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Palladium Catalysis

Construction of Tetrahydrofurans by Pd^{II}/Pd^{IV}-Catalyzed Aminooxygenation of Alkenes**

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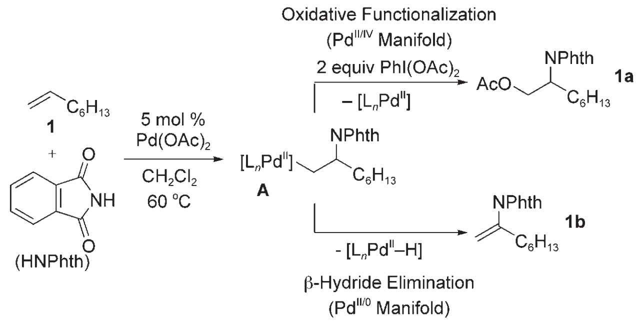
Catalytic transformations involving Pd^{II} σ-alkyl or σ-aryl intermediates are widely used in organic synthesis and offer attractive routes to many valuable products.[1] However, the vast majority of these reactions proceed by Pd^0/Pd^{II} mechanisms. As a result, the diversity of structures/bonds that can be constructed is constrained by the limitations of this redox cycle. Recent studies have explored the generation of Pd^{II} σ-alkyl/aryl species in the presence of strong oxidants (e.g., $PhI(OAc)_2$, oxone, *N*-halosuccinimides, iodine) to access alternative Pd^{II}/Pd^{IV} reaction manifolds.[2–4] Importantly, these oxidative transformations often yield highly complementary organic products to those formed by traditional $Pd^{0/II}$ catalysis.[2–4]

Our group is interested in exploiting Pd^{II}/Pd^{IV} catalytic cycles for the development of new organic transformations.[2a–e,4a] As part of these efforts, we reasoned that Pd^{II} β-aminoalkyl species (generated by the aminopalladation of olefins)[5] might be oxidatively intercepted with $PhI(OAc)_2$ (Scheme 1). If successful, such reactions would provide an attractive Pd^{II}/Pd^{IV}-catalyzed route from alkenes to amino-oxygenated products, which are valuable building blocks in organic synthesis.[6] Importantly, while this work was in progress, several other groups disclosed related transformations.[3] We report herein the successful application of this strategy to the stereospecific and diastereoselective conversion of 3-alken-1-ols into 3-aminotetrahydrofurans.[6] Mechanistic details are discussed and offer insights into the further design and development of Pd^{II}/Pd^{IV}-catalyzed reactions.



Scheme 1. Pd-catalyzed aminoacetoxylation of 1-octene.

Our initial studies focused on generating Pd^{II} β-aminoalkyl species **A** by the intermolecular aminopalladation of 1-octene with phthalimide (Scheme 1).[3a] Complex **A** would typically undergo β-hydride elimination; however, we anticipated that this species could react competitively with $PhI(OAc)_2$ to generate a Pd^{IV} intermediate. Reductive elimination from this intermediate should then provide aminoacetoxylated product **1a**. We were pleased to find that treatment of 1-octene with 5 mol% $Pd(OAc)_2$, one equivalent phthalimide, and two equivalents $PhI(OAc)_2$ for 12 h at 60 °C afforded **1a** in 41% yield. However, consistent with results recently disclosed by Liu and Stahl,[3a] the β-hydride product **1b** was also obtained in 27% yield.[7]

We hypothesized that competing β-hydride elimination might be suppressed by tethering a hydroxyl group to the alkene. In a substrate like 3-buten-1-ol (**2**), the hydroxyl group could coordinate to the Pd center during/after aminopalladation to form palladacycle **B** (Scheme 2), thereby slowing β-hydride elimination relative to oxidative functionalization. Gratifyingly, treatment of **2** with 5 mol% $Pd(OAc)_2$, one equivalent phthalimide, and two equivalents $PhI(OAc)_2$ did not produce any of the β-hydride elimination product **2d**. However, surprisingly, the intermolecular aminoacetoxylated species **2c** was not observed in this reaction. Instead, tetrahydrofuran product **2a**, resulting from an intramolecular oxygenation, was formed in a modest 30% yield along with a second THF compound (**2b**).[8,9] A screening of reaction additives revealed that 10 mol% $AgBF_4$ increased the yield of **2a** to 37%.[10] Two sequential additions of catalyst, silver salt, oxidant, and alcohol further improved the yield of **2a** to 45% (based on phthalimide as the limiting reagent). Importantly, control reactions (in the absence of Pd or oxidant) did not afford any of the tetrahydrofuran products **2a** or **2b**.

