

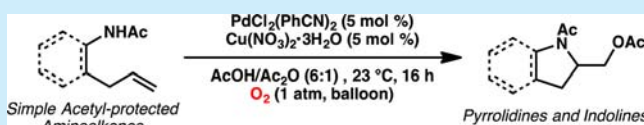
## Palladium-Catalyzed Aerobic Intramolecular Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate

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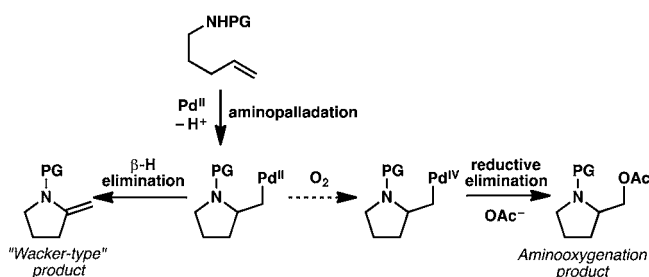
## Supporting Information

**ABSTRACT:** A mild aerobic intramolecular aminoacetoxylation method for the synthesis of pyrrolidine and indoline derivatives was achieved using molecular oxygen as the oxidant. A catalytic  $\text{NO}_x$  species acts as an electron transfer mediator to access a high-valent palladium intermediate as the presumed active oxidant.



Numerous alkene difunctionalization reactions enabled by palladium catalysts have been developed as efficient transformations for the construction of useful organic building blocks.<sup>1</sup> For example, palladium-catalyzed amination of alkenes has been applied as a new strategy to synthesize nitrogen-containing heterocycles.<sup>2</sup> Arising from a key aminopalladation step, an alkylpalladium(II) intermediate can undergo versatile pathways to generate different structural motifs (Scheme 1).<sup>2a</sup> In

Scheme 1. Aminopalladation and Subsequent Transformations



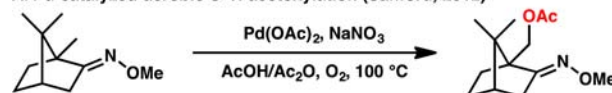
the past decade, amino-oxygenation has been achieved by oxidizing the alkylpalladium(II) intermediate into high-valent palladium ( $\text{Pd}^{\text{IV}}$  or  $\text{Pd}^{\text{III}}$ ) followed by C–O bond-forming reductive elimination. However, a stoichiometric amount of a strong oxidant, such as  $\text{PhI}(\text{OAc})_2$ <sup>3</sup> or NFSI,<sup>4</sup> is typically required to access the high-valent palladium intermediate. Recently, milder conditions have also been developed using  $\text{H}_2\text{O}_2$  as an environmentally tractable and inexpensive oxidant,<sup>5</sup> but aerobic conditions are still in high demand from a sustainable perspective.

A classic and well-studied example of a palladium-catalyzed aerobic homogeneous transformation is the Wacker process. This transformation was developed in the 1950s using  $\text{O}_2$  as the terminal oxidant in combination with a Cu salt as a redox cocatalyst to facilitate the reoxidation of  $\text{Pd}^0$  to  $\text{Pd}^{\text{II}}$ .<sup>6</sup> In contrast, reports of alkene difunctionalizations under aerobic conditions

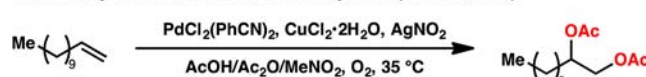
are rare, presumably because the oxidation of the intermediate alkylpalladium(II) species using  $\text{O}_2$  as the sole oxidant is kinetically challenging;<sup>7</sup> hence, care must be taken to avoid facile  $\beta$ -hydride elimination immediately (Scheme 1). Recently,  $\text{NO}_x$  species have been shown to be effective electron transfer mediators capable of facilitating the aerobic oxidation of alkylpalladium(II) intermediates to their high-valent counterparts.<sup>8</sup> Sanford and co-workers reported that nitrate/nitrite could serve as a redox cocatalyst in the aerobic acetoxylation of unactivated  $\text{C}(\text{sp}^3)\text{--H}$  bonds via C–O bond reductive elimination of a high-valent palladacycle (Scheme 2A).<sup>9</sup> Very

Scheme 2. Pd-Catalyzed Aerobic Methods Enabled by  $\text{NO}_x$  Species

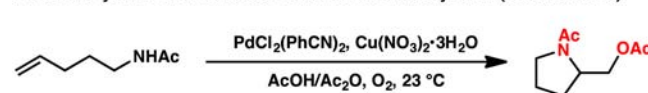
## A. Pd-catalyzed aerobic C–H acetoxylation (Sanford, 2012)



