Highly Selective Palladium-Catalyzed Intramolecular Aminonitroxylation of Alkenes

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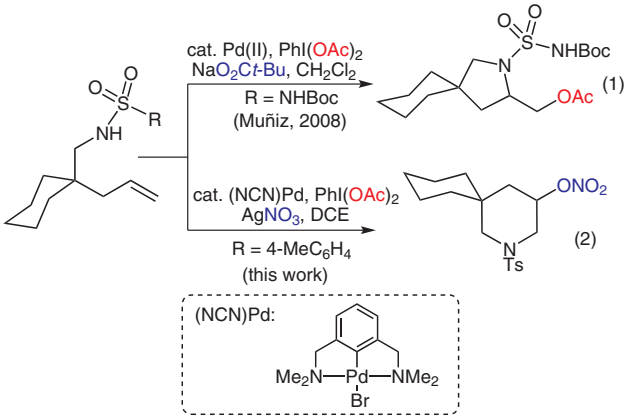
Abstract: A palladium-catalyzed intramolecular oxidative aminonitroxylation of unactivated alkenes, in which $AgNO_3$ functioned as a mild nitrate reagent in the presence of $PhI(OAc)_2$, has been developed. Mechanistic studies suggest that this selective aminonitroxylation reaction likely resulted from a new oxidant $PhI(ONO_2)_2$ generated in situ from $AgNO_3$ and $PhI(OAc)_2$.

Key words: palladium, alkenes, difunctionalization, silver, aminonitroxylation

Palladium-catalyzed oxidation reactions are important transformations in organic synthesis.[1] Recently, a number of palladium-catalyzed difunctionalization reactions of olefins that provide versatile strategies to synthesize molecules with vicinal diheteroatom substitution have been reported.[2] Transformations involving these alkyl-Pd^{IV} intermediates are particularly attractive because these complexes can readily undergo reductive elimination reactions to form C–O, C–N, and C–C bonds, which have proven to be difficult to achieve with catalytic Pd^{II}/Pd^{0} cycles.[3–5] For instance, Sorensen, Stahl, and others have reported that Pd-catalyzed aminoacetoxylation and diacetoxylation employing $PhI(OAc)_2$ to trap the intermediate C–Pd bond and lead to the formation of C–OAc bond.[4a–d] Muñiz have reported a systematic study on the intramolecualr palladium-catayzed diamination of alkene with a similar strategy.[5a–c] It was found that the reaction of alkene bearing sulfonylurea protecting group in nitrogen atom afforded aminoacetoxylation of alkenes, rather than diamination.[5c] This reaction occurs with high selectivity regarding the transfer of the second nucleophile, which orginated from the oxidant [e.g., $PhI(OAc)_2$] but not from the anionic base (Scheme 1, equation 1). Herein, we report a palladium-catalyzed intramolecular aminonitroxylation of alkenes by using $PhI(OAc)_2$ as the oxidant, in which the second nucleophile comes exclusively from the additive $AgNO_3$. In addition, both pincer palladium complex and silver nitrate played important roles in this highly selective transformation (Scheme 1, equation 2).



Scheme 1

Very recently, we reported a palladium-catalyzed intramolecular aminofluorination reaction of alkenes, in which AgF played an important role for the C–F bond formation.[6] During the course of the study, a remarkable effect of selectivity by silver salt was also discovered: treating *N*-tosyl aminoalkene **1a** with $PhI(OAc)_2/AgNO_3$ in the presence of $Pd(OAc)_2$ catalyst afforded an unexpected aminonitroxylation product **2a** as the major product. It is noteworthy that the second nucleophile was originated from $AgNO_3$, rather than oxidant. The aminoacetoxylation of alkenes leading to product **4a** occurred as a side product (Table 1, entry 1). After a series of optimizations, the highly selective aminonitroxylation was achieved with (NCN)Pd complex, which completely inhibited the aminoacetoxylation reaction (entry 2). Furthermore, when $NaNO_3$ was used instead of $AgNO_3$, **4a** was the only product. This observation is reminiscent of the corresponding results reported by Muñiz (entry 3). The reaction with (NCN)PdBr catalyst still provided aminoacetoxylation product **4a** as the major product, along with a small amount of **2a** (entry 4). These observations indicated that $AgNO_3$ is crucial to this high selectivity of aminonitroxylation reaction.[7]

