ORGANIC LETTERS

2004
Vol. 6, No. 3
373−376

# A Readily Synthesized and Highly Active Epoxide Carbonylation Catalyst Based on a Chromium Porphyrin Framework: Expanding the Range of Available *β*-Lactones

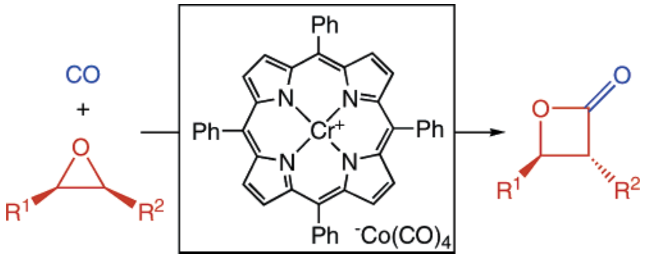
**Joseph A. R. Schmidt, Viswanath Mahadevan, Yutan D. Y. L. Getzler, and Geoffrey W. Coates***

*Department of Chemistry and Chemical Biology, Baker Laboratory,*
*Cornell University, Ithaca, New York 14853-1301*

*gc39@cornell.edu*

Received November 17, 2003

## ABSTRACT



**Catalytic carbonylation of epoxides to *β*-lactones was effected by a highly active and selective bimetallic catalyst comprised of a chromium(III) porphyrin cation and a cobalt tetracarbonyl anion. The complex is readily synthesized from commercially available compounds in high yield. Carbonylation of numerous linear epoxides, as well as bicyclic epoxides derived from 8- and 12-membered hydrocarbons, proceeded with high activity, selectivity, and yield.**

The use of *β*-lactones in organic synthesis has been documented in numerous reports.[1] *β*-Lactones display a range of reactivity including decarboxylation in a syn fashion to produce the corresponding alkene, Lewis acid promoted ring-expansion to yield *γ*-lactones, and enolate reactions.[1] Another useful reaction sequence involves nucleophilic attack of the carbonyl moiety, followed by ring-opening of the acyl-oxygen bond and trapping with an electrophile.[1] A recent elegant example invoking similar reaction intermediates involves the in situ carbonylation of isopropyl glycidyl ether in the presence of 4-(trimethylsilyl)morpholine to yield a *β*-silyloxy morpholine amide.[2] *β*-Lactones also find wide utility as monomers in polymer synthesis; ring-opening polymerization yields poly(hydroxyalkanoate)s (PHAs),[3] biodegradable polyesters presently targeted for commercial production.

Although a wide array of synthetic methods exist for the synthesis of lactones of larger size, the four-membered rings found in *β*-lactones are among the most challenging to synthesize due to their inherent ring strain.[4] We have investigated the catalytic synthesis of *β*-lactones through the carbonylation of epoxides, since epoxides are easy to

---

(1) For a review of *β*-lactone reactivity see: Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441−459.

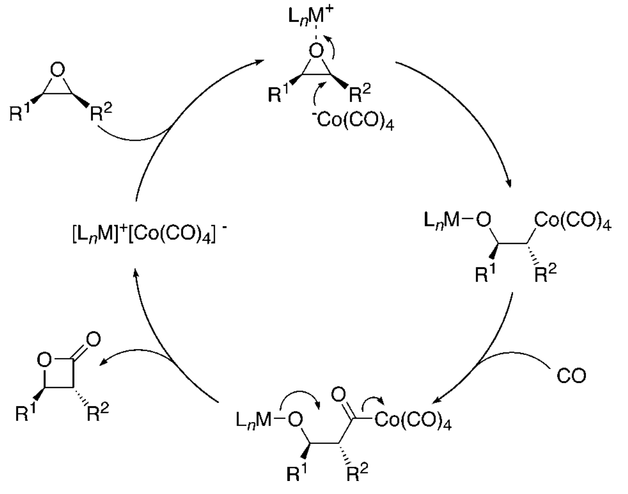
(2) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703−4705.

(3) Rieth, L. R.; Moore, D. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 15239−15248.

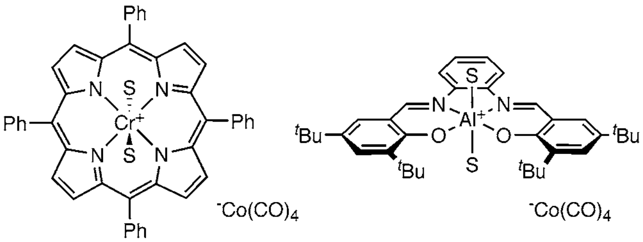
(4) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434.

