Exploration, Optimization, and Application of Supramolecular Thiourea−Amine Catalysts for the Synthesis of Lactide (Co)polymers

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ABSTRACT: The structural flexibility and efficacy of thiourea−amine catalysts for the supramolecular activation and ring-opening polymerization (ROP) of lactide are described. The nature of the hydrogen bonding group and its strength as well as the steric congestion have been altered, leading to shorter polymerization times, better control, and pathways to influence the stereochemistry of the resulting polymer. The tolerance to functionality and the mild conditions of the ROP mechanism allow for block copolymer synthesis by combination of nitroxide-mediated polymerization as well as reversible addition fragmentation and chain transfer polymerization using dual-headed initiators. Tandem hydrogen bond activation to organocatalyze ROP of lactide is an effective, versatile means to generate polymers with predictable molecular weights, narrow polydispersities, control of microstructure and a variety of complex architectures and block copolymers.

Introduction

Control over the macromolecular architecture of a polymer is a necessity for the design of advanced materials in nanotechnology applications, including microelectronics and drug delivery.[1,2] Aliphatic polyesters are excellent candidates to function in such applications due to their facile degradability and good materials properties.[3] Ring-opening polymerization (ROP) of cyclic esters such as lactide is a common method to provide polyesters with controlled properties, and an excellent review on the different ROP pathways for lactide based on organometallic catalytic polymerization reactions has recently appeared.[4] In addition to polymerization techniques that give predictable molecular weights, low polydispersity indices and high end group fidelity, many advanced applications require removal of undesired contaminants such as heavy metal ions from catalysts. Toward this goal, we have initiated a research program on organocatalytic synthetic approaches to ROP of cyclic esters that are metal-free. Among the successful organocatalysts for ROP that we have surveyed are 4-(dimethylamino)pyridine (DMAP),[5] phosphines,[6] N-heterocyclic carbenes,[7] and guanidines.[8]

Recently we reported the first use of a thiourea-containing bifunctional organocatalyst, **1a**, for ROP of lactide (Scheme 1).[9] Urea and thiourea scaffolds have previously been shown to be effective for a variety of enantioselective reactions,[10] including Strecker,[11] Mannich,[12] Pictet−Spengler,[13] hydrophosphorylation[14] and cyanosilylation reactions,[15] by activating one of the substrates through hydrogen bonding. Bifunctional (thio)urea−amine catalysts have been employed to noncovalently activate multiple reactants, such that the (thio)urea moiety activates the electrophile and the amine activates the nucleophile. The close vicinity of both activating groups in the same molecule has resulted in enantioselective aza-Henry and Michael-reactions using nitro-containing compounds[16] and a dynamic kinetic resolution of azlactones.[17] We proposed a similar mechanism for thiourea−amine catalyzed ROP of lactide (Scheme 1): the carbonyl group of the lactide monomer is activated by the thiourea to become more electrophilic, and either the initiating or propagating alcohol is activated by the tertiary amine to become more nucleophilic. The polymerization itself is enthalpically driven by the release of ring strain of the monomer. Remarkably, little transesterification of the resulting poly(lactide) is observed, even after complete monomer consumption and prolonged reactions times, allowing unprecedented control over the polymerization of lactide as shown by the high molecular weights and the extremely low polydispersities of the polymers obtained.[9] A perceivable drawback of the thiourea−amine catalyst is the long reaction time (48−72 h under typical conditions).

Scheme 1. Structure of 1a and Its Proposed Activation Pathways in ROP of Lactide

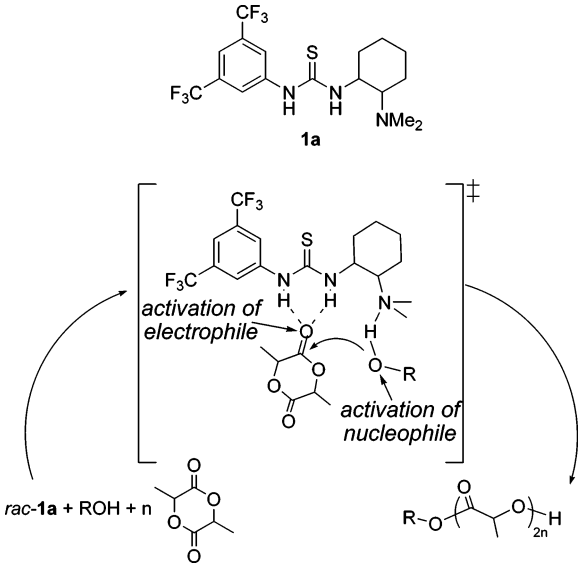

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Table 1. L-Lactide Polymerization Using Bifunctional Thiourea−Tertiary Amine Catalysts[a]

catalyst	loading (mol %)	solvent	$[LA]_0$ (mol L^{-1})	$[LA]_0/[I]_0$[b]	time (h)	convn (%)	M_n (g mol^{-1})	PDI
rac-**1a**	5	CH_2Cl_2	1.0	20	24	97	5200	1.08
rac-**1a**	5	CH_2Cl_2	1.0	50	32	98	12 300	1.05
rac-**1a**	5	CH_2Cl_2	1.0	100	72	94	21 100	1.09
rac-**1a**	5	CH_2Cl_2	1.0	200	105	97	42 000	1.05
rac-**1a**	10	$CDCl_3$	0.7	100	24	51	*c*	*c*
1b	10	$CDCl_3$	0.7	100	24	7	*c*	*c*
1c	10	$CDCl_3$	0.7	100	24	0	*c*	*c*

[a] Reaction conditions: $T = 25$ °C. [b] 4-Pyrene-1-butanol initiator (I). [c] Not measured.

Our optimization of thiourea−amine catalyzed ROP focused on the catalyst structure. The thiourea scaffold is very versatile, and the previously mentioned studies on (thio)urea organocatalysis included a number of structural variants. Owing to the availability of a wide variety of commercially available iso(thio)cyanates and amines, testing of different thiourea−amine linkages, different electron-donating or withdrawing groups, and groups contributing more or less steric bulk was readily possible, with goals of shortening polymerization times and/or reducing catalyst loads while maintaining excellent control of polymer molecular weights and dispersities. Similar systematic studies have been conducted by Takemoto et al. on catalyst variations for enantioselective Michael additions.[16c,d]

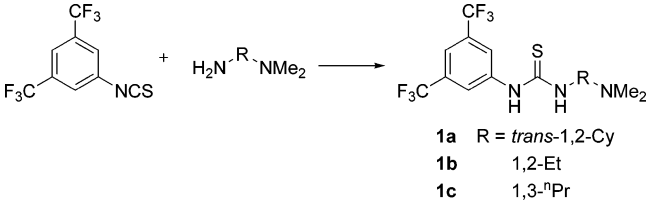
In this paper we report the results of exploring structural variations of thiourea−amine organocatalysts and their effect on ROP efficiencies. Several approaches were taken, including varying the alkyl linkage in tethered bifunctional thiourea−amines, and separating the thiourea and amine functionalities into two separate compounds, allowing the components to be varied more easily and over a greater range of structures. Because chiral amines can be used, we have also made initial investigations into possible stereocontrol of *rac*-lactide polymerization. Further, to demonstrate the versatility of thiourea−amine catalysts for ROP of lactide, we report the synthesis of lactide polymers using nonalcoholic initiators, and the syntheses of lactide block copolymers using macroinitiators resulting from nitroxide mediated polymerizations (NMP)[18] and reversible addition fragmentation and chain transfer (RAFT) polymerizations.[19]

Results and Discussion

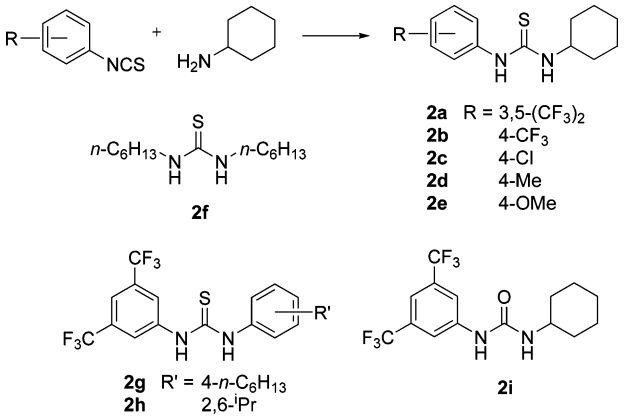
In our earlier communication,[9] the **1a**-catalyzed ROP of lactide (LA) was studied at 25 °C in CH_2Cl_2 solution ($[LA]_0 = 1.0$ M) using a primary alcohol initiator (I). Narrow polydispersity polymers were obtained (polydispersity index (PDI) = weight-average molecular weight (M_w)/number-average molecular weight (M_n) ≤ 1.07) and the degree of polymerization (DP) was controlled by adjusting the $[LA]_0$:$[I]_0$ ratio as determined by gel permeation chromatography (GPC; see Table 1). Characteristics of a living polymerization were further evidenced by the linear correlation between M_n and conversion.[20] No adverse transesterification of the polymer backbone was found even after extended times after complete monomer conversion. Chain extension experiments after complete monomer conversion showed that the catalyst remains active for ring opening of lactide. In polar solvents (acetone, tetrahydrofuran (THF), dimethylformamide) the polymerization is retarded or does not even take place, a result of competitive hydrogen bonding of the substrates.

