

## The Mechanism of Epoxide Carbonylation by [Lewis Acid]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> Catalysts

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**Abstract:** A detailed mechanistic investigation of epoxide carbonylation by the catalyst [(salph)Al(THF)<sub>2</sub>]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> (**1**, salph = *N,N'*-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran) is reported. When the carbonylation of 1,2-epoxybutane (EB) to  $\beta$ -valerolactone is performed in 1,2-dimethoxyethane solution, the reaction rate is independent of the epoxide concentration and the carbon monoxide pressure but first order in **1**. The rate of lactone formation varies considerably in different solvents and depends primarily on the coordinating ability of the solvent. In mixtures of THF and *cis/trans*-2,5-dimethyltetrahydrofuran, the reaction is first order in THF. From spectroscopic and kinetic data, the catalyst resting state was assigned to be the neutral ( $\beta$ -aluminoxy)acylcobalt species (salph)AlOCH(Et)CH<sub>2</sub>COCO(CO)<sub>4</sub> (**3a**), which was successfully trapped with isocyanates. As the formation of **3a** from EB, CO, and **1** is rapid, lactone ring closing is rate-determining. The favorable impact of donating solvents was attributed to the necessity of stabilizing the aluminum cation formed upon generation of the lactone.

### Introduction

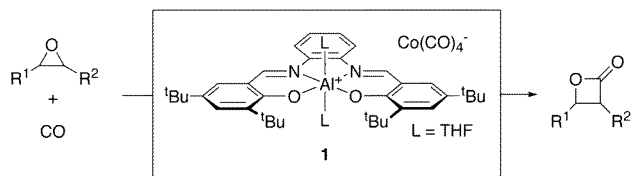
$\beta$ -Lactones are an important class of heterocycles having a wide range of applications in synthetic,<sup>1–3</sup> natural product,<sup>2,4</sup> and polymer<sup>5</sup> chemistry. A number of synthetic methods yielding  $\beta$ -lactones exist, and most can be described as intramolecular substitutions, cycloadditions, ring expansions, or ring contractions.<sup>1,3,4,6</sup> Among these reaction types, two have received considerable recent attention due to their ability to produce enantiopure  $\beta$ -lactones. The discovery of chiral catalysts (nucleophilic,<sup>7–9</sup> Lewis acidic,<sup>10–14</sup> or both<sup>15,16</sup>) has made net [2+2] addition of ketenes and aldehydes a useful route to stereopure  $\beta$ -lactones, and this topic has been reviewed.<sup>6,17</sup> As well, recent research efforts have begun to focus on catalytic epoxide carbonylation, which is attractive because enantiopure

epoxides are easily obtained by well-established methods such as hydrolytic kinetic resolution<sup>18</sup> and asymmetric epoxidation.<sup>19,20</sup> The first contemporary report of epoxide carbonylation directed toward the synthesis of  $\beta$ -lactones, by Drent and Kragtwijk, described the use of Co<sub>2</sub>(CO)<sub>8</sub> and 3-hydroxypyridine to carbonylate epoxides (in particular propylene oxide, PO), producing mixtures of lactone and oligoesters.<sup>21</sup> Following this discovery, Alper and co-workers reported increased activity and selectivity for lactone using combinations of [PPN]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> and neutral Lewis acids (PPN = bis(triphenylphosphine)iminium).<sup>22</sup> Carbonylation of a number of substituted epoxides by this catalyst system was demonstrated; however, turnover frequencies were limited to <13 h<sup>-1</sup>. Subsequently, we reported the bimetallic salt [(salph)Al(THF)<sub>2</sub>]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> (**1**, salph = *N,N'*-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran), which catalyzes the selective carbonylation of epoxides to lactones at lower temperature and without the use of solvent (Scheme 1).<sup>23</sup> We have since reported additional catalysts for this reaction, all of the general form [Lewis acid]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>,<sup>24–28</sup> and have expanded their substrate scope to include aziridines,<sup>24</sup> lactones,<sup>29</sup> oxetane,<sup>29</sup> and a diverse array

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**Scheme 1.** Catalytic Carbonylation of Epoxides to Lactones by [(salph)Al(THF)<sub>2</sub>]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>, **1**

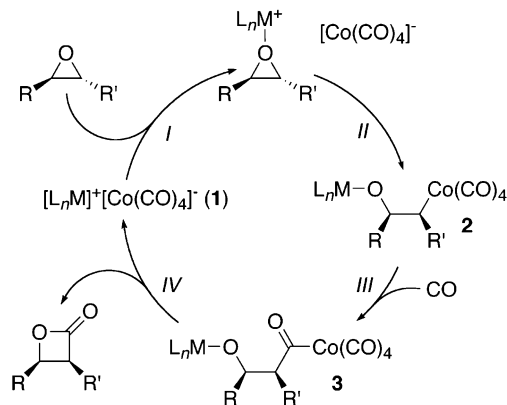
of functionalized and bicyclic epoxides.<sup>27,28</sup> Recently, researchers collaborating at BASF and University of Ulm have carbonylated PO to  $\beta$ -butyrolactone ( $\beta$ -BL) using catalyst mixtures composed of readily available Lewis acids and cobalt carbonyl sources, and used spectroscopic and theoretical studies to examine the effect of catalyst precursors on the reaction.<sup>30–32</sup> In a related study, Kim et al. have used  $\text{Co}_2(\text{CO})_8$  with a number of ligated zinc salts to carbonylate ethylene oxide to methyl  $\beta$ -hydroxypropionate in methanol solution.<sup>33</sup>

We<sup>23–25,27–29</sup> and others<sup>30–32,34</sup> have discussed mechanistic aspects of epoxide carbonylation using Lewis acid/[Co(CO)<sub>4</sub>]<sup>-</sup> catalysts. The coordination environment around the cobalt center has been studied in detail, as the attached carbonyl ligands provide convenient and informative spectroscopic handles. Specifically, in situ IR spectroscopy has been exploited for this purpose.<sup>30–32</sup> Conversely, the transformations taking place at the Lewis acid component of the catalyst have received less consideration in mechanistic studies. This is not surprising, as many of the commercially available Lewis acids used with this system (in particular aluminum alkyls) not only lack convenient spectroscopic handles, but also exhibit complex solution behavior.

In an effort to develop improved catalysts for heterocycle carbonylation, we sought a detailed mechanism of lactone formation. Specifically, we aimed to elucidate the complete catalytic cycle, identify the form of the catalyst during the reaction, and uncover the rate-determining step. The discrete, well-defined nature of our ligand-supported Lewis acid cations proved advantageous in this endeavor. Herein, we present kinetic, spectroscopic, labeling, and reactivity data that permit the construction of a detailed mechanistic picture of epoxide carbonylation by **1**. We believe this study will set the stage for similar investigations with related catalysts of the type [Lewis acid]<sup>+</sup>[M(CO)<sub>n</sub>]<sup>-</sup> and with different substrate classes.

## Results and Discussion

Analysis of the catalyst components necessary for epoxide carbonylation, as well as the reaction products, has provided an initial understanding of the course of this reaction. Notably,

**Scheme 2.** Preliminary Mechanism for Epoxide Carbonylation by Catalysts of the Type [L<sub>n</sub>M]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>

a Lewis acid must be present; reactions using the [Co(CO)<sub>4</sub>]<sup>-</sup> ion with non Lewis acidic cations, such as [PPh<sub>4</sub>]<sup>+</sup>, [PPN]<sup>+</sup>, [Cp<sub>2</sub>Co]<sup>+</sup>, or [<sup>n</sup>Bu<sub>4</sub>N]<sup>+</sup>, were not successful.<sup>22,23,32</sup> Interestingly, lactone is produced in the presence of Na<sup>+</sup>,<sup>23</sup> a very weak Lewis acid.<sup>35</sup> As Lewis acids catalyze the ring-opening of epoxides,<sup>36,37</sup> they likewise have the potential to activate the epoxide substrate for the carbonylation reaction.