With these results in hand, we next sought to investigate the mechanism of the Pd-catalyzed formation of **2a**. We initially hypothesized that **2a** might be formed in a two-step sequence. In the first step, Pd-catalyzed reaction between **2** and $PhI(OAc)_2$ would afford either **2b**[9,11] or **2c** (Scheme 2). Product **2b** could then undergo an intermolecular S_N2 reaction with free phthalimide (Scheme 3, route a), or **2c** could undergo intramolecular S_N2 ring closure (Scheme 3, route b) to afford **2a**. To test the viability of these pathways,

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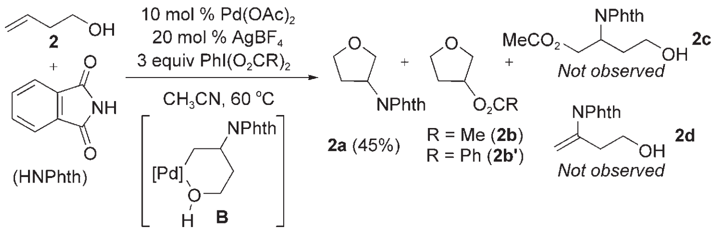
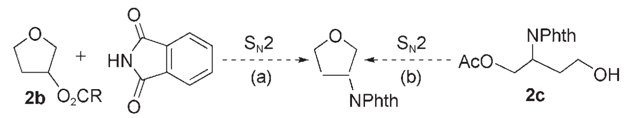


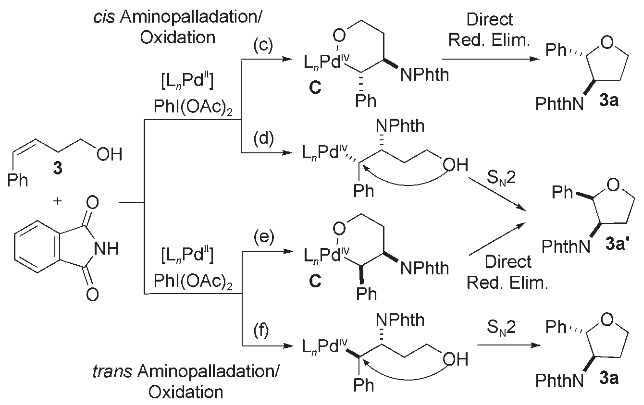
Scheme 2. Pd-catalyzed aminooxygenation of 3-buten-1-ol.



Scheme 3. Possible S_N2 mechanisms for aminooxygenation.

authentic samples of **2c** and **2b′** (in which O_2CMe is substituted with O_2CPh)[9] were subjected to the catalytic reaction conditions. However, in both cases, product **2a** was not observed by GC or ^1H NMR spectroscopy, indicating that neither mechanism is operational.

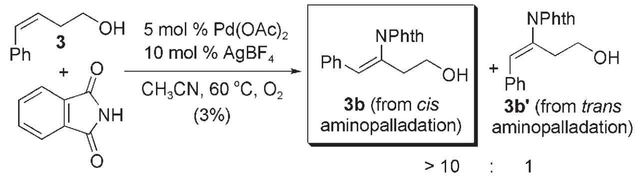
Four alternative Pd^{II}/Pd^{IV}-catalyzed routes to **2a** were next considered.[12] The first two (Scheme 4, routes c and d)



Scheme 4. Possible Pd^{II}/Pd^{IV} mechanisms for aminooxygenation.

begin with *cis* aminopalladation of the olefin, while the latter two (Scheme 4, routes e and f) involve an initial *trans*-aminopalladation step. Oxidation of the resulting Pd^{II} intermediate to Pd^{IV} could then form cyclic or acyclic complexes, which could undergo direct reductive elimination with retention of the stereochemistry (Scheme 4, routes c and e) or S_N2-type reductive elimination with inversion of the stereochemistry (Scheme 4, routes d and f). To gain insights into these mechanistic possibilities, *Z* olefin **3** was examined as a substrate. Subjection of **3** to our standard conditions afforded *trans*-disubstituted tetrahydrofuran **3a** in 60% yield of isolated product as a single diastereomer.[13] This result rules out mechanistic possibilities d and e, which should both selectively provide the *cis*-disubstituted isomer **3a′**.

