Enantiomerically-enriched organic reagents *via* polymer synthesis: enantioselective copolymerization of cycloalkene oxides and CO$_2$ using homogeneous, zinc-based catalysts†

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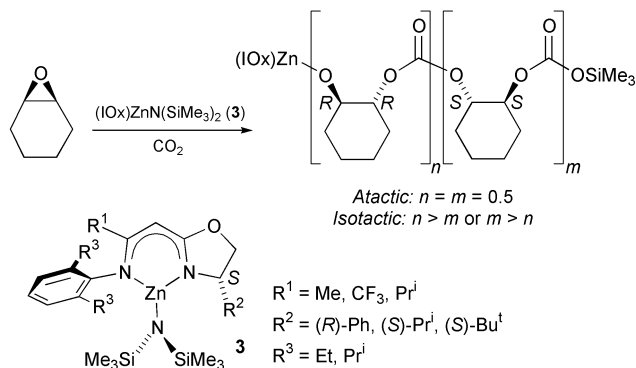*E-mail: gc39@cornell.edu*

Enantiomerically pure zinc complexes have been designed and synthesized for the enantioselective copolymerization of cycloalkene oxides and CO$_2$.

The desymmetrization of *meso* molecules with chiral catalysts or reagents is rapidly emerging as valuable strategy for the synthesis of enantiomerically-enriched products.[1,2] *Meso* epoxides are particularly attractive substrates for desymmetrization reactions: ring-opening with a variety of nucleophiles yields a range of valuable synthetic intermediates.[3] Remarkable advances in the development of chiral catalysts have yielded highly enantioselective systems for the delivery of halide, azide, alcohol, thiol, cyano and carboxylic acid nucleophiles to epoxides. Despite the recent intense interest in developing enantioselective catalysts for the synthesis of optically-active polymers,[4,5] there are few examples of *meso*-desymmetrization in polymerization reactions.[6,7] We have recently developed a new class of single-site catalysts (**1**, Scheme 1)[8] for the
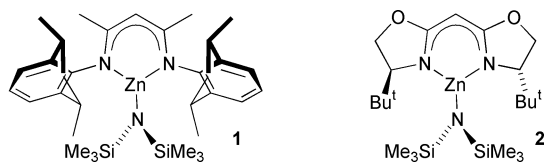
Scheme 1

copolymerization of CO$_2$ and cyclohexene oxide (CHO); (Scheme 2).[9,10] Following reaction of the amido ligand with CO$_2$, extrusion of trimethylsilyl isocyanate and reinsertion of CO$_2$,[11–13] the ring-opening of the epoxide monomer in this system occurs with inversion of stereochemistry thus producing stereogenic centers in the polymer backbone. We reasoned that a chiral ligand set would have the potential to control the

absolute stereochemistry of the ring-opening process, and that hydrolysis of the resultant polycarbonate[14] would yield valuable enantiomerically-enriched diols.[8] During the course of our research Nozaki and coworkers reported a chiral catalyst system for the enantioselective copolymerization of CO$_2$ and CHO,[15] prompting us to communicate our preliminary results. Herein we report a chiral, homogeneous catalyst system which exhibits unprecedented activity, stereoselectivity and molecular weight control for the polymerization of CO$_2$ with both cyclopentene and cyclohexene oxide, even under mild reaction conditions.

