Synthesis of β-Lactones by the Regioselective, Cobalt and Lewis Acid Catalyzed Carbonylation of Simple and Functionalized Epoxides

Jong Tae Lee,† P. J. Thomas,‡ and Howard Alper*,†

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5, and Corporate R&D, The Dow Chemical Company, Midland, Michigan 48674

halper@uottawa.ca

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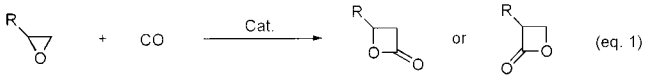
The $PPNCo(CO)_4$ and $BF_3{\cdot}Et_2O$ catalyzed carbonylation of simple and functionalized epoxides in DME gives the corresponding β-lactones regioselectively in good to high yields. The carbonylation occurred selectively at the unsubstituted C−O bond of the epoxide ring, and this reaction tolerates various functional groups such as alkenyl, halide, hydroxy, and alkyl ether.

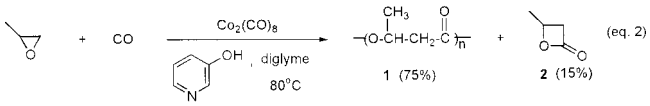
In recent years, metal-catalyzed carbonylative ring expansion reactions of heterocyclic compounds have been shown to be useful and efficient one-step procedures for the syntheses of lactams,[1] lactones[2] and thiolactones.[3] The insertion of carbon monoxide into a heterocycle is a simple, atom economical method for organic synthesis. The use of this strategy for the direct synthesis of β-lactones from epoxides and carbon monoxide has industrial potential, not only because of the nature of the reaction but also because the reactant epoxides and carbon monoxide are readily available at low cost (eq 1).



(eq. 1)

While the cobalt-catalyzed carbonylation reaction of *aliphatic* epoxides to β-lactones[4] or β-hydroxy esters[5] has been known for a long time, the yields and selectivities are very low. In the case of styrene oxide, an epoxide having an aromatic substituent, α-phenyl-β-propiolactone, was obtained in 67% yield by using $RhCl(CO)(PPh_3)_2$ as the catalyst.[6]

In 1993, an improved method was claimed for the carbonylation of aliphatic epoxides to β-lactones using $Co_2(CO)_8$ as catalyst and 3-hydroxypyridine as cocatalyst.[7] In connection with our continued efforts for the development of carbonylative ring expansion reactions of various heterocyclic compounds, we became interested in the noted claims. However, when we repeated this reaction at both Dow Chemical and at the University of Ottawa, we obtained polyester as a dominant product with only a small amount of the desired β-lactone. For example, repetition of the reported reaction of propylene oxide under the described reaction conditions afforded 75% of polyester **1**(M_w = 3,350, M_w/M_n = 1.21) and only 15% of β-butyrolactone(**2**) (eq 2). Drent and Kragtwijk[7] reported the formation of **2** in 93% conversion and 90% selectivity. One might consider that polyester **1** was



(eq. 2)

formed from lactone **2** generated under the reaction conditions. To confirm this possibility we reacted **2**, or a mixture of **2** and propylene oxide, under exactly the same reaction conditions, but **2** was recovered in almost quantitative yield. Note, however, that the $Co_2(CO)_8$/3-hydroxypyridine catalyst system was applied successfully for the carbomethoxylation of epoxides with carbon monoxide/methanol.[8] Given these findings, we endeavored to develop a new catalyst system for the realization of the synthesis of β-lactones from epoxides and carbon monoxide in a reproducible manner.

Following numerous unsuccessful attempts with complexes of different metals (Pd, Rh, Ru, Ni, and Co) as catalysts (e.g., $Pd(OAc)_2/PPh_3$ or dppp, $[Rh(COD)Cl]_2/PCy_3$ or dppp, $Ru_3(CO)_{12}$/±BINAP, $Ni(acac)_2$/dppp, $Co_2(CO)_8/PBu_3$ or 2,2′-bipyridine, etc.), we found that $PPNCo(CO)_4$ [**3**, PPN = bis(triphenylphosphine)iminium, $[(C_6H_5)_3P{=}]_2NCo(CO)_4$], used in conjunction with a Lewis acid such as $BF_3{\cdot}Et_2O$ or $SnCl_4$ in DME or THF, can catalyze the carbonylation of epoxides, affording β-lac-

† University of Ottawa.
‡ Corporate R&D, The Dow Chemical Company.

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(6) Kamiya, Y.; Kawato, K.; Ohta, H. *Chem. Lett.* **1980**, 1549.

(7) Drent, E.; Kragtwijk, E. Eur. Pat. Appl. EP 577, 206; *Chem. Abstr.* **1994**, *120*, 191517c.

