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Stereoselective amination *via* vinyl-silver intermediates derived from silver-catalyzed carboxylative cyclization of propargylamine†

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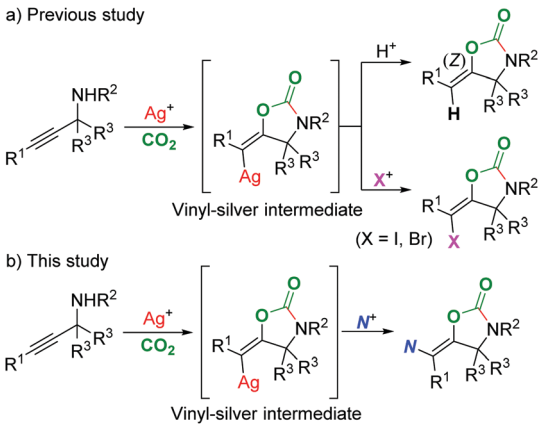
The stereoselective synthesis of aminovinyloxazolidinones based on the electrophilic amination of a vinyl-silver intermediate, generated by silver-catalyzed carbon dioxide incorporation on a propargyl amine, was achieved. The geometry of the aminated product was determined by a single crystal X-ray analysis and NOE measurement and it was elucidated that the geometry was proved to be opposite to the geometry predicted from the previous silver-catalyzed carbon dioxide fixation on a propargyl amine derivative. This unexpected stereoselectivity could be successfully explained by a radical mechanism.

Carbon dioxide is one of the attractive carbon sources, having a low toxicity and availability at low cost as well as easy handling.[1] Several reactions were evaluated for carbon dioxide fixation, however, it sometimes leads to synthetic difficulty due to the instability of the carboxylate generated from the addition of a nucleophile and carbon dioxide.[2] Therefore, a sequence to stabilize the carboxylate is required in many cases to incorporate carbon dioxide into a substrate.[3]

The successive intramolecular cyclization based on the transition metal-catalyzed activation of an alkyne is one of the most utilized and reliable methods to afford a variety of heterocycles. We have reported silver-catalyzed carbon dioxide incorporation reactions on propargyl alcohols[4] and propargyl amines.[5a] In these reactions, the corresponding cyclic carbonates and carbamates bearing *Z exo*-olefin were obtained through the *anti*-addition of a hemicarbonate or -carbamate to the internal alkyne activated by a silver catalyst, followed by the protonation of the vinyl-silver intermediate. The theoretical calculation also supported this reaction mechanism.[4] It was elucidated that the vinyl-silver intermediate generated from the carbon dioxide fixation on the propargyl amine through the *anti*-addition could also be applied for further transformation, such as iodination[5b] and bromination,[5c] to give functionalized vinyloxazolidinones without the loss of the geometry (Scheme 1a).



Scheme 1 Silver-catalyzed CO_2 incorporation into a propargylamine.

The formation of a vinyl-silver complex has been often proposed as an intermediate in the silver-catalyzed reactions,[6] although, due to their instability, few successful reports were found about the isolation of vinyl-silver complexes.[7,8] Therefore, the reactivity of a vinyl-silver complex is not completely understood. Perfluoroalkenylsilvers are known as isolable vinyl-silver complexes, and their applications for halogenation, methylation, silylation, and transmetalation have been studied.[7] The direct transformation of the *in situ* generated vinyl-silver intermediate was also examined in the silver-catalyzed reaction, but was limited to halogenation[8a–e] and stannylation.[8f] Thus, it is considered that the catalytic reaction based on the vinyl-silver intermediates is still being developed. In this paper, we report the amination of the vinyl-silver intermediate generated from the silver-catalyzed carbon dioxide incorporation reaction on the propargyl amine (Scheme 1b). Based on this study, an interesting reactivity of the vinyl-silver intermediate and the unexpected stereoselectivity were discovered.