Thiourea—Amine Tethers. Though the procedures are straightforward, the most time-consuming stage in the synthesis of catalyst **1a** is the synthesis of *N*,*N*-dimethyl-1,2-*trans*-diaminocyclohexane, which is not commercially available in either racemic or chiral form.[21] While the use of the cyclohexyl bridge between the thiourea and tertiary amine moieties introduce the possibility of chiral site-controlled selectivity in polymerization of *rac*-lactide (vide infra), this complexity is unnecessary for polymerization of enantiopure L-lactide. Ethylene and propylene linkages are more easily introduced into candidates **1b** and **1c**, respectively, using commercially available diamines (Scheme 2), and the products could be purified by simple recrystallization. However, evaluation of **1b** and **1c** as ROP catalysts showed that their activities were strongly attenuated: under the same reaction conditions, **1b** achieved only 7% conversion and **1c** showed no activity, comparing poorly to 51% conversion catalyzed by **1a** (Table 1). In the literature, lower reaction rates in Michael addition reactions were also observed when **1b** or **1c** was substituted as catalyst for **1a**.[16d] The additional flexibility afforded by the linear alkyl bridges in **1b** and **1c** may allow stronger interaction between the Lewis acidic and basic functional groups, neutralizing their efficacy in activating the monomer and propagating alcohol, whereas the rigidity of the cyclohexyl bridge prevents close interaction of the thiourea and amine in simple ball-and-stick molecular models.

Scheme 2. Syntheses of Tethered Thiourea−Amines



Scheme 3. Syntheses and Structures of Thiourea and Urea Cocatalysts



Variation of Thiourea. To demonstrate that both the thiourea and tertiary amine in **1a** are necessary for ROP catalysis, compounds **2a** (Scheme 3) and *N*,*N*-dimethylcyclohexylamine, $NCyMe_2$, containing only the thiourea or tertiary amine, respectively, were tested for catalytic activity. As expected, neither **2a** nor $NCyMe_2$ alone can catalyze ROP of lactide, but

Table 2. Effect of Thiourea Variation on LLA Polymerization in Presence of $NCyMe_2$[a]

thiourea[b]	time (h)	convn (%)	M_n	PDI
2a	72	98	17 800	1.09
2b	72	44	9400	1.04
2c	72	26	5600	1.04
2d	72	17	3800	1.04
2e	72	16	3600	1.04
2f	72	0		
2g	72	98	18 300	1.06
2h	72	51	10 100	1.04
2i	72	42	8400	1.05

[a] Reaction conditions: 0.7 M LLA in $CDCl_3$, 1% 4-pyrene-1-butanol, 10% $NCyMe_2$, 10% thiourea, and $T = 25$ °C. [b] See Scheme 3 for structures.

when both **2a** and $NCyMe_2$ are present, polymerization of lactide does take place with rates and control similar to what is observed for **1a**. Clearly, the inclusion of both thiourea and amine into a single molecule is unnecessary for this catalytic system. Furthermore, without the constraint of incorporating the thiourea and amine into a single molecule, variation of this catalytic system to explore the scope and effect of catalyst structures became facile (Scheme 3). For instance, combination of commercially available isothiocyanates with cyclohexylamine quickly provided crystalline thioureas **2a**−**e** bearing a range of electron-withdrawing and donating substituents on the phenyl ring. The catalytic activities for ROP of L-lactide (LLA) were screened using equimolar $NCyMe_2$ as base, with results listed in Table 2. Thiourea **2a** bearing the most electron-withdrawing substituents had the highest activity of those surveyed and the activities of the catalysts declined as the substituents became more electron-donating, matching results found in other thiourea-catalyzed organic transformations. Electron-withdrawing groups presumably increase the acidity of the thiourea, enhancing its ability to hydrogen bond and electrophilically activate the lactide.

Other changes to the thiourea structure were also investigated. Commercial di-*n*-hexylthiourea (**2f**) proved ineffective, presumably because the alkyl groups do not acidify the thiourea protons sufficiently to achieve good hydrogen bonding to lactide. Replacement of the cyclohexyl group with aryl rings bearing solubilizing alkyl substituents gave active cocatalysts (**2g**, **2h**). While it was hoped that a mild electron-withdrawing effect of the additional phenyl group would enhance activity, the activity of **2g** was only equal to that of **2a**. Cocatalyst **2h** gives quite slow reaction rates, owing to steric hindrance of the thiourea site by the bulky 2,6-diisopropyl substituents. The urea analogue of **2a**, **2i**, was synthesized and tested for activity under similar conditions, and could catalyze ROP of lactide. However, its relative effectiveness was difficult to gauge due to its noticeably lower solubility, as **2i** did not completely dissolve under the reaction conditions used due to strong self-complementary hydrogen bonding. In general, the preferential reactivity of isothiocyanate precursors with amines relative to water or alcohols and the higher observed solubility of thioureas vs ureas favor the thiourea cocatalysts.

Variation of Tertiary Amine. Commercially available amines were screened for efficacy of ROP of lactide using **2a** as the thiourea cocatalyst, with results for the various amines given in Table 3. Pyridine, *N*,*N*-dimethylaniline, and Proton Sponge were ineffective cocatalytic bases for catalyzing ROP of lactide, presumably because they are insufficiently basic to activate the alcohol moiety. DMAP, which is already known to catalyze ROP,[5] is a poor catalyst in the absence of a thiourea component under the conditions used, but in combination with **2a** could reach complete conversion of lactide in shorter times

Table 3. Effect of Amine on LLA Polymerization in the Presence of 2a[a]

amine[b]	time (h)	convn (%)	M_n (g mol^{-1})	PDI
pyridine	72	0		
N,*N*-dimethylaniline	72	0		
Proton Sponge	72	0		
TMEDA	72	38	7100	1.04
DABCO	72	88	16 900	1.06
triethylamine	72	91	18 000	1.06
$NCyMe_2$	72	97	18 200	1.08
DMAP	48	94	22 900	1.06
rac-TMCHD	24	91	20 700	1.05
rac-TMCHD	72	99	21 700	1.07
(−)-sparteine[c]	24	99	25 600	1.06
(−)-sparteine[c]	72	99	25 400	1.13

[a] Reaction conditions: 0.7 M LLA in $CDCl_3$, 1 mol % 4-pyrene-1-butanol, 10 mol % **2a**, 10 mol % amine, $T = 25$ °C. [b] See text for full names. [c] 5 mol % loading.

Table 4. Stereoerrors and Thermal Analysis of Poly(LLA)s[a]

catalyst	% nonisotactic	T_g (°C)[c]	T_m (°C)[c]
1a	<1	54	160
2a + $NCyMe_2$	35	56	not observed
2a + *rac*-TMCHD	11	52	147
2a + DMAP	4	55	155
2a + (−)-sparteine[b]	4	58	157

[a] Reaction conditions: $[LLA]_0 = 0.7$ M in $CDCl_3$, 1 mol % 4-pyrene-1-butanol, 10 mol % thiourea, 10 mol % amine, $T = 25$ °C, and $t = 24$ h. [b] 5 mol % amine. [c] DSC analyses up to 250 °C.

than **1a**. The simple trialkylamines $NCyMe_2$ and triethylamine (NEt_3) were competent for catalysis and had similar efficacies to each other and to **1a**. The diamines 1,4-diazabicyclo[2.2.2]-octane (DABCO) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) did not perform significantly better than the simple amines, despite the enforced pyramidalization in DABCO or potential chelation by TMEDA. However, when chelation by the diamine is enforced as in *N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-diaminocyclohexane (TMCHD), a significant improvement in the rate of reaction is observed. Ultimately, the most effective amine tested was the natural product (−)-sparteine, also a chelating diamine, which achieved full conversion of LLA in 24 h with only 5% loading (vs 10% for other amines). Further study showed that 95% conversion was achieved using (−)-sparteine in only 2 h, a 25-fold improvement in reaction rate when compared to the parent systems **1a** or **2a** + $NCyMe_2$.