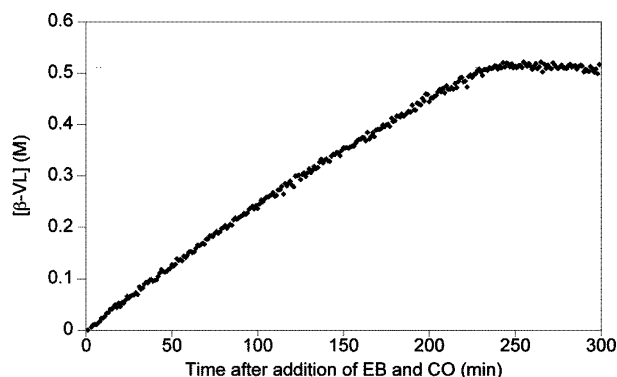
When catalytic carbonylation of epoxides is attempted in the absence of CO or with low pressures of CO, epoxide isomerization to ketone (the Meinwald rearrangement<sup>38</sup>) is also observed. Catalysis of this type of rearrangement by [Lewis acid]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> has been reported for the conversion of PO to acetone using methanolic solutions of  $\text{Co}_2(\text{CO})_8$ .<sup>39</sup> These solutions contain [Co(MeOH)<sub>6</sub>]<sup>2+</sup> and [Co(CO)<sub>4</sub>]<sup>-</sup> (in a 1:2 ratio) as the primary cobalt species.<sup>40</sup> Regiochemical evidence is consistent with the ions [Co(MeOH)<sub>6</sub>]<sup>2+</sup> and [Co(CO)<sub>4</sub>]<sup>-</sup> effecting epoxide rearrangement via a ( $\beta$ -metalloxy)alkylcobalt intermediate (Scheme 2, **2**).<sup>39,41</sup> This type of structure is also accessible in our system, and **2** is believed to be on the reaction path to lactone.

The preliminary mechanism we proposed for the carbonylation of epoxides by **1** and related catalysts (of the form [Lewis acid]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>)<sup>23–25,27,28</sup> is based on these observations and on stereochemical investigations (vide infra). The epoxide, once activated by coordination to the Lewis acid, is ring-opened through nucleophilic attack by [Co(CO)<sub>4</sub>]<sup>-</sup> to form intermediate **2**. Migratory insertion of CO into the cobalt–alkyl bond forms a cobalt acyl (intermediate **3**) that subsequently undergoes an intramolecular attack by the metal alkoxide to form a four-membered lactone ring and release the catalyst.

The skeletal reaction sequence of (I) substrate activation, (II) nucleophilic ring-opening, (III) CO insertion and uptake, and (IV) product ring-closing is consistent with catalytic cycles proposed for epoxide,<sup>23–25,27,28,30–32,34</sup> aziridine,<sup>24,42</sup> and lactone<sup>29</sup> carbonylation in our and related systems. Alternatively, Stirling

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**Figure 1.** Plot of the formation of  $\beta$ -valerolactone from 1,2-epoxybutane (EB) as a function of time. Reaction performed in 1,2-dimethoxyethane solution and monitored using in situ IR spectroscopy.  $[1] = 4.6$  mM,  $[EB]_0 = 0.51$  M,  $P_{CO} = 300 \pm 10$  psi,  $T = 25.0 \pm 0.5$  °C.

and co-workers<sup>34</sup> have proposed that another mechanism, in which ring closing precedes CO uptake, may also be operable under some conditions; this possibility will be discussed later. The catalytic cycle as depicted in Scheme 2 served as the starting point from which we conducted our mechanistic investigation.

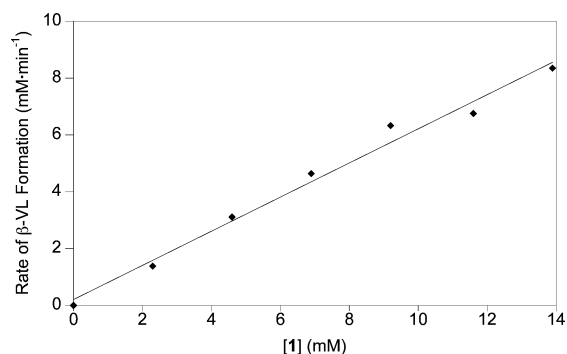
**(I) Activation of the Epoxide Substrate by Catalyst 1.** We undertook kinetic studies to determine the order of the carbonylation reaction in each of its components (eq 1). Though the

$$d[\beta\text{-VL}]/dt = k[EB]^x P_{CO}^y [1]^z \quad (1)$$

carbonylation of PO to  $\beta$ -BL has been the most studied reaction of this type, we chose to examine the formation of  $\beta$ -valerolactone ( $\beta$ -VL) from 1,2-epoxybutane (EB) in 1,2-dimethoxyethane (DME) solution. EB has a higher boiling point than PO, which makes it easier to manipulate quantitatively at room temperature. In situ IR spectroscopy<sup>43</sup> has been used to study the carbonylative formation  $\beta$ -lactones,<sup>30–32</sup> polyesters,<sup>44,45</sup> and poly- $\beta$ -peptoids<sup>46</sup> and was used in this study to monitor the emergence of the lactone carbonyl stretch (for  $\beta$ -VL in DME,  $\nu(\text{C}=\text{O}) = 1827$   $\text{cm}^{-1}$ ). As the intensity of this band was found to vary nonlinearly with the concentration of  $\beta$ -VL (particularly at high concentration), a calibration curve was constructed from 31 independently prepared samples of  $\beta$ -VL in DME and fit to a function such that the concentration of  $\beta$ -VL could be calculated directly from the absorbance.<sup>47</sup> Figure 1 shows a plot of  $\beta$ -VL concentration versus time for a representative experiment in which the pressure of CO was held constant while EB was consumed. The reaction rate,  $d[\beta\text{-VL}]/dt$ , was unchanged throughout the reaction, indicating that the rate of lactone formation is independent of epoxide concentration (viz.,  $x = 0$ ). Thus, for a given CO pressure and concentration of **1**, the rate law is given by eq 2. This suggests that EB does not enter

$$d[\beta\text{-VL}]/dt = k[EB]^0 P_{CO}^y [1]^z \quad (2)$$

the catalytic cycle between the resting state and the transition state of the rate-determining step. To rule out the possibility of



**Figure 2.** Effect of the concentration of catalyst **1** on the rate of  $\beta$ -valerolactone formation from 1,2-epoxybutane (EB). Reactions performed in 1,2-dimethoxyethane solution and monitored using in situ IR spectroscopy.  $[EB]_0/[1] = 110 \pm 1$ ,  $P_{CO} = 300 \pm 10$  psi,  $T = 25.0 \pm 0.5$  °C.

coincidental effects from the starting epoxide and product lactone, the carbonylation was performed with  $\beta$ -VL present initially ( $[\beta\text{-VL}]_0 = 0.32$  M). Notably, this did not alter the reaction rate; the time required for complete epoxide consumption was unchanged ( $\pm 5$  min). Thus, neither epoxide nor lactone concentration affect the rate of reaction, and epoxide binding is eliminated as the rate-determining step.

As the octahedral aluminum in **1** is coordinatively saturated, the intimate mechanism of substitution (replacing THF with an epoxide) at this center is tentatively assigned as dissociative. This is consistent with the lack of order in epoxide, though a rate-limiting dissociation of THF can be neither verified nor excluded based solely on this observation.

