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Synthesis of vinyloxazolidinones by palladium-catalyzed CO_2-recycling reaction of 4-(benzylamino)-2-butenyl carbonates

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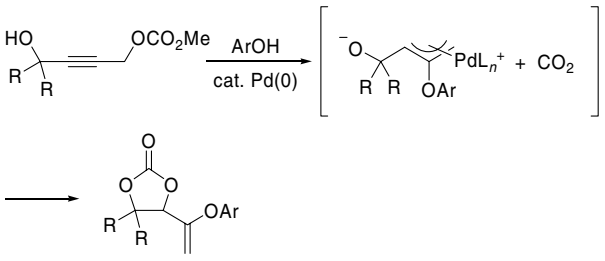
Abstract—A CO_2-recycling reaction using (*E*)-4-(benzylamino)-2-butenyl methyl carbonates has been examined and substituted vinyloxazolidinones were obtained via a CO_2 fixation–elimination process, carried out in the presence of palladium catalyst with DBU.

A number of 5-substituted oxazolidinones are shown to have high potency as biologically active molecules, and are widely used in the pharmaceutical industry.[1] Consequently, much attention and extensive study have been focused on the synthesis of oxazolidinones, and the chemical fixation of CO_2 with aziridines[2] or propargylic amines[3] is one of the most useful and efficient methods.[4] In these reactions, an external CO_2 source has been mostly utilized by carrying out the reactions under high or atmospheric pressure of CO_2 gas. However, an excess amount of CO_2 is required in these methodologies, which is less efficient from a viewpoint of atom economy.[5] Recently, we have developed a novel type of palladium-catalyzed reaction using propargylic carbonates with phenols, which involves a CO_2-recycling process (Scheme 1).[6] The reaction proceeds through a pathway involving decarboxylation–fixation of liberated CO_2 to afford phenoxy-substituted cyclic carbonates. This process can be successfully applied to a palladium-catalyzed reaction using allylic and 2,4-dienylic carbonates.[7] In these reactions, the formation of π-allylpalladium intermediate followed by fixation of CO_2 is a key step. We expected that this CO_2-recycling process could apply for the synthesis of oxazolidinones by using allylic carbonates bearing an amino group at the allylic position. Palladium-catalyzed fixation of CO_2 has been widely



Scheme 1. Palladium-catalyzed CO_2-recycling reaction of propargylic carbonates with phenols.

applied in the synthesis of cyclic carbonates,[6a] but the examples about the synthesis of oxazolidinones are limited.[3c,d] We report here a palladium-catalyzed reaction of 4-(benzylamino)-2-butenyl carbonates to produce 5-vinyloxazolidinones via a CO_2-recycling process.

The initial reactions were carried out using the 4-cyclohexyl-substituted substrate **1a**.[8] When **1a** was subjected to the reaction with 10 mol % of $Pd(PPh_3)_4$ in MeCN at 50 °C, aziridine **3a**,[9] having a non-CO_2 moiety, was produced in 51% yield (Table 1, entry 1).[10] Further attempts toward the CO_2-recycling process revealed that the desired oxazolidinone **2a** was predominantly yielded by carrying out the reaction in the presence of amine base. Thus, vinyloxazolidinone **2a** was obtained in 46% yield when 2 equiv of triethylamine was added (entry 2). The reactions in the presence of pyridine and

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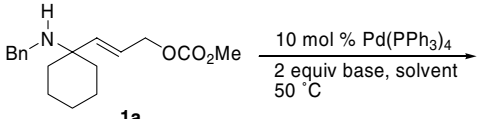
Table 1. Initial attempts for the palladium-catalyzed CO_2-recycling reactions of **1a**



1a → **2a** + **3a**

Entry	Base	Solvent	Yields (%)	
			2a	**3a**
1	—	MeCN	—	51
2	NEt_3	MeCN	46	—
3	Pyridine	MeCN	52	18
4	DABCO	MeCN	52	—
5	DBU	MeCN	57	—
6	Cs_2CO_3	MeCN	—	81
7	NaOMe	MeCN	N.R.	
8	DBU	DMF	51	—
9	DBU	HMPA	47	4
10	DBU	Toluene	—	80
11	DBU	THF	—	68

DABCO also proceeded (entries 3 and 4), and the yield of **2a** was increased to 57% by the addition of DBU (entry 5). On the other hand, inorganic bases such as Cs_2CO_3 or NaOMe were not effective (entries 6 and 7), which implies that the presence of amine base is necessary for the CO_2-recycling reaction. Oxazolidinone **2a** was also afforded in moderate yields when DMF and HMPA were used as solvents (entries 8 and 9), but aziridine **3a** was selectively yielded from the reactions in toluene and THF (entries 10 and 11).

