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Vanadium-Catalyzed Oxidative Intramolecular Coupling of Tethered Phenols: Formation of Phenol-Dienone Products

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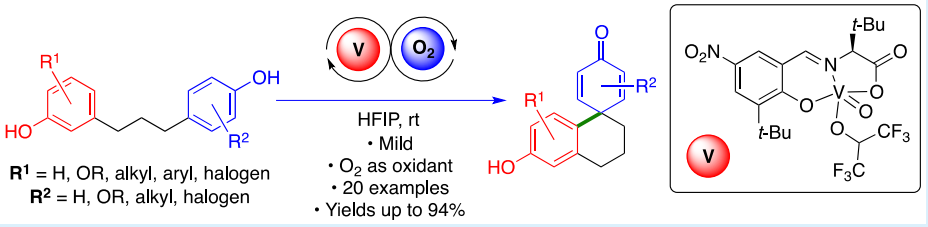


ABSTRACT: A mild and efficient method for the vanadium-catalyzed intramolecular coupling of tethered free phenols is described. The corresponding phenol-dienone products are prepared directly in good yields with low catalyst loadings. Electronically diverse tethered phenol precursors are well tolerated, and the catalytic method was effectively applied as the key step in syntheses of three natural products and a synthetically useful morphinan alkaloid precursor.

Bisphenols constitute an important class of molecules with utility as both complex molecule precursors and biologically active natural products.[1,2] Such biologically active compounds often incorporate the bisphenol biaryl motif as part of a polycyclic system (Figure 1A).[3] Other phenol-containing natural products arise from the direct oxidative coupling of tethered free phenols to afford a phenol-dienone motif (Figure 1B,C).[4,5] Since the discovery that direct phenol oxidation plays a critical role in the biosynthesis of such compounds,[6−8] analogous reagent-based approaches have been of considerable interest for their potential application in the synthesis of plant metabolites.

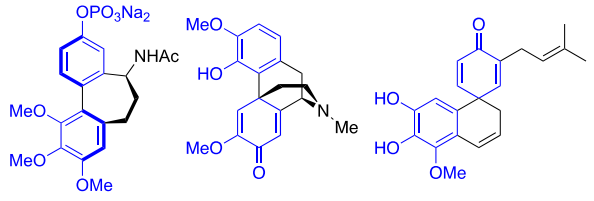
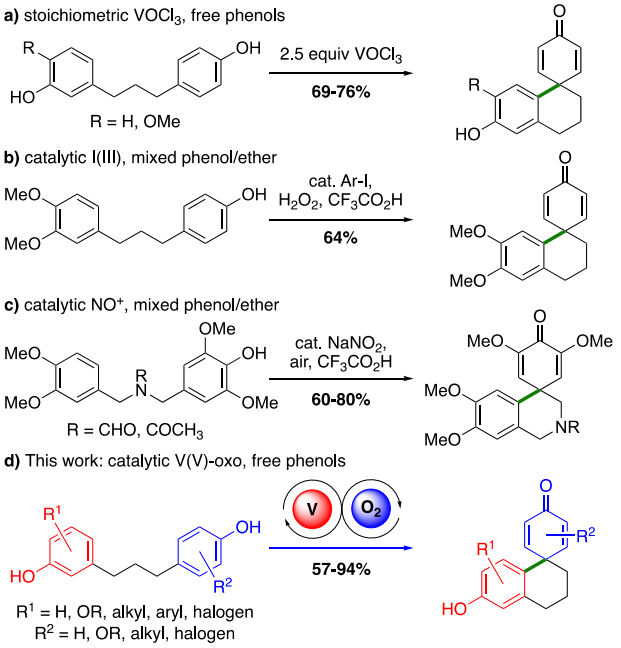


Figure 1. Compounds derived from linked phenols.