**(II) Opening of the Epoxide Ring.** The regio- and stereochemical outcomes of the carbonylation of epoxides as catalyzed by complex **1** provide insight regarding the ring-opening event. In most cases, the carbonylation of a monosubstituted epoxide by **1** yields the corresponding  $\beta$ -substituted  $\beta$ -lactone as the exclusive lactone product, indicating that attack by  $[\text{Co}(\text{CO})_4]^-$  occurs at the less-substituted carbon atom.<sup>48</sup> Further, carbonylation of enantiopure (*R*)-PO (Scheme 2,  $R = (R)\text{-Me}$ ,  $R' = \text{H}$ ) occurs with retention of stereochemistry, yielding (*R*)- $\beta$ -BL.<sup>23</sup> Finally, *cis*- and *trans*-2-butene oxide afford *trans*- and *cis*- $\alpha,\beta$ -dimethylpropiolactone, respectively.<sup>24,25</sup> Therefore, attack of the  $[\text{Co}(\text{CO})_4]^-$  ion on the epoxide occurs in an  $\text{S}_{\text{N}}2$  fashion,<sup>24,25</sup> leading to inversion of stereochemistry at the carbon atom  $\alpha$  to the inserted CO, and retention at the  $\beta$ -carbon. Similarly,  $\text{S}_{\text{N}}2$  pathways have been assigned for the stoichiometric ring opening of epoxide by  $\text{HCo}(\text{CO})_4$ <sup>49</sup> and  $\text{Ph}_3\text{SiCo}(\text{CO})_4$ .<sup>50</sup>

The kinetics for the carbonylation of EB were also measured while varying the catalyst concentration (Figure 2) to determine the reaction order in **1**. As the concentration of EB does not affect the rate of carbonylation, this study was carried out while maintaining a constant ratio of  $[EB]_0/[1]$ .<sup>51</sup> From these experiments, we found that the rate of  $\beta$ -VL formation depended linearly on the concentration of catalyst **1**, so the reaction is

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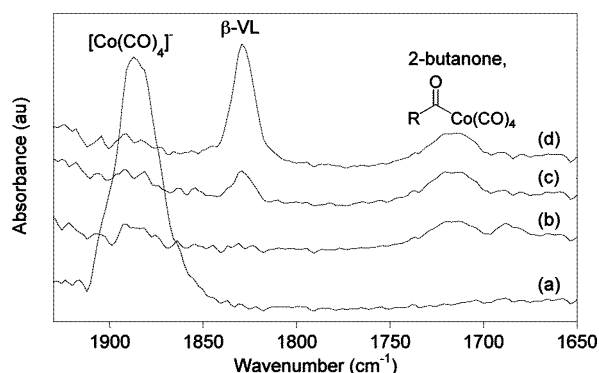
(47) See Supporting Information for details.

(48) Carbonylations of the substrates isobutylene oxide<sup>23</sup> and styrene oxide (Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W.; unpublished results) yield some  $\alpha$ -substituted- $\beta$ -lactones, indicating that reaction of  $[\text{Co}(\text{CO})_4]^-$  with the more substituted carbon is possible for the special cases of aryl-substituted or gem-disubstituted epoxides.

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(51) Consequentially, potential side reactions of **1** with undetected impurities in the EB were not magnified at low catalyst concentration.



**Figure 3.** IR spectra of (a) catalyst **1** in 1,2-dimethoxyethane solution, (b) immediately following addition of 1,2-epoxybutane and CO ( $t = 0$  min), (c)  $t = 1$  min, and (d)  $t = 5$  min.

first-order in **1** (eq 3). The reaction rate was unaltered by the

$$d[\beta\text{-VL}]/dt = k[\text{EB}]^0 P_{\text{CO}}^y [\mathbf{1}] \quad (3)$$

addition of excess  $[(\text{salph})\text{Al}(\text{THF})_2]^+$  (as the  $[\text{BPh}_4]^-$  salt) or  $[\text{Co}(\text{CO})_4]^-$  (as the  $[\text{PPh}_4]^+$  salt). As the activated epoxide is attacked by  $[\text{Co}(\text{CO})_4]^-$  in an  $\text{S}_{\text{N}}2$  fashion, the absence of an order in  $[\text{Co}(\text{CO})_4]^-$  suggests that either (a) the epoxide ring opening is not rate-limiting, or (b) following the dissociative substitution of an epoxide for THF on the cation of **1**, attack by  $[\text{Co}(\text{CO})_4]^-$  occurs within the ion pair  $[(\text{salph})\text{Al}(\text{THF})(\text{EB})]^+[\text{Co}(\text{CO})_4]^-$ , to the exclusion of other ions. These situations can be distinguished by the form of the cobalt in solution. If the ring opening is fast, then  $[\text{Co}(\text{CO})_4]^-$  should not be present, whereas it should be observed in the event of slow substitution within an ion pair. Using in situ IR spectroscopy, we monitored the  $[\text{Co}(\text{CO})_4]^-$  ion directly over the course of the carbonylation (Figure 3). The IR spectrum of **1** in DME (Figure 3a) shows a strong absorption at  $1887\text{ cm}^{-1}$ , assigned to the  $\nu(\text{CO})$  of the  $[\text{Co}(\text{CO})_4]^-$  ion (cf.  $1885\text{ cm}^{-1}$  for solid-state  $\text{I}^{23}$ ). Within one minute of the addition of EB and CO, this band disappears completely (Figure 3b); the  $\nu(\text{C}=\text{O})$  for lactone then appears at  $1827\text{ cm}^{-1}$  (Figure 3c,d). Given the immediate and total disappearance of  $[\text{Co}(\text{CO})_4]^-$  from solution, epoxide ring opening must be very fast on the time scale of the overall reaction and, therefore, is not the rate-determining step. Although  $[\text{Co}(\text{CO})_4]^-$  is only a modest nucleophile,<sup>52,53</sup> rapid ring opening is not unexpected in this system; computational studies found a low barrier to ring opening for epoxides activated by strong Lewis acids<sup>30,34</sup> and, in particular, by aluminum cations.<sup>30</sup>

The cationic  $[(\text{salph})\text{Al}(\text{THF})(\text{EB})]^+$  is converted to a neutral aluminum alkoxide upon the ring opening of epoxide. In both solid and solution phases, aluminum cations supported by ligands of the salen(Bu) family (i.e., having the general form  $N,N'$ -alkylene (or arylene) bis(3,5-di-*tert*-butylsalicylidene-imine)) are almost always six-coordinate;<sup>54–56</sup> the only reported

exceptions cannot be prepared in the presence of donor solvents.<sup>57</sup> Conversely, aluminum alkoxides and siloxides supported by these ligands are five-coordinate at room temperature in solution ( $\text{C}_6\text{D}_6$  and  $\text{CDCl}_3$ ) and in the solid phase, even when crystallized from donor solvents.<sup>56,58–64</sup> Further, the binding of 4-(*N,N*-dimethylamino)pyridine, a strong donor, to the aluminum alkoxide (TPP)AlOR has been shown to be much weaker than to the related carbonate and carboxylate, (TPP)AlO<sub>2</sub>COR and (TPP)AlO<sub>2</sub>CR (TPP = tetraphenylporphyrin), respectively.<sup>60</sup> Given this preference of salen(Bu)-supported aluminum alkoxides for pentacoordination, the conversion of the aluminum center from a cation to a neutral alkoxide likely results in the dissociation of the trans-coordinated solvent molecule. Therefore, we formulate the aluminum-alkoxide/cobalt-alkyl species that results from opening of EB as (salph)AlOCH(Et)CH<sub>2</sub>Co(CO)<sub>4</sub> (Scheme 2, intermediate **2**,  $L_n\text{M} = (\text{salph})\text{Al}$ ,  $\text{R} = \text{Et}$ ,  $\text{R}' = \text{H}$ ).

