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Research Article

Catalyst-Controlled Regioselective Carbonylation of Isobutylene Oxide to Pivalolactone

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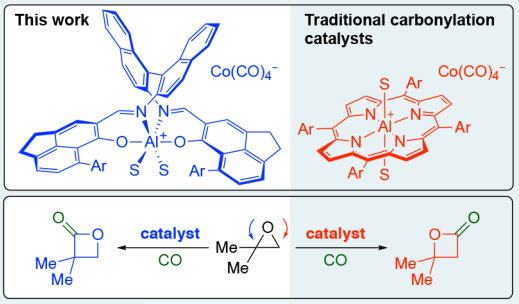
ABSTRACT: Poly(pivalolactone) (PPVL) is a crystalline polyester with attractive physical and mechanical properties; however, prohibitively expensive syntheses of pivalolactone have thwarted efforts to produce PPVL on an industrial scale. Therefore, we developed a class of highly regioselective sandwich-type catalysts for the carbonylation of isobutylene oxide. These sterically encumbered complexes install carbon monoxide at the substituted epoxide carbon, generating a high level of contrasteric selectivity (up to >99:1). Further catalyst development improved catalyst solubility and reproducibility while maintaining high regioselectivity. In addition, a dibasic ester solvent extended catalyst lifetimes and suppressed side product formation. This contrasteric carbonylation of isobutylene oxide offers a route to sought-after pivalolactone and, therefore, PPVL.



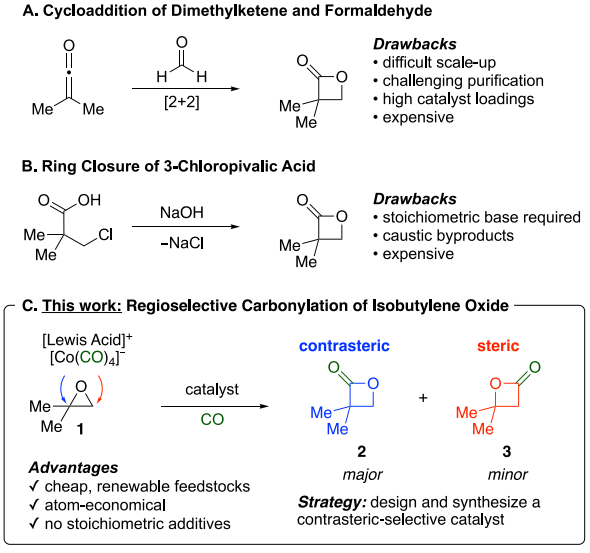
KEYWORDS: *epoxide carbonylation, catalysis, pivalolactone, poly(pivalolactone), isobutylene oxide*

INTRODUCTION

While useful polymer properties dictate material applications, cost-effective monomer syntheses are also critical for practical commercialization. Poly(pivalolactone) (PPVL), for example, has demonstrated promise in the textile fiber industry because of its high crystallinity, thermal stability, elastic recovery, chemical resistance, and low deformation at elevated temperatures.[1] The chemical stability of PPVL, which is superior to that of poly(ethylene terephthalate) fibers,[1b] is attributed to the methyl groups adjacent to the carbonyl. This α-disubstitution prevents intramolecular α-proton abstraction, which leads to chain scission and polymer degradation.[2] Given that aliphatic polyesters like PPVL are often biodegradable,[3] PPVL offers an attractive alternative to many common materials. This polymer's desirable physical properties justified pilot-plant scale industrialization of two pivalolactone polymerization processes.[4] However, the cost of monomer synthesis proved to be economically unfeasible, limiting the overall success of PPVL commercialization.[4,5] Thus, alternative monomer production strategies are necessary.

