**ABSTRACT:** A Pd(II)/bis-sulfoxide/Brønsted acid catalyzed allylic C–H oxidation reaction for the synthesis of oxazolidinones from simple N-Boc amines is reported. A range of oxazolidinones are furnished in good yields (avg 63%) and excellent diastereoselectivities (avg 15:1) to furnish products regioisomeric from those previously obtained using allylic C–H amination reactions. Mechanistic studies suggest the role of the phosphoric acid is to furnish a Pd(II)bis-sulfoxide phosphate catalyst that promotes allylic C–H cleavage and π-allylPd functionalization with a weak, aprotic oxygen nucleophile and to assist in catalyst regeneration.

**RESULTS AND DISCUSSION**

**Reaction Development.** At the outset of our investigation, we evaluated the reaction of homoallylic Boc-amine 2a with Pd(II)/bis-sulfoxide catalyst 1 under standard allylic amination conditions and observed low conversion to the desired product.

**Scheme 1. Pd/Bis-Sulfoxide Catalyzed Allylic C–H Oxidations To Form 1,2-Amino Alcohol Motifs**

**Previous work:**

- **NbsNs**
- **R**
- **C–O**
- Cat. 1
- Ref. 12

**This work:**

- **NbsBoc**
- **R**
- **R**
- **C–O**
- **Ref. 11**
- Cat. 1
- DBP

Reactions wherein these aprotic moieties are able to functionalize highly activated iodonium electrophiles, we endeavored to discover an activation mode to generate a highly electrophilic π-allylPd intermediate while providing a source of exogenous proton for efficient catalyst regeneration. Herein we describe the merging of C–H activation catalysis with Brønsted acid catalysis to effect the synthesis of anti-oxazolidinones from simple N-Boc homoallylic amines.

**INTRODUCTION**

Brønsted acid catalysis is increasingly being recognized as a powerful strategy for electrophile activation. Such organocatalytic modes of activation hold tremendous potential for cooperative catalysis with organometallic systems, as has been recently demonstrated in Pd2,3 and Ir4/phosphoric acid catalyzed allylic functionalizations and C–H activation/rearrangement reactions. We reasoned that for C–H activation reactions that do not tolerate exchangeable, dative ligands that are often used in Lewis acid catalysis, this mode of electrophile activation may be especially powerful. Herein we report the successful application of this concept toward the synthesis of oxazolidinones from simple N-Boc-amines.

