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Brønsted Base-Modulated Regioselective Pd-Catalyzed Intramolecular Aerobic Oxidative Amination of Alkenes: Formation of Seven-Membered Amides and Evidence for Allylic C−H Activation

Liang Wu, Shuifa Qiu, and Guosheng Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, China, 200032

gliu@mail.sioc.ac.cn

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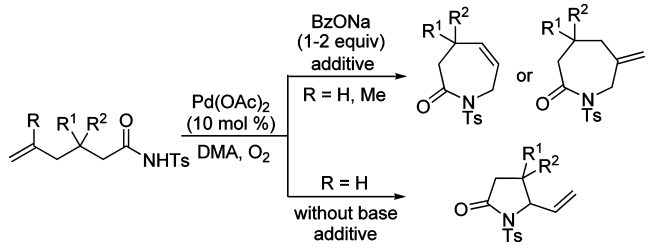
ABSTRACT



A novel palladium-catalyzed intramolecular aerobic oxidative allylic C−H amination of olefins has been developed. Brønsted base can modulate the regioselectivity, favoring the formation of 7-membered rings. Mechanistic studies using deuterium-labeled substrates as probes support a rate-determining allylic C−H activation/irreversible reductive elimination pathway.

The prominence of nitrogen-containing heterocycles in natural products and biologically active molecules has prompted considerable efforts toward their synthesis.[1] Among transition-metal promoted cyclizations of alkenes, palladium-catalyzed oxidative aminations represent one of the most efficient synthetic routes for nitrogen-containing heterocycles.[2] An even more desirable approach for catalytic C−N bond formation is the dioxygen-coupled oxidative amination of olefins.[3] While formations of five- and six-membered heterocycles have dominated palladium-catalyzed oxidative intramolecular aminations of alkenes, formations of seven-membered nitrogen-containing heterocycles under oxidative conditions are quite rare.[4] Herein, we report a Brønsted base-modulated regioselective Pd-catalyzed intramolecular aerobic oxidative amination of alkenes for seven-membered amides

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(2) For reviews on oxidative amination methods, see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

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(4) (a) van der Schaaf, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. *J. Am. Chem. Soc.* **1994**, *116*, 5134. (b) Grellier, M.; Pfeffer, M.; Van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 2877.

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(6) For palladium catalyzed aerobic allylic C-H functionalization, see: (a) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugako, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (b) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (c) Beccalli, E. M.; Broggini, G.; Paladino, G.; Penoni, A.; Zoni, C. *J. Org. Chem.* **2004**, *69*, 5627. For single example, see: (d) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584.

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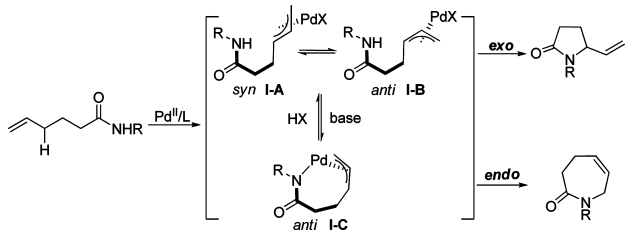
formation.[5,6] Mechanistic studies support the allylic C−H activation pathway.

Recently, significant progress has been made in the area of metal-catalyzed amination of C−H bonds;[7,8] for instance, Rh-catalyzed C−H amination through highly reactive metallo-niteneoids,[7a−d] Pd- or Cu-mediated C−H oxidative amination assisted by directing groups,[7e−g,8] and Pd-catalyzed allylic C−H oxidative amination.[6b,c,9] The latter have proposed a π-allylpalladium species as key intermediates. For intramolecular cyclizations, since the π-allylpalladium intermediate normally exists as an equilibrium mixture of *syn* (**I-A**) and *anti* (**I−B** and **I−C**), the subsequent nucleophilic attack may afford five- and/or seven-membered rings depending on whether the attack proceeds through *exo* or *endo* fashion (Scheme 1). We hypothesized that Brønsted

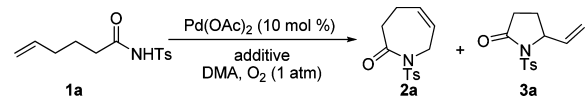
Scheme 1. Pd^{II}-Mediated Intramolecular Oxidative Allylic C−H Amination of Alkenes



base can promote the Pd−N bond formation[10] to favor intermediate **I−C**, leading to selective generation of seven-membered rings (Scheme 1, bottom).

