ChemInform Abstract: Pd-Catalyzed Intramolecular Aminohydroxylation of Alkenes with Hydrogen Peroxide as Oxidant and Water as Nucleophile.

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JANUARY 2014

Impact Factor: 12.11 · DOI: 10.1021/ja412023b · Source: PubMed

3 AUTHORS:

Peter Zhu
Chinese Academy of Sciences
3 PUBLICATIONS **35** CITATIONS
SEE PROFILE

Pinhong Chen
Chinese Academy of Sciences
56 PUBLICATIONS **1,050** CITATIONS
SEE PROFILE

Guosheng Liu
Chinese Academy of Sciences
83 PUBLICATIONS **2,633** CITATIONS
SEE PROFILE

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Pd-Catalyzed Intramolecular Aminohydroxylation of Alkenes with Hydrogen Peroxide as Oxidant and Water as Nucleophile

Haitao Zhu, Pinhong Chen, and Guosheng Liu*

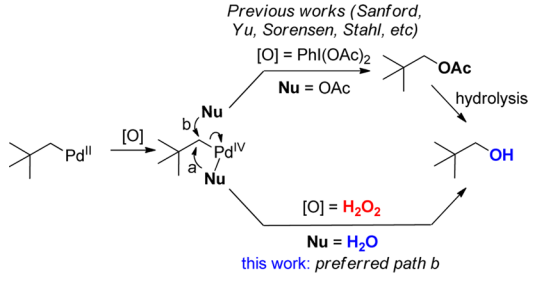
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: A palladium-catalyzed intramolecular aminohydroxylation of alkenes was developed, in which H_2O_2 was applied as the sole oxidant. A variety of related alkyl alcohols could be successfully obtained with good yields and excellent diastereoselectivities, which directly derived from oxidation cleavage of alkyl C-Pd bond by H_2O_2. Facile transformation of these products provided a powerful tool toward the synthesis of 2-amino-1,3-diols and 3-ol amino acids. Preliminary mechanistic studies revealed that major nucleophilic attack of water (S_N2 type) at high-valent Pd center contributes to the final C-O(H) bond formation.

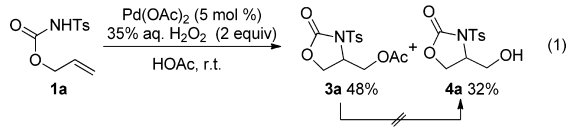
Palladium-catalyzed oxidative reactions are important transformation in organic synthesis.[1] In the past decade, high-valent palladium catalysis has been received much attention, and a number of palladium-catalyzed oxidative C-H functionalization and alkene difunctionalization reactions have been developed.[2] Among these reactions, stoichiometric amount of strong oxidants are generally required to generate Pd^{IV} (or Pd^{III}) intermediates, which readily undergoes reductive elimination to yield the new chemical bonds.[3,4] For instance, alkyl C-Pd^{II} species, which was generated from C-H activation or nucleopalladation of alkene, can be efficiently oxidized by $PhI(OAc)_2$ or other oxidant to deliver alkyl C-OAc,[5] which can be further transformed to related alkyl alcohols (Scheme 1, top).