Palladium(II)/bis-sulfoxide catalysis has emerged as a general platform for allylic C–H esterification,5 alkylation,6 dehydrogenation,7 fluorination,8 and amination.9 Common to these C–H functionalization reactions is the use of acidic, protic nucleophiles that become deprotonated in situ and activated toward functionalization while concomitantly acting as proton sources for Pd(0) → Pd(II) reoxidation.10 In many cases, aprotic nucleophiles are desirable because of their ease of preparation and potential as surrogates for highly unstable protic analogues. For example, we previously reported that allylic N-tosyl carbamates undergo C–H amination to furnish N-tosyl 5-alkyl-4-vinylloxazolidinones (Scheme 1).11 Important pharmacophores in their unprotected form and precursors to amino-alcohols motifs.12 The only method to furnish the regioisomeric N/O motif starts with N-nosyl ureas and gives 2-aminooxazoline heterocycles12 (Scheme 1). We considered that a direct regiodivergent C–H oxidation method may be possible from readily accessible N-Boc amines (Scheme 1, this work). In addition to being a common protecting group for amines, the N-tert-butoxycarbonyl (N-Boc) group is an aprotic surrogate for highly unstable carbamic acids. Inspired by iodofunctionalizations wherein these aprotic moieties are able to functionalize highly activated iodonium electrophiles,13 we endeavored to discover an activation mode to generate a highly electrophilic π-allylPd intermediate while providing a source of exogenous proton for efficient catalyst regeneration. Herein we describe the merging of C–H activation catalysis with Brønsted acid catalysis to effect the synthesis of anti-oxazolidinones from simple N-Boc homoallylic amines.
Typical scale with little change in e (63% yield, entry 8) and highly scalable up to nearly 20-fold the substoichiometric amounts, we found 50 mol % to be optimal (entry 7). Lowering the loading of DBP to 0.5 equiv, 1.5 equiv BQ, 2 M 1,4-dioxane, 45 °C, 24 h, furnished a promising 54% yield of products (entry 6). Phosphoric acids with lower pKa values gave useful diastereoselectivities (Table 1, entry 1). We reasoned that Brønsted acids may activate the α-allylpalladium species by protonating anionic ligands (e.g., acetate) and/or promoting breakdown of the α,β-unsaturated ester.13 For example, ortho-nitrobenzoic acid, (entry 5), led to 78% overall conversion but only 27% yield of oxazolidinones as one diastereomer (entry 5). For substrate scope of the reaction (Table 2). N-Boc homoallyl amine substrates possessing varying degrees of steric congestion and functionality were prepared using Ellman’s sulfinamido auxiliary or other standard methods.3,4,14 Substrates having at least one branching element adjacent to the amine afforded good yields of oxazolidinones as one diastereomer (3b, 3c, 3d). Significantly, small substituents like isobutyl and even methyl gave useful diastereoselectivities (3e, 3f). Such high diastereoselectivities are rare for allylic C–H oxidation processes and may be attributed to the conformational rigidity of the carbamate tether resulting from amide A(1,3) strain. Oxygen- and nitrogen-containing functionality (e.g., ethers, esters, amides) may also be present on the substrates, furnishing densely functionalized products with functional group handles for further elaboration (3g, 3h, 3i, 3j). It is significant to note that acid labile functionality such as primary silyl ethers, tert-butyl esters, and even a distal Boc-amino group are all stable under these mildly acidic conditions. Notably, aryl substitution in the homoallyl position gave product in good yields and excellent diastereoselectivities: previous allylic C–H functionalization reactions did not tolerate such substitution due to formation of stable diene products (3k). Benzyl-substituted amines furnished products in good yields as one diastereomer (3l, 3m). Significantly, substrate 2m containing an indole moiety, was well-tolerated under these acidic, oxidative conditions providing 3m. Indoles have been previously reported to undergo oxidation on the ring with Pd(II) salts under acidic conditions.15 Finally, we probed the reaction tolerance of high levels of steric bulk on the amine-bearing center given that stereocontrolled methods for efficient access to β/β-disubstituted amino alcohol motifs are scarce.16 Gratifyingly, the reaction proved to be tolerant of highly congested stereocenters, providing oxazolidinones 3n, 3o, and 3p in good yield and diastereoselectivity.

In addition to providing a direct and highly selective route to oxazolidinones, we recognized that such compounds could be readily elaborated to valuable α-hydroxy-β-amino acid com-

