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Highly Stereo- and Regioselective Hydrocarboxylation of Diynes with Carbon Dioxide

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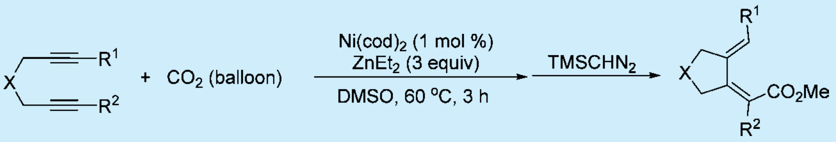
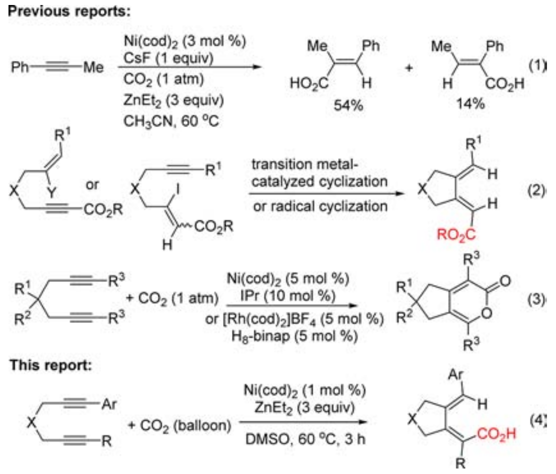
Ⓢ *Supporting Information*



ABSTRACT: A nickel-catalyzed three-component hydrocarboxylation of diynes with $ZnEt_2$ and CO_2 (1 atm) is disclosed. With this method, symmetric/nonsymmetric diynes could be reacted smoothly with very high stereo- and regioselectivity, affording conjugated 2,4-alkadienoic acids incorporated with five- or six-membered rings efficiently. A stepwise non-oxidative cyclometalation mechanism was proposed based on careful mechanistic studies.

As an abundant, inexpensive, and nontoxic gas, utilizing carbon dioxide as a C1 starting material for carboxylic acids or esters in organic reactions has attracted much attention.[1−5] Carboxylation of alkynes with CO_2 should be an efficient approach for synthetically attractive α,β-unsaturated alkenoic acid derivatives. In fact, stoichiometric nickel-mediated carboxylation reactions have been achieved through a five-membered nickelaoxacyclic intermediate.[6] Recently, we have succeeded in hydrocarboxylation of alkynes with $ZnEt_2$ and CO_2 under catalysis with only 1−3 mol % of $Ni(cod)_2$, through a zinc nickelation mechanism;[7a] Tsuji and co-workers also realized this transformation by a NHC−Cu catalytic system with hydrosilanes.[7b] In both protocols, the regioselectivity was poor (Scheme 1, eq 1). Later, we developed amino-[7a] and hydroxyl-group[8]-directed carboxylation reactions, forming lactams and lactones, respectively, which successfully resolved the regioselectivity issue. On the other hand, 2,4-alkadienoic acid derivatives are an important class of compounds as synthetic intermediates and are present in naturally occurring products, thus, much attention has been paid to them (Scheme 1, eq 2).[9,10] We reasoned that conjugated alkadienoic acids incorporated with a cyclic skeleton may be formed efficiently if diynes are used as starting materials for the hydrocarboxylation reaction,[7a] and the regioselectivity issue may be addressed. The reaction of CO_2 with diynes has rarely been reported. The only example is a nickel-[11a,b] or rhodium[11c]-catalyzed [2 + 2 + 2] cycloaddition to afford pyrones from carbon-tethered symmetric 1,6- or 1,7-diynes (Scheme 1, eq 3). Herein, we report our recent studies on the highly regio- and stereoselective cyclic hydrocarboxylation of diynes, affording 2,4-alkadienoic acids with excellent regioselectivity and stereochemistry, contrary to what has been reported[10] (Scheme 1, eq 4 vs eq 2).

