Multicomponent Coupling

International Edition: DOI: 10.1002/anie.201609338
German Edition: DOI: 10.1002/ange.201609338

Nickel-Catalyzed CO_2 Rearrangement of Enol Metal Carbonates for the Efficient Synthesis of β-Ketocarboxylic Acids

*Ryo Ninokata, Tatsuya Yamahira, Gen Onodera, and Masanari Kimura**

Abstract: *4-Methylene-1,3-dioxolan-2-ones underwent oxidative addition of a Ni^0 catalyst in the presence of $Me_2Al(OMe)$, followed by a coupling reaction with alkynes, to form δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivity. The reaction proceeds by [1,3] rearrangement of an enol metal carbonate intermediate and the formal reinsertion of CO_2.*

β-Ketocarboxylic acids are useful and valuable key intermediates en route to biologically active molecules.[1] For example, crassulacean acid metabolism (CAM) is an important carbon-resource-utilization process in the photosynthesis of oxaloacetate from CO_2 by pyruvate carboxylase of green plants.[2] However, as β-ketocarboxylic acids are thermodynamically unstable, many problems, such as the ready extrusion of CO_2 by decarboxylation processes, often arise.[3] Although metal enolates are highly reactive and convenient nucleophilic intermediates for the synthesis of carbonyl compounds, little attention has been focused on the fixation of CO_2 by metal enolates.[4]

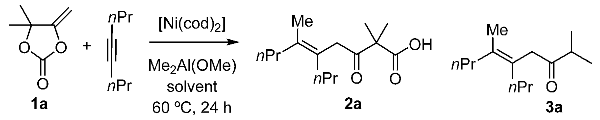
1,3-Dioxolan-2-ones are among the most important industrial materials, for example, as electrolytes in lithium-ion-battery half-cells and as predominant monomers for polycarbonates.[5] Although cyclic carbonates are utilized as fine chemicals and as monomers for polymerization in modern industrial synthesis, most synthetic applications of 1,3-dioxolan-2-ones face difficulties due to decarboxylation.[6]

Nickel-catalyzed C−C bond transformations are powerful tools in modern organic synthesis.[7] Insertion reactions of CO_2,[8] reductive coupling with alkynes and enones,[9] and multicomponent coupling reactions with unsaturated hydrocarbons[10] are extremely attractive methods for efficient organic synthesis. Recently, we developed a nickel-catalyzed multicomponent coupling of diketene and alkynes with organometallic reagents to provide unsaturated carboxylic acids and phenylacetic acids.[11] In that case, the combination of a Ni catalyst and $Et_2Al(OEt)$ had a very important role in promoting the C=C double-bond cleavage of diketene to enable reconstruction of the molecular framework through cycloaddition and migratory processes.

Herein, we disclose a highly efficient method for the synthesis of β-ketocarboxylic acids from 4-methylene-1,3-dioxolan-2-one as a CO_2 and enolate equivalent, by treatment with alkynes and $Me_2Al(OMe)$ in the presence of a Ni^0 catalyst. This reaction directly provides δ,ε-unsaturated β-ketocarboxylic acids under a N_2 atmosphere without decarboxylation occurring.

The reaction was examined with the catalyst $[Ni(cod)_2]$, 1,3-dioxolan-2-one **1a**, and 4-octyne by treatment with $Me_2Al(OMe)$ at 60°C under a N_2 atmosphere in a wide variety of solvents (Table 1). Nonpolar solvents, such as hexane, toluene, and cyclic ethers were ineffective, with the desired product **2a** obtained in low yields and most of substrate **1a** remaining (Table 1, entries 1–5). Among aprotic polar solvents, DMSO was especially efficient and afforded **2a** in 82% yield, along with ketone **3a** as a minor product, even in the presence of 5 mol% of the $[Ni(cod)_2]$ catalyst (Table 1, entry 9).

Table 1: Coupling of cyclic carbonate **1a** with 4-octyne and $Me_2Al(OMe)$.[a]



Entry	Solvent	Product(s) (yield [%][b])
1	hexane	trace
2	toluene	**2a** (20)
3	DME	trace
4	dioxane	**2a** (10)
5	THF	trace
6	DMA	**2a** (34)
7	DMF	**2a** (27)
8	DMSO	**2a** (70)
9[c]	DMSO	**2a** (82), **3a** (14)

