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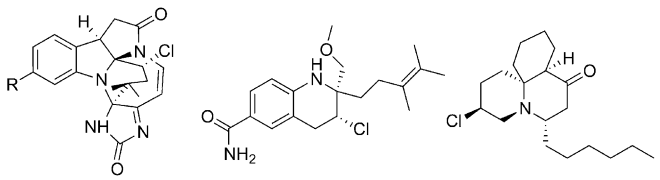
Highly Selective Palladium-Catalyzed Intramolecular Chloroamination of Unactivated Alkenes by Using Hydrogen Peroxide as an Oxidant

Guoyin Yin, Tao Wu, and Guosheng Liu*[a]

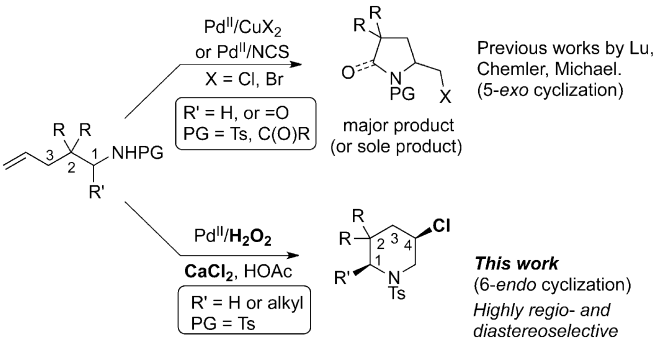
Palladium-catalyzed intramolecular oxidative difunctionalizations of alkenes,[1] such as aminooxygenation,[2] diamination,[3] and dioxygenation[4] have attracted much attention. However, these transformations usually require co-oxidants such as Cu^{II} salts, $PhI(OAc)_2$, oxone, NXS, and $PhICl_2$ for the catalytic cycles, which often produce a large amount of byproducts. Compared with these oxidants, clean oxidants, such as hydrogen peroxide and dioxygen, should be preferred because they are inexpensive, environmental benign, and readily available. Nevertheless, palladium-catalyzed oxidative difunctionalization of alkenes using clean oxidant are quite rare.[5]

Halogenated piperidine moieties are common in natural products and biological active molecules, such as securamine C and D, benzastatin C, and cylindricine B (Scheme 1).[6]



Scheme 1. Selective examples of isolated natural products containing chlorinated piperidine moieties.

Thus, the synthetic utility of the stereoselective construction of C–X bond on the piperidine rings necessitate further development. Palladium-catalyzed aminohalogenation presented an efficient strategy for the synthesis of nitrogen-containing heterocycles.[7] However, these reactions generally undergo 5-*exo* cyclization to afford five-membered rings as sole or major products (Scheme 2).[8] For instance, Lu[7a] and Chemler[7b] simultaneously reported Pd-catalyzed intramolecular haloamination reactions by using $CuCl_2$ or $CuBr_2$ as



Scheme 2. Pd-catalyzed intramolecular aminohalogenation of alkenes.

oxidants. Very recently, the similar chloroamination of alkenes using NCS (*N*-chlorosuccinimide) was also addressed by Michael et al.[7c] In contrast, the preferential formation of piperidine via 6-*endo* cyclization is quite rare under related oxidative condition.[9] Herein, we report an efficient palladium-catalyzed oxidative intramolecular chloroamination of alkenes at mild condition, which employs H_2O_2 as terminal oxidant and a very cheap, low-toxic reagent $CaCl_2$ as chlorine source. This reaction presents an environment benign methodology to synthesize substituted 2-chloropiperidine derivatives with very high regioselectivity. It is worth noting that the configuration of C–Cl bond is well-controlled by the substituents on the adjacent carbon of nitrogen moiety.

In our previous studies, we reported a palladium-catalyzed oxidative enyne cyclization, in which the formation of C–Cl bond can be achieved from oxidative cleavage of $C–Pd^{II}$ bond by using H_2O_2.[10] Thus, if the $C–Pd^{II}$ bond generated from aminopalladation of alkene can be also cleaved in the presence of hydrogen peroxide, environmental benign process for the synthesis of nitrogen-containing heterocycles might be expected. In order to test this hypothesis, the initial studies focused on the reaction of **1a** by using H_2O_2 as an oxidant. When substrate **1a** was treated by $Pd(OAc)_2$ (5 mol%), LiCl (4 equiv), and H_2O_2 (aq, 30%; 2 equiv) in HOAc at room temperature, the reaction afforded a small amount of six-membered chloroamination product **2a**, and five-membered product **3a** was not observed. Instead, alkene isomer **4a** became a major product (Table 1, entry 1). After the screening of chlorine source, we found that $CaCl_2$ was a good choice to give desired product **2a** in good yield (Table 1, entries 2–6). The best yield was ob-

