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## Nickel-Catalyzed Hydrocarboxylation of Ynamides with CO<sub>2</sub> and H<sub>2</sub>O: Observation of Unexpected Regioselectivity<sup>†</sup>

Ryohei Doi,<sup>a</sup> Iman Abdullah,<sup>a</sup> Takahisa Taniguchi,<sup>a</sup> Nozomi Saito,<sup>b</sup> and Yoshihiro Sato\*<sup>a</sup>Received 00th January 20xx,  
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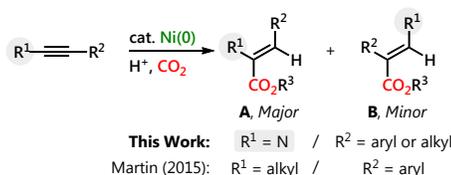
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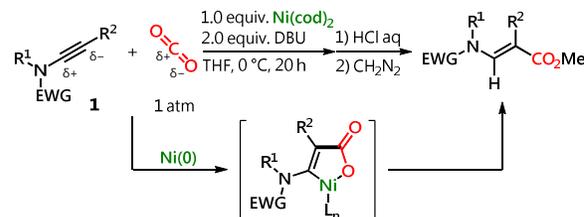
We describe the nickel-catalyzed hydrocarboxylation of ynamides with CO<sub>2</sub> and H<sub>2</sub>O to afford a variety of  $\alpha$ -amino- $\alpha,\beta$ -unsaturated esters with high regioselectivities. Selective  $\alpha$ -carboxylation of ynamide with this catalytic protocol is unexpected in view of the electronic bias of ynamide and is in sharp contrast to our previous study in which a stoichiometric amount of Ni(0) was used to form a  $\beta$ -carboxylated product exclusively. We revealed that this unexpected C–C bond formation was induced by the combination of Zn and MgBr<sub>2</sub>.

Homogeneous nickel catalysis has emerged in the past few decades as a highly efficient tool for organic synthesis.<sup>1</sup> The intrinsic chemical properties of some nickel catalysts to construct a C–C bond have been applied to incorporation of CO<sub>2</sub>, which is an abundant, non-toxic and renewable carbon source.<sup>2</sup> Especially, reactions using compounds bearing a C–C double bond or triple bond as a coupling partner of CO<sub>2</sub> enable transformation of these building blocks into carboxylic acid derivatives without prefunctionalization such as halogenation or metalation.<sup>3–5</sup> Since all carbons constituting an unsaturated bond are potentially reactive, controlling the regioselectivity is a common concern of these promising reactions employing CO<sub>2</sub>. Recently, Martin's group has developed regioselective hydrocarboxylation of alkyl aryl acetylenes with CO<sub>2</sub> employing alcohol as a proton source.<sup>4f</sup> They speculated that an equilibrium would exist between two possible nickelalactones derived from alkyne and CO<sub>2</sub> and that steric repulsion between an alkyl group and alcohol would be a key factor for preferential formation of carboxylic acid **A** behind **B** (Scheme 1). Their proposed mechanism let us assume another strategy for nickel-catalyzed regioselective hydrocarboxylation of a C–C triple bond with CO<sub>2</sub> in which the selectivity would be engendered by taking advantage of an electronic factor.

Herein, we report a nickel-catalyzed regioselective hydrocarboxylation of ynamide, which is known to have an electronic bias on the C–C triple bond, by use of H<sub>2</sub>O and CO<sub>2</sub>.<sup>6</sup> Consequently, we observed an interesting selectivity switching triggered by additives.



Scheme 1. Regioselective oxidative cyclization of ynamide and CO<sub>2</sub> with Ni(0). R<sup>3</sup> = H or Me.



Scheme 2. Our previous work: Nickel-mediated hydrocarboxylation of ynamide with CO<sub>2</sub>.

