<u>Cramic</u> LETTERS

Nickel-Catalyzed Double Carboxylation of Alkynes Employing Carbon Dioxide

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Supporting Information

ABSTRACT: The nickel-catalyzed double carboxylation of internal alkynes employing carbon dioxide (CO_2) has been developed. The reactions proceed under CO_2 (1 atm) at room temperature in the presence of a nickel catalyst, Zn powder as a reducing reagent, and MgBr₂ as an indispensable additive.



Various internal alkynes could be converted to the corresponding maleic anhydrides in good to high yields. DFT calculations disclosed the indispensable role of $MgBr_2$ in the second CO_2 insertion.

C arbon dioxide (CO_2) is a readily available, nontoxic, and renewable carbon source.¹ Its environmental impact due to its overabundance makes it especially attractive as a raw material in *carbon–carbon bond–forming reactions*.² Recently, the highly efficient transition-metal catalyzed *mono*carboxylations of arylboranes,^{3a–d} organozincs,^{3e,f} organic halides,⁴ esters,⁵ and C–H bonds⁶ using CO₂ have been reported. Furthermore, the transition-metal catalyzed hydrocarboxylation of styrenes,^{7a} allenes,^{7b} alkynes,^{7c,d} and 1,3-dienes^{7e} as well as heterocarboxylations of alkynes⁸ have also been explored. In all these reactions, only *one* CO₂ was incorporated into the unsaturated substrates.

By extension, double carboxylation, in which two CO₂ molecules are introduced simultaneously into a substrate, would be very promising for the efficient synthesis of dicarboxylic acids. However, to date, such methods have not been extensively developed. Electrochemical double carboxylation was reported,⁹ but disappointingly, it was not efficient at all in terms of applicable substrates and/or product selectivity. Other than the electrochemical reactions, stoichiometric Ni complexes have been used to facilitate the double carboxylation of 1,3-butadienes, although the reaction did not proceed catalytically.¹⁰ The single reported catalytic double carboxylation used 1-(trimethylsilyl)-3-alkyl-substituted allenes as substrates (Scheme 1a).¹¹ Unfortunately, the substrate scope was limited and the trimethylsilyl moiety was necessary for the double carboxylation. Herein, we report the Ni-catalyzed double carboxylation of internal alkynes with CO₂, affording highly versatile maleic anhydrides¹² as products (Scheme 1b). The reactions proceed selectively under CO2 at 1 atm and room temperature in the presence of Zn powder as a reducing reagent and MgBr₂ as an indispensable additive.

Initially, the reaction of 5-decyne (1a) was surveyed with $Ni(acac)_2(bpy)$ (10 mol %, acac = acetylacetonate; bpy = bipyridine) as a catalyst, zinc powder (3.0 equiv) as a reducing

Scheme 1. Catalytic Double Carboxylation Using CO₂

(a) Silylallenes¹¹

$$\begin{array}{c} \text{Me}_3\text{S}_{\text{i}} \\ R \\ R \end{array} + \begin{array}{c} 2 \text{ CO2} \\ R \\ \text{THF, rt} \end{array} \xrightarrow{\begin{array}{c} \text{Ni(COD)}_2 (20 \text{ mol }\%) \\ \hline \text{DBU (10 equiv)} \\ \text{H}^+ \\ \text{Me}_3\text{Si} \\ \hline \text{H}^+ \\ \text{COOH} \end{array} \xrightarrow{\begin{array}{c} \text{COOH} \\ \text{R} \\ \end{array} \xrightarrow{\begin{array}{c} \text{COOH} \\ \text{COOH} \end{array}}$$



reagent, and MgBr₂ (2.0 equiv) as an additive, in the presence of molecular sieves 3 Å (MS 3 Å, powder) in dimethylformamide (DMF) at room temperature under a CO_2 pressure of 1 atm (Table 1). The yield of the double-carboxylated product (2a) was determined by gas chromatography (GC) after acidification. Under these conditions, the double-carboxylated product 2a was obtained in 74% yield (entry 1). A small amount of a hydrocarboxylated product (3a), which was analyzed by GC after derivatization to the corresponding methyl ester, was also detected. With Ni(acac)₂ as the catalyst (i.e., without the bpy ligand), the reaction did not proceed (entry 2). In the absence of MgBr₂, 2a was not detected (entry 3). The Zn powder was indispensable for the reaction (entry 4). Without MS 3 Å, the yield of 2a was slightly reduced while that of 3a increased (entry 5). Employing MgCl₂^{4c} in place of MgBr2, the yield of 2a considerably decreased and 3a was obtained in 23% yield (entry 6). ZnBr₂ and ZnCl₂ in place of MgBr₂ suppressed the double carboxylation (entries 7 and 8).

