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Nickel-mediated carboxylative cyclization of enynes

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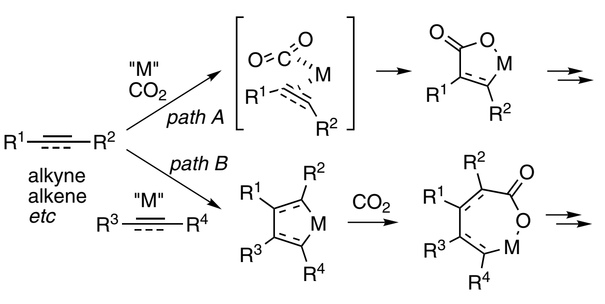
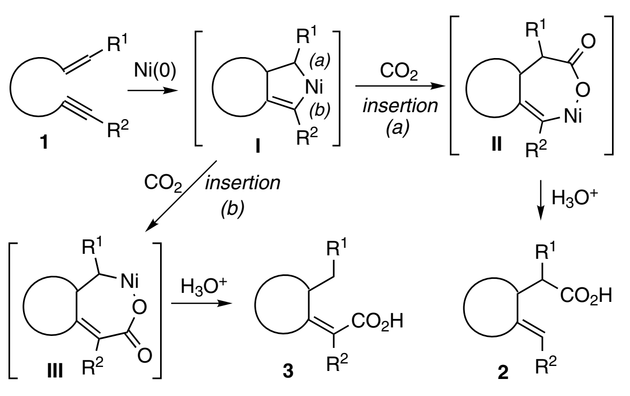
Abstract—Nickel-mediated carboxylative cyclization of α,ω-enyne using carbon dioxide was investigated. Oxidative cycloaddition of enynes having an electron withdrawing group on alkene to a zero-valent nickel complex smoothly proceeded to provide nickelacyclopentene intermediates, which regioselectively reacted with CO_2 at the Csp^3–nickel bond, giving cyclized carboxylation products in good yields.

Carbon dioxide (CO_2) is regarded as an important natural carbon resource because of its abundant reserve and low degree of toxicity. However, the range of its utility in synthetic organic chemistry has been restricted due to its lower reactivity. To overcome such difficulties, various methods employing transition metal complexes have been investigated.[1] One particular grouping of CO_2 incorporation process that has received much attention is the oxidative cycloaddition of CO_2 and unsaturated hydrocarbons to low-valent transition metal complexes (Scheme 1, path a). Especially, nickel-promoted processes have been extensively studied.[2,3] On the other hand, the insertion of CO_2 into metallacycle intermediates (Scheme 1, path b), which are readily prepared by oxidative cycloaddition of two unsaturated hydrocarbon components to low-valent transition metals, has been rarely explored except co-oligomerization of 1,3-dienes with CO_2, although this should be a potentially useful CO_2 incorporation process.[4–9] This prompted us to investigate a novel reaction using such a process. Here, we report the results of our study on nickel-promoted carboxylative cyclization of enynes that proceeds through the intermediary of CO_2 insertion into nickelacyclopenetenes.



Scheme 1.

Our initial plan is shown in Scheme 2. It was envisioned that α,ω-enynes will readily react with a zero-valent nickel complex to form oxanickelacyclopentene **I**.[10–13] If complex **I** undergoes insertion of CO_2 at the Csp^3–nickel bond (path a), oxanickelacycloheptene **II** would be formed, and this would be hydrolyzed to provide carboxylic acid **2**. On the other hand, α,β-unsaturated carboxylic acid **3** would be formed through the



Scheme 2.

Keywords: Nickel; Carboxylation; Cyclization; Carbon dioxide.

