Stereochemistry of Epoxide Carbonylation using Bimetallic Lewis Acid/Metal Carbonyl Complexes: Stereospecific and Stereoelective \([\beta]\)-Lactone Synthesis

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Abstract: The stereochemistry of epoxide carbonylation using bimetallic [Lewis Acid][Co(CO)₆] complexes is reported. The achiral complex [(salph)Al(THF)₂][Co(CO)₄] stereospecifically carbonylates cis- and trans-2-butene oxide to the trans- and cis-\([\beta]\)-lactones, respectively. Preliminary experiments regarding the stereoelective carbonylation of racemic trans-2-butene oxide using the enantiomerically-pure complex [(R,R-salcy)Al(THF)₂][Co(CO)₄] are also reported.

INTRODUCTION

\([\beta]\)-Lactones are highly attractive synthetic targets due to their versatility in organic synthesis [1] as well as their presence in natural products with biological activity [2]. They are also attractive monomers for the synthesis of poly(\([\beta]\)-hydroxyalkanoate), a naturally-occurring class of biodegradable polyesters [3]. A route to \([\beta]\)-lactones which is drawing considerable recent interest is the selective carbonylation of epoxides [4-13]. A major advance in this field was the report that Co₂(CO)₈ in combination with 3-hydroxypropyridine formed an active catalyst for the carbonylation of epoxides of ethylene and propylene; depending on the reaction conditions, either \([\beta]\)-lactones [7] or poly(\([\beta]\)-hydroxyalkanoate)s [9, 14] are formed. Recently, Alper and Lee reported the regioselective carbonylation of epoxides and aziridines using a catalyst system consisting of a mixture of [Ph₃P=N=PPh₃][Co(CO)₄] and BF₃·Et₂O [9]. Our research has focused on the development of a class of discrete bimetallic catalysts of the general formula [Lewis Acid][Co(CO)₄] [10, 11, 15]. These catalysts exhibit high selectivities as well as excellent activity for a range of epoxide and aziridines carbonylations.

In developing these bimetallic Lewis acid/metal carbonyl catalysts, we envisioned a mechanism (Scheme 1) whereby the cationic Lewis acid would coordinate and activate the substrate for attack by an anionic metal carbonyl. Following migratory insertion of CO into the metal alkyl bond and re-coordination of CO, an intramolecular attack of the Lewis acid metal-alkoxide with the metal acyl would form the \([\beta]\)-lactone [10, 11]. Rieger and coworkers have recently reported DFT calculations which are in agreement with this mechanism [13]. We have been searching for further experimental evidence in support of this mechanism, and have turned to the stereochemistry of epoxide carbonylation as a mechanistic probe. Based on the mechanism in Scheme 1, an epoxide with cis-1,2 substitution should be converted to a trans-\([\beta]\)-lactone upon carbonylation. We therefore initiated research regarding the carbonylation of epoxides of 2-
butene, and the preliminary results of these studies employing [Cp₂Ti][Co(CO)₄] were recently published [11]. In short, our experimental stereochemical studies support our proposed mechanism. In addition, we have discovered chiral catalysts capable of kinetically resolving racemic epoxides. Herein we report a full account of the stereochemistry of the carbonylation of 2-butene oxides using achiral and chiral [(salen)Al][Co(CO)₄] complexes.

RESULTS AND DISCUSSION

[(Salen)Al]⁺[Co(CO)₄]⁻ complexes are readily synthesized by adding NaCo(CO)₄ to (salen)AlCl. The steric and electronic nature of salen ligand of the Lewis acidic aluminum cation can be readily modified, making these catalysts easily tuned for the efficient carbonylation of a wide range of epoxides [16]. We therefore chose to study the stereochemistry of epoxide carbonylation using achiral [(salph)Al(THF)]₂[Co(CO)₄] (1) and enantiomerically-pure [(R,R-salcy)Al(THF)]₂[Co(CO)₄] (2) complexes (Figure 1).