There are several reports on intermolecular oxidative phenol coupling, including transition metal-mediated[9−13] and electrochemical[14,15] phenol homocoupling and cross-coupling reactions. Despite this, the intramolecular coupling of tethered free phenols for the formation of phenol-dienone products is not well studied. Schwartz et al. disclosed one of the first examples of this transformation, coupling propyl-tethered phenols with stoichiometric $VOCl_3$ in good yield (Scheme 1a).[16] This work

Scheme 1. Intramolecular Phenol-Type Couplings



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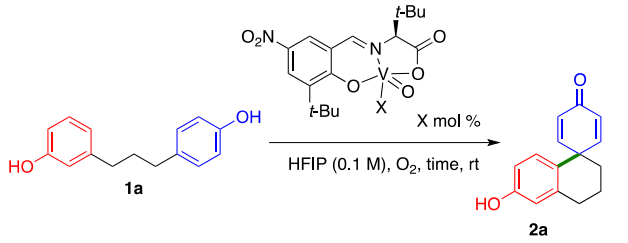
with stoichiometric $VOCl_3$ was also utilized in the formation of *N*-(ethoxycarbonyl)-2-hydroxynorsalutaridine,[17] an analogue of salutaridine (**B**, Figure 1), a key intermediate in the biosynthesis of morphine. In addition to V(V), phenol-dienone products have been prepared directly from tethered free phenols using stoichiometric Fe(III)[18,19] or Tl(III)[20,21] as the oxidant. Despite success with these stoichiometric reagents, limitations include the air sensitivity of $VOCl_3$, the toxicity of Tl(III), the need for a significant excess of oxidant, and reduced yields in converting electron-neutral and electron-deficient substrates. A catalytic variant of this direct transformation using stable, easily accessible reagents would therefore be of great utility from the perspective of atom economy and accessing structurally diverse phenol-dienone substrates.

An alternative approach for the formation of phenol-dienone products proceeds via oxidation of the corresponding tethered aryl ethers or mixed phenol/ether species, followed by subsequent deprotection. Considerable work in this area has shown that stoichiometric Mo(V)[22] and I(III)[23] are competent in the intramolecular oxidative coupling of tethered aryl ethers. The stoichiometric nature of the I(III)-mediated transformation was addressed by Kita et al. in 2008, as they coupled mixed tethered phenol/ethers with catalytic amounts of aryl iodide, which is activated to I(III) by H_2O_2 in the presence of trifluoroacetic acid (Scheme 1b).[24] A complementary approach was also disclosed by Wang et al., wherein they oxidized similar substrates using a catalytic system of sodium nitrite in the presence of air and Brønsted acid (Scheme 1c).[25] While both of these reports reflect catalytic variants of the intramolecular coupling of tethered arenes, both require the use of electron-rich substrates. Additionally, both approaches utilize mixed tethered phenol/ether substrates, which precludes the direct formation of the phenol-dienone motif. Deprotection of aryl ethers to generate the phenol-dienones can be challenging in the presence of the newly formed dienone motif, which is sensitive to acidic and reducing conditions. The orthogonality of protecting groups also becomes a challenge when multiple ether moieties are present in the ether-dienone product.

An important distinction should be made among bis-ether, mixed ether/phenol, and bisphenol intramolecular coupling reactions. These transformations are fundamentally different and are proposed to proceed via different mechanisms. In the case of ether systems, a polar, two-electron mechanism invoking a cationic intermediate is often proposed. In the case of tethered bisphenol cyclizations to form phenol-dienone products, the reaction is more likely to proceed through sequential single-electron oxidation of both coupling partners, akin to the mechanisms proposed in the biosynthesis of phenol-derived polycyclic natural products. To the best of our knowledge, there have been no reports detailing the catalytic oxidation of tethered free phenols for the formation of phenol-dienone products.

Inspired by the work of Schwartz[16,17] and our prior work with vanadium Schiff base catalysts,[12,26] we envisioned the development of a catalytic system for the oxidation of tethered free phenols to form phenol-dienone products directly (Scheme 1d). Initial reaction studies were conducted with substrate **1a**, 20 mol % vanadium catalyst **V1**, and O_2 as the co-oxidant (Table 1). When 1,2-dichloroethane (DCE) was utilized as the solvent, there was little consumption of **1a** and the catalyst system failed to form **2a** (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



entry	X	loading (mol %)	time (h)	**2a** (%)[b]
1[c]	OEt	20	24	<5
2	OEt	20	24	56
3	OEt	20	48	(89)[d]
4	OEt	10	18	24
5	O*t*-Bu	10	18	12
6	F	10	18	<5
7	$OCH(CF_3)_2$	10	18	70
8	$OCH(CF_3)_2$	10	24	(80)[d]
9	$OCH(CF_3)_2$	5	24	31

[a]Reaction conditions: **1a** (0.10 mmol), **V** (10–20 mol %), HFIP (0.1 M), O_2 (1 atm) for 18–48 h. [b]Determined by ^{1}H NMR spectroscopy with an internal standard (4,4′-di-*tert*-butylbiphenyl). [c]DCE as the solvent. [d]Isolated yield.