An additional concern when using increasingly strong bases to catalyze ROP of lactide is that they could cause epimerization, leading to stereoerrors in polymers even when starting with enantiomerically pure L-lactide. The methine region of the homonuclear decoupled ^{1}H NMR spectra of poly(LLA) obtained using **2a** with different amines indeed shows variable amounts of stereoerrors (polymers prepared using **1a** show no epimerization). Stereoerrors in poly(LLA) formed using **2a** and selected amines were quantified as percentages of the methine signals corresponding to irregular stereosequences (Table 4). The amine giving the slowest polymerization rates in this part of the study, $NCyMe_2$, also led to the greatest proportion of epimerization. Higher stereospecificity is observed when using TMCHD, DMAP, or (−)-sparteine cocatalysts. Thermal analysis of poly(LLA) samples obtained with the various **2a**/amine combinations (DP = 100) shows that the $NCyMe_2$-derived poly(LLA) no longer has a well-defined melting point due to the presence of large numbers of stereoerrors (Table 4).[22] The melting point of the TMCHD-derived poly(LLA) containing fewer stereoerrors is slightly depressed relative to those obtained using either DMAP or sparteine, or the original bifunctional catalyst **1a**. ^{1}H NMR spectra of these polymerizations taken in situ prior to

Table 5. Polymerization of L-Lactide Using 2a and (−)-Sparteine[a]

2a (%)[b]	(−)-sparteine (%)[b]	$[LA]_0$ (mol/L)	$[LA]_0/[I]_0$	time (h)	convn (%)	M_n (g/mol)	PDI
10	5	0.7	50	2	99	12 600	1.05
10	5	0.7	100	2	99	25 500	1.06
10	5	0.7	200	6	99	54 700	1.09
10	5	0.7	500	8	97	70 000	1.14
5	2.5	0.7	100	24	99	28 600	1.07
2.5	1.25	0.7	100	24	82	21 900	1.05
5	2.5	1.4	100	2	99	26 900	1.07
2.5	1.25	2.8	100	2	99	22 300	1.05

[a] Reaction conditions: $CDCl_3$, 4-pyrene-1-butanol initiator, $T = 25$ °C. [b] Relative to monomer.

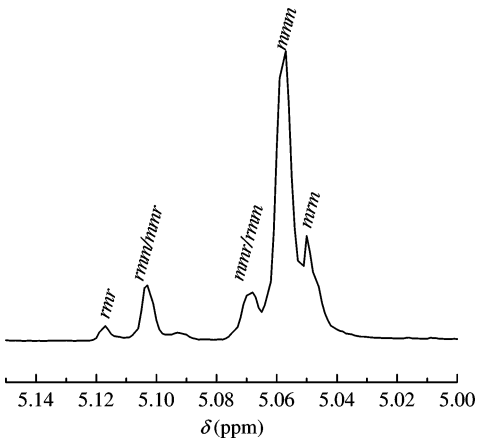


Figure 1. Methine region of the homonuclear decoupled ^1H NMR spectrum of poly(LA) prepared from *rac*-lactide using **2a** and (−)-sparteine as cocatalysts. Tetrad assignments follow ref 23.

complete monomer consumption show a small doublet upfield of the L-lactide methyl resonance attributable to *meso*-lactide, suggesting that the stereoerrors result from epimerization of the monomer prior to incorporation. The results with DMAP and sparteine show that stereocontrol can be retained while retaining polymerization efficiency by judicious choice of the amine component.

The enhanced rate observed in the presence of (−)-sparteine as cocatalyst allows for reasonable reaction times when the loading and mass of catalyst are decreased significantly. When thiourea **2a** and (−)-sparteine concentrations were decreased by half, full conversion could still be achieved in 24 h; when the concentrations were quartered, 82% conversion was achieved in 24 h. Use of less solvent to concentrate all the reagents restored the short reaction times (<2 h) for full monomer conversion even with the lower catalyst loadings (Table 5).

Polymerization of *rac*-Lactide. The stereoselective polymerization of *rac*- and *meso*-lactide is an appealing strategy for generating stereoregular polylactides with novel stereosequence distributions. In this regard, the thiourea−tertiary amine catalyst systems offer several ways of introducing chirality and/or steric bulk to induce either site control or chain end control of the polymerization. Several of the more effective catalyst systems were applied to polymerization of *rac*-lactide. The resulting polymers were analyzed by homonuclear decoupled ^1H NMR spectroscopy (Figure 1 and Table 6).

In all cases, the intensity of the *mmm* tetrad was noticeably increased, indicating isotactic enhancement of the poly(LA) stereochemistry. Concurrently, the ratio of the *rmr* to the *mmr*/*rmm* tetrad intensities is low, which is indicative of chain-end control of the stereochemistry. Isotactic enrichment and chain-end control appear to be common to ROP organocatalysts in contrast to their organometallic counterparts.[23]

Table 6. Polymerization of *rac*-Lactide Using Thiourea−Tertiary Amine Catalysts[a]

catalyst	time (h)	convn (%)	M_n (g mol^{-1})	PDI	P_m	T_m (°C)[c]
rac-**1a**	72	94	21 100	1.09	0.67	*d*
(*R*,*R*)-**1a**	72	90	16 700	1.07	0.76	*d*
2a + $NCyMe_2$	72	95	17 100	1.07	0.64	*d*
2a + DMAP	48	90	20 700	1.06	0.68	none
2a + *rac*-TMCHD	48	99	21 900	1.07	0.72	*d*
2a + (*R*,*R*)-TMCHD	48	99	21 300	1.06	0.73	*d*
2a + (−)-sparteine[b]	2	99	20 700	1.05	0.77	none

[a] Reaction conditions: 0.7 M *rac*-LA in $CDCl_3$, 1 mol % 4-pyrene-1-butanol, 10 mol % thiourea, and 10 mol % amine. [b] 5 mol % amine. [c] DSC analyses up to 250 °C. [d] Not measured.

The ability of a catalyst to enhance isotactic stereocontrol of lactide ROP can be summarized by the ratio P_m, determined from the homonuclear decoupled ^1H NMR spectrum, which quantifies the probability that a catalyst will propagate with retention of stereochemistry (i.e. L-chain end reacting with L-monomer); $P_m = 0.5$ indicates a random insertion pattern, while $P_m = 1.0$ indicates perfect retention.[24] Clearly, all of the thiourea−amine catalysts show modest stereoselectivities at room temperature as their P_m values range from 0.64 to 0.77 (Table 6). For certain systems, epimerization of the monomer to form *meso*-lactide (as seen for L-lactide polymerization, vide supra) is likely to erode stereocontrol. Use of the enantiomerically pure organocatalysts listed in Table 6 does not significantly change the poly(LA) stereochemistry when compared to the racemates, indicating that chain-end stereocontrol dominates any enantiomorphic site stereocontrol. Additionally, if reactions with chiral organocatalysts were quenched at 90% conversion, the remaining unreacted lactide did not show measurable enrichment of either the D- or L-enantiomers. Finally, the catalytic system using (−)-sparteine gives the highest P_m value (0.77), but thermal analysis did not show the presence of a melting point for the resulting polymer which would indicate a high level of stereoregularity; i.e., despite some stereocontrol, the bulk properties resemble those of atactic polylactide.

Initiating Functionalities. Thioureas and tertiary amines are tolerant of many functional groups, allowing **1a** to remain active under many different conditions. Several protic functional groups were found to serve as initiators for lactide polymerization, including alcohols, thiols, and silanols, with good control over molecular weight retained in all cases (Table 7). It is also possible to initiate from a primary amine using **1a** to give amide-terminated polylactide, a result which did affect our choices of amines to screen as cocatalysts. The compatibility of **1a** with a wide range of functional groups and initiators could provide interesting alternatives for developing polymer architectures.