[a] G. Yin, T. Wu, Prof. G. Liu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai, 200032 (P.R. China)
Fax: (+86) 21-64166128
E-mail: gliu@mail.sioc.ac.cn

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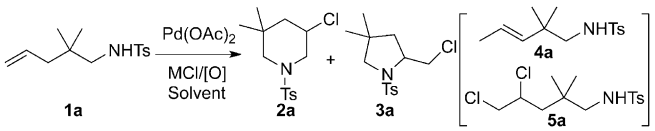
Table 1. The screening results of reaction of **1a**.[a]



Entry	MCl	[O]	Yield [%][b]			
			2a	**3a**	**4a**	**5a**
1	LiCl	H_2O_2	8	–	41	–
2	$BaCl_2$	H_2O_2	32	–	25	–
3	$ZnCl_2$	H_2O_2	–	–	–	–
4	$MgCl_2$	H_2O_2	29	–	26	–
5	Bu_4NCl	H_2O_2	–	–	74	–
6	$CaCl_2$	H_2O_2	71	–	<5	–
7[c]	$CaCl_2$	H_2O_2	83	–	<5	–
8[d]	$CaCl_2$	H_2O_2	<5	–	63	–
9	$CaCl_2$	$PhI(OAc)_2$	14	17	–	25
10[e]	$CaCl_2$	H_2O_2	–	15	8	44

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), MCl (4 equiv), H_2O_2 (30% wt, 2 equiv), and **1a** (0.1 mmol) in HOAc (0.5 mL) at room temperature. [b] Yield obtained by ^1H NMR with 1,3,5-tribromobenzene as an internal standard. [c] $CaCl_2$ (5 equiv) in HOAc (0.4 mL). [d] Ac_2O as solvent. [e] Without palladium catalyst.

tained with a high concentration of $CaCl_2$ (1.25 M; Table 1, entry 7). In addition, only alkene isomerization was observed when Bu_4NCl was employed or Ac_2O was used as solvent (Table 1, entries 5 and 8). In comparison with H_2O_2, $PhI(OAc)_2$ as oxidant gave low selectivity (Table 1, entry 9). Finally, no six-membered product **2a** was observed in the absence of palladium catalyst (Table 1, entry 10).

With the optimized reaction conditions, the substrate scope was further examined. As shown in Table 2, the alkenylamines **1** with a variety of protecting group were firstly explored, and substrates **1a**–**1c** with sulfonyl group were proved to be good for this transformation to give desired product with high regioselectivity (Table 2, entries 1–3). The reactions did not occur for the substrates **1d**–**1e** with carbonyl protecting group, such as Cbz and Boc (Table 2, entries 4 and 5). The following studies demonstrated that various substituents, such as alkyl, ether, ester and alcohol on C-2 position, were compatible to this chloroamination, and these reactions afforded the six-membered rings **2f**–**2k** with high regioselectivity in good yields (Table 2, entries 6–11). However, substrate **1l** without substituent showed the poor regioselectivity (Table 2, entry 12). Very interesting, while cyclic substrate **1m** was treated under standard reaction condition, a single isomers **2m** was selectively formed (Table 2, entry 13). Further studies demonstrated that good diastereoselectivity were also achieved in the reaction of substrates **1n**–**1r** which had substituents in adjacent carbon of NTs, and the formed C–Cl bond located in the same face of six-membered ring with this substituent (Table 2, entries 14–18). The configuration of products **2m** and **2o** were determined by X-ray analysis (Figure 1).

To gain deeper insight into the mechanism of this transformation, deuterium-labeled substrate (*E*)-[D_1]**1a** was prepared[9b] and subjected to the standard reaction conditions. A single isomer *trans*-[D_1]**2a** was obtained (Scheme 3). A