Table 1. Reaction Developmenta

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>pKa</th>
<th>equiv.</th>
<th>% yield</th>
<th>anti/sym</th>
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<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>—</td>
<td>—</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>4.78</td>
<td>1.5</td>
<td>40</td>
<td>19:1</td>
</tr>
<tr>
<td>3</td>
<td>BuOH</td>
<td>4.20</td>
<td>1.5</td>
<td>54</td>
<td>20:1</td>
</tr>
<tr>
<td>4</td>
<td>p-NOSBzOH</td>
<td>3.44</td>
<td>1.5</td>
<td>41%</td>
<td>8:1</td>
</tr>
<tr>
<td>5</td>
<td>o-NOSBzOH</td>
<td>2.17</td>
<td>1.5</td>
<td>27%</td>
<td>15:1</td>
</tr>
<tr>
<td>6</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>1.5</td>
<td>54</td>
<td>20:1</td>
</tr>
<tr>
<td>7</td>
<td>(Ph4P)2PdO2H</td>
<td>1.12</td>
<td>1.5</td>
<td>42</td>
<td>15:1</td>
</tr>
<tr>
<td>8</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.5</td>
<td>59</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>9</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.5</td>
<td>59</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>10</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.2</td>
<td>45</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>11</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.5</td>
<td>65</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>12</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.5</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>(Bu4O)2PdO2H</td>
<td>1.72</td>
<td>0.5</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>Cr(salen)Cl</td>
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<td>0.1</td>
<td>61</td>
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</tr>
<tr>
<td>15</td>
<td>AgOTf</td>
<td>—</td>
<td>0.1</td>
<td>45</td>
<td>11:1</td>
</tr>
<tr>
<td>16</td>
<td>B(C6F5)3</td>
<td>—</td>
<td>0.1</td>
<td>25</td>
<td>11:1</td>
</tr>
<tr>
<td>17</td>
<td>Cu(OTf)2</td>
<td>—</td>
<td>0.1</td>
<td>40</td>
<td>6:1</td>
</tr>
</tbody>
</table>

aConditions: 0.3 mmol (1.0 equiv) 2a, 10 mol % 1, acid (indicated equiv), 1.5 equiv BQ, 2 M 1,4-dioxane, 45 °C, 24 h. 1 Determined by 1H NMR of the crude reaction mixture. 2 Obtained 20% isolated yield of allylic p-nitrobenzoate (see Supporting Information). 3 Obtained 51% isolated yield of allylic o-nitrobenzoate (see Supporting Information). 4 DBP added in three 0.17 mmol portions at t = 0, 1.5, and 3 h. 5 Reaction run without 1; 97% recovered starting material. 6 2,6-Dimethylbenzoquinone (1.5 equiv) employed as oxidant; 94% recovered starting material. 7 97% recovered starting material.
pounds, such as those found in the biologically active molecules Taxol, Bestatin, and Amastatin (Scheme 2). Vinylloxazolidinone 3a can be readily transformed into syn-3-amino-2-hydroxy-4-phenylbutyric acid (AHPBA, 4), the hydroxyamino acid component of the dipeptide aminopeptidase inhibitor Bestatin, via a sequence of olefin oxidation and oxazolidinone hydrolysis to the free amino alcohol (Scheme 2A). Additionally, the high functional group tolerance of this method enables the direct C−H amination of Boc-protected β-allylglycine residues within a peptide setting. For example, the dipeptide leucine-β-allylglycine (-)-5 underwent Pd(II)bis-sulfoxide/phosphoric acid catalyzed C−H amination to afford a 57% yield of oxazolidinone 6 (Scheme 2B).

Table 2. PdII /Bis-sulfoxide/Phosphoric Acid-Catalyzed Allylic C−H Oxidation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>dr</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>77%</td>
<td>&gt;20:1</td>
<td>1.0 equiv substrate 2, 10 mol % 1, 50 mol % (BuO)2PO2H, 1.5 equiv BQ, 2.0 M in 1,4-dioxane, 45 °C, 24 h.</td>
</tr>
<tr>
<td>3c</td>
<td>69%, 7:1</td>
<td>&gt;20:1</td>
<td>1.0 equiv substrate 2, 10 mol % 1, 50 mol % DBP (3 × 17 mol % at 0 h, 1.5 h, and 3 h), 1.5 equiv BQ, 2.0 M in 1,4-dioxane, 45 °C, 24 h.</td>
</tr>
</tbody>
</table>

Scheme 2. Application to Hydroxyamino Acid Motifs

A. Vinylloxazolidinone to Hydroxyamino Acid

B. Late-Stage C−H Oxidation on a Preassembled Dipeptide

Conditions and Reagents: “RuCl3·xH2O, H5IO6, CCl4/H2O/MeCN, rt, 5h, 89%; 6 M HCl, 100 °C, 16 h, 97%.” Conditions: 1.0 equiv substrate (-)-5, 10 mol % 1, 50 mol % DBP (3 × 17 mol % at 0 h, 1.5 h, and 3 h), 1.5 equiv BQ, 2.0 M in 1,4-dioxane, 45 °C, 24 h. dr determined by 1H NMR of crude reaction mixture.

