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

Jingjing Liu, Cheng Chen, Zhenjiang Li, Wenzhuo Wu, Xu Zhi, Qiguo Zhang, Hao Wu, Xin Wang, Saide Cui and Kai Guo*

* State Key Laboratory of Materials-Oriented Chemical Engineering, College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, 30 Puzhu Rd S., Nanjing 211816, China.

Contents

EXPERIMENTAL

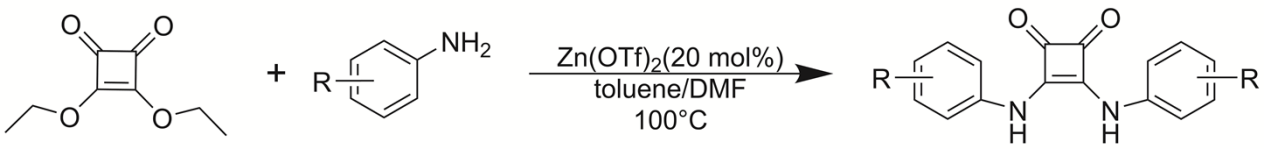
Materials

Dichloromethane (DCM) was purchased from Sinopharm Chemical Reagent Co, and distilled over CaH_2 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 CaH_2 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

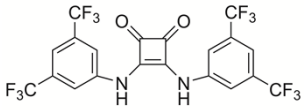
^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AV-300 or a Bruker AV-500 spectrometer at room temperature. The monomer conversion and the number-average molecular weight ($M_{n,\ NMR}$) were determined by ^{1}H NMR spectrum. Melting points were determined on a Shanghai Jingke WRS-2A digital melting point instrument. High resolution mass spectra (HRMS) were obtained on Agilent Acrrurate-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 $CHCl_3$ 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



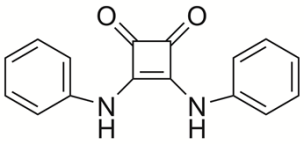
Sq1 : R= 3,5-$(CF_3)_2$
Sq2 : R= H
Sq3 : R= 4-t-Bu

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 ℃ 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**.



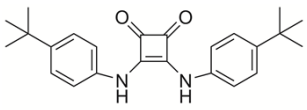
Sq1

yield 90%; m.p. > 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.64 (2 H, s), 7.90 (4 H, s), 7.69(2 H, s); ^{13}C NMR (101 MHz, Pyr-d_5): δ (ppm) 185.24, 166.25, 140.84, 131.60 (q, $J_{C\text{-}F}$ = 33 Hz), 124.36 (q, $J_{C\text{-}F}$ = 272 Hz), 119.33, 116.11; ^{19}F NMR (282 MHz, DMSO-d_6): δ (ppm) -35.70; HRMS (ESI+): calcd for $C_{20}H_8F_{12}N_2O_2$ ([M+H]+) 537.0394, found *m/z* 537.0493.



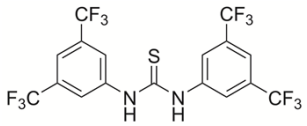
Sq2

yield 95 %; m.p. > 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 9.93 (2 H, s), 7.49 (4H, d, J = 7.3 Hz), 7.39 (4H, app t, J =7.4 Hz), 7.09 (2H, app t, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 181.54, 165.58, 138.48, 129.31, 123.22, 118.41; HRMS (ESI+): calcd for $C_{16}H_{12}N_2O_2$ ([M+H]+) 265.0899, found *m/z* 265.0986.



Sq3

yield 95 %; m.p. > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.81, 7.40, 1.27; ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 181.48, 165.46, 145.85, 136.04, 126.12, 118.34, 39.52, 34.11, 31.21; HRMS (ESI+): calcd for $C_{24}H_{28}N_2O_2$ ([M+H]+) 377.2151, found *m/z* 377.2241.



TU

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): δ (ppm)10.64 (s, 2H), 8.21 (s, 4H), 7.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 180.57, 141.14, 130.54 (q, CF_3), 124.07, 121.31, 117.67; ^{19}F NMR (282 MHz, DMSO-d_6): δ -35.70; HRMS (ESI+): calcd for $C_{17}H_9F_{12}N_2S$ ([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 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_2Cl_2 in cold methanol and dried under high vacuum. Yield, 68.2%; $M_{n,NMR}$ = 4430 g mol^{-1}; $Đ$ = 1.07; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.57(m, 3H × n, $(–CH_3)_n$), 4.34(m, –$CH(CH_3)$OH), 5.13-5.21 (q, 1H× n-1, J= 7.0,–$CH(CH_3)$O–; 2H, ArCH_2O–), 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 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%; $M_{n,NMR}$ = 7490 g mol^{-1}; $Đ$ = 1.07; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.59(m, 3H × n, (–CH_3)$_n$), 2.05 (m, 2H × m, (–OCH_2CH_2–)$_m$), 4.23 (t, 4H × m, (–OCH_2CH_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, $ArCH_2O$–), 7.33-7.38 (m, 5 H, aromatic).

