Organic LETTERS

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

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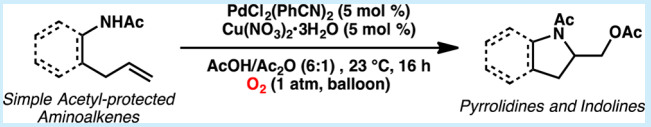
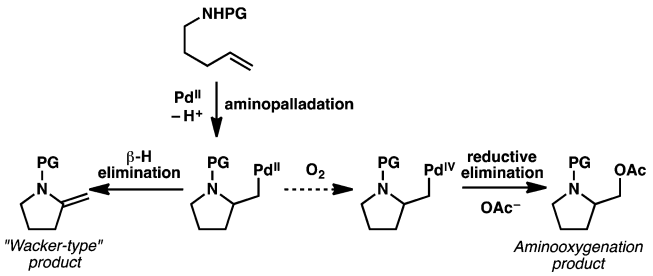
Supporting Information

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 NO_x species acts as an electron transfer mediator to access a high-valent palladium intermediate as the presumed active oxidant.



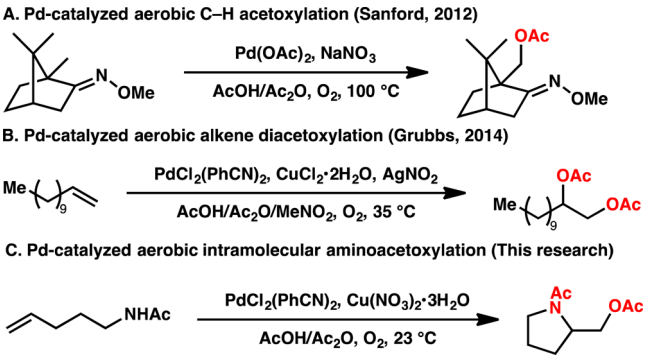
Numerous alkene difunctionalization reactions enabled by palladium catalysts have been developed as efficient transformations for the construction of useful organic building blocks.[1] For example, palladium-catalyzed amination of alkenes has been applied as a new strategy to synthesize nitrogen-containing heterocycles.[2] Arising from a key aminopalladation step, an alkylpalladium(II) intermediate can undergo versatile pathways to generate different structural motifs (Scheme 1).[2a] In the past decade, aminooxygenation has been achieved by oxidizing the alkylpalladium(II) intermediate into high-valent palladium (Pd^{IV} or Pd^{III}) followed by C−O bond-forming reductive elimination. However, a stoichiometric amount of a strong oxidant, such as $PhI(OAc)_2$[3] or NFSI,[4] is typically required to access the high-valent palladium intermediate. Recently, milder conditions have also been developed using H_2O_2 as an environmentally tractable and inexpensive oxidant,[5] but aerobic conditions are still in high demand from a sustainable perspective.

Scheme 1. Aminopalladation and Subsequent Transformations



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 O_2 as the terminal oxidant in combination with a Cu salt as a redox cocatalyst to facilite the reoxidation of Pd^0 to Pd^{II}.[6] In contrast, reports of alkene difunctionalizations under aerobic conditions are rare, presumably because the oxidation of the intermediate alkylpalladium(II) species using O_2 as the sole oxidant is kinetically challenging;[7] hence, care must be taken to avoid facile β-hydride elimination immediately (Scheme 1). Recently, 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.[8] Sanford and co-workers reported that nitrate/nitrite could serve as a redox cocatalyst in the aerobic acetoxylation of unactivated $C(sp^3)$−H bonds via C−O bond reductive elimination of a high-valent palladacycle (Scheme 2A).[9] Very recently, the Grubbs group reported a palladium-catalyzed aerobic alkene diacetoxylation method mediated by a catalytic amount of silver nitrite (Scheme 2B).[10] We reasoned that a palladium-catalyzed aerobic aminooxygenation reaction might be possible using this electron transfer mediator strategy, as an NO_x species could be a kinetically suitable mediator in the

Scheme 2. Pd-Catalyzed Aerobic Methods Enabled by NO_x Species



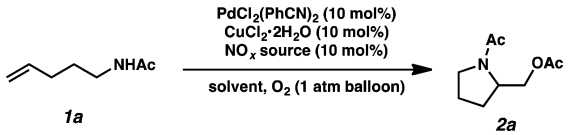
Received: September 9, 2016

DOI: 10.1021/acs.orglett.6b02722
Org. Lett. XXXX, XXX, XXX−XXX

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, entry 1).[10] 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 $MeNO_2$ as the cosolvent (entry 2). Since the NO_x 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_x 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_x sources (entry 11). Copper nitrate trihydrate gave the highest yield among the tested NO_x species, while other types of NO_x species showed marginally lower reactivity. Finally, by lowering the temperature to 23 °C and increasing the ratio of Ac_2O, we achieved a further improvement in the yield (entry 12).