10.1021/ol036244g CCC: $27.50

**Scheme 1.** Proposed Mechanism of Epoxide Carbonylation



synthesize, inexpensive, and readily available in an enantiomerically pure form.[5,6] The initial reports of epoxide carbonylation catalysts can be found in the patent literature, where a mixture of $Co_2(CO)_8$ and hydroxypyridine was employed.[7] The work of Alper using $[Ph_3P{=}N{=}PPh_3][Co(CO)_4]$ activated with Lewis-acidic $BF_3{\cdot}OEt_2$ for regioselective epoxide carbonylation advanced the field substantially, providing lactones at turnover frequencies as high as 3.2 $h^{-1}$.[8] Our initial contributions included the isolation and characterization of two well-defined bimetallic Al/Co and Ti/Co catalysts of the general form [Lewis acid][$Co(CO)_4$], which exhibited higher activities and selectivities than previous systems.[9,10] On the basis of known reactions,[11,12] a plausible catalytic cycle for this epoxide carbonylation was proposed (Scheme 1).[9,10] Rieger and co-workers have recently reported DFT calculations that support this mechanism,[13] and have found that a mixture of $Co_2(CO)_8$ and $Me_3Al$ exhibits excellent activity and moderate selectivity for the conversion of propylene oxide to $\beta$-butyrolactone.[14] Ongoing investigation in our research group has included screening a wide array of complexes of the form [Lewis acid][$Co(CO)_4$] as a means for discovery of the next generation of epoxide carbonylation catalysts. Herein, we report the development of a new catalyst in which a Cr(III) porphyrin comprises the cationic Lewis acid. This compound exhibits substantially increased activity compared to previously published Al and Ti catalysts, and produces $\beta$-lactones in exceptionally high yield and purity. In addition, the catalyst has proven useful in the production of an array of mono- and bicyclic $\beta$-lactones.



[(TPP)Cr(THF)$_2$][Co(CO)$_4$]
**1**

[(salph)Al(THF)$_2$][Co(CO)$_4$]
**2**

**Figure 1.** Catalysts for epoxide carbonylation (S = THF).

The porphyrin catalyst [(TPP)Cr(THF)$_2$][Co(CO)$_4$] (**1**, Figure 1) was synthesized by the metathesis of (TPP)CrCl[15] with $NaCo(CO)_4$. Catalyst workup was minimal, as filtration of the resulting reaction mixture removes the NaCl byproduct, in addition to a small amount of a chromium oxo species that was found to contaminate the commercially available (TPP)CrCl. Evaporation of the reaction solvent gave a paramagnetic purple solid in 81% yield, and the complex was employed without further purification.[16]

Initially, screening of **1** carried out with simple 1,2-epoxyalkanes revealed activities much higher than had been previously observed in our Al- and Ti-based systems. Consequently, optimization of this new catalyst (**1**) was pursued. The following reaction parameters were chosen by means of convenience and versatility: neat substrate, 900 psi of CO, 60 °C, 6 h. Under these conditions, the maximal substrate to catalyst loadings were determined, with generation of >99% yield of the product lactone, whenever possible.

As shown in Table 1, catalyst **1** reacted with numerous epoxides to form the corresponding $\beta$-lactones. Carbonylation of 1,2-epoxyalkanes was effective for a variety of chain lengths ($C_4$−$C_{12}$), with complete conversion at substrate to catalyst loadings of 300:1 or higher (Table 1, entries 1−4). The product lactones from these reactions have potential utility in the synthesis of poly(hydroxyalkanoate) (PHA) copolymers with tailored composition.[3] The highest epoxide loading (800:1) was achieved in the carbonylation of *tert*-butyloxirane (Table 1, entry 5), yielding a $\beta$-*tert*-butyl-$\beta$-lactone. Catalyst **1** is tolerant of alkene functionality, as noted by its ability to effectively carbonylate 250 equiv of 1,2-epoxy-5-hexene (Table 1, entry 6). Additionally, glycidyl ethers could be carbonylated effectively to form hydroxy-

---

(5) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.

(6) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(7) Drent, E.; Kragtwijk, E. Shell Internationale Research Maatschappij B. V., Netherlands, European Patent Application EP 577206; *Chem. Abstr.* **1994**, *120*, 191517c.

(8) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 5424−5426.

(9) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174−1175 and references therein.

(10) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781−2784 and references therein.

(11) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518−521.

(12) Roe, D. C. *Organometallics* **1987**, *6*, 942−946.

