Nickel-Catalyzed Hydrocarboxylation of Ynamides with CO_2 and H_2O: Observation of Unexpected Regioselectivity†

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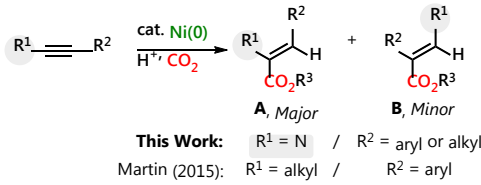
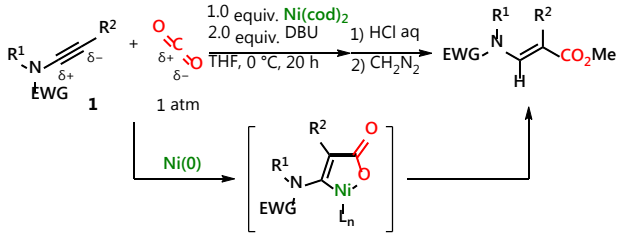
We describe the nickel-catalyzed hydrocarboxylation of ynamides with CO_2 and H_2O to afford a variety of α-amino-α,β-unsaturated esters with high regioselectivities. Selective α-carboxylation of ynamide with this catalytic protocol is unexpected in view of the electronic bias of ynamide and is in sharp contrast to our previous study in which a stoichiometric amount of Ni(0) was used to form a β-carboxylated product exclusively. We revealed that this unexpected C–C bond formation was induced by the combination of Zn and $MgBr_2$.

Homogeneous nickel catalysis has emerged in the past few decades as a highly efficient tool for organic synthesis.[1] The intrinsic chemical properties of some nickel catalysts to construct a C–C bond have been applied to incorporation of CO_2, which is an abundant, non-toxic and renewable carbon source.[2] Especially, reactions using compounds bearing a C–C double bond or triple bond as a coupling partner of CO_2 enable transformation of these building blocks into carboxylic acid derivatives without prefunctionalization such as halogenation or metalation.[3-5] Since all carbons constituting an unsaturated bond are potentially reactive, controlling the regioselectivity is a common concern of these promising reactions employing CO_2. Recently, Martin's group has developed regioselective hydrocarboxylation of alkyl aryl acetylenes with CO_2 employing alcohol as a proton source.[4f] They speculated that an equilibrium would exist between two possible nickelalactones derived from alkyne and CO_2 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_2 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_2O and CO_2.[6] Consequently, we observed an interesting selectivity switching triggered by additives.



Scheme 1. Regioselective oxidative cyclization of ynamide and CO_2 with Ni(0). R^3 = H or Me.



Scheme 2. Our previous work: Nickel-mediated hydrocarboxylation of ynamide with CO_2

We previously described a nickel-mediated regioselective synthesis of functionalized β-amino-α,β-unsaturated esters from ynamides **1** and CO_2.[7] The selectivity was controlled by a regioselective oxidative cyclization step in which a negative β-carbon of an ynamide forms a C–C bond with CO_2 on Ni(0) (Scheme 2). The resulting β-carboxylated products were shown to be precursors of enantio-enriched β-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_2 in the presence of Zn/$MgBr_2$ as reducing agents.[4g] We applied their reaction conditions to catalytic hydrocarboxylation of ynamides with CO_2 and H_2O. In the presence of 10 mol% of $Ni(cod)_2$ and 2,2'-bipyridyl (bpy) and 3 equiv. of Zn/$MgBr_2$, hydrocarboxylation of ynamide **1a** with CO_2 and H_2O 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 α-carboxylation product **2a** over β-carboxylation product **3a** is an unexpected result since our previous study employing a stoichiometric amount of Ni(0) afforded only a β-carboxylation product. Actually, treatment of the ynamide **1a** with a stoichiometric amount of $Ni(cod)_2$ and bpy followed by addition of aqueous

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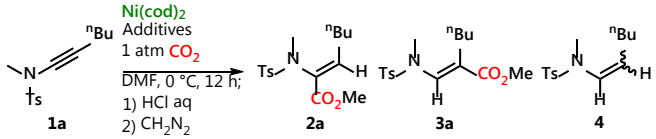
†Electronic Supplementary Information (ESI) available: experimental procedures, crystallographic data for **2n** (CCDC 1545491), **5** (CCDC 1545492) and characterization data of other compounds. See DOI: 10.1039/x0xx00000x

HCl gave β-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).[8] Similar results were obtained in the presence of either $MgBr_2$ or Zn (runs 3 and 4). Contrary to these outcomes, hydrocarboxylation in the presence of both Zn and $MgBr_2$ afforded **2a** as a major product even though stoichiometric amounts of $Ni(cod)_2$ 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 $MgBr_2$.