The intramolecular aminonitroxylation of alkenes is proposed to consist of two important steps: an aminopalladation (AP) of alkene and subsequent oxidative C–O bond formation via reductive elimination (RE). This sequence raises the question of the stereochemical course. Deuterium-labeled substrate (*E*)-**1a**-d_1 was shown to transform

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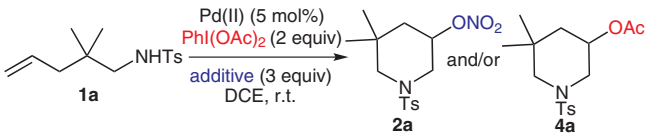
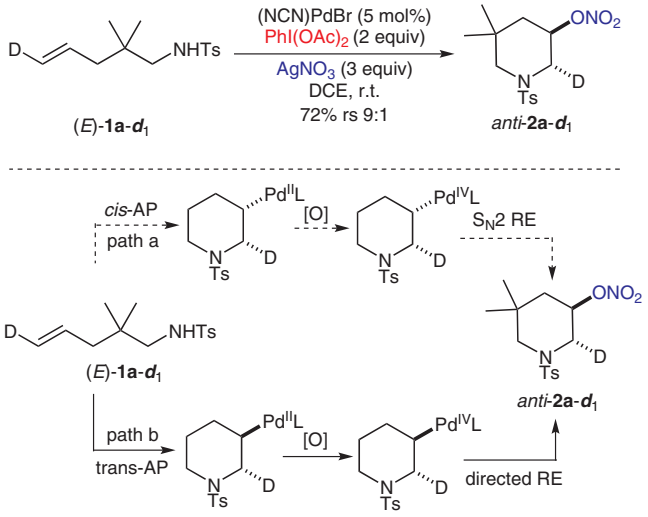
Table 1 The Screen Results on Intramolecular Aminooxygenation[a]



Entry	Pd	Additive	Time (h)	Yield (%)[b]	Ratio of **2a**/**4a**[c]
1	$Pd(OAc)_2$	$AgNO_3$	19	73	3.2:1
2	(NCN)PdBr	$AgNO_3$	24	71	100:0
3	$Pd(OAc)_2$	$NaNO_3$	48	54	0:100
4	(NCN)PdBr	$NaNO_3$	48	78	1:2.7

[a] All the reactions were conducted on a 0.1 mmol scale.
[b] ^{1}H NMR Yield with 1,3,5-trimethoxybenzene as internal standard.
[c] Determined by ^{1}H NMR.

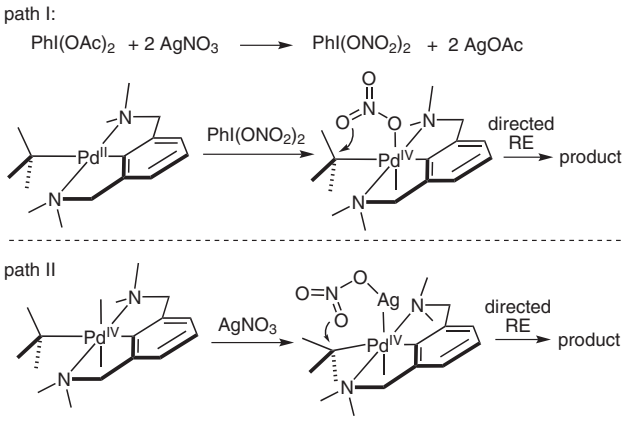
into diastereomerically pure *anti*-**2a**-d_1 selectively (Scheme 2). The overall stereochemical outcome suggested that the inversion of configuration happened during the reaction:[8] The reaction either proceed through *cis*-AP followed by S_N2-type RE (path a)[4b,5b] or *trans*-AP followed by directed RE (path b).[4a] For the former step, although both *cis*- and *trans*-AP of alkenes have been reported to address the 5-*exo* fashion, the *6-endo* ring closure generally proceeded via *trans*-AP.[9] Thus, the directed RE pathway of Pd^{IV} complex should be expected for the C–O bond formation.[4c,10]