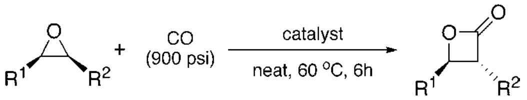
(13) Molnar, F.; Luinstra, G. A.; Allmendinger, M.; Rieger, B. *Chem. Eur. J.* **2003**, *9*, 1273−1280.

(14) Allmendinger, M.; Eberhardt, R.; Luinstra, G. A.; Molnar, F.; Rieger, B. *Z. Anorg. Allg. Chem.* **2003**, *629*, 1347−1352.

(15) TPP = 5,10,15,20-tetraphenylporphyrin.

(16) Despite repeated crystallization attempts, crystals of X-ray quality proved elusive for catalyst **1**.

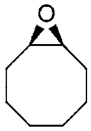
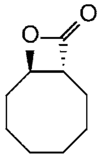
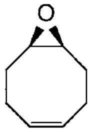
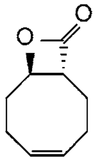
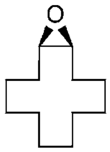
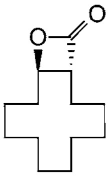
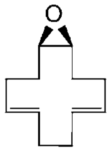
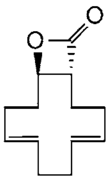
**Table 1.** Epoxide Carbonylation with [(TPP)Cr(THF)$_2$][Co(CO)$_4$] (**1**) and [(salph)Al(THF)$_2$][Co(CO)$_4$] (**2**)



| entry | R$^1$ | R$^2$ | substrate: catalyst | yield$^a$ (%) | |
|---|---|---|---|---|---|
| | | | | 1 | 2 |
| 1 | Et | H | 300:1 | >99 | 60 |
| 2 | *n*Bu | H | 350:1 | >99 | 40 |
| 3 | $CH_3(CH_2)_4$ | H | 350:1 | >99 | 40 |
| 4 | $CH_3(CH_2)_9$ | H | 450:1 | >99 | 10 |
| 5 | *t*Bu | H | 800:1 | >99 | 0 |
| 6 | $H_2C{=}CH(CH_2)_2$ | H | 250:1 | >99 | 40 |
| 7 | *n*BuOCH$_2$ | H | 200:1 | >99 | >99 |
| 8 | TBDMSOCH$_2$$^b$ | H | 400:1 | >99 | 30 |
| 9 | *trans*-CH$_3$ | CH$_3$ | 75:1 | >99 | 74 |
| 10 | *cis*-CH$_3$ | CH$_3$ | 75:1 | 56 | 20 |

[a] Determined by $^1$H NMR spectroscopy. [b] TBDMS = *tert*-butyldimethylsilyl.

**Table 2.** Carbonylation of Bicyclic Epoxides with [(TPP)Cr(THF)$_2$][Co(CO)$_4$] (**1**) and [(salph)Al(THF)$_2$][Co(CO)$_4$] (**2**)[a]

| entry | substrate | substrate: catalyst | product | yield$^b$ (%) | |
|---|---|---|---|---|---|
| | | | | 1 | 2 |
| 1 |  | 250:1 |  | > 99% | 10% |
| 2 |  | 175:1 |  | > 99% | 20% |
| 3 | <br>66% *cis* | 450:1 |  | 66% (97% *trans*) | 0% |
| 4 | <br>13% *cis* | 200:1 |  | 35% (34% *trans*) | 0% |

[a] Conditions: 60 °C, 6 h, 900 psi of CO. [b] Determined by $^1$H NMR spectroscopy.

lactone derivatives, as evidenced by the use of *n*-butyl glycidyl ether and *tert*-butyldimethylsilyl glycidyl ether as carbonylation substrates (Table 1, entries 7 and 8). It was also found that **1** carbonylated 2,3-epoxybutanes; however, reaction with *cis*-2,3-epoxybutane suffered from deleterious polymerization pathways, limiting product yield to 56% (Table 1, entries 9 and 10). In all cases, the product lactones were readily purified by vacuum distillation.

In our previous reports, [(salph)Al(THF)$_2$][Co(CO)$_4$] (**2**, Figure 1) was shown to be an effective carbonylation catalyst.[9,17] To the best of our knowledge, **2** was the most active and selective catalyst known for the carbonylation of a wide range of epoxides.[18] Thus, we compared the activity of **2** to the newly developed catalyst, **1**. Table 1 shows the activity of catalyst **2** with identical reaction conditions to those reported for **1**.[19] From these data, it can be seen that **1** is substantially more active than **2** in nearly every case. In addition, catalyst **1** does not suffer significantly from the detrimental side reactions sometimes present with **2**, such as polymerization and isomerization to ketones.