Powerful features of this allylic C−H oxidation reaction are its predictably high diastereo- and site-selectivity. When coupled with our previously reported intramolecular allylic C−H amination, these two Pd(II)bis-sulfoxide catalyzed methods function as regiodivergent synthetic transforms for the synthesis of oxazolidinones and 1,2-amino alcohols starting from a common aldehyde precursor (Scheme 3). For example, starting from aldehyde (-)-7, derived from commercially available (-)-ethyl lactate, conversion to homoallylic, Boc-amine (+)-8 was achieved via Ellman’s auxiliary. Cyclization via Pd(II)bis-sulfoxide/DBP catalyzed C−H oxidation proceeded smoothly, affording oxazolidinone (-)-9 in 63% yield as a single diastereomer. N-methylation and hydroboration/oxidation of the terminal olefin yielded (-)-10, a known synthetic intermediate to perosamine, an aminosugar found in pyrrolosporin A, an antitumor antibiotic. Alternatively, starting...
from (−)-7, the previously reported Pd(II)bis-sulfoxide mediated allylic C–H amination route efficiently provides the regioisomeric oxazolidinone which is an intermediate in the synthesis of (−)-N-methylacosamine, a sugar found in epirubicin.

Mechanistic Investigations. An important question raised by these studies relates to the mechanism by which catalytic phosphoric acids promote allylic C–H oxidation with N-Boc amines. The phosphoric acid additive may promote loss of t-butyl cation from the Boc group, forming a transient carbamic acid species that functionalizes the α-allyl. However, we have observed the preservation of distal Boc groups under the reaction conditions (Table 2, 3j and 3m), as well as greater than 90% recovery of starting material in the absence of Pd(II)/bis-sulfoxide catalyst or 2,6-dimethylbenzoquinone as oxidant (Table 1, entries 12 and 13), suggesting that the reaction does not proceed by simple acid promoted decomposition of Boc groups.

The second mechanistic possibility is that phosphate anion—generated in equilibrium concentrations with acetate—acts as a nucleophile catalyst to form a transient allylic phosphate via intermolecular π-allylPd substitution. The allylic phosphate may then undergo carbamate displacement to furnish oxazolidinone and regenerate the phosphate catalyst. A competition experiment between independently synthesized allylic phosphate and terminal olefin substrate resulted in preferential reactivity of the olefin (Scheme 4A). Consistent with this, initial rate studies on isopropyl olefin substrate versus under standard reaction conditions show a faster reaction rate for olefin (k2c ≈ 1.8, Scheme 4B). In view of this, taken together with the fact that allylic phosphates are not observed under these reaction conditions, leads us to conclude that it is unlikely the reaction proceeds primarily via a phosphate nucleophile-catalyzed pathway.

Finally, we investigated our hypothesis that the phosphoric acid acts as Bronsted acid cocatalyst to generate an electrophilic π-allylPd(phosphate) intermediate highly activated toward nucleophilic attack. A Pd(II)bis-sulfoxide-phosphate complex was generated in situ via metathesis of Pd(II)bis-sulfoxide-Cl2 with AgO2P(OBn)2 and the resulting solution was used as a catalyst under otherwise identical conditions (Scheme 5A). The reaction proceeded in comparable yields, reaction times, and selectivities as that using acetate catalyst. In the absence of silver phosphate under otherwise identical conditions, 12 is inactive toward allylic oxidation. Prior to this, only Pd(II)bis-sulfoxide complexes having carboxylate counterions have shown competence for allylic C–H cleavage. Consistent with a Pd(II)bis-sulfoxide-phosphate complex being a competent catalyst, a stoichiometric study under mock catalytic conditions showed the Pd(II)bis-sulfoxide-phosphate complex e effects C–H cleavage (Scheme 5B). Significantly, the role of the Bronsted acid cocatalysis extends beyond generation of a Pd(II)bis-sulfoxide-phosphate complex; removal of phosphoric acid from the reaction results in significantly diminished yields (19%, 5A). This may be due to the requirement for acid to assist in catalyst regeneration (Scheme 6, vide infra).

