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Palladium-Catalyzed Intramolecular Chloroamination of Alkenes

Forrest E. Michael,* Paul A. Sibbald, and Brian M. Cochran

Department of Chemistry, University of Washington, Box 351700, Seattle, Washington 98195-1700

michael@chem.washington.edu

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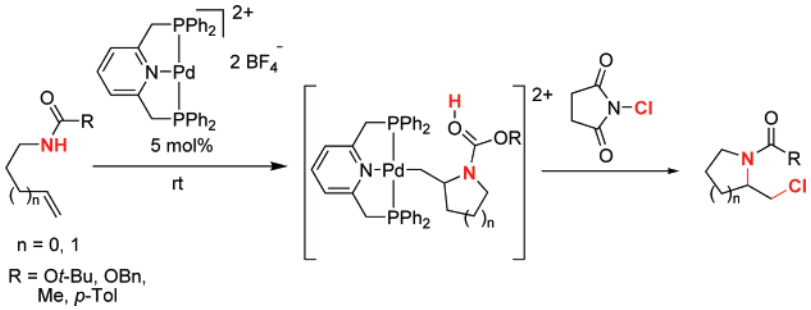
ABSTRACT



A mild and facile Pd-catalyzed intramolecular chloroamination of unactivated alkenes has been described. This reaction takes place at room temperature and is tolerant of synthetically useful acid-sensitive functional groups. Generally high *exo*-selectivities are observed in the formation of a variety of 5- and 6-membered rings. This system is unique in its ability to tolerate multidentate ligands on palladium, which opens up the possibility of controlling the absolute sense of induction using a chiral ligand.

The direct addition of a halogen- and a nitrogen-containing functional group to alkenes and alkynes is a powerful means of introducing two distinct functional groups across a carbon−carbon multiple bond.[1] The vicinal haloamines generated in this fashion have applications as potential medicinal agents[2] but are primarily used as versatile synthetic intermediates.[3]

Intramolecular haloaminations (halolactamizations) can occur directly upon treatment of alkenylamides with relatively active halogen sources such as I_2 or Br_2.[1b,4] However, precautions must often be taken to avoid cyclization via oxygen instead of nitrogen.[5] This approach is simple and effective but precludes the possibility of controlling the absolute stereochemistry of addition.

Transition metal-catalyzed intramolecular haloaminations remain relatively rare.[6,7] Chemler[6a] and Lu[6b] have both reported Pd-catalyzed intramolecular haloamination reactions. Lu reported that alkenes bearing pendant acylsulfonamides could be cyclized with $Pd(OAc)_2$ catalyst, using $CuCl_2$ or $CuBr_2$ as the halogen source. Chemler described the cyclization of sulfonamidoalkenes with $Pd(TFA)_2$, also using copper halides as the halogen sources. These reactions proceeded in high yield but were often plagued by poor regioselectivity (*endo*/*exo* = 1:1.7 to 100:0, depending on substrate). Although the use of transition metal catalysis opens up the possibility of asymmetric catalysis, no enantioselective haloamination reaction has yet been reported. Herein, we report a selective palladium-catalyzed chloroamination of

(1) Reviews: (a) Li, G. G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745−2758. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408.

(2) Qiu, J.; Silverman, R. B. *J. Med. Chem.* **2000**, *43*, 706−720.

(3) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 469−513.

(4) (a) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491−5501. (b) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063−1066.

(5) (a) Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906−7909. (b) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006−4014. (c) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233−3235.

(6) (a) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618−5621. (b) Lei, A. W.; Lu, X. Y.; Liu, G. S. *Tetrahedron Lett.* **2004**, *45*, 1785−1788.

(7) From azides: Danielec, H.; Klugge, J.; Schlummer, B.; Bach, T. *Synthesis* **2006**, 551−556. From *N*-Cl amines: Sjoholm, A.; Hemmerling, M.; Pradeille, M.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 891−899.

