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Catalytic Double Carbonylation of Epoxides to Succinic Anhydrides: Catalyst Discovery, Reaction Scope, and Mechanism

John M. Rowley, Emil B. Lobkovsky, and Geoffrey W. Coates*

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

Received September 25, 2006; E-mail: gc39@cornell.edu

Abstract: The first catalytic method for the efficient conversion of epoxides to succinic anhydrides via one-pot double carbonylation is reported. This reaction occurs in two stages: first, the epoxide is carbonylated to a β-lactone, and then the β-lactone is subsequently carbonylated to a succinic anhydride. This reaction is made possible by the bimetallic catalyst $[(ClTPP)Al(THF)_2]^+[Co(CO)_4]^-$ (**1**; ClTPP = *meso*-tetra(4-chlorophenyl)porphyrinato; THF = tetrahydrofuran), which is highly active and selective for both epoxide and lactone carbonylation, and by the identification of a solvent that facilitates both stages. The catalysis is compatible with substituted epoxides having aliphatic, aromatic, alkene, ether, ester, alcohol, nitrile, and amide functional groups. Disubstituted and enantiomerically pure anhydrides are synthesized from epoxides with excellent retention of stereochemical purity. The mechanism of epoxide double carbonylation with **1** was investigated by in situ IR spectroscopy, which reveals that the two carbonylation stages are sequential and non-overlapping, such that epoxide carbonylation goes to completion before any of the intermediate β-lactone is consumed. The rates of both epoxide and lactone carbonylation are independent of carbon monoxide pressure and are first-order in the concentration of **1**. The stages differ in that the rate of epoxide carbonylation is independent of substrate concentration and first-order in donor solvent, whereas the rate of lactone carbonylation is first-order in lactone and inversely dependent on the concentration of donor solvent. The opposite solvent effects and substrate order for these two stages are rationalized in terms of different resting states and rate-determining steps for each carbonylation reaction.

Introduction and Background

Succinic anhydrides and their derivatives have many applications in organic and polymer chemistry.[1] For example, their copolymerization with epoxides[2] or diols[3] yields biodegradable polyesters.[4] Anhydrides are also useful synthetic intermediates,[5] readily ring opened to diacids or other succinate derivatives; some examples of succinates include biologically active natural products,[6] pharmaceuticals,[7] and metalloprotease inhibitors.[8]

Substituted succinic anhydrides have previously been synthesized by a number of methods,[9] most often by the dehydration of the corresponding diacid or from maleic anhydride via Diels–Alder or Ene reactions.[10] They have also been made by metal-catalyzed carbonylation of alkynes,[11] alkenoic acids,[12] and lactones;[13,14] however, most of these catalytic reactions proceed either in low yield, with significant side products, or without demonstrating substrate generality or product stereochemical purity. Thus, the development of more efficient and stereoselective syntheses remains an important goal.

Over the past 6 years, our group has developed a class of well-defined bimetallic catalysts of the general type [Lewis acid]$^+$[Co(CO)$_4$]$^-$ for the ring-expanding carbonylation of strained heterocycles.[14–22] Within this class of catalysts, we have found that the identity of metal and ligand in the Lewis acid component has a profound effect on the activity and substrate scope of carbonylation. In particular, we recently reported that

(1) Fumagalli, C. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Kroschwitz, J. I., Howe-Grant, M., Eds.; John Wiley & Sons: New York, 1997; Vol. 22, pp 1074–1102.
(2) Maeda, Y.; Nakayama, A.; Kawasaki, N.; Hayashi, K.; Aiba, S.; Yamamoto, N. *Polymer* **1997**, *38*, 4719–4725.
(3) Ranucci, E.; Liu, Y.; Lindblad, M. S.; Albertsson, A. C. *Macromol. Rapid Commun.* **2000**, *21*, 680–684.
(4) Okada, M. *Prog. Polym. Sci.* **2002**, *27*, 87–133.
(5) For example, see: (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247–254. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2983. (c) Stoncius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2005**, 1829–1837.
(6) Wilkinson, R. A.; Strobel, G.; Stierle, A. *J. Nat. Prod.* **1999**, *62*, 358–360.
(7) (a) Yamaguchi, T.; Yanagi, T.; Hokari, H.; Mukaiyama, Y.; Kamijo, T.; Yamamoto, I. *Chem. Pharm. Bull.* **1998**, *46*, 337–340. (b) Bergmeier, S. C.; Ismail, K. A.; Arason, K. M.; McKay, S.; Bryant, D. L.; McKay, D. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3739–3742.
(8) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735–2776.
(9) Arason, K. M.; Bergmeier, S. C. *Org. Prep. Proced. Int.* **2002**, *34*, 337–366 and references therein.
(10) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
(11) For example, see: Chiusoli, G. P.; Costa, M.; Cucchia, L.; Gabriele, B.; Salerno, G.; Veltri, L. *J. Mol. Catal. A: Chem.* **2003**, *204*, 133–142 and references therein. In related chemistry, alkynes have been carbonylated to maleic anhydrides: Zargarian, D.; Alper, H. *Organometallics* **1991**, *10*, 2914–2921.
(12) For example, see: Osakada, K.; Doh, M. K.; Ozawa, F.; Yamamoto, A. *Organometallics* **1990**, *9*, 2197–2198.
(13) Mori, Y.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 777–779.
(14) Getzler, Y. D. Y. L.; Kundnani, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2004**, *126*, 6842–6843.

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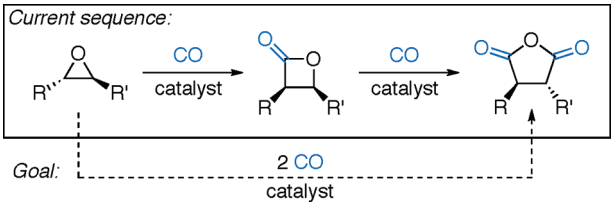
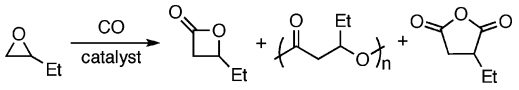
Scheme 1. One-Pot Double Carbonylation of Epoxides to Succinic Anhydrides



one such catalyst can carbonylate β-lactones to succinic anhydrides in high yields while preserving stereochemical purity.[14] Given the many syntheses of enantiomerically pure epoxides[23,24] and the recent advances in epoxide carbonylation to β-lactones, subsequent carbonylation of these lactones constitutes a versatile two-step method for the stereoselective synthesis of succinic anhydrides (Scheme 1). However, this method would be far more synthetically useful if the two steps could be consolidated, eliminating isolation and rigorous purification of toxic lactone intermediates, saving time and catalyst, and increasing overall yield. One-pot double carbonylations are known;[25] however, there are very few instances with an epoxide as the substrate. A rare example is the conversion of styrene oxide to the enol tautomer of 4,5-dihydro-4-phenylfuran-2,3-dione.[26] Our originally reported lactone carbonylation catalyst, $[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (**2**; salph = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-phenylenediamine; THF = tetrahydrofuran), produced trace amounts of succinic anhydrides directly from epoxides,[14] but we were unable to obtain anhydrides cleanly and in good yields with this or any of our previously reported carbonylation catalysts (vide infra). Herein, we report on $[(ClTPP)Al(THF)_2]^+[Co(CO)_4]^-$ (**1**; ClTPP = *meso*-tetra(4-chlorophenyl)porphyrinato), the first highly active and selective catalyst for the one-pot double carbonylation of epoxides to succinic anhydrides.

In the course of optimizing the double carbonylation of epoxides, we found that both carbonylation stages were rapid, yet none of the lactone intermediate was consumed until all of the epoxide had first been carbonylated, and that solvent greatly impacted the rate of each step. We[16,17,22] and others[27] have studied the mechanism of epoxide carbonylation, but no studies have investigated the mechanism of the catalytic interaction of $[Lewis\ acid]^+[Co(CO)_4]^-$ with other substrates.[28] Thus, we undertook a mechanistic investigation of double carbonylation with the following goals: (1) to compare the mechanism of epoxide to lactone carbonylation in this system with that of a previously reported system,[22] (2) to elucidate the mechanism and rate-determining step of lactone carbonylation, and (3) to understand the interplay between these reactions in double carbonylation, specifically the important role that solvent plays in these bimetallic $[Lewis\ acid]^+[Co(CO)_4]^-$ catalytic systems.

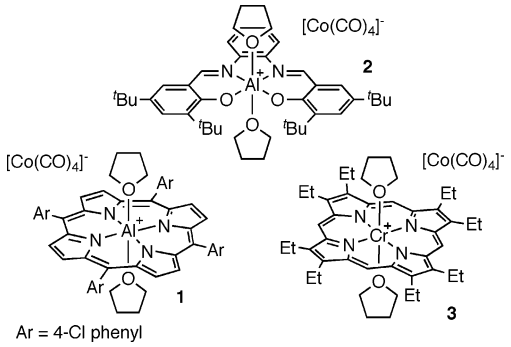
Table 1. Screening for One-Pot Double Carbonylation of 1-Butene Oxide[a]



			product distribution (%)		
entry	catalyst	solvent	lactone	polymer	anhydride
1	**2**	neat	99		
2	**2**	toluene	58[b]		
3	**3**	neat		93	7
4	**3**	toluene		67	33
5	**1**	neat		78	22
6	**1**	toluene			99

[a] Reaction conditions: 1.0 mol % catalyst, [epoxide] = 1.8 M in toluene or neat, 850 psi CO, 6 h, 60 °C. Product distribution determined by ^{1}H NMR spectra of crude reaction. [b] Remainder is starting epoxide.