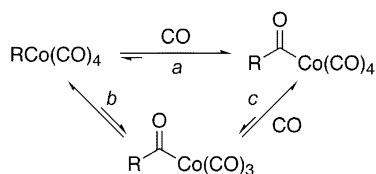
**(III) Insertion of Carbon Monoxide into the Cobalt–Alkyl Bond.** The effect of carbon monoxide pressure on the reaction rate was observed by in situ IR spectroscopy. From four runs with  $[\text{EB}]_0 = 1.24 \pm 0.01\text{ M}$ ,  $P_{\text{CO}} = 300 \pm 10\text{ psi}$ ,  $[\mathbf{1}] = 11.6 \pm 0.1\text{ mM}$ , and  $T = 25.0 \pm 0.5\text{ }^\circ\text{C}$ , the reaction rate was calculated to be  $6.2 \pm 0.5\text{ mM}\cdot\text{min}^{-1}$ . The same reaction was repeated at a range of CO pressures from 220 to 1045 psi (see Table S1, Supporting Information). In each case, the rate was found to be within error of the rate determined for  $P_{\text{CO}} = 300\text{ psi}$ . Thus, the reaction rate is independent of CO pressure over the range considered (eq 4).

$$d[\beta\text{-VL}]/dt = k[\text{EB}]^0 P_{\text{CO}}^0 [\mathbf{1}] \quad (4)$$

The insertion of CO into the cobalt–alkyl bond was also observed spectroscopically. The IR spectra of tetracarbonyl-cobalt alkyls and acyls have been extensively studied.<sup>65</sup> Although the spectra for the alkyl and corresponding acyl species are very similar in most cases, the latter type contains an additional  $\nu(\text{C}=\text{O})$  absorbance associated with the cobalt acyl group. The frequency of this stretch depends on the nature of the alkyl/acyl group but is generally close to  $1700\text{ cm}^{-1}$ .<sup>65</sup> When we added EB and CO to a solution of **1**, we observed a broad absorption, centered at  $1715\text{ cm}^{-1}$  (Figure 3b–d), which persisted in solution during the carbonylation. This band could be assigned to the  $\nu(\text{C}=\text{O})$  of a cobalt acyl; similar assignments (of bands at  $1717$  or  $1710\text{ cm}^{-1}$ ) have been made in related systems.<sup>30–32,45,46</sup> However, catalysts of the type  $[\text{Lewis acid}]^+[\text{Co}(\text{CO})_4]^-$  are known to produce small amounts of ketone (isomeric to the starting epoxide) as byproducts of epoxide carbonylation,<sup>22,23,30</sup> and these are also expected to have

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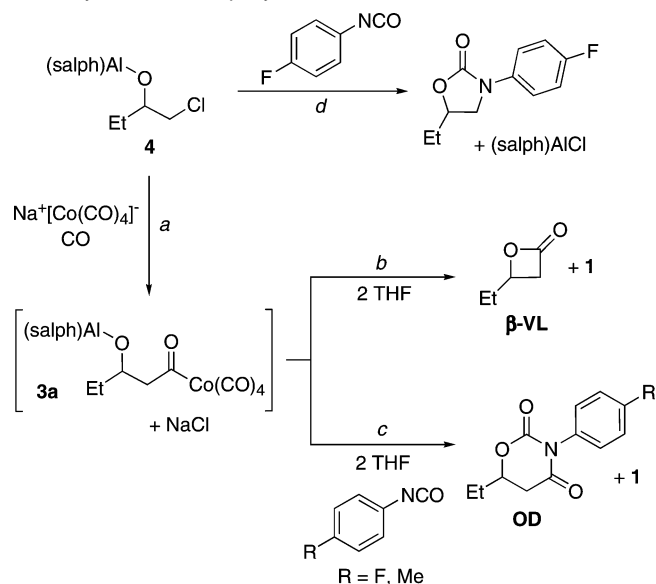
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**Scheme 3.** Equilibria between Alkyl- and Acyl-Cobalt Carbonyls

$\nu(\text{C}=\text{O})$  absorptions at  $\sim 1715\text{ cm}^{-1}$ .<sup>66</sup> To confirm that the peak at  $1715\text{ cm}^{-1}$  is due to a cobalt acyl, we repeated the carbonylation reaction using  $^{13}\text{CO}$ . We expected this isotopic substitution to affect the stretching frequency of cobalt-acyl intermediates but not of ketones formed from isomerization of epoxide. In fact, the IR spectra of the reaction run with  $^{13}\text{CO}$  revealed multiple  $\nu(\text{C}=\text{O})$  peaks. First, a new band at  $1783\text{ cm}^{-1}$  grew in during the reaction and was assigned to  $\nu(^{13}\text{C}=\text{O})$  of  $\beta$ -VL (cf.  $1786\text{ cm}^{-1}$  predicted by Hooke's Law<sup>66</sup>). In addition, two smaller bands were present immediately after adding EB and CO. One was similar to that observed in the spectra of the unlabeled reaction, though less broad, and centered at  $1719\text{ cm}^{-1}$ ; this is attributed to small amounts of 2-butanone (confirmed to be present by GC of the final reaction mixture). The other, a new peak, appeared at  $1677\text{ cm}^{-1}$ , which agrees with the predicted  $\nu(^{13}\text{C}=\text{O})$  of a cobalt acyl. Thus, in spectra collected with unlabeled CO, both ketone and cobalt-acyl moieties coincidentally absorb at  $\sim 1715\text{ cm}^{-1}$ . However, these species can be distinguished using isotopically labeled CO. In the present system, a persistent cobalt-acyl species appears in solution immediately upon addition of epoxide and CO, indicating that carbon monoxide insertion is rapid.

The insertion of CO into alkylcobalt tetracarbonyl and related alkylcobalt monophosphine tricarbonyl complexes has been examined in detail for a variety of systems<sup>65,67</sup> and is generally thought to occur in two steps (Scheme 3, *b* and *c*).<sup>52,68</sup> First, an intramolecular CO insertion yields an unsaturated intermediate, which is believed to be stabilized by  $\eta^2$ -coordination of the cobalt acyl.<sup>67,69</sup>

The rapidity of the CO insertion in this system is not surprising, given the propensity of saturated alkylcobalt carbonyls to insert CO. In the cases of primary R groups without electron-withdrawing substituents, equilibrium *a* in Scheme 3 lies far to the acyl side.<sup>70</sup> The rate of the reverse reaction has been studied for R = Me; release of CO from acetylcobalt tetracarbonyl in an argon atmosphere is rapid.<sup>71</sup> Further, as the equilibrium strongly favors the acyl complex in that case,<sup>71</sup> the insertion of CO into the cobalt-alkyl bond is faster, particularly under the conditions of our study (i.e.,  $220\text{ psi} \leq P_{\text{CO}} \leq 1045\text{ psi}$ ). Indeed, an NMR spectroscopic study of  $^{13}\text{CO}$  exchange between  $\text{MeCoCo}(\text{CO})_4$  and free CO under comparable pressures found acyl formation to be significantly faster than alkyl formation.<sup>72</sup> It is the swift nature of CO insertion into the cobalt-alkyl bond that allows lactone, rather than ketone, to be produced in this system. At low pressures of CO, intermediate

**Scheme 4.** Proposed Resting State **3a** in the 1-Catalyzed Carbonylation of 1,2-Epoxybutane<sup>a</sup>

<sup>a</sup> (a) Formation of **3a** from [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (**4**) and Na<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>. (b) Decay of **3a** to  $\beta$ -VL. (c) Trapping of **3a** with isocyanates to form 1,3-oxazine-2,4-diones, OD. (d) Reaction of the model aluminum alkoxide **4** with isocyanate.

**2** can be diverted to ketone. A plausible mechanism for this rearrangement has been proposed,<sup>41</sup> though it is supported only by regiochemical data. In it,  $\beta$ -H elimination occurs from a ( $\beta$ -metalloxy)cobaltalkyl (such as **2**) to form a vinyloxy metal species and HCo(CO)<sub>4</sub>. Protonation of the vinyloxy group and subsequent tautomerization yields the ketone and regenerates the catalyst.

Calculations suggest that during catalytic epoxide carbonylation, the alkoxide oxygen, still bound to a Lewis acid, may stabilize the RCoCo(CO)<sub>3</sub> intermediate through the reversible formation of a 2-metalla-3-oxo-furan species.<sup>34</sup> Though this process was calculated to be competitive with CO uptake when BF<sub>3</sub> was used as a Lewis acid, the steric bulk of the salph ligand would likely preclude its formation in our system. The same calculations found that lactone ring closing could actually precede CO uptake when a soft Lewis acid (such as B(CH<sub>3</sub>)<sub>3</sub>) was used, but that this pathway is very high in energy ( $\Delta H^\ddagger \approx 35\text{ kcal/mol}$ ) for the harder, more Lewis acidic BF<sub>3</sub>. The aluminum cation used in our system is a hard Lewis acid,<sup>73,74</sup> so this pathway is not expected to be significant.

