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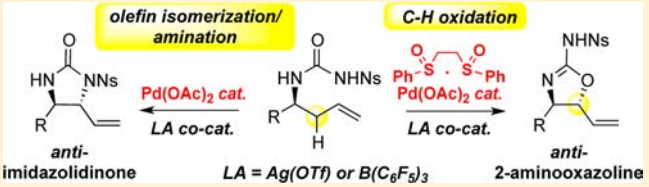
# Catalyst-Controlled C−O versus C−N Allylic Functionalization of Terminal Olefins

Iulia I. Strambeanu and M. Christina White*

Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois, 61801, United States

Supporting Information

**ABSTRACT:** The divergent synthesis of *syn*-1,2-aminoalcohol or *syn*-1,2-diamine precursors from a common terminal olefin has been accomplished using a combination of palladium(II) catalysis with Lewis acid cocatalysis. Palladium(II)/bis-sulfoxide catalysis with a silver triflate cocatalyst leads for the first time to *anti*-2-aminooxazolines (C−O) in good to excellent yields. Simple removal of the bis-sulfoxide ligand from this reaction results in a complete switch in reactivity to afford *anti*-imidazolidinone products (C−N) in good yields and excellent diastereoselectivities. Mechanistic studies suggest the divergent C−O versus C−N reactivity from a common ambident nucleophile arises due to a switch in mechanism from allylic C−H cleavage/functionalization to olefin isomerization/oxidative amination.

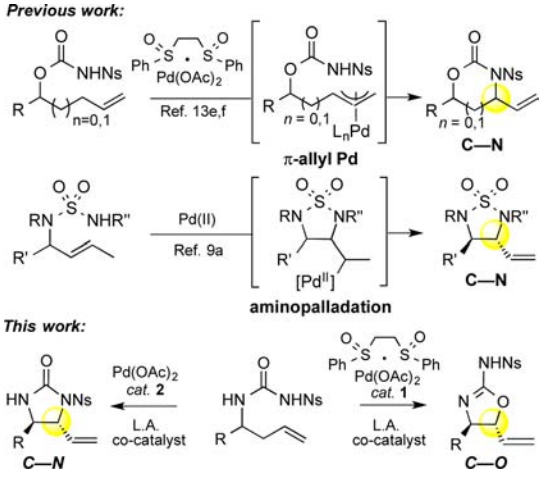



## INTRODUCTION

The advent of powerful C−H oxidation reactions[1] enables reactive oxygen and nitrogen functionality to be carried through synthetic sequences "masked" as inert C−H bonds and strategically unveiled at late stages to improve efficiency and increase diversity.[2] A powerful approach to increase diversity would be to take a common hydrocarbon starting material with an appended ambident nucleophile and, by fully exploiting its distinguishable reactive centers, selectively transform a C−H bond into multiple functionalized products. In this regard, homoallylic ureas could produce either imidazolidinones (cyclic ureas, C−N functionalization) or 2-aminooxazolines (isoureas, C−O functionalization), two medicinally important heterocycles[3] and precursors to 1,2-diamines or 1,2-aminoalcohols (Scheme 1).[4] While C−O olefin functionalizations with ureas have been demonstrated using stoichiometric hypervalent iodine reagents with limited scope,[5] in palladium-catalyzed reactions proceeding through either $\pi$-allylPd or amino-palladated intermediates,[6−11] ambident O/N nucleophiles have reportedly provided primarily[8e] C−N functionalization products (Scheme 1).

**Design Principles.** Palladium(II)/sulfoxide catalysis has proven itself to be a general platform for allylic C−H to C−O[12] and C−N[13] reactions of terminal olefins under mildly acidic, oxidative conditions. For example, 1,2- and 1,3-aminoalcohol precursors are readily accessible from homoallylic and bis-homoallylic carbamates, respectively (Scheme 1). Under similar conditions, homoallylic ureas could furnish either valuable 1,2-diamine (C−N) precursors or 1,2-aminoalcohol (C−O) precursors. Under the reductive, basic conditions of Pd(0)-catalyzed allylic substitutions, ambident urea nucleophiles have provided exclusively C−N products in the form of imidazolidinones.[6] This is thought to be due to both a kinetic (base-promoted deprotonation at nitrogen) and thermodynamic preference for C−N alkylation [Pd(0)-catalyzed equilibration].[14] Given that Pd(II)/sulfoxide catalysis proceeds under acidic, oxidative conditions that do not favor nitrogen deprotonation or promote reversible functionalization, O-alkylation may compete with N-functionalization using urea terminal olefin substrates. Additionally, O-alkylation may be further promoted by the addition of an azaphilic Lewis acid additive that binds to the nitrogen and retards nucleophilic attack. Significantly, the 1,2-aminoalcohol products furnished by this method would have the regiochemistry opposite to that of products previously obtained from carbamate nucleophiles