Scheme 1. Oxygenation of Alkyl C-Pd^{II} Intermediates



However, these reactions often produce a large amount of byproducts due to utilizing above oxidants. In order to avoid these byproducts, exploration of environmental benign, such as dioxygen or H_2O_2 to achieve these oxidative transformations is an important new trend.[6] Among them, 30−35% aqueous H_2O_2 solution is a preferred oxidant with regard to two aspects: (1) 30−35% aqueous H_2O_2 solution is broadly used in industry, and those processes usually present "green" properties;[7] (2) H_2O_2 has enough oxidative potential to oxidize Pd^{II} species. Elegant studies from the Vedernikov group demonstrated that H_2O_2 can oxidize aryl C-Pd^{II} complex with special ligand to yield aryl C-Pd^{IV}(OH) complex.[6a,8] We hypothesized that if related alkyl C-Pd^{IV}(OH) could undergo reductive elimination, or external water could act as a potential nucleophile to react with this Pd^{IV} intermediate, the direct formation of alkyl alcohol product might be expected (Scheme 1, bottom). In Shilov reaction, water was reported as a nucleophile to attack carbon center of Me-Pt^{IV} complex (S_N2 type), which accounted for the formation of MeOH.[9] But the related water substitution reaction is quite rare due to its poor nucleophilicity.[10] Herein, we report a novel Pd-catalyzed intramolecular aminohydroxylation of alkenes using H_2O_2 as oxidant under mild reaction conditions. Notably, the final C-O bond formation was mainly achieved through external water substitution at the carbon center of alkyl C-Pd^{IV} (or Pd^{III}) intermediate via S_N2-type nucleophilic attack pathway (Scheme 1, bottom).

Recently, our group revealed that H_2O_2 can be used as the sole oxidant to achieve Pd-catalyzed chlorination of alkenes.[11] However, acidic solvent (HOAc) is crucial for these transformations. During further studies, we were delighted to find that an aminohydroxylation product **4a** (32% yield) was observed in the absence of chloride additives, along with aminoacetoxylation product **3a** in 48% yield. Further treatment of **3a** under standard condition could not deliver product **4a** (eq 1). Thus, we believed that **4a** should be generated from direct reductive elimination of alkyl-Pd^{IV}(OH) or external water nucleophilic attack at carbon center of alkyl-Pd^{IV} complex.



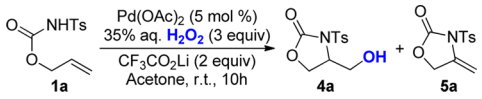
(1)

Inspired by the above understanding, we thought replacing an acidic solvent with another solvent could avoid the formation of **3a**, which is beneficial for aminohydroxylation. After extensive screening of different reaction parameters, the optimized reaction condition was obtained as follows (Table 1): $Pd(OAc)_2$ (5 mol %), 35% aqueous H_2O_2 (3 equiv), LiO_2CCF_3 (2 equiv), and substrate **1a** in acetone at room temperature. The reaction

Received: November 28, 2013
Published: January 13, 2014

   dx.doi.org/10.1021/ja412023b | J. Am. Chem. Soc. 2014, 136, 1766−1769

Table 1. Optimization of the Reaction Conditions[a]



