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Practical β-Lactone Synthesis: Epoxide Carbonylation at 1 atm

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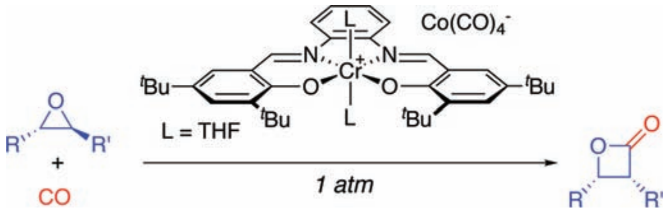
ABSTRACT

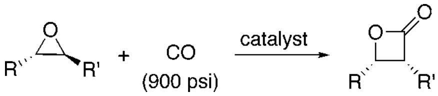


A readily prepared bimetallic catalyst is capable of effecting epoxide carbonylation to produce β-lactones at substantially lower CO pressures than previously reported catalyst systems. A functionally diverse array of β-lactones is produced in excellent yields at CO pressures as low as 1 atm. This procedure allows for epoxide carbonylation on a multigram scale without the requirement of specialized, high-pressure equipment.

There is a wide range of applications for β-lactones in both organic chemistry and polymer synthesis.[1] In organic chemistry, β-lactones are attractive intermediates and are frequently targeted as potentially bioactive compounds due to their prevalence in natural products.[2] The majority of reactions involving β-lactones entails ring opening, including polymerization to yield poly(β-hydroxyalkanoate)s (PHAs), a class of biodegradable polymeric materials.[3,4] Given the relationship between PHA structure and properties,[5] access to a diverse array of β-lactones allows the production of new PHAs for use in a variety of applications, ranging from commodity materials to biomedical products.[3,5] Despite the established relevance of β-lactones in synthetic chemistry, their syntheses have been limited to a few methods.[6] Among these methods, epoxide carbonylation is emerging as a versatile route because of the extensive availability of substrates in both racemic and enantiomerically pure form.[7]

Catalytic carbonylation of epoxides to β-lactones (Scheme 1) was first disclosed over a decade ago.[8] Further investigation highlighted the importance of a Lewis acid component for enhanced catalytic activity.[9] Though a number of systems capable of effecting epoxide carbonylation have since been

Scheme 1. β-Lactone Synthesis by Epoxide Carbonylation.



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[1] For a review of β-lactones in organic chemistry, see: Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605−658. For a review of relevant polymers, see: Müller, H.-M.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 477−502.

[2] Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729−744.

[3] For a review of PHAs, see: Lenz, R. W.; Marchessault, R. H. *Biomacromolecules* **2005**, *6*, 1−8.

[4] For ring-opening polymerization of β-lactones, see: (a) Tanahashi, N.; Doi, Y. *Macromolecules* **1991**, *24*, 5732−5733. (b) Hori, Y.; Suzuki, M.; Yamaguchi, A.; Nishishita, T. *Macromolecules* **1993**, *26*, 5533−5534. (c) Rieth, L. R.; Moore, D. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 15239−15248.

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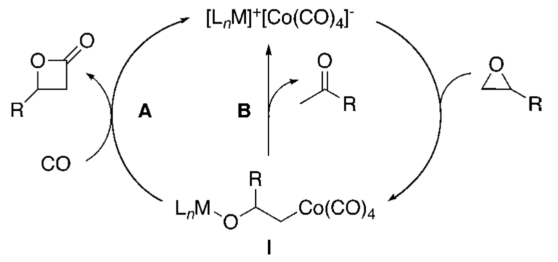
reported,[10] the well-defined catalysts of the general form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ developed in our laboratory are the most active and selective.[11] Unfortunately, the high pressure of CO (200−900 psi) necessary for efficient and selective carbonylation limits the use of these catalysts in general laboratory applications. Thus, a catalyst that is efficient under mild conditions and low pressures of CO would be a significant advance, enabling the widespread use of epoxide carbonylation as a route to β-lactones. Herein, we report a readily synthesized catalyst that is capable of epoxide carbonylation to produce a functionally diverse set of β-lactones with minimal side-product formation at CO pressures as low as 1 atm.