**Scheme 1. Ambident Nucleophile Reactivity**

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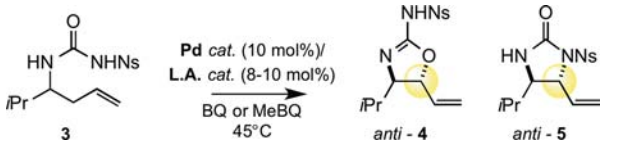
(Scheme 1). With the goal of increasing diversity by tuning the reactivity of an ambident urea nucleophile, herein we show that readily accessible homoallylic *N*-nosyl urea substrates can be transformed into 2-aminooxazolines (C−O) or imidazolidinones (C−N) by a simple switch in the Pd(II) catalyst in the presence of azaphilic Lewis acid cocatalysts.

## RESULTS AND DISCUSSION

**Reaction Discovery: C−O Functionalization.** We began our study by subjecting *N*-nosyl urea **3** to our standard Pd(II)/sulfoxide catalysis. Interestingly, we found that, although C−N (**5**) product was formed in slight excess, an appreciable amount of C−O (**4**) product was present (Table 1, entry 1). As expected, inclusion of a Brønsted base cocatalyst (Table 1, entry 2) completely shut down the C−O functionalization pathway and resulted in a strong preference for C−N functionalization. However, we found that catalytic $B(C_6F_5)_3$[15] (entry 3) or silver triflate[16,17] (entry 4), previously shown to have azaphilic properties with amides, increased the overall selectivity *favoring* the formation of the desired 2-aminooxazoline (4.9:1 and 7:1, respectively) furnishing **4** in 50% and 76% yield, respectively. In contrast, inclusion of an oxophilic Lewis acid cocatalyst [Cr(salen)Cl],[13a] previously shown to activate intermediate $\pi$-allylPd(BQ) electrophiles toward functionalization, led to diminished yields and did not change the C−O to C−N selectivity (entry 5). As had been previously observed with carbamate nucleophiles, *N*-tosyl ureas are less reactive (entry 6). Catalytic triflic acid (TfOH) additive promotes reactivity but with lower selectivity for *anti*-aminooxazoline **4** (entry 7). This result is consistent with experimental observations that water, which may form triflic acid in situ, erodes C−O:C−N ratios. Deletion experiments showed that the Pd/bis-sulfoxide catalyst **1** was critical for reactivity (entries 8 and 9). To the best of our knowledge, this represents the first example of successfully tuning the reactivity of an ambident O/N nucleophile under palladium catalysis to favor C−O bond formation.

**Table 1. Reaction Development**




| entry[a,b] | R | Pd catalyst (10 mol%) | L.A. co-catalyst (8 - 10 mol%) | Yield of 4 (%)[c,d] | Yield of 5 (%)[c,d] | 4:5 | |
|---|---|---|---|---|---|---|---|
| 1[e] | Ns | **1** | none | 19% | 28% | 1:1.6 |  Pd(OAc)$_2$ *cat.* **1** |
| 2[f] | Ns | **1** | DIPEA | 0% | 38% | 1:>20 | |
| 3[e] | Ns | **1** | $B(C_6F_5)_3$ | 50% | 7% | 4.9:1 | |
| 4[g] | Ns | **1** | AgOTf | 76% | 9% | 7:1 | |
| 5[h] | Ns | **1** | Cr(salen)Cl | 8% | 8% | 1:1 | |
| 6[g] | Ts | **1** | AgOTf | 56% | trace | >20:1 | |
| 7[g] | Ns | **1** | TfOH | 64% | 28% | 2.3:1 | |
| 8[i] | Ns | **none** | TfOH | 0% | 0% | - | |
| 9[g,i] | Ns | **none** | AgOTf | 0% | 0% | - | |
| 10[e] | Ns | **2** | AgOTf | 0% | 46% | 1:>20 | Pd(OAc)$_2$ *cat.* **2** |
| 11[j] | Ns | **2** | AgOTf | 0% | 59% | 1:>20 | |
| 12[j] | Ns | **2** | $B(C_6F_5)_3$ | 0% | 62% | 1:>20 | |
| 13[j] | Ns | **2** | none | 0% | 32% | 1:>20 | |
| 14[i,j] | Ns | **none** | $B(C_6F_5)_3$ | 0% | 0% | - | |