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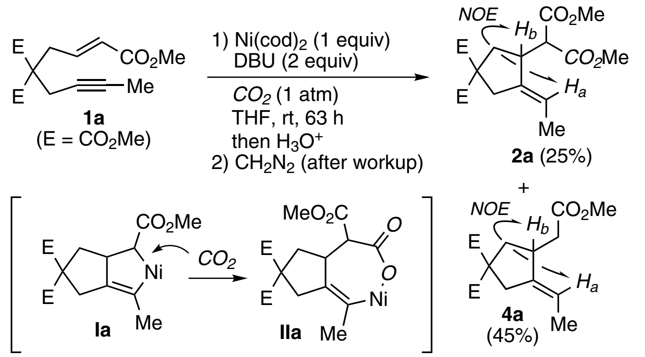


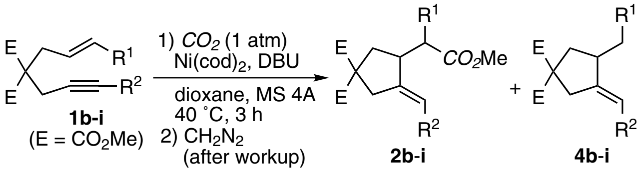
Scheme 3.

intermediary of oxyanickelacycloheptene **III** if the insertion of CO_2 into the Csp^2–nickel bond occurs.

Our investigation began with the reaction of enyne **1a**. Enyne **1a** was first treated with a stoichiometric amount of $Ni(cod)_2$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equiv to nickel) in THF at room temperature for 63 h under an atmosphere of CO_2 (Scheme 3). After hydrolysis of the reaction mixture, the crude product was treated with diazomethane to give tetraester **2a**, a desired product of the intended carboxylative cyclization, in 25% yield along with 45% of **4a**. The results of NOE experiments for **2a** and **4a** showed that these products have an exocyclic *E*-olefin moiety. The formation of **2a** indicated that CO_2 was inserted into the Csp^3–nickel bond of nickelacycle **Ia**. Furthermore, the presence of cyclization product **4a**, which is thought to be a hydrolyzed product of **Ia**, strongly suggests the participation of **Ia** in this carboxylation reaction.

To improve the yield of **2a**, carboxylative cyclization of **1a** was carried out under various conditions (Table 1). The reaction conducted at 40 °C in THF afforded **2a** in 48% yield, while that conducted under reflux conditions gave **2a** in only 9% yield (entries 1 and 2). A shorter reaction time at 40 °C resulted in a slight increase in the yield of **2a** (entry 3). The use of dioxane as a solvent was more suitable for this carboxylative cyclization, and **2a** was obtained in 60% yield (entry 4). Gratifyingly, the yield of **2a** was improved to 70% when the reaction was carried out in the presence of MS 4A in dioxane at 40 °C (entry 5).[14] Thus, these conditions were used as the standard ones in the following investigations.[15]

Table 2. Substituent effects of enynes



Entry	Enyne	R^1	R^2	Yields (%)		
				2	**4**	**2+4**
1	**1b**	H	Me	0	0	0
2	**1c**	Me	Me	0	0	0
3	**1d**	COMe	Me	0	54	54
4	**1e**	CN	Me	44	2	46
5	**1f**	CO_2Me	CH_2OMe	56	16	72
6	**1g**	CO_2Me	Ph	51	24	75
7	**1h**	CO_2Me	CO_2Me	27	61	88
8	**1i**	CO_2Me	$SiMe_3$	0	61	61

Carboxylative cyclizations of enynes **1b–i**, having various substituents at the terminus of alkene or alkyne, were examined (Table 2). Effects of substituents at the terminus of alkene were investigated first. Reactions of enyne **1b**, having no substituent on alkene, afforded neither the desired carboxylation product **2b** nor simple cyclization product **4b** (entry 1). Reaction of **1b** also gave a similar result (entry 2). These results indicated that oxidative cycloaddition of **1b** and **c** did not proceed under these conditions. Reaction of enyne **1d**, having an electron withdrawing keto-carbonyl group on alkene, also gave no carboxylative cyclization product (entry 3). However, in this case, cyclization product **4d** was obtained in 54% yield. This result indicated that oxidative cycloaddition of **1d** took place. In contrast to these results (entries 1–3), enyne **1e**, having a cyano group on alkene as an electron withdrawing one, underwent carboxylative cyclization to form **2e** in 44% yield (entry 4).