Table S1. Catalytic performances in the ROP of L-lactide [a)]

Catalyst	Sq1	Sq2	Sq3	TU
Reaction time	2 h	18h	18h	2h
Conv. % [b)]	97	53	41	84

[a)] L-LA/ BnOH/ catalysts/ (−)-sparteine = 30/ 1/ 1.5/ 1.5 and $[L\text{-}LA]_0$ = 1.0 mol L^{-1} in CH_2Cl_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]

Catalytic System	Monomer Conversion (%) After 18 h [b]
Sq1/DMAP	91
Sq1/(–)-sparteine	100
Sq1/NMe_2Cy [c]	51
Sq1DABCO[d]	30
Sq1/DIEA[e]	20
Sq1/TMEDA[f]	13
Sq1/PMDETA[g]	48

[a] L-LA/ BnOH/ Sq1/ (–)-sparteine = 30/ 1/ 1.5/ 1.5 and $[L\text{-}LA]_0$= 1.0 mol L^{-1} in CH_2Cl_2 at rt.

[b] As determined by ^1H NMR spectroscopy.

[c] NMe_2Cy = *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″,N″*-Pentamethyldiethylenetriamine

Figure S1. Molecular weight ($M_{n,\ NMR}$) and polydispersity ($Đ$) versus the monomer conversion of L-LA (Theoretical M_n (solid line)) in the [M]/[I] ratio of 50.

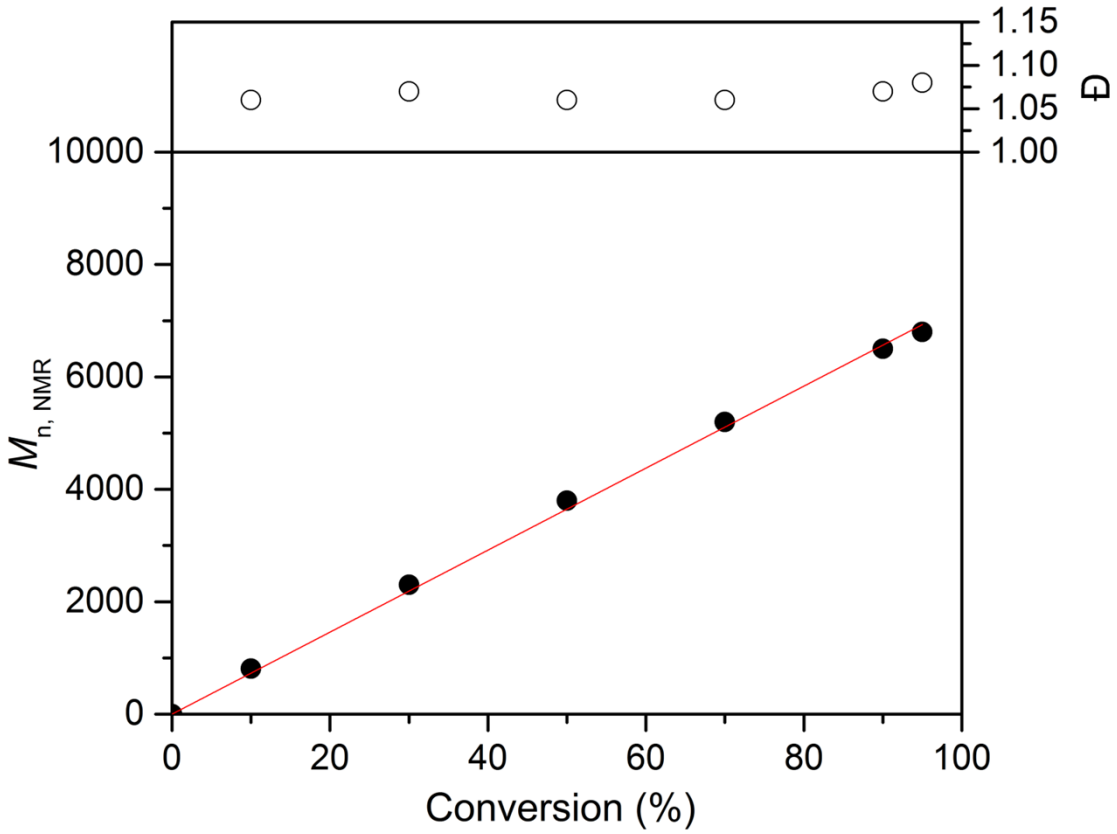


Figure S2. Semi-logarithmic kinetic plot for the polymerization of L-LA ($[L\text{-LA}]_0$ / $[BnOH]_0$ / $[\mathbf{Sq1}]_0$ / $[(-)\text{-sparteine}]_0$ = 30/ 1/ 1.5/ 1.5.