Owing to the well-defined nature of β-diiminate zinc complexes (**1**) for the synthesis of aliphatic polycarbonates, we first decided to investigate structurally-related bisoxazoline-derived zinc complexes (**2**) to attempt stereochemical control. Complex **2** was readily formed in quantitative yield from the reaction of the bisoxazoline ligand with Zn[N(SiMe$_3$)$_2$]$_2$. Despite the structural similarity of the diimine and bisoxazoline ligands, complex **2** is inactive for the copolymerization of CO$_2$ and CHO at 20 °C. Although the cause of inactivity is currently unknown, we believe that either decomposition to a bis-ligated zinc species or irreversible aggregation of the catalytic species occurs early in the polymerization reaction. To impede such deleterious processes we designed a hybrid imine–oxazoline ligand (IOx) that is sterically incapable of forming strongly aggregated or bis-ligated complexes (**3**, Scheme 2). Despite lacking the high symmetry which is often the hallmark of highly selective catalysts, these ligands have the advantage that efficient synthetic strategies allow the systematic variation of the ligand structure to optimize catalyst behavior. The ligands are formed by the nucleophilic attack of imidoyl chlorides with chiral, deprotonated 2-methyloxazolines.[16–18] Reaction of the ligand with Zn[N(SiMe$_3$)$_2$]$_2$ gives **3** in quantitative yield.

Complexes of type **3** are active catalysts for the copolymerization of cycloalkene oxides and CO$_2$ (Table 1). In general, the reaction of a 2.5 M solution of CHO in toluene under 100 psi of CO$_2$ at 20 °C using 1 mol% **3** yields an alternated polycarbonate (ether linkages cannot be detected by ^{1}H NMR) with narrow molecular weight distribution (M_w/M_n is significantly less than 2). To optimize this class of catalysts with respect to stereoselectivity, we employed a condensed version of an improvement strategy earlier described by Snapper and Hoveyda.[19,20] By investigating the variation of substituent R^1 (**3a** Me; **3b** CF$_3$; **3c** Pr^i) while keeping the structures of R^2 (*R*-Ph) and R^3 (Pr^i) constant, we found that the methyl and isopropyl substituents had the best enantioselectivities. Owing to the higher activity of **3c**, we selected the isopropyl group as the substituent to fix at R^1. To probe the effect of R^2 on stereoselectivity, we examined ligands whose chirality was derived from phenylglycine (**3c**), valine (**3d**), and *tert*-leucine (**3e**). Interestingly, complex **3e** exhibits both the highest activity and stereoselectivity, producing a quantitative yield of polymer with an *RR*:*SS* ratio of 86:14. With R^1 fixed as isopropyl and R^2 set as *tert*-butyl, we investigated the effect of varying R^3. Unfortunately, modification of the *ortho*-aryl with the less bulky ethyl group significantly diminishes the activity and slightly decreases the stereoselectivity of the catalyst. Owing to

Atactic: n = m = 0.5
Isotactic: n > m or m > n

R^1 = Me, CF$_3$, Pr^i
R^2 = (*R*)-Ph, (*S*)-Pr^i, (*S*)-Bu^t
R^3 = Et, Pr^i

Scheme 2

Table 1 Enantioselective copolymerization of cycloalkene oxides and CO_2 using 3^a

Catalyst	R^1	R^2	R^3	Monomer[b]	t/h	Conversion (%)	M_n ($\times 10^{-3}$)[c] (g mole^{-1})	M_w/M_n[c]	$RR:SS$ ($n:m$)[d]
3a	Me	(R)-Ph	Pr^i	CHO	24	17	1.37	1.24	29:71
3b	CF$_3$	(R)-Ph	Pr^i	CHO	10	100	11.8	1.13	39:61
3c	Pr^i	(R)-Ph	Pr^i	CHO	24	45	7.69	1.12	31:69
3d	Pr^i	(S)-Pr^i	Pr^i	CHO	24	26	4.81	1.20	82:18
3e	Pr^i	(S)-Bu^t	Pr^i	CHO	24	100	14.7	1.35	86:14
3f	Pr^i	(S)-Bu^t	Et	CHO	24	23	3.56	1.13	84:16
3g	CF$_3$	(S)-Bu^t	Pr^i	CHO	10	100	27.1	1.78	82:18
3e	Pr^i	(S)-Bu^t	Pr^i	CPO	24	48	12.4	1.21	88:12

