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Selectivities in Nickel-Catalyzed Hydrocarboxylation of Enynes with Carbon Dioxide

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Supporting Information Placeholder

ABSTRACT: A three component hydrocarboxylation of enynes with $ZnEt_2$ and CO_2 is realized. Highly selective cyclizative carboxylation of the C-C triple bond was observed. Preliminary mechanistic studies indicated both the concerted cyclometalation mechanism and the stepwise C=C bond-directed carboxylation were possible in this reaction. **KEYWORDS:** nickel, enyne, diethyl zinc, carbon dioxide, cyclic hydrocarboxylation

As one of the most important fundamental organic compounds, carboxylic acid plays an irreplaceable role in life science,¹ chemical industry,² and daily life. Traditionally, carboxylic acids are prepared mainly through oxidation of primary alcohols³ or aldehydes,² oxidative cleavage of C-C bonds,⁴ or hydrolysis of nitriles, esters, and amides. In recent vears, carboxylation of alkynes or alkenes with carbon dioxide under mild conditions has become a powerful method to prepare synthetically useful alkenoic or alkanoic acids.⁵⁻⁷ We envisioned that carboxylation of enynes may provide cyclic alkenoic or alkanoic acids, providing that the selectivity issue between C-C double and triple bonds may be addressed. Y. Sato and M. Mori et al. reported the stoichiometric nickel-mediated cyclizative carboxylation of enyne S1 with a methoxycarbonyl group connected to the C=C bond⁸ resulting in malonate derivative P1 (Scheme 1, Eq. 1). However, the simple enyne substrate S2 with a terminal C=C bond did not react at all (Scheme 1, Eq. 2).8 Herein, we report a nickel-catalyzed cyclizative carboxylation of enynes S3 providing 2-alkenoic acids P3 (Scheme 1, Eq. 3).^{9,10}

Initially, enyne with a nitrogen tether **1a** was treated with 1 mol% of Ni(cod)₂ and 3 equiv of ZnEt₂ with a balloon of CO₂ in CH₃CN at 60 °C. Hydrocarboxylation product *E*-**2a** was obtained in 40% NMR yield accompanied with 30% of the protonolysis product *Z*-**3a**. The structure of *E*-**2a** was confirmed by X-ray single crystal study (Figure 1).¹¹ In addition, based on the analysis of crude NMR spectra, the stereoisomer *Z*-**2a** and **P1**-type product with the C=C bond being carboxylated (**2a'**) was not observed (Scheme 2).









Figure 1. ORTEP representation of E-2a.

Encouraged by these initial results, we turned to optimize the selectivity between E-2a and Z-3a (Table 1). Surprisingly, when CsF was added to the reaction, the yield of E-2a was remarkably improved (Table 1, Entries 1-4). With 2 equiv of CsF, the yield of E-2a reached 83% and only 8% of Z-3a was formed (Table 1, Entry 4). Further increasing the amount of CsF to 3 equiv did not affect the yield of E-2a (Table 1, Entry 5). However, when 2 equiv of ZnEt₂ were used, E-2a was formed only in 64% yield with 16% of 1a recovered (Table 1, Entry 6). Ligands such as PPh₃ and IPr would more or less suppress the reaction (Table 1, Entries 7,8). Finally, 1 mol % of Ni(cod)₂, 2 equiv of CsF, 3 equiv of ZnEt₂ and a balloon of CO₂ in CH₃CN at 60 °C have been defined as the standard conditions for further study.

