Cobalt-catalyzed Reductive Carboxylation on a, β-Unsaturated Nitriles with Carbon Dioxide

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The reductive carboxylation of α,β -unsaturated carbonyl compounds with carbon dioxide was studied. After the screening of various transition-metal complex catalysts and reducing agents, it was found that the combination of bis(acetylaceto-nato)cobalt(II) and diethylzinc could effectively afford the corresponding α -carboxylate in high yield from α,β -unsaturated nitriles. The product was obtained after esterification by trimethylsilyldiazomethane. The highly selective carboxylation was observed at the α -position in the present study.

Carbon-carbon bond formation is one of the most important reactions in organic chemistry. Since the report¹ by Mukaiyama in 1973 on the Lewis acid-catalyzed crossed aldol reaction using silvl enol ether as a metal enolate analogue, this reaction has been employed as a standard method in organic synthesis. In principle, the Mukaiyama aldol reaction proceeds in the presence of a catalytic amount of Lewis acid to exclusively afford the cross addition product. As no strong base is required, this reaction has been welcomed by various organic chemists as a reliable carbon-carbon bond formation reaction, especially in natural product chemistry.² In order to improve the catalytic efficiency or stereoselectivity of this reaction system, various metal elements have been screened as Lewis acid catalysts.³ Much effort has also been made for designing ligands in enantioselective catalytic version. As an alternative solution for the metal-catalyzed crossed aldol reaction, conjugate reductions have been employed using a catalytic amount of rhodium(III) chloride and stoichiometric trimethylsilane for α . β -unsaturated carbonyl compounds, the resulting metal enolate equivalents were employed for the following aldol reaction.⁴ Since both the enolate generation and aldol reaction proceed in one pot, the reductive aldol reaction has been examined especially for the catalytic version of carbon-carbon forming reactions. Isayama and Mukaiyama reported the reductive aldol reaction from α,β unsaturated nitriles catalyzed by bis(acetylacetonato)cobalt(II) and phenylsilane in 1989.5 The reaction mechanism is presumed to be as follows: phenylsilane could act on the cobalt complex as a reducing agent to generate "cobalt hydride." Its 1,4-addition to an α , β -unsaturated nitrile would afford the corresponding cobalt enolate equivalent, which would produce the cobalt alkoxide of the aldol adducts by a nucleophilic attack on the electrophile such as aldehydes and ketones (Sheme 1). The successive transmetalation between the cobalt and silane could regenerate the catalytic cobalt hydride and silvl ether of the aldol adduct. As the carbon-carbon bond-forming reaction was selectivity observed at the α -position, the Michael addition-type reaction should be essential during the first step with cobalt hydride equivalent. During the course of our continuing studies on cobalt(II) complex catalysts with the combined use of reducing agents, various synthetic reactions were reported; the oxidationreduction-hydration of various alkenes was proposed in the



Scheme 1. Cobalt-catalyzed C–C bond formations via enolate equivalents.

presence of 2-propanol and molecular oxygen.⁶ With the combined use of sodium borohydride, the catalytic enantioselective reduction of various carbonyl compounds into optically active secondary alcohols or amines was realized.⁷ Under similar conditions, the enantioselective 1,4-reduction of α , β -unsaturated carboxamides was also reported.⁸

Carbon dioxide is a safe and abundant C1 resource. Since it contains a carbonyl group in its structure, the reaction of CO₂ with various carbon nucleophiles has been examined for new carbon-carbon bond formation. Our laboratory has reported the reactions of carbon dioxide with epoxides catalyzed by cobalt(II) complexes9a and propargyl alcohols and amines catalyzed by silver(I) salts, 9b,9c respectively. In these reactions, however, an oxygen or nitrogen nucleophile attacked the carbon dioxide to afford the corresponding cyclic carbonates or oxazolidinones. Although these products will release carbon dioxide on hydrolysis, the corresponding products, formed via a carboncarbon bond-forming reaction with carbon dioxide, should be stable enough to be employed as further synthetic intermediates for carbon-carbon frameworks. Various methods^{10,11} have been reported for the carbon-carbon bond-forming reaction with carbon dioxide. Our laboratory has proposed the reactions of enolates with carbon dioxide. In the presence of a silver(I) catalyst, various ketones containing an alkyne group at the appropriate position afforded the corresponding y-lactone derivatives^{9d} or dihydroisobenzofuran derivatives^{9e} in good to high yields under mild conditions, respectively. In this communication, the reductive carboxylation reaction of α , β -unsaturated nitriles with carbon dioxide in the presence of cobalt(II) catalysts and reducing agents is reported.

The initially reported standard conditions were used for the reductive aldol reaction of 5-phenylpent-2-enenitrile (1a) with benzaldehyde to afford the corresponding aldol adduct in 88% yield. Under the same reaction conditions, but with the aldehyde being replaced by carbon dioxide, the desired product 2a was not obtained at all; the corresponding reduced product was produced instead. Since the reduced product was obtained, it was assumed that the 1,4-reduction of the α , β -unsaturated nitrile would proceed to generate the corresponding enolate equivalent, which cannot capture carbon dioxide (Table 1, Entry 1). By

 Table 1. Examination of various reductant for reductive carboxylation

Ph	CN 1a	cat.[Co(acac) ₂], CO ₂ Reductant (2.0 equiv)	Ph	
Entry ^a	Reductant	Amount of Co(II) complex/mol%	CO ₂ pres. /MPa	Yield/%
1 ^b	PhSiH ₃	5	1.0	0
2 ^b	PhSiH ₃	100	1.0	10
3	Et_3B	100	1.0	10
4	Et ₂ AlCl	100	1.0	26
5	Et_2Zn	100	1.3	62
6	Et_2Zn	5	1.0	87°
7	Et_2Zn	5	0.1	>99 ^c

