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

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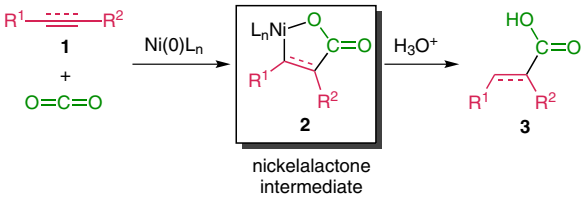
Received: 21.11.2013; Accepted after revision: 18.12.2013

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.

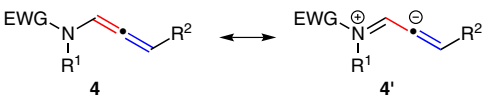
Key words: nickel, allenamide, carbon dioxide, fixation, β-amino acid

Carbon dioxide (CO_2) is an abundant, ubiquitous, cheap, and relatively nontoxic one-carbon source in synthetic organic chemistry, and various methods for the incorporation of CO_2 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, the 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 CO_2 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 the synthesis of various carboxylic acids in synthetic organic chemistry. From the viewpoint of development of a new synthetic methodology using an atmospheric pressure of CO_2, several synthetic utilizations of carboxylation via nickelalactone have recently been demonstrated using alkynes,[4] 1,3-dienes,[5] allenes,[6] and diynes[7] as well as enynes[8] as platforms.



Scheme 1 Synthesis of carboxylic acids from unsaturated compounds and CO_2 via a nickelalactone intermediate

N-Allenylamides (allenamides, Scheme 2, **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.

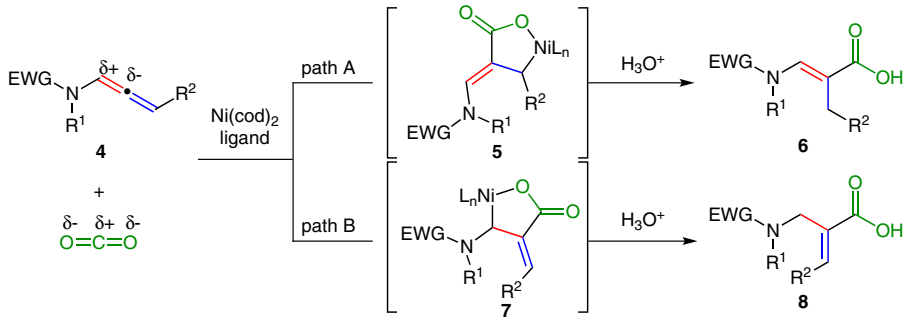


Scheme 2 Structure of allenamide **4**

In this context, we planned the nickel-promoted carboxylation of allenamides (Scheme 3). Thus, if oxidative cycloaddition of the allenamide **4** and CO_2 to a nickel(0) complex proceeds in a manner similar to that of previously reported carboxylation of allene,[6,10] carbon–carbon bond formation would occur between the negatively polarized sp carbon atom of **4** and the positive sp carbon atom of CO_2 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.

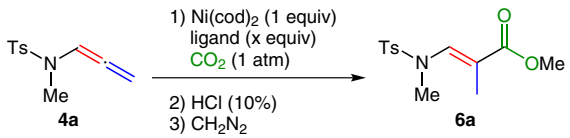
To examine the feasibility of the plan, we set out to conduct condition screening of the carboxylation of allenamide (Table 1). According to previous reports on carboxylation of allene,[6] tosylamide-derived terminal allenamide **4a** was reacted with an atmospheric pressure of CO_2 in the presence of a stoichiometric amount of $Ni(cod)_2$ and two equivalents of DBU as a ligand (Table 1, entry 1). After acidic workup with 10% aqueous HCl solution followed by methylation by CH_2N_2, CO_2-incorporated compound **6a** was produced in 76% yield as a single regio- and stereoisomer.[11] When the amount of DBU was increased to four equivalents, the yield of **6a** increased to 89% (Table 1, entry 2). The use of 1,10-phenanthroline and 1,2-bis(dicyclohexylphoshino)ethane (DCPE) gave **6a** in low yields (Table 1, entries 3 and 4). Furthermore, TMEDA ligand was applicable to the carboxylation of **4a**, giving **6a** in 82% yield (Table 1, entry 5).

SYNLETT 2014, 25, 0736–0740
Advanced online publication: 29.01.2014
DOI: 10.1055/s-0033-1340628; Art ID: ST-2013-U1076-L



Scheme 3 Plan for carboxylation of allenamide with CO_2 via nickelalactone intermediate

