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Enantioselective, Stereoconvergent Resolution Copolymerization of *Racemic cis*-Internal Epoxides and Anhydrides

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Abstract: Enantioselective copolymerization of unsymmetric disubstituted epoxides (e.g. *racemic cis*-internal epoxides) is a very challenging issue, due to their poor reactivity, and complicated stereo-/regio-selectivity. Herein, we present an unprecedented enantioselective resolution copolymerization of *racemic cis*-internal epoxides and anhydrides mediated by dinuclear aluminum complexes with multiple chirality, affording optically active polyesters with two contiguous stereogenic centers, and the unreacted substrates in good enantioselectivity. An unexpected stereoconvergence is observed in this resolution copolymerization, where the selectivity factor (*s*-factor) for the enantioselective formation of copolymer significantly exceeds the kinetic resolution coefficient (k_{rel}) based on the unreacted epoxide at various conversions. The catalytic activity and copolymer enantioselectivity are revealed to be strongly influenced by the phenolate *ortho*-substituents of the ligand set, as well as the axial linker and its chirality. The use of enantiopure binaphthol-linked bimetallic (*R,R,R,R,R*)-Al(III) complex without any substituent at the phenolate ortho-positions of the ligand allows not only a stereoconvergent access to the highly stereoregular semi-crystalline polyesters with an unprecedented levels of enantioselectivities of up to 99% *ee* (with a *s*-factor of 437), but also a concomitant kinetic resolution of the epoxide substrates (with a k_{rel} of 118). Mechanistic studies performed by combining experimental observations and density functional theory calculations suggest that both the enantiomorphic site of the ligand set and the propagating chain-end control mechanisms determined the enantioconvergent access to enantioenriched copolymers.

Introduction

Most of the naturally occurring polymers are optically active, and some of these exhibit unique characteristics, such as molecular recognition ability, resulting from their distinctive chiral structure.[1,2] In the realm of synthetic chemistry, asymmetric polymerization is one of the most challenging methods to prepare enantioenriched polymers with configurational main-chain chirality.[3] In terms of the reaction process, asymmetric polymerization can be classified into two categories: asymmetric synthesis polymerization of optically inactive prochiral monomers *via* enantioselective catalysis; and enantiomer-selective polymerization of only one enantiomer of the *racemic* monomers with completely configurational retention in the kinetic resolution.[4] As most of the *racemate*s are readily available and inexpensive, the latter method has attracted significant interest and affords two separable products, an enantiopure isotactic polymer and the unreacted enantiomer in the solution. A representative example is the binaphthol-linked dinuclear cobalt complex mediated enantioselective resolution polymerization of *racemic* terminal epoxides to afford isotactic polyethers and enantiopure epoxides, which exhibited high activity and enantioselectivity with a selectivity factor (*s*-factor) in the range of 60−370.[5-7]

When this powerful strategy is applied to the enantioselective resolution copolymerization of *racemates* with achiral nucleophiles, optically active copolymers with main-chain chirality can be formed.[8] Employing this strategy, several groups independently explored the kinetic resolution copolymerization of *racemic* terminal epoxides and CO_2 to afford the alternating polycarbonates with more than 95% head-to-tail linkages; however, the kinetic resolution coefficients (k_{rel}) for all tested chiral catalyst systems were less than 25.[9-12] Contrary to the limited success of this type of kinetic resolution copolymerization, the asymmetric copolymerization of *meso*-epoxides and CO_2 or cyclic anhydrides achieved significant progress through the use of enantiopure bimetallic catalyst systems (Scheme 1A), where the resulting polycarbonates or polyesters possessed completely alternating microstructures, low polydispersity index, and up to 99% enantioselectivity.[13-16] Prior to these studies, Williams and coworkers significantly contributed toward developing distinct bimetallic catalysts for the copolymerization of epoxides with CO_2 or anhydrides.[17-19] More recently, our group achieved highly enantioselective resolution copolymerization of *racemic* terminal epoxides and anhydrides mediated by binaphthol- or hydrogenated binaphthol-linked bimetallic complexes, exhibiting both k_{rel}s and *s*-factors of greater than 300 (Scheme 1B).[20]

In comparison with simple terminal epoxides with a chiral center, unsymmetric disubstituted epoxides contain two chiral carbons, as well as *trans-* and *cis*-structure. Although enantioenriched *cis*-epoxides can be efficiently synthesized *via* the asymmetric epoxidation of *cis*-olefins,[21] the use of readily available and inexpensive *racemic* epoxides through the catalytically kinetic resolution provides a competitive alternative route to afford an enantiomerically pure form.[22,23] However, in sharp contrast to the extensive literatures on the kinetic resolution of *racemic* terminal epoxides, only few studies on the catalytically kinetic resolution of *racemic cis*-internal epoxides have been reported. In 2004, Umani-Ronchi *et al*. reported an effective methodology for the kinetic resolution of 2,3-disubstituted aromatic epoxides through a C−C bond forming reaction using 2-methylindole as the resolving reagent and chiral Cr(salen) complexes as catalysts, affording the indolyl derivatives and the unreacted epoxides in high enantiomeric excess (*ee*).[24] Later, Kobayashi and coworkers discovered that the niobium complex of a tetradentate binaphthol derivative, a *meso*-desymmetrization catalyst, was also effective in the regio- and stereoselective ring-opening of unsymmetrical *cis*-epoxides through a kinetic resolution process using anilines as nucleophiles.[25] A practically useful kinetic resolution of *racemic* epoxides was achieved by using chiral phosphoric acid as a catalyst and carboxylic acids as activators at an extremely low reaction temperature of −50 ºC.[26] More recently, Chen *et al.* reported a catalyst-site-controlled diastereoselective polymerization methodology that directly polymerized the diastereomeric mixtures of eight-membered diolide monomers into stereosequenced crystalline polyhydroxyalkanoates with adjustable properties.[27]