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

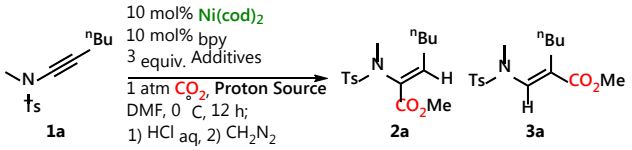


Run	Condition	Yield (%) 2a + 3a	Yield (%) 4
1	10 mol% $Ni(cod)_2$ / bpy 3 equiv. Zn / $MgBr_2$, 0.5 equiv. H_2O	78[a] (83/17)[b]	11
2	1 equiv. $Ni(cod)_2$ / bpy	31[c] (0/100)[b]	29
3	1 equiv. $Ni(cod)_2$ / bpy 3 equiv. $MgBr_2$	29[c] (7/93)[b]	35
4	1 equiv. $Ni(cod)_2$ / bpy 3 equiv. Zn	29[c] (0/100)[b]	32
5	1 equiv. $Ni(cod)_2$ / bpy 3 equiv. Zn / $MgBr_2$	76[c] (84/16)[b]	<5

[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 ^1H 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, $MgCl_2$ showed an effect similar to that of the bromide counterpart, whereas LiBr, $ZnBr_2$ 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).[9]

Table 2. Reaction condition screening



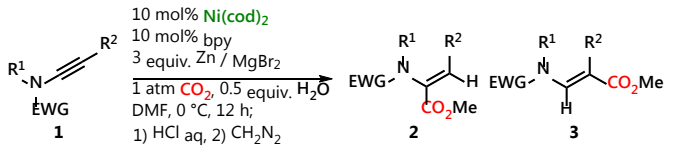
Run	Additive (3 equiv.)	Proton Source		Yield[a] (%)	Selectivity[b] (2a/3a)	
1	Zn/$MgBr_2$	0.5 equiv.	H_2O	78[c]	83	17
2	Mg/$MgBr_2$	0.5 equiv.	H_2O	11	63	37
3	Mn/$MgBr_2$	0.5 equiv.	H_2O	29	55	45
4	Zn/$MgCl_2$	0.5 equiv.	H_2O	71	92	8
5	Zn/LiBr	0.5 equiv.	H_2O	13	23	77
6	Zn/$ZnBr_2$	0.5 equiv.	H_2O	trace	-	-
7	Zn/TBAB	0.5 equiv.	H_2O	trace	-	-
8[d]	Zn/$MgBr_2$	1.0 equiv.	MeOH	81	80	20
9[d]	Zn/$MgBr_2$	1.0 equiv.	^{i}PrOH	64	83	17
10[d]	Zn/$MgBr_2$	1.0 equiv.	^{t}BuOH	46	76	24
11[d]	Zn/$MgBr_2$	1.0 equiv.	CF_3CH_2OH	57	72	28