Scheme 1. Previous Work and This Report of Hydrocarboxylation of Diynes



Initially, 2,7-diyne **1a** was treated with 5 mol % of $Ni(cod)_2$, 3 equiv of $ZnEt_2$, and 1 equiv of CsF in DMSO at 60 °C. Fortunately, the expected product (*Z*,*E*)-**2a** was indeed produced in 71% NMR yield with a *Z*,*E*/*E*,*E* ratio of 92:8, and the structures of these two stereoisomers were confirmed by an X-ray single-crystal study.[12] We found that the monoalkyne hydrocarboxylation products (**A** and **B**) were not observed (Table 1, entry 1). With this preliminary result, we turned to optimize the yields and *Z*,*E*/*E*,*E* selectivity.

Surprisingly, with a lower loading of $Ni(cod)_2$ (1 mol %), the yield of (*Z*,*E*)-**2a** reached 93%, with the *Z*,*E*/*E*,*E* ratio being 97:3, indicating that the loading of $Ni(cod)_2$ would affect both the yield and *Z*,*E*/*E*,*E* selectivity. The influence of CsF and $ZnEt_2$

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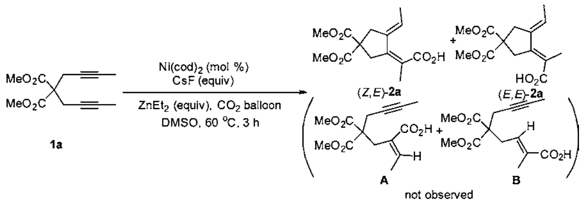
Table 1. Optimization of the Hydrocarboxylation of Diyne 1a[a]



entry	Ni(cod)$_2$ (mol %)	CsF (equiv)	ZnEt$_2$ (equiv)	yield of (Z,E)-2a (%)[b]	Z,E/E,E[b]
1[c,d]	5	1	3	71	92:8
2[c]	3	1	3	84	92:8
3[e]	1	1	3	93	97:3
4	1	0.5	3	94	98:2
5	1	0	3	94	97:3
6	1	0	2	88	98:2

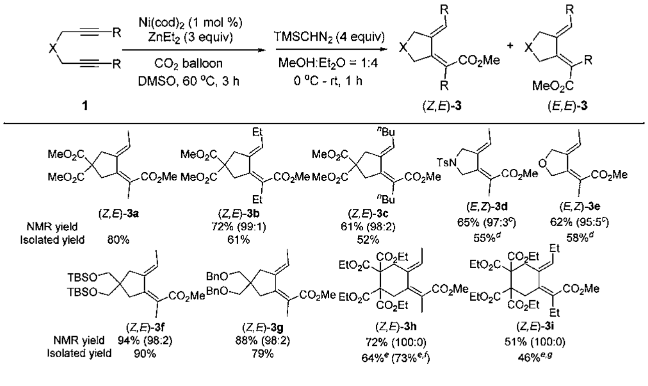
[a] Reaction was carried out with **1a** (0.5 mmol), Ni(cod)$_2$, CsF, ZnEt$_2$ (1.5 M in toluene), and a balloon of CO$_2$ (about 1 L) in 5 mL of DMSO at 60 °C. [b] Determined by ^{1}H NMR analysis with CH$_2$Br$_2$ as the internal standard. [c] Reaction was carried out with **1a** (0.3 mmol) in 3 mL of DMSO. [d] Reaction time was 10.5 h. [e] Reaction was carried out with **1a** (0.5 mmol) in 3 mL of DMSO.

was investigated. Interestingly, we observed that adding CsF was unnecessary (Table 1, entries 3–5). However, when the amount of ZnEt$_2$ was reduced to 2 equiv, the yield of (*Z*,*E*)-**2a** was slightly lower (Table 1, entry 6). Finally, 1 mol % of Ni(cod)$_2$ and 3 equiv of ZnEt$_2$ in DMSO at 60 °C have been defined as the standard conditions for further investigation (Table 1, entry 5).