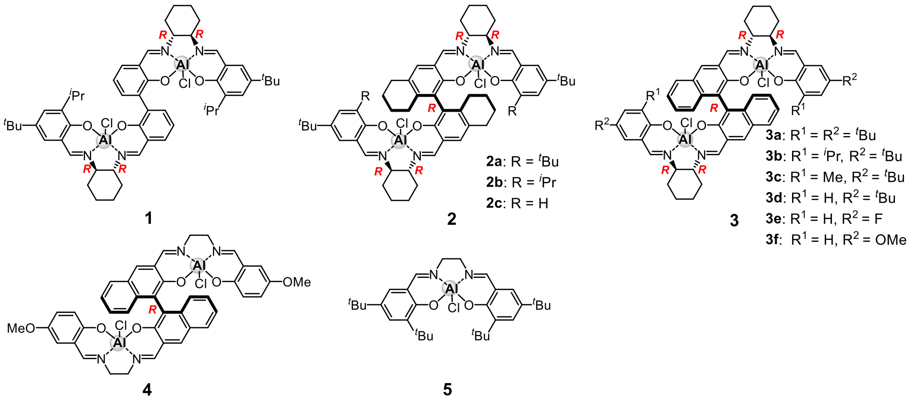
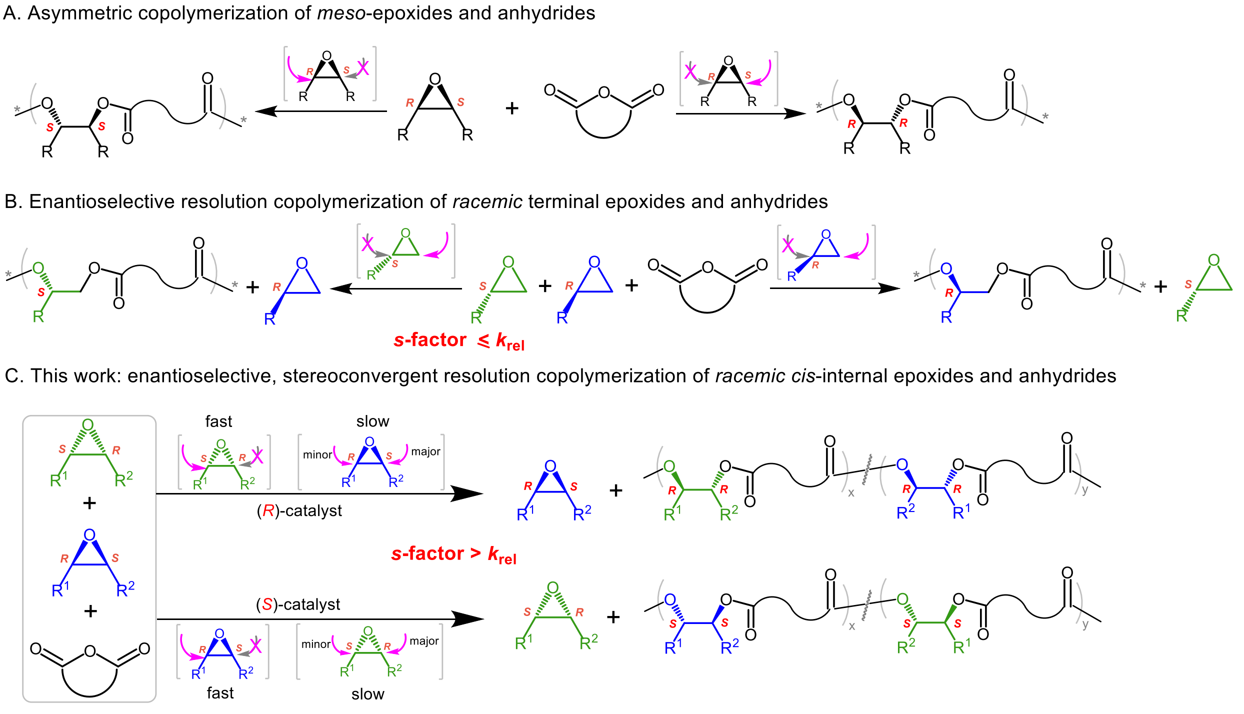


Figure 1. Structure of employed Al(III) complexes

Herein, we present an unprecedented stereoconvergent resolution copolymerization of *racemic cis*-internal epoxides with anhydrides using multi-chiral and bimetallic synergistic catalysis, where the *s*-factors for the enantioselective formation of copolymers are significantly higher than the k_{rel}s based on the unreacted epoxides, as the catalyst systems predominantly dictate the configuration of the newly formed stereogenic centers *via* stereoselective ring-opening, regardless of the extant stereochemistry of the substrate (Scheme 1C). This phenomenon is distinct to the principle in a traditional kinetic resolution process, where the k_{rel} is defined as being equal to the *s*-factor.

Results and Discussion

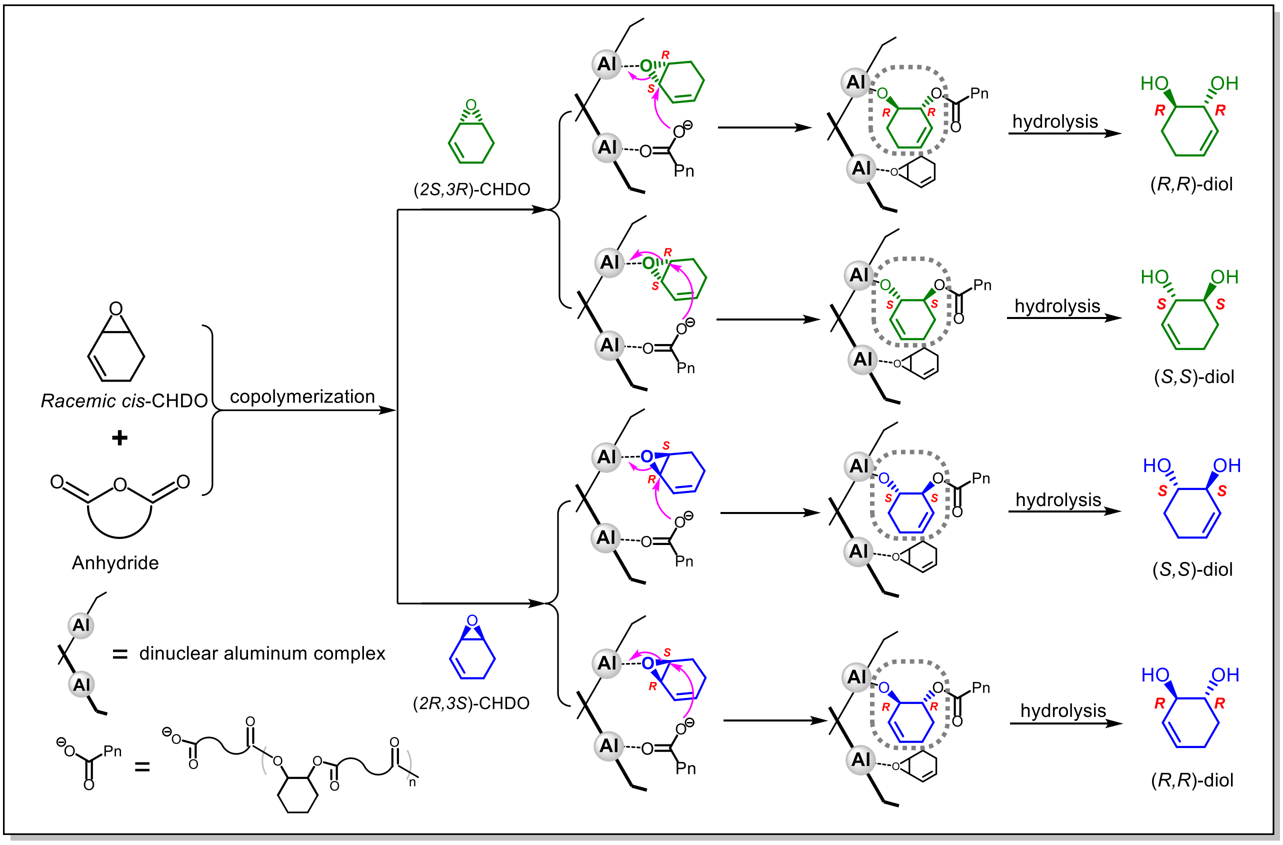
Enantioselective resolution copolymerization of *racemic* 7-oxabicyclo[4,1,0]hept-2-ene (CHDO) and phthalic anhydride (PA). We initiated our studies by using the alternating copolymerization of *racemic* 7-oxabicyclo[4,1,0]hept-2-ene (CHDO) and phthalic anhydride (PA) as a model reaction, and an enantiopure dinuclear Al(III) complex **1** based catalyst system, which has been reported to be highly active and enantioselective for copolymerizing *meso*-epoxides and cyclic anhydrides.[15] When activated with bis(triphenylphosphine)-iminium chloride (PPNCl), the biphenol-linked dinuclear Al(III) complex **1** with (*R*,*R*,*R*,*R*)-configuration showed moderate activity with a turnover frequency (TOF) of 123 h^{-1} at ambient temperature (Table 1, entry 1). This enantioselective resolution copolymerization afforded enantioenriched (+)-(2*R*,3*S*)-CHDO with 76% enantiomeric excess (*ee*) at 49% conversion, and an optically active polyester with a specific rotation value of $[\alpha]_D^{20}$ = -129º (*c* = 1 in CHCl$_3$),