Chart 1. Epoxide Carbonylation Catalysts



Results and Discussion

Catalyst Discovery. Our initial attempts to effect clean one-pot double carbonylation focused on the catalysts and conditions we have previously reported for ring-expansive epoxide and lactone carbonylation. The results of these studies are summarized in Table 1, entries 1−4. Although $[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (**2**, Chart 1) is the only catalyst reported for both epoxide[16] and β-lactone[14] carbonylation, these two independent reactions were found to be orthogonal, such that the reaction conditions, particularly solvent (vide infra), which facilitated the first carbonylation, severely limited the second, and vice

(15) For a review, see: Church, T. L.; Getzler, Y. D. Y. L.; Byrne, C. M.; Coates, G. W. *Chem. Commun.* **2007**, 657−674.
(16) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174−1175.
(17) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781−2784.
(18) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *Pure Appl. Chem.* **2004**, *76*, 557−564.
(19) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373−376.
(20) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426−11435.
(21) Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709−3712.
(22) Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc.* **2006**, *128*, 10125−10133.
(23) (a) Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; Wiley−VCH: Weinheim, 2006 and references therein. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488−496.
(24) 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.
(25) For a review, see: des Abbayes, H.; Salaun, J. Y. *J. Chem. Soc., Dalton Trans.* **2003**, 1041−1052.
(26) Alper, H.; Arzoumanian, H.; Petrignani, J. F.; Saldana-Maldonado, M. *J. Chem. Soc., Chem. Commun.* **1985**, 340−341.
(27) (a) Molnar, F.; Luinstra, G. A.; Allmendinger, M.; Rieger, B. *Chem.-Eur. J.* **2003**, *9*, 1273−1280. (b) Allmendinger, M.; Eberhardt, R.; Luinstra, G. A.; Molnar, F.; Rieger, B. *Z. Anorg. Allg. Chem.* **2003**, *629*, 1347−1352. (c) Allmendinger, M.; Zintl, M.; Eberhardt, R.; Luinstra, G. A.; Molnar, F.; Rieger, B. *J. Organomet. Chem.* **2004**, *689*, 971−979. (d) Stirling, A.; Iannuzzi, M.; Parrinello, M.; Molnar, F.; Bernhart, V.; Luinstra, G. A. *Organometallics* **2005**, *24*, 2533−2537.
(28) Mechanisms for lactone carbonylation have been proposed, but not studied in detail.[13,14]

versa. For example, whereas lactone formation was facile in neat epoxide (entry 1) or ether solvents, nonpolar conditions that favor anhydride formation[14] severely reduced epoxide carbonylation (entry 2). $[(OEP)Cr(THF)_2]^+[Co(CO)_4]^-$ (**3**, Chart 1; OEP = octaethylporphyrinato),[20] the most active catalyst reported for epoxide carbonylation, was considered with the hope that inhibition by nonpolar solvent would be mediated by the exceptional activity of the catalyst. Under typical conditions and catalyst loadings (<0.03 mol %), β-lactone was the only product observed for this system. However, significantly increasing the amount of catalyst to 1 mol % resulted in very rapid lactone formation, followed by slower conversion of lactone to low molecular weight poly(lactone) and a small amount of anhydride (entry 3). Even under favorable (nonpolar and diluted) conditions, polymer remains the major product (entry 4). Given the failure of these previously reported catalysts, conditions, and permutations thereof, it was clear that, to effect clean anhydride formation, the efficient double carbonylation of epoxides would require either a new catalyst, a new solvent, or both.

In the course of investigating the variation of metal and ligand in the cationic portion of our catalysts, we synthesized a series[29] of catalysts with porphyrin aluminum cations such as **1** (Chart 1). As expected, the solid-state structure of **1** (Figure 1) had several key features in common with previously reported

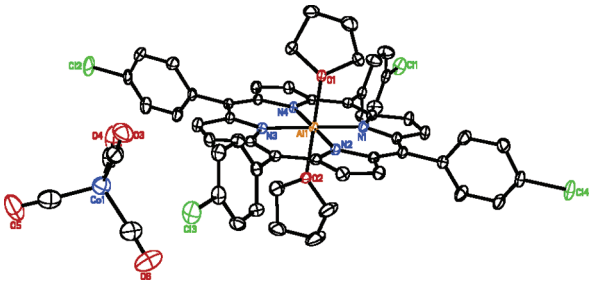
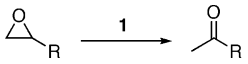


Figure 1. Solid-state structure of **1**. Hydrogen atoms omitted for clarity. Displacement ellipsoids drawn at 40% probability.

bimetallic carbonylation catalysts:[16,18,20,21] a well-separated ion pair with a tetrahedral cobaltate and a pseudo-octahedral cationic metal, which is coordinated by a tetradentate ligand and two axial molecules of THF. Upon screening this new complex, we discovered that it rapidly catalyzed both epoxide and lactone carbonylation, though some low-molecular-weight polymer[30] was formed in the absence of solvent (Table 1, entry 5). Addition of solvent resulted in the first clean, one-pot double carbonylation of epoxide to succinic anhydride (entry 6).

Reaction Optimization. With the first highly active and selective catalyst for one-pot double carbonylation in hand, we sought to optimize the reaction. At 40 °C, anhydrides were formed cleanly using CO pressures as low as 100 psi. Increasing the temperature to 90 °C greatly increased the rate of reaction, but at high temperature and low pressure or in the absence of CO, **1** catalytically isomerizes epoxides to ketones (eq 1).[16,21] Thus, higher pressures (>200 psi) were employed to maintain selectivity along with rapid conversion to anhydride.[31]



(1)

Based upon mechanistic studies of epoxide carbonylation with **2**,[22] we expected that solvent would significantly impact the rate of reaction, and therefore we attempted epoxide double carbonylation in a range of solvents. Conversion to succinic anhydride varied widely with solvent, as illustrated by a representative selection of solvents in Figure 2. Hexane was a poor solvent, yielding mostly polymer. Acyclic monofunctional ether solvents such as diethyl ether were effective for double carbonylation, though polymer remained a significant byproduct. Moderately coordinating, cyclic, or multifunctional ether solvents resulted in the cleanest reactions. In particular, the double carbonylation was distinctively rapid in 1,4-dioxane, and this became the solvent of choice for future reactions. Strongly coordinating solvents such as acetonitrile severely inhibited lactone carbonylation (vide infra).

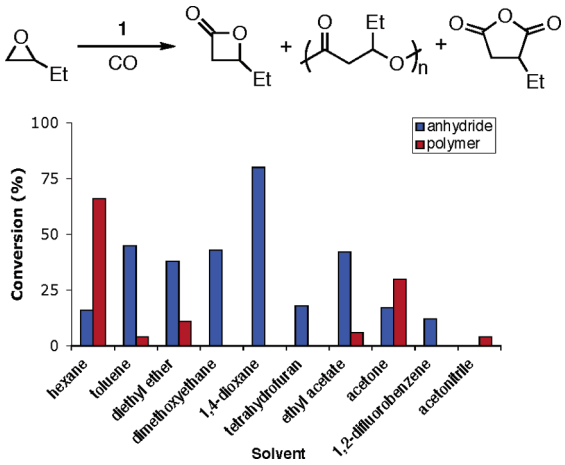
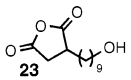
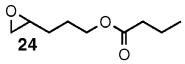
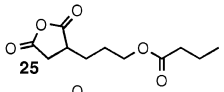
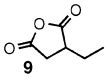
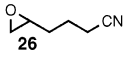
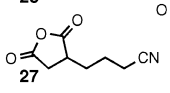
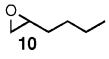
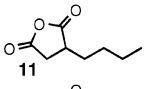
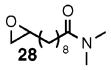
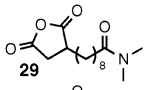
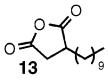
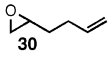
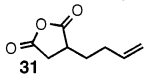
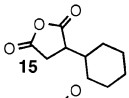
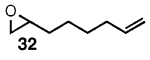
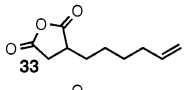
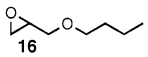
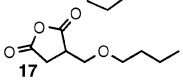
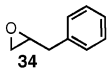
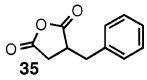
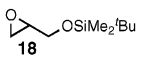
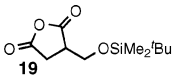
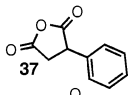
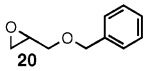
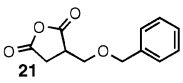
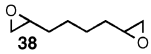
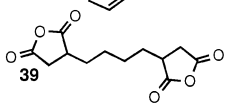


Figure 2. Solvent screen for epoxide double carbonylation. Reaction conditions: 2.0 mmol of epoxide in 1.0 mL of solvent, 0.20 mol % **1**, 850 psi CO, 2 h, 90 °C. Product distribution determined by ^{1}H NMR spectrum of crude reaction mixture. Epoxide was completely converted to lactone (not shown) in all of these solvents; subsequent conversion of lactone to anhydride and polymer is shown.

With an optimum solvent for epoxide double carbonylation, we returned to screen a number of new and previously reported catalysts of the general form $[(ligand)M(THF)_2]^+[Co(CO)_4]^-$. These catalysts were also more active in 1,4-dioxane than other solvents; however, none showed greater activity than **1**.[29] Variation of substituents in the para position of the porphyrin phenyl rings had little effect on the reactivity of the resulting catalysts;[29] however, the *p*-Cl complex (**1**) was chosen for future study, as Cl was an economical para substituent, and this substitution imparted greater crystallinity to the isolated com-

(29) See Supporting Information for details.
(30) By gel permeation chromatography, M_n = 6000 g/mol. Porphyrin Al alkoxides and carboxylates are known polymerize lactones to polyesters, see: Aida, T.; Inoue, S. *Acc. Chem. Res.* **1996**, *29*, 39−48.
(31) Further reactions used 850 psi CO to avoid significant loss of pressure due to CO consumption. At this pressure, ketone was only formed during the delay after mixing the epoxide with **1** and before pressurization with CO, but once the system was saturated with CO, ketone formation ceased. Rearrangement to ketone was minimized by keeping the epoxide and catalyst solution cold until pressurization with CO (small scale, screening),[16] or eliminated entirely by partially pressurizing the reactor with CO prior to epoxide addition (large scale, kinetics). Ketone formation was also observed when insufficient stirring hindered the effective dissolution of CO. Good selectivity (<1% ketone) was retained at pressures as low as 40 psi if the reaction was kept at room temperature until epoxide was converted to lactone, then heated to convert lactone to anhydride.

Table 2. Double Carbonylation of Functionalized Epoxides[a]

entry	epoxide	epoxide/**1**	anhydride	yield (%)[b]	entry	epoxide	epoxide/**1**	anhydride	yield (%)[b]
1	 **4**	1500	 **5**	98 (93)	10	 **22**	150	 **23**	93 (72)[c]
2	 **6**	650	 **7**	99 (89)	11	 **24**	300	 **25**	99 (89)
3	 **8**	250	 **9**	99 (80)	12	 **26**	100	 **27**	99 (77)
4	 **10**	250	 **11**	97 (88)	13	 **28**	20	 **29**	98 (79)[d]
5	 **12**	300	 **13**	99 (93)	14	 **30**	50	 **31**	90 (82)[d]
6	 **14**	150	 **15**	97 (81)	15	 **32**	100	 **33**	99 (85)
7	 **16**	100	 **17**	99 (80)	16	 **34**	100	 **35**	99 (78)
8	 **18**	250	 **19**	98 (83)	17	 **36**	50	 **37**	93 (72)[e]
9	 **20**	50	 **21**	96 (87)	18	 **38**	150	 **39**	98 (89)

[a] Unless specified otherwise, reactions run for 3 h at 850 psi CO and 90 °C in 1,4-dioxane (1.8 M epoxide). [b] Yield of anhydride determined by ^{1}H NMR spectroscopy of crude reaction mixture and verified by internal standard; corresponding lactone and ketone[31] were the only other products detected. Unoptimized isolated yields are in parentheses. [c] [epoxide] = 0.5 M. [d] [epoxide] = 1.0 M, 24 h. [e] [epoxide] = 1.0 M at 50 °C for 12 h.

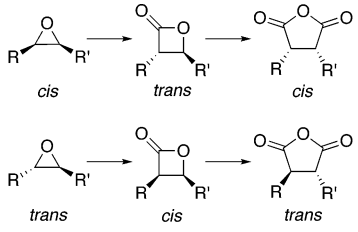
plex. In summary, under optimized conditions, **1** effects the double carbonylation of an epoxide to succinic anhydride with unprecedented activity, yield, and selectivity.

