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Author(s)	Doi, Ryohei; Okano, Taichi; Abdullah, Iman; Sato, Yoshihiro
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Nickel-Catalyzed β -Carboxylation of Ynamides with Carbon Dioxide

Ryohei Doi^a
Taichi Okano^a
Iman Abdullah^b
Yoshihiro Sato^{*a}

^a Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

^b Current position: Department of Chemistry, Faculty of Mathematic and Natural Sciences, Universitas Indonesia, Depok 16424, Indonesia

* indicates the main/corresponding author.

biyo@pharm.hokudai.ac.jp

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Abstract: Described herein is nickel-catalyzed β -selective hydrocarboxylation of ynamide to obtain protected dehydro- β -amino acids. The key to exclusive β -selectivity is the use of diethylzinc as a reductant in the presence of a magnesium salt. The reaction was conducted with $\text{Ni}(\text{acac})_2$ instead of costly and sensitive $\text{Ni}(\text{cod})_2$. In addition, the optimized ligand was inexpensive 1,5-cyclooctadiene. Investigation of the substrate scope revealed that both nitrogen and alkyne substituents have considerable influence on the reaction efficiency. We obtained experimental clues that indicated the formation of a vinylzinc intermediate forging a C–C bond with CO_2 .

Key words: Ynamide, Hydrocarboxylation, Carbon Dioxide, Nickel catalysis, β -Amino Acid

Carbon dioxide (CO_2) is an attractive C-1 building block because of its inexpensiveness, low toxicity and easy manipulation. However, chemical transformation of CO_2 is hampered by its low reactivity, which traditionally requires harsh conditions or a strong nucleophile such as organolithium or Grignard reagent for C–C bond construction. Recently, a transition-metal complex have played an important role for dramatic improvement of this chemistry; a variety of unique, mild and chemoselective carboxylation reactions using CO_2 have been developed under transition-metal catalysis.¹ Nickel catalysts have been used for carboxylation of unsaturated C–C bonds such as alkyne,² alkene³ 1,2- and 1,3-dienes,⁴ which are not able to forge a C–C bond with CO_2 in the absence of a catalyst due to their poor nucleophilicity.

In this context, we have been engaged in carboxylation of ynamides for synthesis of amino acid derivatives because of their importance as biologically active molecules.^{5–7} Consequently, we have reported nickel-mediated hydrocarboxylation of ynamides using CO_2 (Scheme 1a).^{2a} The polarity of a C–C triple bond of ynamide allowed the oxidative cyclization process with CO_2 and $\text{Ni}(0)$ to occur in a regioselective manner to yield a β -carboxylation product exclusively.⁸ It is noteworthy that Rh-catalyzed enantioselective hydrogenation of the products

enabled access to chiral β -amino acids.^{2a} Our next challenge was directed toward establishment of a catalytic carboxylation to bypass the cost and troublesome instability of $\text{Ni}(\text{cod})_2$.⁹ We succeeded in developing Ni-catalyzed hydrocarboxylation of ynamide by use of Zn as a reductant and water as a hydrogen source.^{2b} Interestingly, the reaction gave an α -carboxylated compound as a major product despite the polarity of an ynamide C–C triple bond, which favors coupling with electrophile at the β -position (Scheme 1b). Herein, we describe nickel-catalyzed β -selective hydrocarboxylation of ynamides with CO_2 (Scheme 1c). Catalytic reactions worked well with the use of $\text{Ni}(\text{II})$ salt instead of sensitive $\text{Ni}(\text{cod})_2$ and costly phosphine- or nitrogen-based ligands.