A. Asymmetric copolymerization of *meso*-epoxides and anhydrides

B. Enantioselective resolution copolymerization of *racemic* terminal epoxides and anhydrides

C. This work: enantioselective, stereoconvergent resolution copolymerization of *racemic cis*-internal epoxides and anhydrides

Scheme 1. Synthetic strategies of chiral polyesters from various epoxides by enantioselective copolymerization with anhydrides



Scheme 2. Stereochemical transformation involved in the ring-opening copolymerization of *racemic cis*-CHDO.

corresponding to 82% *ee* for (*R*,*R*)-configuration based on the resulting diol after the copolymer hydrolysis. Notably, both (2*S*,3*R*)-CHDO and (2*R*,3*S*)-CHDO have two available chiral carbons for the nucleophilic ring-opening reaction, resulting in four divergent ring-opening pathways with different regioselectivities or stereoselectivities in the copolymerization with cyclic anhydrides. However, only two types of configured chiral diol-units ((*R*,*R*)-units and (*S*,*S*)-units) could be obtained through the hydrolysis of the resultant polyesters (Scheme 2). Considering the unknown and complexity of the four possible chiral transformation processes, the $k_{rel} = \ln[(1\text{-c})(1\text{-}ee_{\text{epoxide}})]/\ln[(1\text{-c})(1+ee_{\text{epoxide}})]$ and *s*-factor=$\ln[1\text{-c}(1+ee_{\text{polyester}})]/\ln[1\text{-c}(1\text{-}ee_{\text{polyester}})]$ were determined to separately evaluate the unreacted epoxide and copolymer enantioselectivities.

The biphenol-linked dinuclear Al(III) complex (*R*,*R*,*R*,*R*)-**1** has two diastereoisomers with (*R*)- or (*S*)-biphenol stereochemistry, (*R*,*R*,*R*,*R*,*R*)- and (*R*,*R*,*S*,*R*,*R*)-stereoisomers, of which the former is the matched configuration for better activity and enantioselectivity in recent studies on the asymmetric copolymerization involving *meso*-epoxides.[14] Therefore, enantiopure dinuclear Al(III) complexes **2** and **3** bearing the configuration-matched binaphthol and hydrogenated-binaphenol linkers were synthesized for CHDO/PA copolymerization. To our delight, most catalyst systems exhibited excellent activities (TOF > 300 h^{-1}) and enhanced enantioselectivities compared to those with the biphenol-linked Al(III) complex **1** catalyst system under same conditions. The steric hindrance of the phenolate ortho-position substituents of the ligand strongly influenced the catalytic activity, the k_{rel}, and polymer enantioselectivity (corresponding to the *s*-factor). For example, no or very low activity was observed with the catalyst system based on hydrogenated-binaphenol-linked complex (*R*,*R*,*R*,*R*,*R*)-**2a** bearing *tert*-butyl groups on the phenolate ortho-positions (Entry 2), while slightly less-hindered (*R*,*R*,*R*,*R*,*R*)-**2b** bearing isopropyl groups showed a high activity of up to 308 h^{-1}, where the k_{rel} and *s*-factor values were 25 and 43, respectively (Entry 3). Replacement with a further less-hindered (*R*,*R*,*R*,*R*,*R*)-**2c** without any substituent increased both the k_{rel} and *s*-factor values to a certain extent (Entry 4). For binaphthol-linked complexes **3a–3f**, similar effects of the steric hindrance of the phenolate ortho-position substituents on the catalytic activity, as well as the k_{rel} and *s*-factor were also observed (Entries 5**–**8), with the highest activity of 363 h^{-1} obtained for the (*R*,*R*,*R*,*R*,*R*)-**3d** system (Entry 8). In this case, a conversion of 43.5% was achieved within 18 minutes at ambient temperature, and the polyester obtained in 98% *ee* exhibited a high *s*-factor of 226, which was significantly greater than the k_{rel} value of 44, indicating an unexpected stereoconvergence for copolymer formation. The change of the phenolate *para*-position substituents from *tert*-butyl to fluoro or methoxyl groups had limited effect on the catalytic activity and polyester enantioselectivity (Entries 9 and 10). The use of the catalyst with (*S*,*S*,*S*,*S*,*S*)-configuration afforded enantioenriched (-)-(2*S*,3*R*)-CHDO and polyester with (*S*,*S*)-configuration (Entry 11). Surprisingly, when (*R*,*R*,*S*,*R*,*R*)-**3f** was employed, the (*S*,*S*)-configured polyester was obtained in 88% *ee* (Entry 12). This result implied the strong chirality inducing ability of the chiral axial linker. For further investigating the influence of the axial linker on the chiral induction, complex **4** bearing (*R*)-binaphenol linker and achiral ethylenediamine backbone was prepared and tested for the *racemic* CHDO/PA copolymerization. The polymerization predominantly afforded (*R*,*R*)-enriched

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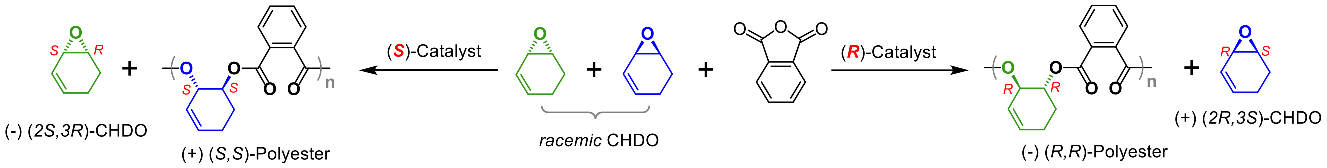
Table 1. Enantioselective copolymerization of *racemic cis*-CHDO and PA[a]