Block Copolymers. In parallel to catalyst studies and optimization, we started the synthesis of block copolymers through the use of dual-headed bifunctional initiators that are capable of initiating ROP of lactide and controlled radical polymerization techniques such as nitroxide mediated polymerization (NMP) (Scheme 4) and reversible addition fragmentation and chain transfer polymerization (RAFT) (Scheme 5). Having a sacrificial polyester block in a well-defined block copolymer has already been shown to be a major advantage in the preparation of nanoporous monoliths, exemplified by Hillmyer.[25]

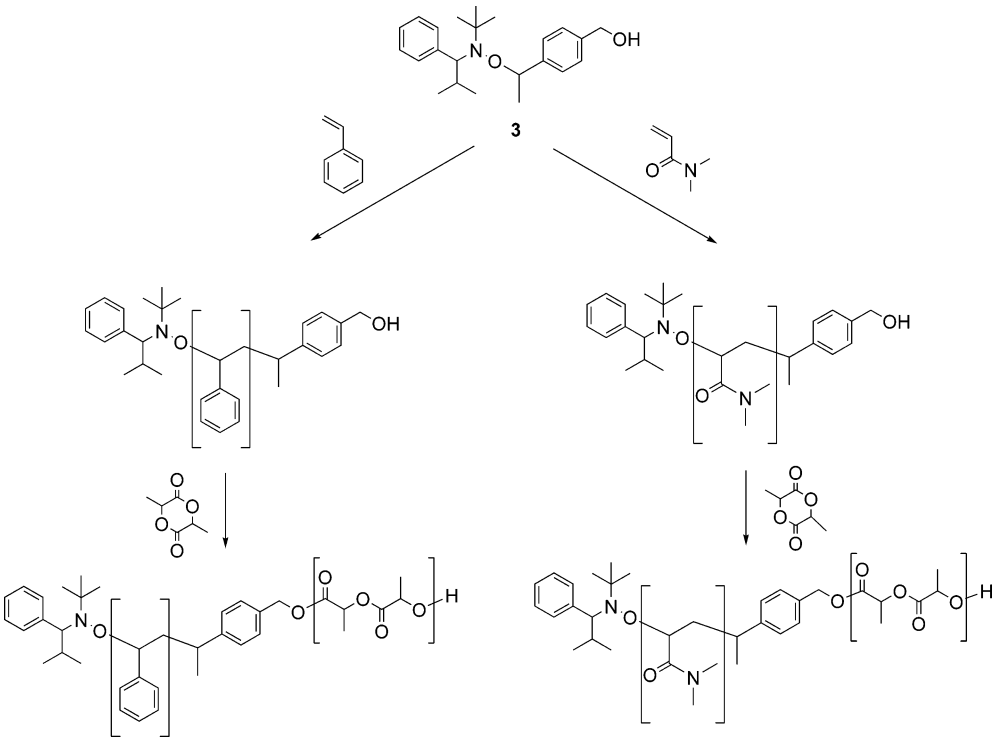
Again, control over both ring-opening and radical polymerization methods is a must for well-defined phase behavior. The NMP initiator **3**[26] and the RAFT agent **4**[27] were prepared according to literature procedures, both of which have been shown to be excellent agents for the preparation of hydroxyl-

Table 7. Initiating Functionalities for ROP of *rac*-LA Using 1a[a]

initiator	**1a** (mol %)	$[rac\text{-LA}]_0$ (mol L^{-1})	$[LA]_0/[I]_0$	time (h)	convn (%)	M_n (g mol^{-1})	PDI
4-pyrene-1-butanol	10	0.7	100	72	99	24 200	1.05
1-pyrenemethylamine	5	1.4	70	55	99	18 000	1.06
octadecylmercaptan	10	1.7	50	20	80	7800	1.06
triethylhydroxysilane	4	0.7	70	72	99	14 200	1.12

[a] Reaction conditions: $CDCl_3$, $T = 25$ °C.

Scheme 4. Synthesis of Block Copolymers from Dual-Function Initiators by Tandem NMP−ROP



end functionalized polymers.[27,28] A series of hydroxyl-functionalized polymer macroinitiators representing styrene, methacrylate, acrylate, and acrylamide monomer classes was prepared and is described in Table 8. With these macroinitiators in hand, a variety of diblock, triblock, and graft copolymers was prepared from *rac*-lactide using **1a** as catalyst in solution at room temperature. Excellent control over both the radical and ring-opening polymerizations is demonstrated by the close matching of the targeted DP with the observed DP and the low polydispersities of both macroinitiators and block copolymers. It is worth noting that the polydispersities generally decrease upon chain extension with lactide showing that the ROP is very well controlled. Once the thiourea−amine ROP catalyst had been optimized, polymerization times could be reduced from 72 to 4 h by using **2a** and (−)-sparteine cocatalysts, without compromising targeted molecular weight and polydispersity. Remarkably, detrimental transesterification was never observed, in particular when using the poly(meth)acrylates as macroinitiators. The high functional group tolerance and selectivity of the thiourea catalysts for ROP is manifested in the retention of the NMP- and RAFT-agent end groups in the block copolymers as judged both from the ^1H NMR spectra and the pink color of block copolymers prepared by the RAFT-technique. Figure 2 shows GPC traces of a hydroxy-terminated PMMA macroinitiator synthesized from a RAFT initiator and its chain-extended PMMA-*block*-PLA obtained using a UV−vis absorbance detector at 350 nm, where only the dithioester moiety shows absorption. The retention of the absorption of the sensitive dithioester functional group shows that it is not affected by the thiourea catalysts and is available for further elaboration of the block copolymer. These data highlight the selectivity of these catalysts and the mild conditions under which thiourea−amine catalyzed ROP of lactide proceeds.

Conclusions

To add to their proven efficacy in catalyzed a variety of enantioselective organic transformations, in this paper we have shown that thiourea−amine catalysts are also extraordinarily selective catalysts for the controlled ROP of lactide to generate well-defined homopolymers and block copolymers of defined molecular weights and narrow molecular weight distributions. Mechanistic studies show that both the hydrogen-bond donating thiourea and hydrogen-bond accepting amine are necessary for high activity in lactide ROP, but that the thiourea and amine need not be incorporated into a single-molecule catalyst. An electron withdrawing group next to the thiourea moiety is necessary for increasing the hydrogen bonding ability to the substrate. (−)-Sparteine was found to be the most effective base for activation of the alcohol of both initiating and propagating species with dramatic shortening of reaction times (25-fold), while excellent control of molecular weight, polydispersity and stereochemistry of the resulting polylactide was retained. (−)-Sparteine also provided the best stereocontrol of *rac*-lactide polymerization so far observed with the thiourea−tertiary amine catalysts via a chain end control mechanism. This catalytic system was shown to be an extremely versatile tool in the preparation of block copolymers by using dual-headed initiators

Scheme 5. Synthesis of Block Copolymers from Dual-Function Initiators by Tandem RAFT−ROP