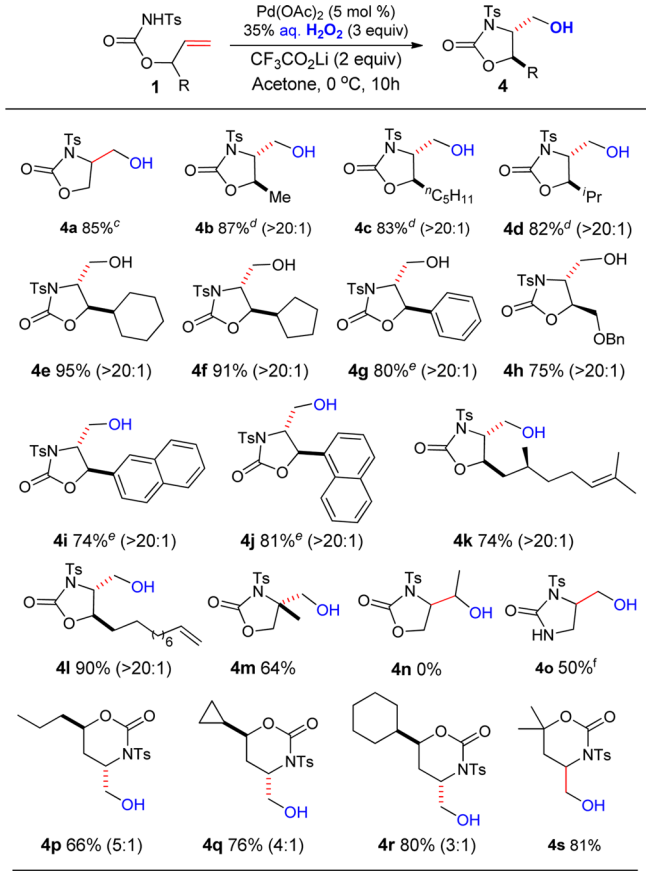
entry	reaction condition	yield (%)[b] 4a	5a
1	**standard condition**	**85**	7
2	no Pd catalyst	0	0
3	$Pd(O_2CCF_3)_2$ instead of $Pd(OAc)_2$	75	7
4	$Pd(CH_3CN)_2Cl_2$ instead of $Pd(OAc)_2$	66	5
5	$Pd(dba)_2$ instead of $Pd(OAc)_2$	20	10
6	**no CF_3CO_2Li**	**80**	**14**
7	CF_3CO_2Na instead of CF_3CO_2Li	35	23
8[c]	CH_3CO_2Li instead of CF_3CO_2Li	40	32
9	CH_3CO_2H instead of CH_3CO_2Li	33	15
10	LiOH instead of CH_3CO_2Li	0	40
11	urea-H_2O_2 instead of aq H_2O_2	50	28
12	Na_2CO_3-H_2O_2 instead of aq H_2O_2	20	5
13	**dioxane instead of acetone**	**80**	**9**
14	THF instead of acetone	67	5
15	toluene instead of acetone	61	9
16	DMF instead of acetone	33	15
17	NMP instead of acetone	trace	30
18	CH_3CN instead of acetone	trace	trace

[a]All the reactions were run at 0.2 mmol scale. [b]Yield obtained by 1H NMR with 1,3,5-trimethoxylbenzene as internal standard. [c]21% aminoacetoxylation product.

provided the desired product **4a** in 85% yield, along with 7% aza-Wacker product **5a** (entry 1). The structure of **4a** was confirmed by X-ray crystallography. The palladium catalyst was required for the successful transformation and $Pd(OAc)_2$ gave the best yield (entry 2−5). The presence of LiO_2CCF_3 is beneficial to give the better result (entry 1 vs 6). However, replacing LiO_2CCF_3 with LiO_2CCH_3, NaO_2CCF_3, or HO_2CCF_3 diminished the reaction yields (entries 7−9). Addition of LiOH could inhibit the aminohydroxylation reaction (entry 10). For the H_2O_2 source, aqueous solution is better than urea·H_2O_2 and Na_2CO_3·H_2O_2 complexes (entries 11−12). Finally, screening of solvents revealed that acetone and dioxane were the best for the aminohydroxylation; THF and toluene were also suitable to give the desired product in moderate yields. However, polar solvents, such as DMF, NMP, and CH_3CN, were not compatible for this reaction (entry 13−18).

With the optimized condition in hand, substrate scope was further examined (Table 2). The substrates synthesized from allylic alcohols were first investigated. All those reactions proceeded very well to provide the desired aminohydroxylation products (**4a**−**4j**) in good yields. For all these γ-substituted terminal alkenes, excellent diastereoselectivities (>20:1) were observed to give single *trans*-isomer products. Interestingly, for the substrates (**1k** and **1l**) bearing two double bonds, the reactions selectively occurred at the double bond of allylic moiety to give products **4k** and **4l** in excellent yields, and another double bond remained intact. It is worth noting that products **4g**, **4i**, and **4j** were obtained from corresponding allylic alcohols with two steps in a one-pot reaction. The 1,1-disubstituted substrate **1m** also afforded product **4m** in 64% yield. But internal alkene (**1n**) was not compatible to the reaction condition. Furthermore, substrate **1o** which was derived from allylic amine was also good for this transformation to give product **4o** in moderate yield.

