Squaramide and (−)-Sparteine: An Excellent Hydrogen-Bonding Pair Organocatalyst for Living Polymerization

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Contents

Experimental S2

Catalytic performances in the ROP of L-Lactide (Table S1) S5

Optimization of the H-bond Acceptor Cocatalyst (Table S2) S6

Kinetic measurements S7

$^1$H NMR and $^{13}$C NMR of the poly (L-Lactide) S9

MALDI-ToF analysis of the polylactide S11

SEC analysis of the poly (L-Lactide) S12

$^1$H NMR and $^{13}$C NMR of poly(trimethylene carbonate)-block-poly(L-lactide) S13

SEC analysis of poly(trimethylene carbonate)-block-poly(L-lactide) S15

$^1$H and $^{13}$C NMR titration experiments S16

Data of computational studies S18

$^1$H and $^{13}$C NMR of catalysts S19

References S23
EXPERIMENTAL

Materials

Dichloromethane (DCM) was purchased from Sinopharm Chemical Reagent Co, and distilled over CaH₂ under an argon atmosphere, and further dried over 4 Å molecular sieve pellets for 48 h before use. Benzyl alcohol (Acros, 99%) was refluxed over CaH₂ for 48 hours prior to its distillation. Commercially available (−)-sparteine were from Sinopharm Chemical Reagent Co. and used as received. L-Lactide (99.5%) were obtained from Jinan Daigang Biomaterial Co. and recrystallised 3 times from toluene. Trimethylene carbonate (TMC) was purified by recrystallization from benzene-n-hexane prior four times to use. All other Reagents were purchased from Aldrich and used without further purification. 3,4-diethoxycyclobut-3-ene-1,2-dione was synthesized by squaric acid with triethyl orthoformate.\(^1\) Squaramide catalysts were prepared according to the literature procedures.\(^2\) Room temperature referred to 20-25 °C.

Instruments

\(^1\)H, \(^13\)C and \(^19\)F NMR spectra were recorded on a Bruker AV-300 or a Bruker AV-500 spectrometer at room temperature. The monomer conversion and the number-average molecular weight (\(M_{n,\text{NMR}}\)) were determined by \(^1\)H NMR spectrum. Melting points were determined on a Shanghai Jingke WRS-2A digital melting point instrument. High resolution mass spectra (HRMS) were obtained on Agilent Accurate-Mass Q-ToF LC/MS 6520 at 135.0 eV. The size exclusion chromatography (SEC) was performed on SSI 1500 pump equipped with Waters 5 μm, 300×7.8 mm column, Wyatt Optilab rEX differential refractive index (DRI) detector with a 658 nm light source. Tetrahydrofurane (THF) was used as eluent with a flow rate of 0.7 ml min⁻¹ at room temperature. The detectors temperature was at 25 °C. All data analyses were performed on Wyatt Astra V 6.1.1 software. Molecular weights and molecular weight distributions of the polymers were determined by size exclusion chromatography (SEC) based on the polystyrene calibration at 25 °C. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF) mass spectrometry was performed on a mass spectrometer (ultraflextreme; Bruker Co.) with Smartbeam/Smartbeam II modified Nd: YAG laser. The MALDI-ToF mass spectra represent averages over 500 laser shots at a 25 KV acceleration voltage. The polymer sample was dissolved in CHCl₃ at a concentration of 5 mg mL⁻¹. The matrix 2,5-DHB (2,5-dihydroxybenzoic acid) was dissolved in solution of trifluoroacetic acid and acetonitrile (volume ratio = 70/30) in water (1%, 10 μL). The final solution (1 μL) by mixing the matrix (20 μL) and polymer (2 μL), was deposited onto the sample target and dried in air at room temperature.
General Procedure for the Synthesis of Symmetrically substituted N, N’-Diarylsquaramides Sq1-3

![Chemical structure](image)

To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (diethyl squarate, 0.65 g, 3.8 mmol, 1.0 equiv) and zinc trifluoromethanesulfonate (0.276 g, 0.76 mmol, 0.2 equiv) in toluene/DMF 19:1 (5.8 mL) was added the corresponding aromatic amines (7.98 mmol, 2.1 equiv). The solution was heated to 100 °C and stirred for 12 h. Upon cooling to room temperature, pale crystals were obtained, isolated by filtration, and further washed with methanol to give N, N’-Diarylsquaramides Sq1-3.