a) Ni-mediated β -hydrocarboxylation of ynamide

b) Ni-catalyzed α -hydrocarboxylation of ynamide

c) This work: Ni-catalyzed β -hydrocarboxylation of ynamide

Scheme 1. Ni-mediated or -catalyzed hydrocarboxylation of ynamides

Table 1. Condition Screening

Run	Catalyst	Solv.	Time	Conc.	Yield ^a
1 ^b	Ni(cod) ₂ /bpy	DMF	12 h	0.2 M	46%
2 ^b	Ni(cod) ₂ /tmeda	DMF	12 h	0.2 M	45%
3 ^b	Ni(cod) ₂ /PPh ₃	DMF	12 h	0.2 M	30%
4 ^b	Ni(cod) ₂	DMF	12 h	0.2 M	47%
5 ^{b,c}	Ni(cod) ₂	DMF	12 h	0.2 M	15%
6	Ni(cod) ₂	DMF	12 h	0.1 M	55%
7	Ni(acac) ₂	DMF	12 h	0.1 M	27%
8 ^d	Ni(acac) ₂	DMF	1 h	0.1 M	58% ^g
9 ^e	Ni(acac) ₂	DMF	1 h	0.1 M	60%
10 ^f	Ni(acac) ₂	DMF	1 h	0.1 M	26%
11 ^d	Ni(acac) ₂	DMPU	1 h	0.1 M	66% ^g
12 ^d	Ni(acac) ₂	NMP	1 h	0.1 M	68% ^g
13 ^d	Ni(acac) ₂	DMA	1 h	0.1 M	63% ^g
14 ^d	Ni(acac) ₂	MeCN	1 h	0.1 M	4%

^aNMR yield. ^bMethylated with CH₂N₂. ^cWithout MgBr₂. ^dWith 1 equiv. COD. ^eWith 1 equiv. NBD. ^fWith 1 equiv. *cis*-4-octene. ^gIsolated yield.

We commenced investigation by using diethylzinc instead of a zinc/water reductant system, which we used in our previous study,^{2b} for catalytic turn-over of active nickel species. As a result, β-carboxylation product **2a** was obtained in 46% yield with 10 mol% Ni(cod)₂ accompanied by a small quantity (<1% yield) of the α-carboxylation product (Table 1, run 1). Interestingly, we found that the reaction was not significantly affected by the addition of an auxiliary ligand such as 2,2'-bipyridine (bpy), *N,N,N',N'*-tetramethylethylenediamine (tmeda) or PPh₃ (runs 1-4). In contrast to ligands, the addition of magnesium salt was found to be indispensable (run 5). A lower concentration gave a better yield (run 6). We assumed that 1,5-cyclooctadiene (COD) is working as a suitable stabilizer of a nickel catalyst in run 4. Then, to circumvent the use of highly sensitive Ni(cod)₂, we tested the use of Ni(acac)₂, which would be reduced to Ni(0) by the action of diethylzinc, and we confirmed that the desired product was isolated in 58% yield in the presence of COD (runs 7,8). In this case, TLC analysis indicated that consumption of the starting material was completed within 1 h. The addition of norbornadiene (NBD) was also effective, while *cis*-4-octene was not a suitable olefin for assisting the nickel catalysis (runs 9,10). Finally, we evaluated several polar solvents in our carboxylation reaction. Reactions in *N,N'*-dimethylpropyleneurea (DMPU) or 1-methyl-2-pyrrolidone (NMP) gave better results than reactions carried out in DMF and DMA (runs 11-13). Acetonitrile was an inappropriate solvent for our system (run 14). NMP gave a better isolated yield due to the ease of chromatographic purification.

We next investigated the substrate scope of our β-selective carboxylation reaction. First, we studied the effect of

nitrogen substituents (Table 2). By comparing ynamides having Ts (**1a**) and mesyl (Ms, **1b**), Ts-ynamide gave a better result. The reaction of an ynamide **1c** having an oxazolidinone ring gave the desired product in 28% yield. Unfortunately, a crude mixture containing **2c** did not allow chromatographic separation from the by-products. The reaction of acyclic carbamate **1d** also worked, but the yield was low. We next screened a partner of the Ts group on nitrogen. Ynamide **1e** protected by a benzyl group delivered the desired product in 65% yield. We found that ynamide **1f** having a Ts and a cyclohexyl group gave the desired product **2f** in 79% yield. We then focused on a bulky and removable protecting group for a synthetic advantage. Hydrocarboxylation with a Ts-ynamide **2g** decorated with a diphenylmethyl group resulted in a low yield even with prolonged reaction time. We then used a *tert*-butyl group, which is known to be deprotected under acidic conditions, to afford the desired product **2h** in 78% yield.

Table 2. Effect of nitrogen substitution^a

Ynamide	Product	Yield
1a (Ts)	2a	68%
1b (Ms)	2b	49%
1c (oxazolidinone)	2c	28% ^b
1d (carbamate)	2d	42% ^b
1e (benzyl)	2e	65%
1f (Ts, cyclohexyl)	2f	79%
1g (diphenylmethyl)	2g	30% ^c
1h (tert-butyl)	2h	78% ^d

^aIsolated yield. ^bNMR yield. ^c24 h. ^d2 h.