 Table 1. Optimization of cyclizative carboxylation of enyne

 1a.^a

TsN	ZnEt ₂ (X	(cod) ₂ (1 mol %) (equiv), CsF (Y e		CO ₂ H
	CO ₂ ball	oon, CH ₃ CN, 60 ^c	PC, 3 h	
	1a		E-2a	Z-3a
entry	Х	Y	yield of $E-2a$ (%) ^b	yield of Z-3a $(\%)^b$
1^c	3	0	40	30
2	3	0.5	57	27
3	3	1	74	17
4^c	3	2	$83(77^d)$	8
5	3	3	83	8
6 ^e	2	2	64	8
71	3	2	6	0
8^g	3	2	61	9

^{*a*} The reaction was carried out with **1a** (0.5 mmol), Ni(cod)₂, CsF, ZnEt₂ (1.5 M in toluene), and a balloon of CO₂ (about 1 L) in 5 mL of CH₃CN at 60 °C. ^{*b*} Yields are determined by ¹H NMR analysis with CH₂Br₂ as the internal standard. ^{*c*} The reaction was carried out with 1 mmol of **1a** in 10 mL of CH₃CN. ^{*d*} Isolated yield. ^{*e*} Recovery of **1a** in 16% yield was observed. ^{*f*} PPh₃ (2 mol%) was added and recovery of **1a** in 86% yield was observed. ^{*g*} IPr (2 mol%) was added and recovery of **1a** in 19% yield was observed.

With the optimized conditions in hand, various alkyl- or aryl-substituted enynes have been investigated (Table 2). With elongated alkyl chain that substituted to C-C triple bond, the yields were slightly decreased (E-2a-c). The substrates with an oxygen tether (E-2d) or dimethyl malonate (Z-2e,f) were also suitable for the reaction. Moreover, the reaction could tolerate varies synthetically useful functional groups, such as cyano (E-2g), acetoxy (E-2h), and acetal (E-2i). In addition, phenyl substituted enynes could be reacted smoothly in this reaction with 5 mol% of Ni(cod)₂ in DMSO at 80 °C (E-4j-l). It is easy to conduct the reaction on one gram scale to afford E-2a in 77% yield (Table 2, Entry 2). However, 1m with a tether of CH₂ was not suitable for the reaction, indicating that the Thorpe-Ingold effect was critical for this cyclization (Table 2, Entry 14). The reaction of 1n yielded a pair of diastereoisomers of E-2n (dr = 1:1), indicating that there is no 1,2-chiral induction (Scheme 3). In all of these cases, the major by-products were the protonolysis products (for details, see the Supporting Information).

Table 2. Cyclizative carboxylation of alkyl- or aryl-substituted enynes $1.^{a}$

	Conditions A or	\xrightarrow{B}	CO ₂ Me
entry	Х	R	yield of 2 or $4 (\%)^b$
1	TsN	Me (1a)	77 (E-2a)
2^{c}	TsN	Me (1a)	77 (E -2a)
3	TsN	Et (1b)	72 (E- 2b)
4	TsN	^{<i>n</i>} Bu (1c)	66 (E-2c)
5	О	Me (1d)	60 (E-2d)
6^d	$C(CO_2Me)_2$	Me (1e)	73 (Z-2e)
7^d	$C(CO_2Me)_2$	^{<i>n</i>} Bu (1f)	43 (Z-2f)
8^e	TsN	$NC(CH_2)_3$ (1g)	42 (E-2g)
9	TsN	$AcO(CH_2)_2$ (1h)	60 (E- 2h)
10	TsN	^ب رمن(1i)	50 (E-2i)
11	TsN	Ph (1j)	42 (E-4j)
12	TsN	$4-\text{MeOC}_6\text{H}_4$ (1k)	42 (E-4k)
13	TsN	$4-FC_{6}H_{4}(11)$	37 (E-41)
14 ^t	CH ₂	^{<i>n</i>} Bu $(\mathbf{1m})$	0

^{*a*} **Condition A** for the syntheses of **2a-i** and the reaction of **1m**: 1 mmol of **1**, 1 mol% of Ni(cod)₂, 2 equiv of CsF, 3 equiv of ZnEt₂ (1.5 M in toluene), and a balloon of CO₂ (about 1 L) in 10 mL of CH₃CN at 60 °C for 3 h followed by addition of HCl (3 M, 10 mL). **Condition B** for the syntheses of **4j-l**: 1 mmol of **1**, 5 mol% of Ni(cod)₂, 2 equiv of CsF, 3 equiv of ZnEt₂ (1.5 M in toluene), and a balloon of CO₂ (about 1 L) in 10 mL of DMSO at 80 °C for 3 h followed by addition of HCl (3 M, 10 mL), and the crude products were reacted with 4 equiv of TMSCHN₂ in 1 mL of MeOH and 4 mL of Et₂O at room temperature for 1 h. ^{*b*} Isolated yields. ^{*c*} The reaction was carried out with 5 mmol of **1a** to afford 1.1962 g of *E*-**2a**. ^{*d*} CsF was not used. ^{*e*} The reaction was carried out with 0.3 mmol of **1g** with 3 mol% of Ni(cod)₂. ^{*f*} Recovery of **1m** (74%) was observed.