**yield 90%; m.p. > 300 °C;** ¹H NMR (300 MHz, DMSO-d₆): δ (ppm) 10.64 (2 H, s), 7.90 (4 H, s), 7.69 (2 H, s); ¹³C NMR (101 MHz, Pyr-d₅): δ (ppm) 185.24, 166.25, 140.84, 131.60 (q, Jₑ-F = 33 Hz), 124.36 (q, Jₑ-F = 272 Hz), 119.33, 116.11; ¹⁹F NMR (282 MHz, DMSO-d₆): δ (ppm) -35.70; HRMS (ESI+): calcd for C₂₀H₈F₁₂N₂O₂ ([M+H]+) 537.0394, found m/z 537.0493.

**yield 95%; m.p. > 300 °C;** ¹H NMR (300 MHz, DMSO-d₆): δ (ppm) 9.93 (2 H, s), 7.49 (4 H, d, J = 7.3 Hz), 7.39 (4 H, app t, J = 7.4 Hz), 7.09 (2 H, app t, J = 7.4 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ (ppm) 181.54, 165.58, 138.48, 129.31, 123.22, 118.41; HRMS (ESI+): calcd for C₁₆H₁₂N₂O₂ ([M+H]+) 265.0899, found m/z 265.0986.

**yield 95%; m.p. > 300 °C;** ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.81, 7.40, 1.27; ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 181.48, 165.46, 145.85, 136.04, 126.12, 118.34, 39.52, 34.11, 31.21; HRMS (ESI+): calcd for C₂₄H₂₈N₂O₂ ([M+H]+) 377.2151, found m/z 377.2241.
Thiourea synthesis: To a solution of 3,5-bis(trifluoromethyl)aniline (0.20 mL, 1.39 mmol) in 2.5 mL abs THF in a 10 mL round-bottom flask was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.25 mL; 1.35 mmol), and the resulting mixture was heated at 50 °C for 80 h. The reaction mixture was concentrated in vacuo to obtain a light yellow solid. Upon cooling, the product was washed with cold dichloromethane (3×2.5 mL). The isolated yield was 0.90 g, 98.0%; m.p. 166.2-167.9 °C; \( ^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) 10.64 (s, 2H), 8.21 (s, 4H), 7.85 (s, 2H); \( ^{13}\)C NMR (75 MHz, CDCl\( _3 \)): \( \delta \) (ppm) 180.57, 141.14, 130.54 (q, CF\( _3 \)), 124.07, 121.31, 117.67; \( ^{19}\)F NMR (282 MHz, DMSO-\( d_6 \)): \( \delta \) -35.70; HRMS (ESI+): calcd for C\( _{17} \)H\( _9 \)F\( _{12} \)N\( _2 \)S ([M+H]+) 501.0295, found 501.0302.

**General procedure for L-lactide polymerization**

In glovebox, L-Lactide (L-LA) (216 mg, 1.5 mmol, 30 equiv) was dissolved in DCM (1.5 mL, \([\text{L-LA}]_0 = 1.0 \text{ mol L}^{-1} \)). The initiator, Benzyl alcohol (5.2 μL, 0.05 mmol, 1.0 equiv) was added by micro syringe. The catalyst system (1.5 equiv squaramide and 1.5 equiv tertiary amine) was then added to the solution to initiate the polymerization. The mixture was stirred at 25 °C until the complete consumption of L-lactide, monitored by \( ^1\)H NMR spectroscopy. An excess of benzoic acid was added to neutralize the catalyst. The polymer was recovered by precipitation from CH\( _2 \)Cl\( _2 \) in cold methanol and dried under high vacuum. Yield, 68.2%; \( M_{n,\text{NMR}} = 4430 \text{ g mol}^{-1} \); \( D = 1.07 \); \( ^1\)H NMR (300 MHz, CDCl\( _3 \)): \( \delta \) (ppm) 1.57(m, 3H × n, \(-\text{CH}_3\)\(_n\)), 4.34(m, \(-\text{CH(\text{CH}_3})\text{OH}\)), 5.13-5.21 (q, 1H× n-1, \( J = 7.0, -\text{CH(\text{CH}_3})\text{O}--\); 2H, ArCH\( _2 \)O--), 7.33-7.34 (m, 5 H, aromatic).