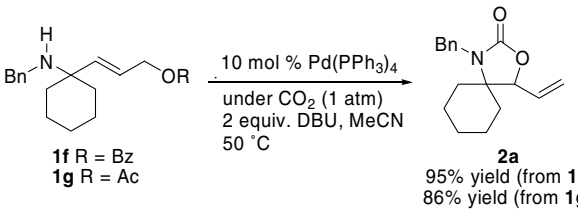
The results of the reactions using allylic carbonates **1b**–**1e**, which contain substituents at the allylic positions, are shown in Table 2. The reaction of diethyl-substituted substrate **1b** under optimized condition yielded oxazolidinone **2b** (19%) along with aziridine **3b** (8%) (entry 1). Although the yield of **2b** was low, it was improved to 57% by carrying out the reaction under a CO_2 atmosphere as an external CO_2 source (entry 2). Substrates **1c**, **1d**, and **1e**, having dipentyl, di-β-cyclohexylethyl, and methylphenyl groups, were also ineffective (entries 3, 5, and 7), presumably because of the difficulty of re-fixation of CO_2 by the steric hinderance of substituents.[11] These substrates were successfully transformed to the corresponding oxazolidinones **2c**, **2d**, and **2e** by carrying out under CO_2 atmosphere (entries 4, 6, and 8).

To examine whether CO_2 dissociates from the substrate in the reaction, several experiments were attempted. We initially examined the reactions of allylic esters **1f** and **1g**, having a non-CO_2 liberating group, in the presence of CO_2 (Scheme 2). When allylic benzoate **1f** and acetate **1g** were subjected to the palladium catalyst in the presence of DBU under an atmosphere of CO_2, the corresponding oxazolidinone **2a** was produced in 95% and 86% yields, respectively. These results indicate that the product was formed by a route in which CO_2 is incorporated from an external source.

Table 2. Reactions using various substituted allylic carbonates **1b**–**1e**.[a]

Entry	Substrate	Product's	
1[b]	**1b**	**2b** 19%	**3b** 8%
2[c]	**1b**	**2b** 57%	
3[b]	**1c**	**2c** 12%	**3c** 3%
4[c]	**1c**	**2c** 62%	
5[b]	**1d**	**2d** trace	**3d** 79%
6[c]	**1d**	**2d** 73%	
7[b]	**1e**	**2e** 8% (dr=1:1)[d]	**3e** 4%
8[c]	**1e**	**2e** 53% (dr = 1:3:1)[d]	

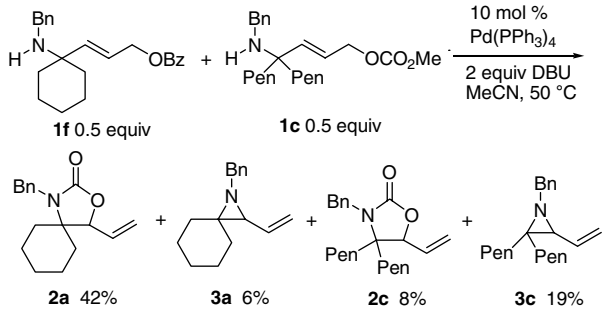
[a] All reactions were carried out with 10 mol % $Pd(PPh_3)_4$ and 2 equiv DBU in MeCN at 50 °C for 4–8 h.
[b] The reaction was carried out under argon atmosphere in a sealed tube.
[c] The reactions were carried out under CO_2 atmosphere.
[d] The ratio of the products was determined by ^1H NMR.



1f R = Bz
1g R = Ac
→ **2a**
95% yield (from **1f**)
86% yield (from **1g**)

Scheme 2. Synthesis of oxazolidinone **2a** from the reactions of allylic esters **1f** and **1g** with external CO_2 source.

A crossover experiment with allylic benzoate **1f** and allylic carbonate **1c** was next performed (Scheme 3). The reaction of an equimolar mixture of **1f** and **1c** under palladium catalyst with DBU resulted in the formation of oxazolidinone **2a** in 42% yield, which was derived from **1f**, along with the formation of the **1c**-derived

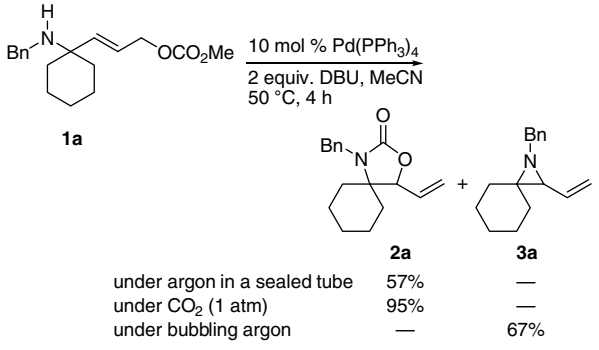


Scheme 3. Crossover experiment using **1c** and **1f**.