^aReactions were carried out in 0.25 mmol scale with 1.5 mL of THF at 20 °C. ^bReaction was carried out in 1.5 mL of 1,2dichloroethane at 70 °C. ^cYield after methylation with trimethylsilyldiazomethane.

using a stoichiometric amount of the cobalt complex, the desired product **2a** was obtained in 10% yield (Entry 2). As it was confirmed that the corresponding reductive carboxylation actually proceeds in the presence of the cobalt complex, various reducing agents were examined. Triethylborane, diethylaluminum chloride, and diethylzinc were used as a reducing agent (Entries 3, 4, and 5).¹² Based on this screening, it was found that diethylzinc is the most suitable reducing agent to capture carbon dioxide. Triethylborane showed a reactivity similar to that of phenylsilane. Diethylaluminum chloride produced a better yield than those obtained by silane and borane; however, diethylzinc gave the best yield. By using diethylzinc and 5 mol% of the cobalt(II) complex, the desired product **2a** was eventually obtained in quantitative yield under mild conditions with atmospheric pressure of carbon dioxide.

The optimized conditions were successfully applied to various α,β -unsaturated nitriles to afford the corresponding carboxylation products (Table 2). The carboxylation reaction with carbon dioxide was selectively observed at the α -position for all substrates in Table 2. 5-Phenylpent-2-enenitrile (1a) and its derivatives with substituents such as alkyls, ethers, esters, and halogens exhibited a good reactivity to afford the corresponding products 3a-3f after methyl esterification in good-to-excellent yields (Entries 1-6). The substrates with a naphthyl group, benzyl group, and shortened alkyl chain 1g-1i also afford the corresponding products in high yields (Entry 7-9). Cinnamonitrile forms the corresponding product 3i in 81% yield (Entry 10). Similar to the standard Michael additions,¹³ though the β-substituted methacryl derivatives were not suitable substrates for this reaction (Entry 12), the α -substituted (Entry 11) and γ -methyl-substituted (Entry 13) α , β -unsaturated nitriles reacted with carbon dioxide to afford the corresponding carboxylation products in moderate-to-good yield. The aphenyl-substituted α , β -unsaturated nitrile was found to react with carbon dioxide to give the carboxylated product in good yield (Entry 14). The dihydronaphthalenes with a nitrile at the α -position **10** and **1p** reacted with carbon dioxide to afford the products in good to high yield (Entries 15 and 16) though no

Table 2. Various α,β -unsaturated nitriles for reductive carboxylation

R	CN 1	^{cat.} [Co(ac CO ₂ , Et ₂	ac)₂] - Zn	TMSCHN	²→ R_)Me N
Entry ^a	Substra	ate		Product			Yield/% ^d
1	Ar a da	Ar = Pl	n		ÇOOMe	3a	>99
2		CN = 4-	Me-Ph	Ar		3b	77
3		= 4-	CO ₂ Et-Ph			3c	85 ^e
4		= 4-	Br-Ph			3d	>99
5		3e	>99				
6		= 4-	OMe-Ph			3f	98
7		= OBn 3					
8		= 1-	Naph			3h	>99
9	C Ph	CN J	Ph		e 3i		78
10 ^b	Ph 🏑	CN	Ph	COOMe	3ј		81
11 ^b	Ph	Me CN	Ph 🏑		Vle 3k		38
12 ^b	Ph	CN /e	Ph		Vle 31		9 ^f
13 ^b	Me Ph	CN	N Ph		Vle 3m		67
14 ^b		Ph CN	\sim		le 3n Me		66
15 ^b					R' = H	30	91
16 ^c					R' = OMe	3p	56
17 ^b	C C	N Me	N		e 3q		0

^aReactions were carried out in 0.25 mmol scale with 1.5 mL of THF at 20 °C under atmospheric pressure of CO₂ with 2 equiv of Et₂Zn (ca. 1.0 M in *n*-hexane) in the presence of 5 mol % of [Co(acac)₂]. ^b10 mol % of [Co(acac)₂] and 4 equiv of Et₂Zn were employed. ^c15 mol % of [Co(acac)₂] and 8 equiv of Et₂Zn were employed. ^dIsolated yield. ^e1.0 MPa of CO₂. ^fD.r. = 60:40.

reaction proceeded for the corresponding β -methyl-substituted nitrile **1q** (Entry 17).

The corresponding ethyl-substituted product at the β position was detected using GC-MS analysis. For the reaction of the α , β -unsaturated nitrile **1p**, the corresponding ethylsubstituted product **4p** was isolated in 12% yield. The ethylsubstituted products were exclusively obtained in the absence of the cobalt complex; however, the desired product was not detected (Scheme 2, eq 1). Therefore, the combined use of a cobalt catalyst and diethylzinc is crucial to generate the metal enolate equivalent hydrated at the β -position (eq 2). It was reported that the transmetalation of the bis(acetylacetonato)nickel(II) complex with alkylaluminum would generate alkyl nickel species, which would result in nickel hydride after β elimination.¹⁴ For this reaction, the cobalt hydride generated by the same process would add the α , β -unsaturated nitrile via a 1,4addition to afford the resulting metal enolate equivalent. Though



Scheme 2. Cobalt hydride 1,4-addition mechanism.

not yet clear whether the cobalt or zinc enolate captures the carbon dioxide, the corresponding carboxylated product was obtained in good-to-high yield for various α , β -unsaturated nitriles.

It is noted that the combination of bis(acetylacetonato)cobalt(II) and diethylzinc could effectively afford the corresponding α -carboxylate in high yield from the α , β -unsaturated nitriles. Further investigation on the detailed mechanism or applications is currently underway.¹⁵

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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