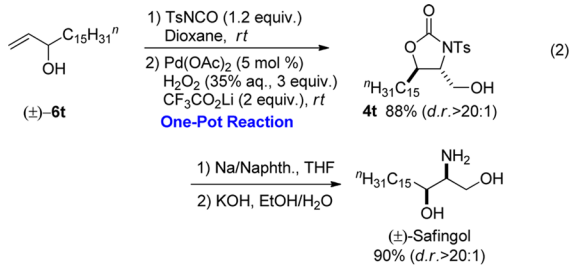
Table 2. Substrate Scope[a]



[a]Reaction condition: substrate (0.2 mmol), H_2O_2 (35% aq, 3 equiv), $Pd(OAc)_2$ (5 mol %), CF_3COOLi (2 equiv) in acetone (2 mL) at 0 °C. [b]Isolated yield, the data in pharenthesis is the ratio of *trans*:*cis*. [c]Room tempertaure. [d]At −5 °C. [e]Reaction was conducted from allylic alcohol in one pot. [f]Without CF_3COOLi.

Beside above allylic alcohol-type substrates, homoallylic substrates **1p**−**1s** were also compatible for the current reaction condition to give aminohydroxylation products **4p**−**4s** in good to excellent yields, *albeit* with moderate diastereoselectivities (3−5:1).

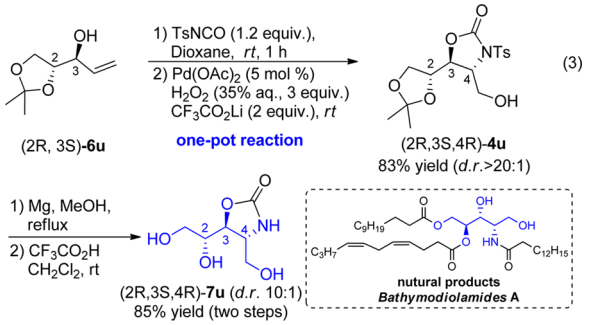
2-Amino-1,3-diol is an important moiety in natural products and bioactive compounds. For instance, safingol, which contains 2-amino-1,3-diol backbond, has been considered as a valuable candidate for antineoplastic and antipsoriatic drugs and is extensively investigated for its role in cell regulation signal transduction and inhibition of protein kinase C.[12] With the current transformation, safingol could be efficiently synthesized from simple allylic alcohol **6t**. As shown in eq 2, the single isomer



of *trans*-**4t** was provided from the reaction of **6t** in high yield and excellent diastereoselectivity in one pot, and further deprotection

dx.doi.org/10.1021/ja412023b | J. Am. Chem. Soc. 2014, 136, 1766−1769

and ring-opening processes delivered racemic safingol in 90% yield. In addition, chiral allylic alcohol (2*R*,3*S*)-**6u** could also be converted to the product (2*R*,3*S*,4*R*)-**4u** in 83% yield with high dr selectivity. Final deprotection steps provided chiral amino-tetraol carbamate (2*R*,3*S*,4*R*)-**7u** in good yields (two steps, 85% overall yields, eq 3). It is worth noting that the core of

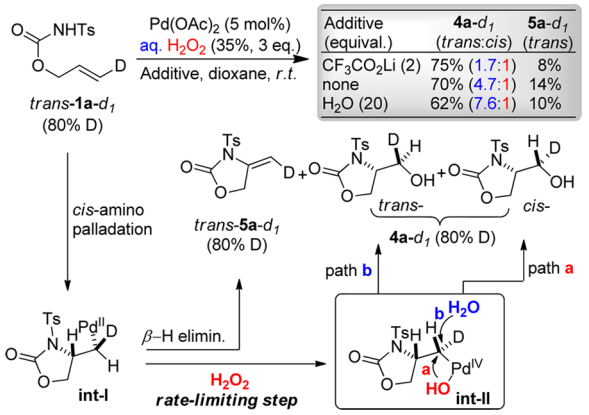


(3)

(2*R*,3*S*,4*R*)-**7u** is an enantiomer of the core of natural products bathymodiolamides A and B, which exhibit the potential activity to inhibit the growth of two cancer cell lines (cervical and breast cancer).[13]