Our experiments were initiated with the intramolecular allylic amination reaction of monosubstituted olefine **1a**. The reaction mediated by Pd $(OAc)_2$ under aerobic condition yielded 20% five-membered ring product **3a** with high regioselectivity (Table 1, entry 1). To our surprise, the seven-membered ring **2a** was formed as the major product in the presence of a base additive (NaOBz, 1 equivalent) under otherwise identical conditions (entry 2). The formation of **2a** can be further enhanced by adding maleic anhydride (MA, 40 mol %) and 4 Å molecular sieves (condition A, entry 3).[11] On the other hand, **3a** can also be obtained in good yield by adding (salen)$Cr^{III}Cl$, an additive first reported by White and co-workers (condition B, entry 4).[9a,12] However, when base is added to the system containing (salen)$Cr^{III}Cl$, the regioselectivity of the reaction was reverted with the generation of 7-membered ring **2a** again (entry 5). The above results indicated that the use of base additive is crucial for the formation of 7-membered ring, as proposed in Scheme 1.[13]

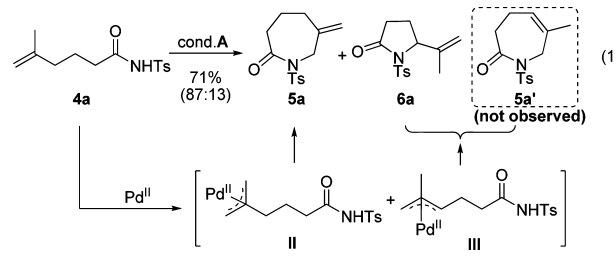
Table 1. Pd-Catalyzed Intramolecular Oxidative Amination of **1a**[a]



entry	additive	yield (**2a:3a**)[b]
1	none	20% (<3:97)
2	NaOBz (100 mol %)	44% (82:18)
3[c]	NaOBz (100 mol %), 4 Å MS (15 mg), MA (40 mol %) **[Condition A]**	91% (86:14)
4	(salen)Cr(III)Cl (10 mol %) **[Condition B]**	65% (<3:97)
5	NaOBz (100 mol %), (salen)Cr(III)Cl (10 mol %)	54% (80:20)

[a] Reactions were conducted at 0.1 mmol scale at 1 mL DMA under 1 atm dioxygen, 50 °C. [b] ^1H NMR yield, 1,3,5-trimethoxybenzene as internal standard. [c] At 70 °C.

The base-promoted regioselective formation of 7-membererd rings is general with respect to monosubstituted alkenes (Table 2). For substrates **1a−1f** tested in our experiments, the optimal condition described above (condition A) favored 7-membered rings **2a−2f** formation (selectivity ranging from 79:21 to 86:14, odd entries). In cases where no base was added (Condition B), 5-membered rings **3a−3f** were formed selectively (even entries). It is worth noting that reactions of **1b−1e** exhibited high stereoselectivity to afford trans products **3b−3e** (entries 4, 6, 8 and 10).



The regioselectivity of 7- over 5-membered rings may be further enhanced by using substrates with a methyl group installed at an internal vinyl position. This is because the

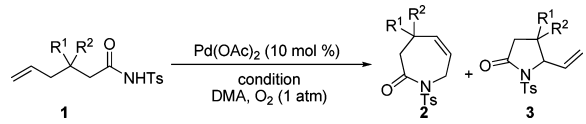
(7) C-H amination via nitrenes: (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (c) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (d) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048 For Cu-catalyzed aminations, see. (f) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (g) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (h) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(8) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (c) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184.

(9) (a) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (b) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (c) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed,* **2008**, *47*, 8224. For allylic C-H alkylation, see: (d) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901. (e) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56.

(10) For the N-Pd bond formation promoted by Brønsted base, see: (a) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

Table 2. Palladium-Catalyzed Oxidative Allylic C−H Amination[a]



entry	substrate	condition	major	product	yield (**2**:**3**)[b]
1	**1a** R^1 = H, R^2 = H	**A**	**2a**		88% (86:14)
2	**1a**	**B**		**3a**	61% (<3:97)
3	**1b** R^1 = Me, R^2 = H	**A**	**2b**		83% (82:18)
4	**1b**	**B**		**3b** (10:1)[c]	66% (<3:97)
5	**1c** R^1 = C_5H_{11}, R^2 = H	**A**	**2c**		64% (81:19)
6	**1c**	**B**		**3c** (6:1)[c]	71% (6:94)
7	**1d** R^1 = ^{i}Pr, R^2 = H	**A**	**2d**		56% (81:19)
8	**1d**	**B**		**3d** (9:1)[c]	41% (<3:97)
9	**1e** R^1 = CH_2OBn, R^2 = H	**A**	**2e**		67% (79:21)
10	**1e**	**B**		**3e** (17:1)[c]	61% (5:95)
11	**1f** R^1 = Me, R^2 = Me	**A**	**2f**		74% (84:16)
12	**1f**	**B**		**3f**	71% (<3:97)