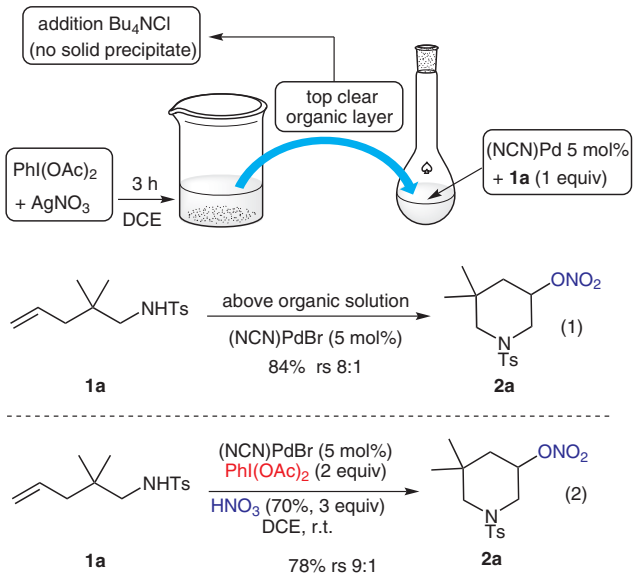
Scheme 2 A possible pathway for the Pd-catalyzed aminonitroxylation of alkenes

There are two possiblities for the formation of aminonitroxylation product: 1) $PhI(NO_3)_2$, generated in situ from $PhI(OAc)_2$ and $AgNO_3$, acts as an oxidant to achieve aminonitroxylation (Scheme 3, path I); 2) a strong interaction between Pd and $AgNO_3$, which was recently reported by Albrecht,[11] possibly results in a intramolecualr nitroxylation to afford the aminonitroxylation product (Scheme 3, path II).

Compared with $NaNO_3$, as mentioned above, the silver ion played an important role for this transformation. According to the path **I**, if the formation of $PhI(ONO_2)_2$ can be achieved, the aminonitroxylation reaction would occur in the absence of silver ion. Otherwise, the silver ion is necessary for the success of the reaction as predicted by path II. Based on this hypothesis, two experiments were conducted: (1) A mixture of $PhI(OAc)_2$ and $AgNO_3$ in DCE were stirred for three hours, then the organic layer was used to react with **1a** in the presence of Pd catalyst.[12] The reaction afforded the aminonitroxylation product in good yield (Scheme 4, equation 1). (2) A reaction was conducted by using HNO_3 instead of $AgNO_3$, and the similar result was obtained (Scheme 4, equation 2). Those results indicated that the silver ion is not necessary for this transformation and are consistent with the mechanism pathway **I**. However, the silver ion should play a role in promoting the formation of $PhI(ONO_2)_2$.

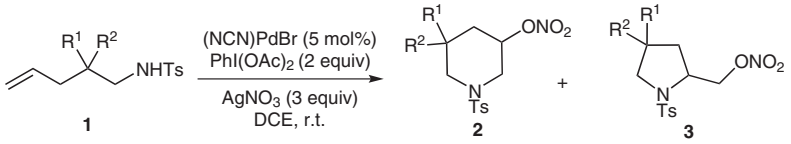


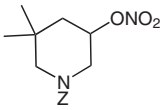
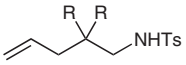
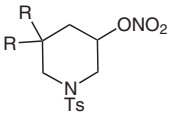
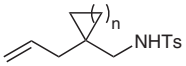
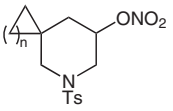
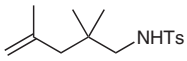
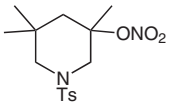
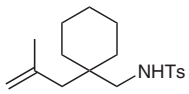
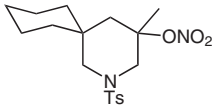
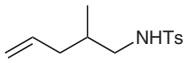
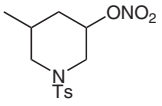
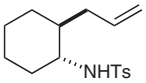
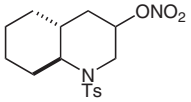
Scheme 3 The possible mechanism for selective C_{sp3}–O reductive elimination



