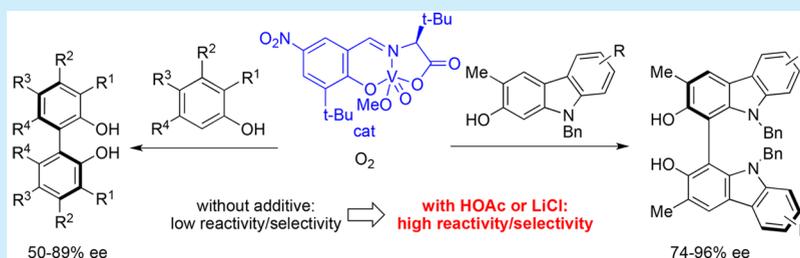


Asymmetric Oxidative Coupling of Phenols and Hydroxycarbazoles

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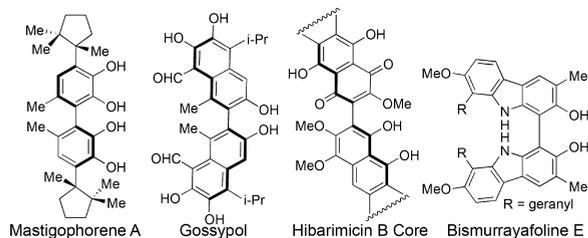
S Supporting Information



ABSTRACT: The first examples of asymmetric oxidative coupling of simple phenols and 2-hydroxycarbazoles are outlined. Generation of a more vanadium catalyst by ligand design and by addition of an exogenous Brønsted or Lewis acid was found to be key to coupling the more oxidatively resistant phenols. The resultant vanadium complex is both more Lewis acidic and more strongly oxidizing. Good to excellent levels of enantioselectivity could be obtained, and simple trituration readily provided the products with $\geq 95\%$ ee.

The axial chiral biaryl motif is found in many natural products (Scheme 1)¹ as well as in structures important in catalysis

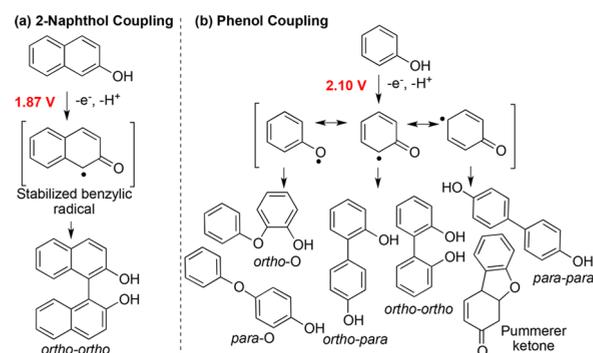
Scheme 1. Examples of Chiral Biphenols and Binaphthols



such as 1,1'-binaphthol.² Approaches involving redox-neutral cross-couplings, in particular Suzuki couplings, have been successful for a range of binaphthyl and biphenyl structures with some limitations on structure.³⁻⁵ Over the past 25 years, oxidative asymmetric catalysis has been successful in generating enantioenriched binaphthol structures by means of Cu,⁶ Ru,⁷ V,⁸ and Fe⁹ catalysts. The absence of any prefunctionalization at the centers undergoing C–C bond formation confers several advantages to this latter approach with respect to overall efficiency.

However, oxidative asymmetric coupling has been noticeably absent with phenols vs 2-naphthols. The phenol substrate type is both more difficult to oxidize and subject to oxidative coupling at a larger number of reactive sites (Scheme 2). The latter feature can be controlled by appropriate substitution and has been addressed with a number of catalytic systems particularly with

Scheme 2. Phenol vs Naphthol Coupling

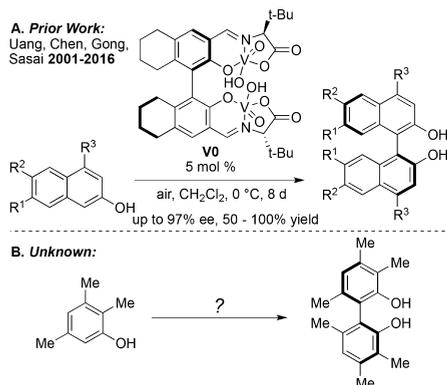


reference to hetero cross-coupling,¹⁰ but the former issue has proved to be a significant impediment with only one coupling having been reported (12% yield, 13% ee).¹¹ There are no reports of highly enantioselective phenol couplings, although organocatalytic approaches using a preoxidized reaction partner (quinone or iminoquinone) have been successful.¹²