We previously described a nickel-mediated regioselective synthesis of functionalized  $\beta$ -amino- $\alpha,\beta$ -unsaturated esters from ynamides **1** and CO<sub>2</sub>.<sup>7</sup> The selectivity was controlled by a regioselective oxidative cyclization step in which a negative  $\beta$ -carbon of an ynamide forms a C–C bond with CO<sub>2</sub> on Ni(0) (Scheme 2). The resulting  $\beta$ -carboxylated products were shown to be precursors of enantio-enriched  $\beta$ -amino acid derivatives by conducting Rh-catalyzed asymmetric hydrogenation. As a next step, we commenced to develop a regioselective catalytic hydrocarboxylation of ynamides. Recently, Sakaki and Tsuji *et al.* reported a nickel-catalyzed double carboxylation of alkyne by the use of CO<sub>2</sub> in the presence of Zn/MgBr<sub>2</sub> as reducing agents.<sup>4g</sup> We applied their reaction conditions to catalytic hydrocarboxylation of ynamides with CO<sub>2</sub> and H<sub>2</sub>O. In the presence of 10 mol% of Ni(cod)<sub>2</sub> and 2,2'-bipyridyl (bpy) and 3 equiv. of Zn/MgBr<sub>2</sub>, hydrocarboxylation of ynamide **1a** with

<sup>a</sup> Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

<sup>b</sup> Meiji Pharmaceutical University, Kiyose, Tokyo 204-8588, Japan  
Email: biyo@pharm.hokudai.ac.jp

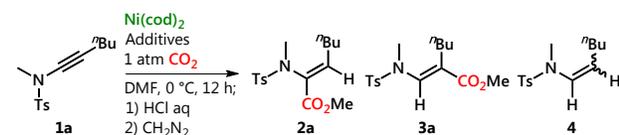
<sup>†</sup> Electronic Supplementary Information (ESI) available: experimental procedures, crystallographic data for **2n** (CCDC 1545491), **5** (CCDC 1545492) and characterization data of other compounds. See DOI: 10.1039/x0xx00000x

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CO<sub>2</sub> and H<sub>2</sub>O occurred to give a mixture of esters **2a** and **3a** in 78% yield with a regioisomer ratio of 83/17 (Table 1, run 1). The structure of compound **2a** was supported by NOE experiments of the corresponding alcohol that was obtained by DIBAL reduction of **2a** (see Supporting Information for details). The preference for generation of  $\alpha$ -carboxylation product **2a** over  $\beta$ -carboxylation product **3a** is an unexpected result since our previous study employing a stoichiometric amount of Ni(0) afforded only a  $\beta$ -carboxylation product. Actually, treatment of the ynamide **1a** with a stoichiometric amount of Ni(cod)<sub>2</sub> and bpy followed by addition of aqueous HCl gave  $\beta$ -carboxylation product **3a** as a sole carboxylation product along with the formation of a considerable amount of a hydrogenated product **4** as a mixture of *cis/trans* isomers (run 2).<sup>8</sup> Similar results were obtained in the presence of either MgBr<sub>2</sub> or Zn (runs 3 and 4). Contrary to these outcomes, hydrocarboxylation in the presence of both Zn and MgBr<sub>2</sub> afforded **2a** as a major product even though stoichiometric amounts of Ni(cod)<sub>2</sub> and bpy were loaded (run 5). This observation clearly suggests that the selectivity switching is induced not by the amount of Ni loading but by the combination of Zn and MgBr<sub>2</sub>.

Table 1. Hydrocarboxylation of ynamide with catalytic and stoichiometric amounts of Ni(0)



