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

Juntao Ye,[†] Suhua Li,[†] and Shengming Ma*[,†,‡]

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

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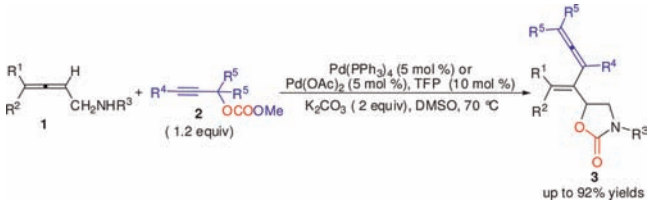
ABSTRACT



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[1] and biologically active molecules.[2] 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.[1a,f,3] 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,[4] palladium-catalyzed transformations of propargylic carbonates have become a powerful tool for constructing carbon−carbon and carbon−heteroatom bonds.[5] Recently, we have developed the Pd-catalyzed cyclization of allenes bearing a nucleophilic

[†] Chinese Academy of Sciences.
[‡] East China Normal University.

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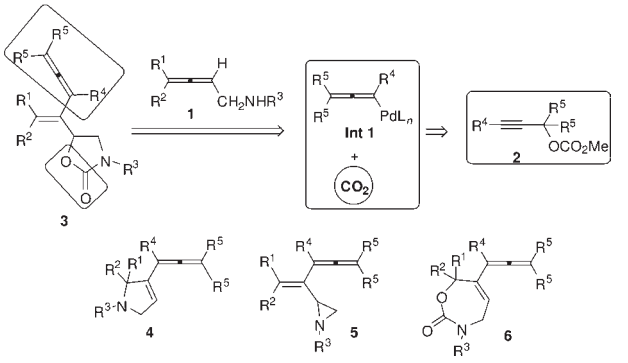
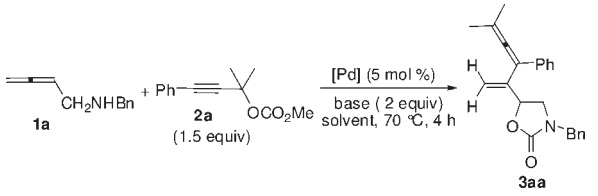
moiety in the presence of propargylic carbonates affording allenyl cyclic products, in which the CO_2 was eliminated and released.[6] Based on these previous works and retrosynthetic analysis, we envisioned that allenic oxazolidin-2-ones **3** may be efficiently constructed by using 2,3-allenyl amines[7] **1** and propargylic carbonate **2** in an atom-economic manner provided that the to-be-released CO_2 can be recycled[8] 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_2 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 % $Pd(PPh_3)_4$, 1.5 equiv of **2a**, and 2 equiv of K_2CO_3 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_2-incorporated cyclization products[9,10] or the **6**-type CO_2-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_2CO_3 or NEt_3 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_2 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 % $Pd(PPh_3)_4$, 1.2 equiv of **2a**, and 2 equiv of K_2CO_3 in DMSO at 70 °C for 4 h were established as the standard conditions for further study.

Table 1. Optimization of Reaction Conditions for the Pd-Catalyzed Cyclization of **1a** with **2a**[a]



entry	[Pd]	solvent	base	yield of **3aa** (%)[b]
1	$Pd(PPh_3)_4$	DMSO	K_2CO_3	94(88)[c]
2	$Pd(dba)_2$/TFP[d]	DMSO	K_2CO_3	52
3	$Pd(OAc)_2$/TFP[e]	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_3	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

[a] The reaction was carried out on a 0.1 mmol scale of **1a** in 1 mL of the indicated solvent. [b] NMR yield of **3aa** determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard. [c] The value in parentheses is the isolated yield of **3aa**. [d] $Pd(dba)_2$ (5 mol %) and TFP (10 mol %) were used; TFP = tri-(2′-furyl)phosphine. [e] $Pd(OAc)_2$ (5 mol %) and TFP (10 mol %) were used. [f] No base was added. [g] Run at 50 °C. [h] Run at 90 °C. [i] **2a** (1.2 equiv) was used. [j] **2a** (2 equiv) was used.

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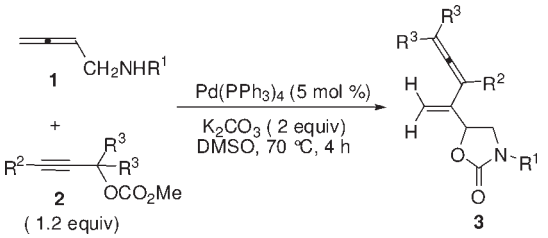
Table 2. Palladium-Catalyzed Cyclization of Unsubstituted 2,3-Allenyl Amines **1a**–**d** in the Presence of Propargylic Carbonates **2a**–**h**[a]



entry	R^1	R^2, R^3, R^3	yield of **3** (%)[b]
1	Bn (**1a**)	Ph, Me, Me (**2a**)	92 (**3aa**)
2[c]	Bn (**1a**)	Ph, Me, Me (**2a**)	90 (**3aa**)
3	Bn (**1a**)	Ph, Et, Et (**2b**)	90 (**3ab**)
4	Bn (**1a**)	Ph, -$(CH_2)_4$- (**2c**)	85 (**3ac**)
5	Bn (**1a**)	Ph, -$(CH_2)_5$- (**2d**)	86 (**3ad**)
6	Bn (**1a**)	4-$NO_2C_6H_4$, Me, Me (**2e**)	85 (**3ae**)
7	Bn (**1a**)	Me, Me, Me (**2f**)	80 (**3af**)
8	Bn (**1a**)	*n*-Bu, Me, Me (**2g**)	83 (**3ag**)
9	Bn (**1a**)	$CH_2OTBDMS$, Me, Me (**2h**)	70 (**3ah**)
10	PMB (**1b**)	Ph, Me, Me (**2a**)	87 (**3ba**)
11	*n*-Bu (**1c**)	Ph, Me, Me (**2a**)	82 (**3ca**)
12	H (**1d**)[d]	Ph, Me, Me (**2a**)	75 (**3da**)