**The Resting State of Catalyst 1.** We have shown that steps I–III in Scheme 2 are fast on the time scale of the catalysis, as (1) neither epoxide nor CO is represented in the rate equation, (2) in situ IR spectroscopy indicates that [Co(CO)<sub>4</sub>]<sup>-</sup> is not observed in solution during lactone formation, and (3) the  $\nu(\text{C}=\text{O})$  for cobalt acyl appears immediately upon CO addition. Therefore, so long as both epoxide and CO remain in the reaction mixture, **1** exists not as the ion pair [(salph)Al(solvent)]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> but as the neutral aluminum-alkoxide/cobalt-acyl **3a**, as depicted in Scheme 4 (cf. Scheme 2, intermediate **3**, where L<sub>n</sub>M = (salph)Al, R = Et, R' = H).

Evidence that **3a** could be an intermediate in the carbonylation of epoxides by **1** was obtained from its independent synthe-

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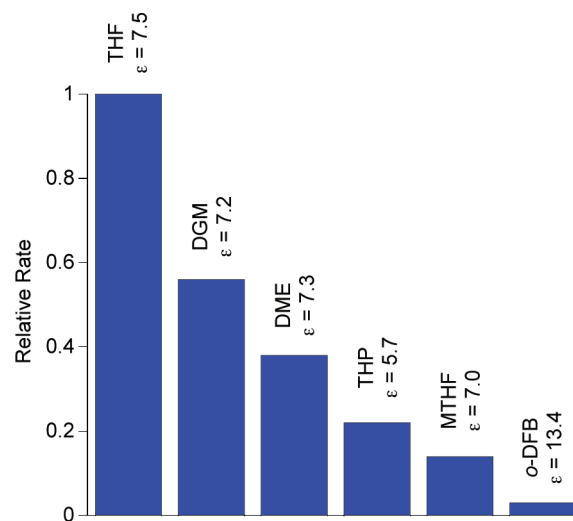
sis. When a model aluminum–alkoxide, [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (**4**), was combined with Na<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>−</sup> in DME solution and under a pressure of 300 psi of carbon monoxide, there was no reaction at room temperature. Heating the reaction mixture to 80 °C resulted in the appearance of β-VL in solution. We propose that **3a** is formed through a slow substitution of [Co(CO)<sub>4</sub>]<sup>−</sup> onto the alkyl chloride of **4** and subsequent CO insertion into the new cobalt–alkyl bond (Scheme 4a). The formation of β-VL then occurs by ring closing (Scheme 4b). Unfortunately, we were unable to measure the rate for this process, as the substitution reaction was rate-determining. However, assuming that the substitution reaction produced **3a**, the ensuing β-VL production supports that **3a** is on the reaction path to lactone.

Further, as we suspected that **3a** is the resting state in the catalytic cycle, we attempted to intercept it via reaction of the aluminum–alkoxide terminus with electrophiles. We used isocyanates for this purpose because they do not participate in side reactions with the catalyst, the epoxide, CO, or the lactone product. We predicted that the aluminum alkoxide of **3a** would react with isocyanate to form an aluminum carbamate, which could then attack the cobalt–acyl moiety to form a six-membered 1,3-oxazine-2,4-dione (OD, Scheme 4c). When the carbonylation of EB in DME was run in the presence of 4-Me-C<sub>6</sub>H<sub>4</sub>NCO ([ArNCO] = 0.50 M, [I] = 0.0115 M, [EB] = 0.55 M), β-VL was the only product detected in the crude reaction mixture; the isocyanate was unchanged. However, when the more electrophilic 4-F-C<sub>6</sub>H<sub>4</sub>NCO was used under identical conditions, the products were 93% β-VL and 7% OD (in this case 6-ethyl-3-(4-fluorophenyl)-1,3-oxazine-2,4-dione). That intermediate **3a** can be diverted during the carbonylation reaction suggests that it has a significant lifetime in solution, consistent with its assignment as the resting state.

**(IV) Closing of the Lactone Ring.** With **3a** as the catalyst resting state, the rate-determining step of the reaction must occur during the lactone ring-closing or dissociation events. To gain further insight into these processes, we examined the effect of solvent on the catalysis. Although epoxide carbonylation by **1** can be run in neat substrate,<sup>23</sup> the rate law was measured in DME, and the reaction was also run in a number of other solvents. The rate of carbonylation was found to vary widely depending on the reaction solvent. It was generally fastest in moderately polar solvents, such as ethers (at 25 °C, the reaction is much faster in DME than in neat epoxide). In nonpolar or weakly polar solvents, such as hexanes or toluene, catalyst **1** was insoluble, and the overall reaction was slowed. Although solutions of **1** are generally red, addition of the catalyst to very polar, strongly donating, acetonitrile resulted in a yellow solution. Carbonylation in this solvent was slow and first-order in epoxide, indicative of a change in mechanism or in rate-determining step compared to the DME case. We suspect that one or both THF molecules of **1** are displaced by CH<sub>3</sub>CN, and that epoxide must displace these strong bases prior to carbonylation. Finally, the use of halomethane solvents resulted in a severe reduction of catalyst activity, presumably due to reaction of [Co(CO)<sub>4</sub>]<sup>−</sup> with these compounds.<sup>75</sup>

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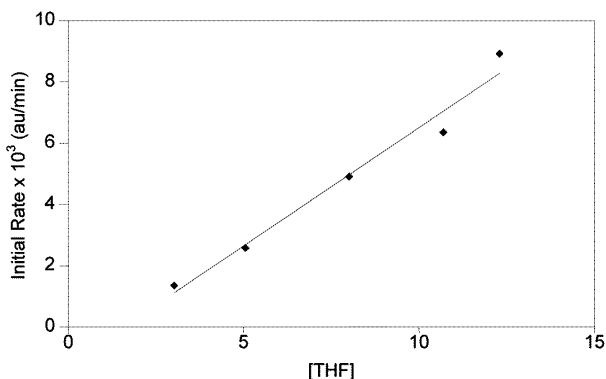
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**Figure 4.** Comparison of the rate of carbonylation of 1,2-epoxybutane (EB) by catalyst **1** in various solvents.  $\epsilon$  = dielectric constant.<sup>76</sup> [I] = 11.6 ± 0.1 mM, [EB]<sub>0</sub> = 1.25 ± 0.01 M,  $P_{\text{CO}}$  = 300 ± 10 psi, T = 25.0 ± 0.5 °C. THF = tetrahydrofuran, DGM = diglyme, DME = 1,2-dimethoxyethane, THP = tetrahydropyran, MTHF = 2-methyltetrahydrofuran, *o*-DFB = 1,2-difluorobenzene.

To investigate the origin of the large solvent dependence of the reaction, we repeated the carbonylation in a number of moderately polar solvents, primarily ethers (Figure 4). Though complete rate laws were not obtained in each solvent, we confirmed that the reaction was zero-order in epoxide for each solvent, as it was in DME. Additionally, isocyanate was added to the slowest and fastest carbonylations to intercept the catalyst resting state in these solvents. In 1,2-difluorobenzene (*o*-DFB, slowest), the carbonylation of EB in the presence of 4-Me-C<sub>6</sub>H<sub>4</sub>NCO ([ArNCO] = 0.58 M, [I] = 0.0116 M, [EB] = 0.63 M) yielded 83% β-VL and 17% OD (cf. 100% β-VL in DME, *vide supra*). Because the reaction is slow in *o*-DFB, **3a** is longer-lived and can be intercepted with the less electrophilic isocyanate (Ar = 4-Me-C<sub>6</sub>H<sub>4</sub>), whereas the stronger electrophile 4-F-C<sub>6</sub>H<sub>4</sub>NCO was required in DME. In THF (fastest), however, no OD was detected with either 4-Me-C<sub>6</sub>H<sub>4</sub>NCO or 4-F-C<sub>6</sub>H<sub>4</sub>NCO present. We believe that this result is likely due to much faster lactone formation than isocyanate insertion in this solvent, and not to a change in resting state for the catalyst. To test this hypothesis, we reacted a model compound, [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (**4**), with 4-F-C<sub>6</sub>H<sub>4</sub>NCO in THF-*d*<sub>8</sub> and monitored the reaction by <sup>1</sup>H NMR spectroscopy (Scheme 4d). Under the conditions employed ([**4**] = 0.0116 M, [4-F-C<sub>6</sub>H<sub>4</sub>NCO] = 0.67 M, T = 25 °C), the reaction was found to proceed quite slowly, with an initial rate (−d[**4**]/dt) of 4.3 × 10<sup>−6</sup> M/min. Based on this rate and the rate of epoxide carbonylation in THF, only 0.03% OD is expected when epoxide carbonylation is run in the presence of 4-F-C<sub>6</sub>H<sub>4</sub>NCO, using THF as a solvent.<sup>47</sup> Thus, the failure to observe OD in carbonylations run in THF is attributed to the inability of isocyanate insertion to compete with rapid lactone formation.