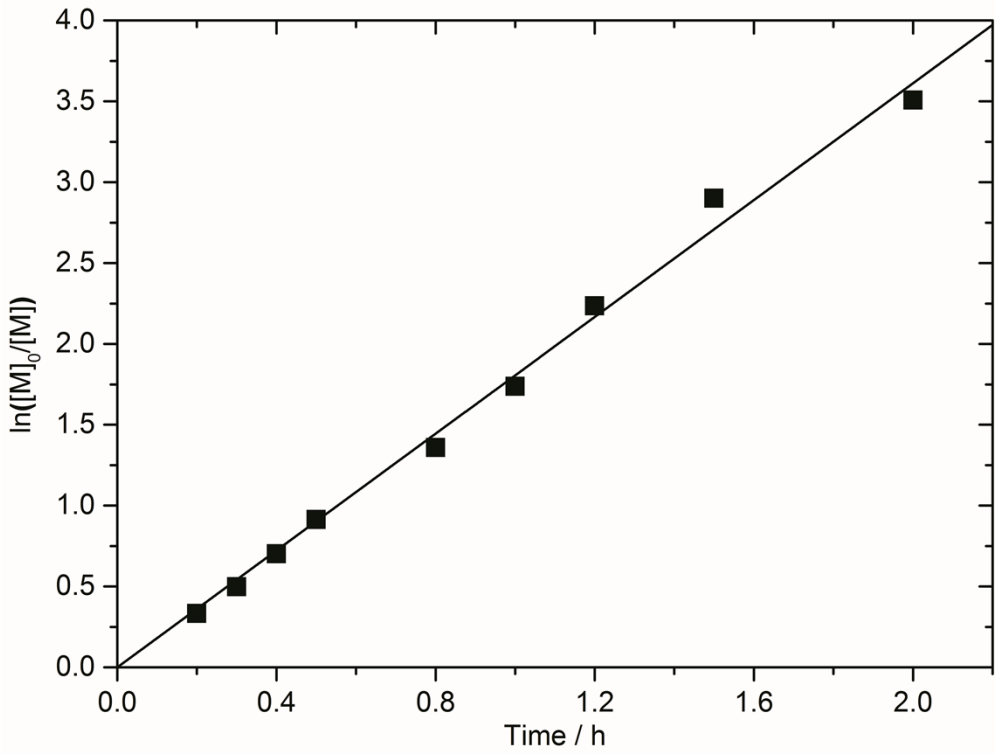


Figure S3. ^{1}H NMR spectrum of poly(L-lactide) initiated by benzyl acohol.