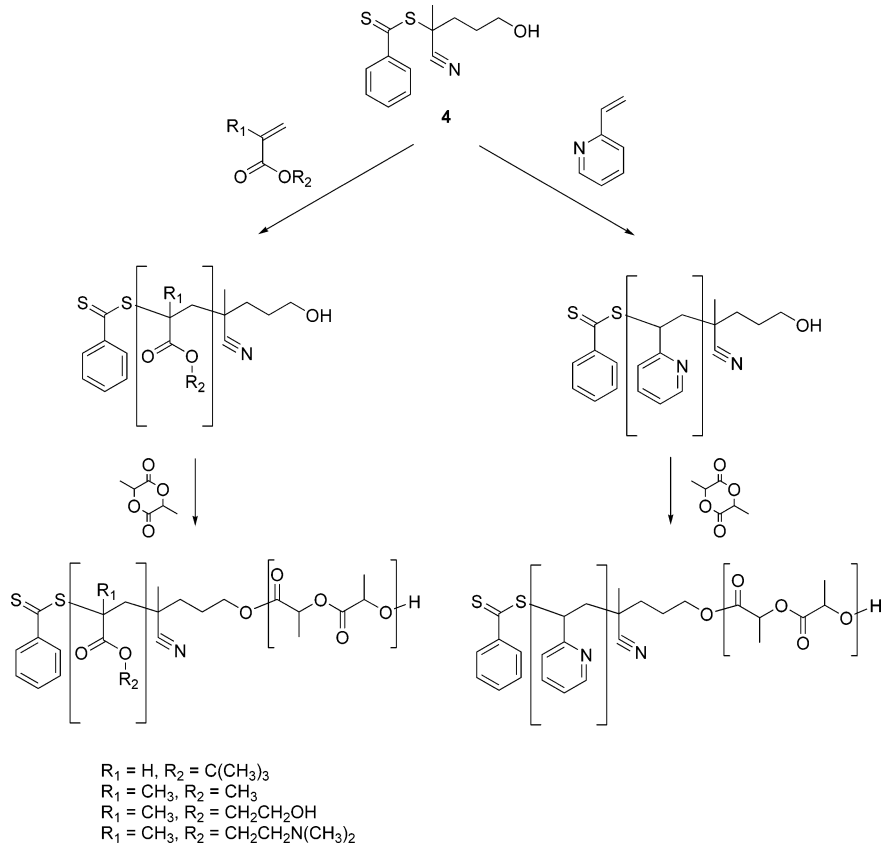


Table 8. Characterization of Macroinitiators and *rac*-Lactide Block Copolymers

macroinitiator				block copolymer				
	macroinitiator				lactide			
structure	DP[a]	M_n	PDI	catalyst	DP[a]	convn (%)	M_n	PDI
poly(ethylene oxide)-OH[b]	125	5000	1.03	**1a**	70	65	17 200	1.04
	125	5000	1.03	**2a** + (−)-sparteine	70	99	26 400	1.05
polystyrene-OH[c]	30	3500	1.05	**1a**	50	95	11 500	1.07
	55	5900	1.06		25	95	9400	1.05
	80	8300	1.07		100	95	29 900	1.07
	105	11 000	1.08		125	95	35 700	1.09
	55	5900	1.06	**2a** + (−)-sparteine	100	99	32 900	1.07
poly(*N*,*N*-dimethylacrylamide)-OH[c]	40	4100	1.11	**1a**	110	99	26 700	1.08
	70	7100	1.13		160	99	33 800	1.08
poly(methyl methacrylate)-OH[d]	140	14 500	1.12	**1a**	150	85	37 600	1.12
	140	14 500	1.12	**2a** + (−)-sparteine	150	99	44 900	1.10
poly(*N*,*N*-DMAEMA)-OH[d,e]	100	13 900	1.24	**1a**	50	99	21 600	1.32
poly(methyl methacrylate-*co*-hydroxyethyl methacrylate)-OH[d]	MMA: 150 HEMA: 25	18 100	1.17	**1a**	125	75	31 700	1.21
					175	80	50 700	1.17
poly(*tert*-butyl acrylate)-OH[d]	175	24 400	1.09	**1a**	150	85	39 500	1.10
	175	24 400	1.09	**2a** + (−)-sparteine	150	99	46 400	1.11
poly(2-vinylpyridine)-OH[d]	90	9200	1.06	**1a**	65	80	21 700	1.09
	90	9200	1.06	**2a** + (−)-sparteine	100	99	33 000	1.10
poly(methyl methacrylate-*block*-styrene)-OH[d]	MMA: 140 St: 185	39 000	1.15	**1a**	55	99	50 500	1.18

[a] DP was determined by ^{1}H NMR. [b] Commercial polymer. [c] Prepared by NMP. [d] Prepared by RAFT. [e] DMAEMA = dimethylaminoethyl methacrylate.

for sequential controlled radical and ring-opening polymerizations.

Experimental Section

Materials and Methods. Reagents (cyclohexylamine, 99%; *N*,*N*-dimethylethylenediamine, 95%; 3-(dimethylamino)-1-propylamine, 99%; 3,5-bis(trifluoromethyl)phenyl isothiocyanate, 98%; 4-(trifluoromethyl)phenyl isothiocyanate, 97%; 4-chlorophenyl isothiocyanate, 99%; *p*-tolyl isothiocyanate, 97%; 4-methoxyphenyl isothiocyanate, 99%; 3,5-bis(trifluoromethyl)phenyl isocyanate, 98%; *N*,*N*′-di-*n*-hexylthiourea, Lancaster, 98%; 4-hexylaniline, 90%; 2,6-diisopropylaniline, 97%) were available commercially from Aldrich and used as received unless otherwise noted. Solvents (THF, toluene) were dried using activated alumina columns. Deuteriochloroform (Cambridge Isotopes, 99.8%) was distilled from CaH_2 under dry N_2 and stored over molecular sieves (3 Å) for a maximum of 2 weeks before use. 4-Pyrene-1-butanol (99%) was stirred in dry THF with CaH_2, filtered, and freed of solvent in vacuo. 1-Pyrenemethylamine was freed from its hydrochloride salt (Aldrich, 95%) using concentrated NaOH and CH_2Cl_2, dried in vacuo, stirred in dry THF with CaH_2, filtered, and freed of solvent in vacuo. L-Lactide and *rac*-lactide (Purac, 99%) were recrystallized from

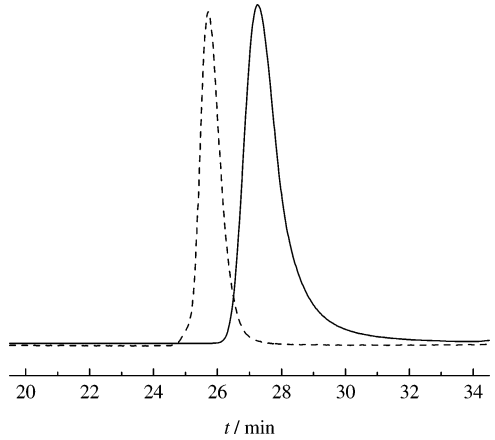


Figure 2. UV−vis absorption (350 nm) traces for GPC analysis of hydroxy-functionalized PMMA macroinitiator prepared by RAFT polymerization (solid line) and the derivative PMMA-*b*-PLA block copolymer (dashed line) using **2a** and (−)-sparteine (see Table 8). The only UV-absorbing agent present is the RAFT end group.

dry toluene 3 times prior to use. Thioureas were dissolved in dry THF, stirred with CaH_2, filtered, and freed of solvent in vacuo. Both *rac*- and (*R*,*R*)-TMCHD were prepared by a literature procedure, twice distilled from CaH_2 under dry N_2 and stored over molecular sieves (3 Å) prior to use.[30] Liquid amine cocatalysts (pyridine (99.8%); $NCyMe_2$ (99%); TMEDA (99%); (−)-sparteine (99%)) were twice distilled from CaH_2 under dry N_2 and stored over molecular sieves (3 Å) prior to use; solid amine cocatalysts (Proton Sponge (99%); DMAP (99%); DABCO (98%)) were recrystallized from dry toluene and dried in vacuo prior to use. Styrene (99%), methyl methacrylate (MMA; 99%), *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA; 98%), 2-hydroxyethyl methacrylate (HEMA; 98%) and *N*,*N*-dimethylacrylamide (DMA; 99%) were purified by stirring overnight over CaH_2 and subsequent distillation under reduced pressure. 2-Vinylpyridine (2VP; 97%) and *tert*-butyl acrylate (tBA; 98%) were passed through a plug of neutral activated aluminum oxide prior to use and used as such. 4,4′-Bisazo(4-cyanopentan-1-ol) (Langfang Hawk Ltd. (China), technical grade), water-wet as received, was dissolved in methylene chloride, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting solid was recrystallized twice from methylene chloride/hexanes yielding off-white crystals. The hydroxy-functionalized alkoxyamine for NMP, 2,2,5-trimethyl-3-(4′-p-hydroxymethylphenylethoxy)-4-phenyl-3-azahexane (**3**),[26] and the hydroxy-functionalized RAFT-agent, 4-cyano-4-((thiobenzoyl)sulfanyl)-pentan-1-ol (**4**),[27] were prepared according to literature procedures. Hydroxy-functional PS-OH[26,29] and PDMA-OH[8,26,29] were prepared by NMP, whereas hydroxyfunctional PMMA-OH,[28] PDMAEMA-OH,[28] P(MMA-*co*-HEMA)-OH,[28] PMMA-*b*-PS-OH[31] and P2VP-OH[32] were prepared by RAFT polymerization according to literature procedures. Macroinitiators from NMP and RAFT polymerizations as well as commercially available poly(ethylene oxide) (PEO; Fluka) were dried in a vacuum oven and further dried by coevaporation of dry distilled toluene 3 times before transferring to a glovebox for assembly of the ROP reaction. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on a Bruker Avance 400 instrument operated at 400, 100, and 376 MHz, respectively. Gel permeation chromatography (GPC) was performed in THF at 30 °C using a Waters chromatograph equipped with four 5 μm Waters columns (300 mm × 7.7 mm) connected in series with increasing pore size (10, 100, 1000, 10^5, 10^6 Å), a Waters 410 differential refractometer for refractive index (RI) detection and a 996 photodiode array detector, and calibrated with polystyrene standards (750 to 2×10^6 g mol^{-1}). Differential scanning calorimetry (DSC) was performed using a TA differential scanning calorimeter 1000 that was calibrated using high purity indium at a heating rate of 10 °C/min. Melting points were determined from the second scan following slow cooling (to remove the influence of thermal history) at a heating rate of 10 °C/min. Mass spectrometry (MS) services were provided by Stanford University Mass Spectrometry (EI = electron impact; ESI = electrospray ionization).