Substrate Scope. The versatility of this reaction was demonstrated with a variety of functionalized epoxides (Table 2). Substrate/catalyst ratios were optimized to achieve near complete conversion of 1−2 mmol of epoxide in 3 h at 90 °C; longer reaction times were used if more than 2 mol % catalyst was required to complete in 3 h. Conversion to anhydride is reported to indicate the high selectivity of the reaction. In most cases, isolation is straightforward, only requiring removal of solvent and catalyst. As shown in Table 2, the reaction was most facile for ethylene oxide (**4**) but still rapid for epoxides with pendent alkyl groups (entries 2−6). Substrates with ether side-chains were less active, but high yields and selectivity were retained (entries 7−9). Surprisingly, good conversion to anhydride was obtained with a seemingly incompatible unprotected alcohol (entry 10). The product, **23**, was stable enough to isolate and characterize by IR, ^{1}H and ^{13}C NMR spectroscopy, though after a few days at room temperature it decomposed from a white solid to a yellow oil. Ester functionality was well tolerated (entry 11), except in the specific case of glycidyl esters, where isomerization to γ-lactone[20] was favored over double carbonylation. Anhydrides with nitrile and amide side-chains were also synthesized (entries 12 and 13), although, in the presence of an amide, carbonylation of the lactone intermediate was very slow, presumably due to competitive coordination (vide infra) with the Lewis acid. Epoxides with pendent alkenes exhibited varied activity depending on chain length (entries 14 and 15). Aryl groups were also tolerated (entries 16 and 17), but styrene oxide (**36**) was run at lower temperature for a longer time to avoid thermal decarboxylation[32] of the lactone intermediate.[33] Substrates with more than one epoxide can undergo multiple double carbonylations; for example, 1,2,7,8-diepoxyoctane (**38**) was quadruply carbonylated to give the bis(succinic anhydride), **39**, in good yield.

1,2-Disubstituted epoxides[34] were carbonylated to the corresponding succinic anhydrides with retention of relative stereochemistry via a double inversion mechanism (vide infra), in which the stereocenter adjacent to the inserted carbonyl is inverted with each carbonylation. *cis*-Epoxides were carbonylated to *cis*-anhydrides via the *trans*-lactones, and *trans*-epoxides were carbonylated to the *trans*-anhydrides via *cis*-lactones (Table 3). At elevated temperatures, some epimerization of the product occurred in the presence of catalyst;[14] however, lower temperatures and thus longer reaction times afforded either *cis*- or *trans*-succinic anhydrides (entries 1 and 2) with good stereochemical purity. The *cis*-anhydride **41** was not formed as easily as the *trans*-anhydride **43** and had to be run at lower concentration to avoid poly(lactone) formation. Increasing steric bulk decreased the rate of carbonylation, but relative stereochemical purity was preserved (entries 3 and 4).[35]

(32) Minato, T.; Yamabe, S. *J. Org. Chem.* **1983**, *48*, 1479−1483.
(33) Unlike the other examples, styrene oxide carbonylates at the more hindered, benzylic carbon to give α-phenyl β-propiolactone.
(34) Although 1,1-disubstituted epoxides readily formed β-lactones, they were unreactive for further carbonylation; see Table 5 (vide infra).
(35) Epoxide **46** is carbonylated to **47** via a ∼1:1 mixture of two regioisomeric β-lactones.

Table 3. Double Carbonylation of Disubstituted Epoxides[a]



entry	epoxide	epoxide/**1**	anhydride	yield (%)[b]	*trans*:*cis*[b]
1[c]	**40**	100	**41**	95	1 : 20
2	**42**	200	**43**	99	> 100 : 1
3	**44**	75	**45**	99	> 100 : 1
4	**46**	100	**47**	99	> 100 : 1

[a] All reactions run for 24 h at 850 psi CO and 50 °C in 1,4-dioxane (1.8 M epoxide). [b] Conversion to anhydride and relative stereochemistry determined from the ^{1}H NMR spectroscopy of crude reaction mixture; lactone and ketone[31] were the only other products detected. [c] [epoxide] = 1.0 M in 1,4-dioxane.

Succinic anhydrides and succinate derivatives with excellent enantiomeric purity were readily accessed via double carbonylation (Table 4). (*S*)-Methylsuccinic anhydride, **(*S*)-7**, was rapidly obtained from (*R*)-propylene oxide, **(*R*)-6**, with a slight loss of enantiomeric purity at 90 °C (entry 1), but at 50 °C, greater than 99% enantiomeric excess is maintained through clean inversion of the stereocenter (entry 2). Likewise, larger alkyl and functionalized epoxides were carbonylated to yield anhydrides with ≥97% ee (entries 3 and 4). Thus, double carbonylation yields anhydrides as useful intermediates for asymmetric synthesis.

Mechanism. The double carbonylation of propylene oxide (PO) to methylsuccinic anhydride (MSA) was monitored by in situ IR spectroscopy. A representative plot of the concentrations of β-butyrolactone (BBL) and MSA as a function of time reveals that the reaction proceeds in two distinct stages (Figure 3). First, catalytic carbonylation of epoxide results in the linear production of β-lactone, which continues until all of the epoxide is

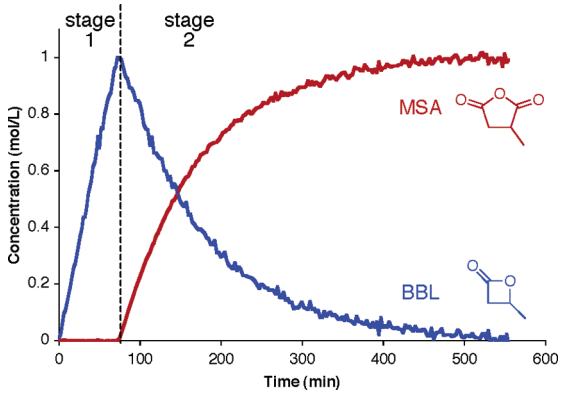


Figure 3. Plot of the concentrations of BBL and MSA during double carbonylation of PO. Reaction performed in 1,4-dioxane and monitored by in situ IR spectroscopy ($\nu_{C=O}$ BBL = 1827 cm^{-1} and $\nu_{C=O}$ MSA = 1787 cm^{-1}). $[PO]_0$ = 1.0 M, [**1**] = 4.0 mM, P_{CO} = 850 psi, T = 40 °C.

carbonylated; only then is there an abrupt change in the reaction, and the lactone intermediate is immediately consumed in a first-order decay, producing succinic anhydride as the product of a second carbonylation. This two-stage behavior was observed under all of the conditions studied. Even in solvents where lactone carbonylation is much faster than epoxide carbonylation, the lactone intermediate is not consumed while it is formed; the two stages remain sequential.

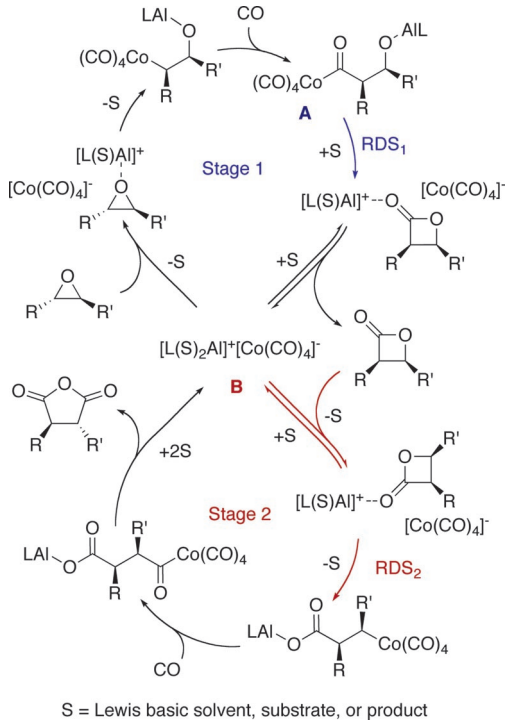
As a starting point, a general mechanistic scheme for double carbonylation is proposed as a combination of the separate mechanisms we have proposed for epoxide[22] and lactone[14] carbonylation (Scheme 2). The cycle is initiated by substitution of epoxide for solvent at the Lewis acidic cation [(ClTPP)Al(S)$_2$]$^+$ (S = solvent, substrate, or product), which binds and activates the epoxide. Subsequent ring-opening nucleophilic attack by [Co(CO)$_4$]$^-$ occurs at the less-hindered carbon, presumably with concomitant loss of solvent,[22] generating a formally neutral, five-coordinate aluminum alkoxide. This is followed by a rapid migratory insertion of CO into the cobalt−alkyl bond and uptake of another CO to form the catalyst resting state (**A**). Recoordination of solvent to Al facilitates release of the alkoxide and subsequent attack on the cobalt-acyl, producing lactone and regenerating [(ClTPP)Al(S)$_2$]$^+$[Co(CO)$_4$]$^-$ (**B**). In an analogous second cycle, the aluminum cation coordinates lactone, activating it for nucleophilic attack by [Co(CO)$_4$]$^-$, which occurs at the β-carbon. The resulting neutral aluminum-carboxylate/cobalt-alkyl complex readily undergoes migratory

Table 4. Double Carbonylation of Enantiomerically Pure Epoxides[a]

entry	epoxide	ee (%)	epoxide/**1**	T (°C)	anhydride	yield (%)[b]	ee (%)[c]
1	***(R)*-6**	>99	650	90[d]	***(S)*-7**	97	97
2	***(R)*-6**	>99	300	50	***(S)*-7**	99	>99
3	***(S)*-10**	>99	300	50	***(R)*-11**	99	>99
4	***(R)*-20**	>99	100	50	***(S)*-21**	96	97 (>99)[e]

[a] Unless specified otherwise, reactions run for 24 h at 850 psi CO in 1,4-dioxane (1.8 M epoxide). [b] Conversion to anhydride determined by ^{1}H NMR spectroscopy of crude reaction mixture; lactone and ketone[31] were the only other products detected. [c] Determined by chiral GC or HPLC of crude product. [d] Reaction run for 3 h. [e] Product recrystallized from ether, 87% isolated yield.

Scheme 2. Proposed Catalytic Cycle of Double Carbonylation



S = Lewis basic solvent, substrate, or product

insertion of CO and coordination of another CO to form an aluminum-carboxylate/cobalt-acyl species. Ring-closing attack of the carboxylate on the cobalt-acyl, which may be aided by solvent coordination to aluminum, forms anhydride and regenerates **B**.

The fact that each carbonylation occurs with separate and non-overlapping rate-determining steps, and that the β-lactone intermediate is readily synthesized, means that each can be studied as an independent reaction. In this paper, we will first describe mechanistic studies of epoxide carbonylation, then investigate the mechanism of lactone carbonylation. In light of these studies, we will discuss why lactone consumption does not begin until epoxide carbonylation is complete. Last, we will address the interplay of these two reactions, and how the separate conditions necessary for efficient catalysis of each stage can be fulfilled in one system, thus enabling one-pot double carbonylation.

Epoxide Carbonylation. Our group has recently completed an in-depth investigation of the mechanism of epoxide carbonylation with **2**, yielding a detailed picture of the essential steps and important intermediates.[22] There are three main criteria with which to compare the present system to this previously reported work: order in substrate and catalyst, solvent effects, and the catalyst resting state. Although the present study differs in temperature (40 vs 25 °C), ligand (ClTPP vs salph), and epoxide (PO vs 1,2-epoxybutane), we found that the basic mechanistic picture remained the same.

