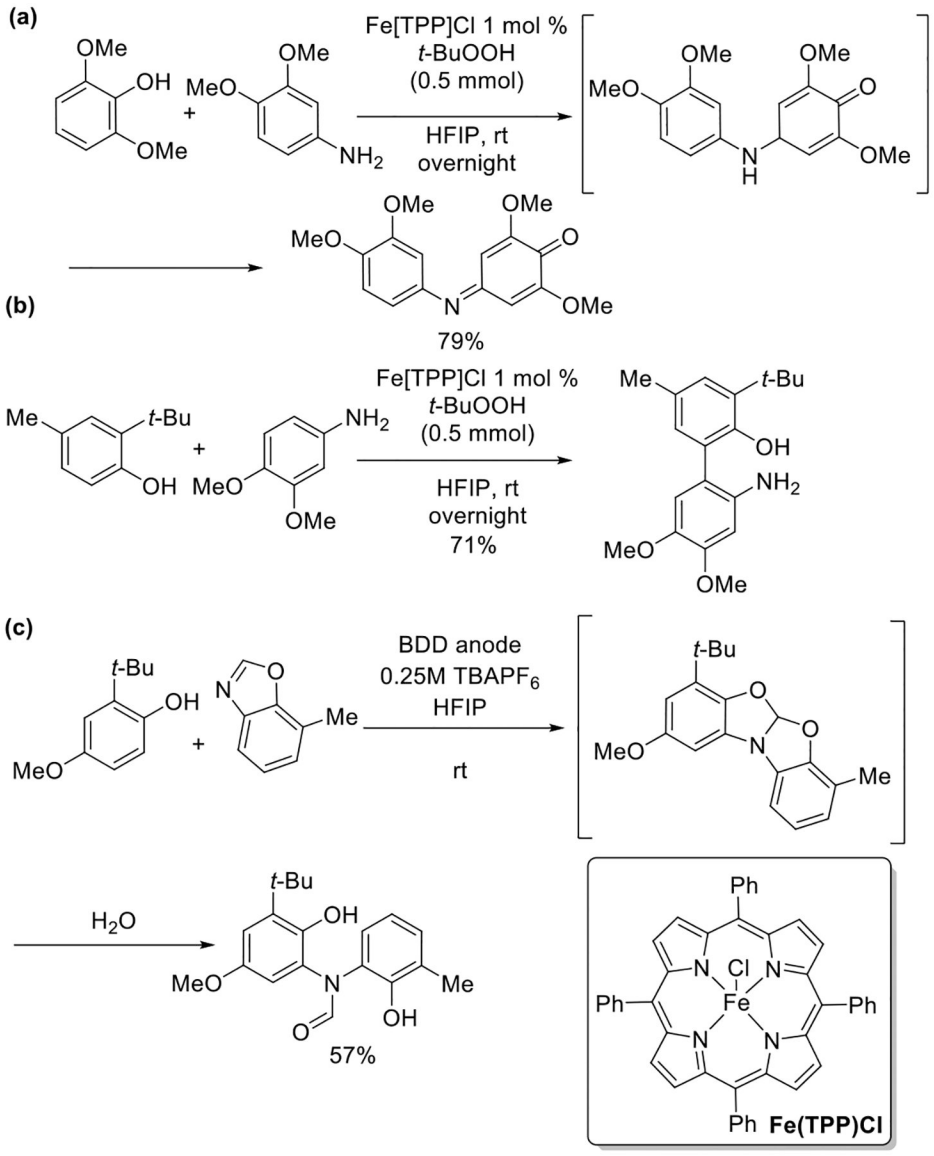
Scheme 31:
β-β Alkenylphenol Coupling with a Vanadium Catalyst



