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（日本語版文献）
Nickel-Promoted Carboxylation/Cyclization Cascade of Allenyl Aldehyde Under an Atmosphere of CO₂

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Abstract: In the presence of a stoichiometric amount of Ni(0) complex, allenyl aldehydes smoothly reacted with carbon dioxide at an ambient temperature and pressure in a regioselective manner. The reaction involves an intramolecular cyclization of aldehyde and allene moieties to afford cyclic carboxylic acid derivatives having a hydroxyl group.

Key words: allenes, aldehydes, carboxylic acid, cyclization, nickel

Development of new methods to incorporate carbon dioxide (CO₂) into organic molecules through carbon-carbon bond formations is still an important subject in synthetic organic chemistry. With the aim of developing novel CO₂ incorporation reactions, transition-metal-promoted carboxylation reaction has attracted much attention.1,2 Nickel-mediated or -catalyzed CO₂ incorporation reactions, 4 we found in the course of our previous studies on nickel-promoted carboxylation of the allenyl aldehyde 1, which would proceed according to the following reaction process: (i) oxidative cyclization of 1 and CO₂ with low-valent nickel species would afford an oxa-nickelacycle 2 and (ii) intramolecular nucleophilic addition of the oxa-nickelacycle moiety of 2 to the tethered aldehyde would give cyclized product 3 (Scheme 1).3

In the course of our previous studies on nickel-promoted or -catalyzed CO₂ incorporation reactions,3 we found that various allenes reacted with CO₂ and a zero-valent nickel complex to form a nucleophilic Oxa-nickelacycle that could react with aldehydes.4c From these results, we envisioned a carboxylation/cyclization cascade of allenyl aldehyde 1, which would proceed according to the following reaction process: (i) oxidative cyclization of 1 and CO₂ with low-valent nickel species would afford an oxa-nickelacycle 2 and (ii) intramolecular nucleophilic addition of the oxa-nickelacycle moiety of 2 to the tethered aldehyde would give cyclized product 3 (Scheme 1).

Scheme 1 Carboxylation/Cyclization cascade

We first examined nickel-promoted carboxylation of the allenyl aldehyde 1a under standard conditions previously developed by us for nickel-promoted CO₂ incorporation reactions. To our delight, the reaction of 1a with CO₂ (1 atm) proceeded in THF at room temperature in the presence of Ni(cod)2 (1 equiv) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 2 equiv) (Scheme 2). After hydrolysis of the reaction mixture followed by diazomethane esterification, the desired cyclic carboxylic acid ester 3a was isolated in 50% yield. Treatment of 3a with NaH afforded bicyclic α-methylene lactone 4a in 92% yield. The observed coupling constant value between H₂ and H₃ in the 1H NMR spectrum of 4a showed that 4a had a trans-fused bicyclic structure, and thus the configuration of the hydroxyl group and alleny moiety on 3a was determined to be trans.

Scheme 2

To improve the yield of 3a, various reaction conditions were examined (Table 1).

Table 1 Carboxylative Cyclization of 1a under Various Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>ligand</th>
<th>time (h)</th>
<th>yields of 3a (%)</th>
<th>total</th>
</tr>
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<tr>
<td>1</td>
<td>toluene</td>
<td>DBU</td>
<td>3</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>DBU</td>
<td>3</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>dioxane</td>
<td>DBU</td>
<td>4</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>dioxane</td>
<td>DBN</td>
<td>1</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>dioxane</td>
<td>bpy</td>
<td>2</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>dioxane</td>
<td>DMF</td>
<td>2</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>dioxane</td>
<td>TEMED</td>
<td>3</td>
<td>59</td>
<td>59</td>
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*The reactions were carried out using 1 equiv of Ni(cod)₂ under an atmosphere of CO₂ (1 atm). †2 equiv to Ni(cod)₂. ‡1 equiv to Ni(cod)₂.
Among the solvents examined (entries 1-3), 1,4-dioxane, a relatively polar solvent gave the best result (entry 3). The effects of ligands were also investigated when dioxane was used as the solvent (entries 5 – 6). The use of DBN, 1,2-bipyridine (bpy) or 1,2-dimethylimidazole (DMI) did not result in any significant improvement compared with DBU. Interestingly, by using tetramethylethylenediamine (TMEDA) as the ligand, the total yield of the cyclized products was improved to 87%, although cis-3a was also formed in 28% yield along with trans-3a.

The reaction of 1b with CO₂ proceeded smoothly in the presence of Ni(cod)₂ and TMEDA at room temperature to give the desired cyclic product with a five-membered ring (Scheme 3). Because the formed carboxylic acid easily underwent dehydration during the purification process, the product was isolated and characterized as 4b (61% yield from 1b) after lactonization in the presence of an acid catalyst. From the results of NOE experiments, the stereochemistry of 4b was determined to be cis, as shown in Scheme 3.