Scheme 4. DBP as a Possible Nucleophilic Catalyst

Scheme 5. In Situ Formation and Reactivity of Pd(II)(phosphate)(bis-sulfoxide) Complex

Scheme 6. Plausible Catalytic Cycle
We present a plausible catalytic cycle that is consistent with our studies in Scheme 6. Catalyst 1 may undergo equilibrium acetate/phosphate exchange to form an intermediate of type A having acetate and/or phosphate ligands (denoted X). Intermediate A binds substrate 2 and subsequently performs C−H cleavage, producing π-allylPd complex B and I equivalent of proton source (HX). The weakly coordinating ligand (X) on B may then dissociate to afford cationic complex C, which undergoes functionalization. Loss of the tert-butyl group during functionalization may proceed by loss of isobutylene gas with concomitant generation of a second equivalent of proton and/or by loss of t-butyl cation and subsequent trapping by DBP or acetate (forming t-BuX products). We have observed (n-BuO)2P(−)=O)(Ot-Bu) in crude reaction mixtures, suggesting that this pathway is operating to some degree.25 Finally, proton-assisted reoxidation of Pd(0) to Pd(II) by BQ reforms A and dihydroquinone (DHQ), completing the catalytic cycle.

## CONCLUSION

We describe a Pd(II)/bis-sulfoxide/phosphoric acid catalyzed intramolecular allylic C−H oxidation of simple homoallylic, Boc-protected amine substrates to furnish anti-ami vinyl oxazolidinones. This method provides unprecedented direct access to these important heterocycles with outstanding stereoselectivities and novel regioselectivities. Mechanistic studies suggest the in situ generation of a Pd(II)/bis-sulfoxide/phosphoric acid complex that is capable of promoting both C−H cleavage and π-allylPd functionalization with the weak, aprotic N-Boc amine nucleophile. These findings have important future implications for effecting asymmetric induction under this general allylic C−H oxidation manifold.26

## EXPERIMENTAL PROCEDURES

### General Procedure for the Allylic C−H Oxidation Reaction (Table 2)

A 1-dram vial was sequentially charged with substrate 2 (1.0 equiv, 0.33 mmol), benzoquinone (48.6 mg, 1.5 equiv, 0.45 mmol), and catalyst 1 (15.1 mg, 0.1 equiv, 0.03 mmol). A stir bar was added to the vial, then 1,4-dioxane (0.15 mL, 2.0 M with respect to substrate) was added to the vial via syringe, followed by dibutyl phosphate (28 μL, 0.5 equiv, 0.15 mmol). The vial was capped with a Teflon cap and stirred at 45 °C for 24 h. The reaction was diluted with CH2Cl2 and transferred to a separatory funnel. The mixture was washed with H2O, the layers were separated, and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). Combined organics were dried over MgSO4, filtered through a pad of Celite, and concentrated. 1H NMR spectroscopy was performed on the crude mixture to determine the diastereomeric ratio. Flash chromatography was performed to isolate pure product 3.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, and 1H and 13C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES


(14) See the Supporting Information.

(15) Significant amounts of olefin isomerization are also observed with AgOTf and B(C6F5)3.


(19) Observation of O½X products is analogous to Corey’s observation of apparent t-Bu+ scavenging by solvent acetonitrile in a...

(25) Our studies suggest that DBP does not simply play the role of $t$Bu$^+$ scavenger. Superstoichiometric amounts of DBP were not optimal compared to substoichiometric loadings. See Table 1, entry 6 vs entry 8.