When our previously reported catalysts are reacted at CO pressures below 200 psi, a reduction in activity is observed, concomitant with the significant production of ketone as a side product.[11d] This ketone is likely the result of the non-carbonylative rearrangement[12] of a ring-opened epoxide intermediate (Scheme 2). Our proposed catalytic cycle for epoxide carbonylation begins with ring opening to form a metal-alkoxide/cobalt-alkyl species (**I**, Scheme 2).[11a] Under high-pressure conditions, rapid CO insertion into the cobalt-alkyl bond followed by ring closing results in β-lactone formation and regeneration of the catalyst (pathway **A**).[13] However, if intermediate **I** is sufficiently long-lived (as we propose is the case under lower CO pressures because of the reversibility of CO insertion),[14] the cobalt-alkyl of **I** can undergo β-hydride elimination followed by enolate protonation and tautomerization (pathway **B**) to afford the observed ketone.[15]

Scheme 2. Mechanism for Epoxide Carbonylation (Pathway **A**) and Competing Ketone Formation (Pathway **B**) from a Common Intermediate (**I**).



During the examination of catalysts containing different Lewis acids, we discovered that [(salph)Cr(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (**1**, Figure 1, salph = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-phenylenediamine) was a highly active catalyst for epoxide carbonylation under our standard conditions (neat epoxide, 900 psi CO, 60 °C). Catalyst **1** is readily synthesized using modified literature procedures.[11a,16,17] In screening reactions at 100 psi CO with several epoxide carbonylation catalysts, **1** displayed the highest activity and selectivity for β-lactone formation.[18] A CO pressure of 100 psi is noteworthy as it allows the carbonylation reactions to be performed in sealed glass reactors[18] which are significantly more practical and less expensive than high-pressure, stainless steel reactors. One possible explanation for the differences between carbonylation catalysts at lower CO pressures is that **1** allows a faster ring-closing event relative to ketone formation; further exploration of this postulate is currently being pursued in our laboratory.

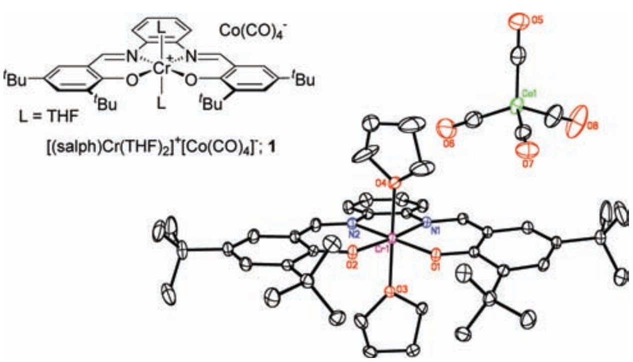


Figure 1. Catalyst **1** with its crystal structure drawn with 40% thermal ellipsoids.

Optimization of the conditions necessary for efficient carbonylation of epoxides by **1** at 100 psi CO highlighted two important features. First, the judicious choice of reaction solvent is necessary to maintain catalyst activity and selectivity for lactone formation. It was found that weakly coordinating, polar solvents such as 1,2-difluorobenzene and 1,2-dimethoxyethane (DME) were optimal. More strongly coordinating solvents such as THF and acetonitrile drastically reduced the rate of catalysis. Second, although higher temperatures increased the rate of reaction, the selectivity for lactone over ketone formation was compromised. Thus, subsequent reactions were performed at room temperature (22 °C) using DME as the solvent to favor efficient and selective lactone formation.

Encouraged by the high activity and selectivity **1** displayed for carbonylation at 100 psi CO, we sought to determine

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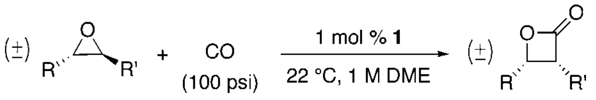
[17] Catalyst **1** was subjected to crystallographic analysis. CCDC-601862 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] See Supporting Information.