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Table 1. Optimization of Reaction Conditions on the Nickel-Catalyzed Double Carboxylation of 5-Decyne $(1a)^a$

1a	CO ₂ (1 atm) Ni(acac) ₂ (bpy) (10 mol %)	(1) 6 N HCl aq	°₹_2°, н	→CO ₂ Me
	Zn (3.0 equiv) MgBr ₂ (2.0 equiv) MS 3 Å, DMF, rt, 20 h	(2) TMSCHN ₂ Et ₂ O/MeOH	Bu Bu Bu 2a	Bu 3a
entry	catalyst system: alternation from the reaction conditions		yield of $2a$ $(\%)^b$	yield of $3a$ $(\%)^b$
1	without any change		74	3
2	without bpy		0	0
3	without MgBr ₂		0	0
4	without Zn powder		0	0
5	without MS 3 Å		62	6
6	MgCl ₂ in place of MgBr ₂		24	23
7	ZnBr ₂ in place of MgBr ₂		0	0
8	ZnCl ₂ in place of MgBr ₂		0	0
9	MeObpy in place of bpy		37	2
10	phen in place of bpy		48	trace
11	Mn in place of Zn		66	2
12	Mg in place of Zn		4	trace
13	MgBr ₂ (3.0 equiv), DMF (2.0 mL)		$78 (71)^c$	2

^aReaction conditions: 5-Decyne (1a, 0.50 mmol), Ni(acac)₂(bpy) (0.050 mmol, 10 mol %), Zn powder (1.5 mmol, 3.0 equiv), MgBr₂ (1.0 mmol, 2.0 equiv), molecular sieves 3 Å (MS 3 Å, powder, 100 mg), under CO₂ (1 atm), in DMF (2.5 mL), at room temperature for 20 h. ^bDetermined by GC analysis. ^cIsolated yield of 2a.

The use of other ligands such as 4,4'-dimethoxybipyridine (MeObpy) and 1,10-phenanthroline (phen) in place of bpy decreased the yield of **2a** (entries 9 and 10). Regarding the ligand, PPh₃, PCy₃ (tricyclohexylphosphine), and dppe (diphenylphosphinoethane) were not effective.¹³ Other reducing agents such as Mn powder or Mg turnings gave the product in moderate or low yields (entries 11 and 12). In 1,3-dimethyl-2-imidazolidinone (DMI) as the solvent in place of DMF, **2a** was obtained in 52% yield, whereas THF and toluene were not good solvents, giving trace amounts of **2a**. Under the optimal reaction conditions, **2a** was obtained in 78% GC yield and in 71% isolated yield as shown in entry 13.

The double carboxylations of various internal alkynes (1b-i)were carried out (Table 2). With 3-hexyne (1b) and 2,9dimethyl-5-decyne (1c) as substrates, the corresponding products (2b and 2c) were obtained in good isolated yields (entries 1 and 2). 2-Octyne (1d) and 5-phenyl-2-pentyne (1e) reacted smoothly, giving the corresponding products (entries 3 and 4). Alkynes with secondary alkyl groups on the sp-carbons (1f and 1g) also provided the double-carboxylated products in good yields (entries 5 and 6). An alkyne having an olefin substituent (1h) was converted to the corresponding product with the C=C bond intact (entry 7). A cyclic internal alkyne (1i) also took part in the reaction, giving the corresponding product in 79% yield (entry 8). In Table 2, 1b-i were fully converted, but side products other than a small amount of monocarboxylated products were not detected by GC and GC-MS analyses. Unfortunately, terminal alkynes and aromatic internal alkynes did not afford the corresponding double carboxylated products.

