## Palladium-Catalyzed Cyclization Reactions of 2,3-Allenyl Amines with Propargylic Carbonates

LETTERS 2012 Vol. 14, No. 9 2312–2315

ORGANIC

## Juntao Ye,<sup>†</sup> Suhua Li,<sup>†</sup> and Shengming Ma<sup>\*,†,‡</sup>

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China, and Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai 200062, P. R. China

masm@sioc.ac.cn

Received March 21, 2012



A highly efficient and atom-economic route to synthesize 5-(1,3,4-alkatrien-2-yl)oxazolidin-2-ones via palladium-catalyzed cyclization reactions of 2,3-allenyl amines with propargylic carbonates was reported. The  $CO_2$  generated in situ from propargylic carbonates is incorporated into the oxazolidin-2-one unit with high efficiency, affording the products in 70–92% yields.

Oxazolidin-2-ones are an important class of compounds of broad interest as both synthetic intermediates<sup>1</sup> and

(2) For reviews, see: (a) Brickner, S. J. Curr. Pharm. Des. 1996, 2, 175.
(b) Barbachyn, M. R.; Ford, C. W. Angew. Chem., Int. Ed. 2003, 42, 2010. (c) Renslo, A. R.; Luehr, G. W.; Gordeev, M. F. Bioorg. Med. Chem. 2006, 14, 4227. (d) Shaw, K. J.; Barbachyn, M. R. Ann. N.Y. Acad. Sci. 2011, 1241, 48.

(3) For some of the most recent examples on the synthesis of oxazolidin-2-ones, see: (a) Paz, J.; Pérez-Balado, C.; Iglesias, B.; Muñoz, L. J. Org. Chem. 2010, 75, 3037. (b) Schindler, C. S.; Forster, P. M.; Carreira, E. M. Org. Lett. 2010, 12, 4102. (c) Phung, C.; Pinhas, A. R. Tetrahedron Lett. 2010, 51, 4552. (d) Fontana, F.; Chen, C. C.; Aggarwal, V. K. Org. Lett. 2011, 13, 3454. (e) Kim, C.; Ko, S. Y. Bull. Korean Chem. Soc. 2011, 32, 4450. (f) Kojima, R.; Sawamoto, S.; Okamura, A.; Takahashi, H.; Tsunoi, S.; Shibata, I. Eur. J. Org. Chem. 2011, 7255. (g) Watile, R. A.; Bagal, D. B.; Patil, Y. P.; Bhanage, B. M. Tetrahedron Lett. 2011, 52, 6383. (h) Grigg, R. D.; Rigoli, J. W.; Pearce, S. D.; Schomaker, J. M. Org. Lett. 2012, 14, 280.

10.1021/ol3007293 © 2012 American Chemical Society Published on Web 04/26/2012 biologically active molecules.<sup>2</sup> Given the versatile utilities of oxazolidin-2-ones, considerable effort has been made in the synthesis of the oxazolidin-2-one skeleton and numerous methodologies have been reported.<sup>1a,f,3</sup> Among the reported methods, the oxazolidin-2-one nucleus is generally prepared from amino alcohols by carbonylation using phosgene or its functional equivalent or by oxidative carbonylation utilizing CO and Pd catalysts, which require the use of either highly hazardous chemicals or harsh reaction conditions. Methods for the preparation of oxazolidin-2-ones containing amendable functionalities for further elaborations have yet to be well established.

Since Tsuji's first report in 1985,<sup>4</sup> palladium-catalyzed transformations of propargylic carbonates have become a powerful tool for constructing carbon–carbon and carbon–heteroatom bonds.<sup>5</sup> Recently, we have developed the Pd-catalyzed cyclization of allenes bearing a nucleophilic

<sup>&</sup>lt;sup>†</sup>Chinese Academy of Sciences.

<sup>&</sup>lt;sup>‡</sup>East China Normal University.

For reviews, see: (a) Dyen, M. A.; Swern, D. Chem. Rev. 1967, 67, 197.
 (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. Pure Appl. Chem. 1981, 53, 1109.
 (c) Evans, D. A. Aldrichimica Acta 1982, 15, 23.
 (d) Ager, D. J.; Prakash, I.; Schaad, D. R. Chem. Rev. 1996, 96, 835.
 (e) Ager, D. J.; Prakash, I.; Schaad, D. R. Aldrichimica Acta 1997, 30, 3.
 (f) Zappia, G.; Gacs-Baitz, E.; Monache, G. D.; Misiti, D.; Nevola, L.; Botta, B. Curr. Org. Chem. 2007, 4, 81.
 (g) Zappia, G.; Cancelliere, G.; Gacs-Baitz, E.; Monache, G. D.; Misiti, D.; Nevola, L.; Botta, B. Curr. 079, 74, 283.