[a] All reactions performed in 2.5 M epoxide solution (toluene) at 20 °C and 100 psi CO_2 using 1 mol % catalyst. [b] CHO = cyclohexene oxide; CPO = cyclopentene oxide. [c] Measured using gel-permeation chromatography *versus* polystyrene standards. [d] Measured by hydrolyzing the polymer and analyzing the resultant diol by chiral GC.

the high activity of the CF$_3$-substituted complex **3b**, we decided to investigate the related complex **3g** with the substituents at R^2/R^3 presumably optimized as *tert*-butyl/isopropyl. Although the high activity of the complex was retained, the stereoselectivity of the complex was inferior to that of **3e** ($RR:SS$ ratio 82:18). Complex **3e** was also investigated for the copolymerization of cyclopentene oxide and CO_2: the polymer formed contained 88% RR-units in the main chain. This result represents not only the first successful asymmetric polymerization of this monomer, but also the highest degree of asymmetric induction achieved to date in a CO_2/epoxide copolymerization.

With complex **3e** identified as the most selective catalyst for the copolymerization we obtained a molecular structure of this catalyst precursor using X-ray diffraction.†,‡ Complex **3e** is a rare example of a three-coordinate zinc complex; the steric bulk of the IOx and the amido ligands precludes dimerization or coordination of Lewis-basic solvents. In agreement with other zinc diimine and bisoxazoline complexes, the aryl group is perpendicular to the nearly planar IOx–Zn chelate,[8] and the *tert*-butyl group adopts a staggered conformation. The origins of asymmetric induction are not understood at the current time, although we anticipate that mechanistic studies currently underway on complexes of type **1** will facilitate the more rational design of improved variants of **3**.

We have studied the chemical structure and physical properties of the CHO/CO_2 polymer derived from **3e** in detail. The carbonyl region (δ_C 152–154) of the ^{13}C NMR spectrum of the polymer appears to exhibit partial tetrad resolution based on comparison of experimental and predicted intensities assuming an enantiomorphic-site control mechanism.§ The large peak at δ_C 153.8 is assigned to the chemical shift equivalent m-centered tetrads ([mmm], [mmr] and [rmr]),[15] while the small shifts at δ_C 153.3 and 153.2 are assigned to the [mrm]/[rrr] tetrads (they cannot be unambiguously determined due to their statistical equivalence in the polymer). Finally, the peak at δ_C 153.1 is assigned to the [mrr] tetrad. The T_g and T_m of the polycarbonate are 120 and 220 °C, respectively. The application of these complexes for other asymmetric transformations, as well as the development of improved catalysts for CHO/CO_2 polymerization, is currently underway in our laboratory.

Notes and references

‡ *Crystal data* for **3e**: C$_{30}$H$_{55}$N$_3$OSi$_2$Zn, M = 595.32, monoclinic, space group $P2_1$, a = 11.4881(1), b = 13.9886(1), c = 22.0242(3) Å, U = 3426.23(6) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.811 mm^{-1}, 20704 reflections measured, 14040 unique (R_{int} = 0.0867) which were used in all calculations. Final $wR(F^2)$ was 0.1158 (all data).
CCDC 182/1767. See http://www.rsc.org/suppdata/cc/b0/b005537i/ for crystallographic files in .cif format.
§ The expressions for the tetrad concentrations in terms of the enantioselectivity parameter (α) are: [mmm] = α^4 + $(1 - \alpha)^4$; [mmr] = [mrr] = $2[\alpha^3(1 - \alpha) + \alpha(1 - \alpha)^3]$; [rmr] = [mrm] = [rrr] = $2\alpha^2(1 - \alpha)^2$. For the CHO/CO_2 polymer formed using **3e** (α = 0.86), the observed (predicted) tetrad concentrations are: [mmm] + [mmr] + [rmr] = 0.76 (0.76); [rrr]/[mrm] = 0.04 (0.03); [mrm]/[rrr] = 0.02 (0.03); [mrr] = 0.18 (0.18).

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