HHS Public Access

Author manuscript

Org Lett. Author manuscript; available in PMC 2017 November 04.

Published in final edited form as:

Org Lett. 2016 November 04; 18(21): 5449–5451. doi:10.1021/acs.orglett.6b02722.

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

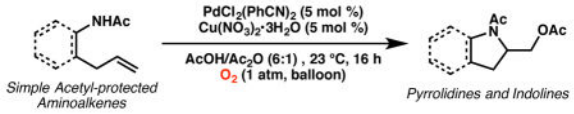
Jiaming Li, **Robert H. Grubbs***, and **Brian M. Stoltz***

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

Abstract

A mild aerobic intramolecular aminoacetoxylation method for the synthesis of pyrrolidine and indoline derivatives was achieved using molecular oxygen as oxidant. A catalytic NO_x species acts as an electron transfer mediator to access a high-valent palladium intermediate as the presumed active oxidant.

Graphical abstract



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.

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

*Corresponding Author: rhg@caltech.edu; stoltz@caltech.edu.

Notes

The authors declare no competing financial interest.

Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

O_2 as the terminal oxidant in combination with a Cu salt as a redox co-catalyst 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 co-catalyst in the aerobic ace-toxylation 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 aerobic oxidation of the alkylpalladium(II) intermediate formed after aminopalladation.

We started our investigation by subjecting acetyl-protected ami-noalkene 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 co-solvent (entry 2). Since the NO_x species is acting 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 yield (entries 2–10). However, the reaction did not give cyclized product without adding 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 of yield (entry 12).

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

Based on 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 intermediate **II** by an NO_x species (possibly be 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 a cationic intermediate **III**,[10] which forms the aminoacetoxylation product **2a** upon ace-tolysis. The source of additional oxygen atoms in

the product is not 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 report a mild, aerobic intramolecular aminoace-toxylation method. This chemistry provides another 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, including a full stereochemical analysis, of this unique catalytic system would be beneficial to the development of novel stereoselec-tive methods. Finally, in today's renaissance of NO_x redox chemistry, we anticipate 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to 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.

References

1. Selected reviews for Pd-catalyzed alkene difunctionalization reactions: Muñiz K. Angew Chem Int Ed Engl. 2009; 48:9412–9423. [PubMed: 19882603] Xu LM, Li BJ, Yang Z, Shi ZJ. Chem Soc Rev. 2010; 39:712–733. [PubMed: 20111789] Sehnal P, Taylor RJK, Fairlamb IJS. Chem Rev. 2010; 110:824–889. [PubMed: 20143876] Hickman AJ, San-ford MS. Nature. 2012; 484:177–185. [PubMed: 22498623] Coombs JR, Morken JP. Angew Chem Int Ed. 2016; 55:2636–2649.
2. For Pd-catalyzed amination reactions: McDonald RI, Liu G, Stahl SS. Chem Rev. 2011; 111:2981–3019. [PubMed: 21428440] Liu G, Stahl SS. J Am Chem Soc. 2007; 129:6328–6335. [PubMed: 17439217] Bertrand MB, Neukom JD, Wolfe JP. J Org Chem. 2008; 73:8851–8860. [PubMed: 18942792] Muñiz K, Hövelmann CH, Streuff J. J Am Chem Soc. 2008; 130:763–773. [PubMed: 18081279] Ye X, Liu G, Popp BV, Stahl SS. J Org Chem. 2011; 76:1031–1044. [PubMed: 21250706]
3. Selected examples of alkene difunctionalization using high-valent iodine reagents: Alexanian EJ, Lee C, Sorensen EJ. J Am Chem Soc. 2005; 127:7690–7691. [PubMed: 15913354] Streuff J, Hövelmann CH, Nieger M, Muñiz K. J Am Chem Soc. 2005; 127:14586–14587. [PubMed: 16231907] Liu G, Stahl SS. J Am Chem Soc. 2006; 128:7179–7181. [PubMed: 16734468] Desai LV, Sanford MS. Angew Chem Int Ed Engl. 2007; 46:5737–5740. [PubMed: 17600808] Neufeldt SR, Sanford MS. Org Lett. 2013; 15:46–49. [PubMed: 23249401] Martínez C, Wu Y, Weinstein AB, Stahl SS, Liu G, Muñiz K. J Org Chem. 2013; 78:6309–6315. [PubMed: 23734834] Chen H, Kaga A, Chiba S. Org Lett. 2014; 16:6136–6139. [PubMed: 25422848]
4. For alkene difunctionalization using NFSI as oxidant: Sib-bald PA, Rosewall CF, Swartz RD, Michael FE. J Am Chem Soc. 2009; 131:15945–15951. [PubMed: 19824646] Liskin DV, Sibbald PA, Rosewall CF, Michael FE. J Org Chem. 2010; 75:6294–6296. [PubMed: 20738146] Engle KM, Mei TS, Wang X, Yu JQ. Angew Chem Int Ed. 2011; 50:1478–1491.Ingalls EL, Sibbald PA, Kaminsky W, Michael FE. J Am Chem Soc. 2013; 135:8854–8856. [PubMed: 23734771]