[a]All reactions were run using THF (1.0 M) as solvent, MeBQ (methyl-*p*-benzoquinone, 1.5 equiv) as terminal oxidant and 8 mol % Lewis acid (LA) cocatalyst for 6 h unless otherwise noted. [b]Reactions with cat. **1** were run with an additional 5 mol % Bis-SO ligand [1,2-bis(phenylsulfinyl)ethane]. [c]Average of two runs. [d]Observed diastereoselectivities in crude reaction mixtures: >20:1 dr *anti:syn* for **4** for all entries; dr for **5**: entry 1, 1.3:1 dr *anti:syn*; entry 2, 4.4:1 dr; entry 4, 1:1 dr; entry 7, 2.5:1 dr; entries 3, 5, 10, 11, 12, 13 >20:1 dr; dr determined by $^1$H NMR analysis of the crude reaction mixture. [e]Reactions run to complete conversion: entry 1, 24 h; entry 3, 2 h; entry 10, 72 h. [f]Reaction stopped at 18 h (37% rsm); no improved conversion was observed at 48 h or 72 h. [g]DCM (dichloromethane, 1.0 M) used as solvent; for entry 4, 1 equiv of DMA was added. [h]Reaction stopped before complete conversion at 2 h. Increased reaction times resulted in product decomposition. [i]>99% rsm, 0% *E*-internal olefin. [j]Reaction run using THF (1.66 M) as solvent, BQ (*p*-benzoquinone, 1.05 equiv) as terminal oxidant and 10 mol % LA cocatalyst for 72 h.

**Reaction Discovery: C−N Functionalization.** We were intrigued by our discovery of a selective C−O bond-forming reaction using Pd(II)/sulfoxide catalysis and questioned whether the sulfoxide ligand was critical for the observed selectivity. After removing the ligand from a standard reaction, we made the unexpected observation of the *exclusive* formation of C−N alkylated product *anti*-imidazolidinone **5** in 46% yield (entry 10). Upon optimization, synthetically useful yields and excellent diastereoselectivity (>20:1 dr) were obtained using either silver triflate (entry 11, 59% yield) or $B(C_6F_5)_3$ (entry 12, 62% yield). Notably, omission of the Lewis acid cocatalyst resulted in lower product formation (32% yield) due to an oxidative amination pathway (aminopalladation/$\beta$-hydride elimination) of the terminal olefin (entry 13). Additionally, omission of the palladium catalyst gave no reactivity (entry 14).

Collectively, these two processes represent the first examples of transforming readily accessible ambident urea nucleophiles into either C−O or C−N alkylated products by simply switching the Pd(II) catalyst.

**Reaction Scope.** As outlined in Tables 2 and 3, a range of *N*-nosyl urea olefin substrates were effectively oxidized and aminated using these heterobimetallic catalytic systems to furnish either *anti*-2-aminooxazolines or *anti*-imidazolidinones in good yields and selectivities. Substrates containing moderate to high levels of steric bulk adjacent to the urea tether (R = ethyl, isopropyl, *t*-Bu) furnished the corresponding products in high yields and selectivities with both systems (**4**, **5**, **6**, **14**, **15**). *anti*-2-Aminooxazolines (**7** and **8**) and *anti*-imidazolidinones (**16** and **17**), derived from common tertiary amines, can also be accessed in excellent yields and selectivities. These represent a class of sterically challenging vicinal diamine and aminoalcohol precursors that are difficult to access otherwise in optically enriched form. In each case, a single starting material was converted selectively into either C−O or C−N functionalized products simply by using the appropriate palladium catalyst. Substrates containing proximal benzylated diols capable of catalyst deactivation via metal chelation are also tolerated under both reaction manifolds [(−)-**11**, (−)-**18**, (−)-**19**]. Aryl moieties were evaluated and the products generated displayed excellent selectivities for either the C−O or the C−N functionalized products [**12**, (−)-**13**, **21**]. The diastereoselectivity for both processes appears to be very high; in most cases examined, only the *anti*-aminooxazolines and *anti*-imidazolidinones are observed by $^1$H NMR of the crude reaction mixtures.


