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Organocatalytic Ring-Opening Polymerization of Cyclic Esters Mediated by Highly Active Bifunctional Iminophosphorane Catalysts

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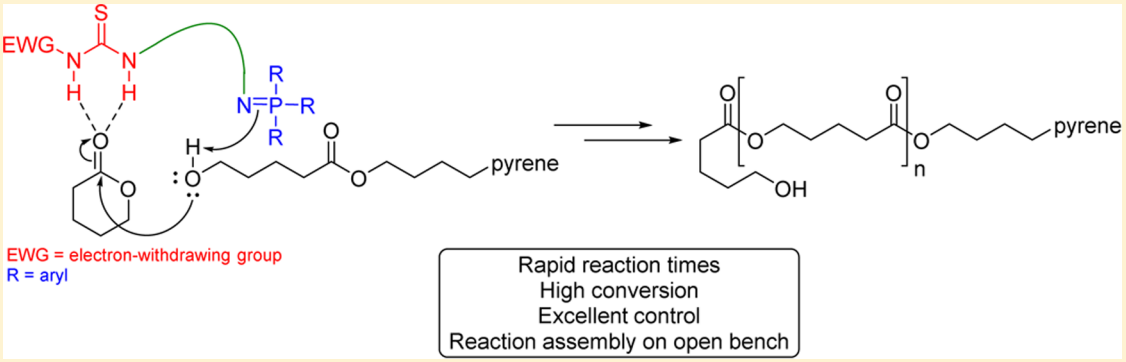
Supporting Information



ABSTRACT: Highly active bifunctional iminophosphorane catalysts have been applied to the organocatalytic ring-opening polymerization (ROP) of L-lactide (LA), δ-valerolactone (VL), and ϵ-caprolactone (CL). LA polymerization using catalyst **2** at 1 mol % loading rapidly gave poly(LA) in full conversion and with excellent control over the molecular weight distribution. VL and CL were polymerized under the control of catalyst **3** at 5 mol % loading. Poly(VL) was obtained in high conversion and with very good control over the molecular weight distribution. The catalyst system was suitable for the formation of short lengths of poly(CL), with good control over the molecular weight distribution. The formation of block copolymers by sequential monomer addition and the use of macroinitiators such as monomethoxy-terminated poly(ethylene glycol) (mPEG) were also demonstrated using the catalyst system. Control experiments using nonbifunctional *N*-alkyl iminophosphorane **5** demonstrated the roles of both components of the bifunctional catalyst in the ROP reaction. Notably, the bifunctional iminophosphorane catalysts are moisture-stable and nonhygroscopic, enabling the assembly of ROP reactions on the open bench.

INTRODUCTION

The ability to prepare a variety of structurally well-defined polymers underlies the design and application of advanced polymeric materials, for example the development of polymersomes for use as nanoreactors[1] or for the encapsulation and controlled release of drugs and medical imaging agents.[2] Of the existing polymerization techniques, organocatalytic ring-opening polymerization, pioneered by Hedrick and co-workers,[3−5] is characterized by its ability to produce polymers with exceptionally low polydispersity and excellent end-group fidelity. In recent years, the development of highly reactive guanidine, amidine and *N*-heterocyclic carbene catalysts, as well as the extension of organocatalytic techniques to a variety of functionalized monomers have made organocatalysis an attractive and practical alternative to traditional, metal-catalyzed ROP.[6] Furthermore, organocatalytic ROP provides unique advantages such as the production of polymers which are entirely free from metal residues and comparative ease of operation compared to metal-catalyzed polymerization.

The bases 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in combination with a simple thiourea cocatalyst, represent the current state-of-the-art in the organocatalytic ROP of cyclic esters.[5] These catalysts have the advantage of being highly active (in the case of TBD in particular), commercially available and competent in facilitating very well-controlled polymerizations. However, the more active catalytic systems (such as TBD) exert decreased levels of control over the polymerization of more reactive monomers such as LA, while the more finely controlled catalytic systems (DBU/thiourea) require prolonged reaction times and, in some cases, result in incomplete monomer conversion. Furthermore, amidines and guanidines are highly hygroscopic, making their handling difficult in the absence of a glovebox. Indeed, ROP reactions using these catalysts are performed in a glovebox[5] and in our hands, attempts to utilize them on the open bench were met with limited success. Accordingly, a catalytic system that is both highly active, exerts exquisite control over ring-opening polymerization and is easy to handle is desirable.

Our group has recently disclosed the invention of a novel class of potent bifunctional iminophosphorane organocatalysts and their application in the asymmetric nitro-Mannich

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reaction.[7] These consist of a triaryl iminophosphorane linked to a hydrogen bond donor, such as a thiourea (Figure 1). The

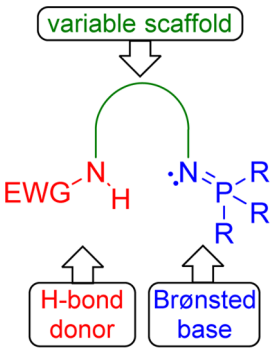

Figure 1. General structure of bifunctional iminophosphorane catalysts. *R* = aryl group; EWG = electron-withdrawing group.

strong basicity of these organocatalysts, comparable to that of guanidines, enables their application in transformations where the low reactivity of traditional tertiary amine organocatalysts is a limiting factor. Conveniently, when combined with a thiourea moiety, triaryl iminophosphoranes were found to be air- and moisture-stable. The catalysts can be isolated and handled in air and have been stored for several months in screw-cap vials at 4 °C with minimal decomposition. In light of the successful application of guanidine and amidine bases in organocatalytic ROP, we undertook to test our bifunctional iminophosphorane catalysts in the ROP of cyclic esters (Figure 2).