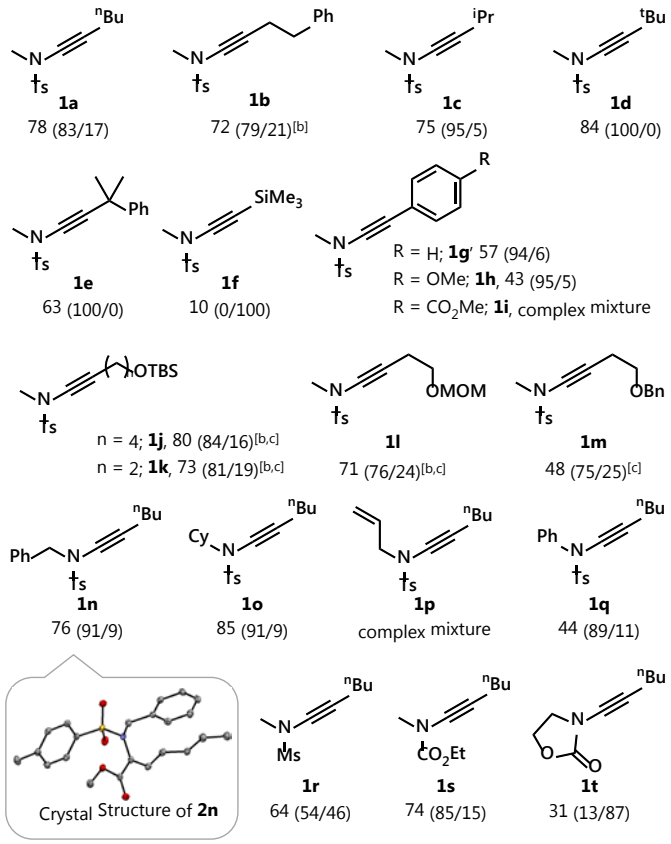
[a] Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] The selectivity refers to the ratio of **2a** and **3a** that was determined by the integration ratio of ^1H NMR signals. [c] Isolated yield. [d] The reactions were conducted for 36 h.

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 β-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[a]





[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 $Ni(cod)_2$, bpy, ynamide **1c** and CO_2. X-ray crystallography of complex **5** revealed that C–C bond formation between ynamide and CO_2 occurred at the negative β-carbon, being in good accordance with our previous report (Figure 1).[7] However, treatment of complex **5** with the $MgBr_2$/Zn/H_2O system in DMF under a CO_2 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_2O under a reductive condition.[10,11] Recently, Gosmini and Gillaizeau group reported Co-catalyzed carbozincation of ynamide, in which regioselectivities similar to those in our reactions were observed in some cases.[12] In addition, Hou's group developed Cu-catalyzed alkylative carboxylation of ynamide that gives α-carboxylated products.[13] 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.

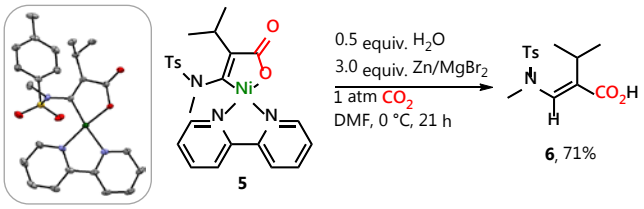
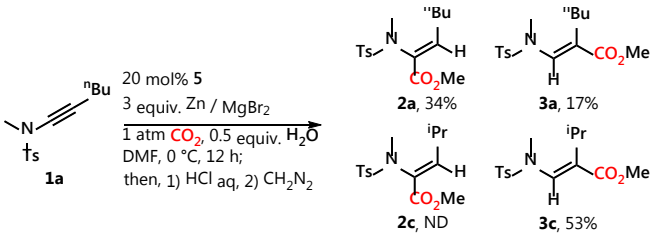


Figure 1. Structure and stoichiometric reaction of nickelalactone **5**.



Scheme 3. Nickelalactone **5**-catalyzed hydrocarboxylation of ynamide **1a**. Yields were determined by ^{1}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_2 and H_2O in the presence of Zn/$MgBr_2$ 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.[14] 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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8 We speculate that nickelalactone intermediates would deliver compound **4**, because the starting material was fully recovered in the reaction in the absence of CO_2.

9 We also conducted screening of ligands, including 1,10-phenanthroline and its derivatives, but the reactions resulted in lower yields. For the results of full ligand screening, see Supporting Information.

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14 The application of an asymmetric hydrogenation condition we developed previously (ref. 7) resulted in formation of the desired α-amino acid derivative in 25% yield and 25%ee. In addition, we obtained racemic α-amino acid quantitatively by reduction under H_2 pressure in the presence of Pd/C or Crabtree's catalyst. Further investigation is ongoing.