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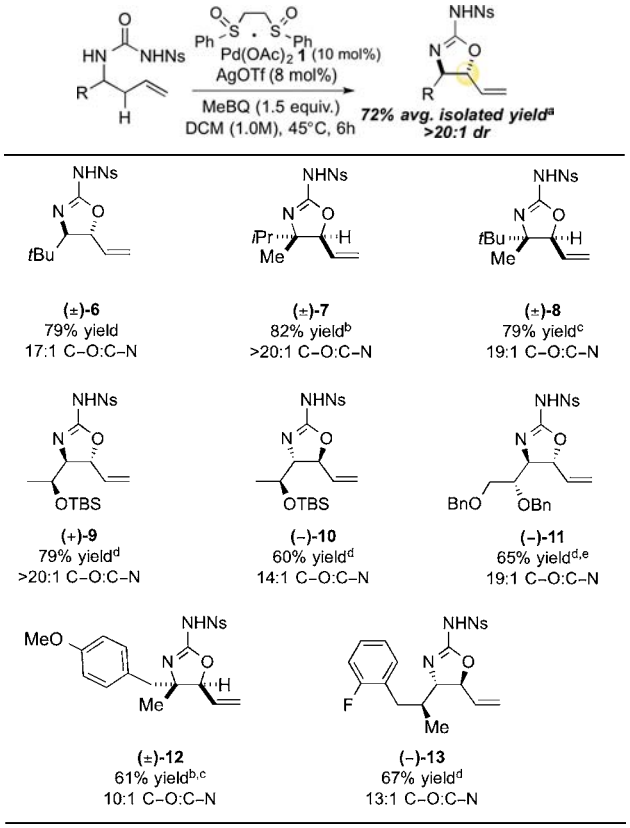
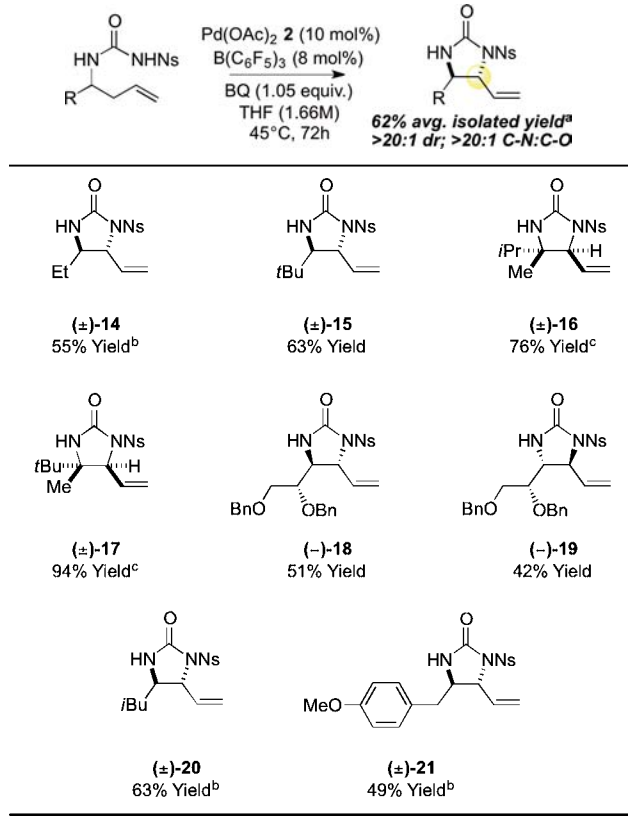
**Table 2. $Pd^{II}$/Bis-sulfoxide/Ag-Catalyzed Allylic C−O Bond Formation**




[a]Diastereoselectivities and C−O:C−N = *anti*-2-aminooxazoline:*anti*-imidazolidinone ratios were measured by $^1$H NMR analysis of the crude reaction mixtures; >20:1 dr unless otherwise noted. All yields are reported for the major diastereomer. [b]**7**: 5.6:1 dr *anti:syn* 2-aminooxazoline; **12**: 4:1 dr. [c]Reaction run at 45 °C with a 0.12:1 DMA:DCM solvent mixture. [d]Reaction run at 40 °C with a 0.12:1 DMA:DCM solvent mixture. [e]Unable to determine crude selectivity due to peak overlap; isolated selectivity reported.