GENERAL EXPERIMENTAL DETAILS

L-Lactide was purchased from Alfa Aesar, D,L-lactide was purchased from Sigma-Aldrich. Both were recrystallized three times from toluene under anhydrous conditions then dried *in vacuo* before use. VL was purchased from Acros Organics and CL was purchased from Alfa Aesar. Both were distilled twice from calcium hydride before use. 1-Pyrenebutanol and monomethoxy-terminated poly(ethylene glycol) (MW ~ 2000) were purchased from Sigma-Aldrich and dried before use by dissolving in THF and stirring over calcium hydride overnight, followed by filtration and recovery by removal of solvent under nitrogen flow. Anhydrous toluene and dichloromethane were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns, followed by standing over activated 4 Å molecular sieves for 24 h. Chlorobenzene was distilled from calcium hydride. 1*H*-Imidazole-1-sulfonyl azide hydrochloride was prepared according to literature procedures.[8] All other reagents purchased from commercial sources were used as supplied. Solvents were stored in sealed Schlenk flasks over activated 4 Å molecular sieves, VL and CL were stored in sealed Schlenk flasks. LA was stored in a desiccator under vacuum over phosphorus pentoxide. Reaction assembly was performed on an open bench under a blanket of nitrogen.

NMR spectra were recorded using a Bruker Avance 250, 400, or 500 MHz spectrometer and chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak. Conversion was measured by the ratio of the integrations of the NMR signals of the α-methylene or methine protons of the monomer compared to those of the polymers. The tacticity of synthesized poly(LA) was determined from the integration of the methine region of the homodecoupled ^{1}H NMR spectrum. P_i, the probability of forming an isotactic dyad, was calculated using literature methods.[9]

MALDI-ToF MS analysis was performed on a Waters MALDI micro equipped with a 337 nm nitrogen laser and an accelerating voltage of 25 kV. The polymer samples were dissolved in THF at a concentration of 1.0 mg mL^{-1}. The cationization agent used was potassium trifluoroacetate (Sigma-Aldrich, >99%) dissolved in THF at a concentration of 5.0 mg mL^{-1}. The matrix used was *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (Sigma-Aldrich) and was dissolved in THF at a concentration of 40 mg mL^{-1}. Solutions of matrix, salt and polymer were mixed in a volume ratio of 2: 1: 2, respectively. The mixed solution was hand spotted on a stainless steel MALDI target and left to air-dry. The spectra were recorded in the reflectron mode.

Polymer molecular weights (M_w, M_n, and PDI) were determined by GPC using a Polymer Laboratories PL-GPC50 Plus instrument equipped with a Polymer Laboratories PLgel MixedD column (300 mm length, 7.5 mm diameter) and refractive index (RI) detector. Samples were dissolved in THF (Fisher, HPLC grade, stabilized with BHT, 2.5 ppm) at a concentration of 2.0 mg mL^{-1} and filtered prior to injection. THF (Fisher, HPLC grade, stabilized with BHT, 2.5 ppm) was used as the eluent at 30 °C and the flow rate was set to 1.0 mL min^{-1}. Linear polystyrenes (Polymer Laboratories) were used as the primary calibration standards and the appropriate Mark−Houwink corrections for poly(LA) and poly(CL) in THF at 30 °C were used to calculate the experimental molecular weights.

EXPERIMENTAL SECTION

Catalyst Precursor 1. To a solution of bromoethylamine hydrobromide (1.00 g, 4.88 mmol) in water (5 mL) at room temperature was added sodium azide (0.952 g, 14.6 mmol) and the reaction mixture was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature then basified with potassium hydroxide (1.60 g, 28.5 mmol). The reaction mixture was then extracted with diethyl ether (3 × 50 mL) and the combined organic extracts washed with brine, dried over anhydrous sodium sulfate and the solvent removed under a flow of nitrogen. The crude aminoazide was dissolved in anhydrous THF (25 mL), treated with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.664 mL, 3.64 mmol) and the reaction mixture stirred under argon atmosphere for 3 h. The solvent was removed *in vacuo* and the crude reaction mixture purified by flash column chromatography over silica (petroleum ether, followed by 10% ethyl acetate in petroleum ether, then 20% ethyl acetate in petroleum ether) to give the product as a colorless solid (1.03 g, 2.89 mmol, 59% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.54 (1 H, br s), 7.81 (2 H, s), 7.74 (1 H, s), 6.54 (1 H, br s), 3.94−3.74 (2 H, m), 3.72−3.54 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 181.1, 138.6, 133.4 (q, J_{FC} = 34.3 Hz), 124.3 (d, J_{FC} = 3.8 Hz),

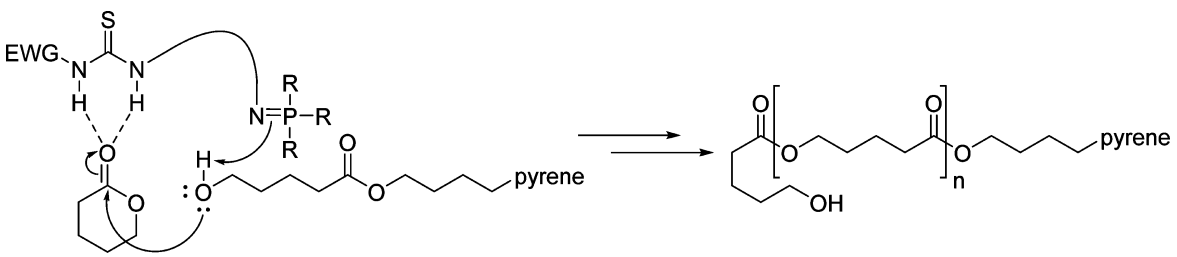

Figure 2. Representation of dual activation of a monomer and growing polymer chain by a bifunctional iminophosphorane organocatalyst. *R* = aryl group; EWG = electron-withdrawing group.

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122.8 (q, J_{FC} = 272.8 Hz), 120.1 (t, J_{FC} = 3.8 Hz), 50.4, 44.4. ^{19}F NMR (470 MHz, $CDCl_3$), δ (ppm): −63.1. Mp: 84−85 °C. IR (ν_{max}/cm^{-1}): 3238, 2116, 1537, 1469, 1379, 1336, 1270, 1166, 1127, 971, 894, 847, 713, 680, 649. HRMS (ES+): calcd for $C_{11}H_9F_6N_5NaS$ $[M + Na]^+$, 380.0375; found, 380.0366.