Sample Thiourea Synthesis. 2a. Cyclohexylamine (1.85 g, 18.5 mmol) was added dropwise at room temperature to a stirring solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (5.0 g, 19 mmol) in THF (20 mL). After the solution was stirred for 4 h, the solvent was evaporated. The white residue was recrystallized from chloroform to give **2a** as a white powder, mp >150 °C. Yield: 5.90 g (86%). ^{1}H NMR: δ = 7.52 (s, 1H, 5-Ar*H*), 7.33 (s, 2H, 2,6-Ar*H*), 6.50 (s, 1H, ArN*H*), 5.17 (s, 1H, CyN*H*), 4.40 (br m, 1H, NCy*H*), 2.03−0.86 (m, 10H, Cy*H*). {^{1}H}^{13}C NMR (benzene-d_6, 100 MHz): δ 179.8 (C=S), 140.1 (C_{aryl}), 133.1 (q, CF_3), 123.2 (C_{aryl}), 122.0 (C_{aryl}), 118.4 (C_{aryl}), 54.2 (C_{alkyl}), 32.8 (C_{alkyl}), 25.9 (C_{alkyl}), 25.2 (C_{alkyl}). ^{19}F NMR (benzene-d_6, 376 MHz): δ −63.5 (s, CF_3). ESI-MS: m/z = 371.882.

1b. This compound was synthesized using the same procedure as for **2a** from *N*,*N*-dimethylethylenediamine (350 mg, 4.0 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.08 g, 4.0 mmol). It was recrystallized from chloroform to give white needles, mp >150 °C. Yield: 1.2 g (86%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.27 (br, 1H, N*H*), 8.27 (s, 2H, 2,6-Ar*H*), 8.10 (br, 1H, N*H*), 7.72 (s, 1H, Ar*H*), 3.58 (m, 2H, CH_2CH$_2$NMe$_2$), 2.44 (m, 2H, CH_2NMe$_2$), 2.20 (s, 6H, N(CH_3)$_2$). {^{1}H}^{13}C NMR (DMSO-d_6, 400 MHz): δ = 180.2 (C=S), 142.0 (C_{aryl}), 129.8 (q, CF_3), 124.6 (C_{aryl}), 121.9 (C_{aryl}), 121.4 (C_{aryl}), 56.8 (C_{alkyl}), 44.8 (C_{alkyl}), 41.6 (C_{alkyl}). ESI-MS: m/z = 345.721.

1c. This compound was synthesized using the same procedure as for **2a** from 3-(dimethylamino)-1-propylamine (408 mg, 4.0 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.08 g, 4.0 mmol). It was recrystallized from chloroform to give a white powder. Yield: 1.1 g (81%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.01 (br, 1H, N*H*), 8.23 (s, 2H, 2,6-Ar*H*), 7.72 (s, 1H, Ar*H*), 3.51 (m, 2H, CH_2CH$_2$CH$_2$NMe$_2$), 2.26 (t, 2H, CH_2NMe$_2$), 2.12 (s, 6H, N(CH_3)$_2$), 1.69 (m, 2H, CH$_2$CH_2CH$_2$). {^{1}H}^{13}C NMR (DMSO-d_6, 400 MHz): δ = 180.4 (C=S), 142.0 (C_{aryl}), 130.2 (q, CF_3), 124.6 (C_{aryl}), 121.9 (C_{aryl}), 121.8 (C_{aryl}), 56.8 (C_{alkyl}), 44.9 (C_{alkyl}), 42.5 (C_{alkyl}), 25.9 (C_{alkyl}).

Sample Procedure for Thiourea-Catalyzed Polymerization of Lactide (Table 2, First Entry). A 0.07 M solution of amine $NCyMe_2$ in $CDCl_3$ (1 mL) was added to L-lactide (100 mg, 0.7 mmol), 4-pyrene-1-butanol (1.9 mg, 7 μmol, $[LA]_0/[I]_0$ = 100), and thiourea **2a** (25.7 mg, 0.07 mmol, 10 mol %) in a screw-cap vial. The contents were swirled until dissolved, transferred to an NMR tube, then left to stand. The reaction was monitored by ^{1}H NMR, with conversion measured by the ratio of the integrations of the methine protons for L-lactide and poly(L-lactide) (~4.9 ppm and ~5.1 ppm, respectively); no byproducts could be observed. After 72 h, 15 mg of benzoic acid was added to quench the polymerization, and the polymer was precipitated in 20 mL of methanol.

For polymerizations targeting a high degree of polymerization and therefore using a small amount of initiator (e.g. Table 5, fourth entry: $[LA]_0/[I]_0$ = 500), the initiator was delivered as 100 μL of a stock solution in $CDCl_3$.

Synthesis of Polylactide Initiated from Pyrenemethylamine. Pyrenemethylamine (2.3 mg, 10 μmol), **1a** (15 mg, 35 μmol) and *rac*-LA (100 mg, 0.7 mmol) were dissolved in $CDCl_3$ (0.5 mL). The reaction was quenched after 55 h by benzoic acid (10 mg). Conversion by NMR was 99%. ^{1}H NMR ($CDCl_3$): δ = 8.28−7.77 (m, 9H; Py), 6.78 (s, 1H; NH), 5.21−5.05 (m, ~140H, CH PLA backbone), 4.31 (q, 1H; C*H*−OH), 4.01 (b, 2H; PyCH$_2$), 1.68−1.44 (m, ~420H; CH_3 PLA backbone). GPC (RI): M_n (PDI) = 18000 g mol^{-1} (1.06).

Synthesis of Polylactide Initiated from Octadecylmercaptan. Octadecylmercaptan (5.0 mg, 18 μmol), **1a** (36 mg, 87 μmol) and *rac*-LA (125 mg, 0.87 mmol) were dissolved in $CDCl_3$ (0.5 mL). The reaction was quenched after 20 h by benzoic acid (10 mg). Conversion by NMR was 80%. ^{1}H NMR ($CDCl_3$): δ = 5.18−5.07 (m, ~80H; CH PLA backbone), 4.31 (q, 1H; C*H*−OH), 2.77 (t, 2H; CH$_2$S(C=O)), 1.52−1.47 (m, ~240H; CH_3 PLA backbone),

1.24−1.16 (m, 32H; CH_2), 0.80 (t, 3H; CH_3). GPC (RI): M_n (PDI) = 7800 g mol^{-1} (1.06).

Synthesis of Polylactide Initiated from Triethylhydroxysilane. Triethylhydroxysilane (1.2 mg, 9.1 μmol), **1a** (11.4 mg, 27.6 μmol), and *rac*-LA (95 mg, 0.66 mmol) were dissolved in $CDCl_3$ (1 mL). The reaction was quenched after 72 h by benzoic acid (10 mg). Conversion by NMR was 99%. ^{1}H NMR ($CDCl_3$): δ = 5.17−5.07 (m, ∼150H; CH PLA backbone), 4.32 (q, 1H; C*H*−OH), 1.55−1.42 (m, ∼450H; CH_3 PLA backbone), 0.68 (t, 9H; C*H*$_3$-CH_2Si), 0.52 (q, 6H; CH_3CH_2Si). GPC (RI): M_n (PDI) = 14200 g mol^{-1} (1.12).

