

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

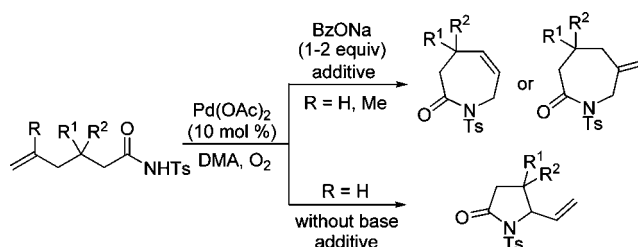
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## ABSTRACT



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.<sup>1</sup> Among transition-metal promoted cyclizations of alkenes, palladium-catalyzed oxidative aminations represent one of the most efficient synthetic routes for nitrogen-containing heterocycles.<sup>2</sup> An even more desirable approach for catalytic C–N bond formation is the dioxygen-coupled oxidative amination of olefins.<sup>3</sup> 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.<sup>4</sup> 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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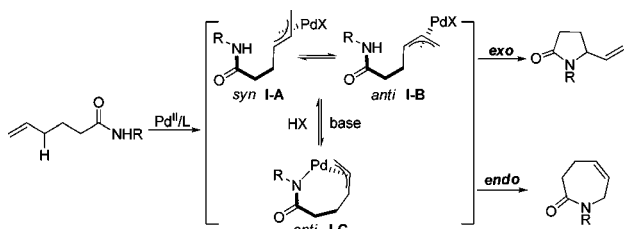
(5) The seven-membered amides are important intermediates for the synthesis of biological compounds and materials, see: (a) Proctor, G. R.; Redpath, J. In *Monocyclic Azepines*; Taylor, E. C. Eds.; Wiley-VCH: New York, 1996. (b) Hutchison, G. I.; Prager, R. H.; Ward, A. D. *Austra. J. Chem.* **1980**, *33*, 2477. (c) Maier, S.; Loontjens, T.; Scholtens, B.; Mülhaupt, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5094, and reference therein.

(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.

formation.<sup>5,6</sup> 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;<sup>7,8</sup> for instance, Rh-catalyzed C–H amination through highly reactive metallo-niteneoids,<sup>7a–d</sup> Pd- or Cu-mediated C–H oxidative amination assisted by directing groups,<sup>7e–g,8</sup> and Pd-catalyzed allylic C–H oxidative amination.<sup>6b,c,9</sup> The latter have proposed a  $\pi$ -allylpalladium species as key intermediates. For intramolecular cyclizations, since the  $\pi$ -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<sup>II</sup>-Mediated Intramolecular Oxidative Allylic C–H Amination of Alkenes



base can promote the Pd–N bond formation<sup>10</sup> 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)<sub>2</sub> under aerobic condition yielded 20% five-membered ring product **3a** with high regioselectivity (Table 1, entry 1). To our surprise, the seven-

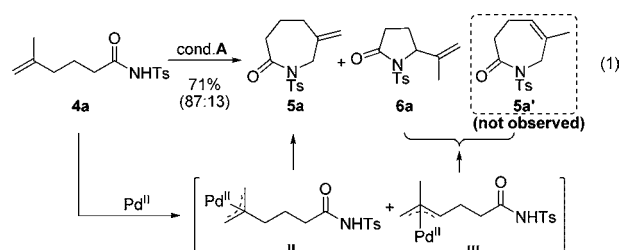
**Table 1.** Pd-Catalyzed Intramolecular Oxidative Amination of **1a**<sup>a</sup>

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

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

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).<sup>11</sup> On the other hand, **3a** can also be obtained in good yield by adding (salen)Cr<sup>III</sup>Cl, an additive first reported by White and co-workers (condition B, entry 4).<sup>9a,12</sup> However, when base is added to the system containing (salen)Cr<sup>III</sup>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.<sup>13</sup>

The base-promoted regioselective formation of 7-membered 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.; Lécourt, 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.

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(10) For the N–Pd bond formation promoted by Brønsted base, see: (a) Muñoz, 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<sup>a</sup>

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

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

reaction of **4a** is expected to favor  $\pi$ -allylpalladium intermediates **II** over **III** due to the higher activity of the terminal methyl over the internal methylene group.<sup>14</sup> 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.<sup>15</sup> 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  $\beta$ -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).<sup>16</sup> The seven-membered rings **5j–5l** containing two heteroatoms 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 proceed through an allylic C–H activation/reductive elimination pathway, or an aminopalladation/ $\beta$ -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**<sup>a</sup>

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

<sup>a</sup> Reaction condition: **4** (0.2 mmol), Pd(OAc)<sub>2</sub> (10 mol %), NaOBz (1 equiv), MA (40 mol %), 4 Å MS (30 mg) in DMA (2 mL) under 1 atm O<sub>2</sub>, 70 °C. <sup>b</sup> Isolated yield. <sup>c</sup> NaOBz (2.5 equiv). <sup>d</sup> NaOBz (1.5 equiv), 20 h. <sup>e</sup> Scale: 1.5 mmol. <sup>f</sup> 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.

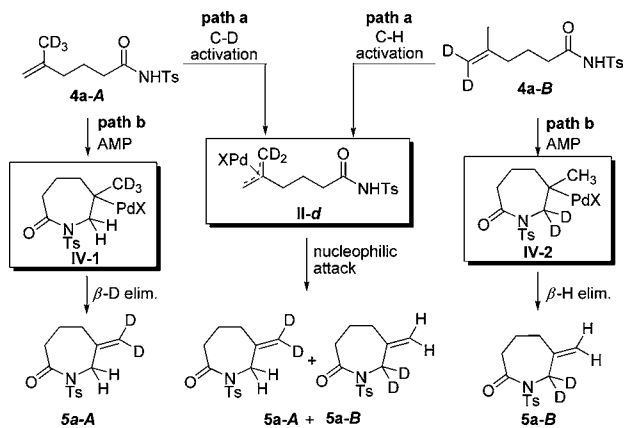
(14) Maitlis, P. M. In *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vol. I, p 175.

(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 2 also excludes this possibility.

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

of **4a-A** and **4a-B** will result the same  $\pi$ -allyl-Pd<sup>II</sup> 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,

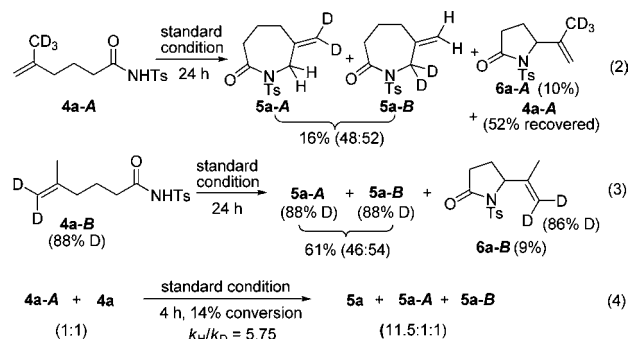
**Scheme 2.** Hypothesis of Two Possible Mechanisms (AMP = Aminopalladation)



if the reaction goes through aminopalladation/ $\beta$ -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%)<sup>17</sup> (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/ $\beta$ -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).<sup>18,19</sup>

(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.

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**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<sub>2</sub> 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.