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Nickel(0)-Promoted Carboxylation of Allenamides with Carbon Dioxide via a Nickelalactone Intermediate

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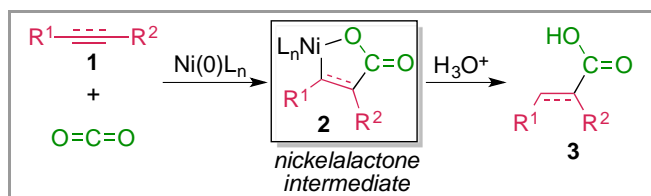
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Abstract: Nickel(0)-promoted carboxylation of *N*-allenylamides (allenamides) with carbon dioxide proceeded via a nickelalactone intermediate to give β -amino acid derivatives. It was also found that the regioselectivity at the oxidative addition stage was strongly affected by the substituents on the allene part.

Key words: nickel, allenamide, carbon dioxide, fixation, β -amino acid

Carbon dioxide is an abundant, ubiquitous, cheap and relatively nontoxic C1 source in synthetic organic chemistry, and various methods for incorporation of carbon dioxide into organic compounds have been demonstrated. Recently, transition metal-promoted direct carboxylation of organic compounds has attracted much attention due to its high efficiency.^{1,2} In particular, zero-valent nickel complex has been widely used for carboxylation of carbon-carbon unsaturated compounds (Scheme 1).³ The reaction proceeds via nickelalactone intermediate **2**, which is generated by oxidative cycloaddition of unsaturated compound **1** and carbon dioxide to a nickel(0) complex, and hydrolysis of the nickelalactone affords the corresponding carboxylic acid **3**. Thus, the nickelalactone can be regarded as a useful intermediate for synthesis of various carboxylic acids in synthetic organic chemistry. From the viewpoint of development of a new synthetic methodology using an atmospheric pressure of carbon dioxide, several synthetic utilizations of carboxylation via nickelalactone have recently been demonstrated using alkynes,⁴ 1,3-dienes,⁵ allenes,⁶ and diynes⁷ as well as enynes⁸ as platforms.



Scheme 1 Synthesis of carboxylic acids from unsaturated compounds and carbon dioxide via a nickelalactone intermediate

N-allenylamides (allenamides, Figure 1, **4**) have been recognized as versatile synthetic units in recent organic synthesis.⁹ Due to delocalization of lone-pair electrons of a nitrogen atom to a double bond of the allene moiety depicted as **4'**, the sp carbon atom of

allenamide has a partial negative charge. Therefore, allenamide could act as a polarized allene, and various organic transformations of allenamide using its unique electronic property have been reported in the past decade.

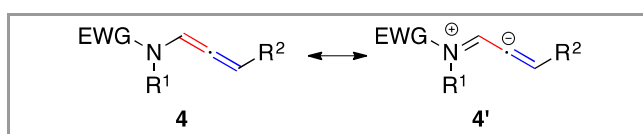
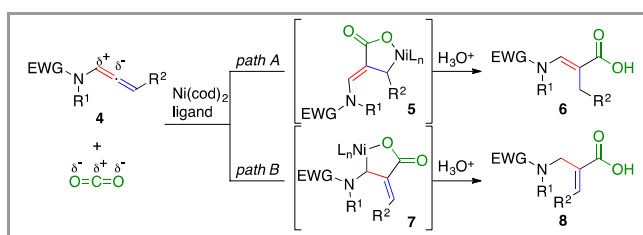


Figure 1. Structure of Allenamide **4**

In this context, we planned nickel-promoted carboxylation of allenamides (Scheme 2). Thus, if oxidative cycloaddition of the allenamide **4** and CO₂ to a nickel(0)-complex proceeds in a manner similar to that of previously reported carboxylation of allene,^{7,10} carbon-carbon bond formation would occur between the negatively polarized sp carbon atom of **4** and the positive sp carbon atom of CO₂ to give nickelalactone **5** or **7**. Finally, hydrolysis of the nickelalactone could give β -amino acid derivative **6** or **8**, the structure of which is often found in some important biologically active compounds.