<sup>(4)</sup> Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. J. Am. Chem. Soc. **1985**, 107, 2196.

<sup>(5)</sup> For reviews on Pd-catalyzed transformations of propargylic carbonates, see: (a) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (b) Tsuji, J. *Palladium Reagents and Catalysts*; JohnWiley & Sons Ltd.: U.K., 2004; pp 543–564. (c) Guo, L.; Duan, X.; Liang, Y. *Acc. Chem. Res.* **2011**, *44*, 111 and references cited therein.

moiety in the presence of propargylic carbonates affording allenyl cyclic products, in which the CO<sub>2</sub> was eliminated and released.<sup>6</sup> Based on these previous works and retrosynthetic analysis, we envisioned that allenic oxazolidin-2ones **3** may be efficiently constructed by using 2,3-allenyl amines<sup>7</sup> **1** and propargylic carbonate **2** in an atomeconomic manner provided that the to-be-released CO<sub>2</sub> can be recycled<sup>8</sup> intermolecularly with high efficiency (**3** and **6** vs **4** and **5**, Scheme 1) and the issue of regioselectivity can be addressed (**3** vs **6**, Scheme 1). Herein, we report an efficient synthesis of 5-(1,3,4-alkatrien-2-yl)oxazolidin-2-one **3** via palladium-catalyzed cyclization reactions of 2,3-allenyl amines in the presence of propargylic carbonates with the *in situ* generated CO<sub>2</sub> recycled under mild conditions.

Scheme 1. Concepts and Selectivity Issue for the Synthesis of Allenic Oxazolidin-2-ones 3



Initially, terminal 2,3-allenyl amine **1a** and propargylic carbonate **2a** were chosen to test the feasibility of our hypothesis. Gratifyingly, the expected product **3aa** was

obtained in 94% NMR yield and 88% isolated yield by using 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>, 1.5 equiv of **2a**, and 2 equiv of K<sub>2</sub>CO<sub>3</sub> in DMSO at 70 °C for 4 h (entry 1, Table 1). Also, we were pleased to find that the formation of 4- and 5-types of non-CO<sub>2</sub>-incorporated cyclization products<sup>9,10</sup> or the 6-type CO<sub>2</sub>-incorportaed regioisomer was not observed. Encouraged by these results, further optimization of the reaction conditions was carried out subsequently. Changing the palladium catalyst (entries 2 and 3, Table 1) or the solvent (entries 4-7, Table 1) led to a decrease in the yield of 3aa. Other bases such as Cs<sub>2</sub>CO<sub>3</sub> or NEt<sub>3</sub> were less effective (entries 8 and 9, Table 1). Notably, 66% and 75% NMR yields of 3aa were observed even in the absence of  $K_2CO_3$ , indicating that the CO<sub>2</sub> trapped in the oxazolidin-2-one indeed comes from propargylic carbonates (entries 9 and 10, Table 1). Lowering or elevating the temperature proved to be deleterious (entries 11 and 12, Table 1) whereas lowering the amount of 2a to 1.2 equiv improved the yield of 3aa to 99% by NMR (entry 13, Table 1). In contrast, increasing the amount of 2a to 2 equiv resulted in a lower yield of 3aa (entry 14, Table 1). Thus, 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>, 1.2 equiv of 2a, and 2 equiv of K<sub>2</sub>CO<sub>3</sub> in DMSO at 70 °C for 4 h were established as the standard conditions for further study.

Table 1. Optimization of Reaction Conditions for thePd-Catalyzed Cyclization of 1a with  $2a^a$ 



entry	[Pd]	solvent	base	yield of <b>3aa</b> (%) <sup>b</sup>
1	$Pd(PPh_3)_4$	DMSO	$K_2CO_3$	$94(88)^{c}$
2	$Pd(dba)_2/TFP^d$	DMSO	$K_2CO_3$	52
3	Pd(OAc) <sub>2</sub> /TFP <sup>e</sup>	DMSO	$K_2CO_3$	67
4	$Pd(PPh_3)_4$	$CH_3CN$	$K_2CO_3$	89
5	$Pd(PPh_3)_4$	DMF	$K_2CO_3$	82
6	$Pd(PPh_3)_4$	THF	$K_2CO_3$	39
7	$Pd(PPh_3)_4$	DCE	$K_2CO_3$	77
8	$Pd(PPh_3)_4$	DMSO	$Cs_2CO_3$	22
9	$Pd(PPh_3)_4$	DMSO	NEt <sub>3</sub>	66
10	$Pd(PPh_3)_4$	DMSO	f	75
$11^g$	$Pd(PPh_3)_4$	DMSO	$K_2CO_3$	72
$12^h$	$Pd(PPh_3)_4$	DMSO	$K_2CO_3$	36
$13^i$	$Pd(PPh_3)_4$	DMSO	$K_2CO_3$	99
$14^{j}$	$Pd(PPh_3)_4$	DMSO	$K_2CO_3$	83