5. (a) Zhu H, Chen P, Liu G. J Am Chem Soc. 2014; 136:1766–1769. [PubMed: 24417595] (b) Zhu H, Chen P, Liu G. Org Lett. 2015; 17:1485–1488. [PubMed: 25742490]
6. For reviews of Wacker oxidation and selected examples: Takacs JM, Jiang X. Curr Org Chem. 2003; 7:369–396.Cornell CN, Sigman MS. Inorg Chem. 2007; 46:1903–1909. [PubMed: 17348721] Keith JA, Henry PM. Angew Chem Int Ed Engl. 2009; 48:9038–9049. [PubMed: 19834921] Dong JJ, Browne WR, Feringa BL. An-gew Chem Int Ed Engl. 2015; 54:734–744.Trend RM, Ramtohul YK, Stoltz BM. J Am Chem Soc. 2005; 127:17778–17788. [PubMed: 16351107] Trend RM, Ramtohul YK, Ferreira EM, Stoltz BM. Angew Chem Int Ed. 2003; 42:2892–2895.Wickens ZK, Morandi B, Grubbs RH. Angew Chem Int Ed. 2013; 52:11257–11260.Wickens ZK, Skakuj K, Morandi B, Grubbs RH. J Am Chem Soc. 2014; 136:890–893. [PubMed: 24410719]
7. (a) Zhang J, Khaskin E, Anderson NP, Zavalij PY, Veder-nikov AN. Chem Commun. 2008; 31:3625–3627.(b) Wang A, Jiang H, Chen H. J Am Chem Soc. 2009; 131:3846–3847. [PubMed: 19292485] (c) Zhang YH, Yu JQ. J Am Chem Soc. 2009; 131:14654–14655. [PubMed: 19788192] (d) Tang F, Zhang Y, Rath NP, Mirica LM. Organometallics. 2012; 31:6690–6696.(e) Khusnutdinova JR, Rath NP, Mirica LM. J Am Chem Soc. 2012; 134:2414–2422. [PubMed: 22239690]
8. Fairlamb IJS. Angew Chem Int Ed. 2015; 54:10415–10427.Gerken JB, Stahl SS. ACS Cent Sci. 2015; 1:234–243. [PubMed: 27162977] Liang YF, Li X, Wang X, Yan Y, Feng P, Jiao N. ACS Catal. 2015; 5:1956–1963.Zultanski SL, Stahl SS. J Organomet Chem. 2015; 793:263–268.For a review on NO_2/NO redox cycle in transition-metal chemistry, see: Ford PC, Lorkovic IM. Chem Rev. 2002; 102:993–1018. [PubMed: 11942785]
9. Stowers KJ, Kubota A, Sanford MS. Chem Sci. 2012; 3:3192–3194. [PubMed: 23050075]
10. Wickens ZK, Guzmán PE, Grubbs RH. Angew Chem Int Ed. 2014; 54:236–240.
11. (a) Theimann, M., Scheibler, E., Wiegand, KW. Nitric Acid, Nitrous Acid, and Nitrogen Oxides. Ullmann's Encyclo-pedia of Industrial Chemistry. Wiley-VCH; Weinheim: 2005. (b) Laue, W., Theimann, M., Scheibler, E., Wiegand, KW. Nitrates and Nitrites. Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH; Weinheim: 2005.
12. Cámpora J, Palma P, del Río D, Carmona E, Graiff C, Tiripicchio A. Organometallics. 2003; 22:3345–3347.
13. See Table S1 in Supporting Information for control experiments, and Table S2 for catalysts ratio studies. Possible heterobi-metallic Pd/Cu catalyst species were suggested by previous computational studies: Jiang YY, Zhang Q, Yu HZ, Fu Y. ACS Catal. 2015; 5:1414–1423.