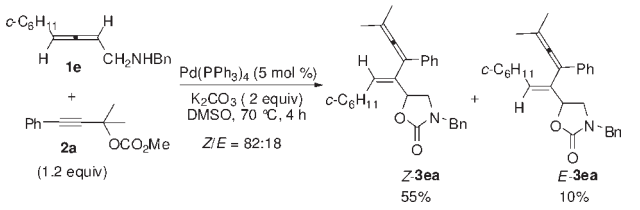
[a] The reaction was carried out on a 0.3 mmol scale of **1** in DMSO (3 mL) in a Schlenk tube unless otherwise noted. [b] Isolated yields. [c] The reaction was carried out with 6.3 mmol of **1a** and 7.56 mmol of **2a** in a three-necked flask. [d] **1d**·HCl was used as the starting material with K_2CO_3 (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 2,3-butadienyl amines **1** were first investigated as shown in Table 2. The substituent on the C–C triple bond of propargylic carbonates 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 ^{1}H NMR analysis of the crude reaction mixture (Scheme 2).

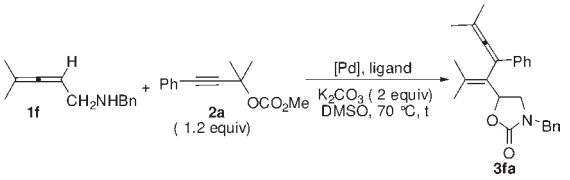
However, when 4,4-disubstituted 2,3-allenyl amine **1f** was subjected to the standard conditions mentioned above, the corresponding product **3fa** was obtained in a rather low yield (entry 1, Table 3). Interestingly, a brief survey of the palladium catalyst and phosphine ligand showed that the combination of $Pd(OAc)_2$ (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).

Table 3. Palladium Catalyst and Ligand Screening for the Cyclization of 4,4-Disubstituted 2,3-Allenyl Amine **1f**[a]

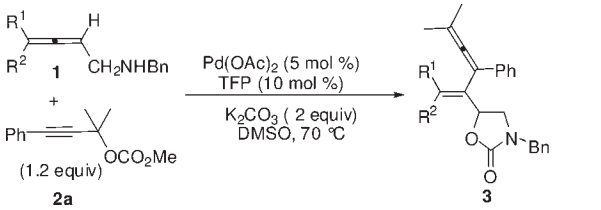


entry	[Pd] (mol %)	ligand (mol %)	*t* (h)	yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	–[c]	4	22
2	$Pd(dba)_2$ (5)	TFP (10)	6	68
3	$Pd(OAc)_2$ (5)	TFP (10)	6	72
4	$Pd(OAc)_2$ (5)	dppe (5)	6	39

[a] The reaction was carried out on a 0.1 mmol scale of **1f** in DMSO (1 mL) in a Schlenk tube. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard. [c] 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**

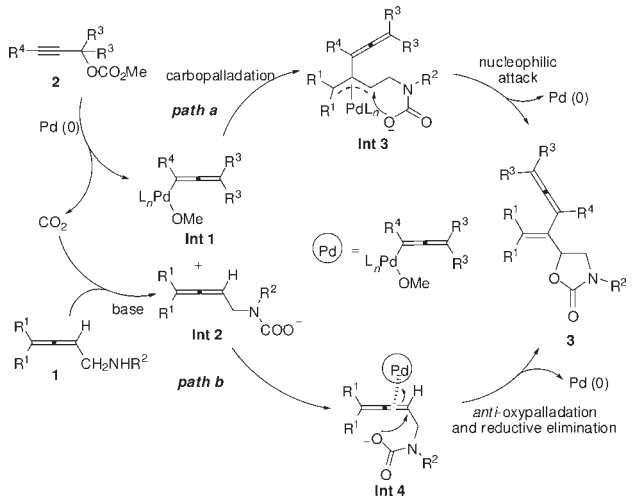


1) $R^1 = R^2$ = Me (**1f**), 5.5 h, 70% (**3fa**)

2) R^1, R^2 = -$(CH_2)_5$- (**1g**), 2 h, 72% (**3ga**)

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,[4,5] which must have been captured by 2,3-allenyl amines **1** efficiently in the presence of a base forming carbamate intermediate **Int 2**.[11] The reaction of **1** with CO_2 may involve a cyclic intermediate with hydrogen bonding.[12] 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 π-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).[9]

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 2,3-allenyl amines with propargylic carbonates with the *in situ* generated CO_2 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.

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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.

The authors declare no competing financial interest.

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