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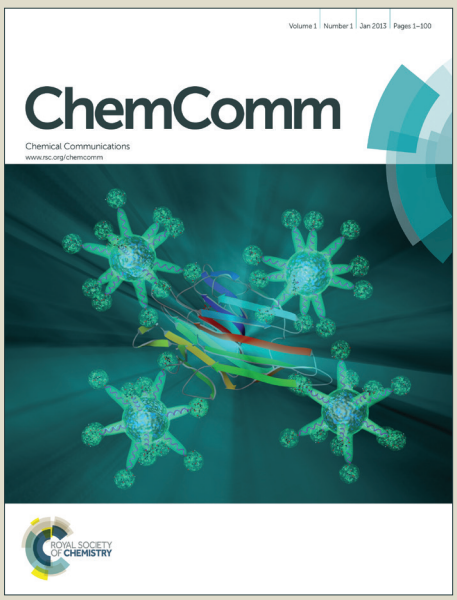

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Binaphthol-Derived Phosphoric Acid as an Efficient Chiral Organocatalyst for the Enantiomer-Selective Polymerization of *rac*-Lactide

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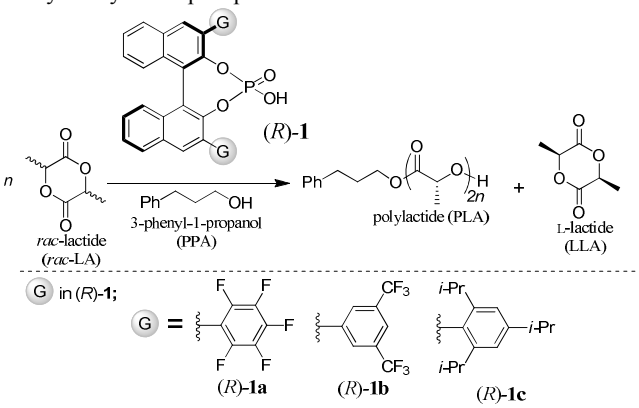
The high enantiomer-selectivity for the polymerization of *rac*-lactide was achieved using chiral binaphthol-derived monophosphoric acids as an organocatalyst. During the polymerization, D-lactide (DLA) preferentially polymerized via kinetic resolution with the maximum selectivity factor (k_D/k_L) of 28.3. The selective polymerization of DLA was derived from a dual activation, i.e., monomer activation and chain-end activation.

Chiral Brønsted acids have been widely utilized for a number of enantioselective organic transformations via activation of a variety of functional groups.[1] Among the reported chiral Brønsted acids, binaphthol (BINOL)-derived monophosphoric acids ((*R*)-**1** in Scheme 1),[1,2] which represent an important and widely applicable class of organocatalysts, have emerged as a powerful tool for enantioselective transformations, and significant progress has been made in their utilization as asymmetric-inducing agents via activation of various prochiral substrates.[3] The high enantioselectivities have been achieved due to the desirable features of the BINOL-derived phosphoric acids as a chiral Brønsted acid catalyst;[2a] the ring structure of the phosphate ester with substituents (G) at the 3,3'-position of the binaphthyl backbone as well as the acid and base dual function of the OH group and the phosphoryl oxygen, respectively, even for monofunctional phosphoric acid catalysts. An appropriate chiral environment for the enantioselective transformations can be created by these sterically, but also electronically adjustable substituents (G) coupled with the acid and base dual function.