Effects of substituents on alkyne were next examined using enynes **1f–i**, having a methyl ester on alkene. In the reaction of enynes **1f** or **g**, having an alkyl or aryl group on alkyne, carboxylative cyclization product **2f** or **g** was predominantly formed in 56% and 51% yields, respectively (entries 5 and 6). However, the reaction of **1h**, having an electron withdrawing group on alkyne, resulted in a lower yield of **2h** (entry 7) and that of **1i** provided only cyclization product **4i** (entry 8). In each

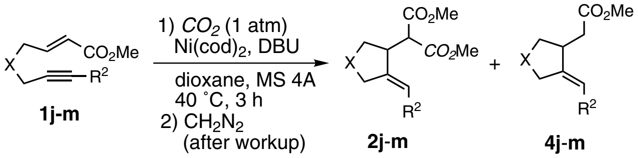
Table 1. Carboxylative cyclization of **1a** under various conditions[a]

Entry	Solvent	Temp	Time (h)	Yields (%)		Recovery of **1a** (%)
				2a	**4a**	
1	THF	40 °C	18	48	38	0
2	THF	reflux	13	9	77	0
3	THF	40 °C	3	55	30	3
4	Dioxane	40 °C	3	60	25	0
5[b]	Dioxane	40 °C	3	70	9	9

[a] All reactions were carried out using 1 equiv of $Ni(cod)_2$ and 2 equiv of DBU under an atmosphere of CO_2 (1 atm). The obtained crude materials were treated with CH_2N_2 before isolation.

[b] The reaction was carried out in the presence of MS 4A.

Table 3. Carboxylative cyclization of various enynes



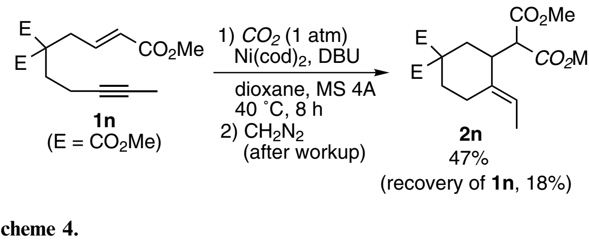
Entry	Enyne	X	R^2	Yields (%)		Recovery of **1** (%)
				2	**4**	
1	**1j**	CH_2	Me	31	22	39
2	**1k**	TsN	Me	54	25	0
3	**1l**	TsN	CH_2OMe	55	34	0
4	**1m**	O	Me	68	12	0

case (entries 5–8), the combined yield of **2** and **4** was good to high. From the results shown in Table 2, the effects of substituents on alkene or alkyne are summarized as follows: (i) the presence of an electron withdrawing substituent on alkene is necessary for oxidative cycloaddition of enynes to a zero-valent nickel complex, which is an initial step of carboxylative cyclization; (ii) if enynes have an electron withdrawing group on alkene, oxidative cycloaddition of enynes proceeds smoothly regardless of the substituents on alkyne; and (iii) the second step, insertion of CO_2 into the resulting nickelacyclopentenes, is greatly affected by substituents on alkene and alkyne (entries 3-8).

To examine the scope of this carboxylative cyclization, syntheses of various ring compounds were tried by using this method (Table 3). Reaction of a simple enyne **1j**, having no substituent on its tether, gave carboxylative cyclization product **2j** in 31% yield along with recovery of a substantial amount of the starting material (Table 3, entry 1). In contrast, enynes **1k**–**m**, which have a hetero atom in the tether, afforded the desired products in good yields (entries 2–4).

It is noteworthy that enyne **1n** underwent carboxylative cyclization under the standard conditions to give carboxylated product **2n**, having a six-membered ring, in 47% yield (Scheme 4).