In order to gain insights into the stereochemical course of the C-N and C-O bond forming steps, *trans*-**1a**-d_1 (80% D) was subjected to the standard condition with different additives (Scheme 2). First, only a single isomer *trans*-**5a**-d_1 was obtained

Scheme 2. Mechanism in Standard Condition

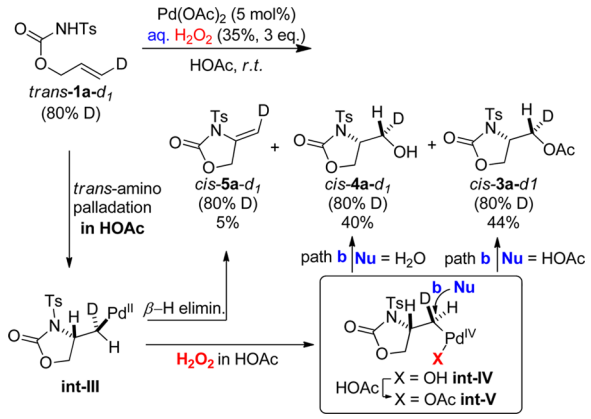


as a side product in ~10% yield in the above reactions, which suggest the reaction involved a *cis*-aminopalladation process to give alkyl C-Pd(II) species (**int-I**). Meanwhile, these reactions also afforded the mixture of two isomers *cis*-**4a**-d_1 and *trans*-**4a**-d_1, in which the *trans*-isomer is predominant. And the ratio of *cis*- and *trans*-isomer varied significantly according to the different additives. For instance, the ratio of *trans*/*cis*-**4a**-d_1 was increased from 1.7:1 to 4.7:1 by removal of CF_3CO_2Li and further increased to 7.6:1 by adding exogenous water.

With the above results, we believe the high-valent palladium complex **int-II** might be involved to account for C-OH bond forming (Scheme 2):[14] (1) *cis*-**4a**-d_1 was delivered from the direct reductive elimination of Pd^{IV} complex **int-II**, resulting the retention of the C(sp^3) center (path **a**); and this process could be promoted by addition of CF_3CO_2Li (see above). (2) For the case of *trans*-**4a**-d_1, the reaction should involve a S_N2 type nucleophilic attack pathway due to the inversion of the C(sp^3) center, and external water acts as a nucleophile (path **b**).[15] As shown in Scheme 2, addition of extra water resulting in highly selective *trans*-**4a**-d_1 formation was consistent with S_N2 nucleophilic pathway **b**. Furthermore, the reaction rate was significantly enhanced by increasing the concentration of H_2O_2 (see the SI), implying that oxidation of Pd^{II} should contribute to the rate-limiting step.

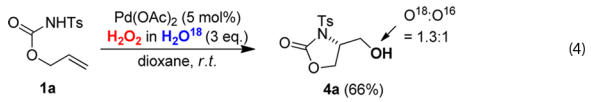
Interestingly, when the reaction was conducted in HOAc, the opposite stereoconfiguration products were obtained (Scheme 3). The reaction of *trans*-**1a**-d_1 gave the mixture of *cis*-**4a**-d_1 and

Scheme 3. Mechanism in HOAc



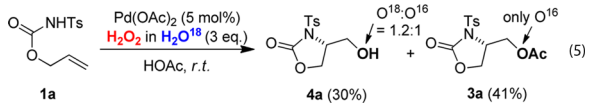
cis-**3a**-d_1 in high diastereoselectivities (>20:1), combined with a small amount of *cis*-**5a**-d_1. The formation of *cis*-**5a**-d_1 indicated that the reaction should be initiated by *trans*-aminopalladation to give **int-III**.[16] After oxidation by H_2O_2, high-valent palladium complex **int-IV** possibly reacts with solvent HOAc to give complex **int-V**. The selective formation of *cis*-**4a**-d_1 and *cis*-**3a**-d_1 revealed that the C-O bond formation undergoes S_N2 nucleophilic attack by H_2O or HOAc at the carbon center of high-valent palladium complex **int-IV** or **int-V**.