With the optimized conditions in hand, various symmetric substrates have been studied (Scheme 2). With diynes that have elongated alkyl R chains, the yields were slightly lower, and *Z*,*E*/*E*,*E* selectivity remains high [(*Z*,*E*)-**3a**, (*Z*,*E*)-**3b**, (*Z*,*E*)-**3c**]. The reaction may be extended to the substrates with the linker of NTs and O, forming tetrahydropyrrole (*E*,*Z*)-**3d** and tetrahydrofuran (*E*,*Z*)-**3e**, respectively. In addition, the substrate bearing acid- or base-sensitive groups, such as a *t*-butyldimethylsilyl group, was tolerated under the standard reaction conditions, maintaining good yield and high selectivity [(*Z*,*E*)-**3f**]. The substrate with a benzyl ether group was also suitable for this transformation [(*Z*,*E*)-**3g**]. When we applied this method to the synthesis of a six-membered ring under the standard conditions, to our surprise, no (*E*,*E*)-isomer was formed [(*Z*,*E*)-**3h**, (*Z*,*E*)-**3i**], indicating that the formation of the (*E*,*E*)-isomer is also affected by ring strain of the products formed. However, only 52% yield of (*Z*,*E*)-**3h** accompanied by 16% yield of the protonolysis product was observed by NMR analysis of the crude product. Luckily, the reaction afforded (*Z*,*E*)-**3h** in 72% NMR yield (64% of isolated yield) with only 4% of the protonolysis product by addition of 2 equiv of CsF at 80 °C, indicating that CsF could enhance the reactivity of the vinyl zinc intermediate with CO$_2$, thus retarding protonolysis.[7a] Moreover, this reaction could be carried out on a 1 g scale with a higher yield (73% vs 64%). In these cases, the difference between NMR yields and isolated yields may be attributed to adsorption of products bearing three ester groups on silica gel.

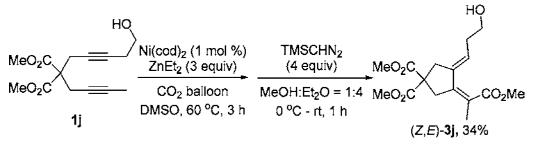
Furthermore, when nonsymmetric substrate **1j** with a free hydroxyl group was treated under the standard conditions, (*Z*,*E*)-**3j** was formed in 34% yield[8] (Scheme 3).

Scheme 2. Hydrocarboxylation of Symmetric 1,6- or 1,7-Diynes[a,b]



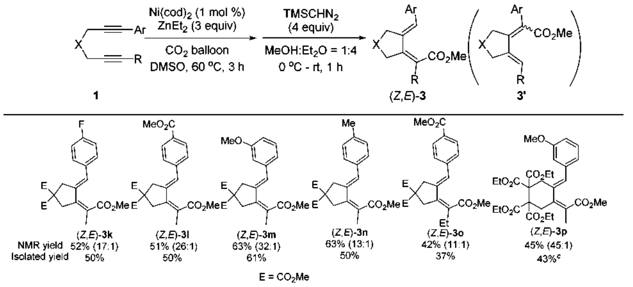
[a] Reaction was carried out with 1 mmol of **1**, 1 mol % of Ni(cod)$_2$, 3 equiv of ZnEt$_2$ (1.5 M in toluene), and a balloon of CO$_2$ (about 1 L) in 10 mL of DMSO at 60 °C and then esterified with 4 equiv of TMSCHN$_2$ to form the methyl esters. [b] Ratio of (*Z*,*E*)-**3**/(*E*,*E*)-**3** determined by ^{1}H NMR analysis of the crude products is shown in parentheses. [c] Ratio of (*E*,*Z*)-**3**/(*Z*,*Z*)-**3**. [d] Ni(cod)$_2$ (0.5 mol %) was used, and reaction time was 6 h. [e] Reaction at 80 °C with 2 equiv of CsF added. [f] Four millimole scale reaction. [g] ZnEt$_2$ (4 equiv) was used, and reaction time was 9.5 h.

Scheme 3. Hydrocarboxylation of 1j



In addition, the reaction of nonsymmetric substrates with an aryl on one end and an alkyl substituent on the other end afforded (*Z*,*E*)-**3** with high regioselectivity (Scheme 4). The phenyl-substituted substrates could bear electron-withdrawing groups [(*Z*,*E*)-**3k**, (*Z*,*E*)-**3l**] and electron-donating groups [(*Z*,*E*)-**3m**, (*Z*,*E*)-**3n**]. The configuration of the two C=C bonds in (*Z*,*E*)-**3n** were established by NOE study. This reaction also showed good selectivity between an aryl and an ethyl substituent [(*Z*,*E*)-**3o**]. The nonsymmetrical 1,7-diyne was also suitable for this transformation, maintaining the high regioselectivity, yielding six-membered (*Z*,*E*)-**3p**. These results

Scheme 4. Hydrocarboxylation of Nonsymmetric 1,6-Diynes[a,b]