Entry	Cat.	Temp. (°C)	Time (h)	Conv. [b] (%)	TOF[c] (h^{-1})	ee_{epo}[d] (%)	k_{rel}[e]	ee_{pro}[f] (%)	*s*-factor[g]	M_n[h] (kg/mol)	*Đ* [h]	Specific rotation [i] (°)
1	(*R,R,R,R*)-**1**	25	1	49.0	123	76(*2R,3S*)	19	82(*R,R*)	24	5.6	1.31	-129
2	(*R,R,R,R,R*)-**2a**	25	4	<2	--	--	--	--	--	--	--	--
3	(*R,R,R,R,R*)-**2b**	25	0.4	49.3	308	80(*2R,3S*)	25	88(*R,R*)	43	5.7	1.43	-146
4	(*R,R,R,R,R*)-**2c**	25	1	45.9	115	74(*2R,3S*)	32	95(*R,R*)	97	5.3	1.24	-172
5	(*R,R,R,R,R*)-**3a**	25	3	45.4	38	60(*2R,3S*)	11	75(*R,R*)	13	5.0	1.18	-114
6	(*R,R,R,R,R*)-**3b**	25	0.4	49.7	311	77(*2R,3S*)	19	94(*R,R*)	110	5.8	1.20	-166
7	(*R,R,R,R,R*)-**3c**	25	0.3	42.5	354	65(*2R,3S*)	30	98(*R,R*)	216	4.8	1.22	-182
8	(*R,R,R,R,R*)-**3d**	25	0.3	43.5	363	70(*2R,3S*)	44	98(*R,R*)	226	5.0	1.12	-183
9	(*R,R,R,R,R*)-**3e**	25	0.4	45.2	283	71(*2R,3S*)	28	96(*R,R*)	119	5.2	1.14	-175
10	(*R,R,R,R,R*)-**3f**	25	0.4	45.7	286	77(*2R,3S*)	52	94(*R,R*)	78	5.4	1.30	-168
11	(*S,S,S,S,S*)-**3f**	25	0.5	49.3	247	87(*2S,3R*)	51	93(*S,S*)	86	5.9	1.11	+168
12	(*R,R,S,R,R*)-**3f**	25	1.5	39.7	66	47(*2S,3R*)	10	88(*S,S*)	28	4.4	1.20	+144
13	(*R*)-**4**	25	1.5	42.7	71	61(*2R,3S*)	19	90(*R,R*)	38	4.7	1.09	-154
14	(*R,R,R,R,R*)-**3f**	0	3	42.7	36	70(*2R,3S*)	67	96(*R,R*)	105	4.6	1.05	-177
15[j]	(*R,R,R,R,R*)-**3f**	0	30	46.9	4	85(*2R,3S*)	142	98(*R,R*)	280	5.5	1.08	-185
16[j]	(*R,R,R,R,R*)-**3d**	0	24	42.4	4	71(*2R,2S*)	118	99(*R,R*)	437	4.6	1.23	-188
17[k]	(*R,R,R,R,R*)-**3d**	25	6	47.2	79	83(*2R,3S*)	70	97(*R,R*)	186	15.3	1.26	-180
18[l]	(*R,R,R,R,R*)-**2b**	25	24	78.1	--	--	--	>99(*R,R*)	--	3.0	1.33	-190
19[l]	**5**	25	96	61.6	--	--	--	>99(*R,R*)	--	3.0	1.21	-190
20[l]	(*S,S,S,S,S*)-**2b**	25	120	53.2	--	--	--	60(*R,R*)	--	2.7	1.16	-89
21[l]	(*S,S,S,S,S*)-**3d**	25	96	54.7	--	--	--	62(*R,R*)	--	2.8	1.12	-91
22[l]	(*S,S,S,S,S*)-**2b**	0	336	73.4	--	--	--	20(*R,R*)	--	3.1	1.13	-45

[a]Conditions: The reaction was performed in toluene (2.7 mL, 25 mmol) in a 20 mL flask; toluene/CHDO/anhydride/catalyst/PPNCl = 500/250/125/1/2 (molar ratio), except for entries 15–22. [b] Calculated using ^{1}H NMR spectroscopy using CHDO as the limiting reagent. [c] Turnover frequency (TOF) = moles of product (polyester)/moles of catalyst per hour. [d] Measured by chiral HPLC, and the (*2R,3S*)-CHDO was the major enantiomer remaining when (*R,R,R,R,R*)-catalyst was used. [e] $k_{rel} = \ln[(1-c)(1-ee_{epo})]/\ln[(1-c)(1+ee_{epo})]$, where *c* is the conversion and ee_{epo} is the enantiomeric excess of the recovered epoxide expressed as %/100. [f] Measured by hydrolyzing the polymer and analyzing the resulting diol by chiral GC, and the (*R,R*)-diol was the major enantiomer when (*R,R,R,R,R*)-catalyst was used. [g] *s*-factor = $\ln[1-c(1+ee_{pro})]/\ln[1-c(1-ee_{pro})]$, where *c* is the conversion and ee_{pro} is the enantiomeric excess of the resulting diol expressed as %/100. [h] Determined by using gel permeation chromatography in THF, calibrated using polystyrene. [i] Specific rotation values of the polymers were determined in chloroform at 20 °C (c = 1) by using a polarimeter; the wavelength of the polarized light was 589.3 nm. [j] Toluene/CHDO/anhydride/catalyst/PPNCl = 2000/250/125/1/2 (molar ratio). [k] Toluene/CHDO/anhydride/catalyst/PPNCl = 2000/1000/500/1/2 (molar ratio). [l] Enantiopure (*2S,3R*)-CHDO was used for entries 18–22, toluene/epoxides/anhydride/catalyst/PPNCl = 4000/200/200/1/2 (molar ratio)

polyester and retained the unreacted epoxide with (*2R,3S*)-isomer excess (Entry 13). Both the k_{rel} and *s*-factor values were higher than those observed with the (*R,R,S,R,R*)-**3f** catalyst system. Notably, the catalytic activity of (*R*)-**4** or (*R,R,S,R,R*)-**3f**

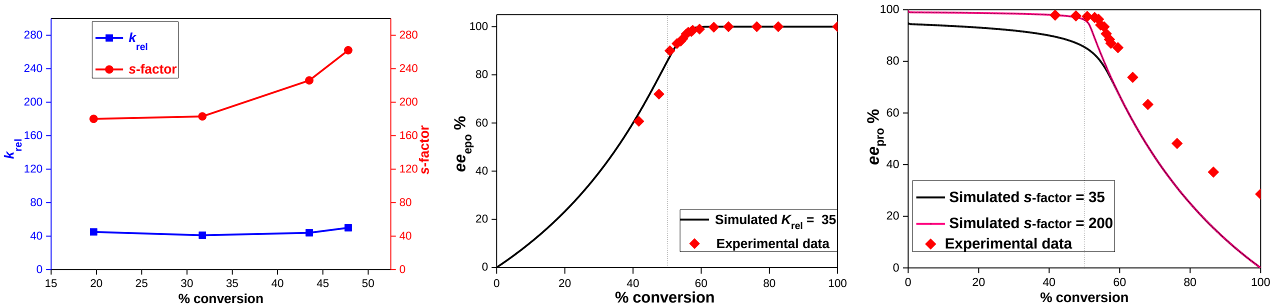


Figure 2. Left: Determination of k_{rel} and *s*-factor using four data points at different conversions mediated by (*R*,*R*,*R*,*R*,*R*)-**3d**/PPNCl. Middle: Comparison of experimental data with the simulated plot of substrate enantioselectivity. Right: Comparison of experimental data with the simulated plot of product enantiooselectivity**.** Experimental data are described in Supplementary tables S1 and S2).

was significantly lower than that of the (*R*,*R*,*R*,*R*,*R*)-**3f** catalyst system. Overall, in the enantiopure dinuclear Al(III) complex mediated *racemic* CHDO/PA copolymerization, the axial chirality determined the chiral induction direction, and the cyclohexanediamine backbones with the same configuration was beneficial for the catalytic activity and product enantioselectivity.