Table 1. Epoxide Carbonylation at 100 psi CO Using **1**[a]



entry	R	R′	time (h)	yield[b] (%)
1	Me	H	2	>98
2	Et	H	1	>98
3	$(CH_2)_9CH_3$	H	2	>98
4	$(CH_2)_2CH{=}CH_2$	H	2	>98
5	$CH_2OCH_2CH{=}CH_2$	H	1	>98
6	CH_2O^nBu	H	1	>98 (88)[c]
7	$CH_2OSiMe_2{}^tBu$	H	1	>98
8	$CH_2OC(O)CH_3$	H	2	>98
9	$CH_2OC(O)Ph$	H	3	>98
10	CH_2Cl	H	3	>98
11[d]	Me	Me	8	>98[e]

[a] All reactions were stirred in a 60-mL Fisher-Porter bottle using 2 mmol of epoxide in 2 mL of DME and 1 mol % of **1** at 22 °C, unless noted otherwise. [b] Yield determined by ^{1}H NMR spectroscopy; β-lactone was the exclusive product. [c] Isolated yield from a 1-g scale reaction. [d] 2 mol % of **1**. [e] Product lactone was >99% cis.

the scope of viable substrates for this reaction. Table 1 shows the results from the carbonylation of a variety of epoxides using 1 mol % of **1** at 100 psi CO. Each monosubstituted epoxide examined was cleanly carbonylated to the corresponding β-lactone within 3 h. The alkyl-substituted epoxides (entries 1−3), epoxides with terminal alkenes (entries 4 and 5), and glycidyl ethers (entries 5−7) were carbonylated quickly, regardless of steric bulk. This is consistent with the proposed mechanism for β-lactone formation, in which $[Co(CO)_4]^-$ ring opens the epoxide at the less-substituted carbon.[19] Glycidyl esters (entries 8 and 9) were also amenable to low-pressure carbonylation. Epichlorohydrin (entry 10) is a traditionally challenging substrate for carbonylation.[9,11a,b] Though epichlorohydrin was slower to react than comparable alkyl-substituted epoxides, the corresponding 4-chloromethyl-2-propiolactone was quantitatively produced in 3 h using **1**.[20] The disubstituted *trans*-2,3-epoxybutane (entry 11) was slower to react, requiring 8 h and 2 mol % of **1** to achieve quantitative conversion to the corresponding *cis*-3,4-dimethyl-2-propiolactone. The observed decrease in reaction rate with *trans*-2,3-epoxybutane is likely the result of cobaltate attack at a more substituted carbon during ring opening.

The carbonylation of cyclooctene oxide, which has been reported at 900 psi CO and 60 °C,[11c,d] initially appeared unattainable under low-pressure conditions. Preliminary attempts at 22 °C and 100 psi CO did not convert any epoxide to lactone. However, upon increasing the epoxide concentration to 2 M in DME and heating the reaction to 60 °C, β-lactone was produced without the significant ketone production that plagued monosubstituted epoxides at elevated temperatures.[21] Thus, in 24 h at 60 °C, cyclooctene oxide was converted to *trans*-9-oxabicyclo[6.2.0]decan-10-one in 94% yield (Figure 2) with just 3% ketone and 3% unreacted epoxide.

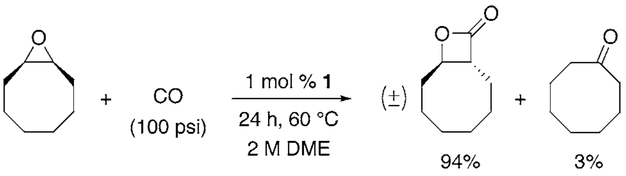
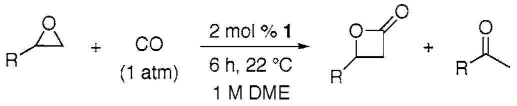


Figure 2. Cyclooctene oxide carbonylation at 100 psi CO.

Because **1** showed excellent results at 100 psi CO, we were inspired to attempt the carbonylation of epoxides at 1 atm CO. There is precedent for epoxide carbonylation at 1 atm CO using $Co_2(CO)_8$,[22] though not for β-lactone synthesis. Toward this end, we devised a simple carbonylation procedure using standard glassware, eliminating the need for any specialized, high-pressure equipment.[18] Table 2 shows the results from a variety of carbonylation reactions using **1** under 1 atm CO. In general, the reaction proceeded more slowly than comparable reactions at higher CO pressures and thus required slightly longer reaction times and 2 mol % of catalyst, but this procedure was very efficient at producing β-lactone despite the mild conditions.[23] Similar to the carbonylation at 100 psi CO, this method was applicable to a variety of functional groups, including alkyls (entries 1−3),