[a] Reaction was conducted at 0.2 mmol scale at 2 mL DMA under 1 atm dioxygen. Condition **A**: $Pd(OAc)_2$ (10 mol %), NaOBz (1 equiv), MA (40 mol %), 4 A MS (30 mg), 70 °C; Condition **B**: $Pd(OAc)_2$ (10 mol %), (salen)Cr(III)Cl (10 mol %), 50 °C. [b] Isolated yield, the data in parentheses is the ratio of **2** and **3**. [c] Ratio of *trans*-3 and *cis*-3.

reaction of **4a** is expected to favor π-allylpalladium intermediates **II** over **III** due to the higher activity of the terminal methyl over the internal methylene group.[14] The intermediate **II** should exclusively give seven-membered product **5a** (eq 1). We found when substrate **4a** was submitted to condition **A**, similar ring-sized selectivity (**5a/6a** = 87:13) was achieved as in the cyclization of **1a** (eq 1). The fact that **5a′** was not observed indicated that intermediate **III** afforded five-membered ring **6a** as the only product.[15] However, for the substrate **4a**, no reaction occurred under condition B.

Subsequent studies of substrate scope were conducted. Interestingly, for substrates **4b**−**4i**, which featured one or two substituents at β-position of carbonyl groups, the reactions afforded the seven-membered products **5b**−**5i** in good yields and excellent regioselectivities (Table 3, entries 2−10). This can be attributed to complete elimination of the activation of allylic C−H bond of the methylene group probably due to steric effect. Product **5f** was successfully prepared on a 1.5 mmol scale in yield comparable to that on small scale (entry 7).[16] The seven-membered rings **5j**−**5l** containing two hetereoatoms were also prepared using our methods in moderate yields (entries 11−13). Finally, for the one methylene less substrates **4m** and **4n**, the reactions proceeded smoothly to six-membered rings with good yields (entries 14−15).

We then conducted preliminary mechanistic studies. The reaction may proceeds through an allylic C−H activation/reductive elimination pathway, or an aminopalladation/β-H elimination pathway. The deuterium labeled experiments can be used to differentiate the above two scenarios. If the reaction involves allylic C−H activation, both the reactions

Table 3. Palladium-Catalyzed Oxidative Allylic C−H Amination of **4**[a]

entry	substrate	product	yield[b]
1[c]	**4a**	**5a**	71% (87:13)[f]
2[d]	**4b** R^1 = H, R^2 = Me	**5b**	76%
3[c]	**4c** R^1 = H, R^2 = Ph	**5c**	58%
4	**4d** R^1 = H, R^2 = OMe	**5d**	82%
5	**4e** R^1 = H, R^2 = COOMe	**5e**	70%
6	**4f** R^1 = Me, R^2 = Me	**5f**	91%
7[e]	**4f**	**5f**	88%
8	**4g** R^1 = Me, R^2 = OMe	**5g**	93%
9	**4h** R^1 = R^2 = $(CH_2)_4$	**5h**	82%
10	**4i** R^1 = R^2 = $(CH_2)_5$	**5i**	81%
11	**4j** X = O, R = H	**5j**	54%
12	**4k** X = NTs, R = H	**5k**	62%
13	**4l** X = NTs, R = Me	**5l**	68%
14	**4m** R = H	**5m**	72%
15	**4n** R = Me	**5n**	77%

[a] Reaction condition: **4** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), NaOBz (1 equiv), MA (40 mol %), 4 A MS (30 mg) in DMA (2 mL) under 1 atm O_2, 70 °C. [b] Isolated yield. [c] NaOBz (2.5 equiv). [d] NaOBz (1.5 equiv), 20 h. [e] Scale: 1.5 mmol. [f] Ratio of **5a:6a**.

(11) For the screening results, see Supporting Information Table S1.

(12) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448 (Salen = 1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-butyl-sali-cylidene).

(13) For Brønsted base-modulated regioselectivity of oxidative amination of styrene, see: Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888.

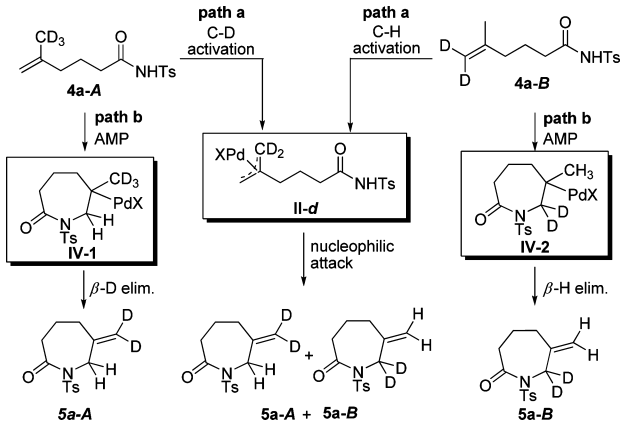
(14) Maitlis, P. M. In *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vol. I, p 175.