Synthesis of Block Copolymers using 2a and Sparteine, Selected Examples. Poly(ethylene oxide)-OH (50 mg, M_n = 5000 g mol^{-1}, PDI = 1.03), **2a** (26 mg, 70 μmol), (−)-sparteine (8.2 mg, 35 μmol) and *rac*-LA (100 mg, 0.69 mmol) were dissolved in CH_2Cl_2 (1 mL). After 2.5 h benzoic acid (10 mg) was added. ^{1}H NMR ($CDCl_3$): δ = 5.20−5.06 (m, ∼140H; CH_{PLA}), 4.33−4.16 (m, 3H; CH_2O(C═O), C*H*−OH) 3.92−3.48 (m, ∼440H; C$H_2CH_2O_{PEO}$), 3.37 (s, 3H; OCH_3), 1.61−1.41 (m, ∼420H; $CH_{3\ PLA}$). GPC (RI): M_n (PDI) = 26 400 g mol^{-1} (1.05).

Polystyrene-OH (40 mg, M_n = 5900 g mol^{-1}, PDI = 1.06), **2a** (26 mg, 70 μmol), (−)-sparteine (8.2 mg, 37 μmol), and *rac*-LA (100 mg, 0.69 mmol) were dissolved in CH_2Cl_2 (1 mL). After 2.5 h benzoic acid (10 mg) was added. ^{1}H NMR ($CDCl_3$): δ = 7.47−6.32 (m, ∼285H; $H_{aromatic}$, $C_6H_{5\ PS}$), 5.19−5.05 (m, ∼200H; CH_{PLA}, HC−ON, PhOCH_2), 4.27−4.07 (b, 2H; C*H*−OH, ON−C*H*), 3.50−0.53 (m, ∼775H; C$H_{2\ PS}$, CH_{PS}, C$H_{3\ PLA}$, C$H_{3\ ini}$, CH_3CHCH_3, $C(CH_3)_3$), CH_3CHCH_3, CH_3CHCH_3). GPC (RI): M_n (PDI) = 32 900 g mol^{-1} (1.07).

Poly(methyl methacrylate)-OH (50 mg, M_n = 14 500 g mol^{-1}, PDI = 1.12), **2a** (19.5 mg, 53 μmol), (−)-sparteine (6.2 mg, 26 μmol), and *rac*-LA (75 mg, 0.53 mmol) were dissolved in CH_2Cl_2 (0.75 mL). After 2.5 h, benzoic acid (7.5 mg) was added.^{1}H NMR ($CDCl_3$): δ = 7.83 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.63 (b, 1H; H_4 aromatic RAFT), 7.48 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.18−5.05 (m, ∼300H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.16 (m, 2H; CH_2OC(═O)), 3.59−3.51 (bs, ∼420H; $OCH_{3\ PMMA}$), 1.95−0.78 (m, ∼1500H; $CH_{2\ PMMA}$, $CH_{3\ PMMA}$, $CH_{3\ PLA}$, $H_{aliphatic\ RAFT}$). GPC (RI): M_n (PDI) = 44 900 g mol^{-1} (1.10).

Poly(*tert*-butyl acrylate)-OH (100 mg, M_n = 24 400 g mol^{-1}, PDI = 1.09), **2a** (23.4 mg, 63 μmol), (−)-sparteine (7.4 mg, 32 μmol), and *rac*-LA (90 mg, 0.62 mmol) were dissolved in CH_2Cl_2 (1 mL). After 2.5 h, benzoic acid (9 mg) was added.^{1}H NMR ($CDCl_3$): δ = 7.83 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.63 (b, 1H; $H_{4\ aromatic\ RAFT}$), 7.48 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.18−5.05 (m, ∼300H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.12 (m, 2H; CH_2OC(═O)), 2.29−1.77 (m, ∼530H; CH_{PtBA}, C$H_{2\ PtBA}$, C$H_2CH_{2\ RAFT}$, C$H_{3\ RAFT}$), 1.68−1.39 (m, ∼900H; $CH_{3\ PLA}$), 1.28 (m, ∼1575H; $C(CH_3)_{3\ PtBA}$). GPC (RI): M_n (PDI) = 46 400 g mol^{-1} (1.11).

Poly(2-vinylpyridine)-OH (50 mg, M_n = 9200 g mol^{-1}, PDI = 1.06), thiourea catalyst **2a** (20.8 mg, 56 μmol), (−)-sparteine (6.6 mg, 28 μmol), and *rac*-LA (80 mg, 0.56 mmol) were dissolved in CH_2Cl_2 (0.8 mL). After 2.5 h, benzoic acid (8 mg) was added to the orange-colored viscous reaction mixture.^{1}H NMR ($CDCl_3$): δ = 8.53−6.12 (m, ∼365H; $H_{aromatic\ RAFT}$, $H_{aromatic\ P2VP}$), 5.20−5.06 (m, ∼200H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.08−3.81 (m, 2H; CH_2OC(═O)), 2.18−0.51 (m, ∼880H; $CH_{3\ PLA}$, $H_{aliphatic\ RAFT}$, $H_{aliphatic\ P2VP}$). GPC (RI): M_n (PDI) = 33 000 g mol^{-1} (1.10).

Synthesis of Block Copolymers Using 1a. Poly(ethylene oxide)-OH (50 mg, M_n = 5000 g mol^{-1}, PDI = 1.03), **1a** (28.7 mg, 69 μmol) and *rac*-LA (100 mg, 0.69 mmol) were dissolved in CH_2Cl_2 (1.5 mL). After 48 h benzoic acid (5 mg) was added. Conversion by NMR was 65%. ^{1}H NMR ($CDCl_3$): δ = 5.20−5.06 (m, ∼90H; CH_{PLA}), 4.33−4.16 (m, 3H; CH_2O(C═O), C*H*−OH) 3.92−3.48 (m, ∼440H; C$H_2CH_2O_{PEO}$), 3.37 (s, 3H; OCH_3), 1.61−1.41 (∼270H; $CH_{3\ PLA}$). GPC (RI): M_n (PDI) = 17 200 g mol^{-1} (1.04).

Polystyrene-OH (50 mg, M_n = 3500 g mol^{-1}, PDI = 1.05), **1a** (12.9 mg, 35 μmol), and *rac*-LA (50 mg, 0.35 mmol) were dissolved in CH_2Cl_2 (0.5 mL). After 72 h benzoic acid (5 mg) was added. Conversion by NMR was 99%. ^{1}H NMR ($CDCl_3$): δ = 7.47−6.32 (m, ∼160H; $H_{aromatic}$, $C_6H_{5\ PS}$), 5.19−5.05 (m, ∼100H; CH_{PLA}, HC−ON, PhOCH_2), 4.27−4.07 (b, 2 H; C*H*−OH, ON−C*H*), 3.50−0.53 (m, ∼400 H; C$H_{2\ PS}$, CH_{PS}, C$H_{3\ PLA}$, C$H_{3\ ini}$, CH_3CHCH_3, $C(CH_3)_3$), CH_3CHCH_3, CH_3CHCH_3). GPC (RI): M_n (PDI) = 11 500 g mol^{-1} (1.07).

Poly(methyl methacrylate)-OH (100 mg, M_n = 14 500 g mol^{-1}, PDI = 1.12), **1a** (10.7 mg, 26 μmol), and *rac*-LA (75 mg, 0.53 mmol) were dissolved in CH_2Cl_2 (0.6 mL). After 48 h benzoic acid (5 mg) was added. Conversion by NMR was 85%.^{1}H NMR ($CDCl_3$): δ = 7.83 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.63 (b, 1H; $H_{4-aromatic\ RAFT}$), 7.48 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.18−5.05 (m, ∼250H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.16 (m, 2H; CH_2OC(═O)), 3.59−3.51 (bs, ∼420H; $OCH_{3\ PMMA}$), 1.95−0.78 (m, ∼1350H; $CH_{2\ PMMA}$, $CH_{3\ PMMA}$, $CH_{3\ PLA}$, $H_{aliphatic\ RAFT}$). GPC (RI): M_n (PDI) = 37 600 g mol^{-1} (1.12).

