

Cobalt-Catalyzed Cyclization of Carbon Monoxide, Imine, and Epoxide

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Supporting Information

ABSTRACT: Cobalt-catalyzed cyclization of CO, imine, and epoxide has been developed. A convenient catalyst system composed of $Co_2(CO)_8$ and LiCl is identified, and the substrate scope has been explored. The reaction provides an efficient method for the synthesis of substituted 1,3-oxazinan-4-ones. N + ArAr R^1 $Co_2(CO)_8/LiCl$ CO 800 psi1,4-dioxane $70 \,^{\circ}C$ Yields up to 98%

M etal-catalyzed carbonylation is a powerful method for the construction of amide and ester bonds.^{1,2} In the past decade, mechanism-based development of well-defined cobalt catalysts resulted in the vast improvement of the efficiency, selectivity, and scope of this type of catalytic reaction. The utility of this type of reaction has been expanded from the synthesis of organic compounds³⁻⁵ to polymer synthesis.⁶⁻⁹

As part of our continuous effort in the area of carbonylative polymerization of heterocycles, we probed the possibility of effecting a triply alternating copolymerization of CO, *N*-benzylidenemethylamine, and propylene oxide using $CH_3COCo(CO)_3P(o-Toly)_3$ (A) as the catalyst (Scheme 1). Instead of the anticipated polymer, the reaction afforded a cyclization product,¹⁰ which was readily diagnosed with mass spectrometry.





Further inspection of the product indicated that it contained a pair of isomers, which were separated by column chromatography. One- and two-dimensional NMR spectroscopic data including ¹H, ¹³C, DEPT, ¹H–¹H COSY, and ¹H–¹H NOESY spectra confirmed that they were *trans*- and *cis*-3,6-dimethyl-2-phenyl-1,3-oxazinan-4-one (*trans*-3aa and *cis*-3aa). The individual diastereomeric configuration was assigned according to the ¹H–¹H NOESY spectra of the two isomers. Correlation of the protons at the C2 and C6 positions was observed in the *cis*-isomer and absent in the *trans*-isomer. The ratio of *trans*-**3aa**/*cis*-**3aa** was approximately 1:3. No regioisomer was observed due to the ring opening at the more hindered carbon of propylene oxide.

1,3-Oxazinan-4-ones are useful intermediates for many important pharmaceutical compounds.^{11a} They are typically synthesized by hetero-Diels—Alder reactions involving multistep substrate preparation.¹¹ The present novel catalytic reaction potentially provides a new and convenient route to the preparation of 1,3-oxazinan-4-ones from very simple and often commercially available starting materials. We therefore followed up on this accidental discovery and report here our preliminary results on catalyst optimization and substrate scouting. Parenthetically, it should be noted that the present accidentally discovered reaction bears a direct analogy to the synthesis of 1,3-oxazinane-2,4-diones from epoxides, isocyanates, and CO developed by Coates and co-workers.¹²

Following the initial discovery, we first attempted to improve the yield of the reaction. With **A** as the catalyst, the best yield was obtained at 70 °C in dioxane (Table 1, entry 3). The yield was lower at higher or lower temperatures (Table 1, entries 2 and 4) and when other solvents were used (Table 1, entries 5 and 6). The reaction conversion of the starting materials was incomplete in all these cases at 5 mol % catalyst loading. Catalysts CH₃COCo(CO)₃PPh₃ (**B**) and PhCH₂COCo(CO)₄ (**C**) also resulted in low yields (entries 7 and 8). The yield is unsatisfactory even under optimized conditions. A more efficient catalyst is necessary for the reaction to be synthetically useful.