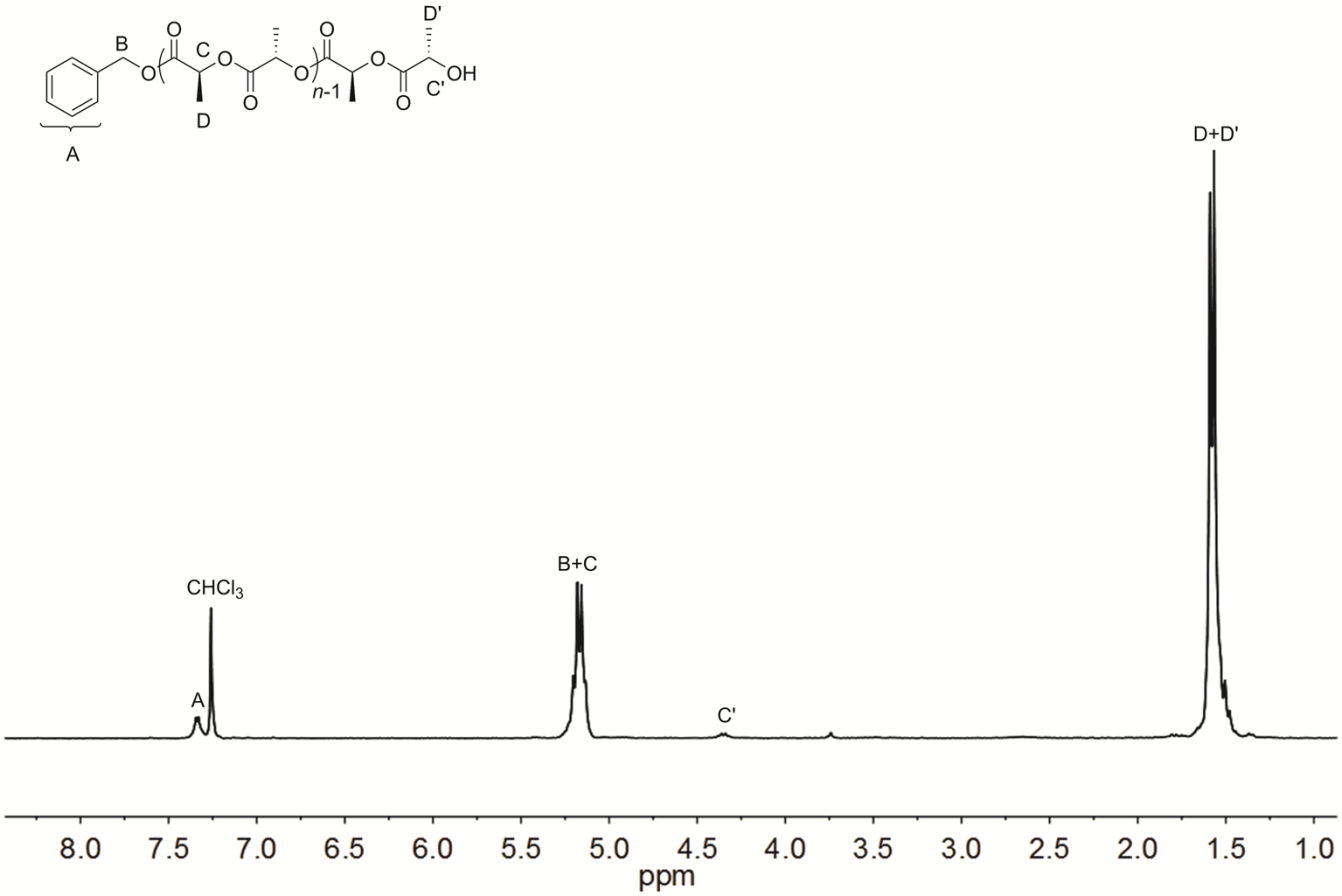


Figure S4 . ^{13}C NMR spectrum of poly(L-lactide).

