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N-Boc Amines to Oxazolidinones via Pd(II)/Bis-sulfoxide/Brønsted Acid Co-Catalyzed Allylic C−H Oxidation

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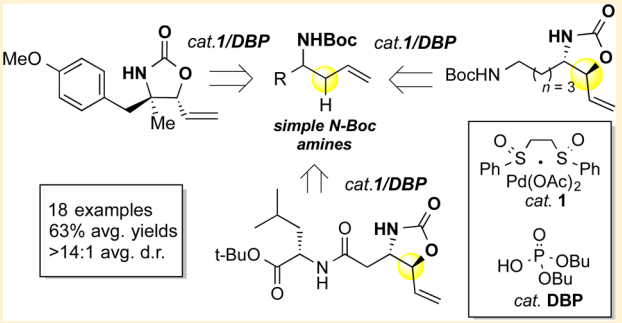
Supporting Information

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.

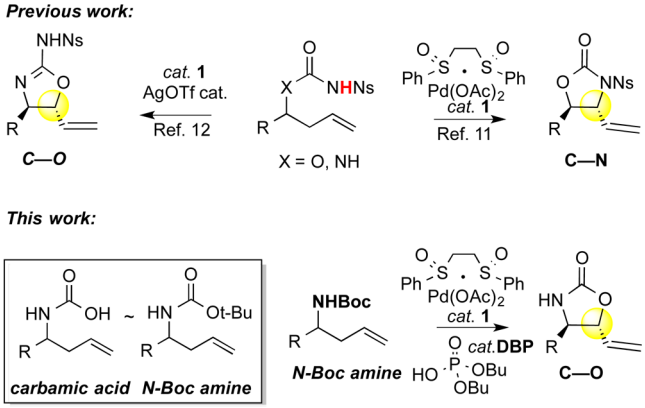


INTRODUCTION

Brønsted acid catalysis is increasingly being recognized as a powerful strategy for electrophile activation.[1] Such organocatalytic modes of activation hold tremendous potential for cooperative catalysis with organometallic systems, as has been recently demonstrated in Pd[2,3] and Ir[4]/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 pronucleophiles 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-vinyloxazolidinones (Scheme 1),[11] important pharmacophores in their unprotected form and precursors to amino-alcohols motifs.[9d] The only method to furnish the regioisomeric N/O motif starts with *N*-nosyl ureas and gives 2-aminooxazoline heterocycles[12] (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.

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



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

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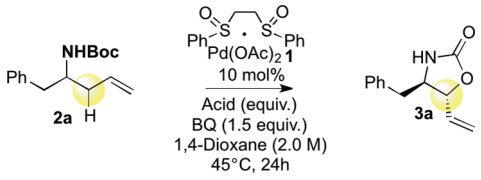
Table 1. Reaction Development[a]



entry	acid	pK_a	equiv.	% yield	*anti:syn*[b]
1	none	---	---	14	---
2	AcOH	4.76	1.5	40	19:1
3	BzOH	4.20	1.5	54	>20:1
4	*p*-NO_2BzOH	3.44	1.5	41[c]	8:1
5	*o*-NO_2BzOH	2.17	1.5	27[d]	15:1
6	$(BuO)_2PO_2H$	1.72	1.5	54	>20:1
7	$(PhO)_2PO_2H$	1.12	1.5	42	15:1
8	$(BuO)_2PO_2H$	1.72	0.5	63	>20:1
9	$(BuO)_2PO_2H$	1.72	0.5	*1.5 g scale* ⇨ 59	>20:1
10	$(BuO)_2PO_2H$	1.72	0.2	45	>20:1
11	$(BuO)_2PO_2H$	1.72	0.5[e]	65	>20:1
12	$(BuO)_2PO_2H$	1.72	0.5	0[f]	---
13	$(BuO)_2PO_2H$	1.72	0.5	0[g]	---
14	Cr(salen)Cl	---	0.1	0[h]	---
15	AgOTf	---	0.1	45	11:1
16	$B(C_6F_5)_3$	---	0.1	25	11:1
17	$Cu(OTf)_2$	---	0.1	40	6:1