Based on the report of vanadyl(IV) acetoacetonate in phenol coupling,¹³ we were inspired to use vanadium complexes as they appear to have the requisite baseline reactivity to catalytically couple phenols. In addition, the success of chiral vanadium catalysts in the asymmetric coupling of naphthols (Scheme 3A)⁸ provides support for use of these architectures in the control of

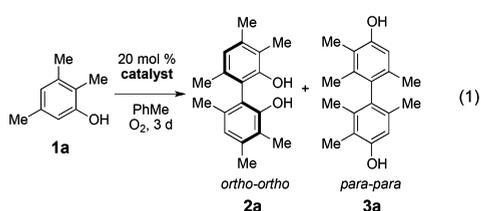
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Scheme 3. Vanadium Catalysts in Oxidative Coupling



atroposelective couplings. In this report, we describe how vanadium catalysts were engineered to create a more reactive system that also enables control of enantioselectivity in oxidative phenol coupling (Scheme 3B).¹⁴

Beginning with one of the most promising vanadium catalysts reported in naphthol coupling, V0 (Scheme 3A),^{8c,d} **1a** was examined (eq 1). Mixtures of two products were observed consisting of *ortho-ortho* coupled **2a** and *para-para* coupled **3a** (eq 1). Notably, none of the other possibilities (Scheme 2) were observed.



However, the reaction was irreproducible, which was attributed to the exact preparation of the catalyst and its resultant hydration state.^{8a-i} Dried samples were less reactive, presumably due to formation of oxo-bridged species. Ultimately, a much more reproducible protocol was developed using VO(OEt)₃ to produce V1.¹⁵ With this procedure, 37% ee was observed for **2a** indicating that the catalyst V1 was capable of controlling the enantioselectivity (Figure 1). However, the overall reactivity was still poor with 51% of starting material **1a** remaining after 3 days. In addition, both the *ortho-ortho* and *para-para* coupling products were formed at about the same rate (**2a**:**3a** 28%:21%, Figure 1)

Reasoning that deprotonation of the substrate or additional activation of the catalyst was necessary, a screen of additives was

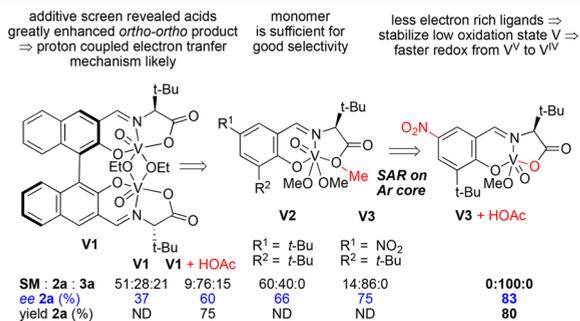
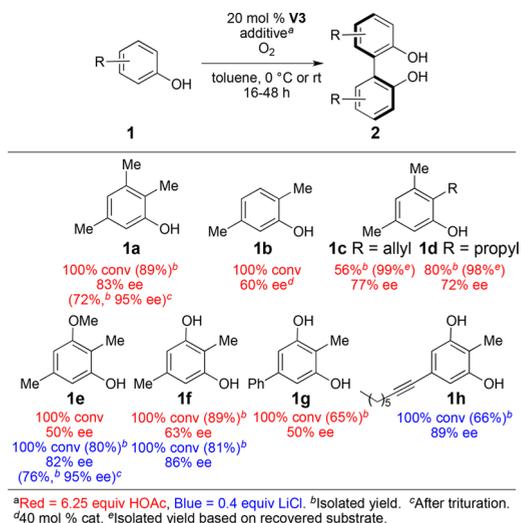


Figure 1. Catalyst evolution in the asymmetric phenol coupling (eq 1).

performed. Protic acids (see Supporting Information (SI)) resulted in the greatest improvement in terms of reactivity and selectivity consistent with protonation of the catalyst being involved. Notably, bases (e.g., Et₃N) resulted in a complete loss of reactivity. Examining concentration, equivalents of acid, and solvent revealed that 0.5 M in CH₂Cl₂ or 1,2-dichloroethane (DCE) with 6.25 equiv of HOAc was optimal with V1 producing 75% of **2a** in 60% ee (Figure 1).

To further improve selectivity, modifications of the catalyst framework were investigated. Changing the amino acid substituent did not offer any advantage. Examination of various dimeric vanadium catalysts with different biaryls and different linkers resulted in no improvement. Reasoning that a large group may be all that is needed in the position formerly occupied by the chiral axis to confer selectivity, a monomeric catalyst with a *tert*-butyl substituent at the R² position was employed (V2) and an improvement in selectivity was seen (66% ee). A study of various R¹ and R² groups of the monomer found that a more Lewis acidic, and hence more strongly oxidizing catalyst (V3), led to both higher reactivity and higher selectivity (86:0 *ortho-ortho/para-para*, 75% ee). When combined with the HOAc additive, full conversion to only the *ortho-ortho* adduct was observed and the enantioselectivity improved to 83% ee.