Table 1. Reaction Optimization



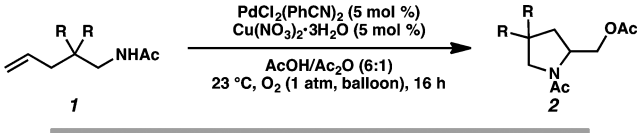
entry	NO_x source	T (°C)	solvent	yield (%)[a,b]
1	$AgNO_2$	35	$AcOH/Ac_2O/MeNO_2$ (10:5:3)	11
2	$AgNO_2$	35	$AcOH/Ac_2O$ (8:1)	50
3	$NaNO_2$	35	$AcOH/Ac_2O$ (8:1)	32
4	NBu_4NO_2	35	$AcOH/Ac_2O$ (8:1)	41
5	*i*-BuONO	35	$AcOH/Ac_2O$ (8:1)	48
6	$NaNO_3$	35	$AcOH/Ac_2O$ (8:1)	35
7	$Fe(NO_3)_3$	35	$AcOH/Ac_2O$ (8:1)	48
8	$AgNO_3$	35	$AcOH/Ac_2O$ (8:1)	40
9	$NOBF_4$	35	$AcOH/Ac_2O$ (8:1)	17
10[c]	$Cu(NO_3)_2·3H_2O$	35	$AcOH/Ac_2O$ (8:1)	56
11	–	35	$AcOH/Ac_2O$ (8:1)	0
12[c]	$Cu(NO_3)_2·3H_2O$	23	$AcOH/Ac_2O$ (6:1)	62

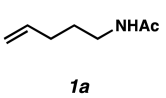
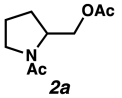
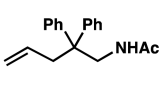
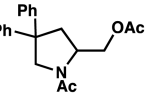
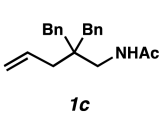
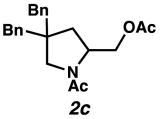
[a]Yields were determined by GC with tridecane as an internal standard. [b]Methyl ketone and alkene isomers were observed as byproducts by ^1H NMR spectroscopy. [c]$CuCl_2·2H_2O$ was not added.

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

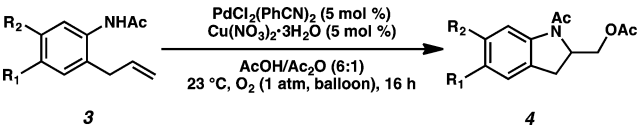
Table 2. Aminoacetoxylation of Aliphatic Amines[a]



entry	amine substrate	product	yield (%)[b]
1			69
2			75
3			83

[a]The amine substrate (0.5 mmol) was treated with $PdCl_2(PhCN)_2$ (5 mol %) and $Cu(NO_3)_2·3H_2O$ (5 mol %) in $AcOH/Ac_2O$ (6:1, 10.5 mL) under an O_2 atmosphere (1 atm) at 23 °C for 16 h. [b]Yields of isolated products.

Table 3. *O*-Allylaniline Substrate Scope[a]



entry	product	R_1	R_2	yield (%)[b]
1	**4a**	H	H	87
2[c]	**4a**	H	H	80
3	**4b**	Me	H	89
4	**4c**	H	Me	95
5	**4d**	F	H	88
6	**4e**	Cl	H	80
7	**4f**	COOMe	H	65
8	**4g**	CF_3	H	58
9	**4h**	NO_2	H	30
10	**4i**	CN	H	32

[a]The amine substrate (0.5 mmol) was treated with $PdCl_2(PhCN)_2$ (5 mol %) and $Cu(NO_3)_2·3H_2O$ (5 mol %) in $AcOH/Ac_2O$ (6:1, 10.5 mL) under an O_2 atmosphere (1 atm) at 23 °C for 16 h. [b]Yields of isolated products. [c]Under 1 atm air instead of oxygen.

intermediate **II** by an NO_x species (possibly NO_2 as suggested by previous literature[11,12]) 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**,[10] which forms the aminoacetoxylation product **2a** upon acetolysis. The source of additional oxygen atoms in the product has not been verified, but a previous ^{18}O labeling study showed that the oxygen came from the AcOH solvent.[10] 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.[13] The other necessary solvent component, Ac_2O, could possibly sequester H_2O generated in the catalytic system.[9]

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

DOI: 10.1021/acs.orglett.6b02722
Org. Lett. XXXX, XXX, XXX–XXX

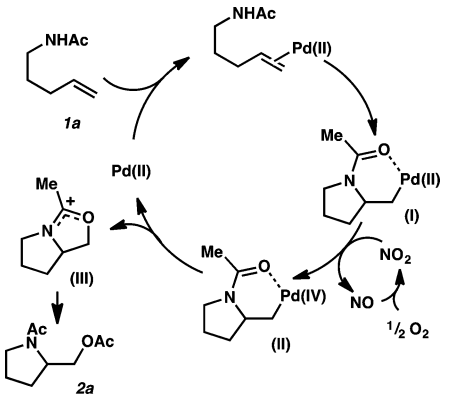


Figure 1. Proposed catalytic cycle. For clarity, the full ligand set on palladium is not shown. Intermediate **II** could be a different high-valent palladium species such as Pd^{III}.

example of a catalytic NO_x 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_x redox chemistry, we anticipate that efficient utilization of the oxidation potential of O_2 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.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the NIH (R01GM031332 and R01GM080269) and Caltech for financial support. Dr. Scott C. Virgil (Caltech) is thanked for assistance with GC analysis. Dr. David VanderVelde (Caltech) and Dr. Mona Shahgholi (Caltech) are acknowledged for help in structural determination and characterizations.

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DOI: 10.1021/acs.orglett.6b02722
Org. Lett. XXXX, XXX, XXX−XXX