As an electrophilic aminating agent, an azodicarboxylate[9] was selected for this investigation. When the propargyl amine

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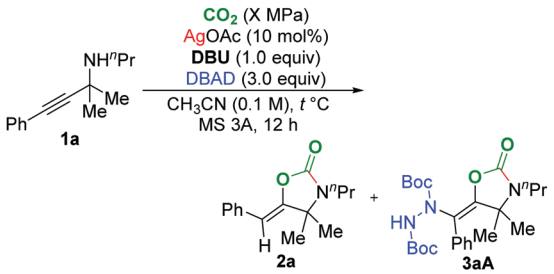
Table 1 Examination of reaction conditions

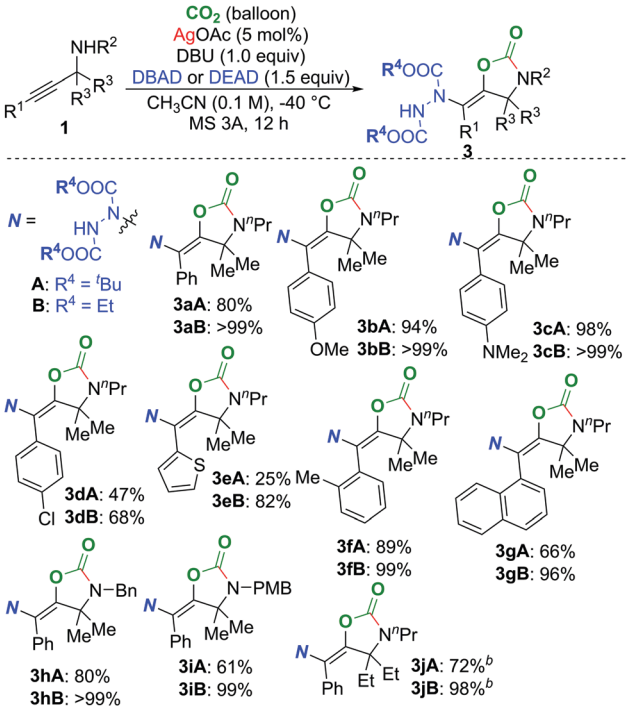


Entry	X/MPa	t/°C	Yield[a]	2a/%	3aA/%	2a : 3aA
1	1.0	30		70	30	70 : 30
2	1.0	50		96	2	>95 : 5
3	1.0	15		65	36	64 : 36
4	1.0	−15		55	45	55 : 45
5	1.0	−30		31	58	35 : 65
6	Balloon	−30		21	67	24 : 76
7	Balloon	−40		10	89	10 : 90
8	Balloon	−45		11	87	11 : 89
9[b,c]	Balloon	−40		9	87 (80)[d]	9 : 91

[a] Determined by ^{1}H NMR. [b] DBAD (1.5 equiv.) was used. [c] AgOAc (5 mol%) was used. [d] Isolated yield.

1a was treated with 1 MPa pressure of carbon dioxide, 1.0 equivalent of DBU (= 1,8-diazabicyclo[5.4.0]undec-7-ene), 3.0 equivalents of DBAD (= di-*tert*-butyl azodicarboxylate), in the presence of a catalytic amount of silver acetate, and molecular sieves 3A in acetonitrile at 30 °C, the desired aminovinyloxazolidinone **3aA** was obtained in 30% NMR yield along with the corresponding vinyloxazolidinone **2a** in 70% NMR yield (Table 1, entry 1). The product **3aA** was clearly identified as a single product without the formation of the other stereoisomer. Next, the reaction of **1a** was carried out under higher temperature conditions (50 °C) but resulted in the formation of **2a** in 96% yield (entry 2). Due to the DBAD decomposition at higher temperature,[10] the protonation of the vinyl-silver intermediate would be preferred rather than the amination. Therefore, a lower temperature was next subjected to this reaction to improve the selectivity of **3aA**. When the reaction was performed at 15 °C, −15 °C, and −30 °C, the yields of **3aA** were increased to 36%, 45%, and 58%, respectively (entries 3–5). It was discovered that the balloon pressure of carbon dioxide was effective to improve the selectivity at −30 °C, and **3aA** was obtained in 67% yield (entry 6). When the reaction was performed at −40 °C, the selective amination reaction proceeded to afford **3aA** in 89% yield (entry 7). Although a further improvement of the yield of **3aA** was not observed at a lower temperature (entry 8), it was found that 1.5 equivalents of DBAD was sufficient to obtain the aminated product **3aA** in 87% yield (80% isolated yield) (entry 9).