When the carbonylation of PO was monitored by in situ IR spectroscopy, the rate of BBL formation was observed to be constant over the course of the reaction (Figure 4), indicating that the rate is zero-order in epoxide. The reaction was performed using five CO pressures in the range 200−1000 psi, and no effect on the rate or selectivity was observed.[29] Next, the reaction was repeated using a range of catalyst concentrations (Figure 5), and the rate of reaction exhibited a first-order

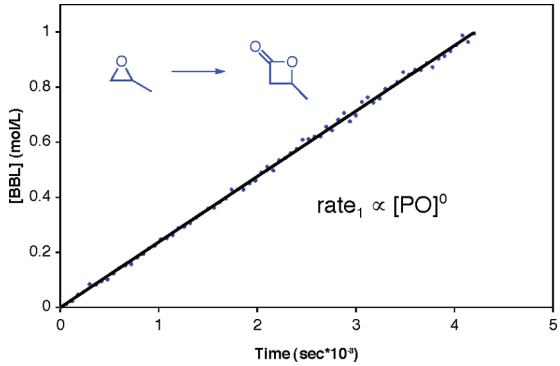


Figure 4. Plot of the formation of BBL as a function of time. Reaction performed in 1,4-dioxane and monitored by in situ IR spectroscopy ($\nu_{C=O}$ = 1827 cm^{-1}). $[PO]_0$ = 1.0 M, [**1**] = 4.0 mM, P_{CO} = 850 psi, T = 40 °C.

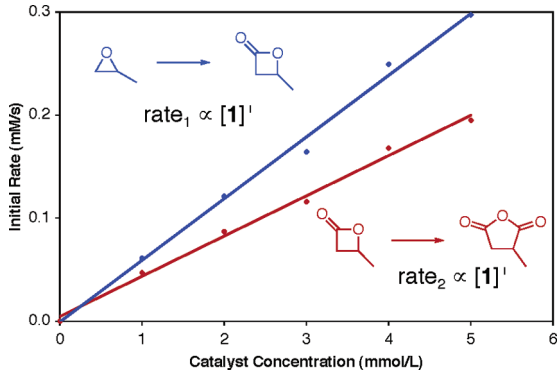


Figure 5. Initial rates of the formation of BBL and MSA as a function of the concentration of **1**. Reactions performed in 1,4-dioxane and monitored with in situ IR spectroscopy ($\nu_{C=O}$ BBL = 1827 cm^{-1} and $\nu_{C=O}$ MSA = 1787 cm^{-1}). $[PO]_0$ = 1.0 M, P_{CO} = 850 psi, T = 40 °C.

dependence on the concentration of **1**. These orders in substrate and catalyst are the same those as reported for **2**.[22]

Solvent effects on the rate of epoxide carbonylation also follow a similar trend to those reported for **2**.[22] In general, coordinating solvents, such as ethers, accelerate the reaction, whereas the carbonylation is slow in non-coordinating solvents such as hexane and toluene (vide infra). Strongly coordinating solvents, such as acetonitrile, inhibit the reaction, and we suspect that substitution of the epoxide for solvent may become rate determining in this case. The effect of solvent donicity can be quantified by examining the reaction in mixtures of THF and 2,5-dimethyltetrahydrofuran (DMTHF).[22,36,37] These solvents have similar properties, except that DMTHF is a much weaker donor due to sterics.[36,37] A plot of initial rate versus concentration of THF in DMTHF shows that the rate of epoxide carbonylation is first-order in the concentration of THF (Figure 6). Because the primary difference between THF and DMTHF as solvents is donicity, the order in THF effectively represents the order in donicity or Lewis base.[22,36] Additionally, the rate laws are the same in both THF/DMTHF and 1,4-dioxane. Addition of THF or other moderately donating solvents accelerates the reaction in 1,4-dioxane, and dilution of 1,4-dioxane or THF with toluene slows the reaction. Thus, the following expression can be written for the carbonylation of PO by **1** in

(36) Wax, M. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 7028−7030.
(37) Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Org. Chem.* **2004**, *69*, 242−249.

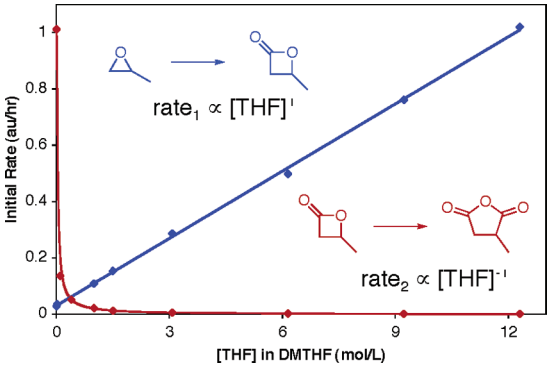


Figure 6. Effect of [THF] on the rate of carbonylation of PO and BBL in mixtures of THF/DMTHF. [THF] = 0 M corresponds to pure DMTHF, and [THF] = 12.3 M corresponds to pure THF solvent. Reactions monitored with in situ IR spectroscopy ($\nu_{C=O}$ BBL = 1827 cm^{-1} and $\nu_{C=O}$ MSA = 1787 cm^{-1}). $[PO]_0$ = 1.0 M or $[BBL]_0$ = 1.0 M, [**1**] = 2.0 mM, P_{CO} = 850 psi, T = 40 °C. Red line calculated from linear fit of initial rate versus $[THF]^{-1}$.[29]

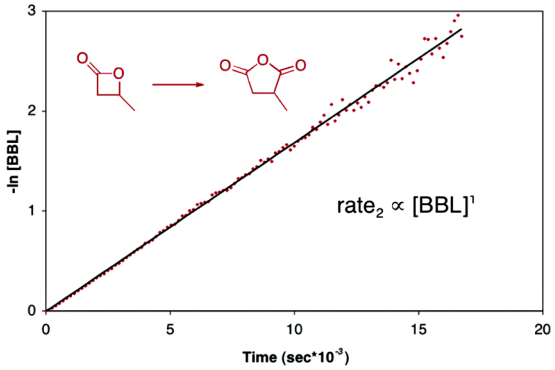


Figure 7. Plot of −ln[BBL] versus time for the carbonylation of BBL to MSA. Reaction performed in 1,4-dioxane and monitored with in situ IR spectroscopy ($\nu_{C=O}$ BBL = 1827 cm^{-1}). [**1**] = 4.0 mM, $[BBL]_0$ = 1 M, P_{CO} = 850 psi, T = 40 °C.

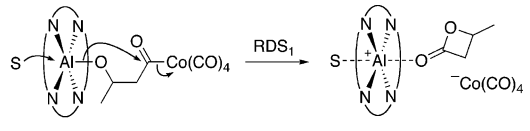
1,4-dioxane, where $\text{rate}_1 = d[BBL]/dt$ and S = THF or 1,4-dioxane:

$$\text{rate}_1 \propto [PO]^0[CO]^0[\mathbf{1}]^1[S]^1$$

The catalyst resting state was also directly observed during the reaction by in situ IR spectroscopy. In 1,4-dioxane solution, the free $[Co(CO)_4]^-$ ion of **1** displays a strong absorption at 1885 cm^{-1}. Upon addition of epoxide and CO, this band immediately disappears and is replaced by a weaker absorbance at 1715 cm^{-1}, which is assigned as the $\nu_{C=O}$ of the cobalt acyl resting state.[22] Furthermore, when the reaction is run in the presence of 4-nitrophenylisocyanate, another product, 6-methyl-3-(4-nitrophenyl)-1,3-oxazinane-2,4-dione, was formed in addition to BBL, indicating that the ring-opened aluminum-alkoxide/cobalt-acyl resting state (**A**; Scheme 2) is sufficiently long-lived to be trapped by an electrophilic isocyanate.[22,38]

From this evidence, we conclude that the mechanistic picture developed for carbonylation of 1,2-epoxybutane with **2** in 1,2-dimethoxyethane at 25 °C also applies to the carbonylation of PO with **1** in 1,4-dioxane at 40 °C. Thus, we propose that the reaction proceeds via rapid epoxide ring opening, CO insertion, and uptake of CO to form the neutral catalyst resting state, an aluminum alkoxide/cobalt acyl (**A**). The rate-determining step is then subsequent solvent-assisted ring closing to lactone (Scheme 3) and regeneration of the catalyst ion pair. Once the

Scheme 3. Proposed Rate-Determining Step of Propylene Oxide Carbonylation (RDS_1)



aluminum cation and cobalt anion are re-formed, epoxide is coordinated and ring opened, immediately returning to the aluminum-alkoxide/cobalt-acyl resting state (**A**). As **1** and **2** are proposed to have the same rate-determining step, we can speculate on the origin of the much greater epoxide carbonylation activity of **1**. We suspect that increased delocalization of charge into the porphyrin ligand stabilizes the rate-determining transition structure as the aluminum center is converted from a formally neutral alkoxide to a cation.

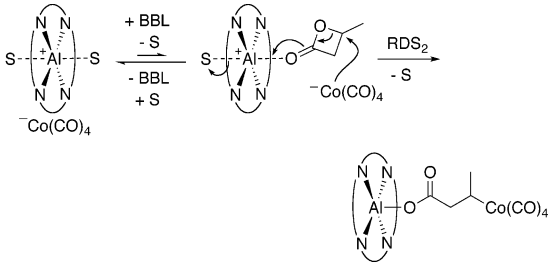
Lactone Carbonylation. The carbonylation of β-butyrolactone to methylsuccinic anhydride was also studied by in situ IR spectroscopy. There are two methods for generating lactone to study its carbonylation, either by first synthesizing and isolating the lactone or by beginning with epoxide and forming the lactone in situ; both methods provide the same results. In this way, we were able to determine a separate rate law for lactone carbonylation.

Unlike the case for epoxide, BBL carbonylation displayed a first-order dependence on substrate concentration, which is evident from the first-order decay of BBL and corresponding production of anhydride (Figure 3). A plot of −ln[BBL] versus time during the carbonylation confirms that the reaction rate is first-order in lactone concentration (Figure 7). When the reaction was repeated, varying CO pressure from 100 to 1000 psi, there was no change in the rate of reaction, and no side products were observed.[29] The reaction was also repeated with different concentrations of **1**, and a plot of initial rate versus catalyst concentration (Figure 5) indicated that the rate of reaction is first-order in the complex **1**, $[(ClTPP)Al(THF)_2]^+[Co(CO)_4]^-$. The resting state of catalyst during the reaction can be observed by in situ IR spectroscopy. During epoxide carbonylation, the catalyst resting state was a cobalt acyl (vide supra), but immediately upon complete conversion of PO to BBL, the cobalt acyl ($\nu_{C=O}$ = 1715 cm^{-1}) disappeared and the signal corresponding to free cobaltate ($\nu_{C=O}$ = 1885 cm^{-1}) reappeared and persisted, indicative of $[Co(CO)_4]^-$ as the cobalt resting state during lactone carbonylation (**B**; Scheme 2).