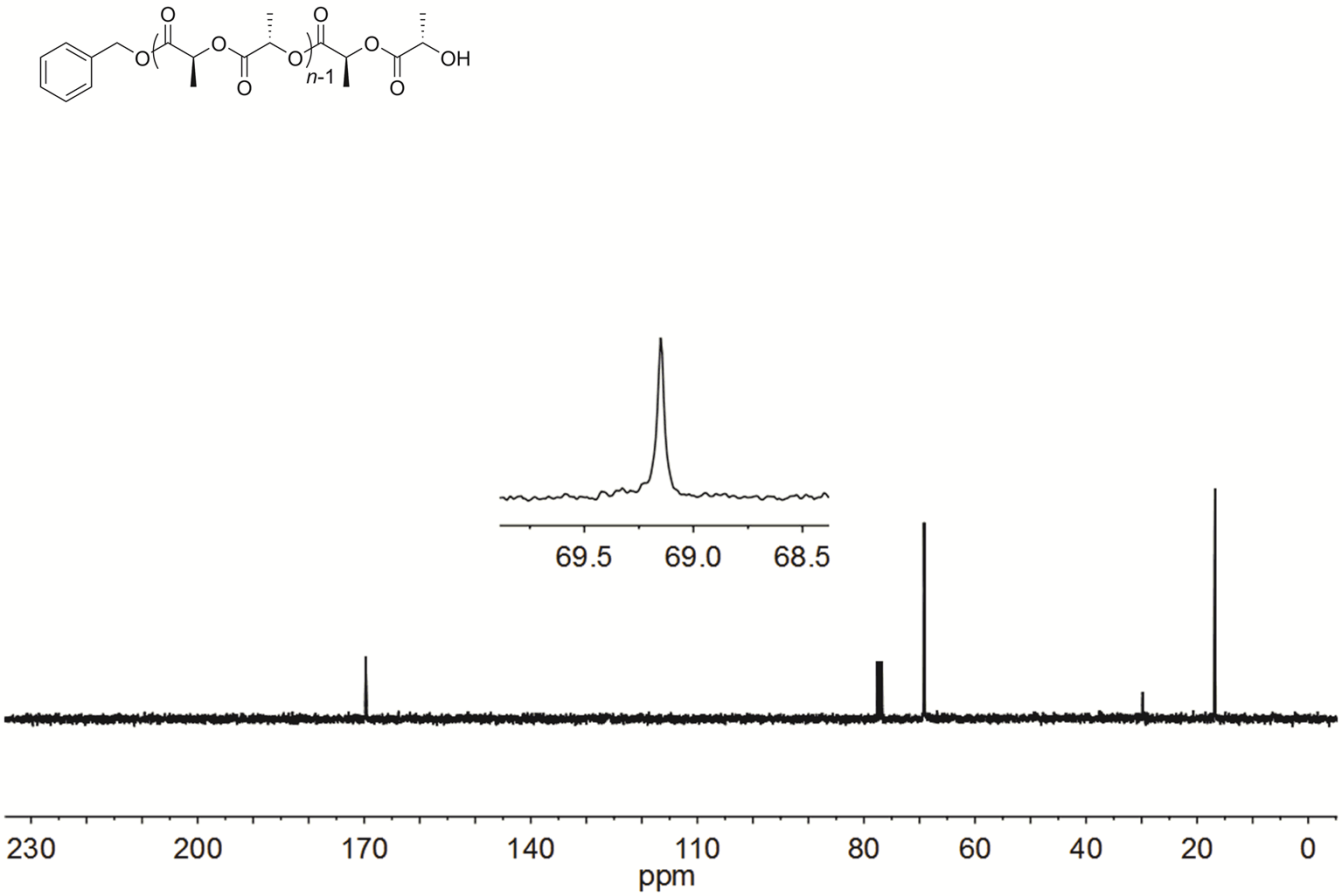


Figure S5. MALDI-ToF MS spectrum of the obtained PLLA ([L-LA]$_0$/ [BnOH]$_0$/ [**Sq1**]$_0$/ [(–)-sparteine]$_0$ = 20/ 1/ 1/ 1, CH_2Cl_2, rt, [L-LA]$_0$ = 0.7 mol L^{-1}). As shown in figure, two main series of peaks were observed with molecular formula of molar mass M=108.06 (M_w of BnOH) + n ×144.04(M_w of L-LA) + 39 (K^+) or M= 108.06 (M_w of BnOH) + n ×144.04(M_w of L-LA) + 23 (Na^+). The mass differences between two adjacent peaks precisely typify the molar mass of L-LA (M = 144.04).