By using ynamides protected with Ts and a *tert*-butyl group, we examined the scope of a substituent on an alkyne moiety (Table 3). Reactions of ynamides carrying primary alkyl groups resulted in good yields (**2i**, **2j**). In contrast, carboxylation of an ynamide having a secondary alkyl group was sluggish, probably due to steric congestion between Z-olefin substituents. In fact, an isopropyl ynamide carrying a methyl group on nitrogen gave the desired product **2k** albeit in low yield. Ynamides derived from phenylacetylene gave the desired product **2l** in 54% yield. The reactions of **1m** and **1n** having a 3-fluoro group and a 4-anisyl group proceeded to give the compounds **2m** and **2n** in 63% and 67% yields, respectively. The structure of **2n** was confirmed by X-ray crystallography (Figure 1).¹⁰

Table 3. Effect of alkyne terminus

^aIsolated yields were shown. ^bYield determined by ¹H NMR analysis.

Figure 1. Structure of **2n**

The displacement ellipsoids for one of two molecules in a lattice are drawn at 50% probability level. Hydrogen atoms were omitted for clarity.

Scheme 2. Scale-up reaction and transformation of the product.

Conditions for transformation: a) Et₂O/HCl, rt; b) Pd/C, H₂, MeOH, rt.

Our reaction could be performed on a 1.5 mmol scale (Scheme 2a). To demonstrate the application of our reaction, we studied deprotection of a *tert*-Bu group on nitrogen. Treatment of **2i** with

HCl in ether gave an unstable deprotected enamine that was subsequently reduced into the amino acid **4** under an H₂ atmosphere with Pd/C. It is noteworthy that an attempt to reduce **2i** with Pd/C under H₂ was unsuccessful, probably due to steric hindrance of the *tert*-Bu group on nitrogen.

Figure 2. Mechanistic study and proposed mechanism

We finally turned our attention to the reaction mechanism. When our standard reaction mixture using an ynamide **1a** was quenched with DCl/Et₂O, deuterium incorporation was not observed (Figure 2a). This result indicates that the α-hydrogen of the product is introduced during the reaction course probably from a β-hydrogen of diethylzinc. Next, we performed the reaction without CO₂ to obtain information on the nucleophilic species that capture CO₂. As a result, reduced enamine was obtained in a catalytic manner. In addition, DCl quenching gave **3a** of which the β-position is deuterated (Figure 2b). This can be interpreted as generation of an organozinc compound *in situ* that is protonated by the addition of HCl or DCl. The addition of iodine gave a corresponding iodinated product **4** of which isolation further supports the existence of a hydrozincation path. Based on these observations and a precedent report, we propose the reaction mechanism illustrated in Figure 2c.¹¹ Coordination of Ni(0), which is added as Ni(cod)₂ or is generated *in situ* by reduction of Ni(II) with ZnEt₂, with an ynamide results in formation of nickelacyclopentadiene intermediate **I**. The electron-donating nature of nitrogen would induce formal anionic charge at the β-carbon, which might interact with an electropositive zinc atom to facilitate regioselective transmetalation.¹² In this step, steric repulsion between substituent R with diethylzinc would have a negative impact on the reaction progress. Meanwhile, an electron-donating *tert*-butyl group on nitrogen would exert a positive

effect for the reaction progress as shown in Table 2. The ethyl nickel moiety of intermediate **II** collapses via β -hydrogen elimination and a reductive elimination sequence to regenerate Ni(0) species. The C–C bond formation of the resulting vinylzinc species **IV** with CO₂ would be accelerated by the addition of magnesium salt via formation of zincate. It is noteworthy that the addition of LiBr, which is known to form reactive zincate species with an organozinc reagent, also promoted our catalytic carboxylation (Figure 2d).¹³

In summary, we have developed a catalytic β -carboxylation of ynamides by using CO₂ as a C1 source to afford a precursor of β -amino acids. Our method used inexpensive and air-stable Ni(acac)₂ as a catalyst instead of Ni(cod)₂, which was previously added in a stoichiometric quantity. A preliminary mechanistic study suggested generation of a vinylzinc intermediate forging a C–C bond with CO₂. Further studies to expand our protocol are currently underway.

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