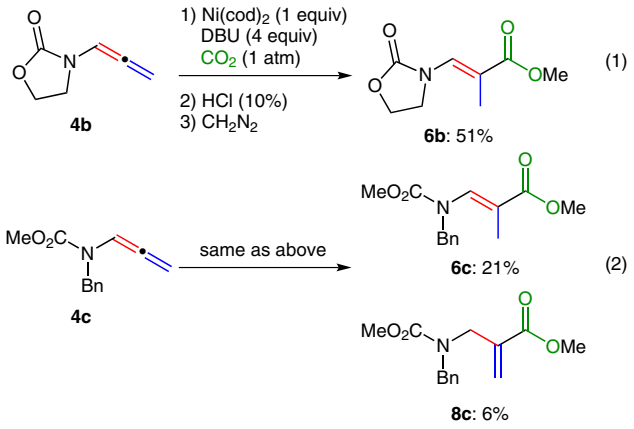
Table 1 Nickel-Promoted Carboxylation of Allenamide **4a**[a]



Entry	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

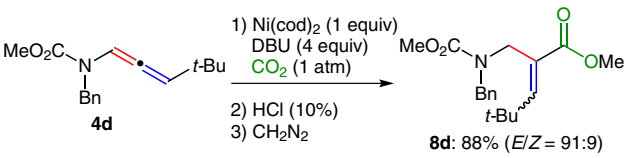
[a] The reaction was carried out in THF at 0 °C.
[b] DCPE = 1,2-bis(dicyclohexylphosphino)ethane.

With optimal conditions in hand, carboxylation of other terminal allenamides was investigated (Scheme 4). Thus, oxazolidione-derived allenamide **4b** was reacted with CO_2 followed by methylation to give the corresponding **6b** in 51% yield (Scheme 4, 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 (Scheme 4, eq. 2).



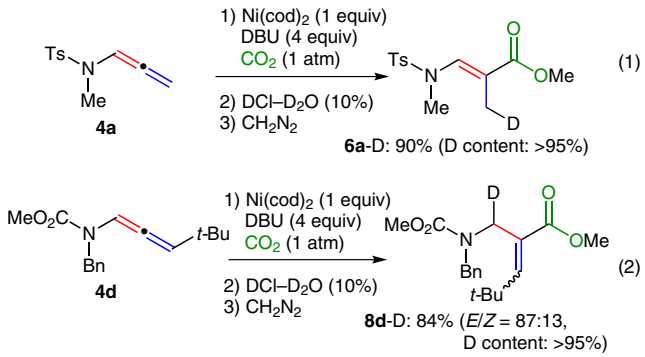
Scheme 4 Nickel-mediated carboxylation of carbamate-derived terminal allenamide

Next, we turned our attention to the carboxylation of allenamide bearing a *tert*-butyl group on the allene moiety (Scheme 5). Thus, the reaction of **4d** and CO_2 (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 5 Carboxylation of *tert*-butyl group substituted allenamide **4d**

Carboxylation of various substituted allenamides was investigated, and the results are shown in Table 2. The Boc group protected allenamide **4e** could react with CO_2, and the desired carboxylation product **8e** was obtained in 91% yield (Table 2, entry 1). Oxazolidinone-derived allenamide **4f** was also applicable to the carboxylation, giving the corresponding coupling product **8f** in 88% yield (Table 2, entry 2). Carboxylation of 2-pyridone derivative **4g** proceeded to give **8g** in good yield as a single isomer (Table 2, entry 3). Oxazolidinone-derived allenamide **4h** having a benzyloxy group was reacted with CO_2 to give the desired CO_2-incorporated product **8h** in 27% yield along with diene **9**, which would be formed from **8h** by debenzyloxylation (Table 2, entry 4). A similar result was obtained in the carboxylation of **4i**, carboxylation compounds **8i** and **9** being produced in a total yield of 42% (Table 2, entry 5). On the other hand, the reaction of siloxylethyl group substituted allenamide **4j** with CO_2 followed by methylation afforded the corresponding product **8j** in 68% yield as a single isomer (Table 2, entry 6). Carboxylation of allenamide having a methyl group **4k** also gave **8k** in 44% yield in a similar regio- and stereoselective manner to that of the carboxylation of *tert*-alkyl group substituted allenamides **4d–j** (Table 2, entry 7). Trisubstituted allenamide **4l** was applicable to the carboxylation, giving the corresponding CO_2-incorporated compound **8l** in 59% yield in a highly regioselective manner (Table 2, entry 8).

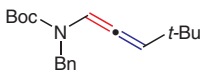
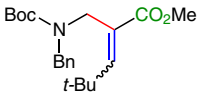
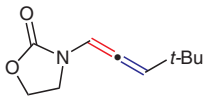
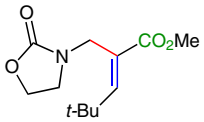
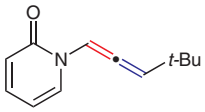
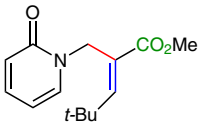
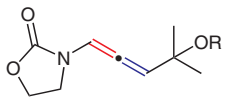
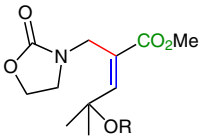
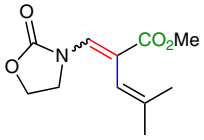
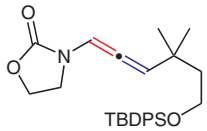
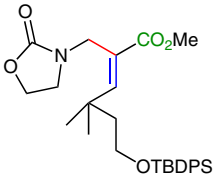
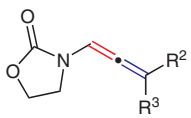
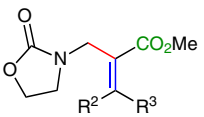