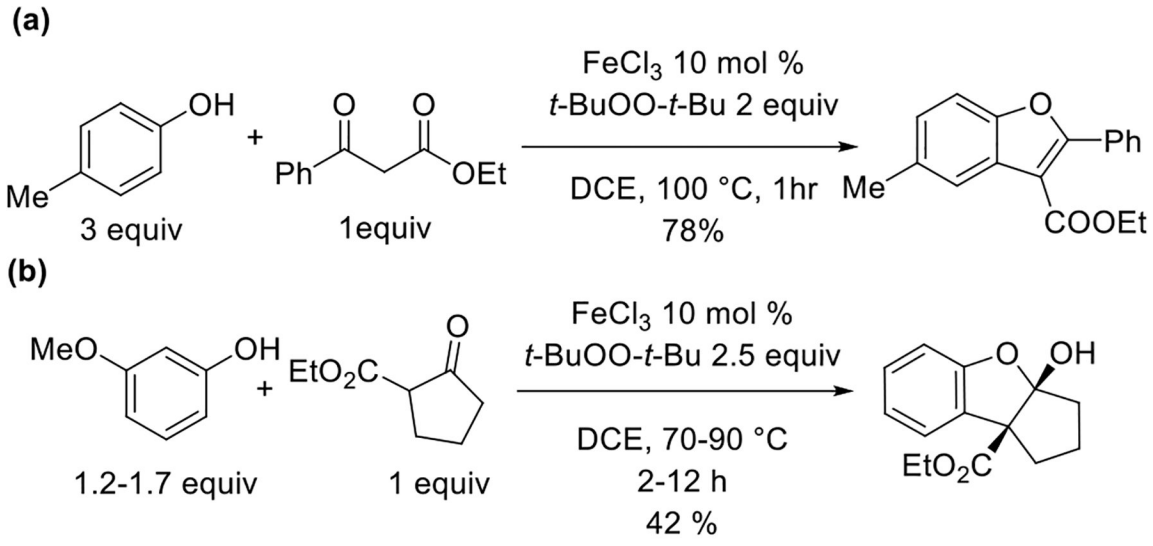
Scheme 32:
Exocyclic Oxidative Phenol Coupling Reaction



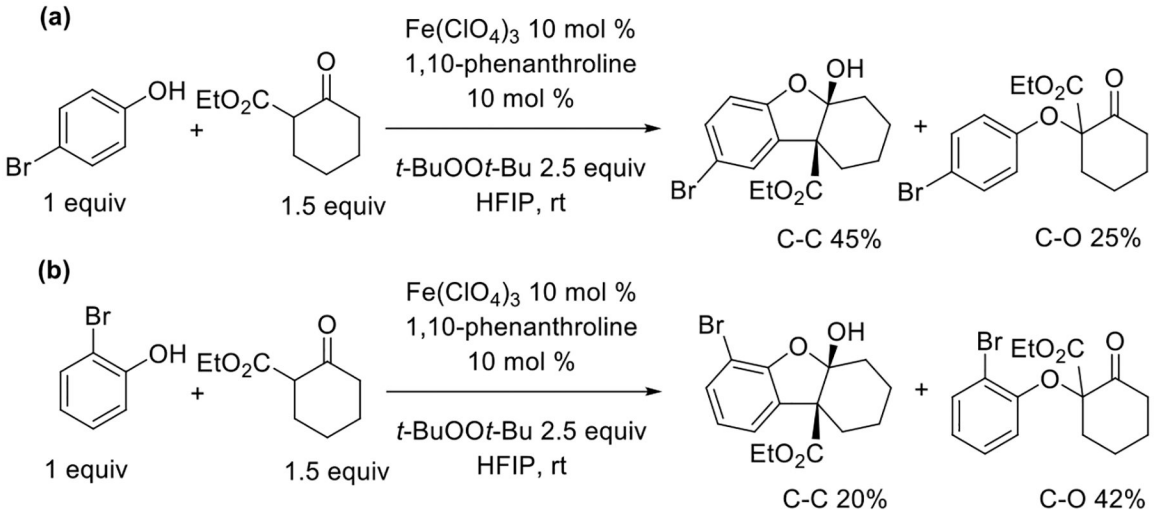
Scheme 33:
Aniline-Phenol/Aminonaphthalene-Phenol Oxidative Couplings