The two most common syntheses of pivalolactone include (1) the (formal) [2 + 2] cycloaddition of dimethylketene and formaldehyde (Scheme 1A)[6] and (2) the ring closure of 3-chloropivalic acid (Scheme 1B).[1b,4,7] The cycloaddition procedure requires precise control of reaction conditions,[6a,c] and, unfortunately, side product formation complicates both scale-up and purification.[6b] In addition, 3-chloropivalic acid ring closure requires a stoichiometric base[1b,4] and separations from metal halides are challenging,[7] rendering the synthesis

Scheme 1. Pivalolactone Syntheses: (A) Cycloaddition of Dimethylketene and Formaldehyde, (B) Ring Closure of 3-Chloropivalic Acid, and (C) an Alternative Regioselective Carbonylation Method



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impractical for large-scale production. In addition to these commonly employed processes, Dow Chemical developed an alternative method to produce pivalolactone via the carbonylation of allylic carbonates.[8] However, superstoichiometric amounts of strong acid and low yields (15%) limit the synthetic utility of this transformation. Most recently, Yu and co-workers reported the palladium-catalyzed β-C(sp^3)−H functionalization of alkyl carboxylic acids, an important advance which generates a variety of α,α-disubstituted β-lactones,[9] including pivalolactone (50% yield from pivalic acid). However, this method requires 10 mol % of a palladium catalyst, near stoichiometric base, and superstoichiometric oxidant. To mitigate these challenges, we propose to use inexpensive and potentially biorenewable isobutylene oxide (**1**)[10] and carbon monoxide (CO)[11] to prepare pivalolactone (**2**) via catalyst-controlled regioselective carbonylation (Scheme 1C). With no stoichiometric additives and low catalyst loadings, this method could potentially facilitate the production of **2** and, therefore, PPVL, on an industrial scale.

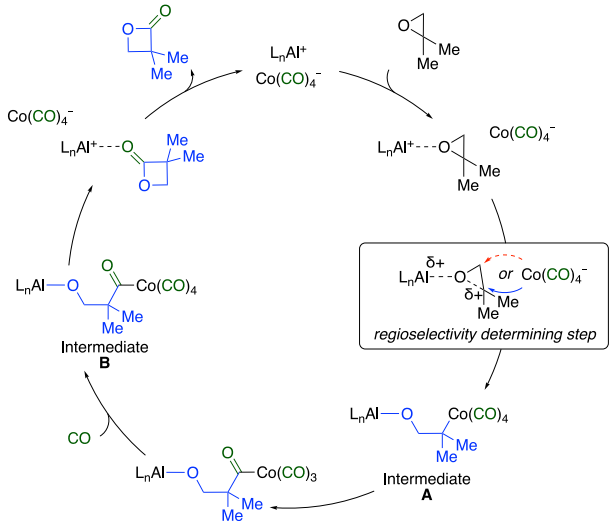
Ring-expansion carbonylation of 2,2-disubstituted epoxides is well-known,[12] and several generations of catalysts have been identified.[13] Drent and co-workers developed the first carbonylation of isobutylene oxide in 1994 using a $Co_2(CO)_8$/3-hydroxypyridine catalyst.[14] However, this system selectively inserted CO at the less-substituted position to form the β,β-disubstituted steric lactone (**3**) and produced various side products. In 2002, our group revisited the carbonylation of isobutylene oxide using $[Cp_2Ti(THF)_2]^+[Co(CO)_4]^-$ and $[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (salph = *N*,*N*′-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran) catalysts, but these methods still favored the production of **3** (20:80 and 8:92 ratio of **2**:**3**, respectively).[15] More recently, we developed a highly regioselective carbonylation of 2,2-disubstituted epoxides for the near-exclusive formation of β,β-disubstituted β-lactones using porphyrin and salen-based catalysts.[16] The high steric selectivity demonstrated by these four reports suggested that achieving large yields of **2** using conventional carbonylation catalysts would be exceptionally challenging.