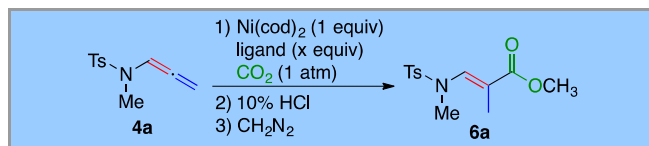


Scheme 2 Plan for carboxylation of allenamide with CO₂ via nickelalactone intermediate

To examine the feasibility of the plan, we set out to conduct condition screening of the carboxylation of allenamide (Table 1). According to previous reports on carboxylation of allene,⁷ tosylamide-derived terminal allenamide **4a** was reacted with an atmospheric pressure of CO₂ in the presence of a stoichiometric amount of Ni(cod)₂ and 2 equivalents of DBU as a ligand (run 1). After acidic work up with 10% aqueous HCl solution followed by methylation by CH₂N₂, CO₂-incorporated compound **6a** was produced in 76% yield as a single regio- and stereoisomer.¹¹ When the amount of DBU was

increased to 4 equivalents, the yield of **6a** increased to 89% (run 2). The use of 1,10-phenanthroline and 1,2-bis(dicyclohexylphosphino)ethane (DCPE) gave **6a** in low yields (runs 3 and 4). Furthermore, TMEDA ligand was applicable to the carboxylation of **4a**, giving **6a** in 82% yield (run 5).

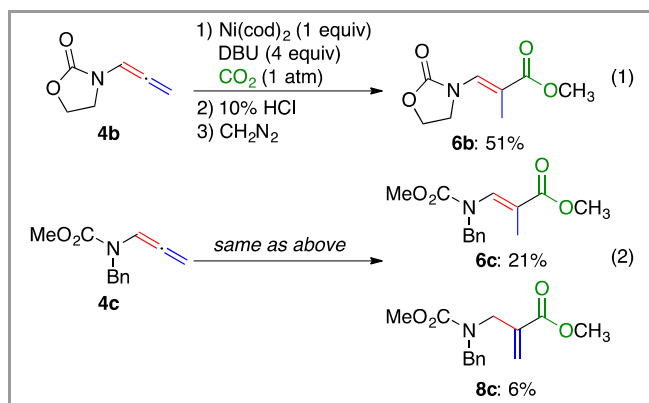
Table 1. Nickel-Promoted Carboxylation of Allenamide **4a**^a



run	ligand (X equiv)	time (h)	yield (%)
1	DBU (2)	2	76
2	DBU (4)	1	89
3	1,10-phenanthroline (1)	1	4
4	DCPE ^b (1)	1	trace
5	TMEDA (1)	1	82

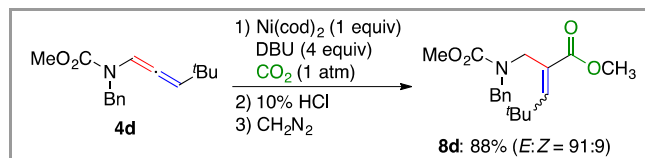
^a The reaction was carried out in THF at 0 °C. ^b DCPE = 1,2-bis(dicyclohexylphosphino)ethane

With optimal conditions in hand, carboxylation of other terminal allenamides was investigated (Scheme 3). Thus, oxazolidinone-derived allenamide **4b** was reacted with CO₂ followed by methylation to give the corresponding **6b** in 51% yield (Eq 1). On the other hand, the carboxylation of methylcarbamate-derived allenamide **4c** gave the desired **6c** in 21% yield, and its regioisomer **8c** was also produced in 6% yield (Eq 2).



Scheme 3 Nickel-mediated carboxylation of carbamate-derived terminal allenamide

Next, we turned our attention to the carboxylation of allenamide bearing a *tert*-butyl group on the allene moiety (Scheme 4). Thus, the reaction of **4d** and CO₂ (1 atm) in the presence of Ni(cod)₂ and DBU followed by methylation gave **8d** in 88% yield as a mixture of geometrical isomers with respect to the alkene moiety.



