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Nickel-Catalyzed Double Carboxylation of Alkynes Employing Carbon Dioxide

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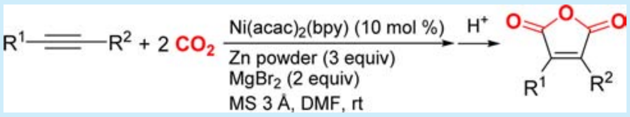
Supporting Information

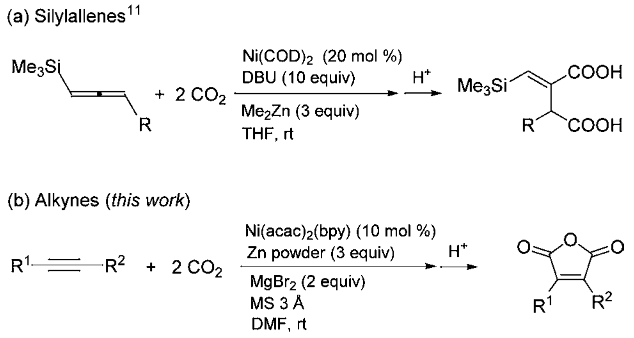


ABSTRACT: The nickel-catalyzed double carboxylation of internal alkynes employing carbon dioxide (CO_2) has been developed. The reactions proceed under CO_2 (1 atm) at room temperature in the presence of a nickel catalyst, Zn powder as a reducing reagent, and $MgBr_2$ as an indispensable additive. Various 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.

Carbon 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 bonds[6] using CO_2 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 alkynes[8] have also been explored. In all these reactions, only *one* CO_2 was incorporated into the unsaturated substrates.

By extension, *double* carboxylation, in which *two* CO_2 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 CO_2, affording highly versatile maleic anhydrides[12] as products (Scheme 1b). The reactions proceed selectively under CO_2 at 1 atm and room temperature in the presence of Zn powder as a reducing reagent and $MgBr_2$ as an indispensable additive.

Scheme 1. Catalytic Double Carboxylation Using CO_2



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 reagent, and $MgBr_2$ (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 $MgBr_2$, **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 $MgCl_2$[4c] in place of $MgBr_2$, the yield of **2a** considerably decreased and **3a** was obtained in 23% yield (entry 6). $ZnBr_2$ and $ZnCl_2$ in place of $MgBr_2$ suppressed the double carboxylation (entries 7 and 8).

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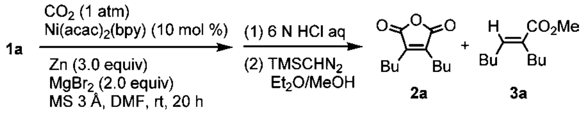
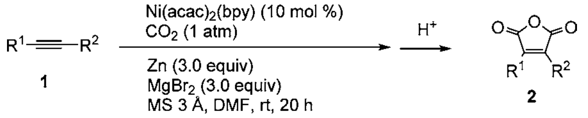
Table 1. Optimization of Reaction Conditions on the Nickel-Catalyzed Double Carboxylation of 5-Decyne (**1a**)[a]

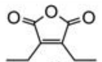
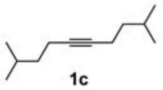
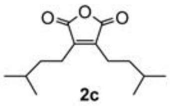
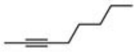
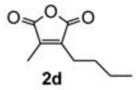
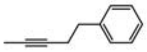
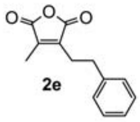
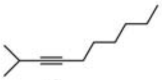
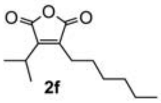
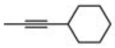
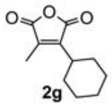
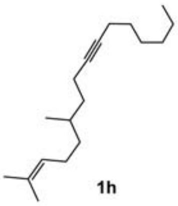
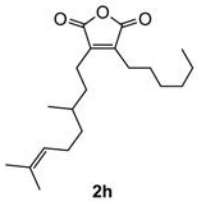
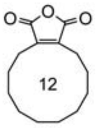


entry	catalyst system: alternation from the reaction conditions	yield of **2a** (%)[b]	yield of **3a** (%)[b]
1	without any change	74	3
2	without bpy	0	0
3	without $MgBr_2$	0	0
4	without Zn powder	0	0
5	without MS 3 Å	62	6
6	$MgCl_2$ in place of $MgBr_2$	24	23
7	$ZnBr_2$ in place of $MgBr_2$	0	0
8	$ZnCl_2$ 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