Examination of a range of phenols (Scheme 4) showed that a methyl group *ortho* to the phenol was required with groups that

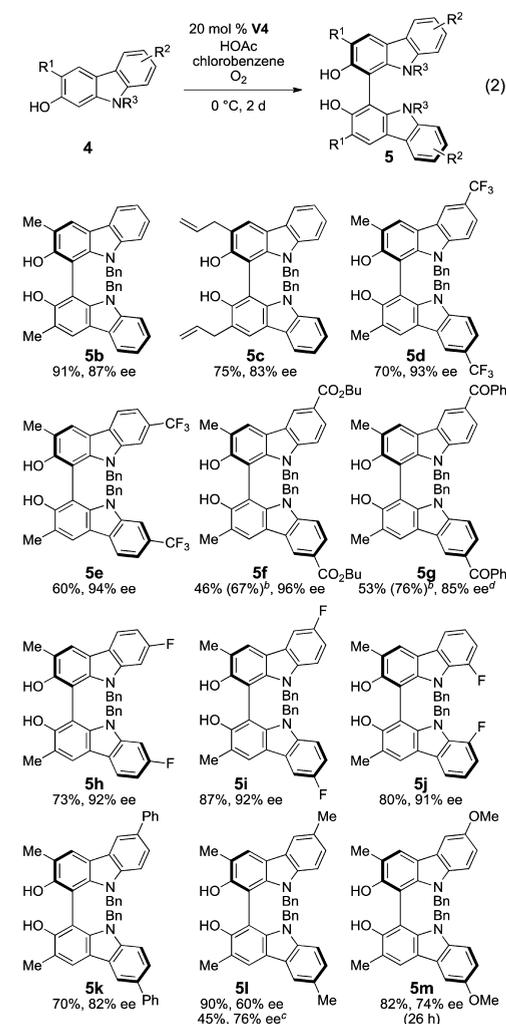
Scheme 4. Scope of Phenol Coupling^d

were smaller (H) or larger (*t*-Bu) leading to very low or no selectivity. However, other substrates with an *ortho*-methyl (**1b**), *ortho*-allyl (**1c**), or *ortho*-propyl group (**1d**) gave similar selectivities. Notably, one trituration was found to increase the enantiomeric excess of the filtrate to ≥95% ee. More electron-rich dioxxygenated substrates **1e**–**1h** reacted quickly even at 0 °C. Screening of additional additives (see SI) revealed that the Lewis acid LiCl afforded higher selectivities for **1e**, **1f**, and **1h**.

It has been theorized that natural products such as bismurrayafoline E (Scheme 1) are synthesized biosynthetically by oxidative coupling.¹⁶ With vanadium catalyst V3, the parent system (**4a**, R¹ = Me, R² = H, NR³ = NH) underwent unselective oxidation, likely due to reaction of the amine. Addition of an *N*-benzyl substituent gave rise to a rapid, chemoselective oxidative coupling with V3 (70% ee). Optimization of the vanadium substituent (see SI) revealed that V4, the isopropoxy analog of

V3, was optimal (Scheme 5, 91% yield, 87% ee). For the N-substituent, smaller (Me, 71% ee) or larger (*i*-Pr, 42% ee; 2,4,6-trimethylbenzyl, 37% ee) groups were deleterious.

Scheme 5. Scope of 2-Hydroxycarbazole Coupling (eq 2)^a



^aReaction conditions: 20 mol % V4, 6.5 equiv of AcOH, O₂, 0.5 M chlorobenzene, 0 °C, 48 h. ^bBased on recovered starting material. ^cReaction was conducted at -15 °C. ^dHFIP/PhCl as a solvent.

Scheme 5 outlines the scope of the asymmetric oxidative couplings of *N*-benzylated-2-hydroxycarbazoles. With an allyl group adjacent to the phenol, good enantioselectivity was observed (5c). Electron-withdrawing groups on the distal ring result in improvements in selectivity (5d–5k, 82–96% ee) with good levels of conversion (67–87% yield). Electron-donating groups such as methyl or methoxy result in good reactivity with moderate selectivity (5l, 5m).

Control experiments with radical inhibitor TEMPO resulted in a dramatic reduction in conversion (Table 1, entry 1 vs 2). In the absence of O₂, 9% and 26% conversions were observed with 20 and 50 mol % catalyst, respectively. This result indicates that each vanadium abstracts one electron as would be the case with a vanadium(V) to vanadium(IV) redox event.