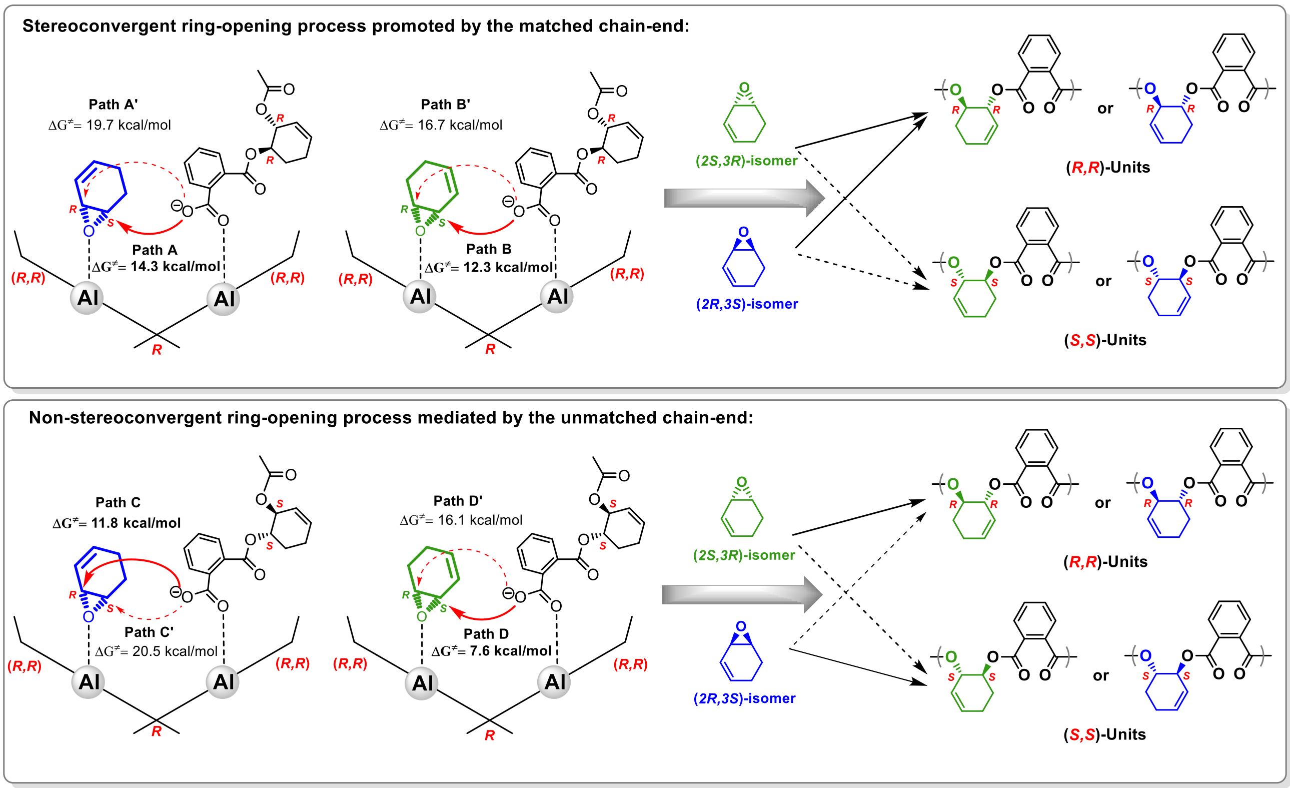
When copolymerization was performed at 0 °C in toluene using (*R*,*R*,*R*,*R*,*R*)-**3f**/PPNCl as the catalyst, the resulting polyester showed a high enantioselectivity of 96% *ee*, and exhibited an enhanced *s*-factor (Table 1, entry 14). The dilution of both the catalyst and monomer concentrations in the reaction system using toluene resulted in a substantial loss in the polymerization rate, but significantly increased both k_{rel} and *s*-factor values (Entries 15 and and 16). The highest *s*-factor of 437 and k_{rel} of 118 was observed for the (*R*,*R*,*R*,*R*,*R*)-**3d**/PPNCl catalyst system at 0 °C, and the resultant copolymer possessed a high enantiopurity of up to 99% *ee* for (*R*,*R*)-configuration, with a specific rotation of $[\alpha]_D^{20}$ = -188° (*c* = 1 in $CHCl_3$). Notably, when the CHDO/catalyst ratio was increased to 1000, the k_{rel} of 70 and *s*-factor of 186 were obtained at 47.2% conversion at room temperature, affording the copolymer with an enhanced molecular weight and a high level enantiopurity of 97% *ee* (Entry 17).

Although the accurate assignment of the microstructure (regio/stereoregularity) of CHDO/PA copolymer is not clear, significant differences in carbonyl, methine and methylene region between the atactic and isotactic polymers are easily identified on the basis of ^{13}C NMR spectroscopy studies (Figure S23). Notably, the isotactic CHDO/PA copolymer (poly(1,3-cyclohexadiene phthalate)) with main-chain chirality was found to be a typical semicrystalline material, possessing a melting endothermic peak at 213 °C with ΔH_m = 18.3 J g^{-1}. Its crystallizability was further identified by powder X-ray diffraction (XRD). Diffraction peaks at 10.9°, 15.3°, 18.1°, 22.2° and 23.3° were observed for the isotactic-enriched poly (1,3-cyclohexadiene phthalate) sample, demonstrating its semicrystalline structure, while no diffraction signal was found in the atactic copolymer (Figure S26).

Comprehensive understanding of enantioconvergent copolymerization behavior (*s*-factor > k_{rel}). As the calculations of k_{rel} and *s*-factor are based on the conversion and the enantioselectivities of the unreacted epoxide and resultant copolymer, their values might deviate from the actual ones, due to the small measurement errors. [23] Therefore, four sets of data for k_{rel} and *s*-factor were calculated at different conversions in the enantioselective CHDO/PA copolymerization mediated by (*R*,*R*,*R*,*R*,*R*)-**3d**/PPNCl at 25 °C. The k_{rel} values ranging from 41 to 50 were obtained between 20 to 48% conversion while the corresponding *s*-factor values varied from 180 to 265, which exceeded the k_{rel} values by a factor of approximately five (Figure 2, left). This result indicated an unexpected enantioconvergent phenomenon in the enantioselective resolution copolymerization. In this case, both enantiomers incorporated into the polyesters afforded the (*R*,*R*)-diol units. Moreover, the *s*-factor increased with the conversion, while the enantioselectivity of the resulting copolymer was maintained at 98% *ee*. For a comparative analysis, the k_{rel} and *s*-factor values at various conversions were calculated for the (*R*,*R*,*R*,*R*,*R*)-**2b**/PPNCl-mediated CHDO/PA copolymerization. Although, no apparent increase in the *s*-factor value was observed with the conversion, a slightly higher *s*-factor than k_{rel} was also identified in this process (Supporting information, figure S34).

Furthermore, for an in-depth understanding of the enantioselective copolymerization process, a monitoring experiment was conducted with a 1:1 feed ratio of *racemic* CHDO and PA at various time points. The experimental data for the enantioselectivity of the unreacted epoxide at various conversions fits well with the simulated plot for k_{rel} of 35 (Figure 2, middle),[28,29] while the data for copolymer enantioselectivity apparently overwhelmed the plot for *s*-factor of 35, or even 200 (Figure 2, right; the simulated k_{rel} and *s*-factor values adopted the experimental values at approximate 50% conversion). Three important differences were observed through the comparative study: (1) the *s*-factor for evaluating the enantioselective copolymerization significantly exceeded the k_{rel} based on the enantioselectivity of the unreacted epoxide at various conversions; (2) the decrease in copolymer enantioselectivity started from approximately 54% conversion, slightly exceeding the maximum efficiency (50%) for the traditional kinetic resolution processes; (3) after complete conversion of the epoxide, the resulting copolymer had an enantioselectivity of 29% *ee*, which was clearly different from 0% *ee* obtained by the traditional kinetic resolution process.[30] These results demonstrated the enantioconvergent phenomenon during the enantioselective resolution copolymerization of *racemic* CHDO and PA, in which approximately 54% conversion was the point of inflexion for the decrease of polyester enantioselectivity.