1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was identified as a suitable solvent for this reaction because of its unique ability to stabilize electron-deficient reaction intermediates.[27] The reaction in HFIP showed good conversion to **2a** over 24 h (Table 1, entry 2), with full conversion observed in 48 h affording an isolated yield of 89% (Table 1, entry 3). Interestingly, only *para*–*para* coupled products were observed in this reaction, despite the fact that prior work with this catalyst uncovered a preference for *ortho* coupling.[12] We hypothesize that the *ortho*–*para* coupled product is not formed because of unfavorable steric interactions between phenoxy-bound vanadium and the other aryl partner during the C–C bond-forming step.

Efforts to reduce reaction time and catalyst loading focused on the catalyst counterion. Vanadium Schiff base catalysts bearing the *tert*-butoxy and fluoride counterions were shown to form product more slowly over 18 h than the corresponding ethoxy catalyst over the same time period (Table 1, entries 5 and 6 vs entry 4). The observation that catalyst activity tracks with the lability of the counterion led to the preparation of a catalyst bearing HFIP as the counterion. Gratifyingly, **V2** proved to be more effective in the transformation, forming **2a** in 70% yield over the same reaction time (Table 1, entry 7). Reaction for a full 24 h with 10 mol % **V2** led to full conversion of **1a** and an 80% isolated yield of **2a** (Table 1, entry 8). A reaction profile for the conversion of **1a** to **2a** with **V2** (see the Supporting Information, control A) is consistent with first-order decomposition through 90% conversion with neither a significant burst nor a significant induction period. Independent experiments in which **2a** was added in variable amounts prior to reaction of **1a** indicate that no product inhibition is occurring, because **1a** is converted to the same extent with various excesses of **2a**. Even so, further reduction of the catalyst loading led to poor conversion over the 24 h reaction period (Table 1, entry 9). A screen of solvents (Table S2) and standard oxidants (Table S3) revealed that HFIP was the optimal solvent for the transformation and that O_2 is the most

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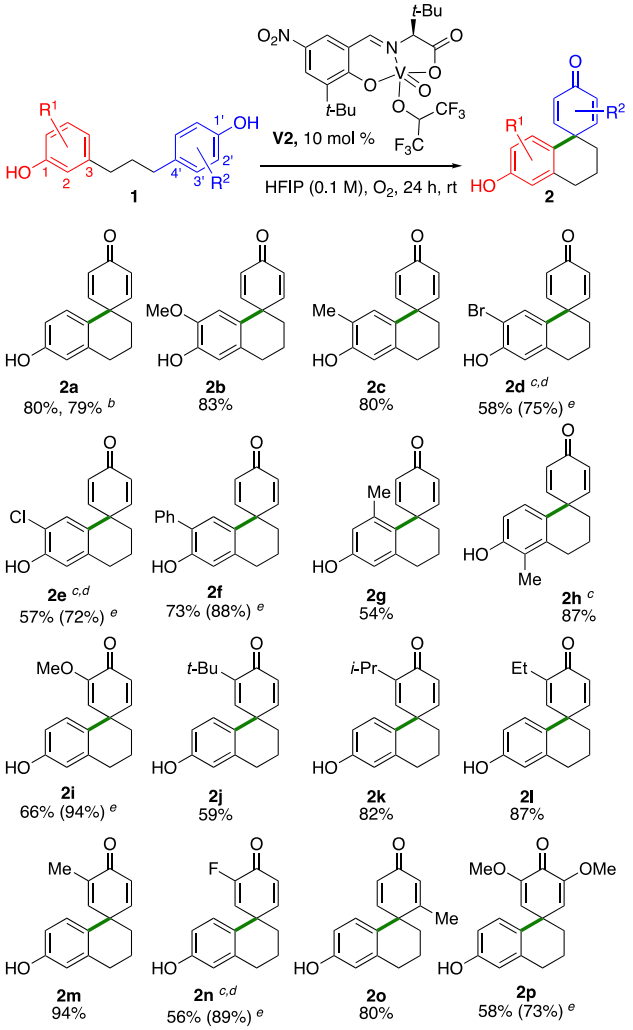
effective oxidant, outperforming an atmosphere of air, inorganic persulfates, and organic peroxides.