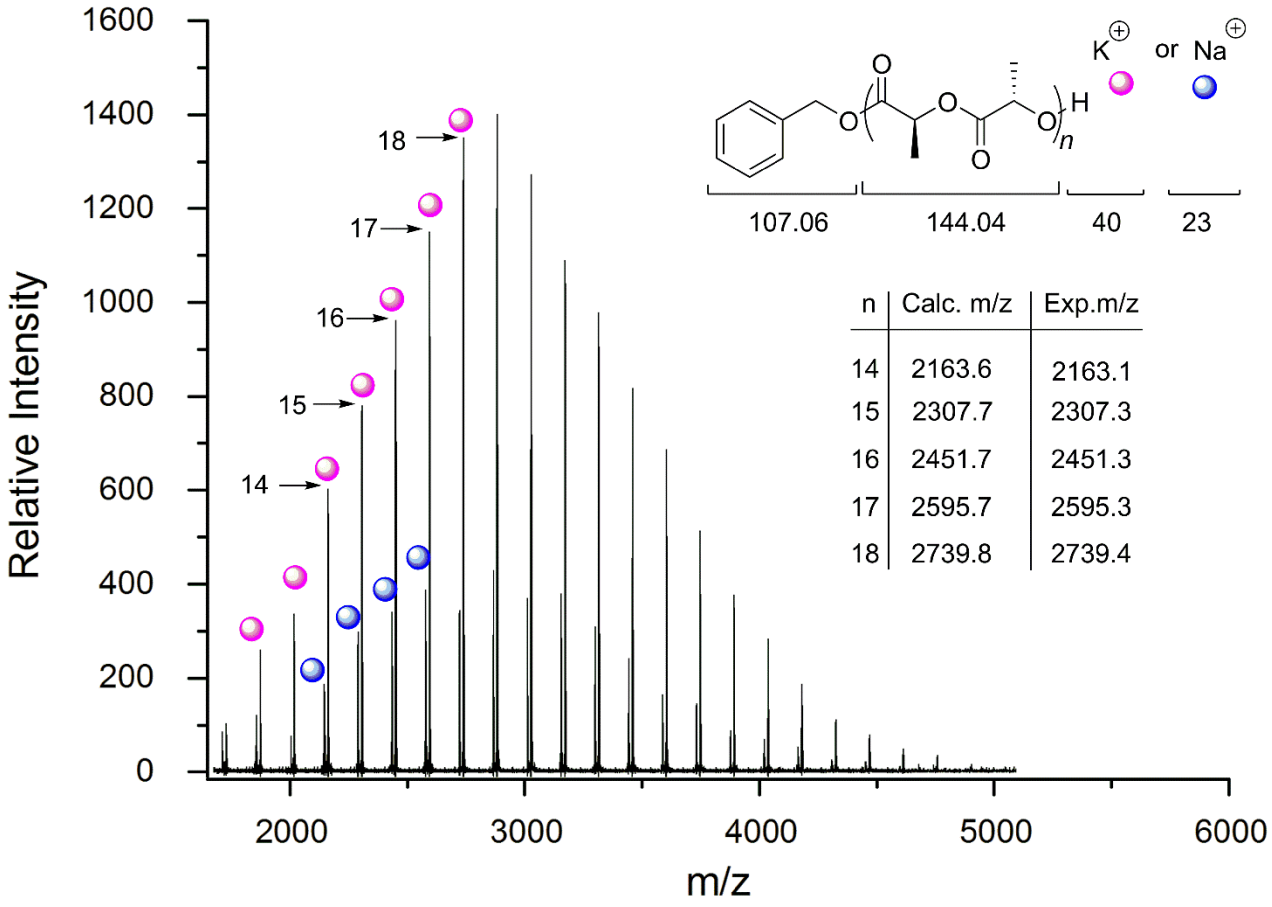


Figure S6. Size exclusion chromatography (SEC) traces for the polylactide samples: (a) obtained after the first feed of L-lactide (L-LA) (CH_2Cl_2, 25 °C, $[L\text{-LA}]_0$/ $[BnOH]_0$/ $[\mathbf{Sq1}]_0$/ $[(–)\text{-sparteine}]_0$ = 50/ 1/ 2.5/ 2.5, $[L\text{-LA}]_0$ = 1.0 mol L^{-1}) and (b) after a second feed of 50 equiv L-Lactide.

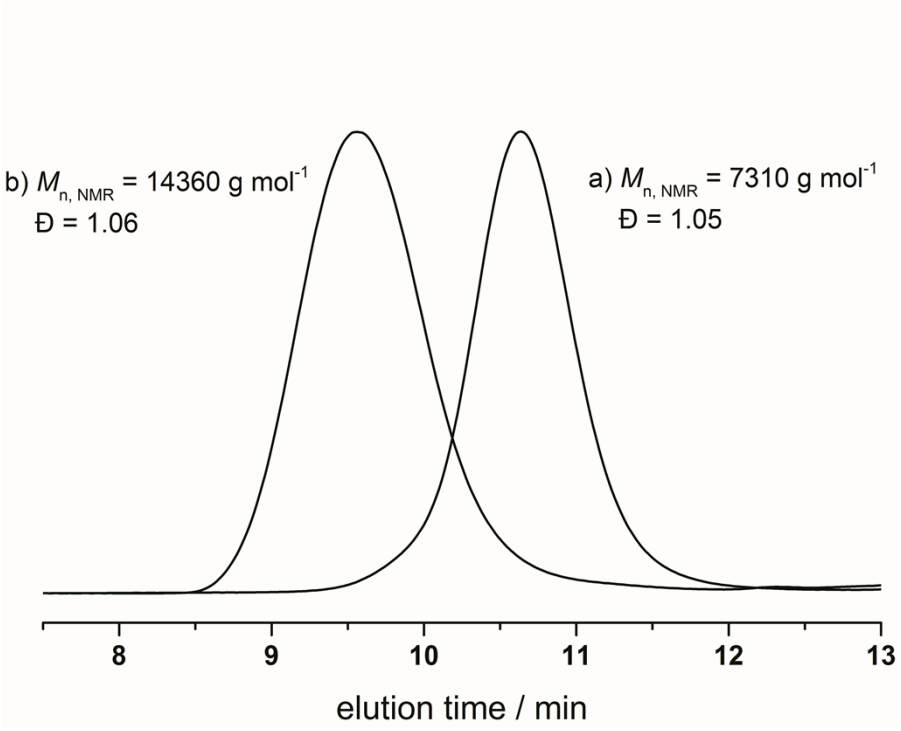


Figure S7. ^{1}H NMR spectrum of the poly(trimethylene carbonate)-*block*-poly(L-lactide).