Scheme 6 Acidic workup with DCl–D_2O

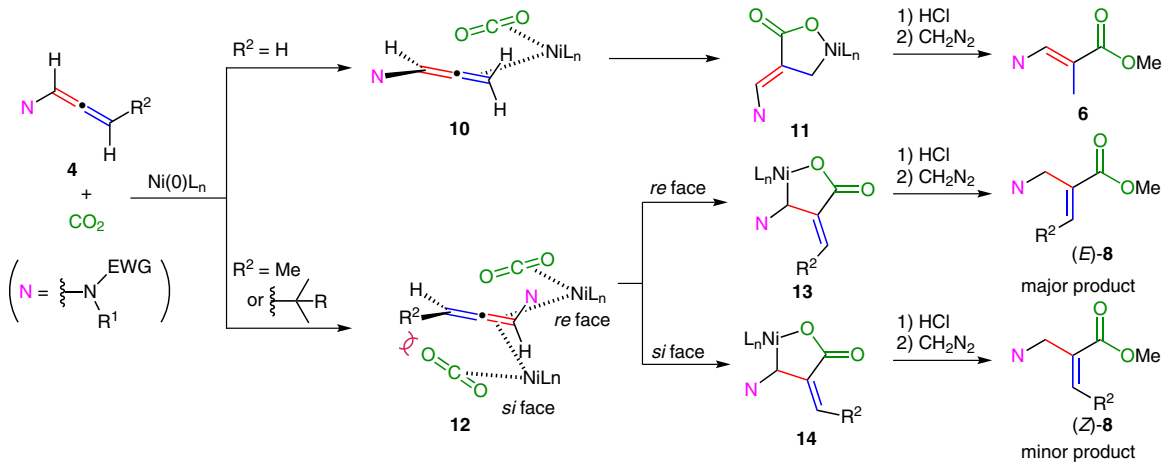
To gain insights into the reaction mechanism, a deuterium incorporation experiment was carried out (Scheme 6). Thus, after the reaction of terminal allenamide **4a** and CO_2, acidic workup with 10% DCl–D_2O followed by methylation by CH_2N_2 was conducted (Scheme 6, eq. 1). As a result, compound **6a**-D, 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 treated under reaction conditions similar to those of **4a**, the allylic methylene position of **8d**-D was deuterated (Scheme 6, eq. 2).

Based on the above results, possible reaction mechanisms of the carboxylation of allenamides were considered (Scheme 7). When terminal allenamides **4** (R^2 = H) were

Table 2 Carboxylation of Various Substituted Allenamides[a]

Entry	Allenamide **4**	Time (h)	Product **8**	
1	 **4e**	15	 **8e** 91% (*E*/*Z* = 89:11)	
2	 **4f**	16	 **8f** 88% (*E*/*Z* = >95:5)	
3	 **4g**	17	 **8g** 60% (*E*/*Z* = >95:5)	
4	 **4h** R = Bn	15	 **8h** R = Bn, 27% (*E*/*Z* = >95:5)	 **9** 41% (*E*/*Z* = 85:15)
5	**4i** R = TBS	18	**8i** R = TBS, 29% (*E*/*Z* = >95:5)	**9** 13% (*E*/*Z* = >95:5)
6	 **4j**	16	 **8j** 68% (*E*/*Z* = >95:5)	
7	 **4k** R^2 = Me, R^3 = H	1	 **8k** R^2 = Me, R^3 = H, 44% (*E*/*Z* = >95:5)	
8	**4l** R^2 = R^3 = Me	1	**8l** R^2 = R^3 = Me, 59%	

[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 CO_2 (1 atm). After acidic workup with 10% HCl, the crude product was treated with CH_2N_2.



Scheme 7 Possible reaction course including origin of regio- and stereoselectivity

used, the less-hindered distal double bond of the allene part and CO_2 would coordinate to the nickel center to give **10** first, from which oxidative cycloaddition would proceed to afford nickelalactone **11**. Hydrolysis of **11** followed by methylation would afford **6**. On the other hand, in the reaction of allenamides having an alkyl group (R^2 = Me or CMe_2R), 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 CO_2 proceeded, nickelalactone **13** could be formed. On the other hand, oxidative cycloaddition of the *si* face of the double bond and CO_2 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 alkyl group in the allenamide and CO_2. 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.

Acknowledgment

This work was partly supported by a Grant-in-Aid for Young Scientists (B) (No. 24790002) and a Grant-in-Aid for Scientific Research (B) (No. 23390001) from JSPS and by a Grant-in-Aid for Scientific Research on Innovative Areas ‘Molecular Activation Directed toward Straightforward Synthesis’ (Nos. 23105501 and 25105701) from MEXT, Japan. N.S. acknowledges Takeda Science Foundation for financial support.

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

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