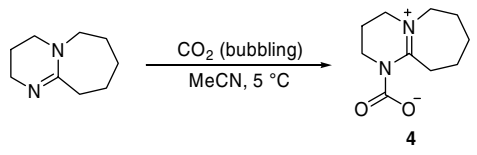
oxazolidinone **2c** and aziridines **3a** and **3c**. It has been clear that **2a** arises by the reaction of in situ generated CO_2 formed by decarboxylation of **1c**.

The reactions in both the presence and the absence of CO_2 source were also conducted (Scheme 4). While the reaction of allylic carbonate **1a** under an argon atmosphere yields oxazolidinone **2a** in 57% yield, the process carried out under 1 atm of CO_2 leads to a 95% of **2a**. On the other hand, when the reaction was carried out under bubbling argon to remove the resulting CO_2, aziridine **3a** was selectively produced in 67% yield. These results support that the process proceeds through a pathway involving decarboxylation–fixation of liberated CO_2.

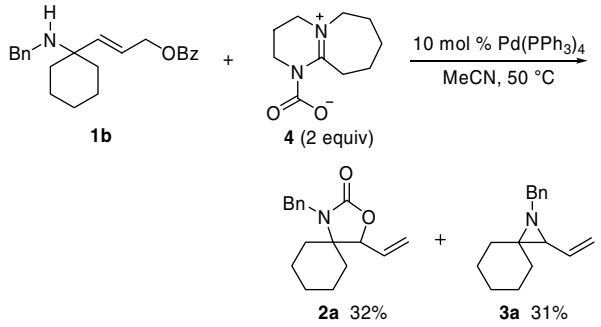
It is known that DBU reacts with CO_2 to form DBU–CO_2 zwitterionic carbamic complex **4** (Scheme 5), which exhibits high activity for transcarboxylation reaction to synthesize various *N*-alkyl carbamates.[12] To examine the reactive species in our CO_2-recycling process, the reaction of allylic ester with DBU–CO_2 complex **4** was attempted. When allylic benzoate **1b** was subjected to the reaction with 2 equiv of **4** in the presence of 10 mol % of $Pd(PPh_3)_4$, the corresponding oxazolidinone **2a** was obtained in 32% yield along with aziridine



Scheme 4. Reactions 'in the presence' and 'in the absence' of CO_2.



Scheme 5. Synthesis of DBU–CO_2 complex **4**.



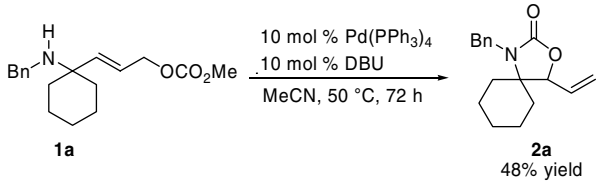
Scheme 6. Synthesis of **2a** using DBU–CO_2 complex **4**.

3a in 31% yield (Scheme 6). Although the yield of the oxazolidinone was low, this result clearly shows that the oxazolidinone arises by fixation of CO_2, which is derived from DBU–CO_2 **4**.

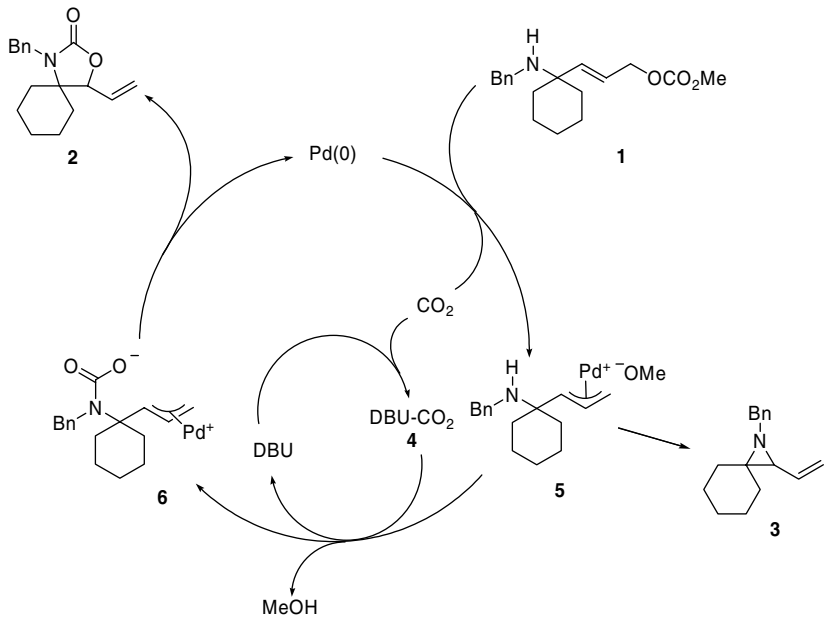
We next examined the required amount of DBU in the CO_2-recycling reaction. As a result, it was clear that the reaction of **1a** successfully proceeded in the catalytic amount of DBU (10 mol %) to afford oxazolidinone **2a** in moderate yield (Scheme 7).