[a] Reaction conditions: **1a** (1.0 mmol), 4-octyne (1.0 mmol), $Me_2Al(OMe)$ (1.2 mmol), $[Ni(cod)_2]$ (0.1 mmol), solvent (3 mL), 60°C, 24 h, nitrogen atmosphere. [b] Yield of the isolated product. [c] The reaction was carried out with **1a** (1.2 mmol), 4-octyne (1.0 mmol), and $Me_2Al(OMe)$ (1.2 mmol) in the presence of $[Ni(cod)_2]$ (0.05 mmol). cod = 1,5-cyclooctadiene, DMA = *N*,*N*-dimethylacetamide, DME = 1,2-dimethoxyethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

We screened a number of organometallic reagents for this reaction (Table 2). In the presence of 5 mol% of $[Ni(cod)_2]$, a mixture of the cyclic carbonate **1a**, 4-octyne, and Me_3B underwent the coupling reaction at 60°C in DMSO to give the expected β-ketocarboxylic acid **2a** in 18% yield, along with the decarboxylated product **3a** in 70% yield (Table 2, entry 1). When Me_2Zn or Me_3Al was used, the desired product **2a** was obtained in 65 and 73% yield, respectively (entries 2 and 3). $Me_2Al(OMe)$ was the most efficient organometallic reagent for the desired coupling reaction

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[*] R. Ninokata, T. Yamahira, Dr. G. Onodera, Prof. Dr. M. Kimura
Graduate School of Engineering, Nagasaki University
Bunkyo-machi 1-14, Nagasaki 852-8521 (Japan)
E-mail: masanari@nagasaki-u.ac.jp

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201609338.

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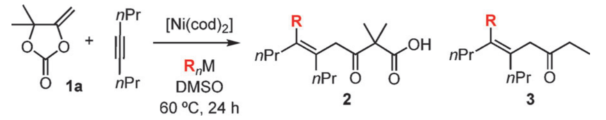
Table 2: Coupling of cyclic carbonate **1a** with 4-octyne and an organometallic reagent.[a]

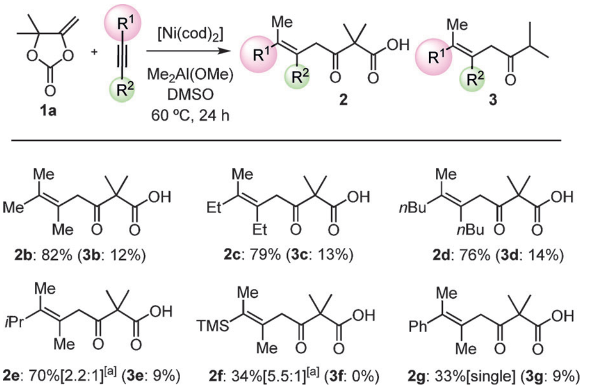


Entry	R$_n$M	Products (yield [%][b])
1	Me_3B	**2a** (18), **3a** (70)
2	Me_2Zn	**2a** (65), **3a** (19)
3	Me_3Al	**2a** (73), **3a** (21)
4	$Me_2Al(OMe)$	**2a** (82), **3a** (14)
5	Et_3Al	complex mixture
6	$Et_2Al(OEt)$	complex mixture

[a] Reaction conditions: **1a** (1.2 mmol), 4-octyne (1.0 mmol), organometal (1.2 mmol), [Ni(cod)$_2$] (0.05 mmol), DMSO (3 mL), 60°C, 24 h, nitrogen atmosphere. [b] Yield of the isolated product.

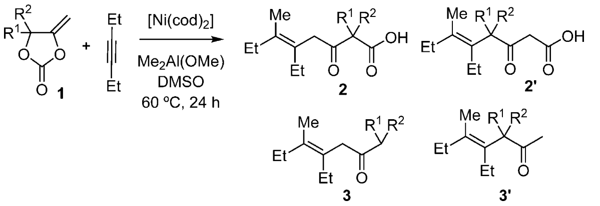
(entry 4). In contrast, Et_3Al and $Et_2Al(OEt)$ were not effective at promoting the coupling reaction with ethyl-group insertion, thus resulting in complex mixtures (Table 2, entries 5 and 6).

Next, we investigated the reaction of cyclic carbonate **1a** with various kinds of alkynes (Scheme 1). The symmetrical alkynes 2-butyne, 3-hexyne, and 5-decyne reacted smoothly with cyclic carbonate **1a** in the presence of $Me_2Al(OMe)$ to provide the corresponding β-ketocarboxylic acids **2b**–**d** in good yields (Scheme 1). In the case of the unsymmetrical alkynes 4-methyl-2-pentyne, 1-trimethylsilyl-1-propyne, and 1-phenyl-1-propyne, the corresponding β-ketocarboxylic acids **2e**–**g** were obtained in modest to good yields. The less hindered substituted acetylenic carbon atom tended to attack the methylene carbon atom of the carbonate. β-Keto acids **2e** and **2f** were obtained as a mixture of regioisomers, whereas **2g** was obtained as a single isomer.