With the optimized conditions for the formation of phenol-dienone products in hand, the substrate scope of this transformation was examined (Scheme 2). In the simplest, unactivated case, the unsubstituted precursor was oxidized in good yield to its corresponding cyclized product (**2a**). In the case of substitution on the ring where the tether is attached at C3 (red ring in Scheme 2), electron-releasing and electron-withdrawing groups were well-tolerated (**2b**–**2h**). Bromo-containing (**1d**) and chloro-containing (**1e**) substrates were oxidized to phenol-dienone products in fair yields requiring an increased catalyst loading. Additionally, substitution is tolerated at all positions of this ring with no loss of coupling efficiency (**2c**, **2g**, and **2h**). A direct assessment against prior art was undertaken to further validate the method. (1) With $Tl(O_2CCF_3)$,[21] a 30% yield of **2c** was obtained with 79% consumption of **1c**. (2) With $VOCl_3$,[16] a 39% yield was obtained after 85% consumption and several other byproducts were observed. (3) With the method reported here, a 76% yield was obtained with 85% consumption. Overall, our catalytic method was easier to undertake [Tl(III) and $VOCl_3$ need special handling], gave a higher yield, provided a much cleaner reaction profile, and resulted in more facile purification.

Scheme 2. Scope of V-Catalyzed Intramolecular Coupling of Tethered Free Phenols[a]

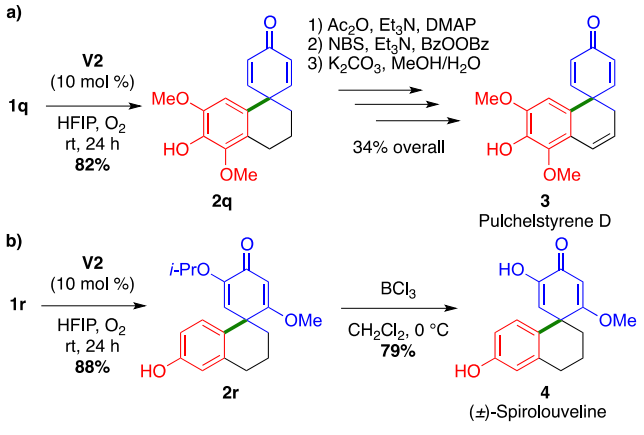


[a]Reaction conditions: **1** (0.10–0.20 mmol), **V2** (10 mol %), HFIP (0.1 M), O_2 (1 atm) for 24–44 h; yields of the isolated material. [b]On a larger scale (5.00 mmol, 1.14 g). [c]With 20 mol % catalyst. [d]HFIP/DCE (0.1 M, 1:1) as the solvent. [e]Yield in parentheses based on recovery of the starting material.

In the case of substitution on the ring where the tether is attached at C4′ (blue ring in Scheme 2), similar results were obtained (**2i**–**2p**). Electron-releasing and electron-withdrawing groups were well tolerated. Notably, dimethoxy-substituted **1p** was converted to its corresponding highly substituted phenol-dienone product in good yield. Fluoro-substituted **2n** was also obtained in fair yield, revealing that deactivated substrates are capable of undergoing oxidation by **V2** to form product. Additionally, substitution is tolerated at other positions of this ring (**2m** and **2o**) with no loss of efficiency. Even though **V2** is a chiral catalyst, no enantioenduction was observed for **2j**–**2m**, likely due to the catalyst binding phenols that are distal to the site of C–C bond formation. The overall substrate scope establishes that this catalyst system is capable of oxidizing a wide variety of tethered phenol compounds and that the transformation is not limited by a need for electron-rich, nucleophilic arenes as is the case for other methods.[24,25] Efforts to increase the reaction scale were successful, with a gram-scale reaction of **2a** giving a nearly identical outcome.