**Table 3. $Pd^{II}$/B-Catalyzed Allylic C−N Bond Formation**



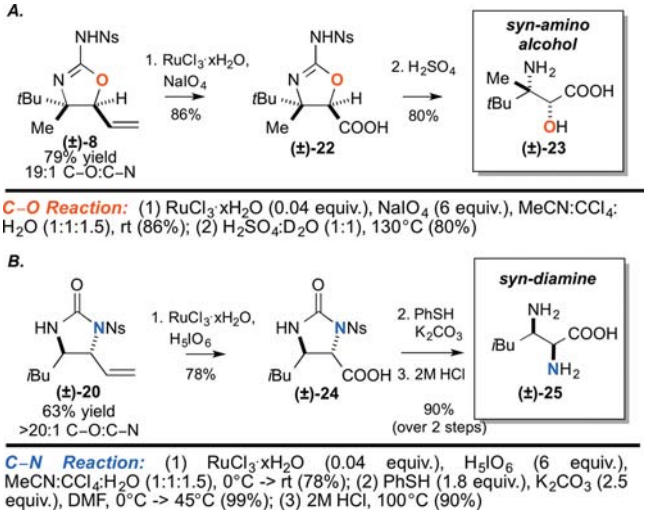

[a]Diastereoselectivities and C−N:C−O ratios were measured by $^1$H NMR of the crude reaction mixtures; >20:1 dr and >20:1 C−N:C−O unless otherwise noted. [b]**14**: 9.8:1 dr; **20**: 7:1 dr; **21**: 12:1 dr. [c]**16**: 10:1 C−N:C−O; **17**: 10:1 C−N:C−O.

For substrates that contain multiple stereogenic centers, the diastereomeric outcome is predictable and controlled entirely by the stereocenter containing the urea ((+)-**9**, (−)-**10**, (−)-**11**, (−)-**13**, (−)-**18**, (−)-**19**). Taken together, these results demonstrate the selective, catalyst-controlled allylic installation of either the O or N functionality using a bifunctional urea nucleophile. It is significant to note that alternative methods to generate these products require de novo syntheses of separate starting materials.[5−11,18] Reactions such as these that take a common intermediate and obtain divergent outcomes based on catalyst control have the potential to significantly advance synthetic efficiency and flexibility.

***α,β*-Diamino Acids and *α*-Hydroxy-*β*-Amino Acids.** The vinyl imidazolidinones (ureas) and aminooxazolines (isoureas) generated via these methods are precursors to valuable 1,2-diamines and 1,2-aminoalcohols. For example, the *α*-olefin moiety can be easily elaborated to furnish *α,β*-diamino acids and *α*-hydroxy-*β*-amino acids, nonproteinogenic amino acids found in numerous biologically active compounds and synthetic peptides.[19]

Beginning with readily accessible homoallylic *N*-nosyl urea precursors (four steps from commercial starting materials, see Supporting Information), application of Pd(II)/bis-sulfoxide/Lewis acid (LA)-catalyzed oxidation or Pd(II)/LA-catalyzed amination methods furnished either the corresponding amino-oxazoline (±)-**8** or imidazolidinone (±)-**20** in excellent yields and selectivities (Tables 2, 3). Elaboration of the vinyl moiety of aminooxazoline (±)-**8** via ruthenium tetraoxide-catalyzed oxidative cleavage affords carboxylic acid (±)-**22** in 86% yield. Hydrolysis of the *N*-nosyl-2-aminooxazoline (±)-**22** under acidic conditions afforded the *α*-hydroxy-*β*-amino acid (±)-**23** in 80% yield (see Scheme 2). Imidazolidinone (±)-**20** could