Scheme 34:
Aniline-Phenol/oxizole -Phenol Oxidative Couplings

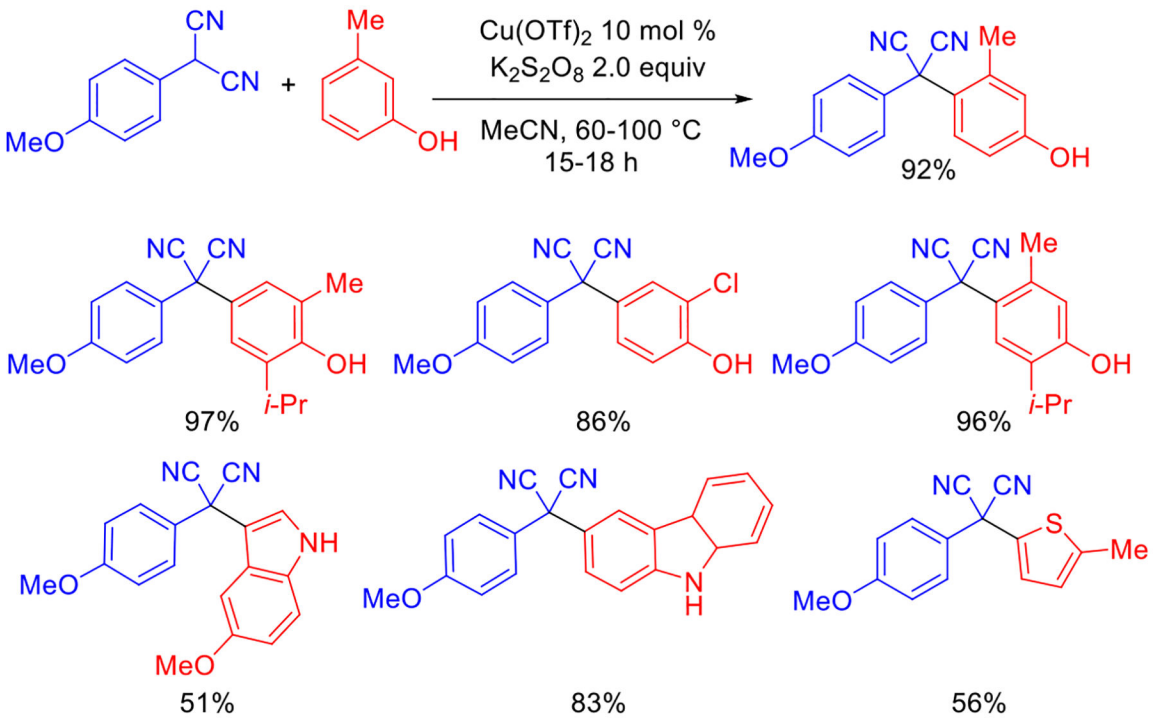


Scheme 35:
β-Ketoesters/Phenols Oxidative Couplings

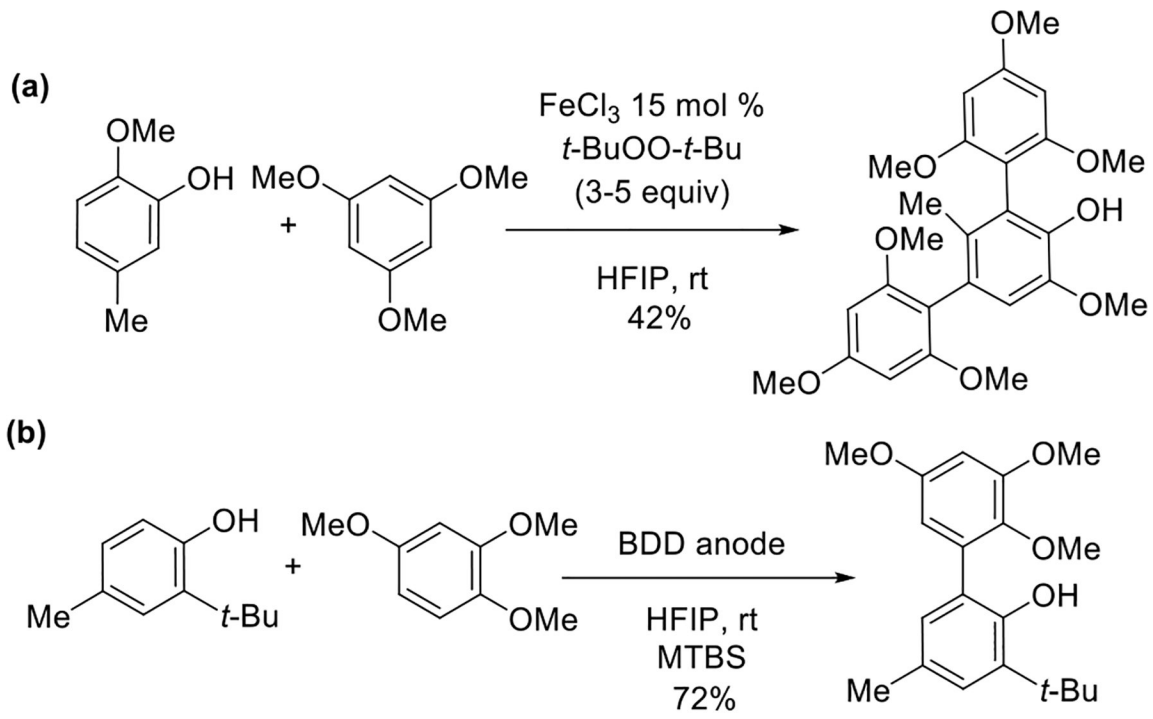


Scheme 36:

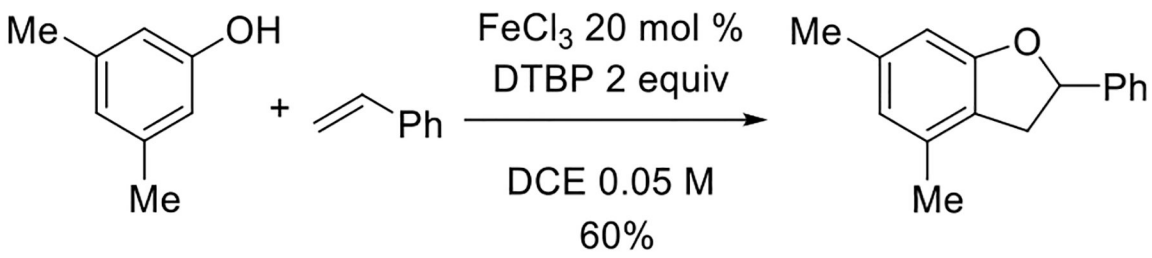
β-Ketoesters/Phenols Oxidative Couplings C–C vs C–O



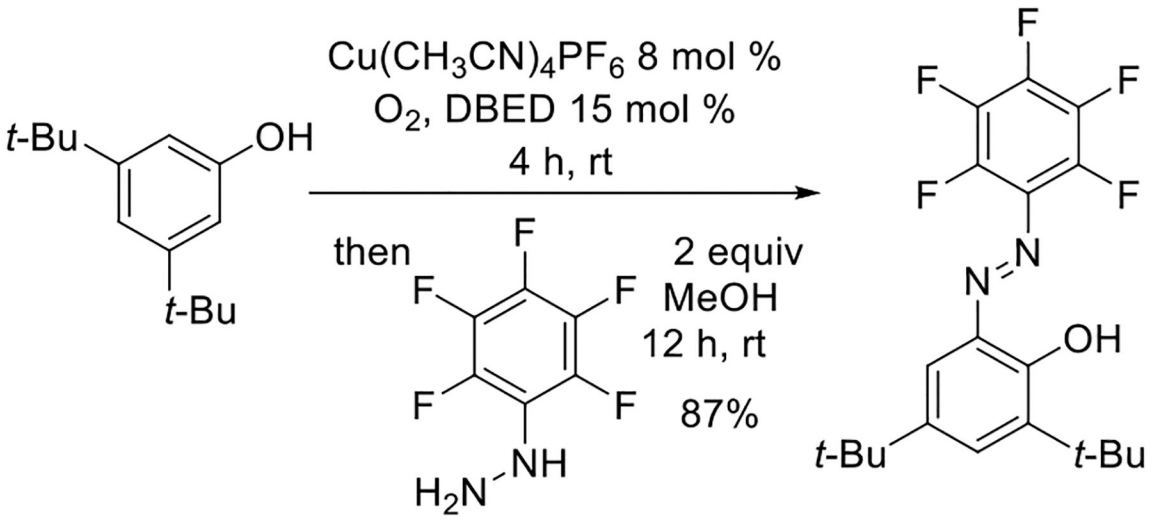
Scheme 37:
Malononitriles-Phenol/Aniline/Heteroarene Oxidative Coupling