Scheme 1. Coupling of cyclic carbonate **1a** with various alkynes and the methylaluminum reagent $Me_2Al(OMe)$. Reaction conditions: **1a** (1.2 mmol), alkyne (1.0 mmol), $Me_2Al(OMe)$ (1.2 mmol), [Ni(cod)$_2$] (0.05 mmol), DMSO (3 mL), 60°C, 24 h, nitrogen atmosphere. Yields are for the isolated product. [a] The ratio shows the regioselectivity with respect to the alkyne substituents. TMS = trimethylsilyl.

Table 3: Coupling of cyclic carbonates with 3-hexyne and $Me_2Al(OMe)$.[a]



Entry	Cyclic carbonate	Products (yield [%][b])
1	R^1 = Me, R^2 = Me (**1a**)	**2c** (79), **3c** (13)
2	R^1 = Me, R^2 = Et (**1h**)	**2h** (52), **3h** (35)
3[c]	R^1 = Me, R^2 = Ph (**1i**)	**2i** (15), **3i** (72)
4[c]	R^1 = H, R^2 = H (**1j**)	**2j** (60), **3j** (25)
5[c]	R^1 = H, R^2 = Me (**1k**)	**2k** (45), **2′k** (18), **3k** (11), **3′k** (9)
6[c]	R^1 = H, R^2 = Ph (**1l**)	**2l** (38), **2′l** (12), **3l** (36), **3′l** (5)

[a] Reaction conditions: **1** (1.2 mmol), 3-hexyne (1.0 mmol), $Me_2Al(OMe)$ (1.2 mmol), [Ni(cod)$_2$] (0.05 mmol), DMSO (3 mL), 60°C, 24 h, nitrogen atmosphere. [b] Yield of the isolated product. [c] β-Ketocarboxylic acids **2** and **2′** were isolated as the methyl ester by treatment of the products with trimethylsilyldiazomethane.

We examined the reaction of 3-hexyne with cyclic carbonates containing different substituents at the 5-position (Table 3). The unsymmetrical 5-disubstituted carbonate **1h** (R^1 = Me, R^2 = Et) was converted into the unsymmetrical α-disubstituted β-keto acid **2h** as the major product, as well as ketone **3h** (Table 3, entry 2). The phenyl- and methyl-substituted cyclic carbonate **1i** was transformed into β-keto acid **2i** in low yield as a mixture with ketone **3i** (entry 3). The unsubstituted cyclic carbonate **1j** (R^1 = H, R^2 = H) underwent a similar coupling reaction to give a mixture of β-keto acid **2j** with ketone **3j** as a minor product (entry 4). In the case of the monosubstituted carbonate **1k** (R^1 = H, R^2 = Me), a mixture of regioisomers of α-methyl-β-keto acid **2k** and γ-methyl-β-keto acid **2′k** were produced in 63 % yield in an approximately 3:1 ratio, along with a small amount of ketone **3k** and **3′k** in 20 % combined yield (entry 5). Apparently, the corresponding 5-phenyl-substituted carbonate underwent the decarboxylation to some extent (entry 6). The ratios of β-keto acid **2** and ketone **3** might depend on the stability of the key metal enolate intermediate, as well as the steric bulk of the R^1 and R^2 groups.

Although it would be premature to provide a complete explanation of the reactivities and selectivities described herein, a plausible mechanism for the multicomponent coupling reaction of 5-substituted 4-methylene-1,3-dioxolan-2-ones with alkynes promoted by the Ni catalyst and $Me_2Al(OMe)$ is proposed in Scheme 2. Thus, oxidative addition of the cyclic carbonate to the Ni^0 catalyst at the allylic position, as promoted by $Me_2Al(OMe)$ as a Lewis acid, gives the oxanickelacycle intermediate **I**, the stability of which seems to depend on the substituents at the 5-position. Metallacycle **I** readily isomerizes to the more stable nickelacycle **III** through σ–π–σ allylnickel interconversion.[12] The insertion of an alkyne proceeds to form an eight-membered oxanickelacycle intermediate **V**, which then undergoes transmetalation with $Me_2Al(OMe)$ to form an enol aluminum carbonate **VII**.[2e,13] This enol metal carbonate **VII** readily undergoes [1,3] rearrangement to afford a β-ketocarboxylic acid,[14] followed by reductive elimination to generate a catalytically active Ni^0 species.