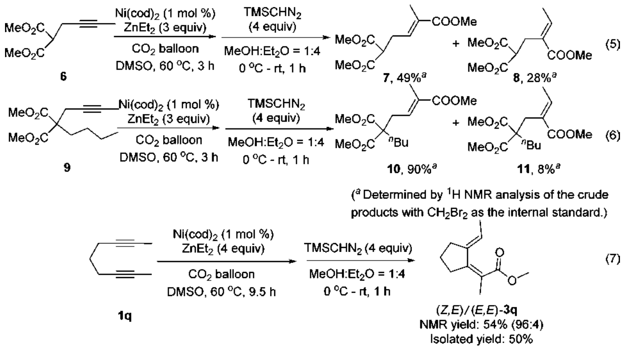


[a] Reaction was carried out with 1 mmol of **1**, 1 mol % of Ni(cod)$_2$, 3 equiv of ZnEt$_2$ (1.5 M in toluene), and a balloon of CO$_2$ (about 1 L) in 10 mL of DMSO at 60 °C and then esterified with 4 equiv of TMSCHN$_2$ to form the methyl esters. [b] Ratio of (*Z*,*E*)-**3**/**3′** determined by ^{1}H NMR analysis of the crude products is shown in parentheses, if any. [c] Reaction was conducted at 80 °C.

indicated that the reaction occurred first with the alkyl-substituted triple bond! In all of these cases, the stereoisomer (*E*,*E*)-**3** formed in <2% yield, if any, as judged by NMR analysis of the crude products.

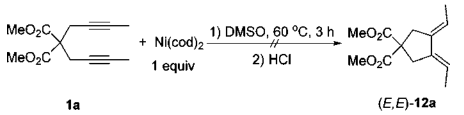
To probe the factors controlling the regioselectivity, we have conducted a series of control experiments (Scheme 5). In the absence of the second C−C triple bond, the reaction of malonate-containing monoalkyne **6** afforded a mixture of two regioisomers **7** and **8** with a ratio of 1.8:1 under standard conditions (Scheme 5, eq 5). The configurations of the C═C bonds in both **7** and **8** were established by the NOE study. As a comparison, when the second C−C triple bond was replaced with a saturated *n*-butyl group (i.e., monoalkyne **9**), its reaction under standard conditions also afforded a mixture of two regioisomers **10** and **11** with a ratio of 11:1, which is much higher than the ratio of **7** and **8**, indicating an obvious steric effect of the two methoxycarbonyl and butyl groups for control of the regioselectivity (Scheme 5, eq 6). However, the reaction of diyne **1q** without the two methoxycarbonyl groups also afforded (*Z*,*E*)-**3q** (Scheme 5, eq 7).

Scheme 5. Hydrocarboxylation of Monoalkynes 6, 9, and Diyne 1q



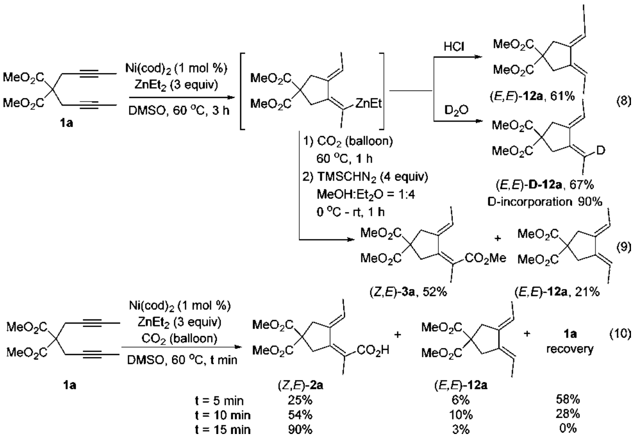
Second, we treated diyne **1a** with 1 equiv of Ni(cod)$_2$ in DMSO in the absence of ZnEt$_2$ under argon. After being quenched with HCl, the double protonolysis product (*E*,*E*)-**12a** was not formed as monitored by ^{1}H NMR analysis of the crude product; instead, the formation of a very complicated mixture of several products was observed (Scheme 6), which excludes the possibility of the cycloaddition of Ni(0) and diynes to form the nickelacyclopentadiene intermediate as the first step.[13] This is also in consistent with the fact that a higher Ni(cod)$_2$ loading results in lower yield of **2a** (Table 1, entries 1−3).