[a]Conditions: 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. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Obtained 20% isolated yield of allylic *p*-nitrobenzoate (see Supporting Information). [d]Obtained 51% isolated yield of allylic *o*-nitrobenzoate (see Supporting Information). [e]DBP added in three 0.17 mmol portions at t = 0, 1.5, and 3 h. [f]Reaction run without **1**; 97% recovered starting material. [g]2,6-Dimethylbenzoquinone (1.5 equiv) employed as oxidant; 94% recovered starting material. [h]87% recovered starting material.

(Table 1, entry 1). We reasoned that Brønsted acids may activate the π-allylPd species by protonating anionic ligands (e.g., acetate) and/or promoting breakdown of the *N*-Boc pronucleophile and provide the necessary protons required for catalyst regeneration (vide infra). We first evaluated carboxylic acid additives that are known to be compatible with the Pd(II)/bis-sulfoxide reaction manifold. The addition of acetic acid provided a significant increase in reactivity with excellent diastereoselectivity (entry 2). Increasing the acidity of the carboxylic acid increased reactivity; however, it led to significant formation of linear allylic ester byproducts (entries 3−5). For example, *ortho*-nitrobenzoic acid, (entry 5), led to 78% overall conversion but only 27% yield of oxazolidinone **3a** and 51% yield of the linear allylic benzoate.[14] We hypothesized that phosphoric acids may similarly promote reactivity with minimized linear functionalization byproducts. Dibutylphosphate (DBP), a phosphoric acid with a comparable pK_a to *ortho*-nitrobenzoic acid, furnished a promising 54% yield of **3a** with excellent diastereoselectivity and no observable allylic phosphate byproducts (entry 6). Phosphoric acids with lower pK_a values gave diminished yields (entry 7). Lowering the loading of DBP to substoichiometric amounts, we found 50 mol % to be optimal (63% yield, entry 8) and highly scalable up to nearly 20-fold the typical scale with little change in efficiency (entry 9). Lower DBP loadings (e.g., 20 mol %) reduced reactivity (45% yield, entry 10). An iterative addition of DBP (3 times 17 mol %) over 3 h was found to only marginally increase the yield of **3a** (entry 11); however, with lower converting substrates we observed that this protocol increases reactivity, possibly by extending the catalyst lifetime (vida infra). Deleting catalyst **1** from the reaction resulted in no observed product and 97% recovered starting material after 24 h, indicating that no deprotection of the Boc group occurs under these mildly acidic conditions in the absence of catalyst (entry 12). Substituting the sterically hindered 2,6-dimethylbenzoquinone for 1,4-benzoquinone resulted in low conversion and no observable **3a**, suggesting that the functionalization step of this reaction is quinone dependent (entry 13).[5b−e] Lewis acid additives, known to promote reactivity with protic nucleophiles under Pd(II)/bis-sulfoxide catalysis,[9a,d,12] were also investigated. Oxophilic Lewis acid Cr(salen)Cl[9a,d] minimally converted starting material with no product formation (entry 14). Azaphilic Lewis acids AgOTf and $B(C_6F_5)_3$,[12] also hypothesized to promote reactivity by enhancing the electrophilicity of the π-allylPd intermediate, were less effective than Brønsted acids.[15] This is consistent with our hypothesis that when using nonacidic pronucleophiles a source of exogenous proton is necessary for effective catalyst regeneration (entries 15 and 16). Interestingly, copper(II) triflate promoted the reaction (entry 17); however, even after extensive optimization, yields and diastereoselectivities of oxazolidinone product **3a** remained moderate.