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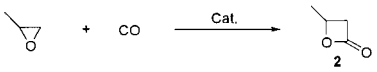
Table 1. Carbonylation of Propylene Oxide to β-Butyrolactone[a]



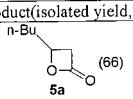
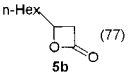
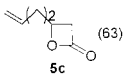
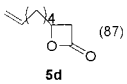
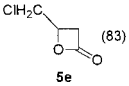
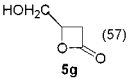
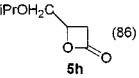
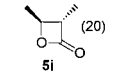
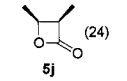
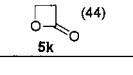
entry	catalyst (mol %)	solvent	GC yield (%)
1	**3** (1) + $BF_3{\cdot}Et_2O$ (1)	THF	64
2	**3** (1) + $BF_3{\cdot}Et_2O$ (1)	DME	77
3[b]	**3** (1) + $B(C_6F_5)_3$ (1)	DME	85
4	**3** (1)	DME	–
5	$Co_2(CO)_8$ (5)	DME	7
6	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (1)	DME	13
7	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (2)	DME	11
8	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (1)	THF	35
9	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (1)	1,4-dioxane	11
10	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	–
11	$Co_2(CO)_8$ (0.5) + PPNCl (1) + $BF_3{\cdot}Et_2O$ (1)	benzene	trace
12	$Co_2(CO)_8$ (1) + PPNCl (2) + $BF_3{\cdot}Et_2O$ (2)	THF	76
13	$Co_2(CO)_8$ (1) + CTAB[c] (2) + $BF_3{\cdot}Et_2O$ (2)	THF	23[d]

[a] All reactions were run on a 10 mmol scale of propylene oxide in 10 mL of solvent (5 mL in the case of THF) at 80 °C under 900 psi of CO for 24 h. [b] Reaction time: 7 h. Mixture of regioisomers was obtained (**2**/regioisomer = 4/1, by ^{1}H NMR). [c] Cetyltrimethylammonium bromide. [d] 15% polyester was also formed.

tones in good to excellent yields. When propylene oxide was reacted with 1 mol % each of **3** and $BF_3{\cdot}Et_2O$, in DME at 80 °C under 900 psi of carbon monoxide for 24 h, the corresponding β-lactone **2** was obtained selectively in 77% yield, with a trace amount of the regioisomer of **2** (determined by GC and ^{1}H NMR) (entry 2, Table 1). The reaction using $B(C_6F_5)_3$ instead of $BF_3{\cdot}Et_2O$ as a Lewis acid was completed within 7 h in 85% yield but produced mixture of regioisomers. By ^{1}H NMR spectroscopy, the ratio of **2**/regioisomer was found to be 4/1 (entry 3, Table 1). Using THF as the solvent for the reaction gave **2** in 64% yield with 9% of polymeric material (entry 1, Table 1). Reaction without a Lewis acid, or using $Co_2(CO)_8$ as the catalyst but no Lewis acid, resulted in the recovery of propylene oxide, or the isolation of **2** in 7% yield, respectively (entries 4 and 5, Table 1). In situ formation of **3**, by adding $Co_2(CO)_8$ and 2 equiv of PPNCl as well as $BF_3{\cdot}Et_2O$, in different solvents gave 0–35% yields of **2** (entries 6–11, Table 1). When propylene oxide was reacted in the presence of 1 mol % of $Co_2(CO)_8$, 2 mol % of PPNCl, and 2 mol % of $BF_3{\cdot}Et_2O$ in THF, 76% of **2** was obtained (entry 12, Table 1) and thus this result was comparable to that in entry 2 of Table 1. Use of cetyltrimethylammonium bromide(CTAB) instead of PPNCl in the latter reaction gave only 23% of **2** with 15% of polyester(entry 13, Table 1). Consequently the very bulky [PPN] cation, by being weakly bound or close to the cobalt center, may enhance the catalytic activity.[9]

The scope of the epoxide carbonylation reaction was investigated with a variety of monosubstituted epoxides under the optimum reaction conditions (entry 2, Table 1). The carbonylation reaction occurred selectively at the unsubstituted C–O bond of the epoxide ring, with only

Table 2. Carbonylation of Epoxides to β-Lactones

entry	epoxide	condition[a]	time	product(isolated yield,%)
1	 **4a**	A	24	 **5a** (66)
2	 **4b**	A	24	 **5b** (77)
3	 **4c**	B	48	 **5c** (63)
4	 **4d**	B	48	 **5d** (87)
5	 **4e**	B	48	 **5e** (83)
6	 **4f**	B	24	- (no reaction)
7	 **4g**	A	24	 **5g** (57)
8	 **4h**	B	48	 **5h** (86)
9	 **4i**	C	48	 **5i** (20)
10	 **4j**	C	48	 **5j** (24)
11	 **4k**	D	24	 **5k** (44)