To clarify the asymmetric induction of the dinuclear Al(III) complex in the ring-opening process of the unmatched CHDO isomer, enantiopure (2*S*,3*R*)-CHDO was prepared for the copolymerization with PA at various reaction conditions (Table 1, entries 18–22). Excellent enantioselectivity was observed with the use of both the matched chiral (*R*,*R*,*R*,*R*,*R*)-**2b** and achiral salenAlCl catalyst **5**, where the copolymerization of (2*S*,3*R*)-CHDO with PA at 25 °C afforded highly isotactic polyester with more than 99% *ee*, and a specific rotation value of $[\alpha]_D^{20}$ = -190° (*c*

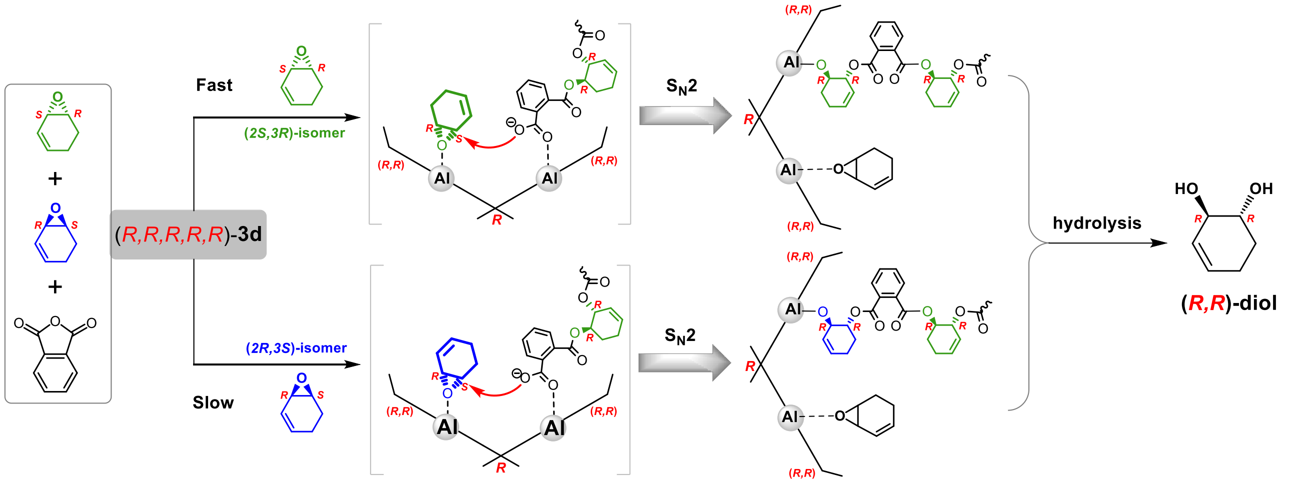


Scheme 3. Gibbs free energy barrier (△G≠) of different ring-opening pathways mediated by (*R,R,R,R,R*)-**3d**. Path A: Attack of unfavorable (*2R,3S*)-CHDO by (*R,R*)-configured chain end; Path B: Attack of favorable (*2S,3R*)-CHDO by (*R,R*)-configured chain end; Path C: Attack of unfavorable (*2R,3S*)-CHDO by (*S,S*)-configured chain end; Path D: Attack of favorable (*2S,3R*)-CHDO by (*S,S*)-configured chain end. The energies are given in kcal mol^{-1}.

= 1 in $CHCl_3$). This result indicated that the copolymerization reaction of a single stereoisomer was highly regioselective and the ring opened at the more active allylic position *via* a S_N2 pathway, resulting in a stereospecific ring-opening reaction. When the reaction was carried out using the unmatched chiral (*S,S,S,S,S*)-**2b** or (*S,S,S,S,S*)-**3d** under same conditions, approximately 20% (*S,S*)-configuration units were detected in the resulting polyester. Moreover, when performed at 0 °C, the enantiomeric ratio of (*S,S*)- and (*R,R*)- figuration units reached to 40:60. These results demonstrated that the multi-chiral environment of the dinuclear Al(III) complex significantly influenced the ring-opening position of the configuration-unmatched CHDO incorporated into the copolymer.

Based on the data shown above, it could be concluded that in the (*R,R,R,R,R*)-**3d**-mediated *racemic* CHDO/PA enantioselective copolymerization, the unfavorable stereoisomer (*2R,3S*)-CHDO was the only source for producing (*S,S*)-units distributed into the (*R,R*)-configuration-enriched polyester. Besides, the almost complete consumption of the favorable (*2S,3R*)-isomer occurred at approximately 54% conversion. Therefore, the incorporation of the favorable (*2S,3R*)-isomer became extremely insufficient at more than 54% conversion, a point of inflection where the copolymer enantioselectivity started to decrease. After the completely consumption of (*2S,3R*)-CHDO, the copolymerization only involved the unmatched (*2R,3S*)-CHDO isomer at a very low rate. Consequently, the ring-opening regioselectivity for the unmatched (*2R,3S*)-CHDO could be different at various conversions, possibly due to the chain-end stereochemical control. It is generally known that both the ligand set of the discrete catalyst and the propagating chain-end influence the stereochemistry of the fresh unit incorporated into the polymer. In prior reports on enantioselective epoxide copolymerization, the enantiomorphic-site mechanism predominantly affected the stereochemistry of the resultant copolymers.[7] To gain insights into the enantioconvergent copolymerization mechanism, the copolymer chain growth processes were simulated using the density functional theory (DFT) calculations. The (*R,R,R,R,R*)-**3d** was selected as a model catalyst, and CHDO/PA copolymerization as a model reaction. The epoxide was coordinated to one Al(III) center and subsequently ring-opened by the benzoate bearing a chiral chain-end bound to the other Al(III) center, affording four pathways for attacking the (*2R,3S*)-CHDO or (*2S,3R*)-CHDO by the (*R,R*)- or (*S,S*)-chain end in the ring-opening process. Each pathway afforded two possible transition states (TSs) for attacking the (*R*)- or (*S*)-methine position (Scheme 3).

It was observed that the benzoate bearing a different chiral ester chain-end unit resulted in a significant difference in the Gibbs free energy barrier for (*2R,3S*)-CHDO ring-opening at either the (*R*)- or (*S*)-methine position. For example, when the coordinated (*2R,3S*)-CHDO was ring-opened by the benzoate bearing an (*R,R*)-ester end unit, the Gibbs free energy barriers for attacking (*S*)-methine (Scheme 3, Path A) and (*R*)-methine C–O bonds (Scheme 3, Path A') of the epoxide were 14.3 and 19.7 kcal/mol, respectively. This implied that it was easier for the ring-opening reaction of the next enchained (*2R,3S*)-isomer to occur at (*S*)-methine to produce a new (*R,R*)-ester unit. In the case of (*2S,3R*)-CHDO ring-opened by the benzoate bearing an (*R,R*)-ester end unit, the Gibbs free energy barriers for attacking (*S*)-methine (Scheme 3, Path B) and (*R*)-methine (Scheme 3, Path



Scheme 4. Enantioconvergent behavior in the enantioselective copolymerizations of CHDO and PA by combining the enantiomorphic-site and chain-end control.