To distinguish between mechanisms c and f, we needed to determine whether initial C–N bond formation proceeded by *cis* or *trans* aminopalladation. As such, the reaction of substrate **3** was next carried out using O_2 (rather than $PhI(OAc)_2$) as the terminal oxidant. Under these conditions, Pd^{IV} intermediates should not be accessible; therefore, the Pd^{II} β-aminoalkyl complex is expected to decompose by β-hydride elimination to afford an olefin,[5] whose geometry should establish the stereochemistry of the aminopalladation.[3a] Subjecting **3** to 5 mol% $Pd(OAc)_2$ and 10 mol% $AgBF_4$ under O_2 produced a greater than 10:1 ratio of **3b** relative to **3b′**, albeit in low (ca. 3%) yield of isolated product (Scheme 5).[14] This result suggests that **3a** is formed predominantly by *cis* aminopalladation;[3a,15] therefore, we propose



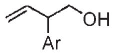
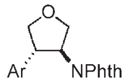
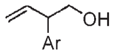
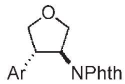
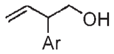
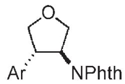
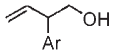
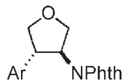
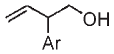
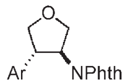
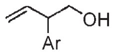
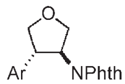
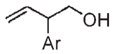
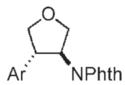
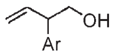
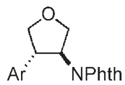
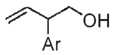
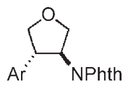
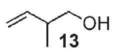
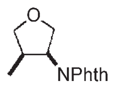
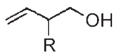
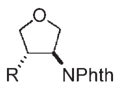
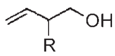
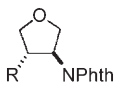
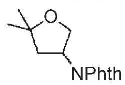
Scheme 5. Determination of stereochemistry of aminopalladation.

that mechanism c, involving *cis* aminopalladation and subsequent C–O bond-forming reductive elimination with retention of stereochemistry,[16,17] is likely operating in this system.

These mechanistic experiments suggested that palladacyclic intermediates **B** and **C** (Schemes 2 and 4) were likely involved in the formation of tetrahydrofuran **3a**. Therefore, we reasoned that incorporation of substituents along the alkyl chain of the substrate would promote metallacycle formation and thereby increase the yields of these reactions. Additionally, since such cyclic intermediates often assume highly ordered transition states, we anticipated that these transformations might proceed stereoselectively. Consistent with these hypotheses, 2-phenyl-3-buten-1-ol (**4**) underwent Pd-catalyzed oxidative cyclization to afford **4a** in 77% yield; furthermore, this product was formed with high (10:1) selectivity for the *trans* diastereomer (Table 1, entry 1). A variety of related substrates containing allylic aryl groups also reacted to form 3,4-*trans*-disubstituted tetrahydrofurans in comparable yields and with modest to excellent diastereoselectivities (entries 2–9). Interestingly, the stereoselectivity of these transformations was sensitive to substitution on the arene. In particular, substitution at the *ortho* position (entries 4 and 9) resulted in substantially decreased levels of diastereoselectivity. Furthermore, modest yields and selectivities were observed with allylic Me, benzyl, or isopropyl groups (entries 10–12). Both experimental and computational efforts are currently underway to develop a transition-state model consistent with all of these observations.

The work described herein reveals several new mechanistic features of Pd^{II}/Pd^{IV}-catalyzed transformations. First, it establishes that C–O bond-forming reductive elimination from Pd^{IV} can proceed with clean retention of configuration.[16,17] This unusual observation is in sharp contrast to closely related studies with $PhI(OAc)_2$, in which C–OAc coupling took place with inversion of configuration at the

Table 1: Scope of palladium-catalyzed formation of 3-aminotetrahydrofuran derivatives.[a]

Entry	Alcohol	Substituents	Major product	Product no.	Yield [%] (d.r.)
1		Ar = Ph (**4**)		**4a**	77 (10:1)
2		Ar = *p*-MeOC$_6$H$_4$ (**5**)		**5a**	62 (15:1)
3		Ar = *m*-MeOC$_6$H$_4$ (**6**)		**6a**	55 (5.4:1)
4		Ar = *o*-MeOC$_6$H$_4$ (**7**)		**7a**	63 (7.8:1)
5		Ar = *p*-CF$_3$C$_6$H$_4$ (**8**)		**8a**	54 (> 20:1)
6		Ar = *m*-CF$_3$C$_6$H$_4$ (**9**)		**9a**	60 (16:1)
7		Ar = *p*-BrC$_6$H$_4$ (**10**)		**10a**	56 (> 20:1)
8		Ar = 2-naphthyl (**11**)		**11a**	80 (12:1)
9		Ar = mesityl (**12**)		**12a**	72 (1.4:1)
10				**13a**	30 (1.4:1)
11		R = benzyl (**14**)		**14a**	27 (1.5:1)
12		R = isopropyl (**15**)		**15a**	< 5
13				**16a**	47

[a] Reagents and conditions: 1 equiv phthalimide, 3 equiv PhI(OAc)$_2$, 3 equiv 3-alken-1-ol, 10 mol% Pd(OAc)$_2$, 20 mol% AgBF$_4$ in 1.4 mL CH$_3$CN at 60°C.

carbon atom.[3a] The stereochemical outcome of the current reactions may be due to the more basic nature of the nucleophile (alkoxide versus acetate) and/or the intramolecularity of the reductive elimination event.