**Procedure for Block Copolymer Formation**

In glovebox, trimethylene carbonate (TMC) (153 mg, 1.5 mmol, 30 equiv) was dissolved in DCM (1.5 mL, \([\text{TMC}]_0 = 1.0 \text{ mol L}^{-1} \)). Benzyl alcohol (5.2 μL, 0.05 mmol, 1 equiv) was added by micro syringe. The catalyst system (1.5 equiv squaramide and 1.5 equiv tertiary amine) was then added to the solution to initiate the polymerization. The mixture was stirred at 25 °C under argon atmosphere. The polymerization was first stirred for 4 h, and then the block copolymerization was started with 30 equiv. of L-lactide (L-LA) (216 mg, 1.5 mmol). Before the polymerization was quenched by the addition of benzoic acid after 3 h, a small portion of the product was sampled to determine the monomer conversion.
via the $^1$H NMR measurements. The polymer was isolated by reprecipitation in cold methanol and dried under vacuum to obtain the poly(trimethylene carbonate)-*block*-poly(L-lactide) (PTMC-*b*-PLLA). Yield, 58.1%; $M_{n,\text{NMR}} = 7490$ g mol$^{-1}$; $D = 1.07$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) 1.59 (m, 3H × n, (–CH$_3$)$_n$), 2.05 (m, 2H × m, (–OCH$_2$CH$_2$–)$_m$), 4.23 (t, 4H × m, (–OCH$_2$CH$_2$–)$_m$), 4.36 (m, –CH(CH$_3$)OH), 5.12-5.22 (q, 1H × n-1, $J = 7.0$, (–CH(CH$_3$)O–)$_{n-1}$; 2H, ArCH$_2$O–), 7.33-7.38 (m, 5 H, aromatic).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Sq1</th>
<th>Sq2</th>
<th>Sq3</th>
<th>TU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td>2 h</td>
<td>18h</td>
<td>18h</td>
<td>2h</td>
</tr>
<tr>
<td>Conv. % $^b$)</td>
<td>97</td>
<td>53</td>
<td>41</td>
<td>84</td>
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</tbody>
</table>

$^a$) L-LA/ BnOH/ catalysts/ (−)-sparteine = 30/ 1/ 1.5/ 1.5 and [L-LA]$_0$ = 1.0 mol L$^{-1}$ in CH$_2$Cl$_2$ at 25 °C. $^b$) Determined by $^1$H NMR.
Table S2. ROP of L-Lactide Catalyzed by the Combination of the squaramides **Sq1** and Different Amines. \(^a\)

<table>
<thead>
<tr>
<th>Catalytic System</th>
<th>Monomer Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sq1/DMAP</td>
<td>91</td>
</tr>
<tr>
<td>Sq1/(–)-sparteine</td>
<td>100</td>
</tr>
<tr>
<td>Sq1/NMe(_2)Cy (^c)</td>
<td>51</td>
</tr>
<tr>
<td>Sq1/DABCO (^d)</td>
<td>30</td>
</tr>
<tr>
<td>Sq1/DIEA (^e)</td>
<td>20</td>
</tr>
<tr>
<td>Sq1/TMEDA (^f)</td>
<td>13</td>
</tr>
<tr>
<td>Sq1/PMDETA (^g)</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^a\) L-LA/ BnOH/ Sq1/ (–)-sparteine = 30/ 1/ 1.5/ 1.5 and [L-LA]\(_0\) = 1.0 mol L\(^{-1}\) in CH\(_2\)Cl\(_2\) at rt.

\(^b\) As determined by \(^1\)H NMR spectroscopy.

\(^c\) NMe\(_2\)Cy = N,N-imethylcyclohexylamine.