These epoxide carbonylation reactions typically proceed via an S_N2 ring-opening mechanism; therefore, cobaltate ($Co(CO)_4^-$) preferentially attacks the least hindered epoxide carbon to generate the β,β-disubstituted steric product (Scheme 2).[16,17] However, to achieve contrasteric regioselectivity, the Lewis acid catalyst must overcome inherent substrate-control and readily promote attack at the *more* substituted site.[16,17b] We hypothesized that this process may be facilitated by the formation of a stable, tertiary carbocation or partial positive charge at the dimethyl-substituted carbon which may promote an S_N1-type pathway. After epoxide ring opening, the remainder of the mechanism likely proceeds similarly to our previously studied carbonylation systems;[17] the alkyl cobalt species (intermediate **A**, Scheme 2) undergoes CO insertion to form a cobalt acyl (intermediate **B**). Next, intramolecular attack by the metal alkoxide produces the β-lactone product and regenerates the active catalyst.

RESULTS AND DISCUSSION

A variety of $[Lewis\ acid]^+[Co(CO)_4]^-$ catalysts (Chart 1) were screened for the contrasteric-selective carbonylation of **1** (Table 1). As expected, first-generation porphyrin and salen catalysts (**4**, **5**, and *rac*-**6a**, Table 1, entries 1−3) resulted in predominantly lactone **3**. However, aldehyde (**10**) and alkene

Scheme 2. Proposed Mechanism for the Contrasteric Carbonylation of Isobutylene Oxide



(**11**) side products were also observed, suggesting a competing epoxide isomerization pathway,[18] as well as steric lactone decarboxylation.[16,19] To improve regioselectivity, previous 2,3-disubstituted epoxide carbonylation[20] and isomerization systems[18b] employed catalysts with additional bulk. Therefore, we screened Lewis acids with large aryl groups in the *ortho*-position of the phenoxide, such as *rac*-**6b**. Although these bulky ligands did increase contrasteric selectivity (**2**:**3** ratio = 42:58; see Table 1, entry 4), **2** remained the minor regioisomer, and isomerization to isobutyraldehyde (**10**) was the major pathway. Next, we screened catalysts with 2,2′-diamino-1,1′-binaphthalene (DABN)-based backbones, which force the ligand out of coplanarity and into a *cis*-α configuration (Chart 1). Although catalyst *rac*-**7a** was previously used for the contrasteric carbonylation of *cis*-epoxides,[20c] it still promoted steric regioselectivity using epoxide **1** (**2**:**3** ratio = 8:92; see Table 1, entry 5). However, increasing bulk at the *para*-position of the catalyst facilitated the contrasteric carbonylation pathway and suppressed isomerization, although the production of **3** still dominated and the formation of an ester side product occurred (**2**:**3** ratio = 33:67, catalyst (*R*)-**7b**; see Table 1, entry 6).[21] We hypothesized that developing a DABN-based ligand with even more steric hindrance would further enhance constrasteric selectivity.

To install this additional substitution, we took inspiration from olefin polymerization literature[22] and replaced the salicylaldimine moiety with an 8-aryl-substituted iminonaphthol to form a sandwich-type catalyst ((*R*)-**8a**). Excitingly, this modification improved the regioselectivity such that only minimal steric product was observed (**2**:**3** ratio >99:1; see Table 1, entry 7). To explore the origin of this unprecedented result, catalyst (*R*)-**8b** was prepared using an iminonaphthol-based salicylaldehyde that lacks an additional aryl substituent. This analogue was unable to inhibit steric attack and therefore favored the production of **3** (**2**:**3** ratio = 21:79; see Table 1, entry 8), demonstrating the importance of additional aryl substituents for regiocontrol.