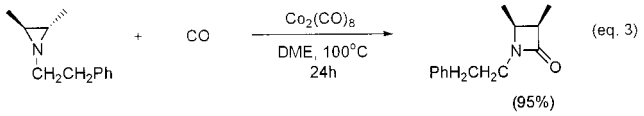
[a] Condition A: 5 mmol of epoxide, 0.1 mmol (2 mol %) of **3** and 0.1 mmol (2 mol %) of $BF_3.Et_2O$ in 10 mL of DME at 80 °C under 900 psi of CO. Condition B: 2.5 mmol of epoxide was used instead of 5 mmol. Condition C: $B(C_6F_5)_3$ was used instead of $BF_3{\cdot}Et_2O$, 2.5 mmol of epoxide, reaction was run at 110 °C. Condition D: 20 mmol of epoxide was used instead of 5 mmol.

a trace amount of the regioisomer detected by ^{1}H NMR in several cases. Furthermore, this reaction tolerates various functional groups such as alkenyl (**4c, 4d**), halide (**4e**), hydroxy (**4g**), and alkyl ether (**4h**), affording the corresponding β-lactones **5** in 57–87% yields. An aryl-substituted epoxide, styrene oxide (**4f**), was recovered unchanged on attempted carbonylation even under higher reaction temperatures (130 °C) (entry 6, Table 2). In the case of alkyl-substituted epoxides, the reactions of longer alkyl chain substituted epoxides (**4a**, **4b**) were slower than that of propylene oxide and needed 2 mol % of catalyst to complete the reactions (compare entry 2 of Table 1 with entries 1 and 2 of Table 2). Reactions of functionally substituted epoxides required 4 mol % of catalyst and longer reaction times (48 h) (entries 3, 4, 5 and 8, Table 2). In the case of disubstituted epoxide, *trans*-2,3-epoxybutane (**4i**), the reaction did not proceed under the optimum conditions. However, when $B(C_6F_5)_3$ was used instead of $BF_3{\cdot}Et_2O$ at 110 °C, the corresponding β-lactone, **5i**, was formed in 20% yield (the unreacted **4i** was recovered) with retention of stereochemistry (entry 9, Table 2).[10] To confirm the stereochemistry of this reaction, we also reacted *cis*-2,3-epoxybutane (**4j**) under the same reaction conditions, and also obtained the corresponding cis-disubstituted β-lactone, **5j**, in 24% yield with retention of stereochemistry (entry 10, Table

(9) Kondo, T.; Okada, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 4123.

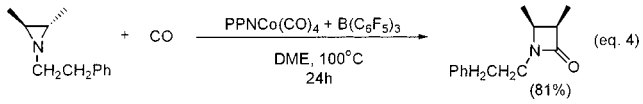
(10) The stereochemistry of **5i** was determined by ^{1}H NMR and is in accordance with literature data. Dervan, P. B.; Jones, C. R. *J. Org. Chem.* **1979**, *44*, 2116.

2). The results of the stereochemistry for these reactions are opposite to those for the $Co_2(CO)_8$-catalyzed synthesis of β-lactams from aziridines and carbon monoxide which resulted in inversion of stereochemistry[1e] (eq 3). To make



certain that the stereochemical results were directly comparable, *trans*-2,3-dimethyl-1-(2-phenylethyl)aziridine was subjected to carbonylation using the **3**/$B(C_6F_5)_3$ catalyst system instead of $Co_2(CO)_8$. Indeed, as in the case of the aziridine $Co_2(CO)_8$ carbonylation reaction, the corresponding *cis*-3,4-dimethyl-1-(2-phenylethyl)-2-azetidinone was obtained in 81% yield with inversion of stereochemistry (eq 4). These results raise intriguing questions regarding the difference in the stereochemistry of carbonylation reactions using epoxides and aziridines with the same catalytic system.

Finally, the parent epoxide, ethylene oxide (**4k**), was carbonylated to β-propiolactone (**5k**), and the reaction was completed within 24 h in the presence of 0.5 mol % of catalyst only. Although, no major side products or polymer were formed, the isolated yield was only 44% due to the instability and low boiling point of **5k** (entry 11, Table 2).



In conclusion, $PPNCo(CO)_4$ and $BF_3{\cdot}Et_2O$ is a useful catalytic system for the regioselective carbonylation of aliphatic epoxides to β-lactones. Yields are often appreciably higher when compared with other known catalyst systems (e.g., $Co_2(CO)_8$, $Co_2(CO)_8$/pyridine, $Co_2(CO)_8$/3-hydroxypyridine, and $RhCl(CO)(PPh_3)_2$).

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Supporting Information Available: Experimental details for the synthesis of β-lactones and spectral and analytical data of new compounds (**5b**, **5c**, **5d**, and **5h**). This material is available free of charge via the Internet at http://pubs.acs.org.

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