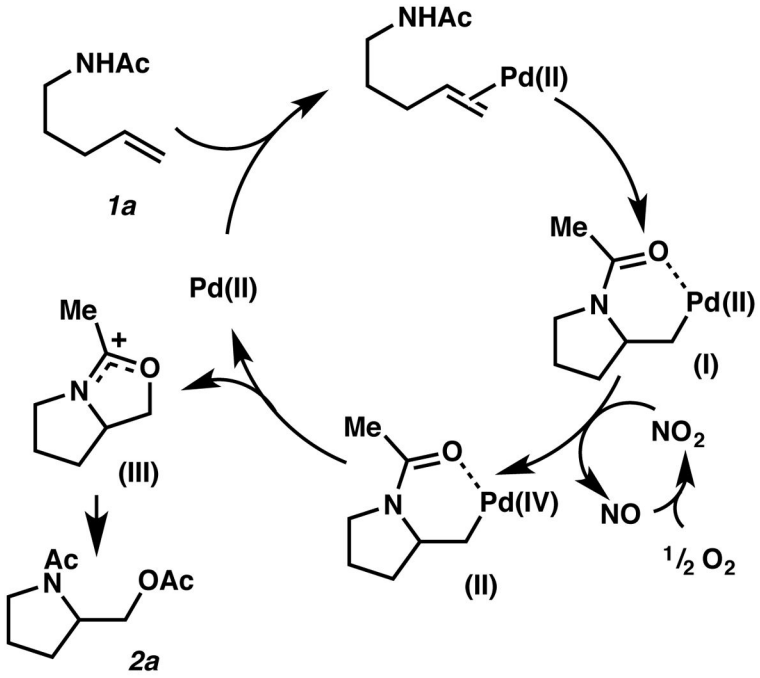
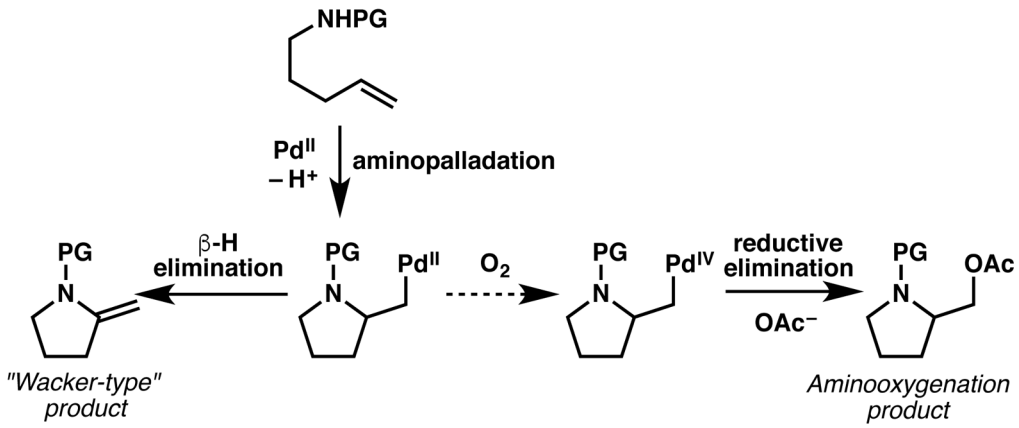
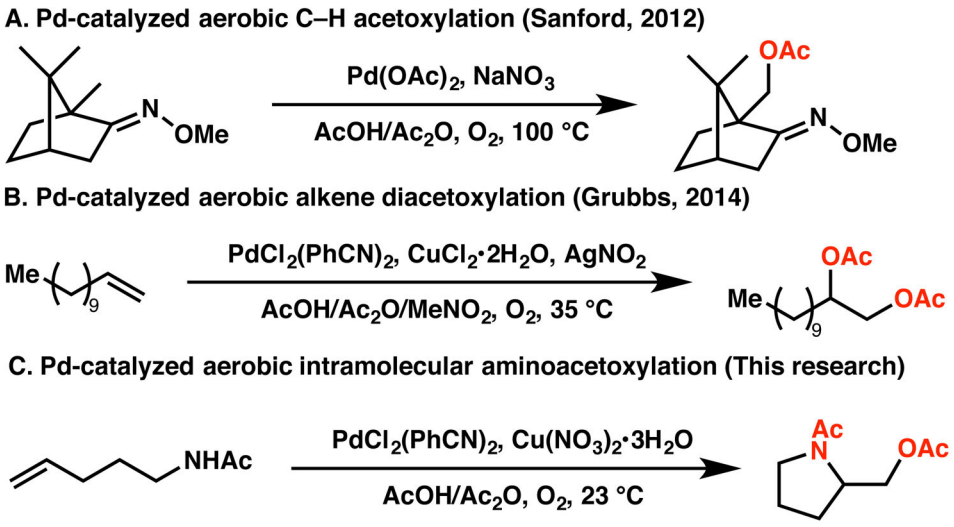