Despite its relative success, (*R*)-**8a** still suffered from several limitations, such as inconsistencies in both conversion and regioselectivity between catalyst batches. We hypothesized that these reproducibility problems arose from poor catalyst

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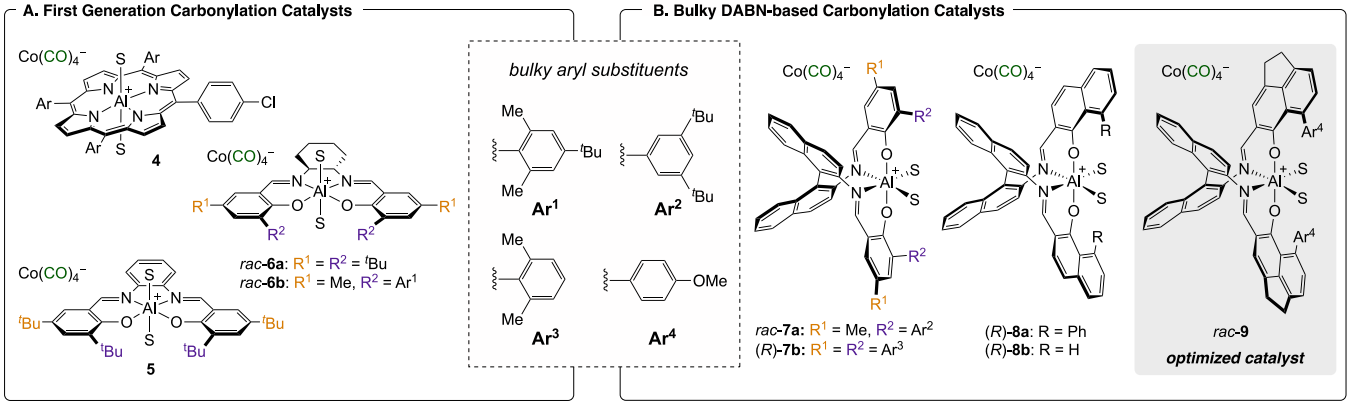
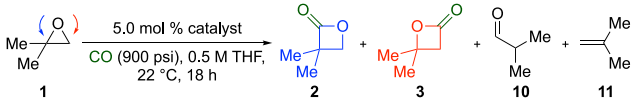
Chart 1. Catalysts Screened for the Contrasteric Carbonylation of Isobutylene Oxide[a]



[a]S = solvent.

Table 1. Initial Catalyst Screen for the Contrasteric Carbonylation of IBO



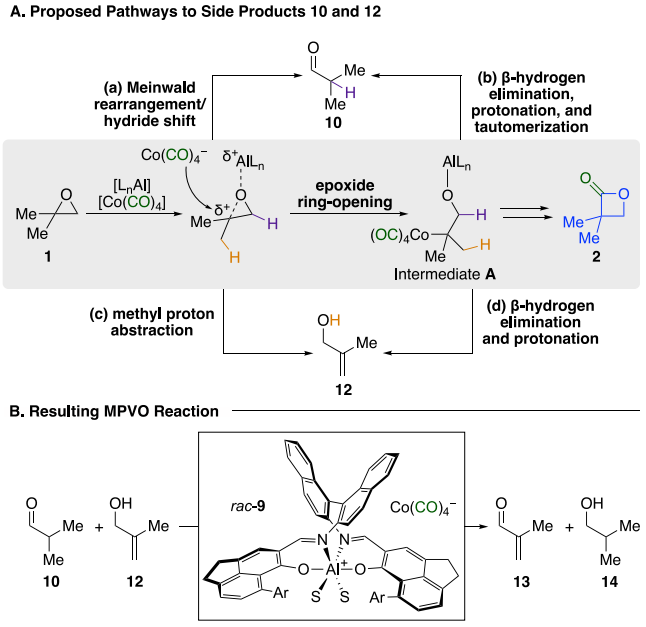
			Conversion[a] (%)		
entry	catalyst	ratio (2:3)	lactone (2+3)	10	11
1	**4**	8:92	96	2	2
2	**5**	4:96	82	3	2
3	*rac*-**6a**	8:92	57	8	2
4	*rac*-**6b**	42:58	39	59	2
5	*rac*-**7a**[b]	8:92	53	8	1
6[c]	(*R*)-**7b**[b]	33:67	27	19	<1
7[c,d]	(*R*)-**8a**[b]	>99:1	14	63	<1
8[d,e]	(*R*)-**8b**[b]	21:79	20	3	<1
9[d]	*rac*-**9**[b]	96:4	22	70	<1