In contrast, seven-membered ring formation from 1c was sluggish under similar conditions, and simply carboxylated product 5c was obtained in 45% (Scheme 4, eq. 1). This result indicated that the reaction did not proceed further from intermediate 2c. However, fortunately, we found that the use of ZnCl₂ (3 equiv to 1c) as an additive promoted the desired cyclization process to afford lactone cis-4c in 41% yield (Scheme 4, eq. 2). The use of other Lewis acids, including BF₃ and TMSOTf, did not work well as promoters. These results suggest that ZnCl₂ did not simply act as a Lewis acid but also as a transmetalating reagent to form a more nucleophilic π-n-allylnickel chloride such as 6c.

With this knowledge in hand, we tried to apply the present carboxylation/cyclization cascade for the synthesis of heterocyclic and benzene-fused bicyclic compounds, and the results are summarized in Table 2.

Carboxylative cyclization of 1d with CO₂ in the presence of a stoichiometric amount of Ni(cod)₂ and TMEDA proceeded smoothly to afford the desired cyclized product 3d in 74% yield as a mixture of two stereo isomers. Although ZnCl₂ was necessary, carboxylation of 1e also gave the desired product 4e in 33% yield.

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Furthermore, the present system was applicable to the synthesis of benzene-fused bicyclic compounds (Table 2, entry 3-5). Benzaldehyde derivative 1f, having a terminal allene moiety at the ortho position, smoothly reacted with CO2 under similar conditions to afford 3f in 66% yield. Interestingly, in the reactions of 1g and 1h having an internal allene moiety, the cyclization process proceeded to give 3g and 3h in 66% and 74% yields, respectively. In both cases, configuration of a newly formed double bond was controlled to be in an E-form. The results of carboxylation of 1c in the absence of ZnCl2 (Scheme 4, eq. 1) strongly supported our initial hypothesis of the carboxylation/cyclization cascade shown in Scheme 1. However, the high regio- and E-selectivity observed in the reactions of 1g and 1h (Table 2, entries 4 and 5) suggest another possible reaction pathway. Montgomery and coworkers reported a nickel-catalyzed cyclization of allenyl aldehydes that involved an oxidative cyclization of the allene and aldehyde moieties to low-valent nickel species as the first step of the catalytic cycle.7a Allenyl aldehydes 1g or 1h would also be able to react with low-valent nickel species in a similar way before the reaction with CO2 (Scheme 5). To undergo such reaction, low-valent nickel species would be preferably placed at the opposite side of the “R” group due to steric repulsion (Scheme 5, intermediate 7). Thus, oxidative cyclization from 7 would give oxa-nickelacycle intermediate 8. Then insertion of CO2 into the nickel-carbon bond would proceed in a stereospecific manner to form 9, which would afford 3g or 3h after hydrolysis and esterification. This cyclization/carboxylation cascade pathway cannot be excluded in the reactions of other allenyl aldehydes. Thus, in the actual system, the reaction course might involve one or both cascades depending on the substrate used.

![Scheme 5 Cyclization/Carboxylation Cascade](image)

In summary, nickel-mediated cyclization of allenyl aldehydes that involved a CO2 incorporation process was developed. The reaction proceeds under mild conditions in a regioselective manner and provides a novel method for synthesis of bicyclic α-methylene-γ-lactones. Further studies on expansion of the scope of this procedure are now in progress.

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

References and Notes

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(4) Other examples for transition metal-catalyzed CO2 incorporation reactions, see: (a) Takimoto, M.; Mori, M. in Modern Organonickel Chemistry (Ed. Y. Tamaru), Wiley-VCH, Weinheim, 2005, pp 205-223.

(6) Hoberg reported the formation of nickelacycles such as 2 by the reaction of allenes, CO₂, and nickel(0) complex, see: Hoberg, H.; Oster, B. *W. J. Organomet. Chem.* **1984**, *266*, 321.  
(7) Related examples for nickel-catalyzed inter- or intramolecular reactions between allene and aldehyde, see:  
(8) Oxidation of the mixture of trans- and cis-3a afforded the corresponding ketone as the sole product in high yield.  
(9) Semmelhack reported a similar transformation involving an intramolecular nucleophilic addition of π-allylnickel bromide intermediate to aldehyde that formed a seven-membered ring fused with α-methylene-γ-lactone. The cis-stereoselectivity observed in Semmelhack’s example shows good accordance with our results: Semmelhack, M. F.; Wu, E. C. *S. J. Am. Chem. Soc.* **1976**, *98*, 3384.
Carboxylation/Cyclization Cascade of Allenyl Aldehyde

\[
\text{CHO} + \text{CO}_2 \xrightarrow{\text{Ni(cod)$_2$, TMEDA, dioxane, rt}} \text{OH} + \text{CO}_2\text{H} \\
(R=H, Me, or Ph)
\]