Catalyst 2. Catalyst precursor **1** (0.945 g, 2.64 mmol) and tris(4-methoxy)phenylphosphine (0.932 g, 2.64 mmol) were dissolved in anhydrous diethyl ether (8 mL) and stirred at room temperature under argon atmosphere overnight. The resulting colorless precipitate was collected by filtration, washed with pentane (10 mL) and dried under vacuum overnight, yielding **2** (1.59 g, 2.33 mmol, 88%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.57−7.45 (8 H, m), 7.28 (1 H, br s), 6.98−6.95 (6 H, m), 3.84 (9 H, s), 3.68−3.61 (2 H, m), 3.10−3.07 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 182.1, 163.9, 134.9 (d, J_{PC} = 11.4 Hz), 130.7 (q, J_{FC} = 32.4 Hz), 125.1, 124.3 (br s), 123.8 (q, J_{FC} = 272.8 Hz), 116.0 (br s), 115.2 (d, J_{PC} = 13.4 Hz), 115.0−114.7 (m), 77.4 (br s), 55.6, 47.1 (br s), 46.5. ^{19}F NMR (470 MHz, $CDCl_3$), δ (ppm): −62.1. ^{31}P NMR (202 MHz, $CDCl_3$), δ (ppm): 27.9 (br s). Mp 96−98 °C. IR (ν_{max}/cm^{-1}): 1595, 1502, 1466, 1416, 1374, 1299, 1273, 1179, 1114, 1013, 867, 836, 804, 699, 678. HRMS (ES+): calcd for $C_{32}H_{31}F_6N_3O_3PS$ $[M + H]^+$, 682.1722; found, 682.1772.

Typical Procedure for LA Polymerization. To a stirred solution of L-lactide (100 mg, 0.694 mmol, 100 equiv) in CH_2Cl_2 (0.1 mL) under argon atmosphere was added a solution of catalyst **2** (4.7 mg, 0.0069 mmol, 1 equiv) and 1-pyrenebutanol (1.9 mg, 0.0069 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 10 min at room temperature, then quenched by the addition of acetic acid (0.05 mL, 1 M in CH_2Cl_2). Solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion. The crude polymer was dissolved in a minimum amount of CH_2Cl_2, then precipitated from methanol and isolated by filtration. The purified polymer was analyzed by GPC to determine its molecular weight and polydispersity. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.25−7.83 (9 H, m, ArH), 5.15 (196 H, q, J = 7.2 Hz, $CH_{PLA\ backbone}$), 4.35 (1 H, q, J = 6.9 Hz, C*H*−OH), 4.20 (2 H, td, J = 6.4, 1.6 Hz, 1-pyrenebutanol CH_2), 1.57 (608 H, d, J = 7.3 Hz, $CH_{3\ PLA\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 169.7 (CO), 69.1 ($CH_{PLA\ backbone}$), 16.8 ($CH_{3\ PLA\ backbone}$). GPC (RI): M_n (PDI) = 27 500 g mol^{-1} (1.04).

Typical Procedure for VL Polymerization. To a stirred solution of catalyst **3** (75.8 mg, 0.100 mmol, 5 equiv) and 1-pyrenebutanol (5.50 mg, 0.0200 mmol, 1 equiv) in chlorobenzene (1 mL) under argon atmosphere was added δ-valerolactone (186 μL, 2.00 mmol, 100 equiv) and the reaction mixture stirred for 9 h at room temperature and then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.27−7.84 (9 H, ArH), 4.12−4.01 (170 H, m, $COOCH_{2\ PVL\ backbone}$), 2.39−2.25 (169 H, m, $CH_2COO_{\ PVL\ backbone}$), 1.73−1.54 (347 H, m, $CH_2CH_{2\ PVL\ backbone}$). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.4 (CO), 64.0 ($COOCH_{2\ PVL\ backbone}$), 33.8 ($CH_2COO_{\ PVL\ backbone}$), 28.2 ($COOCH_2CH_{2\ PVL\ backbone}$), 21.5 ($CH_2CH_2COO_{\ PVL\ backbone}$). GPC (RI): M_n (PDI) = 10 100 g mol^{-1} (1.13).

Typical Procedure for CL Polymerization. To a stirred solution of catalyst **3** (75.8 mg, 0.100 mmol, 5 equiv) and 1-pyrenebutanol (5.50 mg, 0.0200 mmol, 1 equiv) in toluene (1 mL) under argon atmosphere was added ε-caprolactone (222 μL, 2.00 mmol, 100 equiv) and the reaction mixture stirred for 100 h at room temperature, then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.30−7.81 (9 H, m, ArH), 4.05 (162 H, t, J = 6.8 Hz, $COOCH_{2\ PCL\ backbone}$), 2.23−2.35 (177 H, m, $CH_2COO_{\ PCL\ backbone}$), 1.56−1.70 (349 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$), 1.32−1.44 (175 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.7 (CO), 64.3 ($COOCH_{2\ PCL\ backbone}$), 34.2 ($CH_2COO_{\ PCL\ backbone}$), 28.5 ($CH_2CH_2CH_{2\ PCL\ backbone}$), 25.6 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 24.7 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$). GPC (RI): M_n (PDI) = 4900 g mol^{-1} (1.23).