Next, we set out to synthesize a series of bicyclic $\beta$-lactones, compounds with broad synthetic utility. It is notable that the ability to synthesize bicyclic $\beta$-lactones catalytically may have relevance to the application of **1** in the synthesis of natural products[20] and pharmaceuticals.[21] As shown in Table 2, catalyst **1** readily carbonylated epoxides of 8- and 12-membered cyclic hydrocarbons. Cyclooctene oxide and cyclooctadiene monoxide, both present as exclusively *cis*-epoxides, were transformed into the *trans*-lactones (Table 2, entries 1 and 2). Although cyclooctene oxide exists as a solid under ambient conditions, within the reactor, carbonylation of this material takes place in the melt. Careful thermolysis of the product lactones yielded the *trans*-alkenes through loss of CO$_2$, confirming the production of *trans*-lactones from these *cis*-epoxides.[22−24] In the case of the 12-membered-ring substrates, the *cis*-epoxides were found to carbonylate much more readily than the trans isomers. For cyclododecene oxide, the commercially available material was composed of 66% *cis*-epoxide, after vacuum distillation from CaH$_2$. Carbonylation of this mixture of isomers showed formation of *trans*-lactone primarily (by consumption of *cis*-epoxide), with only trace *cis*-lactone production. Table 2 shows the results for a loading of 450:1 (entry 3), while the results with other substrate:catalyst ratios are provided in the Supporting Information. Finally, cyclododecatriene monoxide was also applied as a substrate for this catalytic system. The material used contained only

---

(17) Salph = *N,N*′-bis(3,5-di-*tert*-butylsalicylidene)phenylenediamine.

(18) Recent reports on the carbonylation of propylene oxide have shown exceptional turnover frequencies (320 h$^{-1}$) when employing conditions of 105 °C and 60 bar of CO, although lactone selectivity in these reactions is limited to 91%, see ref 14.

(19) Due to differences in heat flow and reactor volume, catalyst activity comparisons are less reliable when data from multiple high-pressure reactors are used. For this reason, all reactions detailed in this report were performed in a single reactor.

(20) Pommier, A.; Pons, J. M. *Synthesis* **1995**, 729−744.

(21) For a review of carbocyclic eight-membered rings see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821.

(22) Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* **1972**, *94*, 2000−2006.

(23) Noyce, D. S.; Banitt, E. H. *J. Org. Chem.* **1966**, *31*, 4043−4047.

(24) Cope, A. C.; Howell, C. F.; Bowers, J.; Lord, R. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1967**, *89*, 4024−4027.

13% *cis*-epoxide;[25] results from a 200:1 loading are presented for this substrate (Table 2, entry 4). Catalyst **2** was also investigated with these substrates for comparison purposes, and yields again confirm the enhanced activity of catalyst **1** (Table 2).

In summary, we report the development of a highly active and versatile new catalyst for the carbonylation of epoxides. By comparison with our previous system **2**, we have shown that $[(TPP)Cr(THF)_2][Co(CO)_4]$ (**1**) is the most active and selective carbonylation catalyst to date for a wide range of epoxides. In addition, catalyst **1** effectively carbonylates bicyclic epoxides, providing an array of new bicyclic $\beta$-lactones for exploration. Our ongoing pursuits include investigation of more cost-effective carbonylation catalysts derived from simple metal-halides directly, as well as exploring the utility of the lactones presented in this paper as monomers for the synthesis of new polymers with interesting properties.

**Acknowledgment.** G.W.C. gratefully acknowledges a Packard Foundation Fellowship in Science and Engineering and an Arnold and Mabel Beckman Foundation Young Investigator Award, as well as funding from the NSF (CHE-0243605) and Metabolix, Inc. This material is based upon work supported in part by the U.S. Army Research Laboratory and the U.S. Army Research Office under grant number DAAD19-02-1-0275 Macromolecular Architecture for Performance (MAP) MURI.

**Supporting Information Available:** Synthesis and characterization of catalyst **1**, general procedure for epoxide carbonylation, full characterization of all previously unpublished lactones, and a table of product distributions for various substrate:catalyst ratios in the carbonylation of cyclododecene oxide. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036244G

---

[25] One *trans*- and two *cis*-lactone isomers are produced upon carbonylation of cyclododecatriene monoxide (see the Supporting Information).