The optimized reaction conditions were successfully applied to various propargyl amines (Scheme 2). In this examination, DBAD (**A:** R^4 = ^{t}Bu) or DEAD (**B:** R^4 = Et) was employed as the aminating reagent. The reaction using propargyl amine **1a** resulted in the corresponding aminovinyloxazolidinones **3aA** and **3aB** in 80% and >99% yields, respectively.[11] The propargyl amines bearing electron donating groups on R^1 (**1b** and **1c**)



Scheme 2 Scope of substrates.

were next evaluated. When the reaction of the substrate having *p*-methoxyphenyl group (**1b**) was carried out, the desired products **3bA** and **3bB** were obtained in 94% and >99% yields, respectively. The propargyl amine bearing *p*-dimethylaminophenyl group (**1c**) also converted to **3cA** and **3cB** in 98% and >99% yields, respectively. The substrate bearing an electron withdrawing group on R^1 was also examined, however, the reactions using the propargyl amine having *p*-chlorophenyl group (**1d**) resulted in moderate yields of **3dA** and **3dB** (47% and 68%, respectively) due to the lower nucleophilicity of the vinyl-silver intermediate. In the examination of substrate bearing a 2-thienyl group on R^1 (**1e**), when DBAD was used, the lower yield (25%) of **3eA** was observed, whereas the use of DEAD resulted in a high yield of **3eB** (82%). The difference in yields between **3eA** and **3eB** might reflect the reactivity of the aminating reagents.[12] Further studies focused on the substituent effect of R^1 on substrates having an *o*-substituted phenyl group (**1f** and **1g**) were carried out. When the substrate bearing *o*-tolyl group (**1f**) was employed, the amination proceeded to afford **3fA** and **3fB** in 89% and 99% yields, respectively. The reaction using 1-naphthyl group-substituted propargyl amine (**1g**) resulted in the formation of the corresponding aminated products **3gA** and **3gB** in 66% and 96% yields, respectively. The effect of the substituent R^2 was next examined. The reaction using the propargyl amine having benzyl group on R^2 (**1h**) successfully proceeded to give **3hA** and **3hB** in 80% and >99% yields, respectively. The substrate bearing *p*-methoxybenzyl group on R^2 (**1i**) also converted to **3iA** and **3iB** in 61% and 99% yields, respectively. For examination of the substituent of R^3, the diethyl substituted propargyl amine (**1j**) was employed for this reaction, and **3jA** and **3jB** were obtained in 72% and 98% yields, respectively.