Block Copolymerization of VL and CL. To a stirred solution of catalyst **3** (26.3 mg, 0.0347 mmol, 5 equiv) and 1-pyrenebutanol (1.9 mg, 0.0069 mmol, 1 equiv) in chlorobenzene (0.34 mL) under argon atmosphere was added δ-valerolactone (32 μL, 0.35 mmol, 50 equiv) and the reaction mixture stirred for 4 h at room temperature. After removal of a 50 μL aliquot of the reaction mixture for analysis of the conversion, molecular weight and polydispersity of the first polymerization, ε-caprolactone (38 μL, 0.35 mmol, 50 equiv) was added and the reaction mixture stirred at room temperature for 48 h, then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.27−7.85 (9 H, m, ArH), 4.09−4.03 (144 H, m, $COOCH_{2\ PCL/PVL\ backbone}$), 2.35−2.29 (157 H, m, $CH_2COO_{\ PCL/PVL\ backbone}$), 1.73−1.61 (309 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$ and $CH_2CH_{2\ PVL\ backbone}$), 1.43−1.35 (67 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.8 ($CO_{\ PCL\ sequence}$), 173.3 ($CO_{\ PVL\ sequence}$), 64.2 ($COOCH_{2\ PCL\ backbone}$), 64.0 ($COOCH_{2\ PVL\ backbone}$), 34.2 ($CH_2COO_{\ PCL\ backbone}$), 33.7 ($CH_2COO_{\ PVL\ backbone}$), 28.4 ($CH_2CH_2CH_{2\ PCL\ backbone}$), 28.1 ($COOCH_2CH_{2\ PVL\ backbone}$), 25.6 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 24.6 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 21.5 ($CH_2CH_2COO_{\ PVL\ backbone}$). GPC (RI): M_n (PDI) VL sequence = 4050 g mol^{-1} (1.10); final polymer = 5920 g mol^{-1} (1.19).

Block Copolymerization of VL and LA. To a stirred solution of catalyst **3** (26.3 mg, 0.0347 mmol, 5 equiv) and 1-pyrenebutanol (1.9 mg, 0.0069 mmol, 1 equiv) in chlorobenzene (0.34 mL) under argon atmosphere was added δ-valerolactone (32 μL, 0.35 mmol, 50 equiv) and the reaction mixture stirred for 5 h at room temperature. After removal of a 50 μL aliquot of the reaction mixture for analysis of the conversion, molecular weight, and polydispersity of the first polymerization, a solution of L-lactide (50.0 mg, 0.347 mmol, 50 equiv) in CH_2Cl_2 (0.5 mL) was added in one portion and the reaction mixture stirred for 10 min and then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.27−7.85 (9 H, ArH), 5.16 (88 H, q, J = 7.1 Hz, $CH_{PLA\ backbone}$), 4.09−4.05 (89 H, m, $COOCH_{2\ PVL\ backbone}$), 2.36−2.29 (87 H, m, $CH_2COO_{PVL\ backbone}$), 1.68−1.67 (180 H, m, $CH_2CH_{2\ PVL\ backbone}$), 1.58 (260 H, d, J = 7.2 Hz, $CH_{3\ PLA\ backbone}$). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.3 ($CO_{\ PVL}$), 169.6 ($CO_{\ PLA}$), 69.0 ($CH_{\ PLA\ backbone}$), 64.0 ($COOCH_{2\ PVL\ backbone}$), 33.7 ($CH_2COO_{\ PVL\ backbone}$), 28.1 (one of $COOCH_2CH_{2\ PVL\ backbone}$), 21.5 (one of $CH_2CH_2COO_{\ PVL\ backbone}$), 16.7 ($CH_{3\ PLA\ backbone}$). GPC (RI): M_n (PDI) VL sequence = 3930 g mol^{-1} (1.12); final polymer = 7530 g mol^{-1} (1.13).

Block Copolymerization of CL and LA. To a stirred solution of catalyst **3** (26.3 mg, 0.0347 mmol, 5 equiv) and 1-pyrenebutanol (1.9 mg, 0.0069 mmol, 1 equiv) in chlorobenzene (0.34 mL) under argon atmosphere was added ε-caprolactone (38 μL, 0.35 mmol, 50 equiv) and the reaction mixture stirred for 48 h at room temperature. After removal of a 50 μL aliquot of the reaction mixture for analysis of the conversion, molecular weight and polydispersity of the first polymerization, a solution of L-lactide (50.0 mg, 0.347 mmol, 50 equiv) in CH_2Cl_2 (0.5 mL) was added in one portion and the reaction mixture stirred for 10 min and then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^{1}H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 8.33−7.88 (9 H, ArH), 5.32−5.21 (124 H, m, $CH_{PLA\ backbone}$), 4.11 (89 H, t, J = 6.7 Hz, $COOCH_{2\ PCL\ backbone}$), 2.37−2.35 (82 H, m, $CH_2COO_{\ PCL\ backbone}$), 1.74−1.68 (171 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$), 1.66−1.61 (396 H,

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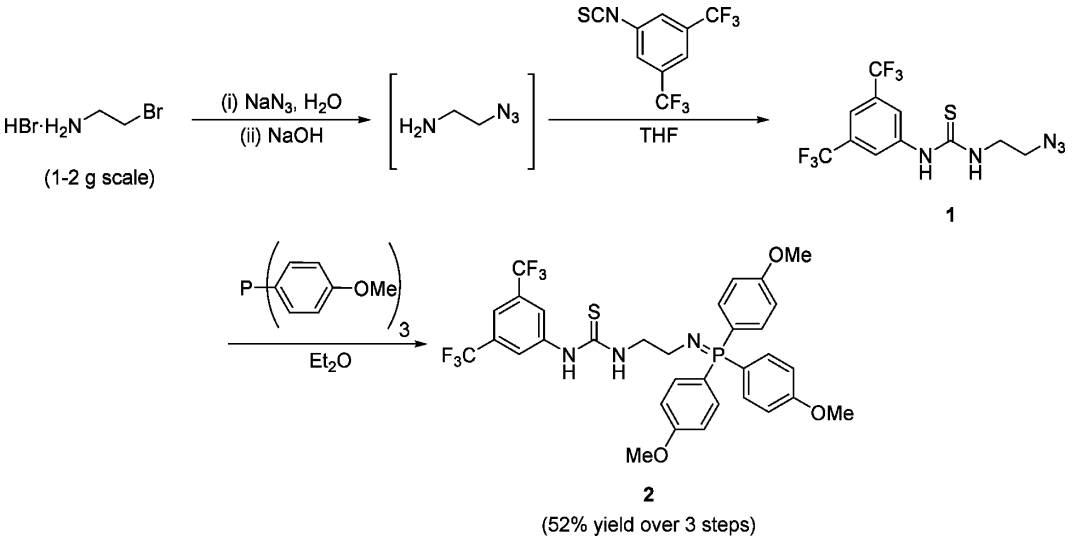
Scheme 1. Synthesis of Bifunctional Iminophosphorane Catalyst 2