Scope and Applications. We next sought to explore the substrate scope of the reaction (Table 2). *N*-Boc homoallylic amine substrates possessing varying degrees of steric congestion and functionality were prepared using Ellman's sulfinamine auxiliary or other standard methods.[14,16] 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 homoallylic 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**, **3p**). 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.[17] 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.[18] 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-

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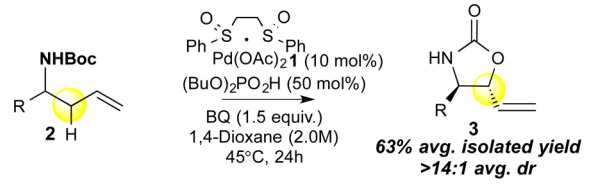
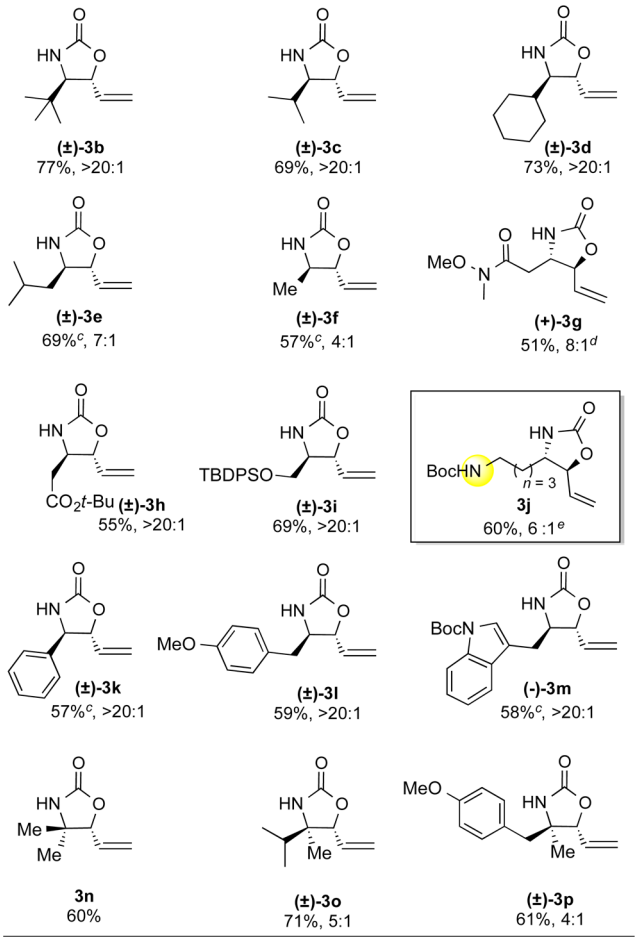
Table 2. Pd^{II} /Bis-sulfoxide/Phosphoric Acid-Catalyzed Allylic C−H Oxidation[a]

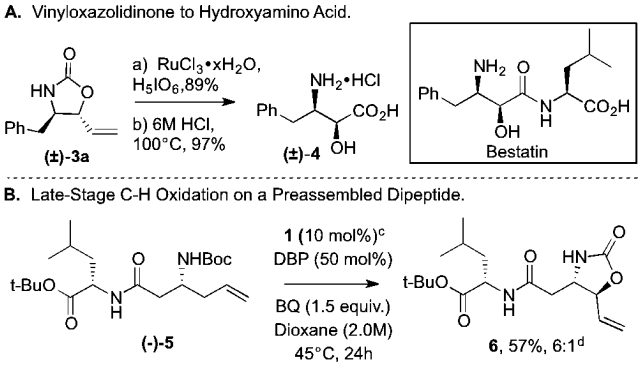




[a]Conditions: 1.0 equiv substrate **2**, 10 mol % **1**, 50 mol % $(BuO)_2PO_2H$, 1.5 equiv BQ, 2.0 M in 1,4-dioxane, 45 °C, 24 h. [b]Diastereomeric ratio (dr) determined by ^1H NMR of crude reaction mixtures. [c]Iterative addition of 17 mol % DBP at 0 h, 1.5 h, 3 h. [d]Optical rotation measured on material in >20:1 dr after additional purification. [e]Isolated as a 15:1 dr mixture after 1 flash chromatographic purification.

pounds, such as those found in the biologically active molecules Taxol, Bestatin, and Amastatin (Scheme 2).[18b] Vinyloxazolidinone **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,[19] 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).