Critical evidence was obtained in the isotope labeling experiments by using H_2O_2 in H_2O^{18} solution.[17] The reaction in dioxane led to the formation of [^{18}O]-**4a** and **4a** with the ratio of 1.3:1 (eq 4), and this result was unequivocally confirmed by



(4)

mass spectrometry. In addition, the mixture of [^{18}O]-**4a** and **4a** with the similar ratio was obtained in the same reaction in AcOH (eq 5). Interestingly, this reaction afforded product **3a** without ^{18}O incorporation, which also implied the formation of **4a** was not derived from product **3a**.



(5)

Vedernikov has reported that the C-O reductive elimination of $LPt^{IV}(OH)_2Me$ in H_2O^{18} via water nucleophilic substitution is much faster than that of $^{16}OH/^{18}OH$ exchange in Pt center. In addition, there is no oxygen exchange between H_2O_2 and H_2O^{18} in the absence or presence of palladium catalyst.[16] Thus, the formation of [^{18}O]-**4a** implied that H_2O^{18} should act a nucleophile to attack the high-valent Pd complex to construct a C-O^{18}H bond via a favorable S_N2-type substitution. To the best

dx.doi.org/10.1021/ja412023b | J. Am. Chem. Soc. 2014, 136, 1766−1769

of our knowledge, this is a rare example of oxidative cleavage of a C-Pd bond involving water as the nucleophile to give an alcohol product. However, the above mechanism could not address the formation of [^{16}O]-**4a**.[18] We assumed that alkyl Pd(IV)^{16}OH complex[19] could also act as a nucleophile to compete with water, allowing for nucleophilic attack of another alkyl Pd(IV)^{16}OH to give [^{16}O]-**4a**.[20]

In conclusion, we have developed a simple catalytic system to achieve intramolecular aminohydroxylation of alkenes with Pd catalyst under mild reaction conditions. In this transformation, aq H_2O_2 solution plays two roles to achieve C-OH bond formation via a favorable S_N2-type substitution pathway: H_2O_2 as oxidant and water as nucleophile reacting with high-valent palladium intermediate to give a C-O bond. Further application of this aminohydroxylation reaction is in progress.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

gliu@mail.sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Basic Research Program of China (973-2011CB808700), the National Nature Science Foundation of China (nos. 21225210, 21202185, and 21121062), the Science and Technology Commission of the Shanghai Municipality (11JC1415000), and the CAS/SAFEA International Partnership Program for Creative Research Teams.

■ REFERENCES

(1) (a) *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. A., Eds.; Pergamon Press: Oxford, 1991.

(2) Some reviews on high-valent Pd catalysis: (a) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (b) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (c) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478. (d) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177. (e) Chen, P.; Liu, G.; Engle, K. M.; Yu, J.-Q. In *Science of Synthesis: Organometallic Complexes of Palladium*, Stoltz, B. M., Ed.; Thieme: Germany, 2013; Vol *1*, p 63.

(3) For selective examples: (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (c) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (e) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (f) Iglesias, A.; Alvarez, R.; de Lera, A. R.; Muniz, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2225.

(4) For selective examples: (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (c) Michael, F. E.; Sibbald, P. A.; Cochran, B. M. *Org. Lett.* **2008**, *10*, 793. (d) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150. (e) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.

(5) For selective examples: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Cuo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (d) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (e) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (f) Wang, A.; Jiang, H. *J. Org. Chem.* **2010**, *75*, 2321. (g) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284.

(6) For some reviews: (a) Vedernikov, A. N. *Acc. Chem. Res.* **2012**, *45*, 803. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Piera, J.; Backvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506. (d) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977.

(7) For safety guideline on H_2O_2: (a) http://en.wikipedia.org/wiki/Hydrogen_peroxide. (b) http://h2o2.evonik.com/product/h2o2/en/pages/h2o2-safety-training-video.aspx.