\(^d\) DABCO = 1,4-Diaza[2.2.2]bicyclooctane.

\(^e\) DIEA = Ethyldiisopropylamine.

\(^f\) TMEDA = N,N,N',N'-Tetramethylethylenediamine.

\(^g\) PMDETA = N,N,N',N''-Pentamethyldiethylenetriamine
Figure S1. Molecular weight ($M_n, \text{NMR}$) and polydispersity ($D$) versus the monomer conversion of L-LA (Theoretical $M_n$ (solid line)) in the [M]/[I] ratio of 50.
Figure S2. Semi-logarithmic kinetic plot for the polymerization of L-LA ([L-LA]₀ / [BnOH]₀ / [Sq1]₀ / [(-)-sparteine]₀ = 30/ 1/ 1.5/ 1.5.
Figure S3. $^1$H NMR spectrum of poly(l-lactide) initiated by benzyl alcohol.
Figure S4. $^{13}$C NMR spectrum of poly(L-lactide).
**Figure S5.** MALDI-ToF MS spectrum of the obtained PLLA ([L-LA]₀/[BnOH]₀/[Sq1]₀/[(−)-sparteine]₀ = 20/1/1/1, CH₂Cl₂, rt, [L-LA]₀ = 0.7 mol L⁻¹). As shown in figure, two main series of peaks were observed with molecular formula of molar mass M=108.06 (Mᵤ of BnOH) + n ×144.04(Mᵤ of L-LA) + 39 (K⁺) or M= 108.06 (Mᵤ of BnOH) + n ×144.04(Mᵤ of L-LA) + 23 (Na⁺). The mass differences between two adjacent peaks precisely typify the molar mass of L-LA (M = 144.04).
Figure S6. Size exclusion chromatography (SEC) traces for the polylactide samples: (a) obtained after the first feed of L-lactide (L-LA) (CH₂Cl₂, 25 °C, [L-LA]₀/[BnOH]₀/[Sq1]₀/[(−)-sparteine]₀ = 50/1/2.5/2.5, [L-LA]₀ = 1.0 mol L⁻¹) and (b) after a second feed of 50 equiv L-Lactide.
Figure S7. $^1$H NMR spectrum of the poly(trimethylene carbonate)-block-poly(L-lactide).
Figure S8. $^{13}$C NMR spectrum of the poly(trimethylene carbonate)-block-poly(L-lactide).
Figure S9. Size exclusion chromatography (SEC) traces for the poly(trimethylene carbonate)-block-poly(L-lactide): (a) obtained after the first feed of trimethylene carbonate (TMC) (CH2Cl2, 25 °C, [TMC]0/ [BnOH]0/ [Sq1]0/ [(-)-sparteine]0 = 30/ 1/ 1.5/ 1.5, [TMC]0 = 1.0 mol L⁻¹) and (b) after a second feed of 30 equiv L-lactide.
Figure S10. $^1$H NMR spectrum of benzyl alcohol, (−)-sparteine and their 1:1 complex in CDCl$_3$ at room temperature.
Figure S11. Chemical shifts of carbonyl carbon in the $^{13}$C NMR spectrum observed by titration of L-LA with squaramide Sq1 in C$_5$D$_5$N.
Details of computational studies

Calculations were carried out with the Gaussian ’09 \textsuperscript{[3]} software package on a windows 7 64 bits ultimate system. In order to study the interaction of L-lactide with catalysts, geometry optimizations were carried out with density functional theory at the B3LYP/6-31+G (d) in the presence of a continuum dielectric $\varepsilon = 8.93$ (dichloromethane) using IEF-PCM as implemented in Gaussian 09.

H-bonding complex between $\textbf{Sq1}$ and L-lactide

Distance N-H…O=C in $\textbf{Sq1} \cdot \text{L-lactide} = 1.945 \text{ Å }$ and $1.977 \text{ Å }$.

H-bonding complex between $\textbf{TU}$ and L-lactide

Distance N-H…O=C in $\textbf{TU} \cdot \text{L-lactide} = 2.046 \text{ Å }$ and $1.982 \text{ Å }$. 
$^1$H and $^{13}$C NMR of catalysts
References