m, $CH_{3\ PLA\ backbone}$), 1.47−1.39 (92 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.4 (CO_{PCL}), 169.8 (CO_{PLA}), 69.1 ($CH_{PLA\ backbone}$), 64.3 ($COOCH_{2\ PCL\ backbone}$), 34.3 ($CH_2COO_{PCL\ backbone}$), 28.5 ($CH_2CH_2CH_{2\ PCL\ backbone}$), 25.7 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 24.7 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 16.8 ($CH_{3\ PLA\ backbone}$). GPC (RI): M_n (PDI) CL sequence = 3480 g mol^{-1} (1.12); final polymer = 5670 g mol^{-1} (1.16).

Polymerization of LA Using mPEG$_{50}$ Macroinitiator. To a stirred solution of L-lactide (100 mg, 0.694 mmol, 100 equiv) in CH_2Cl_2 (0.8 mL) under argon atmosphere was added a solution of catalyst **2** (23.6 mg, 0.0347 mmol, 5 equiv) and mPEG$_{50}$ (13.9 mg, 0.00694 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 10 min at room temperature, then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). Solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^1H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): (selected peaks) 5.16 (193 H, q, J = 7.1 Hz, $CH_{PLA\ backbone}$), 3.64 (169 H, br s $CH_{2\ mPEG}$), 3.38 (3 H, s, $CH_{3\ mPEG\text{-}OMe}$), 1.58 (618 H, d, J = 7.1 Hz, $CH_{3\ PLA\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 169.7 (CO), 70.7 ($CH_{2\ mPEG}$), 69.1 ($CH_{PLA\ backbone}$), 55.8 ($CH_{3\ mPEG\text{-}OMe}$), 16.7 ($CH_{3\ PLA\ backbone}$). GPC (RI): M_n (PDI) = 16 800 g mol^{-1} (1.07).

Polymerization of VL Using mPEG$_{50}$ Macroinitiator. To a stirred solution of catalyst **3** (13.1 mg, 0.0173 mmol, 5 equiv) and mPEG$_{50}$ (13.9 mg, 0.00694 mmol, 1 equiv) in chlorobenzene (0.34 mL) under argon atmosphere was added δ-valerolactone (32 μL, 0.35 mmol, 50 equiv) and the reaction mixture stirred for 5 h at room temperature, then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^1H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): (selected peaks) 4.06−4.03 (64 H, m, $COOCH_{2\ PVL\ backbone}$), 3.61 (127 H, $CH_{2\ mPEG}$), 3.35 (3 H, s, $CH_{3\ mPEG\text{-}OMe}$), 2.36−2.29 (67 H, m, $CH_2COO_{PVL\ backbone}$), 1.67−1.64 (146 H, m, $CH_2CH_{2\ PVL\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.3 (CO), 70.6 ($CH_{2\ mPEG}$), 64.0 ($COOCH_{2\ PVL\ backbone}$), 33.7 ($CH_2COO_{PVL\ backbone}$), 28.1 ($COOCH_2CH_{2\ PVL\ backbone}$), 21.5 ($CH_2CH_2COO_{PVL\ backbone}$). GPC (RI): M_n (PDI) = 4600 g mol^{-1} (1.04).

Polymerization of CL Using mPEG$_{50}$ Macroinitiator. To a stirred solution of catalyst **3** (13.1 mg, 0.0173 mmol, 5 equiv) and mPEG$_{50}$ (13.9 mg, 0.00694 mmol, 1 equiv) in toluene (0.34 mL) under argon atmosphere was added ε-caprolactone (38 μL, 0.35 mmol, 50 equiv) and the reaction mixture stirred for 72 h at room temperature, then quenched by the addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2). The solvent was removed *in vacuo* and the crude reaction mixture analyzed by ^1H NMR to determine conversion and GPC to determine the molecular weight and polydispersity. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): (selected peaks) 4.06−4.03 (64 H, t, J = 6.6 Hz, $COOCH_{2\ PCL\ backbone}$), 3.63 (186 H, $CH_{2\ mPEG}$), 3.37 (3 H, s, $CH_{3\ mPEG\text{-}OMe}$), 2.33−2.25 (67 H, m, $CH_2COO_{PCL\ backbone}$), 1.68−1.54 (140 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$), 1.41−1.32 (74 H, m, $CH_2CH_2CH_{2\ PCL\ backbone}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): (selected peaks) 173.6 (CO), 70.5 ($CH_{2\ mPEG}$), 64.1 ($COOCH_{2\ PCL\ backbone}$), 34.1 ($CH_2COO_{PCL\ backbone}$), 28.3 ($CH_2CH_2CH_{2\ PCL\ backbone}$), 25.5 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$), 24.6 (one of $CH_2CH_2CH_{2\ PCL\ backbone}$). GPC (RI): M_n (PDI) = 4910 g mol^{-1} (1.18).

Azide 4. Phenethylamine (100 mg, 0.825 mmol), copper(II) sulfate pentahydrate (2.1 mg, 0.0083 mmol) and potassium carbonate (193 mg, 1.40 mmol) were taken up in methanol (4.1 mL) at room temperature. 1*H*-imidazole-1-sulfonyl azide hydrochloride (205 mg, 0.990 mmol) was added portionwise with stirring and the reaction was stirred overnight at room temperature. The solvent was removed under a flow of nitrogen and the residue was partitioned between water and diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent removed under a flow of nitrogen. The residue was purified by flash column chromatography over silica (petroleum ether, then 10% diethyl ether in petroleum ether) to give the product as a colorless oil (79 mg, 0.54 mmol, 65%). ^1H NMR (250 MHz, $CDCl_3$), δ (ppm): 7.43−7.27 (5 H, m), 3.57 (2 H, d, J = 7.3 Hz), 2.96 (2 H, d, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 138.2, 128.9, 128.8, 126.9, 52.6, 35.5.