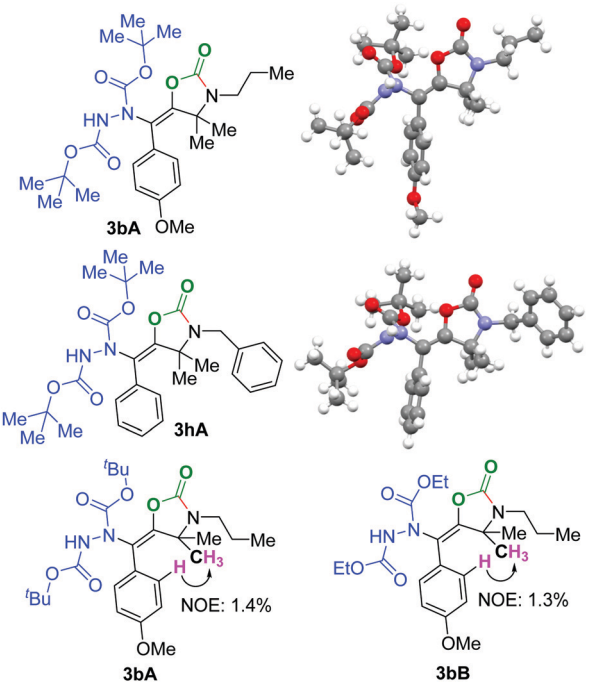
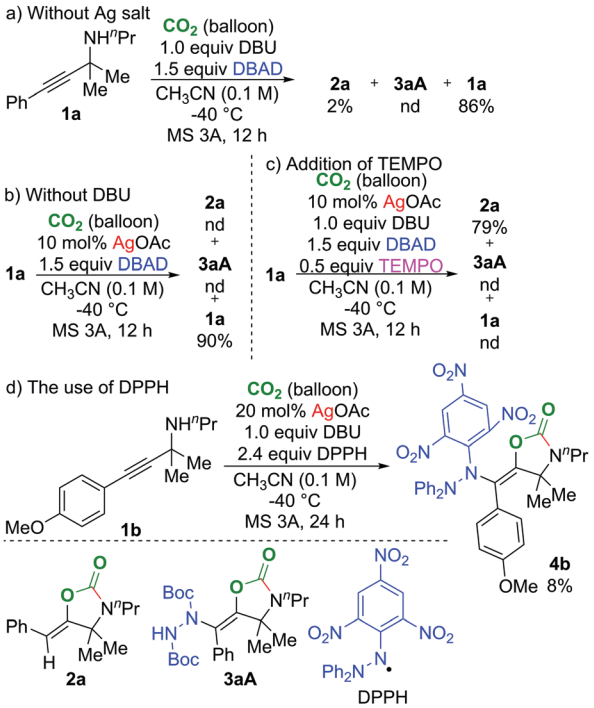


Fig. 1 X-ray crystallographic data and NOE experiment.



Scheme 3 Control experiments.

The geometry of the *exo*-olefin was next confirmed. The single crystals of aminovinyloxazolidinone **3bA** and **3hA** were obtained from the reaction using DBAD as an aminating reagent for the substrates bearing *p*-methoxyphenyl group on R^1 (**1b**) and benzyl group on R^2 (**1h**) and an X-ray analysis was performed using these single crystals. When NOE experiment of **3bA** was performed, the correlation of the protons between the methyl and PMP groups (1.4%) was observed to also support the geometry resulting from the X-ray analysis. As a result, the *exo*-olefin geometry of **3bA** and **3hA** were determined to be *Z*[13] and surprisingly proved to be opposite to the geometry predicted from our past findings (Fig. 1).[4,5] In the reactions using DEAD as an aminating reagent, no single crystal was obtained, thus the *exo*-olefin geometry was determined by NOE experiment. The aminated product **3bB** synthesized from **1b** using DEAD was measured, and the proton interaction between the PMP group and the methyl groups was observed as **3bA**. Based on these analyses, it was confirmed again that the *exo*-olefin geometries of the aminated products in this reaction were opposite to the already reported silver-catalyzed vinyloxazolidinone synthesis.[5] This result suggested that the mechanism of this reaction could be different from the previously reported transformations of the vinyl-silver intermediates.[4,5]