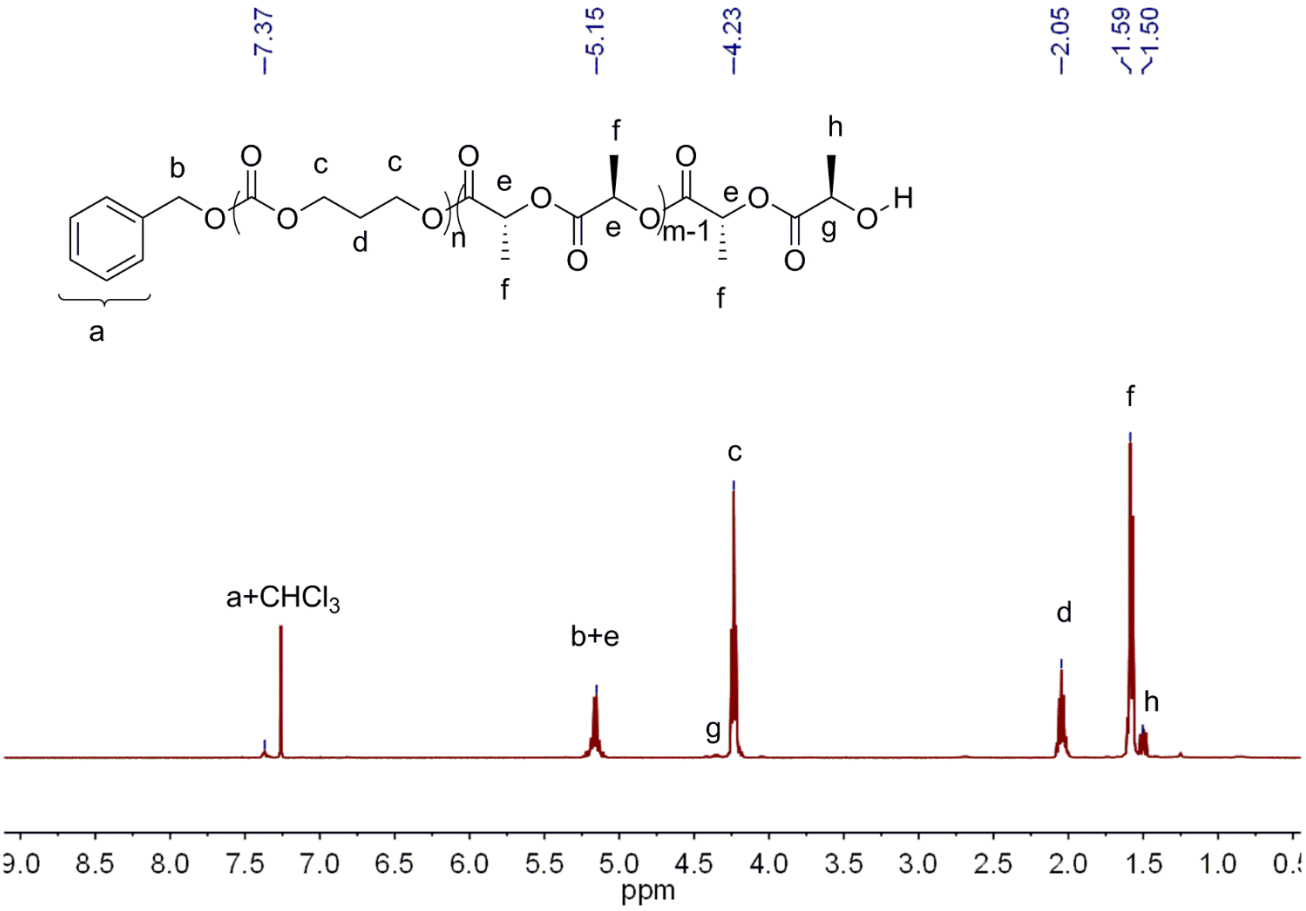


Figure S8 . ^{13}C NMR spectrum of the poly(trimethylene carbonate)-*block*-poly(L-lactide).