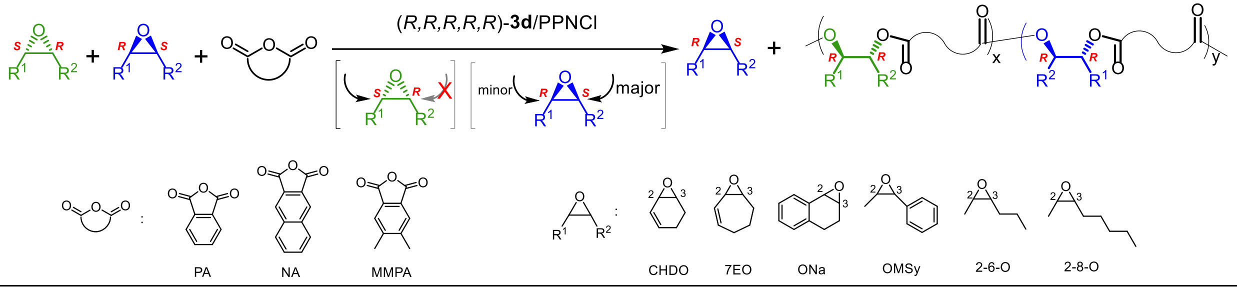
B') of the epoxide were 12.3 and 16.7 kcal/mol, respectively, with the same tendency to produce a new (*R*,*R*)-ester unit.

Alternately, when the coordinated (2*R*,3*S*)-CHDO was ring-opened by the benzoate bearing an (*S*,*S*)-ester end unit, the Gibbs free energy barriers for attacking (*S*)-methine (Scheme 3, Path C') and (*R*)-methine (Scheme 3, Path C) were calculated to be 20.5 and 11.8 kcal/mol, respectively, implying the tendency to produce a new (*S*,*S*)-ester unit. Whereas, in the case of (2*S*,3*R*)-CHDO ring-opened by the benzoate bearing an (*S*,*S*)-ester end unit, the Gibbs free energy barrier for attacking (*S*)-methine (Scheme 3, Path D) and (*R*)-methine (Scheme 3, Path D') were calculated to be 7.6 and 16.1 kcal/mol, respectively, implying the inclination toward ring-opening at (*S*)-methine to afford the (*R*,*R*)-unit. Briefly, with the use of (*R*,*R*,*R*,*R*,*R*)-**3d**, it was easier for the ring-opening of the favorable (2*S*,3*R*)-CHDO to occur at (*S*)-methine to produce a new (*R*,*R*)-unit regardless of the chirality of the chain end, whereas the chain-end chirality significantly affected the ring-opening direction of the unfavorable (2*R*,3*S*)-CHDO. Therefore, it could be concluded that both the enantiomorphic-site of the ligand set in the(*R*,*R*,*R*,*R*,*R*)-**3d** and propagating (*R*,*R*)-ester chain-end control mechanisms determined the regioselective ring-opening at (*S*)-methine C-O bond for either (2*S*,3*R*)- or (2*R*,3*S*)-CHDO incorporated into the copolymer before the 54% conversion.

Based on the above-mentioned studies, a reasonable explanation for the enantioconvergent behavior (*s*-factor > k_{rel}) observed in the enantioselective copolymerization of *racemic* CHDO with PA mediated by complex (*R*,*R*,*R*,*R*,*R*)-**3d** catalyst systems could be proposed (Scheme 4). In this system, the effective kinetic resolution process proceeded smoothly to preferentially consume (2*S*,3*R*)-isomer and retain (2*R*,3*S*)-isomer. The favorable (2*S*,3*R*)-isomer was stereospecifically ring-opened at (*S*)-methine C-O bond *via* S$_N$2 mechanism, affording poly(1,3-cyclohexadiene phthalate) with (*R*,*R*)-configuration. Importantly, the simultaneous influence of both the enantiomorphic-site control and the propagating (*R*,*R*)-ester chain-end control resulted in the incorporation of a very low amount of the unfavorable (2*R*,3*S*)-isomer into the copolymer as an (*R*,*R*)-unit *via* ring-opening at the (*S*)-methine C-O bond. Pathways A' and B' involving ring-opening at the (*R*)-methine C-O bonds of both (2*S*,3*R*)- and (2*R*,3*S*)-CHDO isomers were inhibited due to their higher Gibbs free energy barriers. Any unavoidable stereochemical error that appeared in the chain-end could be corrected by the enchainment of the next favorable (2*S*,3*R*)-isomer until it was completely consumed. After the favorable (2*S*,3*R*)-isomer was consumed, the benzoate bearing the (*S*,*S*)-configured ester end was beneficial for the ring-opening of the next enchained (2*R*,3*S*)-isomer at its (*R*)-methine C−O bond to produce (*S*,*S*)-ester units, thereby changing the ring-opening tendency to cause an irreversible collapse of the copolymer stereoselectivity. Therefore, the enantioconvergence (*s*-factor > k_{rel}) was attributed to the same asymmetric ring-opening direction of both isomers, prior to the complete consumption of the favorable stereoisomer.

Substrate scope of enantioselective *racemic cis*-disubstituted epoxide/anhydride copolymerization. With highly active and enantioselective (*R*,*R*,*R*,*R*,*R*)-**3d** catalyst system in hand, we evaluated the substrate scope of both the *racemic cis*-internal epoxides and anhydrides with toluene as a solvent. Because of its relatively high reactivity, PA was selected as a model cyclic anhydride for investigating the catalytic activity and enantioselectivity. Various *racemic cis*-internal epoxides, including alicyclic 8-oxabicyclo[5.1.0]oct-2-ene (7EO), aromatic 1,2-dihydronaphthalene oxide (ONa) and *cis*-beta-methylstyrene oxide (OMSy), and aliphatic *cis*-2,3-epoxyhexane (2-6-O) and *cis*-2,3-epoxyoctane (2-8-O), exhibited reactivities at ambient temperature, affording (*R*,*R*)-configuration-enriched polyesters with 84~99% *ee* (Table 2, entries 1-7). Additionally, the enantioconvergent copolymerization behavior was observed in these systems. For example, the enantioselective resolution copolymerization of 7EO and PA showed a k_{rel} value of 31 at room temperature, and a corresponding s-factor of 88 at 49.5% conversion (Entry 1). A decrease in the reaction temperature from 25 to 0 °C resulted in great increases in both k_{rel} (61) and *s*-factor (126) (Entry 2). The resultant polyester had a high enantiopurity of 96% *ee*. Similar enantioconvergent behavior was also observed in the ONa/PA copolymerization system, where k_{rel} of 21 and *s*-factor of 65 were obtained at room temperature (Entry 3), and the corresponding values of 40 and 131, respectively, were found at 0 °C, affording polyesters with an enantiopurity of 97% *ee* (Entry 4). In the case of OMSy, a moderate kinetic resolution process proceeded with a k_{rel} of 9 and *s*-factor of 39 at 25 °C (Entry 5). Surprisingly, (*R*,*R*,*R*,*R*,*R*)-**3d** was found to be ineffective in catalyzing the enantioselective resolution copolymerization of PA with 2-6-O or 2-8-O. However, to our delight, the (*R*,*R*,*R*,*R*,*R*)-**3b** catalyst system was highly