[a] Reaction conditions: 5-Decyne (**1a**, 0.50 mmol), $Ni(acac)_2(bpy)$ (0.050 mmol, 10 mol %), Zn powder (1.5 mmol, 3.0 equiv), $MgBr_2$ (1.0 mmol, 2.0 equiv), molecular sieves 3 Å (MS 3 Å, powder, 100 mg), under CO_2 (1 atm), in DMF (2.5 mL), at room temperature for 20 h. [b] Determined by GC analysis. [c] Isolated yield of **2a**.

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



entry	substrate	product	yield (%)[b]
1	 **1b**	 **2b**	60
2	 **1c**	 **2c**	65
3	 **1d**	 **2d**	65
4	 **1e**	 **2e**	50
5	 **1f**	 **2f**	58
6	 **1g**	 **2g**	67
7[c]	 **1h**	 **2h**	69
8	 **1i**	 **2i**	79

[a] Reaction conditions: **1** (0.50 mmol), $Ni(acac)_2(bpy)$ (0.050 mmol, 10 mol %), $MgBr_2$ (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.

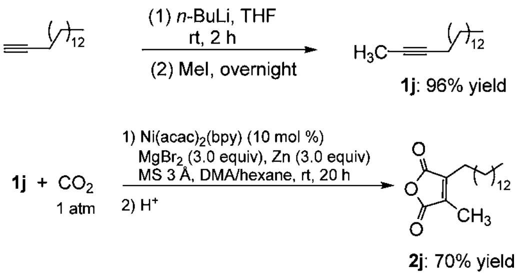
The use of other ligands such as 4,4′-dimethoxybipyridine (MeObpy) and 1,10-phenanthroline (phen) in place of bpy decreased the yield of **2a** (entries 9 and 10). Regarding the ligand, PPh_3, PCy_3 (tricyclohexylphosphine), and dppe (diphenylphosphinoethane) were not effective.[13] Other reducing agents 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 2,9-dimethyl-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.

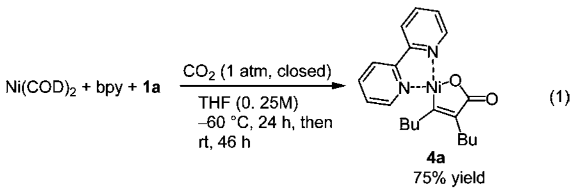
The present reaction was applied to the fast and highly efficient synthesis of Chaetomellic acid A anhydride, which is isolated from the coelomycete *Chaetomella acutiseta*. The dianionic form of this compound is a potent and selective inhibitor of ras farnesyl protein transferase.[14] As shown in Scheme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

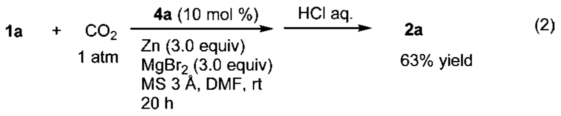
In terms of a mechanism, it is well-known both experimentally[16a,b] and theoretically[16c,d] that the oxidative