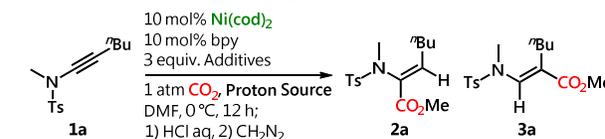
Run	Condition	Yield (%)	
		2a + 3a	4
1	10 mol% Ni(cod) <sub>2</sub> / bpy 3 equiv. Zn / MgBr <sub>2</sub> , 0.5 equiv. H <sub>2</sub> O	78 <sup>[a]</sup>	11
		(83/17) <sup>[b]</sup>	
2	1 equiv. Ni(cod) <sub>2</sub> / bpy	31 <sup>[c]</sup>	29
		(0/100) <sup>[b]</sup>	
3	1 equiv. Ni(cod) <sub>2</sub> / bpy 3 equiv. MgBr <sub>2</sub>	29 <sup>[c]</sup>	35
		(7/93) <sup>[b]</sup>	
4	1 equiv. Ni(cod) <sub>2</sub> / bpy 3 equiv. Zn	29 <sup>[c]</sup>	32
		(0/100) <sup>[b]</sup>	
5	1 equiv. Ni(cod) <sub>2</sub> / bpy 3 equiv. Zn / MgBr <sub>2</sub>	76 <sup>[c]</sup>	<5
		(84/16) <sup>[b]</sup>	

[a] Isolated Yield. [b] NMR yield with the aid of 1,1,2,2-tetrachloroethane as an internal standard. [c] Ratio of **2a** and **3a** determined by comparison of peak areas of <sup>1</sup>H NMR signals.

We further investigated the effects of reaction conditions on the yield and selectivity (Table 2). As a result, the reaction was found to be quite sensitive to the choice of a reductant. When the reaction was conducted by use of Mg or Mn as a reductant, both the yield and selectivity were significantly decreased (runs 2 and 3). Addition of magnesium salt was indispensable for this catalytic reaction; indeed, MgCl<sub>2</sub> showed an effect similar to that of the bromide counterpart, whereas LiBr, ZnBr<sub>2</sub> and tetrabutyl ammonium bromide (TBAB) were

totally ineffective (runs 4-7). Next, the reactions were conducted by using other proton sources. In contrast to Martin's system in which repulsion between an alcohol and an alkyl group is supposed to be a key factor, the selectivity of the hydrocarboxylation of ynamide was not significantly affected by the difference in proton source, though some alcohols gave the desired product in lower yields (runs 8-11).<sup>9</sup>

