Stereoselective polymerization of *rac*- and *meso*-lactide catalyzed by sterically encumbered *N*-heterocyclic carbenes†

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New sterically encumbered *N*-heterocyclic carbene catalysts were synthesized and used to polymerize *rac*-lactide to give highly isotactic polylactide or *meso*-lactide to give heterotactic polylactide.

Polylactide (PLA) has emerged as a relatively new commodity polymer derived from renewable feedstocks for packaging, fiber and biomedical applications.[1] The mechanical properties of PLA are critically linked to its microstructure, and hence, the stereoselective polymerization of lactide (LA) has become a subject of considerable attention.[2] Metal alkoxides,[3] which control the stereochemistry of the resultant polymers by two distinct mechanisms: chain end control, in which the stereochemistry of the last inserted monomer defines the stereochemistry of the subsequent ring-opening step; and enantiomorphic site control polymerization, in which the chirality of the catalyst defines the stereochemistry of the monomer insertions.[4] Various achiral organometallic catalysts for stereoselective lactide polymerization have been reported, and chain end control was proposed for such selectivity,[5] whereas chiral metal complexes have achieved stereospecific polymerization by a proposed enantiomorphic site control.[6–9] Furthermore, polymer microstructure has been found to be highly dependent upon the ancillary ligand substituents[5] and solvent.[10] Recently, it was reported that a *N*-heterocyclic carbene (NHC) and the Zn complex of the same carbene give strikingly different stereoselectivity patterns.[11] Herein we report our investigations into organocatalytic stereoselective ring-opening polymerization (ROP) by employing new sterically encumbered NHCs that catalyze the formation of highly isotactic polylactide from *rac*-LA monomer at low temperature with high activity, and the formation of heterotactic PLA using *meso*-LA monomer under similar conditions.

The results of our and others' studies have shown 1,3-dimesitylimidazol-2-ylidene, **1** (Fig. 1), to produce mainly atactic PLA.[11,12] In order to gain a greater degree of control over the stereochemistry of the PLA produced in these organocatalytic polymerizations, we targeted the synthesis of more sterically hindered NHCs.

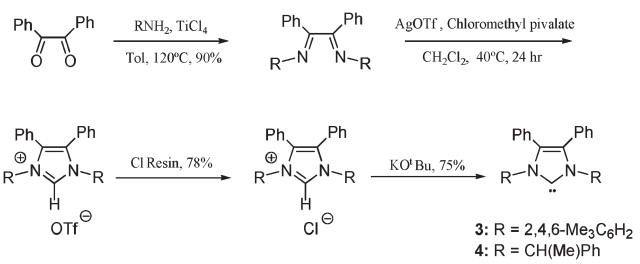
1 **2**

Fig. 1 NHCs **1** and **2**.

Our initial investigations focused on the synthesis and testing of carbene **2** (Fig. 1), a sterically hindered saturated chiral carbene previously reported by Grubbs.[13] Treatment of this species with one equivalent of initiating alcohol (either methanol or isopropanol) and *rac*-LA resulted in no observable polymerization activity even at elevated temperatures. Given the propensity of saturated NHCs to form alcohol adducts,[14] we postulated that the adduct formed with this carbene was unusually thermally stable and thus inhibited polymerization activity.

The formation of alcohol adducts is generally prohibited with the unsaturated NHC analogues however, access to sterically encumbered NHCs is synthetically challenging. The synthesis of NHCs **3** and **4** was achieved and is outlined in Scheme 1. The steric bulk from the phenyl rings in the carbene backbone resulted in the failure of traditional synthetic methods for cyclization.[15] A new methodology developed by Glorius *et al.*[16] that generates the alkylating reagent *in situ* was successfully adopted to cyclize these sterically demanding structures. After ion exchange and deprotonation, **3** was isolated in an overall yield of 52%. NHCs (*R*,*R*)-**4** and (*S*,*S*)-**4** were obtained in similarly high yields providing access to highly sterically hindered unsaturated chiral and achiral NHCs.[17]

The conditions and stereoselectivity for *rac*-LA polymerization were surveyed by varying catalyst. The use of **3** as catalyst provides polymers with low polydispersities and molecular weights that closely track the monomer-to-initiator ratio (Table 1). Catalyst activities are remarkably high, with turnover frequencies of



Scheme 1 Synthesis of **3** and **4**.