**Scheme 2. Diversification to Biologically Relevant Motifs**





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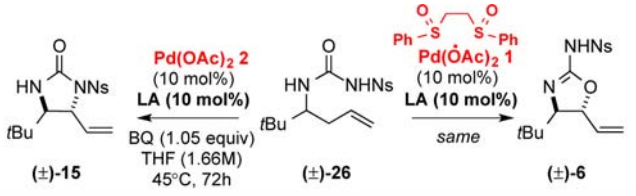
also be readily elaborated to $\alpha,\beta$-diamino acid (±)-**25** via a three-step sequence involving oxidative cleavage of the olefin (78%), mild $PhSH/K_2CO_3$ removal of the *N*-nosyl group, and acidic hydrolysis (90% over two steps) (see Scheme 2). These methods enable the selective and efficient generation of heterocyclic and acyclic polyoxidized pharmacophores and may expedite discovery of new medicinal agents.

**Mechanistic Considerations.** Data from the reaction discovery studies suggested that the C−O versus C−N selectivities obtained with the ambident urea nucleophile are dictated by the choice of $Pd^{II}$ catalyst (Table 1). In order to confirm that it is a switch in palladium catalyst alone that is causing the selectivity for C−O vs C−N bond formation in these two reactions, we subjected a common starting material **26** to either 10 mol % Pd(II)/bis-sulfoxide catalyst **1** or $Pd(OAc)_2$ **2** under otherwise identical reaction conditions of azaphilic Lewis acid cocatalyst, solvent, oxidant, and temperature (Scheme 3). Remarkably, both Lewis acid cocatalysts

**Scheme 3. Ligand Effects on Selectivity**



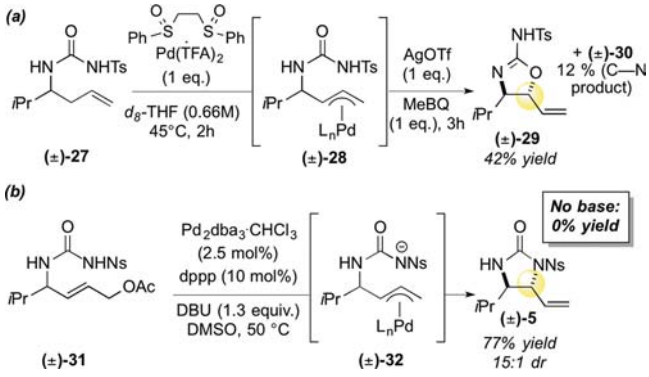

[a]Isolated yield, average of 2 runs at 0.3 mmol. [b]The ratios were determined by $^1H$ NMR analysis of crude reaction mixture.

$B(C_6F_5)_3$ and Ag(OTf) furnished imidazolidinone product *anti*-**15** and 2-aminooxazoline product *anti*-**6** in comparable yields with excellent C−O vs C−N selectivities of >20:1 that are dependent solely on the nature of the palladium catalyst.

A critical question raised by these studies relates to the means by which a switch in palladium catalyst results in divergent product outcomes from a common urea starting material. We hypothesized that the observed difference in the reactivity of the urea nucleophile when switching from Pd(II)/bis-sulfoxide **1** to $Pd(OAc)_2$ **2** arises from a change in mechanism from allylic C−H oxidation that furnishes *anti*-2-aminooxazoline products to olefin isomerization/oxidative olefin amination that generates *anti*-imidazolidinones. Pd(II)/sulfoxide catalysis with terminal olefins has been well established to proceed via an allylic C−H cleavage/$\pi$-allylPd functionalization mechanism with a wide range of oxygen and nitrogen nucleophiles under varying reaction conditions.[12,13] Consistent with C−O alkylation proceeding via such a mechanism, stoichiometric $\pi$-allyl intermediate **28** affords *anti*-aminooxazoline **29** as the major product in the presence of AgOTf (Scheme 4a).