With the presumption that epoxide carbonylation occurs via the same mechanism in each of the solvents shown in Figure 4, we continued to analyze the effect of solvent on the rate of carbonylation. Though moderately polar solvents generally accelerate the carbonylation, the disparity in rates we observed cannot be explained solely on polarity. For example, although



**Figure 5.** Effect of tetrahydrofuran (THF) concentration on the rate of carbonylation of 1,2-epoxybutane (EB) to  $\beta$ -valerolactone, in mixtures of THF/2,5-dimethylTHF. Reaction was monitored by in situ IR spectroscopy, and initial rates taken for 5 to 15% conversion. [1] =  $11.5 \pm 0.1$  mM, [EB] =  $1.27 \pm 0.01$  M,  $P_{\text{CO}} = 300 \pm 10$  psi,  $T = 25.0 \pm 0.5$  °C.

THF, DME, and diglyme (DGM) have very similar dielectric constants  $\epsilon$ ,<sup>76</sup> the reaction rate using THF as a solvent is nearly twice that using DGM, and nearly three times that using DME. Further, the reaction is slower in 2-methyltetrahydrofuran (MTHF) than in tetrahydrofuran (THF), though the former has a significantly higher dielectric constant. When polar but noncoordinating *o*-DFB ( $\epsilon = 13.4$ <sup>76</sup>) was used, the reaction was extremely slow, reaching only 52% conversion after 28 h (cf. 100% conversion after 90 min in THF). Thus, the polarity of the solvent used for the carbonylation reaction is not a consistent predictor of the relative rate of catalysis.

The large rate difference between reactions conducted in THF and MTHF (Figure 4) suggests that solvent Lewis basicity has a significant impact on the reaction, as the increased steric bulk about the O atom of MTHF makes it a weaker donor. To further probe the effect of solvent basicity on the rate of carbonylation, we examined the reaction in mixtures of THF and the more sterically encumbered DMTHF (DMTHF = 2,5-dimethyltetrahydrofuran, 56% *cis*, 44% *trans*), which allow the concentration of THF to be varied with minimum impact on polarity.<sup>77</sup> We varied the THF concentration from 3.02 to 12.3 M (neat THF)<sup>78</sup> and found that the rate of carbonylation exhibited a first-order dependence on THF (Figure 5). Additionally, when the carbonylation was performed in a 1:1 mixture of DME and DMTHF,  $\beta$ -VL formation was  $\sim 3.6$  times slower than in DME. Thus, the rate law formulated in eq 4 is incomplete; a solvent term is necessary (eq 5).

$$d[\beta\text{-VL}]/dt = k[\text{EB}]^0 P_{\text{CO}}^0 [\mathbf{1}][\text{solvent}] \quad (5)$$

The appearance of solvent in the rate law for catalysis implies that a solvent molecule must enter the catalytic cycle between the resting state and rate-limiting transition state. This could be explained if a slow, solvent-assisted displacement of the product lactone from the aluminum center was necessary before another epoxide could be activated. This possibility is discarded, however, because the reaction rate is independent of the concentration of lactone and because [Co(CO)<sub>4</sub>]<sup>-</sup> (regenerated upon lactone ring closing) is not detected in solution during the reaction.

Instead, we propose that the coordination of a Lewis base to the aluminum center is necessary to facilitate the transformation from the neutral aluminum alkoxide, which exists in the ground state, to an aluminum cation. Whereas the aluminum alkoxide is stable as a five-coordinate species, the cation is not; addition of a Lewis base is required for stabilization (*vide supra*). Coordination of a Lewis base to an unsaturated aluminum cation is likely favorable and rapid; thus, the presence of solvent in the rate law indicates that the coordination event must occur immediately before, or concurrently with, lactone ring closing. Although we are unable to distinguish between these cases, the former evokes the ability of neutral, nitrogen-containing donors to accelerate the catalytic copolymerization of epoxides and CO<sub>2</sub> by LAIX complexes (L = porphyrin, X = Cl, OR). In this case, the Lewis base has been proposed to facilitate CO<sub>2</sub> insertion by weakening the Al–O bond of the aluminum–alkoxide intermediates.<sup>60,79</sup>

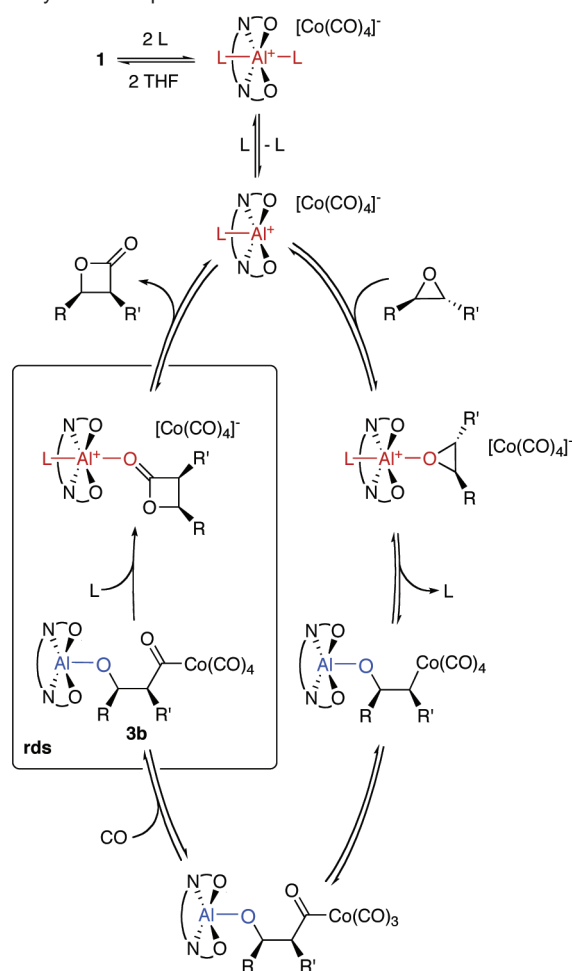
The importance of stabilizing the cationic aluminum accounts for the strong influence of solvent on the rate of this reaction, even among solvents having similar polarities. Coordinating solvents, such as THF or other unhindered ethers, successfully stabilize the aluminum in this form, so the reaction is fast. Polar solvents that are weak donors (such as MTHF, DMTHF, or *o*-DFB) stabilize the aluminum cation less effectively, and result in slower carbonylation. Very polar solvents, such as CH<sub>3</sub>CN, likely coordinate to the aluminum strongly and inhibit epoxide binding. In the absence of solvent, the reaction is first-order in epoxide. In this case, an equivalent of epoxide or lactone, or a THF molecule from **1**, must solvate the aluminum cation, resulting in an order in epoxide. Presumably, epoxide or lactone could fulfill this role even when a donor solvent is available. However, neither epoxide nor lactone is represented in the rate equation for the solvated reaction. Therefore, the donor solvents examined are considerably better at stabilizing the aluminum cation, rendering the effects of epoxide and lactone negligible (i.e.,  $k_{\text{solvent}}[\text{donor solvent}] \gg k_{\text{epoxide}}[\text{epoxide}], k_{\text{lactone}}[\text{lactone}]$ ).