Carbonylation Employing [(salph)Al(THF)]₂[Co(CO)₄] (1)

[(Salph)Al(THF)]₂[Co(CO)₄] (1) was used to carbonylate cis- and trans-2-butene oxide (Figure 2). Neat 2-butene oxide was carbonylated using 1 at 800 psi of CO for 20 hours at 50 °C. The trans-isomer proved to react faster and with higher selectivity than the cis-isomer (100% versus 25% lactone formation). The cis-2-butene oxide reaction also produced oligomeric materials in addition to 2-butanone. The lactones were isolated by vacuum distillation and subjected to NMR spectroscopy. By comparing the spectra to those in the literature, it was determined that 1 stereospecifically converts cis-2-butene oxide to trans-2,3-dimethylxetan-2-one and trans-2-butene oxide to cis-2,3-dimethylxetan-2-one [17, 18]. Given there are conflicting literature reports regarding the NMR spectra of the epimeric 2,3-dimethylxetan-2-ones, we chose to further confirm the stereochemistry by syn-decarboxylation of the lactones. Thermolysis of the lactones produces CO₂ and an alkene; the reaction has been shown to proceed with retention of stereochemistry of the carbon framework [19, 20]. By comparing the ¹H NMR spectra (Figure 3) (as well as the ¹³C NMR spectra) of the 2-butenes formed to those of known compounds, the assignment of the configurations shown in Figure 2 was confirmed [11].

Carbonylation Employing [(R,R-salcy)Al(THF)]₂[Co(CO)₄] (2)

The synthetic value of lactones in both organic as well as polymer chemistry is largely determined by the availability of these building blocks in their enantiomerically-pure forms [2, 21]. We have previously shown that optically active epoxides such as propylene oxide are carbonylated to lactones with complete retention of configuration [10, 11]. Given that enantiopure epoxides are readily available by a range of synthetic methods, catalytic carbonylation of optically-active epoxides with discrete complexes provides a reliable route to a wide range of chiral lactones. Despite the fact that enantioselective catalysts for lactones have been developed [22], to the best of our knowledge enantioselective catalysts for epoxide carbonylation have not been reported. We initially chose to investigate [(salen)Al]⁺[Co(CO)₄] complexes given the great successes of related chiral salen complexes in asymmetric catalysis [23]. Following the successful discovery of achiral catalyst 1, we decided to explore the synthesis and utility of enantiopure 2 in epoxide carbonylation. [(R,R-salcy)Al(THF)]₂[Co(CO)₄] (2) is synthesized in the same manner as 1. Crystals of 2 were examined by x-ray diffraction. The molecular structure of 2 is virtually isostructural to that of 1 (Figure 4; see Experimental Section for refinement data) [10]. Complex 2 was investigated for the carbonylation of racemic trans-2-butene oxide, and was found to have comparable activity to complex 1. The carbonylation of racemic trans-2-butene oxide was then carried out at 30 °C for 4 hours to give cis-2,3-dimethylxetan-2-one; ¹H NMR revealed a
clean 49% conversion. Using chiral GC (see Experimental Section for conditions), a percent enantiomeric excess (%ee) of 44% was measured. Since the correlation between optical rotation and absolute configuration of cis-2,3-dimethylxetan-2-one has not been reported, we do not know the absolute configuration of the major enantiomer. However assuming that the reaction is first order in epoxide, we calculate the relative ratio of the rate constants ($k_{rel}$) for consumption of the two enantiomers using the equation [24]:

$$k_{rel} = \frac{\ln[1-C(1+ee)]}{\ln[1-C(1-ee)]}$$

where $C$ is the reaction conversion and ee is the enantiomeric excess of the $\gamma$-lactone product. At 30 °C, we calculate $k_{rel} = 3.8$, where at 0 °C $k_{rel} = 4.1$. Although these selectivities are not synthetically efficient, they provide important mechanistic evidence that the enantiomerically-pure aluminum Lewis acid is intimately involved in reaction, possibly as depicted in Scheme 1. We are confident that further empirical modifications to the [Lewis acid][Co(CO)$_4$] catalyst framework will yield much higher stereoselectivities.