Organocatalysts have also been used for many polymerization reactions. The organocatalytic ring-opening polymerization (ROP) of cyclic esters was one of the most researched subjects from the view point of producing metal-free biodegradable and biocompatible polymers.[4-7] Recently, the controlled/living polymerizations of cyclic monomers, such as ε-caprolactone, δ-valerolactone, lactide, and cyclic carbonates, were achieved using various organocatalysts leading to aliphatic polyesters and polycarbonates with controlled molecular weights and a narrow polydispersity; e.g., we reported that the ROPs of cyclic esters and cyclic carbonates using diphenyl phosphate proceeded in a controlled/living manner.[8,9] On the other hand, an organocatalytic enantiomer-selective polymerization has rarely been reported, in which one of the two enantiomers is preferentially polymerized through the kinetic resolution of a racemic monomer, whereas several achiral organocatalysts produced stereoregulated polylactide through chain-end control with no enantiomer-selectivity.[10,11] As the only example in the field of organocatalytic enantiomer-selective ROP, the cinchona alkaloid performed the enantiomer-selective polymerization of *rac*-lactide (*rac*-LA) with the maximum selectivity factor (k_L/k_D)[12] of 4.4 at a 48.4 % monomer conversion.[13] Thus challenging tasks still remain in the field of organocatalytic enantiomer-selective polymerization. To achieve the enantiomer-selective polymerization with a high selectivity, we focused on the kinetic resolution method using chiral BINOL-derived monophosphoric acids ((*R*)-**1**).

Scheme 1. Enantiomer-selective polymerization of *rac*-lactide catalyzed by chiral phosphoric acid



In order to obtain a high enantiomer-selectivity for the ROP of *rac*-LA using (*R*)-**1**, we first evaluated the substituent (G) effect of (*R*)-**1** (Scheme 1). The polymerization was conducted using 3-phenyl-1-propanol (PPA) as the initiator and (*R*)-**1a-c** as a catalyst with the initial monomer-to-initiator ratio of $[rac\text{-LA}]_0/[\text{PPA}]_0 = 50$ (runs 3, 8, and 10 in Table 1). All the polymerizations homogeneously proceeded at 75°C and the monomer conversions reached ca. 50 % within 18 h. After quenching the polymerization, the residual monomer was recovered as the hexane/isopropanol soluble part and the enantiomeric excess (*ee*) of the unreacted

Table 1. Enantiomer-selective Ring-opening Polymerization of *rac*-Lactide using (*R*)-**1** as Organocatalyst [a]

run	catalyst	$[rac\text{-LA}]_0/[PPA]_0$	temp (°C)	time (h)	conv. (%) [b]	$M_{n,calcd}$ (g mol^{-1}) [c]	$M_{n,NMR}$ (g mol^{-1}) [b]	M_w/M_n [d]	*ee* (%) [e]	k_D/k_L [f]
1 [g]	(*R*)-**1a**	50	60	24	51.4	3840	1780	1.16	24.4	1.99
2 [g]		50	70	24	52.1	3890	4130	1.11	35.6	2.73
3		50	75	18	49.0	3670	3730	1.13	80.6	28.3
4		50	80	15	49.2	3680	3810	1.08	74.8	17.3
5		50	90	12	54.4	4060	3950	1.11	74.9	9.60
6		100	75	90	50.0	7340	7290	1.09	73.1	13.9
7 [g]	(*R*)-**1b**	50	70	24	49.9	3730	3610	1.13	22.2	1.92
8		50	75	18	45.7	3430	3310	1.16	62.3	12.6
9 [g]	(*R*)-**1c**	50	70	24	50.4	3770	4170	1.11	5.22	1.16
10		50	75	18	56.1	4180	3660	1.06	0.09	1.00

[a] Solvent, toluene; initiator (I), 3-phenyl-1-propanol; (*R*)-**1a**, (*R*)-3,3'-bis(pentafluorophenyl)-1,1'-binaphtyl-2,2'-diyl-hydrogenphosphate; (*R*)-**1b**, (*R*)-3,3'-bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphtyl-2,2'-diyl-hydrogenphosphate; (*R*)-**1c**, (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphtyl-2,2'-diyl-hydrogenphosphate; $[rac\text{-LA}]_0/[PPA]_0/[cat.]_0$, 50/1/1; $[rac\text{-LA}]_0$, 3.0 mol L^{-1}. [b] Determined by ^{1}H NMR in $CDCl_3$. [c] Calculated from $([rac\text{-LA}]_0/[PPA]_0) \times$ conv. × (M.W. of *rac*-LA) + (M.W. of PPA). [d] Determined by SEC in $CHCl_3$ using PSt standards. [e] Enantiomeric excess of unreacted monomer measured by chiral HPLC. [f] Calculated from $\{\ln[(1\text{-conv.})(1\text{-}ee)]\}/\{\ln[(1\text{-conv.})(1+ee)]\}$. [g] Partially insoluble in toluene.