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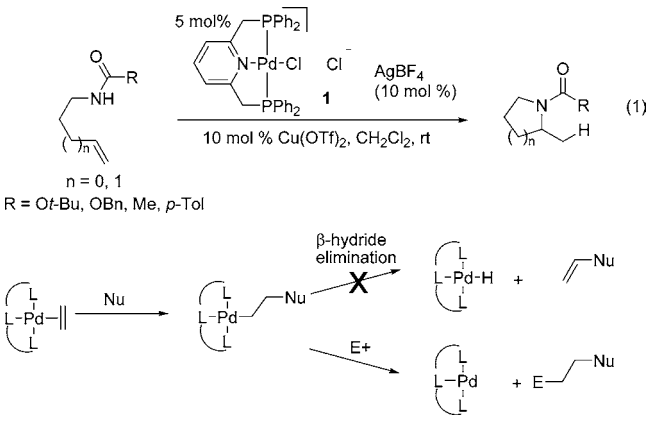
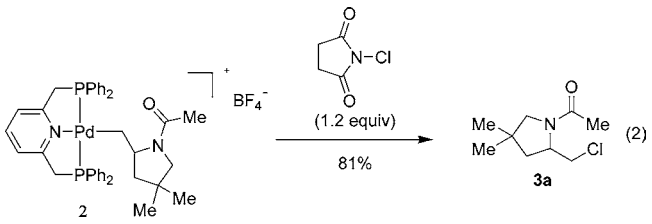
protected aminoalkenes that generally gives high regioselectivity for *exo* cyclization and has the potential for future enantioselective development.

We have recently reported that Pd complex **1** is highly effective for the intramolecular hydroamination of unactivated alkenes (eq 1).[8] The tridentate ligand on Pd prevents the normally rapid β-hydride elimination of the intermediate Pd−alkyl complex, allowing protonolysis to occur instead (Scheme 1). The success of this strategy prompted an

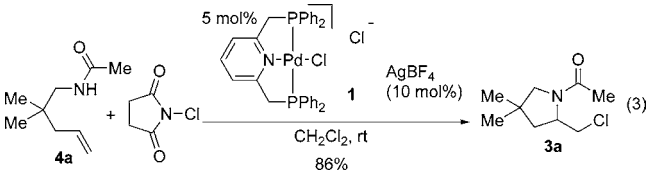
Scheme 1. Hydroamination via Inhibition of β-hydride Elimination



investigation of whether this Pd−alkyl complex could also be intercepted by other electrophiles, resulting in a catalytic difunctionalization of alkenes.



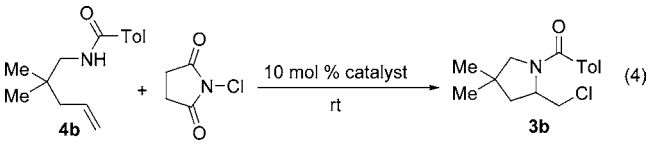
Palladium−alkyl complex **2** can be isolated by treatment of the protected aminoalkene with the palladium complex in the presence of mild base. Exposure of **2** to acid afforded the expected hydroamination product.[9] Similarly, treatment of **2** with 1.2 equiv of *N*-chlorosuccinimide (NCS) at room temperature resulted in clean conversion to chloroamination product **3a** in 81% yield (eq 2).



Having demonstrated the feasibility of the key halogenation step, catalytic conditions were developed. Reaction of protected aminoalkene **4a** with NCS using a catalytic amount of Pd complex **1** (5 mol %) and $AgBF_4$ (10 mol %) at room temperature also resulted in clean conversion to chloroamination product **3a** in 86% yield (eq 3). In contrast, aminoalkene **4a** failed to react with NCS in the absence of Pd catalyst (both with and without $AgBF_4$), returning only unreacted starting material and confirming that the reaction is specifically catalyzed by Pd.

Other Pd complexes were also effective in the chloroamination reaction (Table 1). The presence of the tridentate

Table 1. Chloroamination of Protected Aminoalkene **2a**

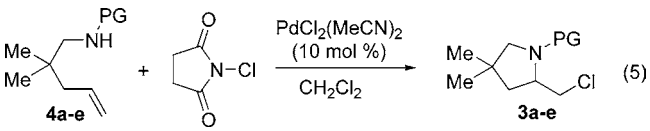


entry	catalyst	solvent	yield %
1	$PdCl_2(MeCN)_2$	CH_2Cl_2	94 (93)[a]
2	$Pd(OAc)_2$	CH_2Cl_2	92
3	$Pd(TFA)_2$	CH_2Cl_2	93
4	$Pd_2(dba)_3$	CH_2Cl_2	88
5	$(pybox)PdCl_2$	CH_2Cl_2	0[b]
6	$(BINAP)PdCl_2$	CH_2Cl_2	0[b]
7	$PdCl_2(MeCN)_2$	MeCN	92
8	$PdCl_2(MeCN)_2$	Et_2O	95
9	$PdCl_2(MeCN)_2$	toluene	90