Table 2. Substrates scope of enantioconvergent copolymerization[a]



Entry	Epoxide/ Anhydride	Temp. (ºC)	Time (h)	Conv. [b] (%)	TOF[c] (h^{-1})	ee_{epo}[d] (%)	k_{rel}[e]	ee_{pro} [f] (%)	s-factor[g]	M_n[h] (kg/mol)	Đ [h]	Specific rotation[i] [º]
1	7EO/PA	25	8	49.5	15	83(2*R*,3*S*)	31	93(*R*,*R*)	88	4.6	1.14	-49
2 [j]	7EO/PA	0	40	46.1	3	79(2*R*,3*S*)	61	96(*R*,*R*)	126	4.0	1.10	-51
3	ONa/PA	25	3	41.7	35	60(2*R*,3*S*)	21	94(*R*,*R*)	65	5.5	1.09	-73
4[j]	ONa/PA	0	72	40.5	1	62(2*R*,3*S*)	40	97(*R*,*R*)	131	5.0	1.08	-75
5	OMSy/PA	25	48	52.6	3	70(2*R*,3*S*)	9	84(*R*,*R*)	39	4.8	1.08	-9
6[k]	2-6-O/PA	25	12	33.2	7	45(2*R*,3*S*)	31	97(*R*,*R*)	106	7.1	1.11	+52
7[k]	2-8-O/PA	25	24	43.9	5	72(2*R*,3*S*)	52	99(*R*,*R*)	470	10.0	1.05	+30
8	CHDO/NA	25	12	41.3	9	60(2*R*,3*S*)	23	94(*R*,*R*)	64	3.7	1.29	-320
9	CHDO/DMPA	25	10	45.9	11	70(2*R*,3*S*)	22	96(*R*,*R*)	124	4.6	1.14	-148

[a] Conditions: The reaction was performed in toluene in a 20 mL flask; toluene/epoxides/anhydride/catalyst/PPNCl = 500/250/125/1/2 (molar ratio), except for entries 6 and 8. [b] Calculated using ^{1}H NMR spectroscopy with epoxides as the limiting reagents. [c] Turnover frequency (TOF)= moles of product (polyester)/moles of catalyst per hour. [d] Measured by chiral HPLC; the absolute configuration was confirmed by determining the specific rotation or from literature results. [e] k_{rel}= ln[(1-*c*)(1-ee_{epo})]/ln[(1-*c*)(1+ee_{epo})], where *c* is the conversion and ee_{epo} is the enantiomeric excess of the recovered epoxide expressed as %/100. [f] Measured by hydrolyzing the copolymer and analyzing the resulting diol by chiral GC or HPLC, and the (*R*,*R*)-diol was the major enantiomer when (*R*,*R*,*R*,*R*,*R*)-catalyst was used. [g] *s*-factor = ln[1-*c*(1+ee_{pro})]/ln[1-*c*(1-ee_{pro})], where *c* is the conversion and ee_{pro} is the enantiomeric excess of the resulting diol expressed as %/100. [h] Determined by using gel permeation chromatography in THF, calibrated with polystyrene.^{i}[i] Specific rotation of the polymers was determined in chloroform at 20 ºC (*c* = 1) by using a polarimeter. The wavelength of the polarized light was 589.3 nm. [j] Toluene/CHDO/anhydride/catalyst/PPNCl = 1000/250/125/1/2 (molar ratio). [k] The reaction was mediated by complex (*R*,*R*,*R*,*R*,*R*)-**3b**.

enantioselective for this copolymerization. The reaction of aliphatic epoxides 2-6-O showed moderate k_{rel} value of 31, but a high *s*-factor value of 106 was obtained, with 97% *ee* for the affording polyester (Entry 6). Notably, both the high K_{rel} (52) and *s*-factor (470) values were obtained for the reaction of 2-8-O with PA, affording the polyester with up to 99% *ee* (Entry 7). Moreover, naphthyl anhydride (NA), and 4,5-dimethylphthalic anhydride (DMPA) were employed for the enantioselective resolution copolymerization using *racemic* CHDO as a model *racemic cis*-internal epoxide monomer at ambient temperature (Entries 8 and 9). As anticipated, the resultant copolymers exhibited perfectly alternating structure and enhanced enantioselectivities of 94% and 96% *ee*, respectively.

Conclusion

In summary, we report the first highly enantioselective resolution copolymerization of *racemic cis*-internal epoxides with anhydrides *via* multi-chiral synergistic catalysis using enantiopure dinuclear aluminum catalyst systems. The steric hindrance of the phenolate ortho-position substituents of the ligand and axial chirality significantly affected both the catalytic activity and enantioselectivity. For the alternating copolymerization of *racemic* 7-oxabicyclo[4,1,0]hept-2-ene (CHDO) and phthalic anhydride (PA), the binaphthol- linked bimetallic Al(III) complex (*R*,*R*,*R*,*R*,*R*)-**3d** without any substituent at the phenolate ortho-positions of the ligand exhibited unprecedented levels of enantioselectivity of up to 99% *ee* for the (*R*,*R*)-configuration copolymer formation with an *s*-factor of 437, affording the unreacted (2*R*,3*S*)-CHDO-enriched epoxides with good enantiopurity, and the highly stereoregular semi-crystalline polyesters with a perfectly alternating structure. Various *racemic* unsymmetric *cis*-disubstituted epoxides with anhydrides were tested, and all of these copolymerization systems showed an unanticipated enantioconvergent behavior, i.e., the *s*-factor significantly exceeded the k_{rel} at various conversions. The DFT theoretical calculations suggested that both the enantiomorphic-site of the ligand set and propagating chain-end control mechanisms influenced the enantioconvergent behavior in the enantioselective resolution copolymerization.

Although enantioconvergent catalysis is emerging as a powerful method for synthesizing single enantiomerically-enriched organic compounds from the *racemic* substrates with a maximum yield of 100%,[31-35] such a strategy has not been applied to the preparation of optically active polymers from a *racemic* starting material. The present study is the first report of the enantioselective, stereoconvergent copolymerization of *racemic cis*-internal epoxides with anhydrides to afford enantioenriched semi-crystalline polyesters with high enantioselectivities of up to 99% *ee* at more than 50% conversion. It is anticipated that the enantioconvergent catalytic polymerization can possibly allow the production of highly isotactic polymers through kinetic resolution polymerization even with an inferior kinetic resolution coefficient.

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Keywords: stereoconvergence • asymmetric ring-opening copolymerization• chain-end control • polyester • *cis*-internal epoxides

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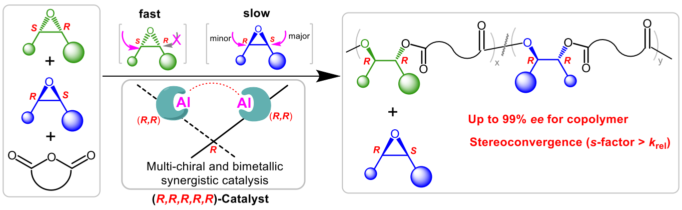

Stereoconvergence is observed in the enantioselective resolution copolymerization of *racemic cis*-internal epoxides and anhydrides mediated by dinuclear aluminum complexes with multiple chirality, where the selectivity factor for chiral copolymer formation significantly exceeds the kinetic resolution coefficient based on the unreacted substrate at various conversions.