Figure 1.

Proposed Catalytic Cycle. The full ligand set on palladium is not shown for clarity. Intermediate (II) could be a different high-valent palladium species such as Pd^{III}.



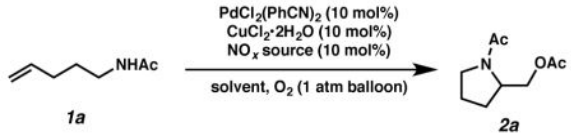
Scheme 1.
Aminopalladation and Subsequent Transformations



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

Table 1

Reaction Optimization



1a *2a*

entry	NO_x source	temperature (°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	*iso*-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]	$Cu(NO_3)_2 \cdot 3H_2O$	35	$AcOH/Ac_2O$ (8:1)	56
11	–	35	$AcOH/Ac_2O$ (8:1)	0
12[c]	$Cu(NO_3)_2 \cdot 3H_2O$	23	$AcOH/Ac_2O$ (6:1)	62

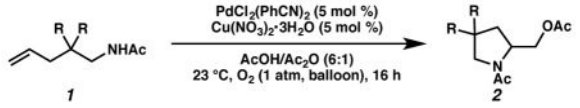
[a] Yields were determined by GC with tridecane as an internal standard.

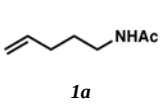
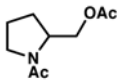
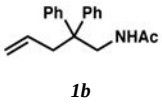
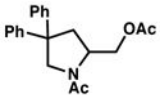
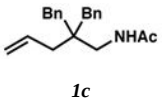
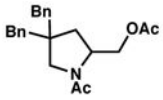
[b] Methyl ketone and alkene isomers were observed as byproducts by ^1H NMR.

[c] $CuCl_2 \cdot 2H_2O$ not added.

Table 2

Aminoacetoxylation of Aliphatic Amines



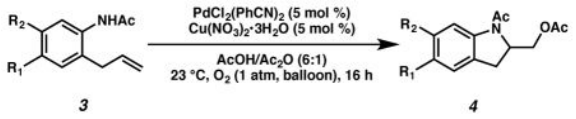
entry	amine substrate	product	yeild (%)[b]
1	 *1a*	 *2a*	69
2	 *1b*	 *2b*	75
3	 *1c*	 *2c*	83

[a] Amine substrate (0.5 mmol) treated with $PdCl_2(PhCN)_2$ (5 mol %), $Cu(NO_3)_2 \cdot 3H_2O$ (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] Yield of isolated product.

Table 3

O-allylaniline Substrate Scope



3 *4*

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] Amine substrate (0.5 mmol) treated with $PdCl_2(PhCN)_2$ (5 mol %), $Cu(NO_3)_2 \cdot 3H_2O$ (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] Yield of isolated product.

[c] Under 1 atm air instead of oxygen.