Polymerization Catalyzed by Iminophosphorane 5. Azide **4** (5.1 mg, 0.035 mmol) and tris(4-methoxy)phenylphosphine (12.2 mg, 0.0347 mmol) were dissolved in THF and stirred at room temperature under argon atmosphere overnight, after which TLC analysis indicated complete consumption of the starting materials and mass spectrometry indicated the presence of iminophosphorane **5**. Maintaining the flask under inert atmosphere, THF was removed under a flow of nitrogen and the residue was dissolved in CH_2Cl_2 (0.2 mL). The CH_2Cl_2 solution of **5** was then added to a solution of L-lactide (100 mg, 0.694 mmol) and 1-pyrenebutanol (1.9 mg, 0.0069 mmol) in CH_2Cl_2 (0.8 mL) under argon atmosphere and the reaction stirred at room temperature for 1 h. The reaction was quenched by addition of acetic acid (0.1 mL, 1 M in CH_2Cl_2), the solvent removed *in vacuo* and the residue analyzed by ^1H NMR to determine conversion and GPC to determine the molecular weight and polydispersity.

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RESULTS AND DISCUSSION

A unique feature of the bifunctional iminophosphorane organocatalysts is the tunability of the modular basic functionality. From mechanistic and pK_a studies within our group,[7] it was known that tris(4-methoxy)phenyl substituted iminophosphoranes were the most strongly basic and the most active of those investigated to date, therefore this iminophosphorane was chosen for use in this work. An achiral variant of the bifunctional iminophosphorane catalyst, featuring an unsubstituted two carbon scaffold, was prepared in a simple, three-step procedure requiring only one purification by flash column chromatography. Bromoethylamine hydrobromide was heated overnight with sodium azide to give crude 2-azidoethylamine, which was treated with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give the thiourea **1**. This was then reacted with tris(4-methoxy)phenylphosphine to give the catalyst **2**, which was isolated by simple filtration and used without further purification (Scheme 1). A racemic phenyl-substituted catalyst, **3** (Figure 3), was prepared from (±)-phenylglycine, following literature procedures.[7]

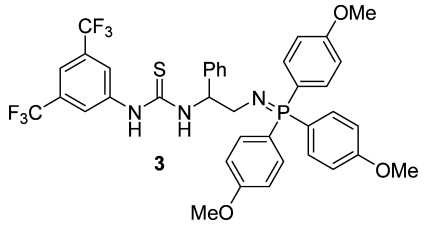

Figure 3. Racemic phenyl-substituted catalyst **3**.

Catalyst **2** was found to be highly effective for the ROP of LA, catalyzing the formation of poly(LA) in short reaction times, high conversion and with excellent control over the molecular weight distribution. At 1 mol % catalyst loading in CH_2Cl_2 and with a monomer to initiator (1-pyrenebutanol) ratio of 100:1, quantitative conversion to poly(LA) with a molecular weight of 27 500 g mol^{-1} and a PDI of 1.04, as determined by GPC using polystyrene standards, was achieved within 10 min. As the catalyst is nonhygroscopic and air-stable, it could be weighed out in air, then transferred to the reaction flask under a blanket of nitrogen. ^{1}H NMR analysis revealed a degree of polymerization of 98 and comparison with literature spectra[5] indicated that the initiator had been entirely incorporated into the polymer chain. MALDI-ToF spectra further confirmed the end-group fidelity (see Supporting Information). Homodecoupled ^{1}H NMR showed that, within the limits of detection, no epimerization had taken place during the polymerization. Poly(LA) with a monomer to initiator ratio of up to 500 was prepared in quantitative conversion (Table 1).

Table 1. Polymerization of LA Catalyzed by 2[a]

$[M]_0/[I]_0$	time (min)	convn (%)[b]	M_n (g mol^{-1})[c]	PDI[c]	DP[b]
25	3	99	6380	1.06	29
50	5	99	11 200	1.05	54
100	10	99	27 500	1.04	98
200	20	99	32 922	1.04	206
500	50	99	*d*	*d*	491

[a]Reaction was performed in CH_2Cl_2 at room temperature with 1 mol % catalyst loading relative to monomer and [LA] = 2.3 M. [b]Measured by ^{1}H NMR. [c]Measured by GPC in THF. [d]Not soluble in THF.

A linear relationship between the conversion and molecular weight and uniform polydispersity with respect to conversion indicated a well-controlled polymerization (Figure 4). Furthermore, the conversion vs time data could be well-fitted by first-order kinetics (see Supporting Information).

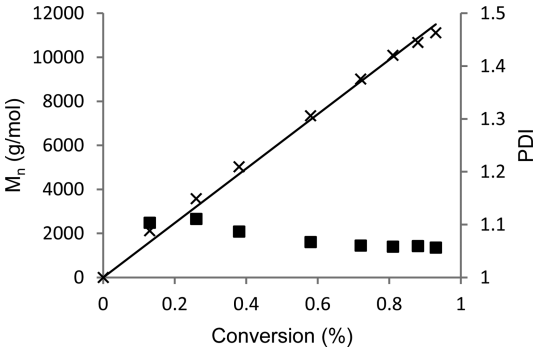

Figure 4. Ring-opening polymerization of LA with $[M_0]/[I_0]$ of 100 catalyzed by **2**. Plot of M_n, (×) and PDI (■), as determined by GPC, vs monomer conversion determined by ^{1}H NMR.

Polymerization of *rac*-lactide at room temperature gave a P_i value of 0.64, indicating a slight isotactic enhancement. Conducting the polymerization at −78 °C increased the P_i slightly to 0.74, but a conversion of only 36% was achieved in 4 h. Changing the catalyst to the more bulky phenyl-substituted catalyst **3** did not significantly affect the tacticity.