While it is required for carbonylative polymerization, the acyl group in A–C may encumber the intramolecular cyclization.¹³ We thus moved away from the acyl-cobalt compounds and tested $Co_2(CO)_8/3$ -hydroxypyridine as the catalyst (Table 1, entries 9, 10).^{3k} The cyclization indeed occurred to afford *trans*-and *cis*-**3aa** in 92% yield. A very small amount of polyester was

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Table 1. Cobalt-Catalyzed Cyclization of N-Benzylidenemethylamine, Propylene Oxide, and CO^a

	$\frac{N}{Ph}$ + $\frac{O}{CO}$ $\frac{Co}{CO}$ 8	00 psi Ph		
entry	catalyst	solvent	temp (°C)	yield (%) ^b
1	Α	1,4-dioxane	50	24 ^c
2	Α	1,4-dioxane	60	43 ^c
3	Α	1,4-dioxane	70	59 ^c
4	Α	1,4-dioxane	80	23 ^c
5	Α	THF	70	35 ^c
6	Α	toluene	70	trace
7	В	1,4-dioxane	70	17^c
8	С	1,4-dioxane	70	20^{c}
9	Co ₂ (CO) ₈ /3-hydroxypyridine	1,4-dioxane	70	$92^{c,d}$
10	Co ₂ (CO) ₈ /3-hydroxypyridine	1,4-dioxane	60	80 ^{c,d}
11	Co ₂ (CO) ₈ /3-hydroxypyridine/ LiCl ^f	1,4-dioxane	70	91 ^{<i>c</i>,<i>d</i>}
12	$Co_2(CO)_8/LiCl^e$	1,4-dioxane	70	40 ^c
13	$Co_2(CO)_8/LiCl^f$	1,4-dioxane	70	95 ^c
14	Co ₂ (CO) ₈ /LiCl ^g	1,4-dioxane	70	90 ^c
15	$Co_2(CO)_8/LiCl^f$	1,4-dioxane	60	89 ^c
16	NaCo(CO) ₄ /LiCl ^f	1,4-dioxane	70	41 ^c
17	NaCo(CO) ₄	1,4-dioxane	70	trace
18	$Co_2(CO)_8$	1,4-dioxane	70	trace
^a React	tion conditions: imine (3.00	mmol), epox	ide (4.50	mmol)

"Reaction conditions: imine (3.00 mmol), epoxide (4.50 mmol), catalyst (0.15 mmol, 5 mol %), solvent (50 mL), 800 psi CO, 24 h. ^bIsolated yield. ^cDiastereomer ratios were determined by HPLC, and all the *trans/cis* ratios were approximately 1:3. ^dPolyester observed. ^eLiCl/Co₂(CO)₈ = 1.0. ^fLiCl/Co₂(CO)₈ = 2.0. ^gLiCl/Co₂(CO)₈ = 3.0.

also observed in the crude product. Since lithium salts often can modulate the rate and selectivity of the ring opening of heterocyclic molecules, 2 equiv of LiCl relative to $Co_2(CO)_8$ (i.e., the mole ratio of $LiCl/Co_2(CO)_8 = 1:1$) were added into the reaction. The outcome of the reaction was not affected to any substantial extent (Table 1, entry 11). However, a subsequent control experiment catalyzed by Co₂(CO)₈/LiCl demonstrated that 3-hydroxypyridine was unnecessary (Table 1, entries 9–13). On the other hand, $Co_2(CO)_8$ alone gave only a trace amount of the anticipated product in the absence of LiCl with the starting materials mostly remaining unreacted (Table 1, entry 18). When only 1 equiv of LiCl was used, the yield was 40% (Table 1, entry 12). When 3 equiv of LiCl were used (Table 1, entry 14), the yield was again somewhat lower than that when 2 equiv of LiCl were used. It appears that the optimal amount of LiCl is 2 equiv (Table 1, entries 12-14). $NaCo(CO)_4$ also gave a modest yield of the anticipated product in the presence of 2 equiv of LiCl (Table 1, entry 16). Again, only trace product was observed in the absence of LiCl with $NaCo(CO)_4$ as the catalyst (Table 1, entry 17). The same approximately 1:3 diastereomeric ratio was observed in all runs discussed above.