A possible mechanism consistent with these results is outlined in Figure 2. Water and other protic additives, which were found to be advantageous, are proposed to prevent aggregation of the vanadium complexes to forms that were less susceptible to ligand

Table 1. Control Experiments in Asymmetric Coupling^a

entry	condition	conversion (%)
1	control	10
2	0.2 equiv of TEMPO	3
3	N ₂ atmosphere	9 (3 days)
4	50 mol % V3, N ₂ atmosphere	26 (3 days)

^aReaction of 1a with 20 mol % V3, 6.25 equiv HOAc, O₂, PhMe, rt, 2 d.

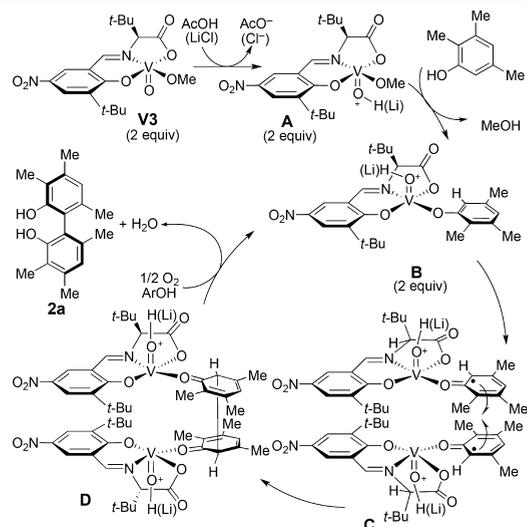
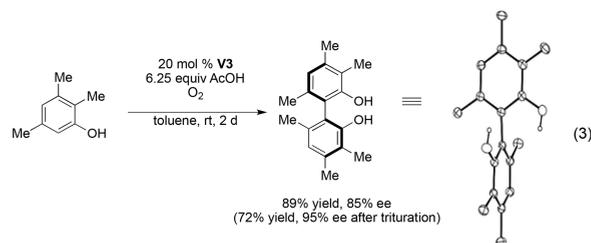


Figure 2. Proposed mechanism.

exchange, and hence reaction, with the phenols. However, the greatly improved results with acetic acid were puzzling since naphthol or phenol deprotonation to effect ligation is often suggested as a first step. In the presence of an excess of acid (6.25 equiv) relative to substrate, such a step seems unlikely under these conditions. Thus, we propose an additional accelerating effect of the acetic acid additive (or the LiCl additive) involving activation of the vanadium complex. Namely protonation of the vanadium oxy group (or coordination of Li⁺ in the case of LiCl) generates a more Lewis acidic species A (Figure 2). The protonated version of A was observed by mass spectrometry, and calculations indicate a favorable association of V3 with acetic acid (see SI). Subsequent associative exchange with phenol would form adduct B, which was also observed by mass spectrometry. Protonation also enhances the oxidizing ability of the vanadium(V) species. Redox transfer to generate a vanadium(IV) keto radical C would account for the radical inhibitor results seen. Coupling via an intermolecular process or, if vanadium aggregates are formed, via an intramolecular process gives rise to D, consistent with the nonlinear effects (see SI). Release and tautomerization lead to product 2a.

X-ray crystallographic analysis of 2a indicated the (*S*) absolute axial configuration was present (eq 3). Circular dichroism



measurements (see SI) support the same (*S*) axial for the bishydroxycarbazoles. On this basis, a preliminary stereochemical model can be proposed as illustrated in intermediate C of Figure 2. The phenol coordinates to minimize steric interactions; namely, the less hindered lone pair of the phenol coordinates to the vanadium and the less substituted *ortho*-position orients closest to the catalyst, placing the larger *ortho*-substituent into unoccupied space. Approach of the second phenol from the face opposite the *tert*-butyl group then gives rise to the observed stereochemistry.

In summary, we report the first enantioselective oxidative coupling of phenols and 2-hydroxycarbazoles to give rise to adducts not available with alternate approaches.^{3–5,12} A much more active vanadium oxidative catalyst was developed capable of acting on these less reactive substrates to form the axial chiral dimers efficiently. Less electron-rich ligands were employed which stabilize the low valent vanadium(IV) and destabilize the high valent vanadium(V) giving rise to a more potent oxidizing species. Counterintuitively, the addition of a Brønsted or Lewis acid was found to accelerate the process, indicating that ligand exchange of the substrate is not driven by deprotonation of the phenol. Rather, the Brønsted acid likely activates the vanadium catalyst enhancing both its oxidizing properties and its ability to coordinate a neutral phenol. Together, these features should prove useful in the design of other asymmetric oxidants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02552.

Experimental procedures for all experiments and characterization data (PDF)

Crystallographic data for 2a (CIF)

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Notes

The authors declare no competing financial interest.

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