[a] 5 mol % catalyst. [b] With and without 20 mol % $AgBF_4$

ligand is not required, as indicated by the activity of several simple Pd salts. A Pd(0) complex (entry 4) can also be employed, as it is presumably oxidized to Pd(II) species under the reaction conditions. On the other hand, other multidentate ligand complexes of Pd, such as $(pybox)PdCl_2$ and $(BINAP)PdCl_2$ failed to catalyze any chlorination of **4a**, both in the presence and absence of silver salts. This unique ability of the PNP pincer ligand to promote cyclization was also observed in the hydroamination reaction. Toluene, ether, acetonitrile, and CH_2Cl_2 were identified as equally suitable solvents for this transformation (entries 7−9).

Table 2. Effect of Nitrogen Protecting Group on Haloamination



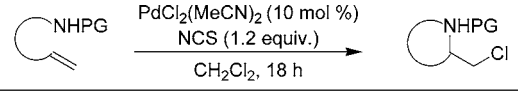
PG	alkene	product	yield %
Ac	**4a**	**3a**	89
p-toluoyl	**4b**	**3b**	94
Boc	**4c**	**3c**	74
Cbz	**4d**	**3d**	67[a]
CONHBn	**4e**	**3e**	91
CONHPMP	**4f**	**3f**	72
Ts	**4g**	**3g**	0

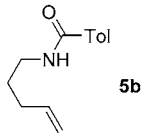
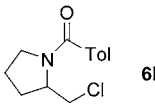
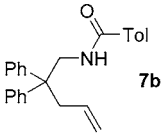
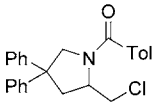
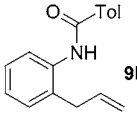
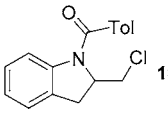
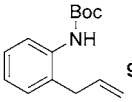
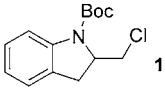
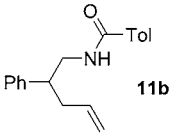
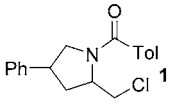
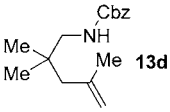
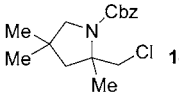
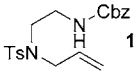
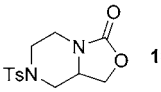
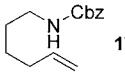
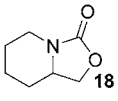
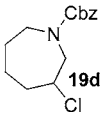
[a] In toluene

Substrates bearing a variety of substituents on nitrogen were effective substrates for chloroamination (Table 2). Amides and carbamates **4a**−**d** cyclize most readily, including the synthetically useful Boc and Cbz protected substrates. Ureas **4d**,**e** also afforded good yields of the chloroamination products. Substrates bearing a toluenesulfonyl substituent on nitrogen failed to cyclize, as was observed in the hydroamination reaction,[8] and in contrast to the Pd-catalyzed haloaminations reported by Chemler and Lu.[6]

Other successful chloroamination reactions are depicted in Table 3. Formation of 5-membered rings is facile with

Table 3. Chloroaminations of Other Aminoalkenes

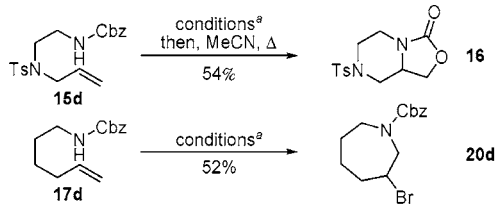


entry	alkene	product	yield %
1	 **5b**	 **6b**	90
2	 **7b**	 **8b**	93
3	 **9b**	 **10b**	63
4	 **9c**	 **10c**	87
5	 **11b**	 **12b**	90
6	 **13d**	 **14d**	60
7[a]	 **15d**	 **16**	91
8[a]	 **17d**	 **18**  **19d**	64/17 (**18**/**19d**)

[a] Then dissolved in MeCN and heated to reflux for 18 h.

various substitution patterns on the tether, including allylaniline derivatives **9b**,**c** (entries 1−5). 1,1-Disubstituted alkenes were also efficiently cyclized (entry 6).