Given that the sulfoxide ligand is known to retard olefin isomerization,[12b] we envisioned that its exclusion allows $Pd(OAc)_2/B(C_6F_5)_3$ to effect isomerization of the terminal olefin starting material to the internal *E*-olefin; subsequently, the internal olefin would be capable of undergoing an oxidative amination pathway (aminopalladation/$\beta$-hydride elimination). Isomerizations of terminal olefins catalyzed by Pd(II)-salts[20] are well documented, and the addition of Lewis acid additives[21] has been shown to promote these processes. To test our

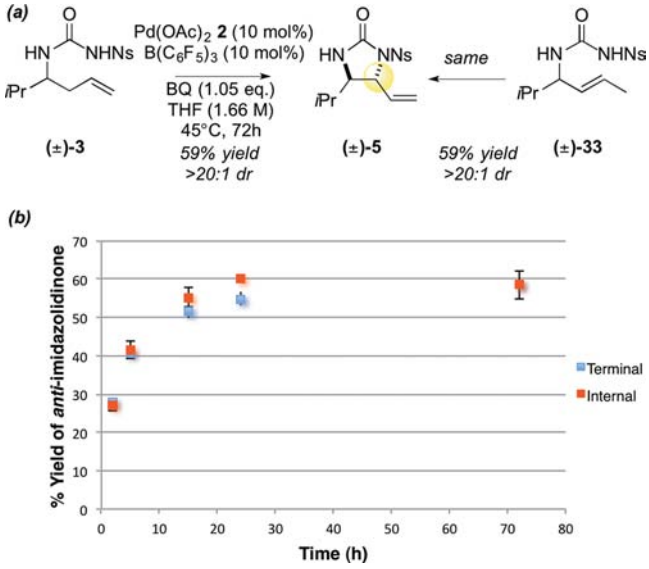
**Scheme 4. Mechanistic Experiments for C−O Functionalization**




(a) Stoichiometric formation and functionalization of a $\pi$-allylPd intermediate. (b) Functionalization of a pre-oxidized *N*-nosyl urea under Pd(0) conditions.

hypothesis, we evaluated the rate of functionalization for terminal olefin substrate **3** and the corresponding *E*-internal olefin substrate **33**, which would lead to the observed *anti*-stereochemistry via an aminopalladation mechanism. Consistent with our hypothesis, both substrates formed the *anti*-imidazolidinone product with comparable overall kinetic profiles, yields, and selectivities (Scheme 5).

**Scheme 5. Mechanistic Experiments for C−N Functionalization**




[a](a) Terminal vs internal olefin functionalization under $Pd^{II}/B$ catalysis. (b) Overall kinetic profile of the terminal olefin and the internal olefin under the standard C−N functionalization conditions

Additionally, $^1H$ NMR analysis of the reaction with terminal olefin substrate **3** revealed complete conversion to the corresponding *E*-internal olefin **33** after only 1 h.[22] Our studies demonstrate that a change in mechanism from allylic C−H oxidation to isomerization/aminopalladation led to catalyst-controlled, divergent C−O and C−N allylic functionalization reactions using tethered urea nucleophiles.

Interestingly, while inclusion of a Lewis acid results in O-functionalization from a $\pi$-allylPd intermediate, exclusive N-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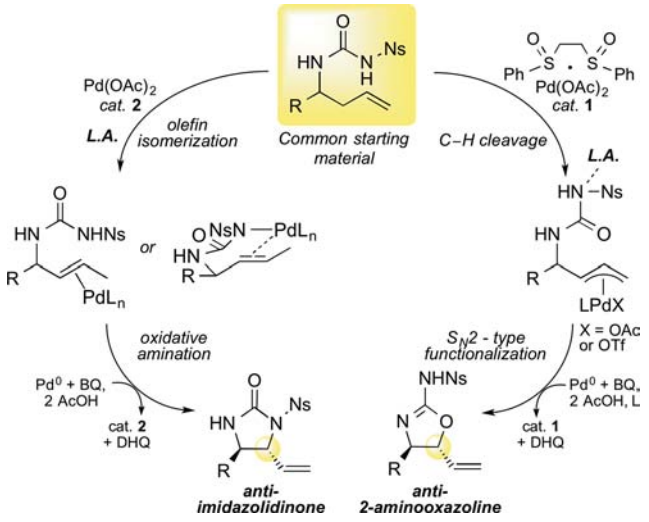
functionalization is observed via an aminopalladation pathway. This outcome may be explained by considering that π-allylPd N-functionalization proceeds via external attack that requires an anionic, nucleophilic nitrogen (Scheme 6). In accord with this,