The present reaction was applied to the fast and highly efficient synthesis of Chaetomellic acid A anhydride, which is isolated from the coelomycete *Chaetomella acutiseta*. The dianionic form of this compound is a potent and selective inhibitor of ras farnesyl protein transferase.¹⁴ As shown in

Table 2. Nickel-Catalyzed Double Carboxylation of Various Internal Alkynes^a

R ¹⁻	$= R^2 $ Ni(acac) ₂ (bpy) (10 mol CO ₂ (1 atm)	%) ► H⁺	0~0~0
	1 Zn (3.0 equiv) MgBr ₂ (3.0 equiv) MS 3 Å, DMF, rt, 20 h		R ¹ R ² 2
entry	substrate	product	yield (%) ^b
1	/ <u>=</u> _/ 1b		60
2	>		65
3	1d	0 0 0 2d	65
4			50
5			-
6		0~0~0 2g	67
7 ^c			69
8	12 1i		79

^{*a*}Reaction conditions: 1 (0.50 mmol), Ni(acac)₂(bpy) (0.050 mmol, 10 mol %), MgBr₂ (1.5 mmol, 3.0 equiv), Zn powder (1.5 mmol, 3.0 equiv), molecular sieves 3 Å (powder, 100 mg), under CO_2 (1 atm), in DMF (2.0 mL), at 25 °C for 20 h. ^{*b*}Isolated yield. ^{*c*}A mixture of DMA/hexane (1.5 mL/0.75 mL) was used as a solvent.

Scheme 2, the reaction of commercially available 1-hexadecyne with methyl iodide afforded 1j quantitatively. The treatment of 1j under the optimized reaction conditions provided the desired product (2j) in 70% isolated yield. To the best of our knowledge, this is the shortest and most efficient synthetic route to Chaetomellic acid A anhydride among the known procedures.^{11,15}

In terms of a mechanism, it is well-known both experimentally $1^{16a,b}$ and theoretically $1^{16c,d}$ that the oxidative

Scheme 2. Synthesis of Chaetomellic Acid A Anhydride



cyclization of Ni⁰, CO₂, and alkynes gives oxanickelacyclopentenones (4). Actually, the reaction of 1a with Ni(COD)₂ (COD = 1,5-cyclooctadiene) in the presence of bpy under CO₂ (1 atm) gave the corresponding complex 4a in 75% yield (eq 1).^{16b} The double carboxylation of 1a to 2a proceeded in the



presence of a catalytic amount (10 mol %) of 4a in 63% yield (eq 2). Hence, nickelacycle (4) must be involved in the catalytic cycle.

After the formation of nickelacycle (4), three possible paths (a-c) may follow for the *second* carboxylation. In path a, direct CO_2 insertion into the Ni^{II}-C bond of 4 occurs without any help by MgBr₂. In path b, 4 forms an adduct with MgBr₂ followed by the insertion of CO_2 into the Ni^{II}-C bond. Finally, in path c, a one-electron reduction of 4 by Zn in the presence of MgBr₂ occurs first to afford a Ni^I intermediate, followed by the insertion of CO_2 into the Ni^I-C bond. ^{5b} These three possible paths were examined by density functional theory (DFT) calculations (Figures 1 and 2).

Direct CO₂ insertion into the Ni^{II}-C bond of 4b (4: R¹ = R² = CH₃) proceeds via TS_{4b-A1} with a large $\Delta G^{\circ\ddagger}$ value of 21.9 kcal/mol (path a, Figure 1). In path b (Figure 1), MgBr₂ first



Figure 1. Gibbs energy profile for the second CO_2 insertion (paths a and b).



Figure 2. Gibbs energy profile for the second CO_2 insertion (path c).

interacts with the nickel carboxylate moiety of **4b** to afford **A2**. Then, CO₂ is inserted into the Ni^{II}–C bond of **A2** via **TS**_{A2-A3} to afford **A3** with a $\Delta G^{\circ \ddagger}$ value of 17.4 kcal/mol. In sharp contrast, in path c (Figure 2), after the one-electron reduction of **4b** to **B**, the insertion of CO₂ into the Ni^I–C bond of **B1** is quite facile ($\Delta G^{\circ \ddagger} = 5.0$ kcal/mol) as compared with paths a and b (cf. 21.9 and 17.4 kcal/mol in Figure 1). In the one-electron reduction, MgBr₂ plays a crucial role to provide a bromide anion to Zn²⁺. During the CO₂ insertion, the resulting MgBr coordinates with both the carboxylate moiety and the incoming CO₂ in **B1** and **TS**_{B1-C} to facilitate the second carboxylation. Thus, MgBr₂ makes the one-electron reduction of **4b** possible and accelerates the CO₂ insertion in **B1**. These crucial roles of MgBr₂ have not been previously recognized.