To further outline the utility of this method, several natural products were identified as synthetic targets due to the presence of the phenol-dienone moiety in their core structure.[17,21,28,29] The natural product pulchelstyrene D (**3**)[28] differs from the simple substrates prepared above (Scheme 2) only in the unsaturation of the propyl tether. Attempts to prepare a version of the substrate with an alkenyl tether were unsuccessful, so an alternative route through the saturated precursor was envisioned. As a result, dimethoxy-substituted substrate **1q** was coupled in good yield to generate saturated phenol-dienone product **2q** (Scheme 3a). Efforts to directly convert **2q** into the natural product **3** were unsuccessful. To overcome this issue, **2q** was subjected to a three-step sequence of acetylation, radical-mediated bromination/elimination, and deacetylation to form natural product **3** in 34% yield over three steps (see the Supporting Information). This synthetic effort represents the first preparation of this naturally occurring compound.

Scheme 3. Formation of Spiro-dienone Natural Products, Pulchelstyrene D and Spirolouveline, via Intramolecular Oxidative Coupling



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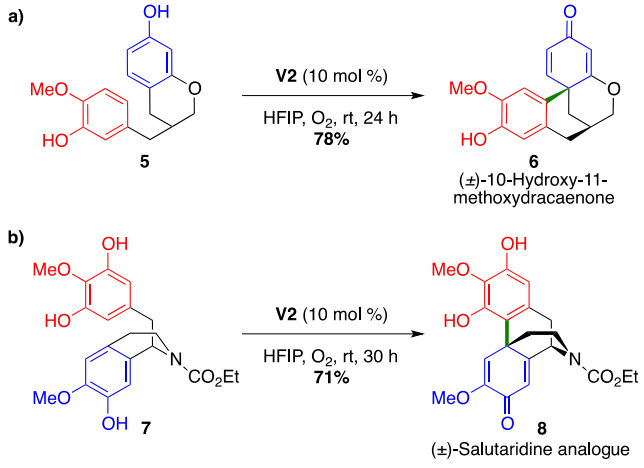
A further natural product, spirolouveline (**4**),[29] is also closely related to the simple substrates prepared in Scheme 2. In addition to a single methoxy group, the compound contains a free hydroxyl group on the dienone moiety. To directly access **4**, a catechol-containing precursor was prepared and subjected to the vanadium-catalyzed oxidation conditions. Unfortunately, a poor reaction profile was observed, likely due to the presence of multiple oxidizable phenolic hydroxyl groups. An alternative approach utilizing a protected form of the catechol was envisioned, and **1r** was coupled successfully in good yield to generate bis-alkoxy phenol-dienone **2r** (Scheme 3b). Selective removal of the more labile *iso*-propoxy group of **2r** with Lewis acid furnished racemic **4**. This synthetic effort also represents the first reported preparation of this naturally occurring compound.

The dracaenone natural products represent a tetracyclic variant of the tethered phenol-dienone motif. The natural product 10-hydroxy-11-methoxydracaenone (**6**) has been prepared previously via direct coupling of the bisphenol in 37% yield[20,21] or by coupling of the protected aryl ether followed by deprotection with 62% yield over the two steps.[21] In each case, a stoichiometric oxidant is required for the key intramolecular coupling step. Using the optimized conditions with **V2**, natural product **6** was obtained in a single step from its corresponding free phenol precursor in 78% yield (Scheme 4a). This preparation represents a protecting group-free synthesis of **6** with improved efficiency in the key intramolecular phenol coupling step.

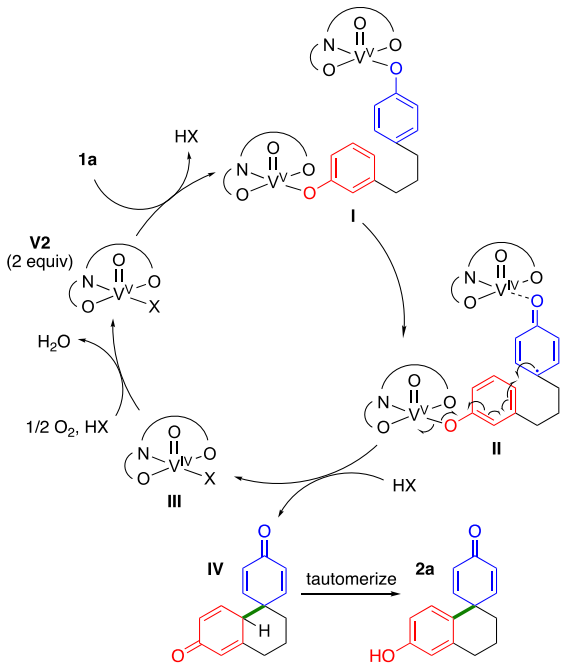
Scheme 4. Formation of Bicyclic Systems, a Dracaenone Natural Product and a Salutaridine Analogue, via Intramolecular Oxidative Coupling