(15) The isomerization from **5a′** to **5a** is unlikely due to relative thermodynamic stability, see: Eskola, P.; Hirsch, J. A. *J. Org. Chem.* **1997**, *62*, 5732. On the other hand, no observation of the double bond isomers within the recovered **4a**-***A*** in eq 2also excludes this possibility.

(16) The product **5f** was treated with Na/Naphthylene and hydrogenation to afford 4,4,6-trimethyl carprolactam in 85% yield.

of **4a-*A*** and **4a-*B*** will result the same π-allyl-Pd^{II} intermediate **II-*d*** and afford the similar results containing the mixture of equal amounts of **5a-*A*** and **5a-*B*** (with negligible secondary isotope effect, see Scheme 2, path a). Otherwise,

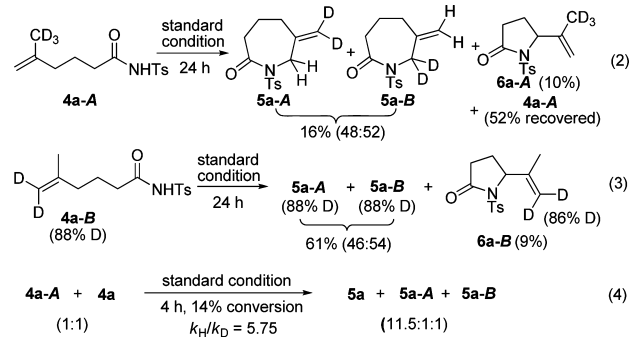
Scheme 2. Hypothesis of Two Possible Mechanisms (AMP = Aminopalladation)



if the reaction goes through aminopalladation/β-H elimination pathway, the reactions of **4a-*A*** and **4a-*B*** would be formed seven-membered products **5a-*A*** and **5a-*B*** respectively (path b).

The reactions with D-labeled substrate **4a-*A*** afforded a mixture of **5a-*A*** and **5a-*B*** with a ratio of 48:52 in low yield (16%), and the five-membered product **6a-*A*** (10%)[17] (eq 2). Substrate **4a-*A*** was recovered in 52% yield without alkene isomerization. For the substrate **4a-*B***, the reaction also produced the mixture of **5a-*A*** and **5a-*B*** with the ratio 46:54 in 61% yield, and **6a-*B*** in 9% yield (eq 3). The formations of mixtures of **5a-*A*** and **5a-*B*** with roughly 1:1 ratio in both reactions exclude the aminopalladation/β-H elimination pathway. Furthermore, the lower conversion of **4a-*A*** is probably resulted from a higher energy barrier of the allylic C-D activation. The kinetic isotopic effect (KIE) of allylic C−H activation was obtained with a 1:1 mixture of **4a** and **4a-*A***, and the large primary KIE value (k_H/k_D = 5.75) supports our hypothesis of a turnover-limiting allylic C−H activation pathway (eq 4).[18,19]

(17) The formation of **6a-*A*** also supports the allylic C-H activation pathway, see Supporting Information Scheme S2 for details.



In conclusion, we have developed a new palladium-catalyzed intramolecular aerobic oxidative allylic amination of unactivated olefins. Brønsted base can modulate the regioselectivity, favoring the formation of 7-membered products. This methodology provides an efficient route for the synthesis of seven-membered cyclic amides. Mechanistic studies support that the reaction proceeds through a rate-determining allylic C−H activation/irreversible reductive elimination pathway to form the C−N bond.

Acknowledgment. This work was supported by the Chinese Academy of Science, the National Natural Science Foundation of China (20821002, 20872155), the National Basic Research Program of China (973-2009CB825300) and the Science and Technology Commission of the Shanghai Municipality (Pujiang Program, 08PJ1411600). G.L. thanks Prof. S. S. Stahl at Unversity of Wisconsin-Madison for helpful discussion.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For the stoichiometric reaction of $PdCl_2$ and methylenecyclo-hexane, the *KIE* values (4.55−5.45) of allylic C−H activation were observed, see: (a) Chrisope, D. R.; Beak, P. *J. Am. Chem. Soc.* **1986**, *108*, 334. (b) Chrisope, D. R.; Beak, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 230.

(19) The formation of seven-membered product **2a** is the kinetically preferred product formation and the C−N bond formation is irreversible step, for more detail see Supporting Information.