

Novel Cobalt-Catalyzed Carbonylation of 2-Aryl-2-oxazolines

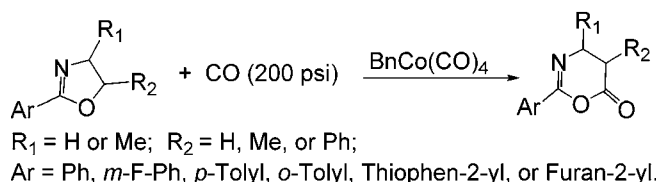
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ABSTRACT



Catalytic ring-expanding carbonylation of 2-aryl-2-oxazolines is reported as a novel method for the synthesis of 4,5-dihydro-1,3-oxazin-6-ones. Various observations suggest the involvement of cobalt radicals as the catalytically active species.

Metal-catalyzed carbonylation is a versatile synthetic method for a broad spectrum of organic carbonyl compounds.¹ Significant innovations have continued to occur in this area, particularly in the carbonylation of heteroatom-containing substrates.^{2–5} Along this line, we have focused our research on the carbonylative polymerization^{6–8} and demonstrated the feasibility of synthesizing poly(β -alanine) and its derivatives via CO–aziridine alternating copolymerization.⁹ In an effort

to broaden the scope of the copolymerization, we attempted to synthesize acyclic polyimides by 2-oxazolines–CO copolymerization under a mechanistic hypothesis similar to that of the aziridine–CO copolymerization.¹⁰ We discovered, to our surprise, that the product of the presumed copolymerization of 2-phenyl-2-oxazoline and CO was 2-phenyl-4,5-dihydro-1,3-oxazin-6-one. This reaction represents, to the best of our knowledge, the first catalytic method for the synthesis of 4,5-dihydro-1,3-oxazin-6-one heterocycles. The 4,5-dihydro-1,3-oxazin-6-ones are interesting molecules because they undergo ring-opening reaction with both nucleophiles and electrophiles resulting in β -amino acid derivatives or β -peptide bonds.^{10–12} Polymerization of this class of molecule has been reported to afford acyclic polyimides,

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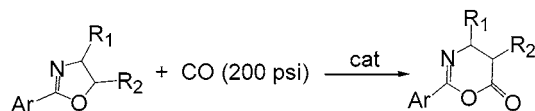
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which are our original targets.¹¹ Since 2-oxazolines as common versatile synthetic intermediates are readily available often in optically pure forms via a variety of synthetic methods,¹³ the novel reaction can be an important addition to the repertoire of β -amino acid/ β -peptide synthesis. Motivated by the above reasons, we followed up on the discovery and wish to report our preliminary results here.

The catalytic reactions were typically carried out at 60 °C under 200–1000 psi of CO pressure in THF in the presence of 5 mol % cobalt complexes **1** and **2**.¹⁴ Complexes **1** and **2** cannot be separated because they are at equilibrium under CO.¹⁴ The most distinct characteristics of the reaction is that an aromatic substituent is required at the C(2) position of the 2-oxazoline substrate.¹⁵ A variety of aryls are suitable substituents. The electron-donating 4-tolyl group renders the highest yield, while the electron-withdrawing 3-fluorophenyl group and the sterically encumbering 2-tolyl group decrease the yield (Table 1,