As in epoxide carbonylation, solvent played a significant role in lactone carbonylation. Coordinating solvents such as THF severely inhibited lactone carbonylation. This reaction was the fastest in toluene, a weakly coordinating solvent (vide infra). The effect of donor solvent was again quantified by measuring the initial reaction rate in mixtures of THF/DMTHF.[22,36] A small increase in [THF] resulted in a dramatic reduction in rate. A plot of initial rate versus $[THF]^{-1}$ in DMTHF indicated that the reaction rate depends inversely on the concentration of THF (Figure 6),[29] exactly opposite the case seen for epoxide carbonylation. Further, the orders in substrates and catalyst in THF solvents were the same as in 1,4-dioxane, and mixtures of THF in 1,4-dioxane resulted in a similar inverse dependence

(38) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.*, submitted.

Scheme 4. Proposed Rate-Determining Step of β-Butyrolactone Carbonylation (RDS_2)



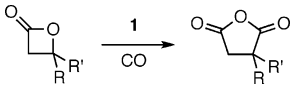
on the concentration of donor solvent or Lewis base. Because the order in THF represents an order in solvent donicity,[22,36] the inverse dependence of rate on THF can thus be applied to the mechanism in 1,4-dioxane and understood as an inverse dependence on the concentration of donor solvent or Lewis base. Thus, the following expression can be written, where $\text{rate}_2 = \text{d[MSA]/d}t$ and S = THF:

$$\text{rate}_2 \propto [\text{BBL}]^1[\text{CO}]^0[\mathbf{1}]^1[\text{S}]^{-1}$$

The inverse dependence of rate on solvent most likely arises from a pre-rate-determining substitution of lactone for solvent at the aluminum center. One possible mechanistic interpretation for this rate law is a reversible substitution (either associative or dissociative) of lactone for donor solvent coordinated to the aluminum cation, followed by a rate-limiting nucleophilic attack of $[Co(CO)_4]^-$, resulting in the ring-opening of lactone (Scheme 4). Another mechanistic interpretation, although unlikely, could be the rate-limiting coordination of BBL after dissociation of donor solvent. These two potential rate-limiting steps could be distinguished if there was an order in either the aluminum or the cobalt ion. To determine if there was an order in the individual ions or the complex **1** as a whole, we independently varied the concentration of both the aluminum and the cobalt components as the salts $[(ClTPP)Al(THF)_2]^+[BPh_4]^-$ and $[PPh_4]^+[Co(CO)_4]^-$. The source of $[(ClTPP)Al(THF)_2]^+$ and $[Co(CO)_4]^-$ (from either the discrete complex **1** or independently added as the respective $[BPh_4]^-$ and $[PPh_4]^+$ salts) did not affect the rate of reaction and indicated that the rate of ion pair exchange is comparable to or faster than catalysis. Independently increasing the concentration of either $[(ClTPP)Al(THF)_2]^+$ or $[Co(CO)_4]^-$ in this manner did not change the observed rate of anhydride formation. Thus, the reaction rate had a first-order dependence on the concentration of the entire complex, but no dependence on the separate cation or anion components. This suggests that the cation and anion may exist as an ion pair in the ground state and is consistent with a rate-limiting attack of a Lewis acid-bound lactone by $[Co(CO)_4]^-$.

In a further attempt to distinguish these two possibilities, we repeated the lactone carbonylation, varying the substitution at the β position of the lactone (Table 5). The relative magnitude of the observed rates of carbonylation of unsubstituted, monosubstituted, and disubstituted lactones is most consistent with a rate-limiting S_N2 attack. However, it is unlikely that the steric hindrance at the β position would have such a large impact on the rate of lactone coordination, particularly because lactone coordination is expected to occur at the carbonyl oxygen,[39] which is far removed from the β position of the lactone. Additionally, coordination to a cationic aluminum center is expected to be facile. Thus, we propose nucleophilic ring-opening attack by an ion paired $[Co(CO)_4]^-$ on lactone coordinated to $[(ClTPP)Al(S)_n]^+$ as the rate-determining step,[40] which is proceeded by a pre-rate-determining associative or dissociative substitution of lactone for solvent.

Table 5. Effect of Substitution on Relative Rate of Lactone Carbonylation[a]



entry	R	R′	relative rate
1	H	H	14
2	Me	H	3.5
3	Et	H	1.0
4	Me	Me	0[b]

[a] Reactions performed in 1,4-dioxane and monitored by in situ IR spectroscopy. $[\text{lactone}]_0 = 1.0$ M, $[\mathbf{1}] = 4.0$ mM, $P_{CO} = 850$ psi, $T = 40$ °C. [b] No anhydride detected.

This proposal for the rate-determining step may be used to interpret the greatly enhanced lactone carbonylation activity of **1** relative to **2**. Porphyrin-aluminum cations are more Lewis acidic than salph-aluminum cations;[41] thus a lactone coordinated to $[(ClTPP)Al]^+$ should be more activated toward ring opening, decreasing the rate-limiting energy barrier.

Double Carbonylation. Although the catalytic cycles proceed via analogous steps for the two substrates, the rate-determining steps appear to be determined by the relative rates of ring opening and closing for epoxide and lactone carbonylation. For ring opening, epoxides have more ring strain than lactones, and thus more driving force for ring opening. Furthermore, in the case of PO, ring opening by $[Co(CO)_4]^-$ occurs at the less substituted carbon of the epoxide; thus, subsequent ring opening of BBL must occur at the more hindered β-carbon of the lactone. On the other hand, ring closing a five-membered anhydride is energetically more feasible than closing a strained four-membered lactone ring. Additionally, because porphyrin aluminum carboxylates are more labile than porphyrin aluminum alkoxides,[42] the necessary transfer of substrate electron density from the aluminum to the cobalt acyl should be more facile for anhydride ring closing than lactone ring closing.

The non-overlapping nature of the two stages of double carbonylation (vide supra, Figure 3) can be understood in terms of the two unique resting states of the catalyst. Although both PO and BBL rapidly and reversibly coordinate the porphyrin aluminum cation, we propose there is a much greater affinity for the ring opening of the epoxide over the lactone. While the ring opening of PO followed by CO insertion and uptake are not rate determining, BBL ring opening is rate determining. Thus, in the presence of both PO and BBL, **1** will rapidly, selectively, and irreversibly react with PO to form the aluminum-alkoxide/cobalt-acyl resting state (**A**; Scheme 2). Upon ring closing of this species, lactone is formed and catalyst is regenerated, followed by another rapid ring opening of PO and

(39) Shimasaki, K.; Aida, T.; Inoue, S. *Macromolecules* **1987**, *20*, 3076−3080.

(40) Another explanation could be that the rate-determining step changes with the substitution. However, this only explains these data if coordination also occurs at the oxygen in the ring, which is unlikely.

(41) Chen, P.; Chisholm, M. H.; Gallucci, J. C.; Zhang, X.; Zhou, Z. *Inorg. Chem.* **2005**, *44*, 2588−2595.

(42) Chisholm, M. H.; Zhou, Z. *J. Am. Chem. Soc.* **2004**, *126*, 11030−11039.

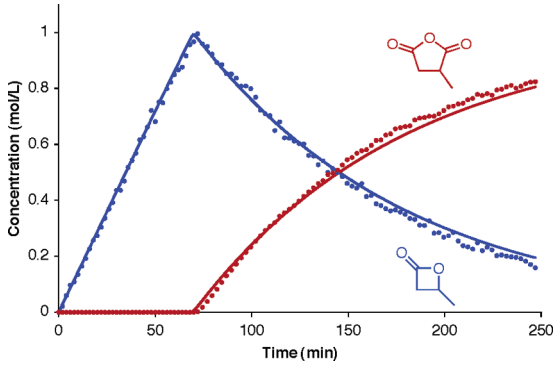


Figure 8. Comparison of simulated (solid lines) with experimental data (points, same as Figure 3) for the double carbonylation of PO in 1,4-dioxane. $[PO]_0 = 1.0$ M, [**1**] = 4.0 mM, $P_{CO} = 850$ psi, $T = 40$ °C.

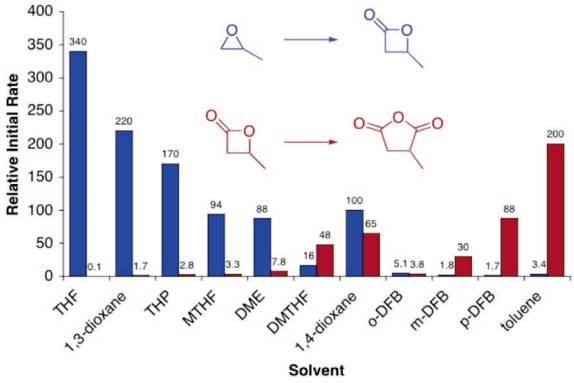


Figure 9. Comparison of relative initial rates for PO (blue) and BBL (red) carbonylation as a function of solvent. Reactions monitored with in situ IR spectroscopy ($\nu_{C=O} = 1827$ cm^{-1}). $[PO]_0 = 1.0$ M or $[BBL]_0 = 1.0$ M, [**1**] = 2.0 mM, $P_{CO} = 850$ psi, $T = 40$ °C.

CO migration. Thus, in the presence of epoxide, the catalyst is continuously returned to the epoxide carbonylation resting state, **A**, thereby excluding ring opening of lactone with **1**. Once all of the epoxide has been consumed, the catalyst resting state then becomes the ion pair, $[(ClTPP)Al(S)_2]^+[Co(CO)_4]^-$ (**B**; Scheme 2, S = solvent, substrate, or product), as evidenced by the abrupt shift in CO stretching frequency for the cobalt carbonyl species, from a cobalt-acyl to free cobaltate, coincident with complete conversion of PO. In this state, the catalyst is free to react with lactone and produce anhydride.

To determine if the proposed mechanism and rate-determining steps predict the observed kinetic behavior, in particular the non-overlapping stages of increase and decay in lactone concentration, we calculated the concentrations of lactone and anhydride predicted by our mechanism as a function of time. From the proposed mechanism, we derived rate equations for the concentrations of the important species. Then from kinetic studies, we extracted rate constants for the proposed rate-determining steps, and estimated larger constants for the faster steps.[29] Using typical experimental conditions as initial concentrations, we solved for the concentration of lactone and anhydride as a function of time. The experimental data from Figure 3 were overlaid with these calculated concentrations (Figure 8), and, not surprisingly, the simulated and experimental initial rates were essentially the same. What was interesting, however, was that the simulated concentrations were in good agreement throughout the reaction, and particularly that the second carbonylation did not occur until the first stage was complete. This simulation confirms that the proposed mechanism, particularly the different catalyst resting states and rate-determining steps, is consistent with the observed two-stage kinetic behavior.