A plausible mechanism for the CO_2-recycling reaction is shown in Scheme 8. A palladium catalyst initially promotes decarboxylation of allylic carbonate to generate a π-allylpalladium complex **5** and CO_2. The resulting CO_2 is successively trapped by DBU to form DBU–CO_2 complex **4**,[13] which causes transcarboxylation with π-allylpalladium **5** leading to carbamate intermediate **6**. Finally, intramolecular nucleophilic attack of **6** produces vinyloxazolidinone **2**. Vinylaziridine **3** results from the direct cyclization of π-allylpalladium **5** without fixation of CO_2. It is expected that the formation of DBU–CO_2 complex **4** suppresses the release of CO_2 from the reaction system, which enables the efficient fixation of CO_2.[14] Since DBU is re-generated from **4** after the elimination of CO_2, the reaction proceeds even in a catalytic amount of DBU.

In conclusion, we have developed a methodology for the synthesis of 5-vinyloxazolidinones by a palladium-catalyzed CO_2-recycling process. It has been made clear that the presence of DBU is necessary for the efficient fixation of CO_2. 5-Substituted oxazolidinones are attractive and important compounds in both medicinal chemistry and synthetic organic chemistry. Although the reaction requires an external CO_2 to give the products in high yields, this reaction would provide a new protocol for the synthesis of substituted oxazolidinones. Further studies about this type of reactions are now in progress.



Scheme 7. Reaction of **1a** in the presence of catalytic amount of DBU.



Scheme 8. Proposed reaction mechanism.

Acknowledgments

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8. *General procedure for the palladium-catalyzed CO_2-recycling reaction (Table 1, entry 5)*. To a stirred solution of allylic carbonate **1a** (33.3 mg, 0.11 mmol) in CH_3CN (1.1 mL) were added $Pd(PPh_3)_4$ (12.7 mg, 11.0 μmol) and DBU (33.0 μL, 0.22 mmol) in a sealed tube at rt. After stirring was continued for 4 h at 50 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give oxazolidinone **2a** (16.7 mg, 57%) as a yellow oil. IR (neat) 2936, 2860, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06–1.23 (2H, m), 1.33–1.49 (2H, m), 1.55–1.78 (6H, m), 4.18 (1H, d, $J = 16.0$ Hz), 4.55 (1H, d, $J = 16.0$ Hz), 4.71 (1H, d, $J = 7.2$ Hz), 5.38 (1H, d, $J = 10.4$ Hz), 5.50 (1H, d, $J = 17.2$ Hz), 5.91 (1H, ddd, $J = 7.2$, 10.4 and 17.2 Hz), 7.22–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 22.6, 24.5, 30.6, 33.4, 43.7, 63.9, 81.5, 119.7, 127.0, 127.1, 128.4, 131.5, 138.5, 157.6; MS *m/z* 271 (M^+); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.37; H, 7.84; N, 5.07.

9. *Spectroscopic data for* **3a**: Yellow oil; IR (neat) 2926, 2853, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31–1.39 (2H, m), 1.43–1.50 (2H, m), 1.53–1.66 (6H, m), 1.96 (1H, d, $J = 7.6$ Hz), 3.75 (1H, d, $J = 14.4$ Hz), 3.87 (1H, d, $J = 14.4$ Hz), 5.15 (1H, dd, $J = 2.0$ and 10.8 Hz), 5.29 (1H, dt, $J = 0.8$ and 16.8 Hz), 5.75 (1H, ddd, $J = 7.6$, 10.8 and 16.8 Hz), 7.19–7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.1, 26.1, 29.6, 33.0, 48.3, 52.5, 55.6, 116.8, 126.3, 127.4, 128.0, 136.3, 140.2; MS *m*/*z* 227 (M^+); HRMS *m*/*z* calcd for $C_{16}H_{21}N$ 227.1647 (M^+), found 227.1657.
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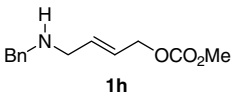
11. When the reaction of **1h**, which has no substituents at the allylic position, was examined, the complex mixture was yielded. In this case, β-elimination of palladium from the intermediate π-allylpalladium complex would occur to cause the undesired reactions.



1h

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