The bifunctional iminophosphorane was also found to be a capable catalyst for the polymerization of VL and CL, though reaction rates were slower than for LA, consistent with previous work on the organocatalytic ROP of cyclic esters.[5] Because of the poor solubility of catalyst **2** in the reaction solvents, toluene and chlorobenzene, the phenyl substituted catalyst **3** was used for the polymerization of these monomers. At 5 mol % catalyst loading in chlorobenzene and with a monomer to initiator (1-pyrenebutanol) ratio of 100:1, 94% conversion to poly(VL) with a molecular weight of 10 100 g mol^{-1} and a PDI of 1.13, as determined by GPC using polystyrene standards, was achieved within 9 h. MALDI-ToF spectra confirmed that the 1-pyrenebutanol initiator was incorporated into the polymer (see Supporting Information). Poly(VL) with molecular weight up to 37 400 g mol^{-1} was synthesized with high conversion and good control over the molecular weight distribution (Table 2).

Similarly, 91% conversion of CL to poly(CL) with a molecular weight of 4860 g mol^{-1} and PDI of 1.23 was achieved in toluene 100 h. In the polymerization of CL, a less reactive monomer, an increasing discrepancy between the target molecular weight and M_n as measured by GPC was observed as the monomer to initiator ratio increased, however

Table 2. Polymerization of VL Catalyzed by 3[a]

$[M]_0/[I]_0$	time (h)	convn (%)[b]	M_n (g mol^{-1})[c]	PDI[c]
50	4	94	7 260	1.10
100	9	94	10 100	1.13
200	16	92	22 400	1.11
500	24	92	37 400	1.08

[a]Reaction was performed in PhCl with 5 mol % catalyst loading relative to monomer and [VL] = 2.0 M. [b]Measured by ^{1}H NMR. [c]Measured by GPC in THF using Mark−Houwink parameters for polystyrene.

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the PDI and conversion remained consistently good. We postulate that in the extended reaction times required for CL, initiation from the catalyst itself (*vide infra*) competes with extension of the 1-pyrenebutanol-initiated chains, leading to consumption of the monomer and the formation of lower molecular weight oligomers. However poly(CL) with catalyst-derived end-groups was not observed directly; only 1-pyrenebutanol initiated chains are seen in MALDI-ToF spectra of poly(CL) (see Supporting Information). Thus, poly(CL) with molecular weight of only up to 9310 g mol^{-1} could be synthesized using this catalytic system (Table 3).

Table 3. Polymerization of CL Catalyzed by 3[a]

$[M]_0/[I]_0$	time (h)	convn (%)[b]	M_n (g mol^{-1})[c]	PDI[c]
50	48	79	3000	1.16
100	100	91	4860	1.23
200	120	91	5370	1.25
500	240	94	9310	1.24

[a]Reaction was performed in PhMe with 5 mol % catalyst loading relative to monomer and [CL] = 2.0 M. [b]Measured by ^{1}H NMR. [c]Measured by GPC in THF.

Block copolymers of LA, VL, and CL were successfully synthesized by the sequential addition of monomers. In a typical example, VL was polymerized in chlorobenzene using 10 mol % catalyst **3** and 1-pyrenebutanol initiator with an $[M]_0/[I]_0$ of 50 for 5 h, at which point an aliquot was removed for NMR and GPC analysis. ^{1}H NMR indicated 87% conversion, while GPC showed a peak with M_n of 4 050 g mol^{-1} and PDI of 1.10. 50 equiv of CL (relative to the initiator) were then added and the reaction continued until 82% conversion was reached, as indicated by ^{1}H NMR, then quenched by addition of acetic acid. GPC analysis of the resulting polymer showed a single, unimodal peak with M_n of 5 920 g mol^{-1} and a PDI of 1.19, indicating that a diblock copolymer had been formed. The final M_n compares favorably with the calculated molecular weight of 9 000 g mol^{-1}, given that this value was calculated directly from the polystyrene calibration curve of the GPC. Poly(VL)-*block*-poly(LA) and poly(CL)-*block*-poly(LA) were also prepared in this fashion (Table 4). In agreement with previous work,[5] the order of monomer addition was an important factor when LA was used.[10] Polymerization could also be initiated from macroinitiators such as mPEG (Table 5).

Although phosphazene bases are established ROP catalysts,[11] to the best of our knowledge, they have not been previously combined with thiourea additives. Consequently, several control experiments were carried out in order to investigate the roles of both the iminophosphorane and thiourea moieties.

First the ability of the bifunctional iminophosphoranes to initiate polymerization was tested. In the presence of 5 mol % catalyst **2**, but with no additional initiating nucleophilic species,

Table 5. Synthesis of Polymers from mPEG$_{50}$ Macroinitiator

monomer	$[M_0]/[I_0]$	time	convn[b] (%)	M_n (g mol^{-1})[a]	PDI[a]
LA	100	10 min	99	16800	1.07
VL	50	5 h	99	4600	1.04
CL	50	27 h	86	4910	1.18

[a]Measured by GPC in THF using Mark–Houwink parameters for polystyrene. [b]Measured by ^{1}H NMR. For mPEG$_{50}$: M_n = 2830 g mol^{-1} and PDI = 1.05 (measured by GPC in THF using Mark–Houwink parameters for polystyrene).

LA, VL, and CL were all polymerized (Table 6), albeit requiring longer reaction times to reach full conversion than in

Table 6. Polymerization of Monomers in the Presence of 5 mol % of Catalyst 2

monomer	time	convn (%)[a]
LA	10 min	75
VL	24 h	70
CL	24 h	20

[a]Measured by ^{1}H NMR.

the presence of an alcohol initiator. On the basis of the known reactivity between esters and iminophosphoranes to form amides in the Staudinger ligation,[12] it is likely that the nitrogen of the iminophosphorane acts as a nucleophile to open the monomer and form an initiating species. This is supported in part by the demonstrated reaction between an iminophosphorane and VL (see Supporting Information), which leads to the opening of the cyclic ester and formation of the corresponding amide upon hydrolysis. In spite of this, we cannot unequivocally rule out the possibility of initiation by adventitious moisture.[13]