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Catalyst made in situ (L_nAlCl + $NaCo(CO)_4$). [c]An additional ester side product formed via the Tishchenko reaction[21] of two isobutyraldehyde molecules in a small amount. [d]Percent conversion determined relative to **1** by ^{1}H NMR spectroscopy, excluding unassigned MPVO products, which were filtered out using alumina plugs (vide infra; see the Supporting Information for additional details). [e]0.5 M 1,4-dioxane/THF (3:1).

solubility, which we previously attempted to improve by using an enantiopure DABN backbone. To overcome this limitation while maintaining high regioselectivity, we synthesized an acenaphthene-derived salicylaldehyde with *p*-methoxy substitution on the pendant aryl group (*rac*-**9**). Although the complex could not be isolated prior to carbonylation, the resulting in situ generated catalyst was soluble under standard reaction conditions and yielded reproducible results between catalyst batches with only a modest decrease in contrasteric selectivity (**2**:**3** ratio = 96:4; see Table 1, entry 9).

Unfortunately, both sandwich catalysts ((*R*)-**8a** and *rac*-**9**) produced several additional side products, initially limiting the overall utility of this process (Scheme 3). Favoring the S_N1-type pathway increased the rate of epoxide isomerization to **10** via Meinwald rearrangement[23] and/or *β*-hydrogen elimination after cobaltate attack[18] (pathways a and b, respectively; see Scheme 3A). In addition, proton abstraction from an isobutylene oxide methyl group and/or *β*-hydrogen elimination of **A** produces *β*-methallyl alcohol (**12**) (pathways c and d, respectively; see Scheme 3A). Because of the adjacent *cis*-coordination sites on the catalyst, **10** and **12** undergo a Meerwein−Ponndorf−Verley−Oppenauer (MPVO) reaction,[24] producing methacrolein (**13**) and isobutyl alcohol (**14**) as additional side products (Scheme 3B).

Scheme 3. (A) Proposed Pathways to Side Products 10 and 12 and (B) the Resulting Meerwein−Ponndorf−Verley−Oppenauer Reaction



Despite these initial drawbacks, we wanted to gain a better understanding of the origin of this unprecedented contrasteric regioselectivity. Single crystals of a BPh_4^- version of *rac*-**9** (*rac*-**9**-BPh_4) were studied by X-ray diffraction (Figure 1), facilitating the generation of two hypotheses: (1) the additional bulk provided by the aryl substituents may guide cobaltate to attack the more sterically congested oxirane carbon, and/or (2) the flanking aryl groups may stabilize positive charge accumulation at the substituted epoxide carbon (Schemes 2 and 3) via noncovalent interactions, prompting contrasteric attack. We are currently performing mechanistic studies to gain a better understanding of this exceptional regiochemical outcome.