Poly(*tert*-butyl acrylate)-OH (100 mg, M_n = 24 400 g mol^{-1}, PDI = 1.09), **1a** (23.4 mg, 63 μmol) and *rac*-LA (90 mg, 0.62 mmol) were dissolved in CH_2Cl_2 (1 mL). After 48 h benzoic acid (10 mg) was added. Conversion by NMR was 85%.^{1}H NMR ($CDCl_3$): δ = 7.83 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.63 (b, 1H; $H_{4-aromatic\ RAFT}$), 7.48 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.18−5.05 (m, ∼250H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.12 (m, 2H; CH_2OC(═O)), 2.29−1.77 (m, ∼530H; CH_{PtBA}, C$H_{2\ PtBA}$, C$H_2CH_{2\ RAFT}$, C$H_{3\ RAFT}$), 1.68−1.39 (m, ∼750H; $CH_{3\ PLA}$), 1.28 (m, ∼1575H; $C(CH_3)_{3\ PtBA}$). GPC (RI): M_n (PDI) = 39 500 g mol^{-1} (1.10).

Poly(2-vinylpyridine)-OH (75 mg, M_n = 9200 g mol^{-1}, PDI = 1.06), **1a** (16.0 mg, 39 μmol), and *rac*-LA (75 mg, 0.52 mmol) were dissolved in CH_2Cl_2 (0.8 mL). After 24 h benzoic acid (5 mg) was added. Conversion by NMR was 80%.^{1}H NMR ($CDCl_3$): δ = 8.53−6.12 (m, ∼365H; $H_{aromatic\ RAFT}$, $H_{aromatic\ P2VP}$), 5.20−5.06 (m, ∼100H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.08−3.81 (m, 2H; CH_2OC(═O)), 2.18−0.51 (m, ∼570H; $CH_{3\ PLA}$, $H_{aliphatic\ RAFT}$, $H_{aliphatic\ P2VP}$). GPC (RI): M_n (PDI) = 21 700 g mol^{-1} (1.09).

Poly(*N*,*N*-dimethylacrylamide)-OH (200 mg, M_n = 4100 g mol^{-1}, PDI = 1.07), **1a** (100 mg, 0.25 mmol), and *rac*-LA (350 mg, 2.5 mmol) were dissolved in CH_2Cl_2 (2.5 mL). After 72 h benzoic acid (15 mg) was added. Conversion by NMR was 99%. ^{1}H NMR ($CDCl_3$): δ = 7.24−7.06 (m, 9H; $H_{aromatic}$), 5.22−5.08 (m, ∼85H; CH_{PLA}, *H*C−ON, PhOCH_2), 4.38−4.18 (m, 2H; C*H*-OH, ON−C*H*), 3.22−0.42 (m, ∼500H; N(CH_3)$_{2\ PDMA}$, C$H_{2\ PDMA}$, CH_{PDMA}, C$H_{3\ PLA}$, C$H_{3\ ini}$, CH_3CHCH_3, $C(CH_3)_3$), CH_3CHCH_3, CH_3CHCH_3). GPC (RI): M_n (PDI) = 16 900 g mol^{-1} (1.07).

Poly(*N*,*N*-dimethylaminoethyl methacrylate)-OH (200 mg, M_n = 13 900 g mol^{-1}, PDI = 1.24), **1a** (28 mg, 68 μmol), and *rac*-LA (100 mg, 0.69 mmol) were dissolved in CH_2Cl_2 (1 mL). After 48 h benzoic acid (8 mg) was added. Conversion by NMR was 99%.^{1}H NMR ($CDCl_3$): δ = 7.82 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.43 (b, 1H; $H_{4-aromatic\ RAFT}$), 7.38 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.24−5.06 (m, ∼100H; CH_{PLA}), 4.32 (q, 1H; C*H*−OH), 4.29−3.76 (m, ∼200H; CH_2O(C═O), C(═O)OC$H_{2\ PDMAEMA}$), 2.72−0.67 (m, ∼1400H; CH_2N(CH_3)$_2$, CH_2N(CH_3)$_2$, C$H_2CH_{2\ ini}$, C$H_{3\ ini}$, $CH_{2\ PDMAEMA}$, $CH_{3\ PDMAEMA}$, $CH_{3\ PLA}$). GPC (RI): M_n (PDI) = 21 600 g mol^{-1} (1.32).

Poly(methyl methacrylate-*co*-hydroxyethyl methacrylate)-OH (200 mg, M_n = 18 100 g mol^{-1}, PDI = 1.17), **1a** (28 mg, 68 μmol) and *rac*-LA (300 mg, 2.1 mmol) were dissolved in CH_2Cl_2 (3 mL). After 24 h benzoic acid (10 mg) was added. Conversion by NMR was 80%.^{1}H NMR ($CDCl_3$): δ = 7.82 (b, 2H; $H_{2,6\ aromatic\ RAFT}$), 7.62 (b, 1H; $H_{4-aromatic\ RAFT}$), 7.41 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 5.19−5.06 (m, ∼280H; CH_{PLA}), 4.35−4.18 (m, 27H; CH_2CH_2OC(═O), C*H*−OH), 4.18−3.95 (m, 16H; C(═O)OCH_2CH_2) 3.81 (m, 9H; CH−O*H*), 3.61−3.36 (bs, ∼450H; $OCH_{3\ PMMA}$), 2.77−2.64 (m, 4H; C$H_2CH_{2\ ini}$), 1.98−0.67 (m, ∼1720H; C$H_{3\ ini}$, $CH_{2\ PMMA}$, CH_3 PMMA, $CH_{2\ PHEMA}$, C$H_{3\ PHEMA}$, $CH_{3\ PLA}$). GPC (RI): M_n (PDI) = 50 700 g mol^{-1} (1.17).

Poly(styrene-*block*-methyl methacrylate)-OH (M_n = 39 000 g mol^{-1}, PDI = 1.15), **1a** (20.8 mg, 56 μmol), and *rac*-LA (80 mg, 0.56 mmol) were dissolved in CH_2Cl_2 (0.8 mL). After 48 h benzoic acid (8 mg) was added. Conversion by NMR was 99%.^{1}H NMR ($CDCl_3$): δ = 7.85 (b, 2H; $H_{2,6-aromatic\ RAFT}$), 7.63 (b, 1H; $H_{4-aromatic\ RAFT}$), 7.44 (b, 2H; $H_{3,5-aromatic\ RAFT}$), 7.38−6.25 (m, ∼925H; $H_{aromatic\ PS}$), 5.19−5.03 (m, CH_{PLA}), 4.29 (m, ∼110H; C*H*−

OH), 4.14 (m, 2H; $CH_2OC(=O)$, 3.62−3.43 (bs, ∼420H; $OCH_{3\ PMMA}$), 2.55−077 (m, ∼1600H; $CH_2CH_{2\ ini}$, $CH_{3\ ini}$, $CH_{2\ PMMA}$, $CH_{3\ PMMA}$, $CH_{2\ PS}$, CH_{PS}, $CH_{3\ PLA}$). GPC (RI): M_n (PDI) = 50 500 g mol^{-1} (1.18).

Sample Procedure for Determining *ee* of Unreacted *rac*-Lactide: *rac*-Lactide (100 mg, 0.7 mmol) was dissolved in a solution of **2a** (25 mg, 0.07 mmol, 10 mol %), (−)-sparteine (9 mg, 0.04 mmol, 5 mol %), and 4-pyrene-1-butanol (1.6 mg, 7 μmol, 1 mol %) in $CDCl_3$. ^{1}H NMR monitoring of the reaction showed 90% conversion of monomer after 1 h, at which time benzoic acid (10 mg) was added to quench the reaction. The solution was loaded onto a small silica column and eluted with CH_2Cl_2. The first fraction isolated was **2a**, and the second fraction was unreacted *rac*-lactide (∼10 mg). To the unreacted *rac*-lactide was added DMAP (5 mg) and (*R*)-*sec*-phenethyl alcohol (50 mg), and the resulting solution was heated to 60 °C for 1 h. The solution was then dissolved in $CDCl_3$ and analyzed by homodecoupled ^{1}H NMR spectroscopy as for stereochemical analyses. Singlet methine peaks appear at 5.93 ppm for opened L-lactide and 5.91 ppm for opened D-lactide. Experiments with genuine L-lactide and D-lactide show that no epimerization/racemization occurs by this procedure.

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Supporting Information Available: Text discussing the determination of P_m values including a table displaying the data, a figure showing {^{1}H}-^{1}H NMR spectra of poly(DL-lactide) and a table giving experimental ratios of stereochemical tetrads and nearest chain-end control fits for poly(DL-lactide). This material is available free of charge via the Internet at http://pubs.acs.org.

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