Next the role of the thiourea moiety was investigated by studying the ROP of LA catalyzed by iminophosphorane **5**, which features an *N*-alkyl substituent rather than a linked H-bond donor. Iminophosphorane **5**, formed *in situ* from azide **4** and tris(4-methoxy)phenylphosphine (Scheme 2), is able to catalyze the polymerization of LA initiated by 1-pyrenebutanol, with a monomer to initiator ratio of 100:1 (Table 7). However, the reaction rate is slower than that achieved with bifunctional catalyst **2**, requiring 1 h to reach 92% conversion and the polydispersity of the resulting polymer is greater than that obtained using the bifunctional catalyst (1.14 vs ≤1.05). This is consistent with the findings of Hedrick and co-workers who show that the association constants of VL and CL and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea are much greater than that of the thiourea and ethyl acetate.[5,14] From this data it is inferred that the preferential activation of cyclic ester monomers over the polymer backbone suppresses transesterification. Thus, the thiourea moiety increases the

Table 4. Synthesis of Diblock Copolymers

		M_n (g mol^{-1})					M_n (g mol^{-1})		
monomer **1**	convn[b] (%)	GPC[a]	NMR	PDI[a]	monomer **2**	convn[b] (%)	GPC[a]	NMR	PDI[a]
VL	87	4050	4200	1.10	CL	82	5920	8000	1.19
VL	92	3930	4500	1.12	LA	99	7530	11 000	1.13
CL	93	3480	5130	1.12	LA	99	5670	14 100	1.16

[a]Measured by GPC in THF using Mark–Houwink parameters for polystyrene. $[M]_0/[I]_0$ for monomer 1 relative to 1-pyrenebutanol = 50; then 50 equiv of monomer 2 relative to 1-pyrenebutanol are added.

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Scheme 2. Preparation of Iminophosphorane 5

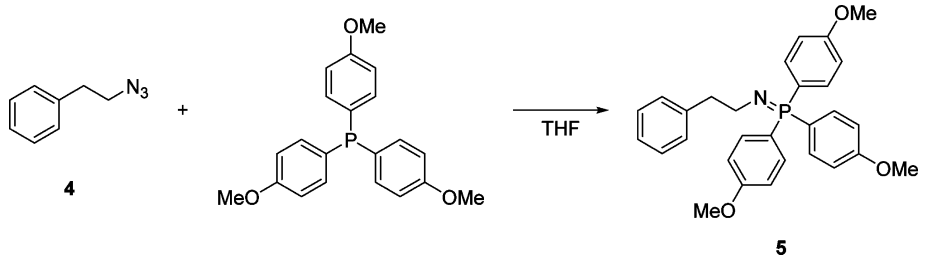

Table 7. Polymerization of LA in the Presence of 5 mol % 5 (Relative to Monomer)

$[M]_0/[I]_0$	initiator	time (h)	convn (%)[a]	M_n (g mol^{-1})[b]	PDI[b]	P_i[c]
100	1-PB	1	92	8190	1.14	0.68
–	–	1	74	8160	1.25	0.66

[a]Measured by ^{1}H NMR. [b]Measured by GPC in THF. [c]Measured by homodecoupled ^{1}H NMR.

rate of polymerization through monomer activation while also suppressing undesirable transesterification reactions.

However, it is also possible that iminophosphorane **5** is more basic and/or more nucleophilic than catalyst **2**. Initiation from the more nucleophilic iminophosphorane **5** may successfully compete with initiation from the alcohol, leading to the formation of lower molecular weight oligomers as well as consumption of the catalyst, which would lead to lower monomer conversion. This is consistent with the low value of M_n when using iminophosphorane **5** (8190 g mol^{-1} vs 27 500 g mol^{-1} for $[M]_0/[I]_0$ = 100 using catalyst **2**). The increased basicity may also result in increased transesterification.

Iminophosphorane **5** also catalyzes the polymerization of LA in the absence of an initiating alcohol—with 5 mol % catalyst loading LA is polymerized in 74% conversion after 1 h. This is slower than polymerization in the absence of an alcohol initiator using bifunctional catalyst **2**, in agreement with the proposed activation of the monomer by thiourea.

Interestingly, significant epimerization occurs when using iminophosphorane **5** and the resulting polymer has a P_i of 0.66–0.68. Stirring a sample of poly(LA) (previously prepared using catalyst **2**) with iminophosphorane **5** in CH_2Cl_2 for 1 h at room temperature does not result in any observable epimerization by homodecoupled ^{1}H NMR. Consequently we conclude that the reduced P_i of the polymer is caused by epimerization of the LA monomer.

CONCLUSION

Bifunctional iminophosphorane organocatalysts **2** and **3** were shown to be excellent catalysts for the synthesis of poly(LA) and poly(VL) giving short reaction times, excellent monomer conversions, low polydispersity and high end-group fidelity. Poly(CL) could also be synthesized, however the utility of the catalysts was limited to relatively short lengths of polymer due to suspected competing initiation from the catalyst. Diblock copolymers could successfully be synthesized through sequential monomer addition and the catalysts were compatible with the use of an mPEG macoinitiator. Importantly, the bifunctional iminophosphoranes represent highly active catalysts for ROP which can be handled on the open bench. Finally, control experiments revealed the requirement for both the iminophosphorane and thiourea moiety in order to achieve rapid and well-controlled polymerization. We anticipate that the ease of handling of these catalysts, combined with their high reactivity and ability to impart exquisite control on ring-opening polymerization will make them useful to the synthetic community.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of catalysts and polymers, first-order linear fit of LA polymerization kinetic data, MALDI–ToF spectra, GPC traces of polymers and copolymers, and the reaction of iminophosphorane with VL. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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CL) was noted by ^{1}H-NMR. This reflects the poor propensity of the terminal secondary alcohol of poly(LA) to initiate ROP.
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(13) Despite repeated attempts at obtaining MALDI-ToF spectra of polymers from Tables 6 and 7, no direct evidence of polymer chains terminated by an iminophosphorane-derived moiety (or by water) was observed.
(14) From preliminary NMR studies, the measurement of an association constant between the catalyst and an ester was not possible due to the complex and dynamic nature of solution phase NMR spectra of the catalyst.