A modified catalytic cycle, which accounts for the new mechanistic data, is shown in Scheme 5. The first four steps (epoxide binding, ring opening, CO insertion, and CO uptake) occur immediately upon addition of epoxide and CO to the catalyst solution, forming the ground-state structure **3b** (Scheme 5; cf. Scheme 2, intermediate **3**, where  $L_nM = (\text{salph})\text{Al}$ ). This species is comprised of a neutral, five-coordinate aluminum alkoxide and a cobalt acyl. The intramolecular nucleophilic attack of the aluminum alkoxide of **3b** on its cobalt acyl yields the four-membered lactone ring. As the lactone is formed, the neutral aluminum alkoxide becomes an aluminum cation, and the [Co(CO)<sub>4</sub>]<sup>-</sup> ion is released. The aluminum cation is highly electrophilic and must be stabilized by the coordination of a Lewis base, either before or during ring closing. This coordination process is analogous to the microscopic reverse of epoxide ring opening; in that case, a donor molecule is released when the aluminum alkoxide is formed. The combination of ring closing and Lewis base uptake is rate-determining; thus, the role of solvent in this system is critical.

On the basis of computational and experimental studies of

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 (78) The reaction rate was not measured in DMTHF. Due to lower solubility, an 11.6 mM solution of **1** cannot be prepared in DMTHF.

(79) It should be noted that this differs considerably from the roles played by nitrogen-containing donors in epoxide/CO<sub>2</sub> copolymerizations catalyzed by (salen)CrX complexes. Darensbourg, D. J.; Mackiewicz, R. *J. Am. Chem. Soc.* **2005**, *127*, 14026–14038.

**Scheme 5.** Expanded Mechanistic Cycle for the **1**-Catalyzed Carbonylation of Epoxides<sup>a</sup>

<sup>a</sup> L = Lewis base (solvent, epoxide, lactone). Neutral aluminum centers are shown in blue, cationic aluminum centers are in red. rds = Rate-determining step.

epoxide carbonylation using  $[\text{Co}(\text{CO})_4]^-$  in concert with some simple Lewis acids, Molnar et al. noted that the relative energetic barriers for epoxide ring opening and lactone ring closing depend strongly on the strength of the Lewis acid.<sup>30</sup> Not surprisingly, strong Lewis acids result in facile ring opening but energetically demanding ring closing; the converse is true for weaker Lewis acids. An aluminum cation such as  $[(\text{salph})\text{Al}(\text{THF})_2]^+$  is a very strong Lewis acid, and as such would be expected to result in fast epoxide ring opening, but slow lactone formation. The high activity of **1** as an epoxide carbonylation catalyst is attributable to the presence of weak, highly labile Lewis bases, which may be solvent or substrate molecules. In reversibly binding to the aluminum center, they modulate its Lewis acidity, resulting in both rapid epoxide opening and rapid lactone closing.

## Conclusions

Compound **1** is known to efficiently carbonylate epoxides to lactones.<sup>23</sup> In this study, we have presented kinetic and spectroscopic data demonstrating that **1** reacts rapidly with epoxide and CO to form the ( $\beta$ -metalloy)acylcobalt species **3b**. Addition of an aryl isocyanate to the carbonylation system traps **3b**, forming a 1,3-oxazine-2,4-dione derivative, which also supports the assignment of **3b** as the catalyst resting state. When **3a** (cf. **3b**, R = Et, R' = H) is synthesized independently from

$[\text{rac}-(\text{salph})\text{AlOCH}(\text{Et})\text{CH}_2\text{Cl}]$  and  $\text{Na}^+[\text{Co}(\text{CO})_4]^-$ , decay to  $\beta$ -VL is observed.

Kinetic and solvent studies of the catalytic carbonylation of 1,2-epoxybutane by **1** also indicate that the rate-determining step in the cycle is generation of lactone product from **3b**. Moreover, this process requires the coordination of a Lewis base to the aluminum center. Though epoxide can perform this function, donating solvents such as THF, DME, and DGM do so more effectively, and result in increased rates of epoxide carbonylation.

In general, epoxide carbonylation catalysts of the form  $[\text{Lewis acid}]^+[\text{Co}(\text{CO})_4]^-$  are highly active. As all of these complexes facilitate very rapid epoxide ring opening, resulting in stable metal alkoxides, stabilization of the cationic form of the Lewis acid provides for faster catalyst turnover (as long as epoxide activation is not compromised). In the present system, we found that donor solvents are effective for this purpose.<sup>80</sup> We hypothesize that through the use of a ligand that more readily delocalizes charge on aluminum, the rate of epoxide carbonylation can be increased.

As this is the first experimental study to examine each step of a catalytic epoxide carbonylation, we believe that the insight gained will be of use in comprehending related catalysts (i.e., of the form  $[\text{Lewis acid}]^+[\text{M}(\text{CO})_n]^-$ ), and the carbonylation of other substrates. All catalysts for this reaction must be able to perform each of the four basic steps shown in Scheme 2. Rational improvement of a carbonylation catalyst entails an appreciation of the challenges at each step. In seeking a strategy for elucidating the mechanism of catalytic epoxide carbonylation, we found it useful to (1) establish the reaction order in the substrates and catalyst (as well as its components), (2) examine the effect of solvent of the reaction, (3) study the IR spectrum of the catalyst, and (4) attempt to intercept the catalyst resting state with an isocyanate. Upon the basis of the results of these mechanistic probes, we have pinpointed the resting state and rate-determining step of the cycle operative for the case of catalyst **1**. We anticipate that this approach will be valuable for the study of related catalysts as well and will aid in the creation of improved catalysts. Investigations into new catalysts are currently underway in our laboratory, as are mechanistic explorations of the carbonylation of other substrate types.

## Experimental Procedures

**General Considerations.** All air- and/or water-sensitive reactions were carried out under dry nitrogen using an MBraun UniLab drybox or standard Schlenk line techniques. All syringes were gastight and were dried overnight in a glassware oven prior to use. NMR spectra were recorded on Varian Mercury 300 (<sup>1</sup>H, 300 MHz; <sup>13</sup>C, 75 MHz), Bruker ASX 300 (<sup>1</sup>H, 300 MHz; <sup>13</sup>C, 75 MHz), or Varian INOVA-400 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz) spectrometers and referenced versus residual solvent shifts. Gas chromatography (GC) analyses were performed on an HP 6890 Series GC equipped with an HP 19091J-413 phenylmethylsilicone column (0.32 mm  $\times$  30 m). All in situ IR spectroscopic reactions were carried out using a 100-mL, stainless steel, high-pressure Parr reactor modified for use with a Mettler-Toledo

(80) Molnar et al. found that  $\text{Co}_2(\text{CO})_8/\text{AlMe}_3$  also rapidly catalyzes epoxide carbonylation.<sup>30</sup> They propose that this mixture forms  $[\text{AlMe}_2\cdot\text{diglyme}]^+$  in diglyme solution. On the basis of DFT calculations, they attribute its ability to carbonylate epoxides to lactones to the availability of a stabilizing interaction between the Co and an H atom of the lactone in the transition state. Although we cannot rule out the participation of such an interaction in our system, the experimental evidence in our study suggests that the participation of solvent allows **1** to effect rapid lactone ring closing.



ReactIR 4000 Reaction Analysis System fitted with a Sentinel DiComp High-Pressure Probe. Data were acquired and analyzed using ReactIR software version 2.21.