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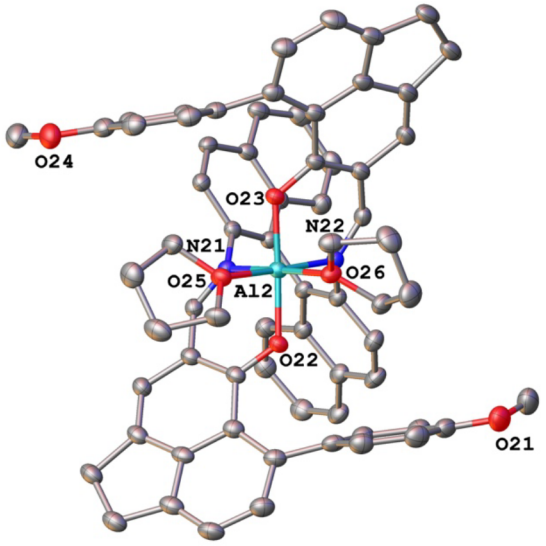
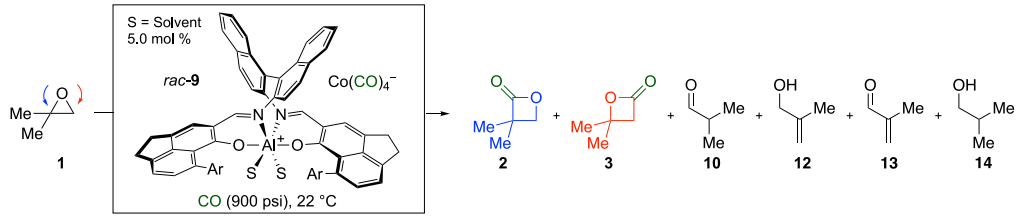


Figure 1. X-ray crystal structure of *rac*-**9**-BPh_4, depicting the restricted catalyst binding pocket. Only one of the two independent molecules is shown; counterions, solvent, and H atoms are omitted for clarity. Displacement ellipsoids shown at 50% probability.

Our group has previously found that solvent can greatly influence product distributions and regioselectivities in epoxide carbonylation reactions.[16,25] Therefore, we screened a variety of solvents for the carbonylation of **1** to maximize regioselectivity while minimizing the formation of **10** and **12** (Scheme 3A). Although *rac*-**9** produced lactone with excellent regioselectivity using THF (**2**:**3** ratio = 96:4; see Table 2, entry 1), **10** was still the major product. 1,4-Dioxane suppressed the formation of this side product (Table 2, entry 2), but regioselectivity suffered. Therefore, we hypothesized that using a combination of THF and 1,4-dioxane could promote the carbonylation pathway selectively and with satisfactory regioselectivity. Indeed, more lactone was formed and regioselectivity was reasonable; however, the desired product **2** still accounted for <50% of the reaction mixture (Table 2, entries 3 and 4). Weakly coordinating diethyl ether (Et_2O) and toluene both reduced overall reactivity (Table 2, entries 5 and 6), and catalyst solubility suffered using ethyl acetate (EtOAc, Table 2, entry 7). Dibasic ester-5 (dimethyl glutarate, DBE-5) increased reactivity, produced excellent regioselectivity (97:3 **2**:**3**), and modestly suppressed side product formation, generating **2** in >50% conversion for the first time (59%, Table 2, entry 8). Further optimization revealed that decreasing the concentration from 0.5 to 0.25 M (Table 2, entry 9) and using $Ph_3SiCo(CO)_4$ instead of $NaCo(CO)_4$ (Table 2, entry 10) decreased side product generation and promoted additional lactone formation (66%).

Interestingly, prior to oxygen exposure, reactions using DBE-5 remain orange in color, characteristic of the catalyst's highly conjugated ligand. However, reactions in other solvents such as THF and 1,4-dioxane turn dark before reaction completion. Cobalt tetracarbonyl hydride, which is formed via β-hydrogen elimination during formation of side products **10** and **12** (see Scheme 3), is known to decompose to hydrogen gas and brown dicobalt octacarbonyl.[26] This visual observation could indicate that catalyst decomposition occurs in certain solvents but is minimized by DBE-5. Because all reactions performed using DBE-5 proceeded to full conversion in 24 h, we

Table 2. Effect of Solvent and $Co(CO)_4^-$ on Product Distribution and Regioselectivity[a]