Based on the experimental results (eqs 1 and 2) and DFT calculations (Figures 1 and 2), a plausible catalytic cycle is suggested in Scheme 3. The active catalyst species must be

Scheme 3. Plausible Reaction Mechanism



 $Ni^{0}(bpy)^{16d}$ which is formed via reduction of the Ni^{II} catalyst precursor by Zn (step a). Then, the oxidative cyclization of $Ni^{0}(bpy)$ with 1 and CO₂ affords the Ni^{II} metallacycle 4 (step b). The reduction of 4 with Zn and MgBr₂ provides Ni^{I} species **B** (step c). **B** must be a key intermediate in this double carboxylation, since the carboxylation of **B** to **C** (step d) is much easier due to the higher nucleophilicity of **B** and the coordinative participation of the MgBr moiety (Figure 2).

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Finally, the reduction of C affords the double-carboxylated product D and regenerates the active Ni^0 catalyst species (step e).

In conclusion, we developed a new nickel-catalyzed double carboxylation of alkynes under CO_2 (1 atm) at room temperature to give maleic anhydride derivatives. The key to the success of the present reaction is the generation of the Ni^I metallacycle intermediate and the participation of MgBr in facilitating the second carboxylation. It should be noted that the crucial roles of MgBr₂ in the one-electron reduction and the second CO_2 insertion into the Ni^I-C bond are first recognized here. Further studies on functional group compatibility and the reaction mechanism are now in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of the products, and computational details. 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 interest.

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REFERENCES

(1) (a) Carbon Dioxide as Chemical Feedstock; Aresta, M., Ed.; Wiley-VCH: Weinheim, 2010. (b) Sakakura, T.; Choi, J.-C.; Yasuda, H. Chem. Rev. 2007, 107, 2365–2387.

(2) For recent reviews, see: (a) Tsuji, Y.; Fujihara, T. Chem. Commun. 2012, 48, 9956–9964. (b) Zang, L.; Hou, Z. Chem. Sci. 2013, 4, 3395– 3403. (c) Huang, K.; Sun, C.-L.; Shi, Z.-J. Chem. Soc. Rev. 2011, 40, 2435–2452. (d) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kühn, F. E. Angew. Chem., Int. Ed. 2011, 50, 8510–8537 and references cited therein.

(3) (a) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. J. Am. Chem. Soc.
2006, 128, 8706-8707. (b) Ohishi, T.; Nishiura, M.; Hou, Z. Angew. Chem., Int. Ed. 2008, 47, 5792-5795. (c) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. Org. Lett. 2008, 10, 2697-2700. (d) Zhang, X.; Zhang, W.-Z.; Shi, L.-L.; Guo, C.-X.; Zhang, L.-L.; Lu, X.-B. Chem. Commun.
2012, 48, 6292-6294. (e) Yeung, C. S.; Dong, V. M. J. Am. Chem. Soc.
2008, 130, 7826-7827. (f) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. Org. Lett. 2008, 10, 2681-2683.

(4) (a) Correa, A.; Martín, R. J. Am. Chem. Soc. 2009, 131, 15974– 15975. (b) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. J. Am. Chem. Soc. 2012, 134, 9106–9109. (c) León, T.; Correa, A.; Martín, R. J. Am. Chem. Soc. 2013, 135, 1221–1224.

(5) (a) Correa, A.; León, T.; Martin, R. J. Am. Chem. Soc. 2014, 136, 1062–1069. (b) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Chem. Commun. 2014, in press (DOI: 10.1039/C4CC03644A).

(6) (a) Sasano, K.; Takaya, J.; Iwasawa, N. J. Am. Chem. Soc. 2013, 135, 10954–10957. (b) Mizuno, H.; Takaya, J.; Iwasawa, N. J. Am. Chem. Soc. 2011, 133, 1251–1253. (c) Zang, L.; Cheng, J.; Ohishi, T.;

Hou, Z. Angew. Chem., Int. Ed. 2010, 49, 8670–8673. (d) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. Angew. Chem., Int. Ed. 2010, 49, 8674–8677. (e) Boogaerts, I. I. F.; Nolan, S. P. J. Am. Chem. Soc. 2010, 132, 8858–8859.