Scheme 4 Carboxylation of *tert*-butyl group-substituted allenamide **4d**

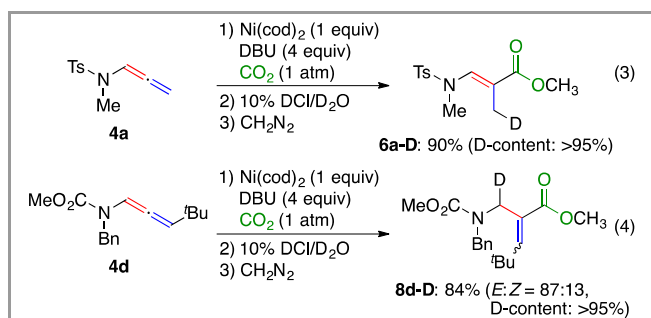
Carboxylation of various substituted allenamides was investigated, and the results are shown in Table 2. Boc group-protected allenamide **4e** could react with CO₂, and the desired carboxylation product **8e** was obtained in 91% yield (run 1). Oxazolidinone-derived allenamide **4f** was also applicable to the carboxylation, giving the corresponding coupling product **8f** in 88% yield (run 2). Carboxylation of 2-pyridone derivative **4g** proceeded to give **8g** in good yield as a single isomer (run 3). Tosylamide-derived allenamides **4h** having a benzyloxy group was reacted with CO₂ to give the desired CO₂-incorporated product **8h** in 27% yield along with diene **9**, which would be formed from **8h** by debenzyloxylation (run 4). A similar result was obtained in the carboxylation of **4i**, carboxylation compounds **8i** and **9** being produced in a total yield of 42% (run 5). On the other hand, the reaction of siloxylethyl group-substituted allenamide **4j** with CO₂ followed by methylation afforded the corresponding product **8j** in 68% yield as a single isomer (run 6).

Table 2. Carboxylation of Various Substituted Allenamides^a

run	allenamide 4	time (h)	product 8
1	Boc-N(Bn)-CH=C=C- <i>t</i> Bu 4e	15	Boc-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me 8e : 91% (<i>E</i> : <i>Z</i> = 89:11)
2	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu 4f	15	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me 8f : 88% (<i>E</i> : <i>Z</i> = >95:5)
3	2-Pyridone-N(Bn)-CH=C=C- <i>t</i> Bu 4g	17	2-Pyridone-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me 8g : 60% (<i>E</i> : <i>Z</i> = >95:5)
4	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-OR 4h (R = Bn)	15	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me + Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-OR 8h (R = Bn): 27% (<i>E</i> : <i>Z</i> = >95:5) 9 : 41% (<i>E</i> : <i>Z</i> = 85:15)
5	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-TBS 4i (R = TBS)	18	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me + Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-TBS 8i (R = TBS): 29% (<i>E</i> : <i>Z</i> = >95:5) 9 : 13% (<i>E</i> : <i>Z</i> = >95:5)
6	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-TBDPSO 4j	16	Oxazolidinone-N(Bn)-CH=C=C- <i>t</i> Bu-CO ₂ Me 8j : 68% (<i>E</i> : <i>Z</i> = >95:5)

^a The reaction of allenamide **4** was carried out in the presence of Ni(cod)₂ (1 equiv) and DBU (4 equiv) in THF at 0 °C under CO₂ (1 atm). After acidic work-up with 10% HCl, the crude product was treated with CH₂N₂.

To gain insights into the reaction mechanism, a deuterium incorporation experiment was carried out (Scheme 5). Thus, after the reaction of terminal allenamide **4a** and CO₂, acidic work-up with 10% DCI/D₂O followed by methylation by CH₂N₂ was conducted (Eq 3). As a result, compound **6a-D**, the allylic methyl group of which was deuterated, was obtained in 90% yield as a single regio- and stereoisomer. On the other hand, when allenamide **4d** having a *tert*-butyl group was reacted under reaction conditions similar to those of **4a**, the allylic methylene position of **8d-D** was deuterated (Eq 4).