					Conversion (%)[b]				
entry	solvent	concentration (M)	time (h)	**2**:**3** ratio[b]	lactone (**2**+**3**)	**10**	**12**	**13**	**14**[c]
1	THF	0.50	18	96:4	19	61	<1	6	6
2	1,4-dioxane	0.50	18	76:24	11	<1	<1	3	3
3[d]	THF:1,4-dioxane (1:1)	0.50	18	84:16	29	19	<1	16	16
4[d]	THF:1,4-dioxane (1:3)	0.50	18	88:12	33	7	1	17	17
5[e]	Et_2O	0.50	18	>99:1	8	<1	2	1	1
6[e]	toluene	0.50	18	>99:1	3	7	<1	2	2
7[d]	EtOAc	0.50	24	91:9	25	<1	9	2	2
8	DBE-5[f]	0.50	24	97:3	59	<1	21	10	10
9	DBE-5[f]	0.25	24	95:5	57	1	15	9	9
10[g]	DBE-5[f]	0.25	24	>99:1	66	1	14	9	9
11[g,h]	DBE-5[f]	0.25	2	>99:1	40	5	10	2	2
12[h,i]	DBE-5[f]	0.25	2	>99:1	71	5	20	2	2

[a]Catalyst made in situ (5.0 mol % L_nAlCl + 5.0 mol % $NaCo(CO)_4$) unless otherwise specified. Product **11** was not observed in any of these reactions. [b]Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c]Diagnostic peak underneath catalyst residue. Determined by conversion to **13** (see the Supporting Information for additional details). [d]An additional ester side product formed through the Tischenko reaction[21] of two isobutyraldehyde molecules. [e]Overall conversion was very low, so integrations of ^1H NMR spectra for determination of regioselectivity may not be reliable. [f]DBE-5 = dibasic ester-5. [g]Catalyst made in situ (5.0 mol % L_nAlCl + 5.0 mol % $Ph_3SiCo(CO)_4$). [h]Percent yield by ^1H NMR spectroscopy using hexamethyldisiloxane as an internal standard, because of product volatility. [i]Catalyst made in situ (5.0 mol % L_nAlCl + 7.5 mol % $Ph_3SiCo(CO)_4$).

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decreased the reaction time to gauge the resulting increase in reaction rate. Within only 2 h, 59% total conversion was achieved (Table 2, entry 11), which is a striking improvement upon reactions in other solvents that did not reach completion within 24 h (Table 2, entries 1−7). This enhanced reactivity, along with the visual observations, indicates that cobaltate degradation, indeed, occurs more slowly in DBE-5. To further increase the turnover frequency, we added additional cobaltate to replenish any cobalt hydride that degrades during the course of the reaction. In the presence of 7.5 mol % $Ph_3SiCo(CO)_4$, full conversion was observed after 2 h (Table 2, entry 12). However, we cannot rule out a ring-opening turnover-limiting step as the reason for this increase in yield. With these improvements, **2** was generated in 71% yield, which is a significant improvement upon previous carbonylation methods.[14−16] Although 20% of this reaction mixture consists of **12**, alumina plugs can be used to remove this alcohol side product (see the Supporting Information for additional details).

CONCLUSION

We report the first contrasteric-selective carbonylation of isobutylene oxide for the production of pivalolactone (**2**:**3** ratio >99:1). The high regioselectivity of this newly developed catalyst is likely due to the epoxide binding pocket in the bulky salen catalyst, which may prevent nucleophilic attack at the less sterically hindered epoxide carbon and/or stabilize the accumulation of positive charge at the more congested site. Using DBE-5 as the solvent suppressed side product formation, minimized catalyst decomposition, and increased reaction rates. This novel regioselective carbonylation is an atom economical and potentially renewable[10,11] route to pivalolactone, which may increase the practicality of commercial PPVL production. Future work will focus on mechanism elucidation to further understand and suppress side product formation and expand this method to other 2,2-disubstituted epoxides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03492.

Crystallographic data for *rac*-**9**-BPh_4 (CIF)

Crystallographic data for (*R*)-8aAlCl (CIF)

Synthetic procedures, characterization data of all new compounds, control reactions, and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This manuscript is dedicated to the memory of our colleague and friend, Jerry Meinwald.

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