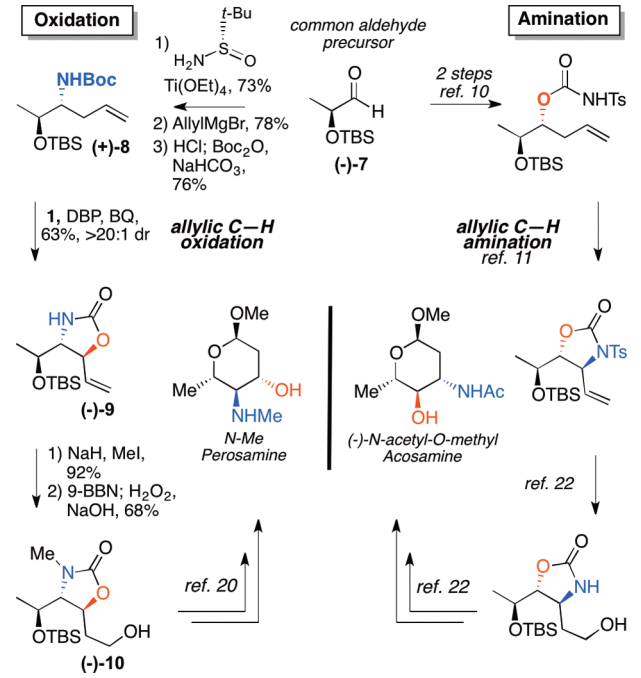
Scheme 2. Application to Hydroxyamino Acid Motifs



Conditions and Reagents: [a]$RuCl_3{\cdot}xH_2O$, H_5IO_6, $CCl_4/H_2O/MeCN$, rt, 5h, 89%; [b]6 M HCl, 100 °C, 16 h, 97%. [c]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. [d]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,[11] 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

Scheme 3. Regiodivergent Synthesis of 1,2-Amino Alcohols



from aldehyde (−)-**7**, derived from commercially available (L)-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,[20] an aminosugar found in pyrrolosporin A, an antitumor antibiotic.[21] Alternatively, starting

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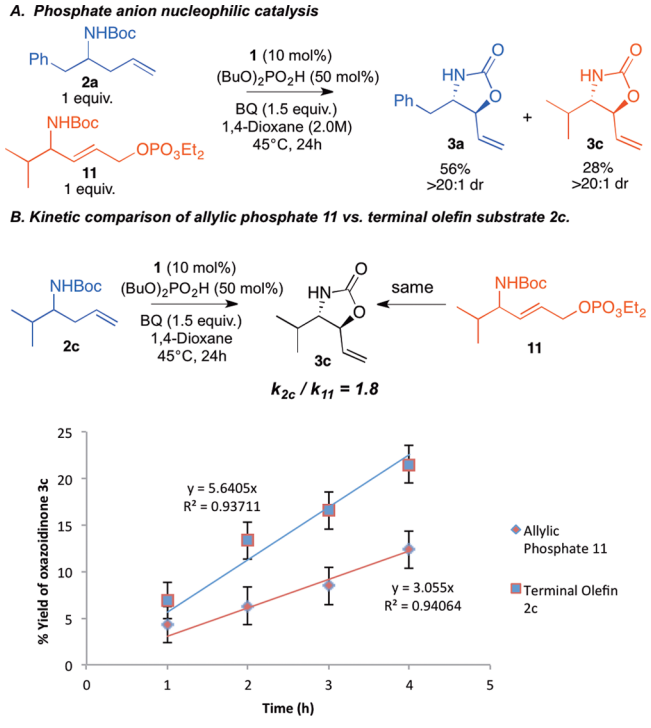
from (−)-7, the previously reported Pd(II)bis-sulfoxide mediated allylic C−H amination route[11] efficiently provides the regioisomeric oxazolidinone which is an intermediate in the synthesis of (−)-*N*-methylacosamine, a sugar found in epirubicin.[22]