Scheme 3. Hydrocarboxylation of 1n.



Notably, when the substrates bearing a homopropargylic hydroxyl (10 and 1p) or amino moiety (1q) were applied, as expected the hydroxyl and amino groups could react further with the in-situ formed carboxylic group to produce lactones (Scheme 4, Eq. 4 and 5) or lactam (Scheme 4, Eq. 6).

Scheme 4. Hydrocarboxylation-lactonization or lactamization.



Interestingly, when substrate 1r that has a non-terminal methyl-substituted C=C bond was reacted under standard conditions, the cyclic hydrocarboxylation product E-2r was formed in only 13% yield, accompanied with non-cyclic regioisomeric C-C triple bond hydrocarboxylation products 7r and 8r, indicating the importance of the terminal C=C bond (Scheme 5, Eq. 7). Similarly, the reaction of the 1,7-envne 1s produced only 8% of the six-membered product (Scheme 5, Eq. 8). Surprisingly, when the S1-type envne 1t was reacted under standard conditions, an ethyl carboxylation product E-9t with the C=C bond being carboxylated was formed as the major product, accompanied with the formation of the **P1**-type product Z-10t (Scheme 5, Eq. 9).

Ē

E-2s, 8%

солн

7r, 16%

E-7s, 10%

со^н

FIZ = 4.0/1

NMR vield E-2r. 13%

NMR vield

Scheme 5. Carboxylation of enynes 1r-t.

Ni(cod)₂ (1 mol%)

ZnEt₂ (3 equiv)

CsF (2 equiv)

CO₂ balloon

CH₃CN, 60°C, 3 h

Ni(cod)₂ (1 mol%)

ZnEt₂(3 equiv)

CsF (2 equiv)

CO₂ balloon CH3CN, 60°C, 3 h

1r. E/Z = 3.8/

1s

1t

18% isolated yield Furthermore, in order to capture any organometallic intermediates, 1a was treated with 1 mol% of Ni(cod)₂, 2 equiv of CsF, and 3 equiv of ZnEt₂ in CH₃CN under Ar in the absence of CO_2 , followed by quenching with D_2O (Scheme 6, Eq. 10). To our surprise, no deuteration occurred to the olefinic position, while the methyl group directly attached to the five-membered ring was deuterated in 29%. As a comparison, when the same reaction of 1a was conducted in CD₃CN and quenched with HCl (Scheme 6, Eq. 11), D-incorporations of the olefinic position and the methyl group directly attached to the five-membered ring are 65% and 10%, respectively. These results indicated that both olefinic carbon-zinc bond and sp3 C-Zn bond may exist and both of them are so reactive that it may abstract a proton from with the solvent, CH₃CN, however, the olefinic carbon-zinc bond is more reactive than the sp³ C-Zn bond. Thus, we proposed the formation of a dizinc species Int 1 (Scheme 6, Eq. 13).¹² In addition, when 1a was reacted in CH₃CN without CsF and CO_2 and quenched with D_2O (Scheme 6, Eq. 12), D-incorporations of the olefinic position and the methyl group directly attached to the five-membered ring are 41% and 27%, respectively, indicating that CsF could enhance the reactivity of olefinic carbon-zinc bond.