This transformation also presents a system in which the key σ-alkyl Pd^{IV} intermediate likely contains multiple different oxygen-donor ligands, including a tethered alkoxide (OR) and at least one acetate (OAc) ligand. This study clearly shows that C–OR bond formation is favored with high selectivity over C–OAc coupling. This may result from the intramolecularity of the ether-forming reductive elimination, but is more likely due to the higher basicity/nucleophilicity of the alkoxide relative to the OAc ligand. Consistent with this hypothesis, stoichiometric C–O bond-forming reductive elimination from Pd^{IV} aryl benzoate complexes was shown to proceed significantly faster with electron-donor substituents on the benzoate ligand.[18] Notably, understanding the relative rates of different C–X couplings at Pd^{IV} centers will likely be critical for the design of catalysts and oxidants for future Pd^{II}/Pd^{IV}-catalyzed transformations.

In conclusion, we have demonstrated that Pd-catalyzed alkene aminopalladation to generate σ-alkyl Pd species can be followed by intramolecular oxidative functionalization to stereoselectively afford tetrahydrofuran products. Mechanistic studies suggest that these transformations proceed by *cis* aminopalladation and subsequent C–O bond-forming reductive elimination with unusual retention of stereochemistry at the carbon atom. Future studies will further probe the mechanism and expand the scope of this reaction.

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[7] β-Hydride elimination remained competitive under all reaction conditions examined.

[8] The modest yield of **2a** was due to competitive formation of **2b** and competitive decomposition of alcohol **2** to an intractable mixture of oxidation products.

[9] Compound **2b′** was isolated from the Pd-catalyzed reaction of **1** with $PhI(O_2CPh)_2$ (see the Supporting Information for details). Compound **2b′** was formed in similar yield when the $Pd(OAc)_2$ catalyst was substituted with $Sc(OTf)_3$, $Cu(OTf)_2$, $BF_3{\cdot}Et_2O$, or $AuCl_3$. This result suggests that $Pd(OAc)_2$ is likely to act as a Lewis acid catalyst for this cyclization rather than to promote a rare 5-*endo-trig* oxypalladation/acetoxylation sequence.

[10] The role of $AgBF_4$ remains to be definitively elucidated. We speculate that it may render the Pd center more electrophilic and thereby promote coordination of the alcohol.

[11] For a rare example of 5-*endo-trig* oxypalladation, see: S. Saito, T. Hara, N. Takahashi, M. Hirai, T. Moriwake, *Synlett* **1992**, 237–238.

[12] A mechanism involving i) 5-*endo-trig* oxypalladation, ii) oxidation to Pd^{IV}, and iii) C–N bond-forming reductive elimination was also considered. However, this mechanism was deemed unlikely based on prior work (references [3a], [9], [11], [15b]). Furthermore, if this mechanism were operating, the exclusion of $PhI(OAc)_2$ would lead to formation of dihydrofuran products by β-hydride elimination from the σ-alkyl Pd product of 5-*endo-trig* oxypalladation. Such products were not observed in reactions of **3** under O_2.

[13] (*E*)-**3** did not form any THF product under these conditions; therefore, the stereochemical outcome of reactions with (*Z*)-**3** appears to reflect a stereospecific transformation of the *Z* isomer and *not* isomerization to (*E*)-**3** with subsequent aminocyclization.

[14] The low yield of **3b** appears to be due to fast catalyst decomposition under these conditions. The remainder of the material is predominantly (ca. 72%) a mixture of *E* and *Z* isomers of **3**. See the Supporting Information for a full discussion.

[15] For rare examples of *cis* aminopalladation, see reference [3a] and: a) J. E. Ney, J. P. Wolfe, *Angew. Chem.* **2004**, *116*, 3689–3692; *Angew. Chem. Int. Ed.* **2004**, *43*, 3605–3608; b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.

[16] Retention of configuration has been observed in some Pd-catalyzed oxidative transformations with $CuCl_2$; for example, see: G. Zhu, S. Ma, X. Lu, Q. Huang, *J. Chem. Soc. Chem. Commun.* **1995**, 271–273.

[17] For examples of oxidative C–O bond formation at Pd that proceed with inversion, see: a) J. E. Bäckvall, E. E. Bjoerkman, *J. Org. Chem.* **1980**, *45*, 2893–2898; b) P. M. Henry, M. Davies, G. Ferguson, S. Phillips, R. Restivo, *J. Chem. Soc. Chem. Commun.* **1974**, 112–113; c) P. K. Wong, J. K. Stille, *J. Organomet. Chem.* **1974**, *70*, 121–132.

[18] A. R. Dick, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 12790–12791.