Scheme 6. Stoichiometric Reaction of 1a and Ni(cod)$_2$



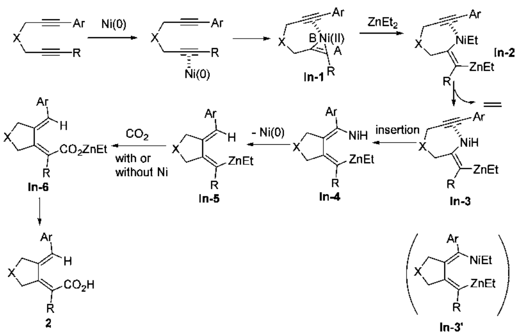
In addition, when **1a** was treated under standard conditions without the CO$_2$ balloon, after complete consumption of **1a**, HCl and D$_2$O were used, respectively, to quench the reaction. Protonolysis product (*E*,*E*)-**12a** and the monodeuterated product (*E*,*E*)-D-**12a** with a D incorporation of 90% were obtained, respectively (Scheme 7, eq 8), indicating the formation of a vinyl zinc intermediate **In-5** (Scheme 8) during the reaction. When an in situ pregenerated vinyl zinc species was treated with CO$_2$ for just 1 h at 60 °C, (*Z*,*E*)-**3a** was obtained in 52% yield after esterification, accompanied by 21% of the protonolysis product (*E*,*E*)-**12a** (Scheme 7, eq 9). Moreover, when the hydrocarboxylation of **1a** was quenched at 5 min, (*Z*,*E*)-**2a** was formed in 25% yield with 6% of (*E*,*E*)-**12a**, along with 58% recovery of **1a**, as determined by ^{1}H NMR analysis of the crude product. When the reaction time was 10 min, (*Z*,*E*)-**2a** was formed in 54% yield with 10% of (*E*,*E*)-**12a**, along with just 28% recovery of **1a**. However, when the reaction was quenched at 15 min, **1a** was completely consumed, and (*Z*,*E*)-**2a** was formed in 90% NMR yield with 3% of (*E*,*E*)-**12a** (Scheme 7, eq 10). These results showed that both the formation of the vinyl zinc intermediate and the carboxylation is very efficient and rapid.

Scheme 7. Detection of the Key Intermediate



Based on the above facts, we propose the following mechanism (Scheme 8): at first, due to the electron-withdrawing property of the aryl group, the aryl-substituted C−C triple bond is less reactive toward coordinating with Ni(0), thus, the first step of the reaction is the highly selective coordination of Ni(0), with the more electron-rich alkyl-substituted C−C triple bond forming **In-1**, in which the remaining C−C triple bond coordinates to Ni(II). Due to such a coordination, transmetalation of the C−Ni(II) bond A of **In-1** with ZnEt$_2$ proceeds highly regioselectively to generate **In-2**, which undergoes *β*-H-elimination to form nickel hydride **In-3**. Insertion and reductive elimination yields the alkenyl zinc **In-5** and regenerates Ni(0). Of course, **In-5** may also be formed via *β*-H-elimination and reductive elimination of **In-3′**. At last, **In-5** reacts with CO$_2$ to generate **In-6**.[2d,e,14] This observed regioselectivity also further excludes the pathway of the oxidative cyclometalation since the transmetalation and carboxylation of the formed nickelacyclopentadiene would most likely form a mixture of carboxylic acids with poor selectivity.[7a]

Scheme 8. Proposed Mechanism



In conclusion, we have developed a simple and efficient hydrocarboxylation of diynes utilizing CO_2. By using this method, conjugated dienoic carboxylates that adopt *Z,E* configuration *exo* to five- or six-membered rings can be synthesized. We proposed a unique C−C triple-bond-directed hydrocarboxylation mechanism. Due to the high efficiency and selectivity as well as the unique mechanism, this reaction may open a door for the highly selective formation of the **In-5**-type of valuable zinc reagents.[15] Related research in this area is being actively undertaken in this laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00028.

Experimental procedure, spectroscopic data, and NMR spectra of all products (PDF)
X-ray data for (*Z,E*)-**2a** (CIF)
X-ray data for (*E,E*)-**2a** (CIF)

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Notes

The authors declare no competing financial interest.

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