CONCLUSION

The stereochemistry of epoxide carbonylation using bimetallic [Lewis Acid][Co(CO)$_4$] complexes is reported. The achiral complex [(salph)Al(THF)$_2$][Co(CO)$_4$] (I) carbonylates cis- and trans-2-butene oxide to the corresponding trans- and cis-$\gamma$-lactones, respectively. Catalyst 1 also has significant potential utility for the synthesis of optically active $\gamma$-lactones by the carbonylation of optically-active epoxides. Preliminary experiments regarding the kinetic resolution of racemic, trans-2-butene oxide using the enantiomerically-pure complex [(R,R-salcy)Al(THF)$_2$][Co(CO)$_4$] (2) revealed $k_{rel}$ values of 3.8-4.1. These results support the mechanism originally proposed for this class of complexes. Future work will center on the development of chiral catalysts that exhibit higher selectivity for the carbonylation of small molecules.

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 Bruker AF300 (1H, 300 MHz; 13C, 75 MHz), Varian Gemini (1H, 300 MHz; 13C, 75 MHz) or Varian Inova (1H, 400 MHz; 13C, 100 MHz) spectrometers and referenced versus residual non-deuterated solvent shifts ($\delta$ = 7.24 for CHCl$_3$). X-ray crystallographic data was collected using a SMART CCD Area Detector System (Mo K$_{\alpha}$, $\delta$ = 0.71073 Å), and frames were integrated with the Siemens SAINT program. The enantiomeric excess of cis-3,4-dimethylxetan-2-one was measured on an HP 6890 Series GC equipped with a Supelco 2-4318 beta-DEX 225 column (0.25mm x 30m) employing helium as the carrier gas. Samples were ramped at 2 °C/min from 120° to 160° then 40 °C/min to 200° C, where they were held for 5 min. The area of the second peak was corrected by a factor of 1.2 after calibration with a racemic sample.

Materials

Tetrahydrofuran and hexanes were dried and degassed over solvent purification columns. Epoxides were distilled from CaH$_2$ under nitrogen and degassed. All other chemicals were commercially available and used as received. NaCo(CO)$_4$ was prepared by standard procedures
Synthesis of Bis(tetrahydrofurano)-R,R,N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-diaminocyclohexylaluminum cobalt tetracarbonyl [(R,R-salcy)Al(THF)]2[Co(CO)4] (2).

All manipulations performed with strict air-free techniques. All reagents and solvent dried and degassed prior to use. In a drybox, R,R-N,N'-bis(3,5-di-tert-butylsalicylaldehyde)-1,2-diaminocyclohexane (1.0 g, 1.8 mmol) was placed in a Schlenk tube equipped with a stir-bar and an air-free addition funnel charged with diethyl aluminum chloride (Aldrich, 1.8 M in toluene) (1.0 ml, 1.8 mmol). Upon removal to the bench top the ligand was dissolved in CH2Cl2, giving a pale yellow solution. Dropwise addition of diethyl aluminum chloride solution resulted in considerable evolution of gas, which was vented, and a yellowing of the solution. After rinsing the addition funnel several times with CH2Cl2 the solution was stirred for 2.5 hours. In vacuo solvent removal gave a yellow solid that was rinsed 3-4 times with hexanes (10-20 ml) and then pumped down. The Schlenk tube was brought into a drybox where white sodium cobalt tetracarbonyl powder (0.35 g, 1.8 mmol), stored at -35 °C under nitrogen, was added. Upon removal to the bench, tetrahydrofuran was added. The foil wrapped tube stirred for two days and was concentrated to 5-10 ml, layered with hexanes (50 ml) and left to sit until well-formed bright yellow X-ray quality crystals appeared. Impurities were washed away with repeated rinses of hexanes allowing isolation of pure catalyst (1.4 g, 88% yield). 1H NMR (CDCl3, 300 MHz): [1.14 (8H, br s), 1.38 (18H, br s), 1.68 (18H, br s), 1.91 (2H, br s), 2.31 (4H, br s), 2.79 (4H, br s), 3.37 (8H, dd, J1 = 6.0 Hz, J2 = 28.1 Hz), 7.66 (br s, 2H), 7.85 (br s, 2H) 8.62 (br s, 2H). 13C NMR (CDCl3, 100 MHz): [24.2, 24.9, 27.6, 29.8, 31.6, 34.4, 35.8, 64.3, 71.0, 119.3, 130.1, 131.7, 139.7, 139.9, 162.3, 167.5. Crystal data for [(R,R-salcy)Al(THF)]2[Co(CO)4] (2): (C28H20AlCoN4O4)(C2H4O)2, M = 885.95, triclinic, a = 12.1629(7), b = 13.1027(7), c = 15.7384(9) Å, α = 101.5810(10), γ = 90.4660(10), β = 90.0100(10)°, U = 2457.0(2) Å3, T = 173(2) K, space group P1, Z = 2, P(Mo-Kα) = 0.418 mm-1, 19377 reflections measured, 14024 unique (Rint = 0.0300) which were used in all calculations. The final R1 was 0.0460 (I>2σ(I)).