Lastly, a synthetically useful salutaridine derivative was prepared using the newly developed catalytic method (Scheme 4b). Reticuline derivative **7** was coupled directly to form salutaridine phenol-dienone product **8** in good yield. Remarkably, only small quantities of the *ortho*−*ortho* coupled aporphine-type product were observed. It has been hypothesized that products of this type are not observed due to an unfavorable *peri*-interaction between the approaching hydroxyl groups in the C−C bond-forming step.[17] Compound **8** is of significant interest in the context of alkaloid synthesis,[30] because the coupling reaction establishes the B ring of the classic morphine scaffold with limited prefunctionalization. Considerable precedent exists for conversion of these phenol-dienone products to downstream morphinan alkaloids.[17,31,32] The efficiency of the coupling reaction to form **8** compares well to that of the stoichiometric variant reported by Schwartz et al.[17] and offers a complementary approach to state-of-the-art electrochemical couplings of the related aryl ethers.[31,32]

A series of control experiments were conducted to aid in understanding the mechanism of the vanadium-catalyzed coupling reaction (see the Supporting Information). Reactions run without **V2** in the presence of dioxygen showed limited conversion of the substrate and no product formation, indicating that the catalyst is key in oxidizing the substrate (Supporting Information, control C). Additionally, a study concerning catalyst ligand identity (Supporting Information, control E) showed that electron-rich ligands (**V1**, with *t*-Bu in place of NO_2) led to slower reaction rates. This result points away from catalyst reoxidation [V(IV) to V(V)] being rate-limiting and suggests substrate−catalyst binding or oxidation by the catalyst [V(V) to V(IV)] as the turnover-limiting step. Attempts to couple mixed phenol/ether substrates (Supporting Information, control F) showed decomposition of the starting material with no detectable phenol-dienone product formation, indicating that oxidation likely occurs through covalent activation by **V2**, as opposed to outer-sphere electron transfer from V(V). Furthermore, no homocoupled dimeric products were observed during a standard reaction with tethered phenols, supporting a mechanism that proceeds through vanadium species (see structure **II** in Scheme 5), as opposed to free radical forms of oxidized **1a**.

Scheme 5. Proposed Mechanism



These control results, combined with prior findings,[12,33] support a proposed mechanism (Scheme 5) in which a phenoxide-bound substrate (**I**) is oxidized by 2 equiv of **V2**. Prior work indicated the formation of a V(IV)−V(V) intermediate (**II**), which undergoes intersystem crossing to react via a triplet.[33] We propose that the radical on the blue ring forms first first, as the presence of the tether at the *para*-position better stabilizes the electron-deficient species formed

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upon oxidation. The subsequent intramolecular coupling followed by substrate displacement affords bis-dienone intermediate **IV** and reduced catalyst species **III**. Bis-dienone intermediate **IV** undergoes a tautomerization to form the phenol portion of the final phenol-dienone product. Catalyst intermediate **III** is then reoxidized in the presence of dioxygen to re-form active catalyst **V2**. Additional mechanistic studies are ongoing, with an emphasis on identifying the nature of the species involved in the key C−C bond-forming step.

In summary, a new vanadium Schiff base catalyst was developed for use in the catalytic intramolecular coupling of tethered phenols to form phenol-dienone products. Modifications to the catalyst counterion revealed that an HFIP-coordinated V(V)−oxo catalyst was superior in mediating the coupling reaction. In total, 20 oxidatively coupled adducts were prepared in yields up to 94%, including three natural products and a morphinan alkaloid analogue. This newly developed catalytic method for intramolecular phenol-dienone coupling serves as a valuable addition to the rich field of oxidative phenol C−H functionalization[34] and represents an effective small molecule catalytic approach to the biomimetic coupling of tethered phenols. Further studies of the mechanism and enantioselective variants of these processes are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00577.

Experimental procedures, reaction optimization, reaction controls, characterization data, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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