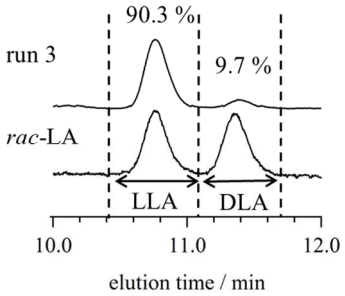
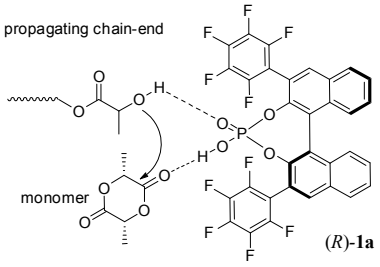


Fig. 1. HPLC chromatograms of unreacted monomer (run 3, upper) and *rac*-LA as a reference (lower) determined by UV (254 nm) detector (Column, Chiralpak IA; flow rate, 0.5 mL min^{-1}; eluent, hexane/isopropanol = 7/3; temperature; 25°C).

monomer was determined by a chiral HPLC measurement (Fig. 1). The chromatograms strongly suggested that D-lactide (DLA), one of the enantiomers, was preferentially polymerized by the effect of these catalysts, resulting in the calculated *ee* values of 80.6, 62.3, and 0.09 for the (*R*)-**1a**, **1b**, and **1c**-catalyzed system, respectively. These results indicated that the electronic nature of the substituent (G) strongly influenced the *ee* compared to the steric hindrance; the highest *ee* was achieved by (*R*)-**1a**. Thus we carried out the ROP of *rac*-LA using (*R*)-**1a** at various temperatures, as listed in Table 1. All the polymerizations were quenched at an ca. 50 % monomer conversion in order to determine the *ee* from the unreacted monomer. Based on the results of runs 1-5, the *ee* strongly depended on the reaction temperature, and the high *ee* of 80.6 was observed at 75°C, i.e., the enantiomer-selectivity decreased with the increasing reaction temperature between 75°C and 90°C, which was the same result as the metal-catalyzed enantiomer-selective polymerization.[14] For considering the increase in selectivity between 60°C and 75°C, the solubility of monomer and catalyst was critically influenced; actually, the polymerization heterogeneously proceeded at 60°C and 70°C leading to the less-controlled molecular weight accompanied by a low enantiomer-selectivity. Thus the suitable reaction temperature should be selected for a good solubility and enantiomer-selectivity. For the polymerization at 75°C, the k_D/k_L was calculated to be 28.3, which was higher than the value obtained from the enantiomer-selective polymerization of *rac*-LA using a metal catalyst;[14-16] for instance, the chiral Schiff-base complex of Al as the representative metal catalysts led to a k_D/k_L = 20 via a kinetic resolution mechanism.[14] Therefore, the (*R*)-**1a**-catalyzed enantiomer-selective ROP could compete with the metal complex-catalyzed ROP, i.e., the chiral phosphoric acid–catalyzed system opened the door for the novel enantiomer-selective ROP as well as enantioselective organic transformations.