(8) Oxidation of stoichiometric amount of Pd(II) by H_2O_2: Oloo, W.; Zavalij, P. Y.; Zhang, J.; Khashin, E.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2010**, *132*, 14400.

(9) For Shilov reaction: (a) Shilov, A. E.; Shul'pin, G. B. *Activation and Catalytic Reactions of Saturated Hydrocarbons in the presence of Metal Complexes*, Kluwer, Dordrecht, 2000. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Kushch, K. A.; Lavrushko, V. V.; Misharin, Y. S.; Moravshky, A. P.; Shilov, A. E. *New. J. Chem.* **1983**, *7*, 729. (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. Mechanistic studies on C-O bond formation: (e) Vedernikov, A. N. *Top. Organomet. Chem.* **2010**, *31*, 101. (f) Luinstra, G. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 3004. (g) Labinger, J. A.; Herring, A. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 5628. (h) Vedernikov, A. N.; Binfield, S. A.; Zavalij, P. Y.; Khusnutdinova, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 82. (i) Khusnutdinova, J. R.; Zavalij, P. Y.; Vedernikov, A. N. *Organometallics* **2007**, *26*, 3466.

(10) Recently, only a few cases were reported with water acting as a nucleophile in allylic substitutions: Ir catalyst (a) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* **2011**, *133*, 2072. Ru catalyst (b) Kanbayashi, N.; Onitsuka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5197. Organocatalyst (c) Zhu, B.; Yan, L.; Pan, Y.; Lee, R.; Liu, H.; Han, Z.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 6894.

(11) (a) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442. (b) Yin, G.; Wu, T.; Liu, G. *Chem.—Eur. J.* **2012**, *18*, 451.

(12) (a) *USP Dictionary of USAN and International Drug Names*, US Pharmacopoeis: Rockville, MD, 2000; P636. (b) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500. (c) Schewartz, G. K.; Jiang, J.; Kelsen, D.; Albino, A. P. *J. Natl. Cancer. Inst.* **1993**, *85*, 402.

(13) Andrianasolo, E. H.; Haramaty, L.; McPhail, K. L.; White, E.; Vetriani, C.; Falkoski, P.; Lutz, R. *J. Nat. Prod.* **2011**, *74*, 842.

(14) Alternative possibilities: (1) involving a sequential epoxidation of olefin and ring-opening amination procedures; (2) nucleophilic attack of H_2O_2 at carbon center of Pd(IV) complex to give peroxide intermediate, then following reduction to afford the corresponding alcohol product. However, both pathways are unlikely. For details, see the SI.

(15) Alternatively, alkyl Pd(IV)OH complex **int-II** could also act as nucleophile to attack another high-valent palladium complex **int-II** to give product trans-**4a**-d_1.

(16) The *trans*-aminopalladation is favorable in the acidic reaction condition: Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

(17) H_2O_2 in H_2O^{18} was derived from the mixture of 50% aq H_2O_2 (0.3 mmol) in H_2O^{18} (98% O^{18}, 9 mmol). Mixture was measured by mass spectrometry. No O^{18} incorporation into H_2O_2 was observed. For details, see the SI.

(18) In the mixture, the ratio of H_2O^{18}:H_2O^{16} is around 200−300:1, and KIE value between ^{18}O and ^{16}O is <1.1. Thus, it is impossible to give the equal amount of ^{18}O and ^{16}O incorporation with a single external water nucleophilic pathway.

(19) Alkyl Pd(IV)^{16}OH complex was proposed to be derived from oxidation of alkyl Pd(II) by $H_2{}^{16}O_2$, but the detailed mechanism is not clear at the moment.

(20) A similar observation on oxygen incorporation and mechanistic analysis was reported in the stoichiometric reaction of Me-Pt(IV)OH complex. And the nucleophilicity of Me-Pt(IV)OH was estimated to be ~10^3 greater than that of water. For details, see refs 9e−9i, and SI.