Table 2. Epoxide Carbonylation at 1 atm CO Using **1**[a]



entry	R	conversion[b] (%)	β-lactone:ketone[b]
1	Me	>98	96:4
2	Et	>98	97:3
3	$(CH_2)_9CH_3$	>98	99:1
4	$(CH_2)_2CH{=}CH_2$	>98	95:5
5	$CH_2OCH_2CH{=}CH_2$	>98	93:7
6	CH_2O^nBu	>98	89:11
7	$CH_2OSiMe_2{}^tBu$	>98	96:4
8	$CH_2OC(O)CH_3$	>98	95:5
9	$CH_2OC(O)Ph$	89[c]	95:5
10	CH_2Cl	35[c]	89:11

[a] Carbonylation reactions performed in a CO-filled round-bottom flask with 2 mmol of epoxide, 2 mL of DME, and 2 mol % of **1**. [b] Conversion and product ratios determined by ^{1}H NMR spectroscopy. [c] Remainder was unreacted epoxide.

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(19) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *Pure Appl. Chem.* **2004**, *76*, 557−564.

(20) Although epichlorohydrin carbonylation has been described (see refs 9, 11a, and 11b), no reported catalysts provide quantitative carbonylation.

(21) Internal epoxides have been reported to rearrange to a ketone much slower than their terminal analogues. See ref 15 for relevant examples.

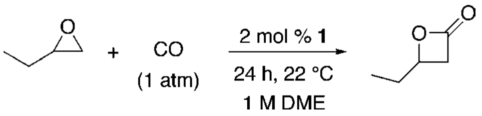
(22) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703−4705.

alkenes (entries 4 and 5), ethers (entries 5−7), and esters (entries 8 and 9). Epichlorohydrin (entry 10) was not carbonylated in high yield under these conditions, though no side reactions were apparent. Though glycidyl ethers without sterically bulky substituents (entries 5 and 6) reacted quickly, they displayed a greater tendency to rearrange to a ketone. The bulkier *tert*-butyldimethylsilyl glycidyl ether (entry 7) did not suffer from increased ketone production.

To increase the preparative value of this procedure, we developed a method to perform the 1-atm carbonylation of an epoxide on a larger scale. An initial reaction with 500 mg (6.9 mmol) of 1,2-epoxybutane (EB) was executed without complications (Table 3, entry 1). However, epoxide carbonylation on the gram scale presented two issues. First, the 500-mL flask held only a substoichiometric quantity of CO; the addition of a balloon of CO eliminated this problem. Second, scaling the reaction to 2 g of EB (Table 3, entry 2) resulted in a noticeable exotherm upon epoxide addition, which caused the observed decrease in selectivity. To control this exotherm, the catalyst solution was cooled to 0 °C and EB was added slowly via an addition funnel.[18] When addition was complete, the ice bath was removed and the reaction was stirred for the indicated time. This method enabled the clean carbonylation of 5 g of EB (Table 3, entry 4) with minimal 2-butanone production.

The increasing significance of β-lactones in synthetic chemistry has generated a great deal of interest in their efficient syntheses. This work reports the first example of epoxide carbonylation to form β-lactones at CO pressures as low as 1 atm. As functionalized and enantiopure epoxides are readily accessible, it is our expectation that the facile synthesis of **1**, coupled with its ability to carbonylate these substrates on a multigram scale under mild conditions, will enable the practical synthesis of β-lactones.

Table 3. Epoxide Carbonylation at a Larger Scale Using **1** at 1 atm CO[a]



entry	epoxide (g)	temp[b] (°C)	conversion[c] (%)	β-lactone:ketone[c]
1[d]	0.5	22	>98	98:2
2	2.0	22	>98	85:15
3	2.0	0	>98	95:5
4	5.0	0	>98	94:6

[a] Reactions performed in a 500-mL, three-neck round-bottom flask with a CO-filled balloon. [b] Temperature at which the epoxide was added to the catalyst solution; all reactions were conducted at 22 °C. [c] Conversion and product ratios determined by ^{1}H NMR spectroscopy. [d] No CO balloon attached.

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Supporting Information Available: Synthesis and characterization of catalyst **1**, screening results with previously reported carbonylation catalysts at low CO pressures, and the general procedures for 100 psi and 1 atm carbonylations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Though this procedure produces small amounts of ketone as a side product, the ketone and lactone can easily be separated because of the large disparity in their boiling points (e.g., acetone bp = 56 °C at 760 mmHg, β-butyrolactone bp = 72 °C at 29 mmHg).