(7) (a) Williams, C. M.; Johnson, J. B.; Rovis, T. J. Am. Chem. Soc.
2008, 130, 14936–14937. (b) Takaya, J.; Iwasawa, N. J. Am. Chem.
Soc. 2008, 130, 15254–15255. (c) Fujihara, T.; Xu, T.; Semba, K.;
Terao, J.; Tsuji, Y. Angew. Chem., Int. Ed. 2011, 50, 523–527. (d) Li,
S.; Yuan, W.; Ma, S. Angew. Chem., Int. Ed. 2011, 50, 2578–2582.
(e) Takaya, J.; Sasano, K.; Iwasawa, N. Org. Lett. 2011, 13, 1698–
1701.

(8) (a) Fujihara, T.; Tani, Y.; Semba, K.; Terao, J.; Tsuji, Y. Angew. Chem., Int. Ed. **2012**, 51, 11487–11490. (b) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. J. Am. Chem. Soc. **2012**, 134, 14314–14317.

(9) (a) Duñach, E.; Dérien, S.; Périchon, J. J. Organomet. Chem. 1989, 364, C33-C36. (b) Dérien, S.; Clinet, J.-C.; Duñach, E.; Périchon, J. J. Organomet. Chem. 1992, 424, 213-224. (c) Dérien, S.; Clinet, J.-C.; Duñach, E.; Périchon, J. Tetrahedron 1992, 48, 5235-5248. (d) Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. Synlett 2001, 418-420. (e) Yuan, G.-Q.; Jiang, H.-F.; Lin, C. Tetrahedron 2008, 64, 5866-5872.

(10) (a) Takimoto, M.; Mori. J. Am. Chem. Soc. **2001**, 123, 2895–2896. (b) Hoberg, H.; Apotecher, B. J. Organomet. Chem. **1984**, 270, C15–C17. (c) Behr, A.; Kanne, U. J. Organomet. Chem. **1986**, 317, C41–C44.

(11) Takimoto, M.; Kawamura, M.; Mori, M.; Sato, Y. Synlett 2005, 2019–2022.

(12) Xiaolong, C.; Zheng, Y.; Shen, Y. Chem. Rev. 2007, 107, 1777– 1830.

(13) See the Supporting Information for details.

(14) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, 49, 5917–5926.

(15) (a) Kshirsagar, U. A.; Argade, N. P. Synthesis 2011, 1804–1808.
(b) Yoshimitsu, T.; Arano, Y.; Kaji, T.; Ino, T.; Nagaoka, H.; Tanaka, T. Heterocycles 2009, 77, 179–186. (c) Kar, A.; Argade, N. P. J. Org. Chem. 2002, 67, 7131–7134. (d) Slade, R. M.; Branchaud, B. P. J. Org. Chem. 1998, 63, 3544–3549. (e) Desai, S. B.; Argade, N. J. Org. Chem. 1997, 62, 4862–4863. (f) Ratemi, E. S.; Dolence, J. M.; Poulter, C. D.; Vederas, J. C. J. Org. Chem. 1996, 61, 6296–6301. (g) Kates, M. J.; Schauble, J. H. J. Org. Chem. 1996, 61, 4164–4167. (h) Branchaud, B. P.; Slade, R. M. Tetrahedron Lett. 1994, 35, 4071–4072.

(16) (a) Burkhart, G.; Hoberg, H. Angew. Chem., Int. Ed. Engl. 1982, 21, 76. (b) Hoberg, H.; Schaefer, D.; Burkhart, G.; Krüger, C.; Romão, M. J. J. Organomet. Chem. 1984, 266, 203–224. (c) Sakaki, S.; Mine,

K.; Taguchi, D.; Arai, T. Bull. Chem. Soc. Jpn. 1993, 66, 3289–3299.
(d) Graham, D. C.; Bruce, M. I.; Metha, G. F.; Bowie, J. H.; Buntine, M. A. J. Organomet. Chem. 2008, 693, 2703–2710.