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Table 1 Polymerization of *rac*-, *meso*-lactide using NHCs at different temperatures[a]

Entry	Catalyst	Monomer	T (°C)	Time (min)	Conversion (%)[b]	DP[b]	M_w/M_n[c]	P_i[18]
1	**3**	*rac*-LA	25	1	95	97	1.24	0.59
2	**3**	*rac*-LA	−15	50	89	96	1.18	0.72
3	**3**	*rac*-LA	−40	90	88	95	1.21	0.80
4	**3**	*rac*-LA	−70	120	91	95	1.20	0.90
5	**1**	*rac*-LA	25	1	96	96	1.18	0.57
6	**1**	*rac*-LA	−70	120	92	94	1.19	0.83
7	(*R*,*R*)-**4**	*rac*-LA	25	1	95	94	1.28	0.59
8	(*R*,*R*)-**4**	*rac*-LA	−70	120	96	95	1.26	0.88
9	(*R*,*R*)-**4** + (*S*,*S*)-**4**	*rac*-LA	−70	120	96	95	1.48	0.88
10	**3**	*meso*-LA	25	2	95	97	1.22	0.62
11	**3**	*meso*-LA	−40	240	90	95	1.25	0.83
12	**1**	*meso*-LA	25	2	93	94	1.27	0.55
13	**1**	*meso*-LA	−40	240	91	93	1.24	0.67
14	(*R*,*R*)-**4**	*meso*-LA	−40	240	95	96	1.46	0.58

[a] Monomer : initiator: 100 : 1. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC (relative to polystyrene in THF).

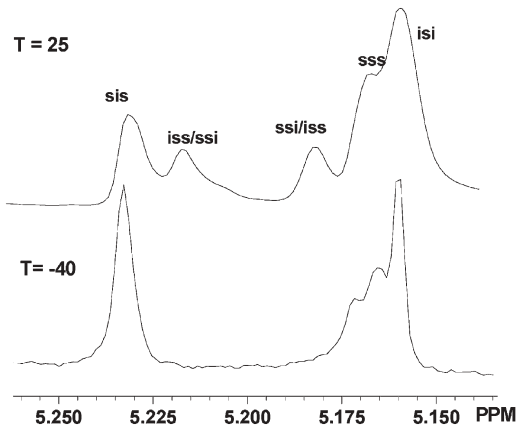


Fig. 3 Methine region of homonuclear decoupled ^{1}H-NMR spectra of poly(*meso*-LA) obtained at different polymerization temperatures using **3** as catalyst (Table 1, entries 10 and 11).[3a]

95 min^{-1} at room temperature (Table 1, entry 1). The high catalytic activity enables the polymerization at low temperatures to generate a highly isotactic polylactide. The P_i increases from 0.59 at room temperature to 0.90 at −70 °C, as shown in Fig. 1 (Table 1, entries 1–4 and Fig. 3).[18] Homonuclear decoupled ^{1}H-NMR spectroscopy (Fig. 2) reveals the isotactic *iii* tetrad, the defect *iis*, *sii*, *isi* tetrads in a 1 : 1 : 1.3 ratio, and a much smaller *sis* tetrad, consistent with isotactic PLA with blocks of (*R*,*R*)-LA and (*S*,*S*)-LA in the main chain.[3a] The polymer produced from entry 4 showed a melting point by differential scanning calorimetry of 153.3 °C (ΔH_{fus} = 12.8 J/g).[6] Under the same polymerization conditions, **3** is more stereoselective than **1**, particularly at lower temperatures (entry 4 *vs.* entry 6). The bulky phenyl groups at the back of **3** can presumably influence the steric hindrance around the catalytic site, and thus enhance the stereoselectivity.

Polymerization of *rac*-LA using the chiral NHCs also resulted in high levels of isotacticity. At 25 °C, these catalysts remain highly active for polymerization however, only a mild preference for stereospecific ROP is observed. Upon lowering the temperature of the polymerization to −70 °C, ROP catalyzed by (*R*,*R*)-**4** demonstrated a marked increase in isotacticity (−70 °C, P_i = 0.59 *vs.* 0.88, Table 1 entries 7 and 8 respectively). This could be a result of the chiral carbene enforcing an enantiomorphic site control or merely a reflection of the sterically hindered active site. In the case of enantiomorphic site control, an initial preference for ROP of one enantiomer of lactide, corresponding to the chirality of the catalyst, would be expected. However, as the chiral purity of the monomer pool is changed towards the enantiomer of lactide opposite to that of the catalyst, the polymer would be expected to slowly reach high conversions resulting in a tapered stereoblock copolymer comparable to that observed by Spassky for the chiral-(SalBINAP)AlOCH_3.[7]

Radano, Smith and Baker[8] have previously demonstrated that employment of an enantiomeric mixture of chiral-(SalBINAP)AlOCH_3 complexes resulted in the generation of stereoblock PLA with each enantiomer of catalyst preferentially polymerizing one enantiomer of lactide.[19] We used *rac*-**4** to initiate the polymerization of *rac*-LA but observed no significant enhancement of the P_i of the polymer obtained under these conditions over that obtained when the single enantiomer, (*R*,*R*)-**4** is employed. These data suggest that the dominating factor determining stereocontrol is the steric congestion of the active site, despite the chirality of the catalyst.