Table 1. Ring-Expanding Carbonylation of 2-Aryl-2-oxazolines^a



entry	precatalyst	Ar	R ₁	R ₂	yield ^b
1	1 and 2	Ph	H	H	95% (92%)
2	1 and 2	4-tolyl	H	H	>98% (88%)
3	1 and 2	2-tolyl	H	H	30% (9%)
4	1 and 2	3-fluorophenyl	H	H	74% (72%)
5	1 and 2	2-furanyl	H	H	45% (32%)
6	1 and 2	2-thiophenyl	H	H	85% (78%)
7	1 and 2	Ph	Me	H	56% (48%)
8	1 and 2	Ph	H	Me	8%
9	1 and 2	Ph	H	Ph	52%
10 ^c	1 and 2	Ph	H	Ph	83% (60%)
11 ^d	3	Ph	H	H	0%
12 ^d	Na ⁺ Co(CO) ₄ ⁻	Ph	H	H	0%
13 ^d	Co ₂ (CO) ₈	Ph	H	H	4%
14 ^{d,e}	Co ₂ (CO) ₈ with AIBN	Ph	H	H	85%
15 ^e	AIBN	Ph	H	H	0%
16 ^{a,f}	1 and 2 with TEMPO	Ph	H	H	0%

^a Reaction conditions unless otherwise specified: 5 mol % Co; 7.60 mmol of 2-oxazoline, 50 mL of THF, 200 psi of CO; 60 °C; 48 h. ^b Yield determined by ¹H NMR, and the isolated yield is given in parentheses. ^c 1000 psi of CO. ^d 10 mol % Co. ^e 5 mol % AIBN. ^f Co/TEMPO molar ratio = 1:1.

entries 2–4). Substrates with heteroaryls at the C(2) position can also be carbonylated in good to moderate yields (entries 5 and 6). Substitution at the C(4) and C(5) positions significantly influences the reactivity of the substrates (entries 7–10). The 4-methyl, 5-methyl, and 5-phenyl derivatives of 2-phenyl-2-oxazoline were converted to the corresponding

products in 56, 8, and 83% yields, respectively (entries 7, 8, and 10). The yield of the carbonylation of 2,5-diphenyl-2-oxazoline decreases to 52% when the reaction is carried out under 200 psi (entry 9). The enamide PhCONHCH=CHPh, which is a simple ring-opened isomer of the substrate, is the major byproduct that apparently escaped from carbonylation.¹⁶ The formation of the enamide byproduct is suppressed by high CO pressure. In contrast, the yields of the carbonylation of the 4-methyl and 5-methyl substrates are unaffected by CO pressure and are limited by the catalyst turnovers, as no byproduct was observed in the reaction mixtures (entries 7 and 8).

Understanding the mechanism of the carbonylation reaction necessarily requires first perception of the catalytically active species. One critical clue came from the fate of the benzyl group in the catalyst precursors. After failing to detect any benzyl-containing byproducts from the reaction, we monitored the catalytic carbonylation of 2-phenyl-2-oxazoline in situ by ¹H NMR in a Wilmad high-pressure NMR tube. The NMR reaction was carried out at 20 mol % catalyst loading under 200 psi of CO pressure in THF-*d*₈ at 60 °C. The concentration of the substrate was chosen so that only 10 psi of CO, i.e., 5% of the total initial pressure in the NMR tube, would be consumed at the completion of the reaction. Toluene was produced during the reaction. Although we are not certain as to the source of the hydrogen atom (not deuterium, the product is toluene-*d*₀), it seems that only abstraction of a hydrogen atom by a benzyl radical provides a reasonable explanation for the formation of toluene. The benzyl radical logically would arise from the homolytic dissociation of the Bn–Co bond,¹⁷ which in turn would leave the 17-electron Co(CO)₄ as the most likely catalytically active species. We have performed several experiments to test the involvement of Co radical species using the parent 2-phenyl-2-oxazoline as the substrate. First, we tested Na⁺Co(CO)₄⁻ and CH₃COC(CO)₃(PPh₃) (**3**) as precatalysts (entries 11 and 12). No reaction was observed as expected. Next, when Co₂(CO)₈ was used as the precatalyst, 4% of the substrate was converted to the product as compared to 95% conversion with **1** and **2** as the catalyst under the identical reaction conditions (entry 13 vs entry 1). In comparison, when an equimolar mixture of AIBN and Co₂(CO)₈ was used as the precatalyst, the conversion was improved to 85% (entry 14), while AIBN alone does not catalyze the carbonylation reaction (entry 15). The catalytic activity of **1** and **2** was completely inhibited by 1 equiv of TEMPO (entry 16). The above observations as well as the fact that the ring-expanding carbonylation requires a 2-aryl substituent ubiquitously prompt a mechanistic hypothesis based on cobalt radicals. We thus propose that the catalytic cycle is composed of 2-oxazoline coordination, intramolecular oxidative addition (cleavage of the O–C(5) bond), CO insertion and coordination, and finally reductive elimination to extrude the product (Scheme 1). The formally 19-electron intermediate **A** is likely an (18 + δ)-electron species, i.e., the spin-delocalized