For the phosphoric acid-catalyzed system, the polymerization should proceed through dual activation of the carbonyl group of the monomer and hydroxyl group of the propagating chain-end, as shown in Scheme 2.[17-19] In order to clarify the catalytic performance of (*R*)-**1a**, the ^{13}C NMR spectra of DLA were measured in the absence/presence of (*R*)-**1a** ([(*R*)-**1a**]/[DLA] = 1.0 and 3.0) (Fig. 2).[9,20] The chemical shift for the carbonyl carbon of DLA at 166.55 ppm shifted to a lower field at 166.58 and 166.61 ppm for [LA]/[(*R*)-**1a**] = 1.0 and 3.0, respectively, corresponding to the interaction between DLA and (*R*)-**1a**, whereas the same result was not obtained for LLA in the presence of (*R*)-**1a** (see ESI† Fig. S1). The carbonyl activation of DLA was also investigated by IR spectroscopy with the [LA]/[(*R*)-**1a**] ratio of 1/1; the carbonyl vibration was observed at a lower wavenumber after the catalyst addition. Thus the carbonyl activation of DLA was strongly suggested and the polymerization of DLA was preferentially induced by the enantiomer-selective monomer activation.

Scheme 2. The proposed polymerization mechanism of dual activation by (*R*)-**1a**



On the other hand, the activation of the propagating chain-end was observed by the ^{1}H NMR and IR analyses for methyl DL-lactate, which was used as a model of the polymer chain-end, with/without (*R*)-**1a** (see ESI† Fig. S2 and S3). For the ^{1}H NMR measurement, the hydroxyl proton signal was shifted to a lower field due to the activation in the presence of (*R*)-**1a**. The IR spectroscopy also supported the results because the hydroxyl group appeared at a lower wavenumber compared to that of the original methyl DL-lactate, which implied that the phosphoryl oxygen acted

as a proton acceptor and the hydroxyl proton of the propagating chain-end was activated through H-bonding. Therefore, the polymerization mechanism was assigned to the enantiomer-selective monomer activation accompanying the chain-end activation, which indicated that (*R*)-**1a** preferentially promoted the polymerization of DLA via dual activation due to the function of the Brønsted acidic site and Brønsted basic site of the catalyst.

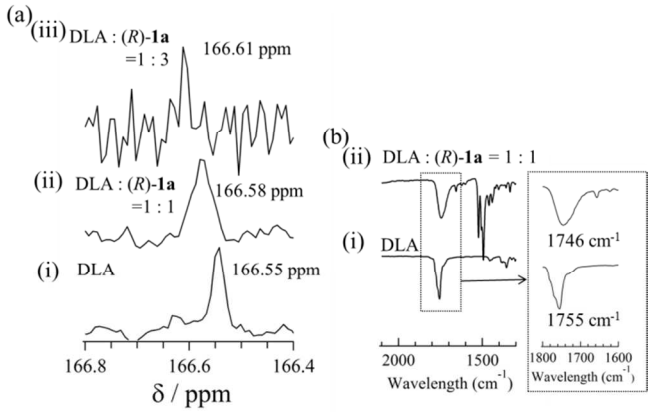


Fig. 2. (a) ^{13}C NMR spectra at 75°C in toluene-d_8 and (b) IR spectra of the carbonyl carbon signals of (i) DLA, (ii) a 1:1 mixture of DLA and (*R*)-**1a**, and (iii) 1:3 mixture of DLA and (*R*)-**1a**.

In conclusion, we achieved a high enantiomer-selectivity for the polymerization of *rac*-LA using chiral phosphoric acid, which is one of the well-known organocatalysts. Actually, the ROP of DLA preferentially proceeded using (*R*)-**1a** at 75°C, and the k_D/k_L was 28.3 at a 49.0 % monomer conversion. To the best of our knowledge, this is the highest value for the enantiomer-selective ROP of *rac*-LA. For the reaction mechanism, the polymerization should have proceeded by dual activation of the monomer and chain-end due to the function of the chiral phoshphoric acid catalyst, and the selective activation contributed to achieving the high k_D/k_L. This strategy for the organocatalytic enantiomer-selective ROP promises to be a new method for synthesizing various stereocontrolled polymers via the selective activation of a monomer and/or propagating chain-end.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization of the obtained polymer, and spectroscopic studies. See DOI: 10.1039/c000000x/

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