## B. Pd-catalyzed aerobic alkene diacetoxylation (Grubbs, 2014)



## C. Pd-catalyzed aerobic intramolecular aminoacetoxylation (This research)



recently, the Grubbs group reported a palladium-catalyzed aerobic alkene diacetoxylation method mediated by a catalytic amount of silver nitrite (Scheme 2B).<sup>10</sup> We reasoned that a palladium-catalyzed aerobic amino-oxygenation reaction might be possible using this electron transfer mediator strategy, as an  $\text{NO}_x$  species could be a kinetically suitable mediator in the

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aerobic oxidation of the alkylpalladium(II) intermediate formed after aminopalladation.

We started our investigation by subjecting acetyl-protected aminoalkene substrate **1a** to our previously published intermolecular diacetoxylation reaction conditions (Table 1,

Table 1. Reaction Optimization

entry	NO <sub>x</sub> source	T (°C)	solvent	yield (%) <sup>a,b</sup>
1	AgNO <sub>2</sub>	35	AcOH/Ac <sub>2</sub> O/MeNO <sub>2</sub> (10:5:3)	11
2	AgNO <sub>2</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	50
3	NaNO <sub>2</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	32
4	NBu <sub>4</sub> NO <sub>2</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	41
5	<i>i</i> -BuONO	35	AcOH/Ac <sub>2</sub> O (8:1)	48
6	NaNO <sub>3</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	35
7	Fe(NO <sub>3</sub> ) <sub>3</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	48
8	AgNO <sub>3</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	40
9	NOBF <sub>4</sub>	35	AcOH/Ac <sub>2</sub> O (8:1)	17
10 <sup>c</sup>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	35	AcOH/Ac <sub>2</sub> O (8:1)	56
11	—	35	AcOH/Ac <sub>2</sub> O (8:1)	0
12 <sup>c</sup>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	23	AcOH/Ac <sub>2</sub> O (6:1)	62

<sup>a</sup>Yields were determined by GC with tridecane as an internal standard.

<sup>b</sup>Methyl ketone and alkene isomers were observed as byproducts by <sup>1</sup>H NMR spectroscopy. <sup>c</sup>CuCl<sub>2</sub>·2H<sub>2</sub>O was not added.

entry 1).<sup>10</sup> We were delighted to find that the desired cyclization product **2a** was indeed formed on the first attempt, albeit in only 11% yield. In order to optimize the reaction, we altered the components of the solvent mixture and observed a substantial boost in yield by removing MeNO<sub>2</sub> as the cosolvent (entry 2). Since the NO<sub>x</sub> species acts as a key catalytic component, we examined a broad range of metal nitrates, metal nitrites, and alkyl nitrites. Most of the tested NO<sub>x</sub> species proved to be capable electron transfer mediators, affording the product in moderate yields (entries 2–10). However, the reaction did not give cyclized product without addition of any NO<sub>x</sub> sources (entry 11). Copper nitrate trihydrate gave the highest yield among the tested NO<sub>x</sub> species, while other types of NO<sub>x</sub> species showed marginally lower reactivity. Finally, by lowering the temperature to 23 °C and increasing the ratio of Ac<sub>2</sub>O, we achieved a further improvement in the yield (entry 12).

Next, we evaluated the substrate scope and functional group tolerance under our optimized conditions. Linear aliphatic amines with geminal disubstitutions were converted to the corresponding pyrrolidine products in good yields (Table 2). We also tested a series of *o*-allylaniline derivatives and obtained a variety of indoline derivatives **4a–i** in moderate to excellent yields (30–95% yield; Table 3). A variety of substituents and functional groups are well-tolerated, including fluoro, chloro, methyl ester, trifluoromethyl, and, to a lesser extent, nitro and cyano groups. Notably, we also tested the reaction under air, and product **4a** was obtained in good yield (80% yield; Table 3, entry 2).