**Scheme 6. Proposed Mechanisms**




we have observed that Pd(0)-catalyzed allylic substitution of an analogous allylic acetate substrate, known to proceed via a π-allylPd intermediate, does not proceed without inclusion of stoichiometric base (Scheme 4b). The Lewis acid cocatalysts used in this study may coordinate to the urea nosyl nitrogen and block its attack on the Pd/π-allyl complex and/or generate highly electrophilic π-allylPd intermediates that are preferentially attacked by the hard oxygen urea nucleophile (Scheme 6). In contrast, aminopalladation is a process that has been noted to proceed under both acidic and basic reaction conditions.[23] Future studies will seek to better understand the divergent reactivity of ambident nucleophiles with π-allylPd and olefin intermediates.

## CONCLUSION

In conclusion, we have developed a novel process that uses palladium catalysis in combination with Lewis acid cocatalysis for the formation of either *anti*-2-aminooxazolines or *anti*-imidazolidinone products from common ambident urea precursors. The inclusion of Lewis acid promotes O-alkylation in reactions proceeding with ambident O/N nucleophiles via π-allylPd intermediates, thereby offering a strategy for expanding the scope of nucleophiles subject to palladium catalysis. Moreover, the discovery of facile isomerization/olefin palladation under LA/Pd(II) conditions may broaden the scope of allylic functionalization reactions available from terminal olefins. We anticipate that the general strategy of taking a common hydrocarbon starting material and selectively transforming it into multiple useful products will find immediate use in streamlining and diversifying the synthesis of medicinal agents and natural products.

## EXPERIMENTAL PROCEDURES

**General Procedure for the Allylic Oxidation (Table 2).** A 1/2 dram borosilicate vial containing a Teflon stir bar was flame-dried, sealed with a Teflon-lined cap, and taken inside a glovebox. The homoallylic *N*-nosyl urea starting material (1 equiv, dried over $P_2O_5$), freshly sublimed methyl-*p*-benzoquinone (1.5 equiv), catalyst **1** (0.10 equiv), 1,2-bis(phenylsulfinyl)ethane (0.05 equiv), and freshly recrystallized AgOTf (0.08 equiv) were added to the 1/2 dram vial in the glovebox, in the order specified. The vial was securely sealed with the Teflon-lined cap and taken out of the glovebox. Dry dichloromethane (1.0 M) (and DMA, if specified in Table 2) was quickly added to the 1/2 dram vial outside of the glovebox, under a flow of argon gas. The vial was then sealed and placed in an aluminum block to stir at 45 °C for exactly 6 h. If the reaction is allowed to run longer than 6 h, an erosion of the C−O:C−N selectivity is observed. The solution was allowed to cool to room temperature and then transferred using dichloromethane to a 250 mL separatory funnel. The solution was diluted with 15 mL of dichloromethane and rinsed with 1 × 15 mL aqueous $NH_4Cl$ (sat.). The organic layer was collected and dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (in general, gradient 25−30% EtOAc/hexanes was used).

**General Procedure for the Allylic Amination (Table 3).** A 1/2 dram borosilicate vial containing a Teflon stir bar was flame-dried, sealed with a Teflon-lined cap, and taken inside a glovebox. The homoallylic *N*-nosyl urea starting material (1 equiv, dried over $P_2O_5$), sublimed benzoquinone (1.05 equiv), $Pd(OAc)_2$ (0.1 equiv), and $B(C_6F_5)_3$ (0.1 equiv) were added to the 1/2 dram vial in the glovebox, in the order specified. The vial was securely sealed with the Teflon-lined cap and taken out of the glovebox. Dry tetrahydrofuran (1.66 M) was quickly added to the 1/2 dram vial outside of the glovebox, under a flow of argon gas. The vial was then sealed and stirred in an aluminum block at 45 °C for 72 h, unless otherwise noted in Table 3. The solution was allowed to cool to room temperature, and the crude reaction mixture was directly purified using flash column chromatography (in general, gradient 20−30% EtOAc/hexanes was used).

## ASSOCIATED CONTENT

### Supporting Information

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

## AUTHOR INFORMATION

### Corresponding Author

white@scs.uiuc.edu

### Notes

The authors declare no competing financial interest.

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