In conclusion, nickel-mediated carboxylative cyclization of enynes, which proceeds via insertion of CO_2 into a nickelacyclopentene intermediate, was investigated. The effects of substituents were investigated in detail, and it was revealed that an electron withdrawing group on alkene is necessary for oxidative cyclization of enynes, which is an initial key step of this carboxylative cyclization. The utility of this novel method was demonstrated by application to the synthesis of various carboxylic acid derivatives having five- to six-membered ring skeletons. Efforts to expand the scope of this reaction and to extend the reaction to a catalytic process are underway.



Scheme 4.

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14. The role of MS 4A has not been clear yet. At present, it is postulated that it prevents nickelacycle **I** from hydrolysis by removing a trace amount of water in the reaction system.

15. Typical procedure: a flame-dried round-bottomed flask was charged with $Ni(cod)_2$ (49 mg, 0.18 mmol), MS 4A (500 mg), and degassed dioxane (1.5 mL). To this was added DBU (0.055 mL, 0.35 mmol) and the flask was immersed in a liquid nitrogen bath. After the mixture had been frozen, the flask was evacuated to 0.05 mmHg. A balloon filled with CO_2, was attached to the flask, and the frozen mixture was slowly thawed at ambient temperature. To this suspension was slowly added a solution of **1a** (50 mg, 0.18 mmol) in degassed dioxane (2 mL) over a period of 1 h. The resulting mixture was stirred at 40 °C for 3 h and then quenched with 10% aqueous HCl after cooling to ambient temperature. The mixture was extracted with AcOEt and the combined organic layers were extracted with saturated aqueous $NaHCO_3$ (acid–base extraction). The basic aqueous layers were acidified with 10% HCl and then extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with diazomethane according to the standard procedure. The obtained crude material was purified by silica gel column chromatography (hexane/AcOEt = 5/1) to afford **2a** (42.4 mg, 70%) as a colorless oil. IR (neat) 2955, 1736, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27–5.21 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.58 (d, $J = 8.0$ Hz, 1H), 3.32–3.25 (m, 1H), 3.02 (d, $J = 16.8$ Hz, 1H), 2.84 (d, $J = 16.8$ Hz, 1H), 2.57 (dd, $J = 7.6, 13.1$ Hz, 1H), 2.27 (dd, $J = 9.5, 13.1$ Hz, 1H), 1.59 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.8, 168.7, 168.3, 139.3, 118.0, 58.3, 54.9, 52.9, 52.8, 52.5, 52.4, 41.9, 36.9, 36.8, 14.8; LRMS (EI, *m*/*z*) 342 (M^+), 311, 282, 250, 222, 191; HRMS (EI, *m*/*z*) calcd for $C_{16}H_{22}O_8$: 342.1315. Found: 342.1308.
From the residual organic layers of the acid–base extraction, **4a** (4.5 mg, 9%) was obtained as a colorless oil after standard workup, and purification by silica gel column chromatography (hexane/AcOEt = 5/1). IR (neat) 2954, 1736, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26–5.20 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.02 (d, $J = 17.4$ Hz, 1H), 2.94–2.92 (m, 1H), 2.84 (d, $J = 17.4$ Hz, 1H), 2.63 (dd, $J = 7.4, 13.0$ Hz, 1H), 2.59 (dd, $J = 5.4, 15.5$ Hz, 1H), 2.28 (dd, $J = 8.7, 15.5$ Hz, 1H), 1.89 (dd, $J = 10.6, 13.0$ Hz, 1H), 1.60 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 172.9, 172.8, 141.9, 117.0, 58.5, 53.1, 53.0, 51.8, 40.2, 38.9, 38.7, 37.2, 14.7; LRMS (EI, *m*/*z*) 284 (M^+), 253, 224, 192; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_6$: 284.1260. Found: 284.1267.