On the basis of our observations and previous mechanistic studies, we propose the catalytic cycle shown in Figure 1. Aminopalladation of the substrate **1a** likely forms Pd(II) intermediate I, which can be oxidized to high-valent palladium

Table 2. Aminoacetoxylation of Aliphatic Amines<sup>a</sup>

$\text{PdCl}_2(\text{PhCN})_2$  (5 mol %)   
 $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (5 mol %)   
 $\text{AcOH}/\text{Ac}_2\text{O}$  (6:1)   
 $23^\circ\text{C}$ ,  $\text{O}_2$  (1 atm, balloon), 16 h

**1** **2**

entry	amine substrate	product	yield (%) <sup>b</sup>
1	<p><b>1a</b></p>	<p><b>2a</b></p>	69
2	<p><b>1b</b></p>	<p><b>2b</b></p>	75
3	<p><b>1c</b></p>	<p><b>2c</b></p>	83

<sup>a</sup>The amine substrate (0.5 mmol) was treated with PdCl<sub>2</sub>(PhCN)<sub>2</sub> (5 mol %) and Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (5 mol %) in AcOH/Ac<sub>2</sub>O (6:1, 10.5 mL) under an O<sub>2</sub> atmosphere (1 atm) at 23 °C for 16 h. <sup>b</sup>Yields of isolated products.

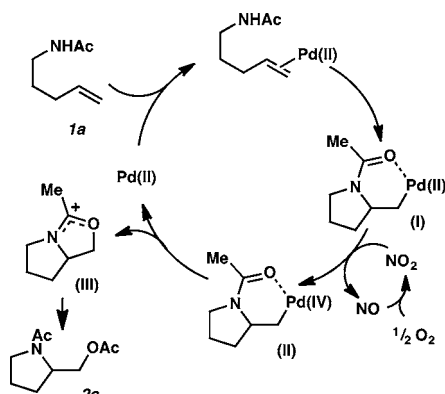
Table 3. *O*-Allylaniline Substrate Scope<sup>a</sup>

entry	product	R <sub>1</sub>	R <sub>2</sub>	yield (%) <sup>b</sup>
1	<b>4a</b>	H	H	87
2 <sup>c</sup>	<b>4a</b>	H	H	80
3	<b>4b</b>	Me	H	89
4	<b>4c</b>	H	Me	95
5	<b>4d</b>	F	H	88
6	<b>4e</b>	Cl	H	80
7	<b>4f</b>	COOMe	H	65
8	<b>4g</b>	CF <sub>3</sub>	H	58
9	<b>4h</b>	NO <sub>2</sub>	H	30
10	<b>4i</b>	CN	H	32

<sup>a</sup>The amine substrate (0.5 mmol) was treated with PdCl<sub>2</sub>(PhCN)<sub>2</sub> (5 mol %) and Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (5 mol %) in AcOH/Ac<sub>2</sub>O (6:1, 10.5 mL) under an O<sub>2</sub> atmosphere (1 atm) at 23 °C for 16 h. <sup>b</sup>Yields of isolated products. <sup>c</sup>Under 1 atm air instead of oxygen.

intermediate II by an NO<sub>x</sub> species (possibly NO<sub>2</sub> as suggested by previous literature<sup>11,12</sup>) with molecular oxygen as the terminal oxidant. We envision that high-valent palladium intermediate II can then undergo the C–O bond-forming reductive elimination to release cationic intermediate III,<sup>10</sup> which forms the aminoacetoxylation product **2a** upon acetylation. The source of additional oxygen atoms in the product has not been verified, but a previous <sup>18</sup>O labeling study showed that the oxygen came from the AcOH solvent.<sup>10</sup> Although the role of copper still remains elusive, the presence of copper is clearly advantageous, as a decrease in yield was observed when no source of Cu was added.<sup>13</sup> The other necessary solvent component, Ac<sub>2</sub>O, could possibly sequester H<sub>2</sub>O generated in the catalytic system.<sup>9</sup>

In summary, we have reported a mild, aerobic intramolecular aminoacetoxylation method. This chemistry provides another



**Figure 1.** Proposed catalytic cycle. For clarity, the full ligand set on palladium is not shown. Intermediate II could be a different high-valent palladium species such as Pd<sup>III</sup>.

example of a catalytic NO<sub>x</sub> species serving as a compatible electron transfer mediator to access a high-valent palladium species with molecular oxygen as the terminal oxidant. Ongoing mechanistic studies of this unique catalytic system, including a full stereochemical analysis, would be beneficial to the development of novel stereoselective methods. Finally, in today's renaissance of NO<sub>x</sub> redox chemistry, we anticipate that efficient utilization of the oxidation potential of O<sub>2</sub> will enable access to even more environmentally benign processes rather than consuming other high-energy/high-cost stoichiometric oxidants.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b02722](https://doi.org/10.1021/acs.orglett.6b02722).

Experimental procedures and compound characterization (PDF)

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### Notes

The authors declare no competing financial interest.

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