1) Ni(cod)₂ (1 mol%) ZnEt₂ (3 equiv) CsF (2 equiv) `Et TMSCHN₂ (4 equiv) 1 (9) CO₂ balloon MeOH:Et₂O = 1:4 CH₂CN, 60°C, 3 h rt. Ĩh 3 М НСІ 2) E-9t Z-10t NMR vield 40% 33% 24%



To further study the nature of the dizinc intermediate Int 1, 1a was reacted with 1 mol% of Ni(cod)₂, 2 equiv of CsF and 3 equiv of ZnEt₂ in CD₃CN under CO₂. After being quenched with D₂O, the methyl-deuterated carboxylation product E-2a-D was obtained in 78% yield with a D-incorporation of 41%, accompanied with 7% of the protonolysis product Z-**3a**-D₁, in which the methyl group directly attached to the five-membered ring was deuterated in 60% (Scheme 7, Eq. 14). The double carboxylation product C was not observed, indicating that the alkyl-zinc was not able to react with CO₂. Interestingly, when the amount of ZnEt₂ was reduced to 1 equiv, the yield of E-2a was 30% with no deuteration at the methyl group and 41% of starting material 1a was recovered (Scheme 7, Eq. 15).

Scheme 7. Detection of the dizinc species Int 1.



Thus, if the reaction started with concerted cyclometalation of 1a and $Ni(cod)_2$ to form Int 1' (Scheme 8),^{12,13} the subsequent transmetalation with ZnEt₂ would form an isomeric mixture of Int 2 and Int 2', which may produce three zinc species Int 3, Int 1, and Int 3', leading to the formation of E-2a, E-2a-D, and Z-3a-D₁, respectively. Since these three products were all observed in the reaction of Scheme 7, Eq. 14, this pathway may be a possible mechanism for the reaction.

Scheme 8. The cyclometalation mechanism.



However, when **1a** was reacted with 1 equiv of Ni(cod)₂, either in the presence or in the absence of CO_2 , only complicated mixtures were obtained, respectively (Scheme 9),

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0₂H

-CO2H

8r, 28%

E/Z = 3.9/1

E-8s, 18%

(7)

(8)

indicating that the concerted cyclometalation mechanism may be less likely.

Scheme 9. Reactions of 1a with stoichiometric amount of $Ni(cod)_2$.



On the other hand, another stepwise mechanism may also be possible or even predominant for this reaction as supported by the results shown in eqs 14 and 15 (Scheme 10): At first, Ni(0) would react with the C-C triple bond of 1a to form a nickelacyclopropene Int 4 with the C=C bond coordinating to nickel,¹⁴ which is critical since the substrate with the methyl-substituted C=C bond 1r failed to perform the reaction smoothly. Subsequent transmetalation with ZnEt₂ highly selectively formed Int 5. The C=C bond was then inserted into the $C(sp^2)$ -Ni bond to form Int 2. There were two possible pathways to finish the observed reaction: when the loading of ZnEt₂ is one equiv (Scheme 7, Eq. 15), Int 2 could undergo β-H elimination and reductive elimination to form a hydrozincation product Int 3 (path A). After being reacted with $CO_2^{7d,15,16}$ followed by quenching with D₂O, Int 3 could produce the non-deuterated product E-2a; In the presence of excess of ZnEt₂, further transmetalatation with ZnEt₂ would form the dizinc intermediate Int 1 and NiEt₂, which underwent reductive elimination to regenerate Ni(0). Int 1 would generate E-2a-D upon reaction with CO_2 and quenching with D₂O (see Eq. 14).

Scheme 10. The C=C bond-directed carboxylation mechanism.



In conclusion, we have developed a highly selective cyclizative hydrocarboxylation of enynes. Two possible mechanisms have been proposed to rationalize the formation of **Int 1**-type dizinc and monozinc **Int 3** species. In **Int 1**, the reactivity of the sp³ C-Zn bond toward carbon dioxide was very low, thus alkanoic acid was not obtained, resulting in highly chemoselective carboxylation of the C-C triple bond. Related research including more detailed mechanism studies and further utilization of such intermediates is undertaken in this laboratory actively.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, spectroscopic data, and the ¹H and ¹³C NMR spectra of all the products; cif files of E-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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