1,2-Dimethoxyethane (DME), diglyme (DGM), 2-methyltetrahydrofuran (MTHF), and 2,5-dimethyltetrahydrofuran (DMTHF) were refluxed with Na/benzophenone for a minimum of 16 h and then distilled under nitrogen and degassed via freeze–pump–thaw cycles. Tetrahydrofuran was dried over columns of alumina<sup>81</sup> and degassed via freeze–pump–thaw cycles. 1,2-Difluorobenzene was stirred over P<sub>2</sub>O<sub>5</sub> for 8 days and then vacuum transferred and degassed via freeze–pump–thaw cycles. Benzene-*d*<sub>6</sub> and tetrahydrofuran-*d*<sub>8</sub> were dried over Na/benzophenone, vacuum transferred, and sparged with dry nitrogen. 1,2-Epoxybutane was purchased from Aldrich, stirred over CaH<sub>2</sub>, then distilled under nitrogen and degassed. Carbon monoxide (Research Grade) was purchased from Matheson and used as received. Labeled <sup>13</sup>C was purchased from Cambridge Isotope Laboratories, Inc., with the aid of a Research Grant, and was also used as received. The complexes [(salph)Al(THF)<sub>2</sub>]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup> (**1**),<sup>23</sup> [PPh<sub>4</sub>]<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup>,<sup>82</sup> and Na<sup>+</sup>[Co(CO)<sub>4</sub>]<sup>-</sup><sup>83</sup> were prepared as previously reported. [(salph)-Al(THF)<sub>2</sub>]<sup>+</sup>[BPh<sub>4</sub>]<sup>-</sup> was synthesized according to the published procedure for [(*R,R*)-salcy(<sup>t</sup>Bu)Al(THF)<sub>2</sub>]<sup>+</sup>[BPh<sub>4</sub>]<sup>-</sup> (salcy = *N,N'*-cyclohexylenebis(3,5-di-*tert*-butylsalicylideneimine),<sup>52,84</sup> and [*rac*-(salph)-AlOCH(Et)CH<sub>2</sub>Cl] (**4**) was formed using the procedure for the related [(*R,R*)-salen(<sup>t</sup>Bu)AlOCH(*S*-Me)CH<sub>2</sub>Cl].<sup>61</sup> β-Valerolactone was prepared from 1,2-epoxybutane and CO using catalyst **1**, washed through Celite with diethyl ether, and distilled. It was then stirred for 1 week with 4 Å molecular sieves, vacuum transferred onto CaH<sub>2</sub>, stirred for 1 week, and vacuum transferred. 4-Methylphenyl isocyanate and 4-fluorophenyl isocyanate were purchased from Aldrich, distilled from P<sub>2</sub>O<sub>5</sub>, and degassed.

**Representative Procedure for In Situ Infrared Experiments.** The assembled Parr reactor was dried at 90 °C under vacuum overnight and allowed to cool. It was then sealed under vacuum and brought into the glovebox. A solution of **1** (0.107 g, 0.122 mmol) in DME (9.09 g, 101 mmol) was prepared in a scintillation vial, and 10.0 mL were drawn into a glass syringe. The needle was inserted through a septum covering the injection port of the reactor. 1,2-Epoxybutane (1.09 mL, 11.6 mmol) was drawn into another syringe, which was also inserted through the septum. The reactor was removed from the glovebox and connected to the React-IR. A heating jacket was added, and the heater was set to 25 °C. After ~5 min, a background spectrum (16 scans) was recorded. Following this, IR spectra (16 scans/spectrum at a gain of 2 and a resolution of 4 cm<sup>-1</sup>) were recorded every minute. After the first spectrum was recorded, the catalyst solution was injected into the reactor, and the solution was stirred until a temperature of 25 °C was reached. The epoxide was then added to the solution, and the system was immediately pressurized with CO to 300 psi. The formation of the product was recorded via the emergence of the carbonyl stretch of lactone. The reaction was allowed to proceed until no more lactone was being formed (i.e., the lactone absorbance was constant). The CO was then vented, and the crude reaction mixture was transferred to a scintillation vial. Product analysis was confirmed by GC and, in some cases, by <sup>1</sup>H NMR spectroscopy.

**Procedure for In Situ Infrared Observation of Reactions in THF/DMTHF.** When carried out in THF/DMTHF mixtures, the carbonylation reaction was performed as described above; however, IR spectra (8 scans/spectrum, at a gain of 2 and resolution of 8 cm<sup>-1</sup>) were collected every 8.3 s, to collect more data during the early stages of the reaction.

**Reaction of [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (**4**) with 4-Fluorophenyl Isocyanate.** In a glovebox, [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (5.46

mg, 8.11 μmol) was dissolved in THF-*d*<sub>8</sub> (0.70 mL, 8.6 mmol), and 0.60 mL of the solution was transferred into a predried NMR tube modified with a Kontes valve. The NMR tube was then charged with 4-F-C<sub>6</sub>H<sub>4</sub>NCO (46 μL, 0.40 mmol) via syringe, and the sample was sealed. The sample was immediately transported to the INOVA 400 MHz NMR spectrometer (equilibrated at 25 °C), and spectra were recorded every 2 min. The integral, *I*, of the imine resonance of the starting material (δ = 9.22 ppm) was used to monitor the progress of the reaction. The initial rate was evaluated over the period *t*<sub>0</sub> → *t* such that *I*<sub>*t*</sub> = 0.95*I*<sub>0</sub>.

**Representative Epoxide Carbonylation in the Presence of Isocyanate.** A Parr reactor, with or without ReactIR modification, was dried and prepared as described above, with the addition of a third syringe containing 4-fluorophenyl isocyanate. The catalyst solution (**1**, 11.5 mM in DME, 10 mL) was injected into the reactor first, followed by 4-fluorophenyl isocyanate (0.57 mL, 5.0 mmol) and finally the epoxide (0.50 mL, 5.8 mmol). The reactor was immediately pressurized with CO (300 psi). After 5h, the reactor was vented, and the reaction mixture was analyzed by <sup>1</sup>H NMR spectroscopy.

**1,3-Oxazine-2,4-diones.** Upon completion of the reactions run with isocyanates, the reactor was vented, and the reaction mixture was transferred to a flask. The solvent was removed in vacuo, and the resulting mixture was washed with hexanes to remove β-VL. The remaining solid was purified as detailed below and analyzed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

**6-Ethyl-3-(4-methylphenyl)-1,3-oxazine-2,4-dione** was purified by crystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes. The melting point, elemental analysis, and partial IR spectrum of this compound have been reported.<sup>85</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.11 (3H, t, *J* = 7.5 Hz), 1.87 (2H, m), 2.39 (3H, s), 2.82 (1H, dd, <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 11.1 Hz), 2.92 (1H, dd, <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 3.9 Hz), 4.59 (1H, dtd, <sup>3</sup>*J* = 11.1, 7.5, 3.9 Hz), 7.07 (2H, pseudo-doublet), 7.26 (2H, pseudo-doublet). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 9.23, 21.48, 27.57, 36.74, 75.81, 128.09, 128.30, 130.22, 130.37, 131.28, 139.52, 149.13, 168.55.

**6-Ethyl-3-(4-fluorophenyl)-1,3-oxazine-2,4-dione** was purified by column chromatography (2:3 EtOAc:hexanes, *R*<sub>f</sub> = 0.30). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.11 (3 H, t, <sup>3</sup>*J* = 7.5 Hz), 1.86 (2 H, m), 2.82 (1 H, dd, <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 11.1 Hz), 2.92 (1 H, dd, <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 3.6 Hz), 4.59 (1 H, m), 7.15 (2 H, m), 7.168 (2 H, br s). <sup>13</sup>C NMR δ 9.20, 27.54, 36.68, 75.87, 116.49, 116.80, 130.20, 130.32, 151.55, 161.08, 164.37, 168.38. HRMS (EI) *m/z* calcd (C<sub>12</sub>H<sub>12</sub>NO<sub>3</sub>F) 237.08012, found 237.07632.

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**Supporting Information Available:** Calibration curve relating Abs<sub>ν(C=O)</sub> to the concentration of β-VL in DME solution, table of values of reaction rates at different values of *P*<sub>CO</sub>, initial kinetics of reaction between [*rac*-(salph)AlOCH(Et)CH<sub>2</sub>Cl] (**4**) and 4-F-C<sub>6</sub>H<sub>4</sub>NCO, and prediction of [β-VL]/[OD] ratio in a carbonylation run in THF with 4-F-C<sub>6</sub>H<sub>4</sub>NCO present. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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