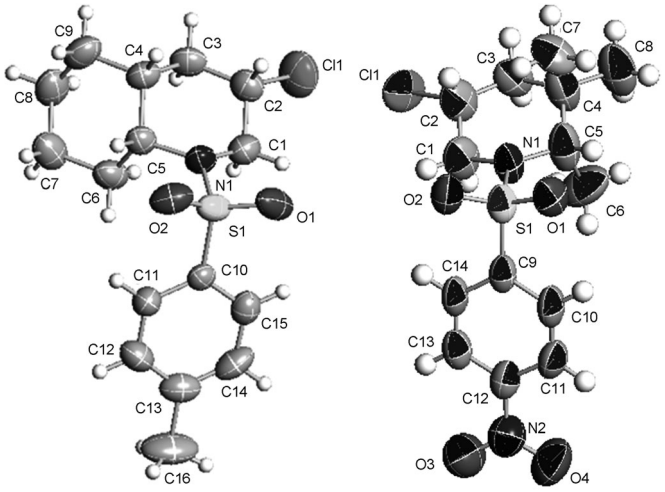
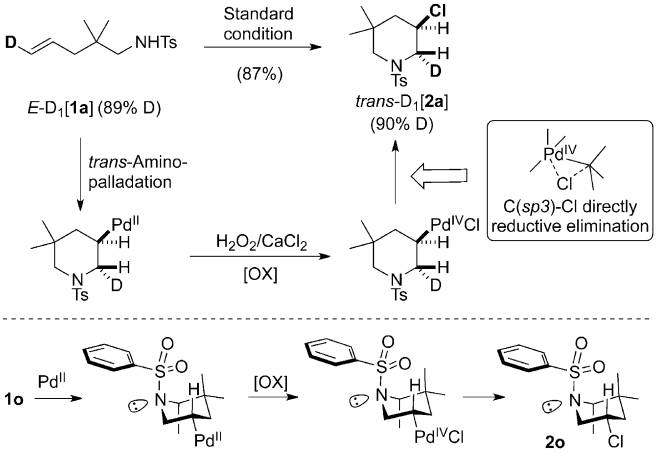


Figure 1. The X-ray structures of compounds of **2m** (left) and **2o** (right).

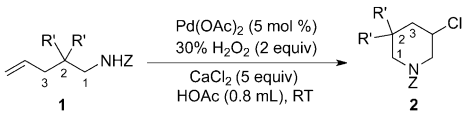


Scheme 3. Proposed mechanism for the high stereoselectivity.

possible catalytic cycle based on our findings is shown below: Pd^{II}-catalyzed *trans*-aminopalladation of the alkene by nitrogen nucleophilic attack at the terminal carbon (6-*endo*)[11,12] generates a Pd^{II} intermediate that undergoes an oxidation step by H_2O_2.[10b] Directly reductive elimination from the Pd^{IV} intermediate generates the C–Cl bond (Scheme 3, top). In addition, it is interesting to note that X-ray structure determination of **2m** and **2o** shows that the substituents adjacent to the amine moiety prefer an axial orientation due to the steric bulky of sulfonyl group (Scheme 3, bottom).[13]

However, the cyclization of alkenylamines like **1a** generally undergoes 5-*exo* model to give five-membered ring, which is opposite to our results.[8] Based on this consideration, there are three different mechanism manifolds to address the six-membered ring **2a** formation (Scheme 4): 1) the reaction yields five-membered product **3a** first, then a isomerization of **3a** occurs to give six-membered ring **2a** via an aziridinium intermediate **III** (path a);[14] 2) the formation of aziridinium intermediate **III** might be formed through in-

Table 2. Pd-catalyzed intramolecular chloroamination of alkenes.[a]

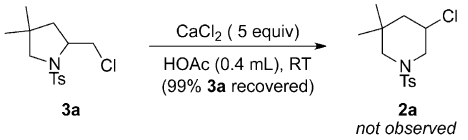


Entry	Substrate		Product		Yield[b]
1		**1a** Z = Ts		**2a**	78 %
2		**1b** Ns		**2b**	75 %
3	NHZ	**1c** SO_3Me	Cl, N, Z	**2c**	71 %
4		**1d** Cbz		**2d**	0
5		**1e** Boc		**2e**	0
6	Bn Bn, NHTs	**1f**	Bn, Bn, Cl, N, Ts	**2f**	75 %
7	OMe, NHTs	**1g**	MeO, Cl, N, Ts	**2g**	81 % (82:18)[c]
8	MeO_2C CO_2Me, NHTs	**1h**	MeO_2C, MeO_2C, Cl, N, Ts	**2h**	86 %[d]
9	HO, OH, NHTs	**1i**	OH, OH, Cl, N, Ts	**2i**	74 %
10	NHTs	**1j**	Cl, N, Ts	**2j**	87 %
11	NHTs	**1k**	Cl, N, Ts	**2k**	90 %
12	NHTs	**1l**	Cl, N, Ts	**2l**	61 %[e]
13	NHTs	**1m**	Cl, N, Ts	**2m**	78 % (>97:3)[f]
14	NHZ, Me	**1n**	Me, Cl, N, Z	**2n**	91 % (93:7)[f]
15		**1o**		**2o**	74 % (>97:3)[f]
16	NHTs, *n*-Bu	**1p**	*n*-Bu, Cl, N, Ts	**2p**	92 % (96/4)[f]
17	NHTs, *n*-Bu	**1q**	*n*-Bu, Cl, N, Ts	**2q**	95 % (95/5)[f]
18	NHTs, Me	**1r**	Me, Cl, N, Ts	**2r**	91 % (90/10)[f]