Scheme 2. Synthesis of Chaetomellic Acid A Anhydride



cyclization of Ni^0, CO$_2$, and alkynes gives oxanickelacyclopentenones (**4**). Actually, the reaction of **1a** with Ni(COD)$_2$ (COD = 1,5-cyclooctadiene) in the presence of bpy under CO$_2$ (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 MgBr$_2$. In path b, **4** forms an adduct with MgBr$_2$ 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 MgBr$_2$ 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 CO$_2$ insertion into the Ni^{II}–C bond of **4b** (**4**: R^1 = R^2 = CH$_3$) proceeds via **TS$_{4b\text{-}A1}$** with a large $\Delta G^{\circ\ddagger}$ value of 21.9 kcal/mol (path a, Figure 1). In path b (Figure 1), MgBr$_2$ first interacts with the nickel carboxylate moiety of **4b** to afford **A2**. Then, CO$_2$ is inserted into the Ni^{II}–C bond of **A2** via **TS$_{A2\text{-}A3}$** 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 CO$_2$ 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, MgBr$_2$ plays a crucial role to provide a bromide anion to Zn^{2+}. During the CO$_2$ insertion, the resulting MgBr coordinates with both the carboxylate moiety and the incoming CO$_2$ in **B1** and **TS$_{B1-C}$** to facilitate the second carboxylation. Thus, MgBr$_2$ makes the one-electron reduction of **4b** possible and accelerates the CO$_2$ insertion in **B1**. These crucial roles of MgBr$_2$ have not been previously recognized.

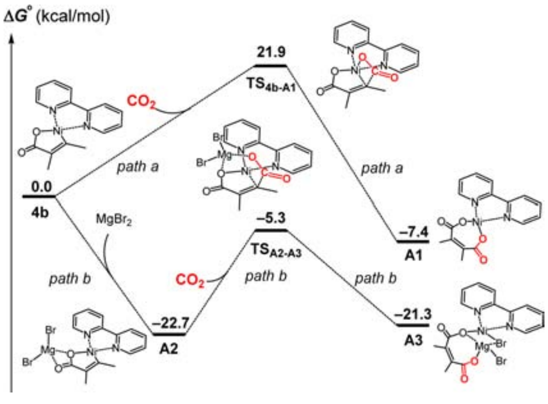


Figure 1. Gibbs energy profile for the second CO$_2$ insertion (paths a and b).

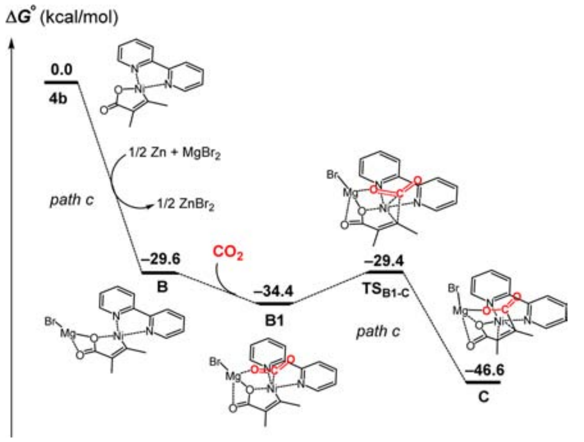
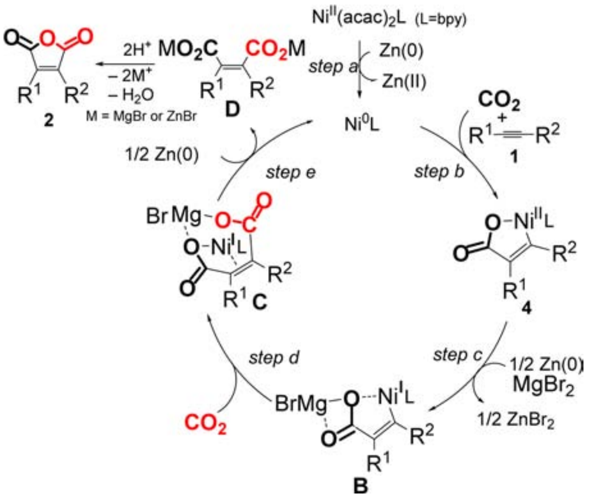


Figure 2. Gibbs energy profile for the second CO$_2$ insertion (path c).

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 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 CO$_2$ affords the Ni^{II} metallacycle **4** (step b). The reduction of **4** with Zn and MgBr$_2$ 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).

Scheme 3. Plausible Reaction Mechanism



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 $MgBr_2$ 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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