After identification of the $Co_2(CO)_8/LiCl$ system as an efficient catalyst, the scope of the substrate for the reaction was explored. With *N*-benzylidenemethylamine serving as the invariant substrate, a few representative epoxides were tested (Table 2, entries 1–4). The reaction of isobutylene oxide afforded the anticipated product in decent but lower yield than that of the reaction of propylene oxide. Ring opening occurred

Table 2. Scope of	Substrates for Cyclization of Imine,
Epoxide, and CO	Catalyzed by $Co_2(CO)_8/LiCl^a$

entry	imine	epoxide	product	yield $\%^b$
1	N 1a	0 2a	Ph-O- 3aa	96 (73:27) ^c
2	N Ia	2b	Ph O 3ab	82
3	N 1a	2c ^{Ph}		0
4		⊘ 2d		0
5	N 1b	2a	N 3ba	90 (89:11) ^{<i>c</i>}
6	N 1c	0 2a	N 3ca	98 (94:6) ^c
7	N 1b	0 2b	N Sbb	78
8	N 1c	о 2b	N O 3cb	85
9	F 1d	⊘ 2b	F 3db	96
10	O N If	<u>с</u> 2b		98
11	Br 1e	<u>е</u> 2b	Br 3eb	50
12	N 1g	<u>о</u> 2b		< 5 ^d

^{*a*}Reaction conditions: imine (3.00 mmol), epoxide (4.50 mmol), $Co_2(CO)_8$ (0.15 mmol, 5 mol %), LiCl (0.30 mmol), 1,4-dioxane (50 mL), 800 psi CO, 70 °C, 24 h. ^{*b*}Isolated yield. ^{*c*}Diastereomer *cis/trans* ratios determined by HPLC. ^{*d*}Detected by LC-Mass.

again selectively at the less hindered carbon. When styrene oxide and cyclohexene oxide were used as the substrate, the expected cyclization did not occur,¹² and the substrates were recovered. The *para*-substituent on the *N*-benzylidenemethylamine affected the diastereoselectivity of the reaction somewhat with propylene oxide serving as the epoxide substrate, but the *cis*-isomer was always the major isomer (entries 1, 5, 6). An increase in the electron-withdrawing ability of the aryl group in the imine substrate increases the yield of the reaction (entries 7–10). In the case of *N*-(*para*-bromo-benzylidene)methylamine (entry 11), the low yield is likely attributable to the participation of the *para*-bromo group in the reaction. Finally,

Scheme 2. Two Plausible Mechanisms for the Cobalt-Catalyzed Cyclization of Imine, Epoxide, and CO



an aryl substituent on the imine substrate is required. For *tert*butylidenemethylamine, only a trace amount of expected product was detected by LC-Mass spectrometry. In regard to the mechanism of the reaction, ^{3e,4a,7d,14} [Lewis

acid⁺[$Co(CO)_4$]⁻ is likely the active species although the identity of the Lewis acid (LA) may vary with the specific catalyst system that is used. Two plausible catalytic cycles can be envisioned that differ in the order in which the imine and epoxide react as shown in Scheme 2. In catalytic cycle I, upon epoxide coordination to the Lewis acid, nucleophilic addition of $Co(CO)_4^-$ onto the activated epoxide gives the ring-opened intermediate. CO insertion affords an acyl-Co species. The imine substrate then nucleophilically attacks the acyl-Co bond to give the iminium intermediate. Intramolecular nucleophilic cyclization between the alkoxide and the iminium gives the product and regenerates the $[LA]^+[Co(CO)_4]^-$ species. In catalytic cycle II, the imine coordinates to the Lewis acid first. Nucleophilic addition of the epoxide substrate onto the activated imine gives the oxonium intermediate, which undergoes intramolecular nucleophilic addition followed by CO insertion to afford an acyl-Co species. Intramolecular nucleophilic cyclization between the amide group and the acyl group gives the product and regenerates the [Lewis acid]⁺[Co- $(CO)_4$]⁻ species. There is no experimental indication at this point as to which mechanism or whether both are operative for the reaction.

In conclusion, we have shown that the readily available imines and epoxides can undergo selective cyclization along with CO to form 1,3-oxazinan-4-ones. The reaction can be catalyzed by the catalyst system composed of the commercially available $\text{Co}_2(\text{CO})_8$ and LiCl. We are currently exploiting the synthetic utilities and investigating the mechanism of the reaction.

ASSOCIATED CONTENTSupporting Information

Typical experimental procedures, full characterization of all new compounds, and ¹H and ¹³C NMR spectra for all substituted 1,3-oxazinan-4-one products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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