Solvent Effects. To further investigate the effect of solvent, we repeated the double carbonylation of PO in a variety of solvents and monitored the reaction by in situ IR spectroscopy. For every solvent studied, the double carbonylation occurred in two distinct and non-overlapping stages; however, the rate of each stage varied greatly as a function of solvent. As seen in Figure 9, the rate of epoxide carbonylation slowed with increasing sterics and decreasing donicity[36] of the substituted THF solvents: THF, 2-methyltetrahydrofuran (MTHF), DMTHF. Similar activity is seen with the moderately donating tetrahydropyran (THP), 1,2-dimethoxyethane (DME), and dioxane, but the reaction is very slow in poorly coordinating toluene and difluorobenzene (DFB). For lactone carbonylation, the trend is reversed, highlighting the difference between these two stages (Figure 9). As expected from the proposed rate-determining step of lactone carbonylation, poorly coordinating solvents (DMTHF, DFB, and toluene) generally result in uninhibited lactone ring opening, whereas the Lewis basic, coordinating solvents severely slow anhydride formation, such that essentially no anhydride is produced in THF.[43] To find a solvent system that has comparable rates for both carbonylations, a possible solution might be to use a mixture of solvents, or a solvent with intermediate donicity. However, simply varying the donicity of a THF solvent system is futile, because the rate will always be much slower for at least one stage of carbonylation (Figure 6). 1,4-Dioxane, however, is unique in that it facilitates both epoxide and lactone carbonylation and is far more active than an optimized mixture of the two solvent extremes.

Although it is clear that Lewis bases affect the rate of these reactions, the origin of enhanced activity seen for both stages in 1,4-dioxane cannot be explained simply in terms of a Lewis base assisting or inhibiting the rate-determining steps. Instead, 1,4-dioxane is unique among the ether solvents studied in that its symmetry results in a low dipole moment. The importance of solvent polarity, separate from donicity, is dramatically illustrated by comparing the rates of carbonylation in the isomers of difluorobenzene (Figure 9). In most respects, *ortho*-, *meta*-, and *para*-difluorobenzene (*o*-DFB, *m*-DFB, *p*-DFB) are similar solvents; however, they vary widely in polarity ($\epsilon = 13$, 5, and 2, respectively);[44] thus differences in rate in these solvents may be primarily attributed to the difference in polarity of each isomer. Epoxide carbonylation was comparatively slow in all three DFB isomers (as expected from their poor donicity), with little change thus attributable to differences in polarity. In agreement with our previous study,[22] donicity appears to have a greater influence than polarity on the rate of epoxide carbonylation.

For lactone carbonylation, however, markedly different rates are observed in each isomer of DFB. *o*-DFB, the most polar isomer, is an extremely slow solvent for lactone carbonylation; *m*-DFB is less polar and exhibits an increased rate; and *p*-DFB

(43) While this is unproductive for double carbonylation, it is synthetically very useful for the rapid and exclusive production of the β-lactone intermediate, because the reaction essentially stops after the first carbonylation. When using **1** in THF, the carbonylation of 1,2-epoxybutane to β-valerolactone is nearly twice as fast as the most active system reported to date,[20] with a TON of over 6000 in 6 h at 60 °C.

(44) Wohlfarth, C. In *CRC Handbook of Chemistry and Physics*, 76th ed.; Lide, D. R., Ed.; CRC Press: New York, 1995; pp 6−149.

is nonpolar and the best isomer for rapid lactone carbonylation (Figure 9). Based solely on their poor donicity, all three isomers should be competent solvents for lactone carbonylation; instead, we see a clear trend of increasing rate with decreasing solvent polarity.

To test this effect of polarity with dioxane, we predicted that 1,3-dioxane ($\epsilon = 13.6$),[45] which is significantly more polar than 1,4-dioxane ($\epsilon = 2.2$),[44] would result in slow lactone carbonylation, comparable to the other more polar ether solvents. In fact, this was exactly what we observed, confirming that polar solvents inhibit lactone carbonylation (Figure 9).

Overall, the rate of epoxide carbonylation is primarily dependent on solvent donicity, whereas the rate of lactone carbonylation is strongly dependent on both solvent donicity and polarity. The ability of 1,4-dioxane to function as a solvent for both epoxide and lactone carbonylation may then be explained in terms of its unique combination of these properties. It retains enough Lewis basic character[46] to assist in ring closing to form lactone, while not significantly inhibiting the subsequent ring opening of lactone. Additionally, its low polarity does not retard epoxide carbonylation, but accelerates lactone carbonylation, due to a nonpolar environment, which may favor the transition of catalyst from an ionic pair to a formally neutral intermediate upon ring opening of lactone. Thus, endowed with the proper combination of donicity and polarity, 1,4-dioxane enables the rapid and efficient double carbonylation of epoxides.

Conclusion

We have reported the double carbonylation of epoxides to give succinic anhydrides in a single synthetic step, using the highly active bimetallic catalyst, **1**. This reaction is compatible with a variety of substituted epoxides with aliphatic, aromatic, alkene, ether, ester, alcohol, nitrile, and amide functional groups. Disubstituted and enantiomerically pure epoxides were doubly carbonylated with excellent retention of stereochemical purity via inversion of each of the two stereocenters. Given the ease of catalyst synthesis (and its impending commercial availability), coupled with the ability to convert readily available epoxides to functionalized and stereochemically pure succinic anhydrides in high yield on multigram scale, we believe this to be an efficient and synthetically useful transformation.

The double carbonylation proceeds through two distinct and non-overlapping stages: epoxide carbonylation to lactone, and subsequent lactone carbonylation to anhydride. Although these two reactions are proposed to follow analogous catalytic cycles, the nature of the substrate determines which step within each cycle will be rate determining. We investigated the mechanism of double carbonylation of PO, and for each stage we determined the rate law with respect to substrates, catalyst, and solvent. The resting state of the catalyst during each stage was observed by in situ IR spectroscopy. In the case of epoxide carbonylation, $\text{rate}_1 \propto [\text{PO}]^0[\text{CO}]^0[\mathbf{1}]^1[\text{S}]^1$ (S = THF or 1,4-dioxane), which is consistent with a rate-limiting, solvent-assisted ring closing to lactone from an aluminum-alkoxide/cobalt-acyl resting state. For lactone carbonylation, $\text{rate}_2 \propto [\text{BBL}]^1[\text{CO}]^0[\mathbf{1}]^1[\text{S}]^{-1}$, which is consistent with substitution of lactone for donor solvent at the porphyrin aluminum cation, followed by a rate-limiting, ring-opening S_N2-type nucleophilic attack by $[Co(CO)_4]^-$. Although the two stages have similar initial rates, ring opening is rapid for PO and rate limiting for BBL. Thus, the catalyst ion pair reacts irreversibly and selectively with epoxide, giving rise to the observed two-stage behavior. The effect of solvent on each stage was explained in terms of both donicity and polarity. Rates of epoxide and lactone carbonylation display an opposite dependence on donor solvent. This unique feature allows for synthetic versatility, in which judicious choice of solvent determines whether the reaction stops cleanly at β-lactone (THF) or immediately continues on to succinic anhydride (1,4-dioxane).

Experimental Section

General Considerations. All manipulations of air- and/or water-sensitive compounds were carried out under dry nitrogen using a Braun Unilab drybox or standard Schlenk line techniques. NMR spectra were recorded on a Varian Mercury spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz) and referenced versus residual non-deuterated or monoprotonated solvent shifts. Standard IR spectra were collected on a Mattson RS-10500 Research Series FTIR. In situ IR data were collected using a 100-mL Parr stainless steel high-pressure reactor modified for use with a Mettler-Toledo ReactIR 4000 Reaction Analysis System fitted with a Sentinel DiComp high-pressure probe, and analyzed with ReactIR software version 2.21. Enantiomeric excesses were measured using either GC (HP 6890 Series equipped with an Astec α-cyclodex TFA chiral capillary column (250 μm × 60 m)), or HPLC (Waters 515 HPLC pump, Waters 2410 refractive index detector, semi-prep Regis Pirkle (*S*,*S*) Whelk-O 1 column (25 cm × 10 mm)). High-resolution mass spectra were obtained using electron impact conditions on a 70-VSE mass spectrometer by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. X-ray crystallographic data were collected using a Bruker X8 APEX II (Mo Kα, λ = 0.71073 Å) at 173(2) K, and frames were integrated with the Bruker SAINT+ Program. Optimization of catalyst loading was performed in custom designed and built six-well, stainless steel, high-pressure reactors,[14,19] which accommodated six 4- or 8-mL glass vials. All high-pressure reactors were dried under vacuum at 90 °C prior to use.

Materials. Carbon monoxide (research grade) was purchased from Matheson and used without further purification. 1,4-Dioxane, 1,3-dioxane, tetrahydropyran, tetrahydrofuran, 2-methyltetrahydrofuran, 2,5-dimethyltetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane were vacuum transferred from purple Na/benzophenone. Hexanes and toluene were dried and deoxygenated on columns of alumina and Q5 copper, respectively. Diethyl ether and methylene chloride were dried on columns of alumina and degassed via repetitive freeze−pump−thaw cycles (FPT). Difluorobenzene, ethyl acetate, acetone, and acetonitrile were dried over 4 Å molecular sieves and vacuum transferred after FPT. Epoxides were stirred for a few days over CaH_2, degassed by FPT, and vacuum distilled, except 10,11-epoxyundecan-1-ol (**22**) and *N*,*N*-dimethyl-10,11-undecylamide (**28**), which were dried over CaH_2, filtered, and degassed by stirring under dynamic vacuum (0.1 Torr). Ethylene oxide (**4**), propylene oxide (**6**), 1,2-epoxybutane (**8**), 1,2-epoxyhexane (**10**), 1,2-epoxydodecane (**12**), *n*-butyl glycidyl ether (**16**), *tert*-butyldimethylsilyl glycidyl ether (**18**), benzyl glycidyl ether (**20**), 1,2-epoxy-5-hexene (**30**), 1,2-epoxy-7-octene (**32**), (2,3-epoxypropyl)-benzene (**34**), styrene oxide (**36**), 1,2,7,8-diepoxyoctane (**38**), β-propiolactone, β-butyrolactone (BBL), 4-nitrophenylisocyanate, and *meta*-chloroperoxybenzoic acid (mCPBA) were purchased from Aldrich. *cis*-2,3-Epoxybutane (**40**) and *trans*-2,3-epoxybutane (**42**) were purchased from GFS Chemicals. Iso-butylene oxide was purchased from TCI America. $Co_2(CO)_8$ and octaethylporphyrin were purchased from Strem. (*R*)-Propylene oxide ((***R***)-**6**),[24] (*S*)-1,2-epoxyhexane ((***S***)-**10**),[24] (*R*)-benzyl glycidyl ether ((***R***)-**20**),[24] 10,11-epoxyundecan-1-ol (**22**),[47] 4,5-

(45) Walker, R.; Davidson, D. W. *Can. J. Chem.* **1959**, *37*, 492−495.
(46) Geerlings, J. D.; Varma, C. A. G. O.; van Hemert, M. C. *J. Phys. Chem. B* **2000**, *104*, 56−64.
(47) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777−7782.

epoxypentyl butyrate (**24**),[20] 5,6-epoxyhexanenitrile (**26**),[48] *N*,*N*-dimethyl-10,11-undecylamide (**28**),[49] *trans*-3,4-epoxyhexane (**44**),[50] *trans*-2,3-epoxyoctane (**46**),[51] $NaCo(CO)_4$,[52] $[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (**2**),[16] $[(OEP)Cr(THF)_2]^+[Co(CO)_4]^-$ (**3**),[20] and $[PPh_4]^+[Co(CO)_4]^-$ [53] were synthesized as previously reported. All other materials were commercially available and used as received.