General procedure for the carboxylation of epoxides with [(salph)Al(THF)]2[Co(CO)4] (1) or [(R,R-salcy)Al(THF)]2[Co(CO)4] (2)

A 100 ml Parr reactor was heated at 90 °C overnight, under vacuum. In a dry-box, the reactor equipped with a test-tube and magnetic stir bar were cooled in a -35 °C freezer for at least 2 h. The test-tube was charged with pre-cooled (-35 °C) epoxides (0.5 ml) and catalyst (1 mol %). Upon removal from a dry-box the reactor was pressured to ~800 psi with carbon monoxide (Matheson, Research Grade) and warmed to the desired temperature with stirring for the amount of time indicated. Finally, the reactor was cooled in a bath of dry ice/acetone until the pressure reached a minimum and the reactor was slowly vented. The resulting reaction mixture was analyzed by 1H NMR for yield, then by 1H/13C NMR and chiral GC following vacuum distillation.

Carboxylation of trans-2-butene oxide using [(salph)Al(THF)]2[Co(CO)4] (1)

Ttrans = 50 °C for 20 h; 100% conversion to cis-3,4-dimethyloxetan-2-one: 1H NMR (CDCl3, 300 MHz): [1.25 (3H, d, J = 7.7 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.72 (1H, m, 4.77 (1H, m). 13C NMR (CDCl3, 75 MHz): [8.28, 15.59, 47.61, 71.99, 172.80.

Carboxylation of cis-2-butene oxide using [(salph)Al(THF)]2[Co(CO)4] (1)

Ttrans = 50 °C for 20 h; 25% conversion to trans-3,4-dimethyloxetan-2-one: 1H NMR (CDCl3, 300 MHz): [1.36 (3H, d, J = 7.5 Hz), 1.52 (3H, d, J = 6.6 Hz), 3.19 (1H, m, 4.32 (1H, m). 13C NMR (CDCl3, 75 MHz): [12.53, 20.20, 52.38, 76.34, 172.10.
Carbonylation of trans-2-butene oxide using [(R,R-salcy)Al(THF)2][Co(CO)4] (2)

\[ \text{Rxn} = 30 \, ^\circ\text{C} \text{ for } 4 \text{ h}; \text{49% conversion to cis-3,4-dimethyloxetan-2-one: } \]  
\[ ^1\text{H NMR (CDCl}_3, \text{ 300 MHz): } \delta \text{ 1.25 (3H, d, } J = 7.7 \text{ Hz), 1.43 (3H, d, } J = 6.3 \text{ Hz), 3.72 (1H, m), 4.77 (1H, m). } \]  
\[ ^13\text{C NMR (CDCl}_3, \text{ 75 MHz): } \delta \text{ 8.28, 15.59, 47.61, 71.99, 172.80. Peaks in the chiral GC chromatograph were found at 16.6 and 17.6 min with areas of 28.1:71.9, respectively.} \]