Formation of 6-membered rings using this method was also successful (entries 7, 8), although the reactions were complicated by partial displacement of the chloride by the carbamate protecting group under the reaction conditions to give the oxazolidinones **16** and **18**. By heating the crude reaction mixture in acetonitrile, full conversion of the *exo* cyclyization products to the oxazolidinones was achieved in good yield. In the case of **17d**, a small amount of the 7-membered *endo* cyclization product **19d** was also formed.

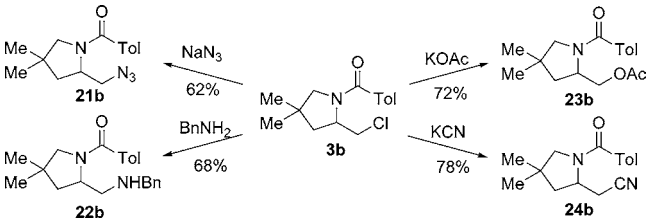


[a] 10 mol% $Pd(TFA)_2$, NBS (1.2 equiv), CH_2Cl_2, 18h

Extension of this method to the corresponding bromoamination reaction required more finesse. Treatment of original substrate **4a**, which is especially prone to cyclization, with NBS and NIS did result in formation of the corresponding bromo- and iodomethylpyrrolidines. However, these reactions also proceeded in the absence of Pd. On the other hand, substrates that are less likely to cyclize, like **15d** and **17d**, did not react with NBS in the absence of Pd but did provide moderate yields of the corresponding oxazolidinone or bromoamination products, respectively, under catalytic conditions (eqs 6, 7).

The presence of an exocyclic chloride functionality in the chloroamination products provided a convenient handle for subsequent functionalization (Scheme 2). Product **3b** easily

Scheme 2. Nucleophilic Substitutions



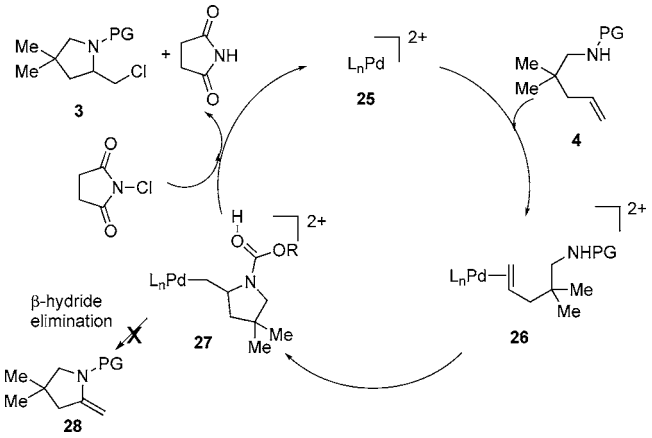
underwent nucleophilic substitutions by treatment with the appropriate nucleophile in refluxing CH_3CN. In this fashion, compounds **21b**−**24b** could be generated in high yield.

The proposed reaction mechanism is illustrated in Scheme 3. Coordination of the alkene to the dicationic Pd **25** to form complex **26** activates the alkene toward nucleophilic attack by the amide or carbamate to form alkylpalladium intermediate **27**. In the presence of NCS, this alkylpalladium species is chlorinated to give the observed chloroamination product and succinamide, regenerating the starting palladium species. Interestingly, chlorination of the alkylpalladium complex

(8) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246−4247.

(9) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, in press.

Scheme 3. Proposed Mechanistic Cycle



appears to be faster than protonolysis, since competitive hydroamination was not observed. The success of unligated palladium sources in this reaction implies that this chlorination is also more rapid than β-hydride elimination.

In conclusion, a mild and facile Pd-catalyzed intramolecular haloamination of unactivated alkenes has been described. This reaction takes place at room temperature and is tolerant of synthetically useful acid-sensitive functional groups. The ability of palladium complexes bearing multidentate ligands to catalyze this reaction opens up the possibility of controlling the absolute sense of induction using a chiral ligand. Studies toward the development of an enantioselective version are underway.

Acknowledgment. The University of Washington is acknowledged for financial support.

Supporting Information Available: Detailed reaction conditions and experimental data for syntheses of all starting materials, catalysts, and cyclization products. This material is available is available free of charge at http://pubs.acs.org.

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