Table 2. Reaction condition screening

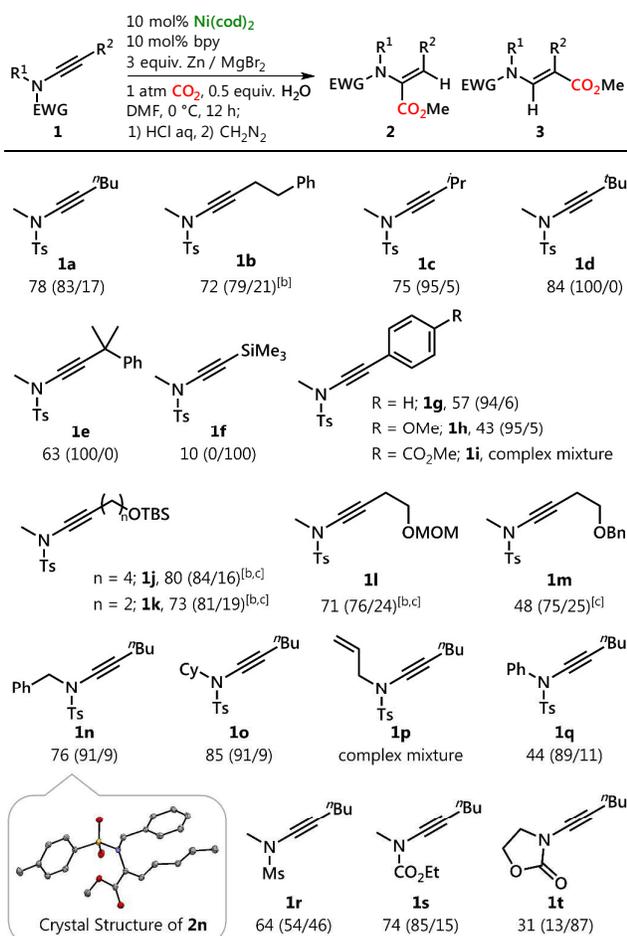


Run	Additive (3 equiv.)	Proton Source	Yield <sup>[a]</sup> (%)	Selectivity <sup>[b]</sup> (2a/3a)
1	Zn/MgBr <sub>2</sub>	0.5 equiv. H <sub>2</sub> O	78 <sup>[c]</sup>	83 17
2	Mg/MgBr <sub>2</sub>	0.5 equiv. H <sub>2</sub> O	11	63 37
3	Mn/MgBr <sub>2</sub>	0.5 equiv. H <sub>2</sub> O	29	55 45
4	Zn/MgCl <sub>2</sub>	0.5 equiv. H <sub>2</sub> O	71	92 8
5	Zn/LiBr	0.5 equiv. H <sub>2</sub> O	13	23 77
6	Zn/ZnBr <sub>2</sub>	0.5 equiv. H <sub>2</sub> O	trace	- -
7	Zn/TBAB	0.5 equiv. H <sub>2</sub> O	trace	- -
8 <sup>[d]</sup>	Zn/MgBr <sub>2</sub>	1.0 equiv. MeOH	81	80 20
9 <sup>[d]</sup>	Zn/MgBr <sub>2</sub>	1.0 equiv. <sup>t</sup> PrOH	64	83 17
10 <sup>[d]</sup>	Zn/MgBr <sub>2</sub>	1.0 equiv. <sup>t</sup> BuOH	46	76 24
11 <sup>[d]</sup>	Zn/MgBr <sub>2</sub>	1.0 equiv. CF <sub>3</sub> CH <sub>2</sub> OH	57	72 28

[a] Yields were determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] The selectivity refers to the ratio of **2a** and **3a** that was determined by the integration ratio of <sup>1</sup>H NMR signals. [c] Isolated yield. [d] The reactions were conducted for 36 h.

Next, we tested a variety of ynamides for the catalytic hydrocarboxylation reaction protocol (Table 3). In addition to an ynamide having a butyl group (**1a**), an ynamide bearing a phenylethyl group (**1b**) afforded the desired hydrocarboxylation product in good yield with similar selectivity. The hydrocarboxylation of ynamides possessing a secondary or tertiary alkyl chain on the alkynyl carbons delivered the esters in high yield with excellent regioselectivity. In contrast to these results, the use of silyl-substituted ynamide **1f** resulted in formation of  $\beta$ -carboxylated product **3f** which contains desilylated product **3f'**. Some ynamides having an aromatic ring such as phenyl (**1g**) or 4-methoxyphenyl (**1h**) were applicable to the reaction, while an ynamide **1i** having a methoxycarbonyl group at the 4-position of the benzene ring gave a complicated mixture. Hydrocarboxylation of alkyl ynamides carrying a terminal silyl ether group (**1j** and **1k**) gave desired products in 80% and 73% yields, respectively, with good regioselectivity. In addition, methoxymethane (MOM) and benzyl (Bn) protections were tolerated, and these substituents exerted very little effect on the selectivity (**1l** and **1m**). However, the reaction of alkyl ynamides having an acetoxy group gave a very small amount of the hydrocarboxylated product. Next, we modified substituents on a nitrogen atom. The reaction of ynamides bearing a benzyl group (**1n**) and a cyclohexyl group (**1o**) afforded the desired products in high yields. The structure of

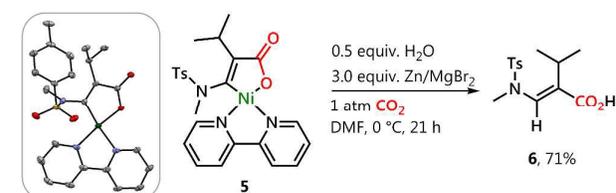
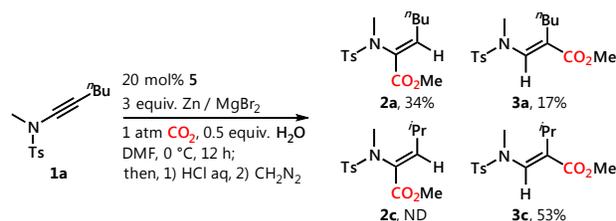
the product **2n** was confirmed by X-ray diffraction study after isolation of **2n** from the mixture of hydrocarboxylated products followed by crystallization. Unfortunately, allyl substituted ynamide **1p** gave a complicated mixture with the catalytic reaction conditions. Ynamide having a phenyl group (**1q**) on nitrogen yielded the desired product in moderate yield. Other electron-withdrawing groups such as mesyl (**1r**) and carbamate (**1s**) were applicable for ynamide protection in this hydrocarboxylation protocol. Interestingly, we observed reverse regioselectivity in the reaction of oxazolidione-derived ynamide **1t**.