\[ \text{Rxn} = 0 \, ^\circ\text{C} \text{ for } 10 \text{ h}; \text{17% conversion to cis-3,4-dimethyloxetan-2-one with the same spectroscopic data. Peaks in the chiral GC chromatograph were found at 16.6 and 17.6 min with areas of 21.7:78.3, respectively.} \]

Thermolysis of 3,4-Dimethyloxetan-2-ones

The lactone was purified by vacuum distillation then placed in a thick-walled Pyrex tube equipped with a Kontes valve. The tube was frozen in N\textsubscript{2} then evacuated. The tube was heated to 171\(^\circ\)\text{C} in an oil bath for 2 hours. The thermolysis tube was connected, via a short-path distillation head, to an NMR tube fitted with a J-Young valve and pre-filled with CDCl\textsubscript{3}. The CDCl\textsubscript{3} was frozen in N\textsubscript{2}, the tube was evacuated, and the apparatus isolated from vacuum. The thermolysis tube was cooled to \textendash78\(^\circ\) and opened to the apparatus, warming of the thermolysis tube resulted in transfer of the volatile compounds into the NMR tube for analysis. The non-volatile compounds were analyzed by NMR as well and revealed primarily residual lactone.

Thermolysis of trans-3,4-dimethyloxetan-2-one

Cis-2-butene: \(^1\text{H NMR (CDCl}_3, \text{ 300 MHz): } \delta \text{ 1.58 (6H, m), 5.44 (2H, m). } \]  
\[ ^13\text{C NMR (CDCl}_3, \text{ 75 MHz): } \delta \text{ 12.35, 124.70. These spectral data were identical to the data of a commercial sample.} \]

Thermolysis of cis-3,4-dimethyloxetan-2-one

Trans-2-butene: \(^1\text{H NMR (CDCl}_3, \text{ 300 MHz): } \delta \text{ 1.61 (6H, m), 5.41 (2H, m). } \]  
\[ ^13\text{C NMR (CDCl}_3, \text{ 75 MHz): } \delta \text{ 18.05, 126.05. These spectral data were identical to the data of a commercial sample.} \]
Scheme 1. Proposed mechanism of epoxide carbonylation using bimetallic [Lewis Acid][Co(CO)₄] complexes; inversion occurs at the carbon adjacent to CO insertion.

Figure 1. Bimetallic [Lewis Acid][Co(CO)₄] carbonylation catalysts [(salph)Al(THF)₂][Co(CO)₄] (1) and [(R,R-salcy)Al(THF)₂][Co(CO)₄] (2).
Figure 2. Stereochemistry of the carbonylation of *trans*- and *cis*-2-butene oxide using [(salph)Al(THF)$_2$][(Co(CO)$_4$]; 1].

Figure 3. Methyl regions of the $^1$H NMR spectra of the 2-butenes resulting from the thermolysis of 3,4-dimethyloxetan-2-ones in comparison with known samples. The peak marked with an asterisk is due to water.
**Figure 4.** Molecular structure of \([\text{(R,R-salcy)Al(THF)}_2][\text{Co(CO)}_4]\) (2) with displacement ellipsoids drawn at 40% probability.

**Figure 5.** Kinetic resolution in the carbonylation of trans-2-butene oxide using \([(\text{R,R-salcy})\text{Al(THF)}_2][\text{Co(CO)}_4]\) (2).
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8. For the use of Co$_2$(CO)$_8$ to carbonylate ethylene oxide to $\alpha$-propiolactone as well as oligomeric polyesters, see: Hattori, N.; Nishida, H. (Tokuyama Soda Co.) Jap. Pat. 09169753; [Chem. Abstr. 1997, 127, 95188].