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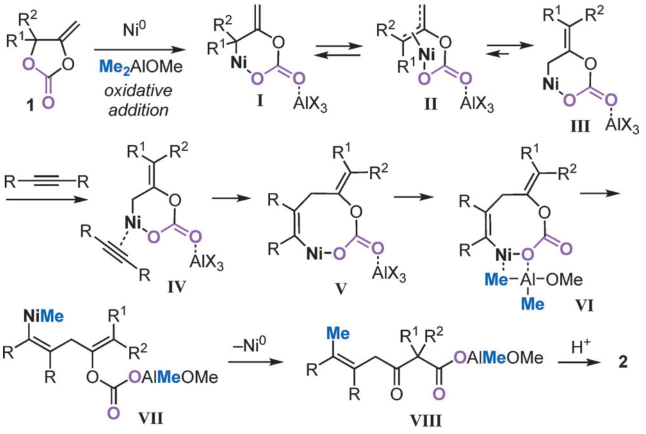

Scheme 2. Plausible reaction mechanism for the multicomponent coupling reaction of cyclic carbonates and alkynes with $Me_2Al(OMe)$.

In conclusion, we have developed an efficient synthesis of β-ketocarboxylic acids from 4-methylene-1,3-dioxolan-2-ones through oxidative addition to a Ni^0 catalyst in the presence of $Me_2Al(OMe)$ and an alkyne. The corresponding enol aluminum carbonate intermediates underwent [1,3] rearrangement to form δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivity. This protocol provides an example of the efficient fixation of CO_2 for carbon-resource utilization, as in the CAM process in biological photosynthesis.

Experimental Section

Typical procedure: Cyclic carbonate **1a** (153.8 mg, 1.2 mmol), 4-octyne (110.2 mg, 1.0 mmol), and $Me_2Al(OMe)$ (1.2 mmol, 1.0 M hexane) were added successively with a syringe to a solution of $[Ni(cod)_2]$ (13.8 mg, 0.05 mmol) in anhydrous DMSO (3.0 mL) under a N_2 atmosphere, and the resulting mixture was stirred at 60 °C for 24 h. The mixture was then diluted with ethyl acetate (30 mL) and washed with 2 N HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was subjected to column chromatography over silica gel (hexane/EtOAc 1:1, v/v) to give **2a** (208.6 mg, 82 %; $R_f = 0.50$, hexane/EtOAc 1:1, v/v) along with **3a** (29.4 mg, 14 %; $R_f = 0.73$).

Acknowledgements

We gratefully acknowledge funding from Grants-in-Aid for Scientific Research (B; 26288052) from the Ministry of Education, Culture, Sports and Technology (MEXT), Japan.

Keywords: alkynes · aluminum · cyclic carbonates · multicomponent reactions · nickel

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[12] In entries 5 and 6 of Table 3, a regioisomeric mixture of β-ketocarboxylic acids **2** and **2′** were produced. Both nickelacycles **I** and **III**, through σ–π–σ allylnickel interconversion, would participate in alkyne insertion to form a regioisomeric mixture of nickelacycle intermediates, thus leading to **2** and **2′** (Scheme 2). However, an alternative reaction mechanism involving a decarboxylation–carboxylation sequence can not be ruled out.

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[14] For the [1,3] rearrangement of an enol zinc carbonate to provide a β-ketocarboxylic acid, see: K. Kataoka, T. Tsuruta, *Polym. J.* **1977**, *9*, 595–604.

Manuscript received: September 23, 2016
Final Article published: ■■ ■■, ■■■■

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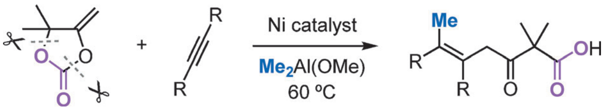
Communications

Multicomponent Coupling

R. Ninokata, T. Yamahira, G. Onodera, M. Kimura* ______ ■■■■–■■■■

Nickel-Catalyzed CO_2 Rearrangement of Enol Metal Carbonates for the Efficient Synthesis of β-Ketocarboxylic Acids



Let all the parts fall into place: A 4-Methylene-1,3-dioxolan-2-one underwent oxidative addition to a Ni^0 catalyst in the presence of $Me_2Al(OMe)$, followed by a coupling reaction with alkynes to form δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivity (see scheme). The reaction proceeds via [1,3] rearrangement of an enol metal carbonate intermediate and the formal reinsertion of CO_2.

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