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 π-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 nucleophilic catalyst[23] 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 **11** and terminal olefin substrate **2a** resulted in preferential reactivity of the olefin (Scheme 4A). Consistent with this, initial rate studies

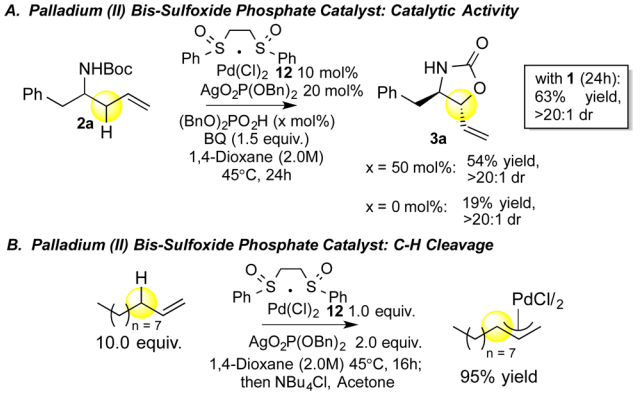
Scheme 4. DBP as a Possible Nucleophilic Catalyst



on isopropyl olefin substrate **2c** versus **11** under standard reaction conditions show a faster reaction rate for olefin **2c** ($k_{rel} \approx 1.8$, 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.

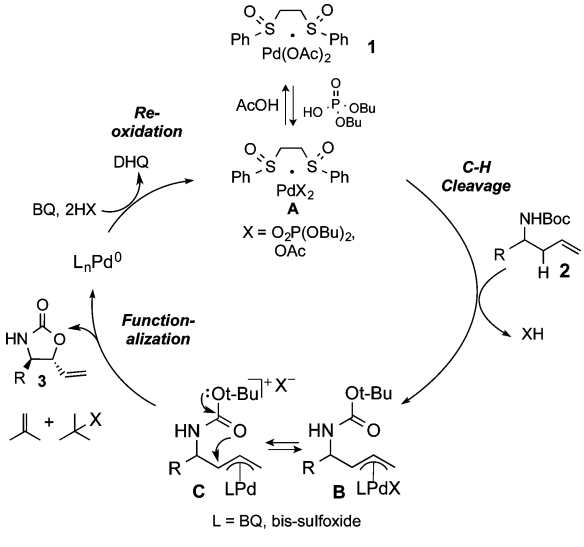
Finally, we investigated our hypothesis that the phosphoric acid acts as Brønsted acid cocatalyst to generate an electrophilic π-allylPd(phosphate) intermediate highly activated toward nucleophilic attack. A Pd(II)bis-sulfoxide-phosphate complex was generated in situ via metathesis of Pd(II)bis-sulfoxide-Cl_2 **12** with $AgO_2P(OBn)_2$ and the resulting solution was used as a catalyst under otherwise identical conditions (Scheme 5A). The

Scheme 5. In Situ Formation and Reactivity of Pd^{II}(phosphate)$_2$(bissulfoxide) Complex



reaction proceeded in comparable yields, reaction times, and selectivities as that using acetate catalyst **1**. In the absence of silver phosphate under otherwise identical conditions, **12** is inactive toward allylic oxidation.[14] 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 effects C−H cleavage (Scheme 5B). Significantly, the role of the Brønsted 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 6. Plausible Catalytic Cycle



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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 1 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 $(n\text{-BuO})_2P(=O)(Ot\text{-Bu})$ in crude reaction mixtures, suggesting that this pathway is operating to some degree.[24,25] 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*-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/phosphate complex that is capable of promoting both C−H cleavage and π-allylPd functionalization with the weak, aprotic *N*-Boc amine pronucleophile. 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, 0.3 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 CH_2Cl_2 and transferred to a separatory funnel. The mixture was washed with H_2O, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). Combined organics were dried over $MgSO_4$, 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 ^{13}C 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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