Bis(tetrahydrofuran)-*meso*-tetra(4-chlorophenyl)porphyrinato Aluminum Tetracarbonyl Cobaltate, $[Cl(TPP)Al(THF)_2]^+[Co(CO)_4]^-$ (1). (Note: This and related catalysts may be commercially available in 2007 from Sigma-Aldrich.) The following synthetic method is analogous to that of related literature compounds.[16−21,54a] According to the method of Adler,[54b] *meso*-tetra(4-chlorophenyl)-21*H*,23*H*-porphyrin ($ClTPPH_2$) was easily synthesized from pyrrole and 4-chlorobenzaldehyde, and dried under vacuum overnight. All subsequent manipulations were performed using strict air-free techniques, and all reagents and solvents were dried and degassed prior to use. Using a modified literature procedure,[55] $ClTPPH_2$ (3.44 g, 4.57 mmol) was placed in a Schlenk tube equipped with a magnetic stir bar in a drybox. Upon removal to the bench top, the dark purple ligand was dissolved in 250 mL of CH_2Cl_2 to form a very dark red solution. Diethyl aluminum chloride (5.0 mL, 5.0 mmol, 1.0 M in heptane, 1.1 equiv) was added via syringe through a septum under flow of N_2. Ethane evolved from the reaction and was vented. The reaction was stirred at room temperature for 3 h, then solvent was removed in vacuo. The residual red-purple solid was dried under vacuum overnight and identified by comparison of its ^{1}H NMR spectrum ($CDCl_3$, 300 MHz, δ) 9.10 (s, 8H), 8.13 (broad d, 8H), 7.76 (m, 8H), to that of free ligand ($CDCl_3$, 300 MHz, δ) 8.92 (s, 8H), 7.88 (d, 8H, $^3J = 8.2$ Hz), 7.49 (d, 8H, $^3J = 8.2$ Hz), −2.19 (s, 2H, *NH*). Having reacted quantitatively, it was used without further purification. The Schlenk tube was brought into a drybox where $NaCo(CO)_4$ (887 mg, 4.57 mmol) was added. Upon removal to the Schlenk line, the solids were dissolved in THF (200 mL) and stirred overnight at room temperature. The very dark, red-purple solution was concentrated to 100 mL in vacuo, and NaCl was allowed to precipitate. The solution was then filtered and layered with hexanes (200 mL). Slow diffusion over the course of a few days afforded large, purple, X-ray quality crystals that were stable under N_2 for over a year. (Intentional mixing of the layers results in rapid precipitation of the complex as a crystalline powder with comparable catalytic activity and selectivity.) The crystals were filtered, washed with hexanes, and dried in vacuo (4.33 g, 87% yield). ^{1}H NMR (300 MHz, THF-d_8, δ): 9.23 (s, 8H), 8.21 (m, 8H), 7.88 (m, 8H), 3.62 (m, 8H), 1.78 (m, 8H); IR (Nujol, NaCl) $\nu_{C=O} = 1875$ cm^{-1}. Crystal data:[29] monoclinic, space group $P2_1/n$, $a = 11.9296(6)$ Å, $b = 22.6420(12)$ Å, $c = 20.4696(10)$ Å, $\alpha = 90°$, $\beta = 102.446(2)°$, $\gamma = 90°$, $V = 5399.1(5)$ Å^3; $Z = 4$, formula weight = 1092.63 for $C_{48}H_{24}AlCl_4CoN_4O_4 \cdot 2C_4H_8O$ and density (calc.) = 1.344 g/mL; $R = 0.0593$, $R_w = 0.1634$ ($I > 2\sigma(I)$).

Bis(tetrahydrofuran)-*meso*-tetra(4-chlorophenyl)porphyrinato Aluminum Tetraphenyl Borate, $[Cl(TPP)Al(THF)_2]^+[BPh_4]^-$. The synthetic procedure was identical to that for **1**, except that $NaBPh_4$ was used in place of $NaCo(CO)_4$. The structure was confirmed by X-ray crystallography.[29]

General Procedure for the Small-Scale Carbonylation of Epoxides. A six-well, stainless steel, high-pressure reactor was loaded with six 4-mL glass vials and magnetic stir bars. In a nitrogen drybox, an appropriate amount of **1** was weighed into each vial, then solvent was added to each, with no effort made to dissolve the catalyst. Epoxide was weighed into the vials, and the catalyst became soluble in the reaction mixture. Each vial was cooled in the drybox freezer (−37 °C for at least 5 min) to limit ketone formation,[16] and then all were placed in the reactor. The reactor was sealed and removed from the drybox, immediately pressured to 850 psi with CO, stirred, and heated to the appropriate temperature. After the indicated time, the reactor was placed on dry ice, cooled to <0 °C, then slowly vented. Crude reaction mixture from each vial was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$.

General Procedure for the Large-Scale Carbonylation of Epoxides. In a nitrogen drybox, a 100-mL Parr high-pressure reactor was charged with the appropriate amount of **1** and solvent, then removed from the drybox. The reactor was first pressured with 200 psi CO and stirred for 10 min, then vented down to 20 psi without stirring. The epoxide was injected via gastight syringe into the CO-filled reactor through a septum at room temperature. (This procedure of presaturating the solution with CO eliminated ketone formation.) The reactor was then immediately pressured to 850 psi CO, followed by rapid stirring and heating to 90 °C. After the appropriate time, the reactor was placed on dry ice, cooled to <0 °C, and slowly vented.

General Procedure for in Situ IR Spectroscopy. In a nitrogen drybox, a React IR modified reactor was charged with catalyst and solvent, and substrate was drawn into a gastight syringe. After removal from the drybox, the reactor was pressured to 850 psi with CO, mechanically stirred, and heated to 40 °C. Once the system equilibrated, a background spectrum was taken (16 scans). The reactor was vented to 20 psi, and at time = 0, substrate was injected through a septum, and the reactor was immediately repressurized to 850 psi CO. IR spectra were collected once per minute (16 scans/spectrum at 4 cm^{-1} resolution). Absorbances of BBL and MSA were measured at 1827 and 1787 cm^{-1}, respectively, and corrected for overlap.

Isocyanate Trapping of Catalyst Resting State. In a nitrogen drybox, an 8-mL glass vial equipped with a magnetic stir bar was charged with **1** (10.4 mg, 9.5 μmol), 4-nitrophenylisocyanate (161 mg, 0.98 mmol), 1,4-dioxane (0.95 mL), and propylene oxide (55 mg, 0.95 mmol), and then placed in a six-well reactor. Upon removal from the drybox, it was immediately pressured to 850 psi CO, stirred, and heated to 40 °C. After 24 h, the reactor was cooled and vented. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy in $CDCl_3$ indicated complete conversion of epoxide to methyl succinic anhydride (48%), β-butyrolactone (45%), and 3-(4-nitrophenyl)-6-methyl-1,3-oxazine-2,4-dione (7%).

Representative Synthesis of Epoxide: Cyclohexyl Oxirane (14). Prepared by a modified literature[56] procedure: vinylcyclohexane (17.4 mL, 13.9 g, 126 mmol) was added dropwise to a cold solution of mCPBA (36.4 g, 77%, 160 mmol) in CH_2Cl_2 (600 mL). The reaction was stirred at 0 °C for 2 h, then at room temperature overnight. The milky white suspension was extracted with 10% $NaHSO_{3\,(aq)}$ (to remove organic peroxides), then twice with saturated $NaHCO_{3\,(aq)}$. The organic layer was washed with saturated $NaCl_{\,(aq)}$, dried over Na_2SO_4, and concentrated to an oil under reduced pressure. Vacuum distillation at 1 mmHg gave **14** as a clear, colorless liquid (13.1 g, 82%).

Representative Synthesis of Lactone: β-Valerolactone. A 100-mL Parr high-pressure reactor with mechanical stirrer was dried overnight at 120 °C under vacuum. In a nitrogen drybox, the reactor was charged with **1** (21 mg, 0.020 mmol), THF (16 mL, 200 mmol), and 1,2-epoxybutane (8.6 mL, 100 mmol), then closed and removed from the drybox. The reactor was pressured with 850 psi CO and stirred at 60 °C for 6 h, by which time the pressure dropped to 400 psi. The

(48) de Raadt, A.; Klempier, N.; Faber, K.; Griengl, H. *J. Chem. Soc., Perkin Trans.* **1992**, 137−140.
(49) Glushko, L. P.; Petukhova, E. I.; Klebanskii, E. O. *Zh. Org. Khim.* **1997**, *33*, 1527−1531.
(50) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101−1133.
(51) Mischitz, M.; Mirtl, C.; Saf, R.; Faber, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2041−2046.
(52) Edgell, W. F.; Lyford, J. *Inorg. Chem.* **1970**, *9*, 1932−1933.
(53) Wei, C. H.; Bockman, T. M.; Kochi, J. K. *J. Organomet. Chem.* **1992**, *428*, 85−97.
(54) (a) Barbe, J. M.; Guilard, R. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 3, pp 225−229. (b) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
(55) Konishi, K.; Aida, T.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 816−820.
(56) Vyvyan, J. R.; Meyer, J. A.; Meyer, K. D. *J. Org. Chem.* **2003**, *68*, 9144−9147.

reactor was cooled and vented. Volatiles were removed in vacuo, and the resulting oil was vacuum distilled to afford β-valerolactone (9.1 g, 91%).

Representative Synthesis of Anhydride: Cyclohexylsuccinic Anhydride (15). A 100-mL Parr high-pressure reactor with mechanical stirrer was dried overnight at 120 °C under vacuum. In a nitrogen drybox, the reactor was charged with **1** (262 mg, 0.240 mmol) and 1,4-dioxane (20 mL), then closed and removed from the drybox. The reactor was pressured with 200 psi CO, stirred for 10 min, and then vented down to 20 psi without stirring. Cyclohexyl oxirane (4.88 mL, 36.0 mmol) was injected via syringe into the CO-filled reactor at room temperature, and then the reactor was immediately repressurized to 850 psi CO, followed by rapid stirring and heating to 90 °C. After 3 h, the reactor was placed on dry ice, cooled to <0 °C, and slowly vented. Volatiles were removed in vacuo, the resulting oil was vacuum distilled to afford a clear oil that solidified on standing, then was recrystallized from cold ether/hexanes to afford **15** (5.32 g, 81% isolated yield).

General Procedures for Anhydride Purification. Anhydrides were obtained by rotary evaporation followed by bulb-to-bulb vacuum distillation (**9**, **11**, **15**, **37**, **45**, **47**) or sublimation (**5**, **7**, **39**, **41**, **43**) of the crude reaction mixture. For higher boiling anhydrides, solvent and any volatile ketones were removed from the crude reaction mixture in vacuo. The catalyst residue was then removed from the resulting oil by elution through a plug of silica gel (with 1:2 EtOAc:hexanes for **13**, **17**, **19**, **21**, **23**, **27**, **29**, **31**, **33**, **35**, and with 4:1 EtOAc:hexanes for **25**). Subsequent concentration by rotary evaporation afforded the product, which could be further purified by vacuum distillation or recrystallization from cold ether/hexane, as appropriate. Anhydrides were stable enough to be isolated and characterized, but reacted slowly with moisture to give the corresponding diacids.