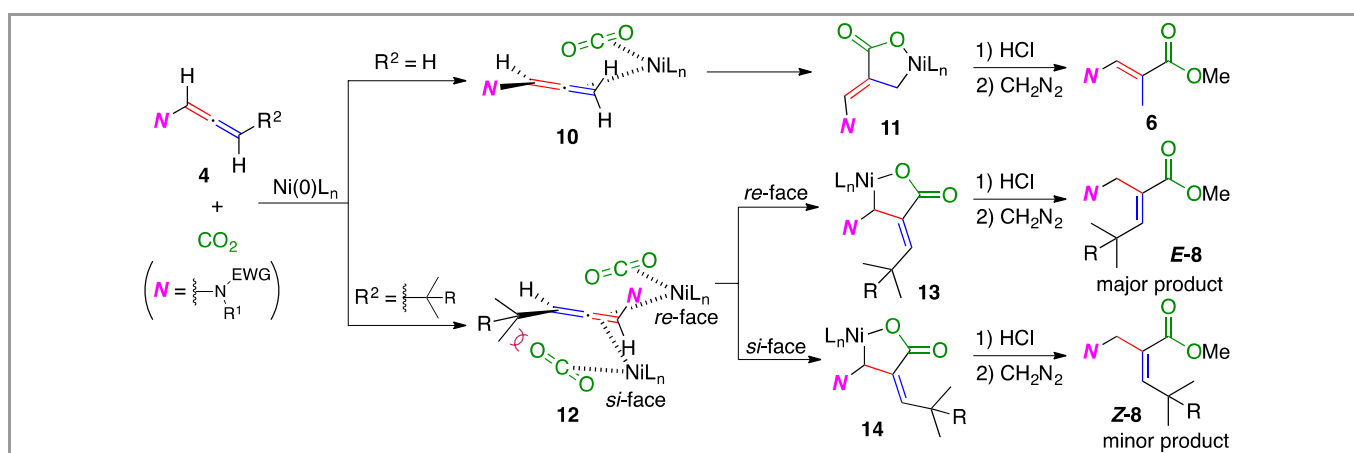
Scheme 5 Acidic work-up with DCI/D₂O

Based on the above results, possible reaction mechanisms of the carboxylation of allenamides were considered (Scheme 6). When terminal allenamides **4** (R² = H) were used, the less-hindered distal double bond of the allene part and CO₂ would coordinate to the nickel center to give **9** first, from which oxidative cycloaddition would proceed to afford nickelalactone **10**. Hydrolysis of **10** followed by methylation would afford **6**. On the other hand, in the reaction of

allenamides having a tertiary-alkyl group (R² = CMe₂R), the less-hindered nitrogen-substituted double bond of **4** would coordinate to the nickel center to give **12**. In this step, two types of coordinated complex could be formed. That is, if oxidative cycloaddition of the *re*-face of the nitrogen-substituted double bond of allenamide and CO₂ proceeded, nickelalactone **13** could be formed. On the other hand, oxidative cycloaddition of the *si*-face of the double bond and CO₂ would give nickelalactone **14**. Obviously, the formation of **14** from **12** seems to be less favorable than the formation of **13** because of steric repulsion between the bulky tertiary-alkyl group in the allenamide and CO₂. Thus, nickelalactone **13** would be formed preferably as compared with **14**, resulting in *E*-**8** being obtained as a major product after hydrolysis followed by methylation.

In summary, we have demonstrated nickel-promoted carboxylation of allenamide with an atmospheric pressure of carbon dioxide. The reaction proceeds via a nickelalactone intermediate from allenamide and carbon dioxide to give the corresponding β-amino acid derivatives. It was also found that the regioselectivity at the oxidative addition stage was strongly affected by substituents on the allene part. Further studies including development of the carboxylation to a catalytic reaction are in progress.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.



Scheme 6 Possible reaction course including origin of regioselectivity

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- (11) Regio- and stereochemistry of the carboxylation compound was determined by NOE experiments, see Supporting Information.

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