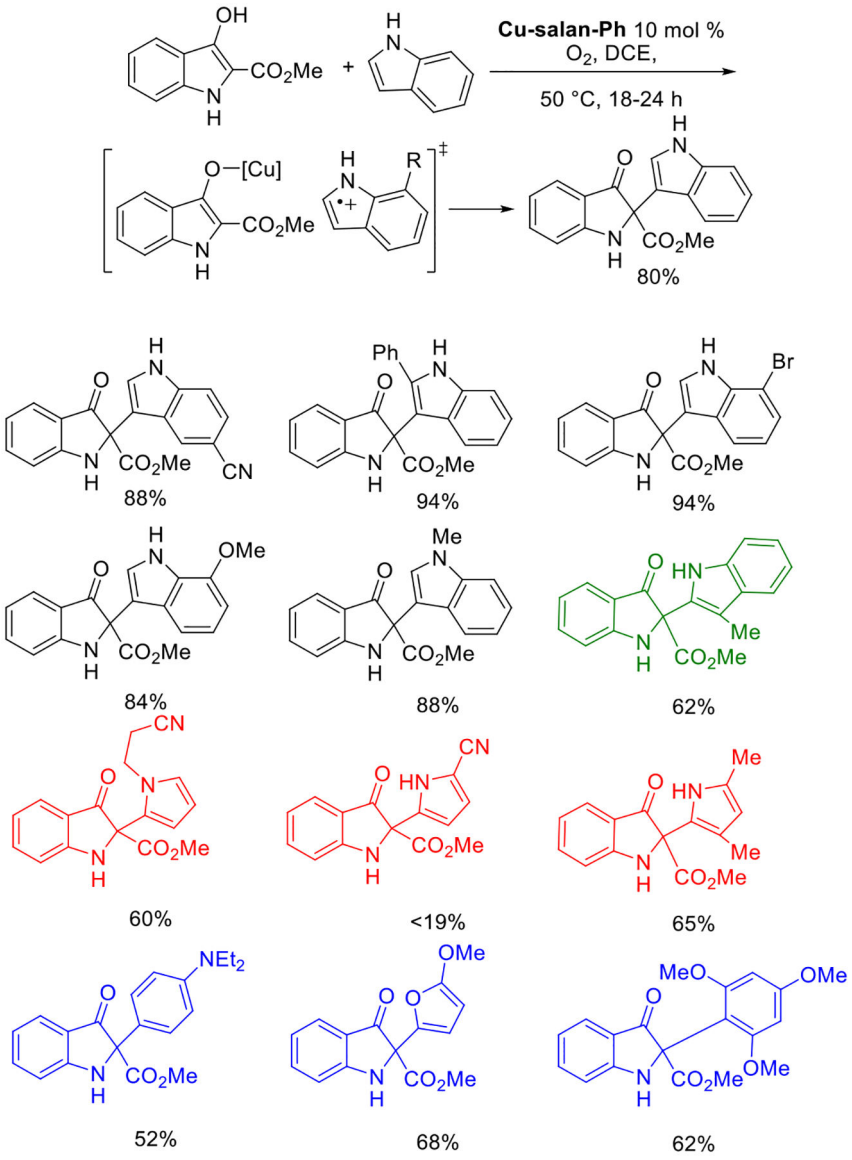
Scheme 38:
Phenol/Arene Oxidative Coupling with Fe Catalyst or Through Electrochemical Processes



Scheme 39:
Oxidative Coupling of Phenols and Alkenes



Scheme 40:
Oxidative Coupling of Phenols and Hydrazides



Scheme 41:
Copper Catalyzed Oxindole Oxidative Coupling Reactions