Scheme 4

Table 2 Palladium-Catalyzed Intramolecular Aminonitrooxylation of Alkenes[a]



Entry	Alkene	Substituents	Major product	Yield of **2** + **3** (%)[b]	Ratio of **2**/**3**[c]
1		**1a** Z = Ts	**2a** 	83	91:9
2		**1b** Z = Ac	**2b**	0	
3		**1c** Z = Cbz	**2c**	0	
4		**1d** R = Ph	**2d** 	89	86:14
5		**1e** R = Bn	**2e**	69	88:12
6		**1f** R = CO_2Me	**2f**	85	90:10
7		**1g** n = 1	**2g** 	78	82:18
8		**1h** n = 3	**2h**	85	88:12
9		**1i** n = 4	**2i**	80	87:13
10		**1j**	**2j** 	92	97:3
11		**1k**	**2k** 	79	97:3
12		**1l**	**2l** 	65	80:20 (**2l** 1.5:1)[d] (**3l** 1.1:1)[d]
13		**1m**	**2m** 	63	85:15 (**2m** 3:1)[d] (**3m** n.d.)

[a] Reactions were conducted on a 0.2 mmol scale.
[b] Isolated yield.
[c] The ratio of regioselectivity which determined by ^{1}H NMR.
[d] The ratio of *trans*/*cis*, the diastereoselectivity determined by ^{1}H NMR.

Based on the optimized conditions, the substrate scope of the aminonitroxylation reaction was then investigated (Table 2). Compared to *N*-tosyl alkene **1a** with a 83% yield in 91:9 regioselectivity, substrates *N*-acetyl alkene **1b** and *N*-Cbz alkene **1c** did not afford any aminonitroxylation products (entries 1–3). The reactions of **1d–i** afforded products **2d–i** in good yields, with moderate to good regioselectivity (entries 4–9). Substrates **1j** and **1k**, with one substituent in the β-carbon position, underwent intramolecular aminonitroxylation to afford the corresponding products with good yields and excellent diastereoselectivity (entries 10 and 11). In contrast, the substrates **1l–m** exhibited good reactivity, moderate regioselectivity, and poor diastereoselectivity (entries 12 and 13).

In summary, a highly chemoselective palladium-catalyzed intramolecular oxidative aminonitroxylation of unactivated alkenes have been developed, in which $AgNO_3$ functioned as a mild nitrate reagent in the presence of $PhI(OAc)_2$. Mechanistic studies suggested that two key

steps in the reaction were possibly involved in the formation of C–N and C–O bonds: *trans*-aminopalladation (*endo*) of alkene and directed reductive elimination of Pd^{IV} complex.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) In comparison to the standard conditions, the reaction of **1a** still afforded the aminonitroxylation product in 78% yield in the absence of palladium catalyst, but the poor regioselectivity of **2a** and **3a** (49:51) and slow rate indicated that this reaction was catalyzed by a palladium complex. For the acid-catalyzed amination of alkene by hypervalent iodine reagents, see: (a) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (b) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188.

(8) The same stereochemical behavior has been reported.[4a,b,5b,6]

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(10) The alternative path a in Scheme 2 is less likely, but cannot be excluded at this moment. This is because the differentiation of *cis*- and *trans*-aminopalladation is very difficult.

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(12) The organic layer contained no Ag ion, which was demonstrated by addition of Bu_4NCl – no AgCl precipitated from the organic layer.