<sup>*a*</sup> The reaction was carried out on a 0.1 mmol scale of **1a** in 1 mL of the indicated solvent. <sup>*b*</sup> NMR yield of **3aa** determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard. <sup>*c*</sup> The value in parentheses is the isolated yield of **3aa**. <sup>*d*</sup> Pd(dba)<sub>2</sub>(5 mol %) and TFP (10 mol %) were used; TFP = tri-(2'-furyl)phosphine. <sup>*e*</sup> Pd(OAc)<sub>2</sub> (5 mol %) and TFP (10 mol %) were used. <sup>*f*</sup> No base was added. <sup>*g*</sup> Run at 50 °C. <sup>*h*</sup> Run at 90 °C. <sup>*i*</sup> **2a** (1.2 equiv) was used.

<sup>(6) (</sup>a) Ma, S.; Gu, Z.; Deng, Y. *Chem. Commun.* **2006**, 94. (b) Shu, W.; Jia, G.; Ma, S. *Org. Lett.* **2009**, *11*, 117. (c) Shu, W.; Ma, S. *Tetrahedron* **2010**, *66*, 2869. (d) Chen, G.; Zhang, Y.; Fu, C.; Ma, S. *Tetrahedron* **2011**, *67*, 2332.

<sup>(7)</sup> For a report on the synthesis of oxazolidin-2-ones by Pd-catalyzed cyclization of 2,3-allenyl amines with pressurized  $CO_2$  in 2–65% NMR yields, see: Kayaki, Y.; Mori, N.; Ikariya, T. *Tetrahedron Lett.* **2009**, *50*, 6491.

<sup>(8)</sup> For reviews on synthesis of cyclic carbonates via intramolecular "CO<sub>2</sub> recycling" from allylic or propargylic carbonates, see: (a) Yoshida, M.; Ihara, M. *Chem.—Eur. J.* **2004**, *10*, 2886. (b) Yoshida, M. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 160and references cited therein. For reports on the synthesis of oxazolidin-2-ones, see: (c) Yoshida, M.; Ohsawa, Y.; Sugimoto, K.; Tokuyama, H.; Ihara, M. *Tetrahedron Lett.* **2007**, *48*, 8678. (d) Yoshida, M.; Komatsuzaki, Y.; Ihara, M. *Org. Lett.* **2008**, *10*, 2083.

<sup>(9)</sup> For reviews on Pd-catalyzed cyclization of allenes with a nucleophilic moiety, see: (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (c) Ma, S. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer-Verlag: Heidelberg, 2005; pp 183–210. (d) Alcaide, B.; Almendros, P.; del Campo, T. M. *Chem.—Eur. J.* **2010**, *16*, 5836.

<sup>(10)</sup> For selected examples on Pd-catalyzed cyclization reactions of 2,3-allenyl amines with organic halides, see: (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Tanaka, T.; Ibuka, T. J. Org. Chem. **1999**, 64, 2992. (b) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. J. Org. Chem. **2001**, 66, 4904 and references cited therein. (c) Dieter, R. K.; Yu, H. Org. Lett. **2001**, 2, 3855. (d) Shibata, T.; Kadowaki, S.; Takagi, K. Heterocycles **2002**, 57, 2261. (e) Ma, S.; Yu, F.; Gao, W. J. Org. Chem. **2003**, 68, 5943. (f) Shu, W.; Yu, Q.; Jia, G.; Ma, S. Chem.—Eur. J. **2011**, 17, 4720.

**Table 2.** Palladium-Catalyzed Cyclization of Unsubstituted 2,3-Allenyl Amines 1a-d in the Presence of Propargylic Carbonates $2a-h^a$ 



<sup>*a*</sup> The reaction was carried out on a 0.3 mmol scale of **1** in DMSO (3 mL) in a Schlenk tube unless otherwise noted. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> The reaction was carried out with 6.3 mmol of **1a** and 7.56 mmol of **2a** in a three-necked flask. <sup>*d*</sup> **1d** ·HCl was used as the starting material with  $K_2CO_3$  (3 equiv) as the base. Bn = benzyl, PMB = *p*-methoxybenzyl, TBDMS = *tert*-butyldimethylsilyl.