Table 3. Substrate scope<sup>[a]</sup>

[a] Isolated yields are given. [b] 20 mol% catalyst was loaded. [c] Acidic work-up was conducted using 10% citric acid solution instead of 10% HCl.

To gain an insight into the origin of the selectivity, we isolated nickelalactone **5** as an orange precipitate formed from the reaction mixture containing Ni(cod)<sub>2</sub>, bpy, ynamide **1c** and CO<sub>2</sub>. X-ray crystallography of complex **5** revealed that C–C bond formation between ynamide and CO<sub>2</sub> occurred at the negative β-carbon, being in good accordance with our previous report (Figure 1).<sup>7</sup> However, treatment of complex **5** with the MgBr<sub>2</sub>/Zn/H<sub>2</sub>O system in DMF under a CO<sub>2</sub> atmosphere followed by HCl quenching only afforded β-carboxylation

product **6**. In addition, hydrocarboxylation of **1a** in the presence of a catalytic amount of nickelalactone **5** produced compounds **2a**, **3a** and **3c** (Scheme 3). The absence of compound **2c** in this reaction mixture implies that nickelalactone only gives a β-carboxylated product and that α-carboxylation might involve another pathway(s). We propose that the reaction proceeds via a nickel hydride species derived from H<sub>2</sub>O under a reductive condition.<sup>10,11</sup> Recently, Gosmini and Gillaizeau group reported Co-catalyzed carboxylation of ynamide, in which regioselectivities similar to those in our reactions were observed in some cases.<sup>12</sup> In addition, Hou's group developed Cu-catalyzed alkylative carboxylation of ynamide that gives α-carboxylated products.<sup>13</sup> Taking these reports into account, the α-selectivity would be induced by steric repulsion between a nickel complex and carbon substitution at the β-position and/or by interaction between a nickel complex and a substituent of nitrogen at the addition step of a nickel hydride species to ynamide.

Figure 1. Structure and stoichiometric reaction of nickelalactone **5**.Scheme 3. Nickelalactone **5**-catalyzed hydrocarboxylation of ynamide **1a**. Yields were determined by <sup>1</sup>H NMR of a crude product. Yields of **2a** and **3a** are based on ynamide **1a**, while that of **3c** is based on nickelalactone **5**.

In summary, we have described a nickel-catalyzed regioselective hydrocarboxylation of ynamide with CO<sub>2</sub> and H<sub>2</sub>O in the presence of Zn/MgBr<sub>2</sub> under mild conditions (0 °C). The selectivity of this catalytic protocol is in sharp contrast to the reaction using a stoichiometric amount of Ni(0) that resulted in exclusive formation of β-amino-α,β-unsaturated esters. The major product is a potential precursor of unnatural α-amino acids.<sup>14</sup> Further investigations of the reaction mechanism to clarify the origin of the selectivity observed in this nickel-catalyzed hydrocarboxylation are currently underway in our laboratory.

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- 14 The application of an asymmetric hydrogenation condition we developed previously (ref. 7) resulted in formation of the desired  $\alpha$ -amino acid derivative in 25% yield and 25%ee. In addition, we obtained racemic  $\alpha$ -amino acid quantitatively by reduction under H<sub>2</sub> pressure in the presence of Pd/C or Crabtree's catalyst. Further investigation is ongoing.