The control experiments were performed to investigate the reaction mechanism (Scheme 3). When the reaction was carried out without the silver salt, the protonation and amination hardly proceeded with recovery of the starting material **1a** (Scheme 3a). This result suggested that a silver salt was necessary for the cyclization of the carboxylate into the alkyne the same as the standard silver-catalyzed carbon dioxide incorporation. The reaction without DBU was also examined and resulted in no reaction. According to our previous study,[5] the silver-catalyzed carbon dioxide incorporation on a propargyl amine can proceed at ambient temperature without a base, thus it was indicated that DBU might increase the nucleophilicity of the nitrogen atom to attack the carbon dioxide under the low temperature conditions. Next, the mechanism of the amination step was investigated. It was reported that the amination using an azodicarboxylate ester proceeded by a radical mechanism.[14] When TEMPO (= 2,2,6,6-tetramethylpiperidine 1-oxyl) was added as a radical scavenger in this reaction, the protonated product **2a** was only obtained in 79% yield (Scheme 3c). Therefore, it is considered that the amination could involve a radical mechanism. According to the literature, the combination of DEAD with triphenylphosphine generated the corresponding *N*-radical species.[15] Also, in this reaction, the similar *N*-radical species can be formed by a single electron transfer to DEAD from DBU. Thus, DBU might play double roles as a base to enhance the nucleophilicity of the substrate at a lower temperature and as a single electron reductant against DEAD to generate the *N*-radical species. The reaction of **1b** was then performed using DPPH (= 1,1-diphenyl-2-picrylhydrazyl free radical) as the *N*-radical species instead of DBAD or DEAD, and the corresponding *N*-substituted vinyloxazolidinone **4b** was certainly obtained in 8% yield (Scheme 3d). This result suggested that the amination of this reaction proceeded through a radical process.

The plausible reaction mechanism is summarized in Fig. 2. The vinyl-silver intermediate **I** is first generated *via* the silver-catalyzed carbon dioxide incorporation on the propargyl amine **1** using DBU as a base. When the vinyl-silver intermediate **I** reacts with a proton source, such as the protonated DBU (H-DBU$^+$), the corresponding vinyloxazolidinone **2** is obtained (Fig. 2, path A).

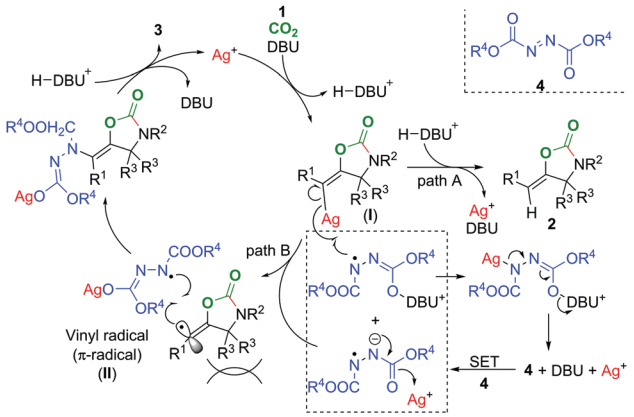


Fig. 2 Plausible reaction mechanism.

On the other hand, the reaction of **I** and *N*-radical species generated from an azodicarboxylate and DBU is assumed to produce the vinyl radical **II** *via* the homolysis of the vinyl-silver bond (Fig. 2, path B). It is known that vinyl radical bearing an aryl group forms a π-radical having a linear structure.[16] Therefore, another *N*-radical species would access and react with **II** while avoiding the sterically demanding substituent R^3 to afford the corresponding aminated product **3**.[14e,17] This might be the reason why the *exo*-olefin geometry of the aminated product **3** was opposite that of the vinyl-silver intermediate **I**.

In conclusion, we have developed the stereoselective synthesis of aminovinyloxazolidinones *via* the silver-catalyzed carbon dioxide incorporation. In this reaction, the nucleophilic addition of a propargyl amine to carbon dioxide and sequential silver-catalyzed cyclization proceeded to generate the vinyl-silver intermediate, and the azodicarboxylate reacted with this intermediate to afford the corresponding aminated product in high yield. This reaction is the first example of the amination of a vinyl-silver bond, and it was suggested that this amination would proceed by a radical mechanism.

Conflicts of interest

The authors declare no conflict of interest.

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