Identification of Anhydrides. Product anhydrides were identified by comparison of their ^{1}H NMR spectra to a commercially available samples for **5** and **7** and by comparison to literature values for **9**,[14] **13**,[14] **17**,[14] **19**,[14] **31**,[14] **35**,[57] **37**,[58] **41**,[58] **43**,[58] and **45**.[59] Anhydrides **11**,[60] **25**,[61] and **39**[62] have previously been reported; however, their ^{1}H NMR spectra are reported in DMSO-d_6 or CCl_4. Anhydrides for which ^{1}H NMR spectra have not been reported in $CDCl_3$ are characterized below.

Methylsuccinic Anhydride (7). Enantiomeric excess determined by chiral GC: inlet (T = 250 °C, 32 psi, 260.0 mL/min, 100:1 split); detector (250 °C, 35 mL/min H_2 flow, 400 mL/min air flow); column (32 psi, 1.5 mL/min); oven (150 °C, isothermal). The (*R*)- and (*S*)-enantiomers elute at 6.9 and 7.2 min, respectively.

***n*-Butylsuccinic Anhydride (11).** ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.10 (m, 2H), 2.67 (m, 1H), 1.95 (m, 1H), 1.65 (m, 1H), 1.38 (m, 4H), 0.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.90, 170.34, 40.85, 34.28, 30.89, 29.00, 22.42, 13.97; IR (melt, NaCl) $\nu_{C=O}$ = 1862, 1786 cm^{-1}; mp = 46 °C; HRMS (EI) *m*/*z* calcd ($C_8H_{12}O_3$), 156.0786; found, 156.0790. Enantiomeric excess determined by chiral GC: inlet (T = 250 °C, 33 psi, 125.0 mL/min, 50:1 split); detector (250 °C, 35 mL/min H_2 flow, 400 mL/min air flow); column (33.0 psi, 1.5 mL/min); oven (160 °C, isothermal). The (*R*)- and (*S*)-enantiomers elute at 11.3 and 12.2 min, respectively. Absolute configuration of **(*R*)-11** was confirmed by hydrolysis to (*R*)-*n*-butylsuccinic acid and comparison of optical rotation ($[\alpha]^{25}_D$ +22.3° (*c* 1.5, H_2O)) to literature values for (*S*)-*n*-butylsuccinic acid, $[\alpha]^{29}_D$ −21.5° (*c* 1.49, H_2O).[63]

Cyclohexylsuccinic Anhydride (15). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.00 (m, 2H), 2.74 (m, 1H), 1.90 (m, 1H), 1.78 (m, 3H), 1.69 (m, 1H), 1.58 (m, 1H) 1.36−0.95 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.14, 170.70, 46.50, 39.12, 31.36, 30.34, 28.47, 26.07, 25.88; IR (melt, NaCl) $\nu_{C=O}$ = 1861, 1785 cm^{-1}; mp = 36 °C; HRMS (EI) *m*/*z* calcd ($C_{10}H_{14}O_3$) 182.0943, found 182.0945.

Benzyloxymethylsuccinic Anhydride (21). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.39−7.24 (m, 5H), 4.58 (d, 1H, ^2J = 12.1 Hz), 4.51 (d, 1H, ^2J = 12.1 Hz), 3.91 (dd, 1H, ^2J = 9.2, ^3J = 3.4 Hz), 3.63 (dd, 1H, ^2J = 9.2, ^3J = 3.1), 3.26 (m, 1H), 3.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 172.66, 170.24, 137.08, 128.79, 128.32, 127.91, 73.69, 67.51, 42.27, 31.70; IR (melt, NaCl) $\nu_{C=O}$ = 1858, 1782 cm^{-1}; mp = 69−70 °C; HRMS (EI) *m*/*z* calcd ($C_{12}H_{12}O_4$) 220.0736, found 220.0732. Enantiomeric excess determined by chiral HPLC: solvent (4.5 mL/min, 93:7 hexanes:isopropanol with 0.1% acetic acid). The (*R*)- and (*S*)-enantiomers elute at 24.4 and 27.0 min, respectively. Absolute configuration was assigned to **(*S*)-21** on the basis of analogy to the other stereochemically pure substrates.

9-Hydroxynonylsuccinic Anhydride (23). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.64 (t, 2H, ^3J = 6.6 Hz), 3.09 (m, 2H), 2.66 (m, 1H), 1.93 (m, 1H), 1.65 (m, 1H), 1.56 (m, 2H), 1.50−1.23 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.06, 170.57, 62.84, 40.69, 34.08, 32.73, 30.90, 29.44, 29.36, 29.22, 29.08, 26.72, 25.73; IR (melt, NaCl) ν_{O-H} = 3380, 1062, $\nu_{C=O}$ = 1861, 1783 cm^{-1}; mp = 48 °C.

3-Butyroxypropylsuccinic Anhydride (25). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.05 (t, 2H, ^3J = 6.2 Hz), 3.11 (m, 2H), 2.64 (m, 1H), 2.23 (t, 2H, ^3J = 7.5 Hz), 1.96 (m, 1H), 1.72 (m, 3H), 1.58 (qt, 2H, ^3J = 7.4 Hz, ^3J = 7.5 Hz), 0.89 (t, 3H, ^3J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.82, 173.77, 170.31, 63.24, 40.44, 36.24, 34.28, 27.71, 26.65, 18.58, 13.85; IR (melt, NaCl) $\nu_{C=O}$ = 1862, 1785, 1728 cm^{-1}; mp = 35 °C; HRMS (EI) *m*/*z* calcd ($C_{11}H_{16}O_5$) 228.0998, found 228.0989.

3-Cyanopropylsuccinic Anhydride (27). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.14 (m, 2H), 2.68 (m, 1H), 2.42 (t, 2H, ^3J = 6.8 Hz), 2.00 (m, 1H), 1.92−1.67 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.62, 170.21, 119.40, 40.18, 34.33, 29.88, 23.04, 17.10; IR (neat, NaCl) $\nu_{C\equiv N}$ = 2247, $\nu_{C=O}$ = 1862, 1784 cm^{-1}; clear colorless oil. HRMS (EI) m/z calcd ($C_8H_9O_3N-CO_2$) 123.0684, found 123.0684.

9-(Succinic anhydridyl)-*N*,*N*-dimethylnonanamide (29). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.09 (m, 2H), 3.00 (s, 3H), 2.93 (s, 3H), 2.66 (m, 1H), 2.30 (t, 2H, ^3J = 7.6 Hz), 1.92 (m, 1H), 1.62 (m, 3H), 1.45−1.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.95, 173.15, 170.42, 40.56, 37.22, 35.24, 33.98, 33.18, 30.74, 29.23, 29.15, 28.99, 28.90, 26.59, 24.98; IR (melt, NaCl) $\nu_{C=O}$ = 1861, 1782, 1642 cm^{-1}; mp = 49 °C. HRMS (EI) m/z calcd ($C_{15}H_{25}O_4N-CO_2$) 239.1885, found 239.1883.

Hex-5-enylsuccinic Anhydride (33). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.76 (ddt, 1H, ^3J = 6.6 Hz, ^3J = 10.2 Hz, ^3J = 17.1 Hz), 4.98 (m, 2H), 3.09 (m, 2H), 2.65 (m, 1H), 2.07 (m, 2H), 1.93 (m, 1H), 1.65 (m, 1H), 1.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.87, 170.34, 138.30, 115.17, 40.78, 34.21, 33.42, 30.91, 28.37, 26.24; IR (neat, NaCl) $\nu_{C=O}$ = 1862, 1786 cm^{-1}; clear colorless oil; HRMS (EI) *m*/*z* calcd ($C_{10}H_{14}O_3$) 182.0943, found 182.0938.

1,4-Bis(succinic anhydridyl)butane (39). 1:1 mixture of the racemic and meso stereoisomers. ^{1}H NMR (300 MHz, acetone-d_6, δ): 3.34 (dddd, 2H, ^3J = 5.3 Hz, ^3J = 6.3 Hz, ^3J = 8.8 Hz, ^3J = 9.9 Hz), 3.22 (dd, 2H, ^3J = 9.8 Hz, ^2J = 18.1 Hz), 2.86 (dd, 2H, ^3J = 6.3 Hz, ^2J = 18.1 Hz), 1.95 (m, 2H), 1.77 (m, 2H), 1.54 (m, 4H); ^{13}C NMR (75 MHz, acetone-d_6, δ): 175.42, 171.77, 41.26, 34.53, 34.51, 30.71, 30.64, 27.10, 27.08; IR (melt, NaCl) $\nu_{C=O}$ = 1857, 1778 cm^{-1}; mp = 105−108 °C; HRMS (EI) *m*/*z* calcd ($C_{12}H_{14}O_6$) 254.0790, found 254.0798.

***trans*-3-Methyl-4-(*n*-pentyl)succinic Anhydride (47).** ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.82 (dq, 1H, ^3J = 7.3 Hz, ^3J = 7.5 Hz), 2.69 (ddd, 1H, ^3J = 5.6 Hz, ^3J = 7.5 Hz, ^3J = 7.7 Hz), 1.88 (m, 1H), 1.66 (m, 1H), 1.51−1.25 (m, 6H), 1.40 (d, 3H, ^3J = 7.3 Hz), 0.87 (t, 3H, ^3J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.84, 173.00, 48.08, 41.27, 31.52, 29.98, 26.40, 22.46, 15.65, 14.06; IR (neat, NaCl) $\nu_{C=O}$ = 1858, 1785 cm^{-1}; clear colorless oil; HRMS (EI) *m*/*z* calcd ($C_{10}H_{16}O_3$) 184.1009, found 184.1094.

(57) Qiao, C. H.; Marsh, E. N. G. *J. Am. Chem. Soc.* **2005**, *127*, 8608−8609.
(58) Crandall, J. K.; Schuster, T. *J. Org. Chem.* **1990**, *55*, 1973−1975.
(59) Bode, J.; Brockman, H. *Chem. Ber.* **1972**, *105*, 34−44.
(60) Bergmeier, S. C.; Ismail, K. A. *Synthesis* **2000**, 1369−1371.
(61) Huang, N.-J.; Xu, L.-H.; Ye, M.-X.; Feng, J. *Youji Huaxue* **1991**, *11*, 174−178.
(62) Bouvier, J. M.; Bruneau, C. M. *Bull. Soc. Chim. Fr.* **1975**, 2195−2201.
(63) Zhou, B.; Xu, Y. *J. Org. Chem.* **1988**, *53*, 4419−4421.

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Supporting Information Available: Screening and characterization of additional catalysts, calibration curve for MSA in 1,4-dioxane, rate dependence on P_{CO}, plot of initial rate versus $[THF]^{-1}$, details of kinetics simulation for double carbonylation, ^{1}H and ^{13}C NMR spectra of all new anhydrides, and X-ray data for **1**, $[(ClTPP)Al(THF)_2]^+[BPh_4]^-$, and $[(OEP)Al(THF)_2]^+[Co(CO)_4]^-$. This material is available free of charge via the Internet at http://pubs.acs.org.

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