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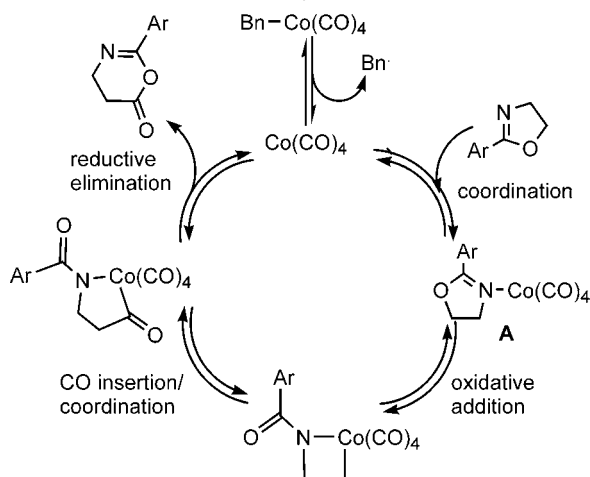
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(15) When the C(2) substituent is an alkyl group, the reaction product is a polymer that appears to contain an acyclic imide structure and the uncarbonylated amide.

(16) A second minor byproduct was also present but was not characterized.

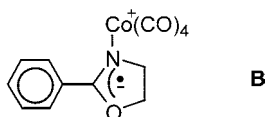
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Scheme 1. Plausible Mechanism of 2-Oxazoline Carbonylation



canonical structure **B** is an important contributor to the bonding of the intermediate **A**.¹⁸ The stability of the odd-electron species is rendered by the ability of the ligand to accept the spin density. The extended π -conjugation of a 2-aryl group in the 2-oxazoline undoubtedly is favorable for the spin delocalization. Note that the addition of organic radicals to the nitrogen atom of N=C double bond has recently been reported when an aromatic substituent at C is present to stabilize the resulting C-centered radical.¹⁹ The same explanation is applicable to the requirement of a 2-aryl substituent for the carbonylation. There are also precedents for C–O bond rupture of the C–OCR₂• structural moiety.^{20,21} The addition of the radical activated C–O bond to Co might

Scheme 2



be either a concerted event or a stepwise process in the present cases depending on the substituent at the C(5) position of the oxazoline substrate. Insertion and coordination of CO are common organometallic reactions. The reductive elimination may involve the first formation of an *N*-aryl- β -lactam intermediate, which then isomerizes to the final product, but we have not observed an *N*-aryl- β -lactam during the reaction by high-pressure ¹H NMR. The combination of two Co(CO)₄ radicals to form Co₂(CO)₈ is the most reasonable pathway for the catalyst deactivation, which limits the conversion of some of the substrates (entries 4 and 6–8).

In summary, we have shown that 2-oxazolines are a new class of organic molecules that undergo the metal-catalyzed carbonylation reaction. All evidence points to the mechanism involving the cobalt radicals as the catalytically active species. The catalysts for the transformation are almost certainly not limited to the cobalt radicals. We expect that a diverse variety of catalysts will be discovered for the novel and potentially useful reaction.

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Supporting Information Available: Synthesis and characterization of 2-aryl-2-oxazolines and 4,5-dihydro-1,3-oxazin-6-ones and experimental procedure for the carbonylation reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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