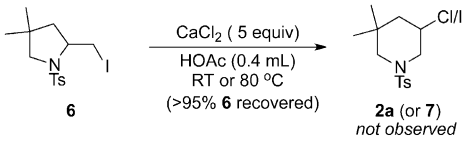
[a] Reactions were conducted in 0.2 mmol scales. [b] Yield of isolated product. [c] The ratio of *trans*- and *cis*-**2g**. [d] **2h**/**3h** = 85:15. [e] **2l**/**3l** = 63:37. [f] Ratio of diastereoisomers (*cis*/*trans*).

tramolecular nucleophilic attack at carbon center of Pd^{IV} intermediate **II** by N moiety with concomitant Pd^{II} release (path b); 3) alternatively, if a reversible 5-*exo* and 6-*endo* aminopalladation was involved, and the oxidative cleavage of C–Pd^{II} bond of intermediate **IV** to generate the C–Cl bond was faster than that of **I**, the reaction might expect to generate six-membered product **2a** as sole or major product (path c).

To differentiating these hypotheses, substrate **3a** was treated with $CaCl_2$ in HOAc. No observation of product **2a** is against the possibility of path a (Reaction (1)). In addition, it is well known that Pd^{IV} is a good leaving group.[1f] If the leaving ability of Pd^{IV} species is similar to iodide atom, substrate **6** should have a similar reactivity with intermediate **II**. Thus, the failure of isomerization of **6** suggests that the possibility of path b is less likely (Reaction (2)).

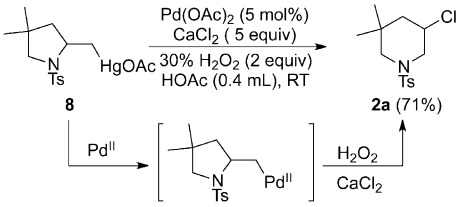


(1)



(2)

Furthermore, when alkyl mercury reagent **8** was subjected to standard reaction condition,[15] a single isomer **2a** was obtained in 71 % yield (Reaction (3)). This observation suggests that the reaction involves a reversible aminopalladation more likely (path c, Scheme 4).[16,17]

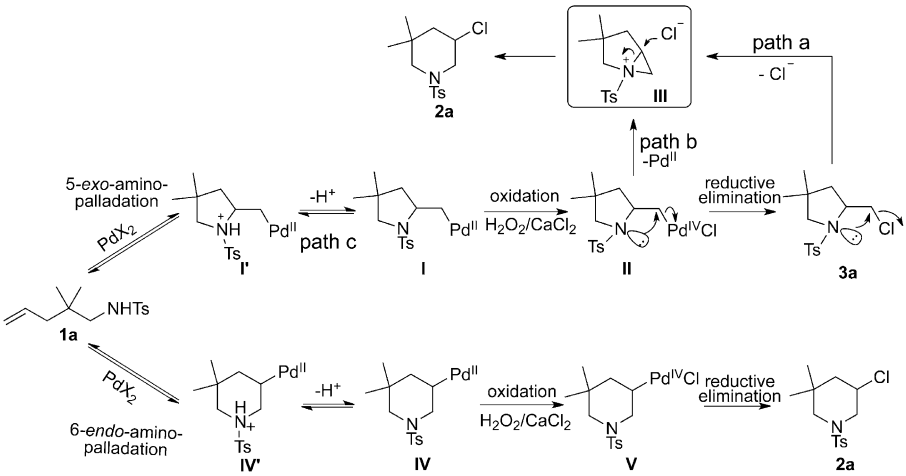


(3)

In summary, a highly selective Pd-catalyzed oxidative intramolecular chloroamination of unactivated alkenes have been developed by using a environment benign catalytic system, in which H_2O_2 was used as oxidant and $CaCl_2$ as chlorine source. A variety of chlorinated piperidine compounds were obtained with good regio- and diastereoselectivities. A reversible *trans*-aminopalladation of alkenes was proposed to address the formation of 6-*endo* product. The asymmetric chloroamination of alkenes is in progress.

Experimental Section

Representative procedure: in a 4 mL sealed glass vial, alkenylamine **1a** (53.4 mg, 0.2 mmol), $CaCl_2$ (111.2 mg, 1.0 mmol) were dissolved in dry acetic acid (0.8 mL). After stirring for a few minutes, $Pd(OAc)_2$ (2.3 mg,



Scheme 4. Mechanistic proposals for **2a** formation.

0.01 mmol) and H_2O_2 (30% aq wt; 0.4 mmol, 46 μL) were added, and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography until **1a** was consumed. Then diethyl ether (25 mL) was added and the mixture was filtered through a plug of Celite to remove excess $CaCl_2$. The mixture was concentrated in vacuum and the crude residue was purified by silica gel column chromatography to give the corresponding product **2a**.

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Keywords: alkene difunctionalization · chloroamination · hydrogen peroxide · oxidation · palladium

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