With the optimized reaction conditions in hand, the scope of the propargylic carbonates **2** and terminal 2,3butadienyl amines **1** were first investigated as shown in Table 2. The substituent on the C–C triple bond of propargylic carbonates  $\mathbb{R}^2$  can be aryl (entries 1–6, Table 2) or alkyl groups (entries 7–9, Table 2), furnishing the corresponding products **3aa–3ah** in good to excellent yields. In addition to **1a**, secondary 2,3-butadienyl amines **1b** or **1c** with a PMB or *n*-butyl protective group (entries 10 and 11, Table 2) or primary 2,3-butadienyl amine **1d** (entry 12, Table 2) are also suitable substrates for the reaction. It is noteworthy that the reaction can be easily conducted using substrate **1a** on a gram scale with 1.2 equiv of **2a**, affording **3aa** in 90% yield (entry 2, Table 2).

Next, we examined the reaction of 4-monosubstituted 2,3-allenyl amine **1e** with propargylic carbonate **2a**. The product **3ea** was obtained as a mixture of stereoisomers with a ratio of Z/E = 82:18 as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture (Scheme 2).

However, when 4,4-disubstituted 2,3-allenyl amine 1f was subjected to the standard conditions mentioned above, the corresponding product 3fa was obtained in a rather low yield (entry 1, Table 3). Interestingly, a brief survey of the palladium catalyst and phosphine ligand showed that the combination of Pd(OAc)<sub>2</sub> (5 mol %) and TFP (10 mol %)

Scheme 2. Cyclization of 4-Monosubstituted 2,3-Allenyl Amines 1e



improved the yield of 3fa to 72% by NMR (entry 3, Table 3).





<sup>*a*</sup> The reaction was carried out on a 0.1 mmol scale of **1f** in DMSO (1 mL) in a Schlenk tube. <sup>*b*</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard. <sup>*c*</sup> No ligand was added. dppe = 1,2-Bis(diphenylphosphino)ethane.

Under this set of improved conditions, 4,4-disubstituted 2,3-allenyl amines **1f** and **1g** underwent the reaction smoothly, affording the corresponding products **3fa** and **3ga** in 70% and 72% yields, respectively (Scheme 3).

Scheme 3. Cyclization of 4,4-Disubstituted 2,3-Allenyl Amines 1f and 1g



A plausible mechanism is proposed as shown in Scheme 4. Oxidative addition of 2 with Pd(0) would afford allenylpalladium intermediate Int 1 with simultaneous generation of

Scheme 4. A Possible Mechanism



the yet *unreleased* molecule of  $CO_2$  probably due to its coordination with Pd,<sup>4,5</sup> which must have been captured by 2,3-allenyl amines **1** efficiently in the presence of a base forming carbamate intermediate **Int 2**.<sup>11</sup> The reaction of **1** with  $CO_2$  may involve a cyclic intermediate with hydrogen

bonding.<sup>12</sup> The subsequent transformation involving **Int 1** and **Int 2** may proceed through two possible pathways: Carbopalladation of the allene moiety of **Int 2** would generate the  $\pi$ -allyl palladium species **Int 3**, and subsequent nucleophilic attack by the oxygen anion would afford the product **3** and regenerate the catalytically active Pd(0) (path a). Alternatively, anti-oxypalladation of **Int 4** followed by reductive elimination would also give **3** and regenerate Pd(0) (path b).<sup>9</sup>

In conclusion, we have developed an efficient method for the synthesis of 5-(1,3,4-alkatrien-2-yl)oxazolidin-2-ones via palladium-catalyzed cyclization reactions of 2,3allenyl amines with propargylic carbonates with the *in situ* generated CO<sub>2</sub> recycled. Due to the easy availability of the starting materials and good to excellent yields of the reaction, this methodology will be of interest to the scientific community. Further studies on the scope and mechanism of the reaction as well as synthetic applications of the products are currently underway in our laboratory.

Acknowledgment. Financial support from National Basic Research Program of China (2011CB808700) and National Natural Science Foundation of China (No. 20732005) is greatly appreciated. We thank Mr. Bo Lü in our group for reproducing the results presented in entry 11 of Table 2 and entry 1 in Scheme 3.

**Supporting Information Available.** Detailed experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

<sup>(11)</sup> Sakakura, T.; Choi, J.; Yasuda, H. Chem. Rev. 2007, 107, 2365. (12) For alkoxide/alcohol exchange of palladium alkoxide complexes with alcohols via hydrogen bonding, see: (a) Kim, Y.-J.; Osakada, K.; Takenaka, A.; Yamamoto, A. J. Am. Chem. Soc. 1990, 112, 1096. (b) Gordillo, A.; Lloyd-Jones, G. C. Chem.-Eur. J. 2012, 18, 2660 and references cited therein. For reports on the reaction of amides with CO<sub>2</sub>, see: (c) Chen, G.; Fu, C.; Ma, S. Org. Lett. 2009, 11, 2900. (d) Chen, G.; Fu, C.; Ma, S. Org. Biomol. Chem. 2011, 9, 105.

The authors declare no competing financial interest.