To further investigate the mechanism of stereo-control by carbene catalysts, the polymerization of *meso*-LA was investigated using NHCs **3** and (*R*,*R*)-**4**. Stereochemical control of *meso*-LA polymerization would be expected to yield markedly different results depending on the mechanism of stereocontrol. For example, syndiotactic PLA is most likely obtained by a site controlled mechanism,[16] whereas heterotactic PLA is expected when a chain end controlled mechanism is in operation.

The polymerization activities of *meso*-LA are lower than those of *rac*-LA and the *meso* isomer is also less soluble at low temperature than the *racemic* mixture. Compared with **1**, **3** exhibits a pronounced higher stereoselectivity for the polymerization of *meso*-LA, particularly at lower temperatures (−40 °C, P_i = 0.83 *vs.* 0.67, Table 1 entries 11 and 13 respectively).[19] Notably, polymerization of *meso*-LA catalysed by the chiral NHC, (*R*,*R*)-**4**, also produces heterotactic polymer (−40 °C, P_i = 0.58, Table 1 entry 14).

We have previously proposed a monomer-activated mechanism for the NHC-catalyzed polymerization of lactide.[12] The observation of highly isotactic polymer from *rac*-LA and heterotactic polymer with *meso*-LA are consistent with a chain end control mechanism for both achiral and chiral NHCs suggesting that even

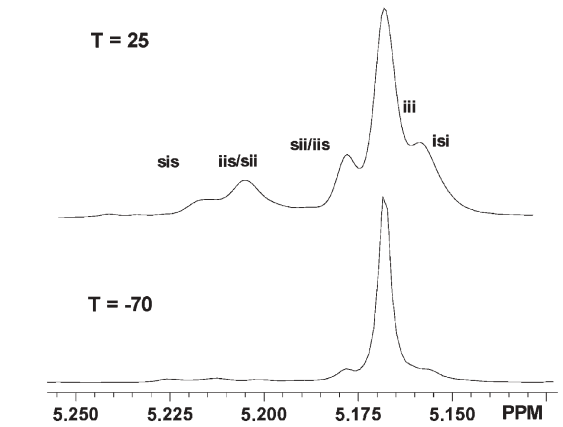
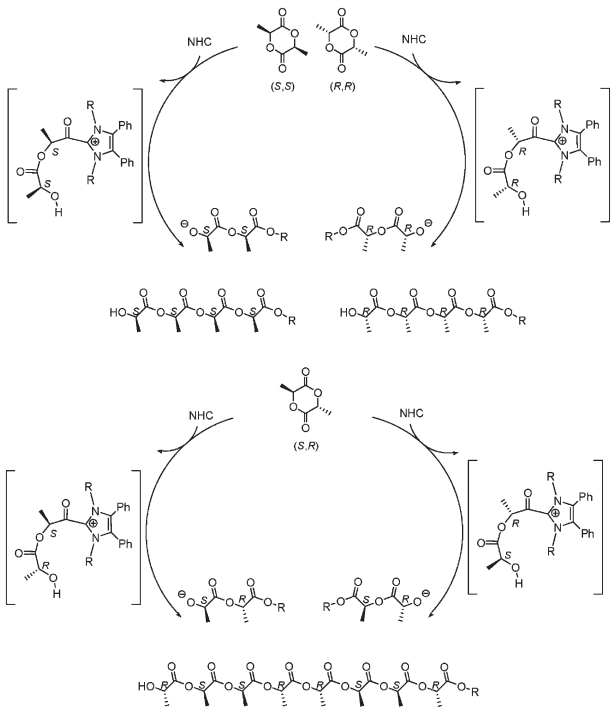


Fig. 2 Methine region of homonuclear decoupled ^{1}H-NMR spectra of poly(*rac*-LA) obtained at different polymerization temperatures using **3** as catalyst (Table 1, entries 1 and 4).[3a]

with the presence of chiral groups close to the active site, a chain end control mechanism predominates. For *rac*-LA, both D- and L-LA should be equally activated with stereoselective attack by the terminal alkoxide of the last inserted monomer in the polymer chain leading to isotactic enchainment (Scheme 2). The formation of heterotactic-enriched PLA from *meso*-LA is also consistent with a chain end control mechanism. In this case, the oxygen adjacent to the last stereogenic center of the polymer chain end (either *R* or *S*) preferentially attacks the activated monomer with the same stereogenic configuration adjacent to it. Repeating these steps, a heterotactic-enriched polymer chain can be achieved.



Scheme 2 Proposed chain end control mechanisms for (top) *rac*-lactide and (bottom) *meso*-lactide polymerizations.

In summary, new sterically encumbered, unsaturated chiral and achiral *N*-heterocyclic carbene catalysts polymerize *rac*-LA to form highly isotactic PLA at low temperature, while *meso*-LA yields heterotactic PLA. A proposed mechanism involving chain end control explains these examples of stereoselective polymerization.

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