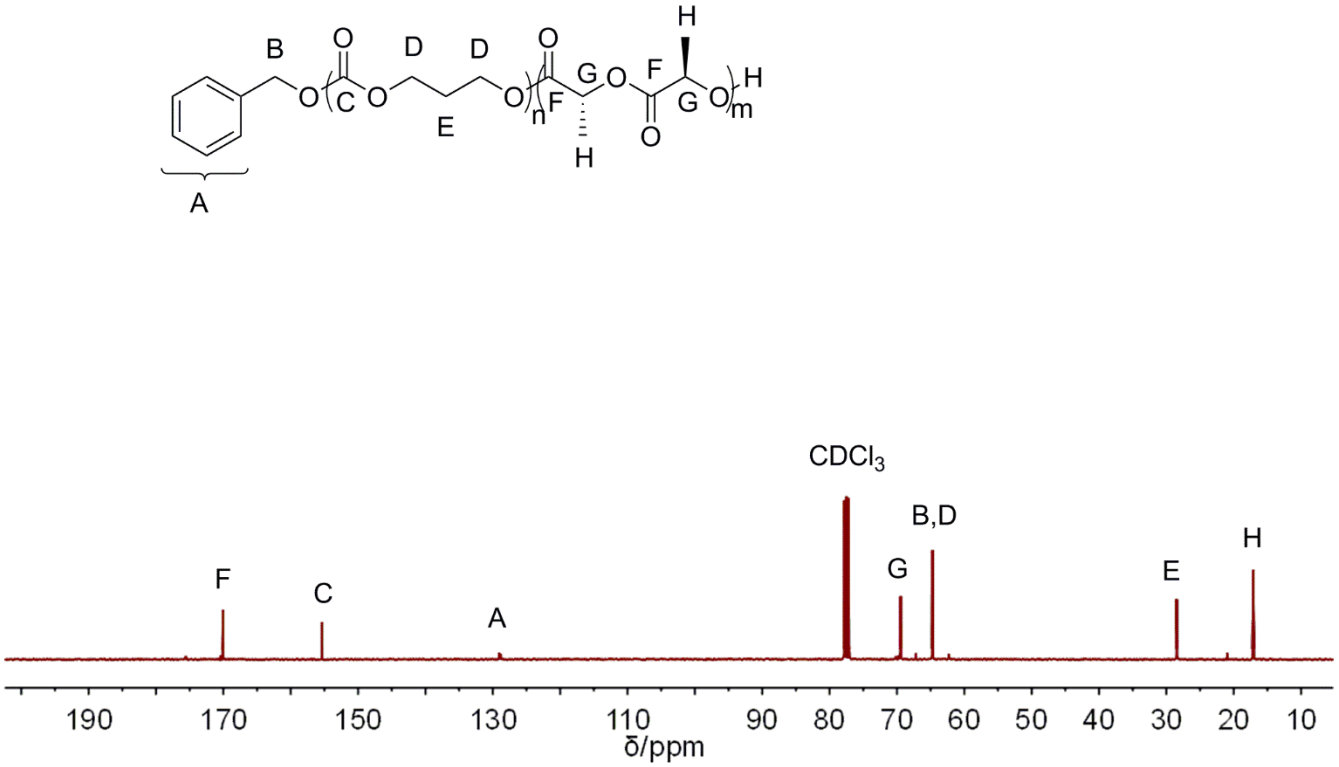


Figure S9. Size exclusion chromatography (SEC) traces for the poly(trimethylene carbonate)-block-poly(L-lactide): (a) obtained after the first feed of trimethylene carbonate (TMC) (CH2Cl2, 25 °C, $[TMC]_0$/ $[BnOH]_0$/ $[Sq1]_0$/ $[(–)\text{-sparteine}]_0$ = 30/ 1/ 1.5/ 1.5, $[TMC]_0$ = 1.0 mol L^{-1}) and (b) after a second feed of 30 equiv L-lactide.

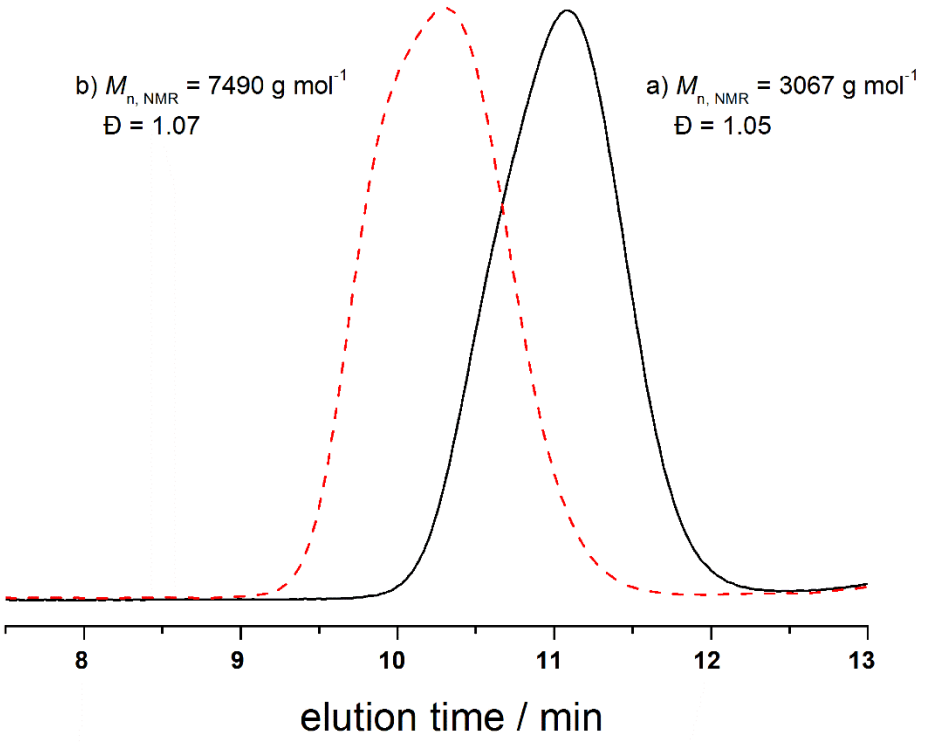


Figure S10. ^{1}H NMR spectrum of benzyl alcohol, (–)-sparteine and their 1:1 complex in $CDCl_3$ at room termpetrue.

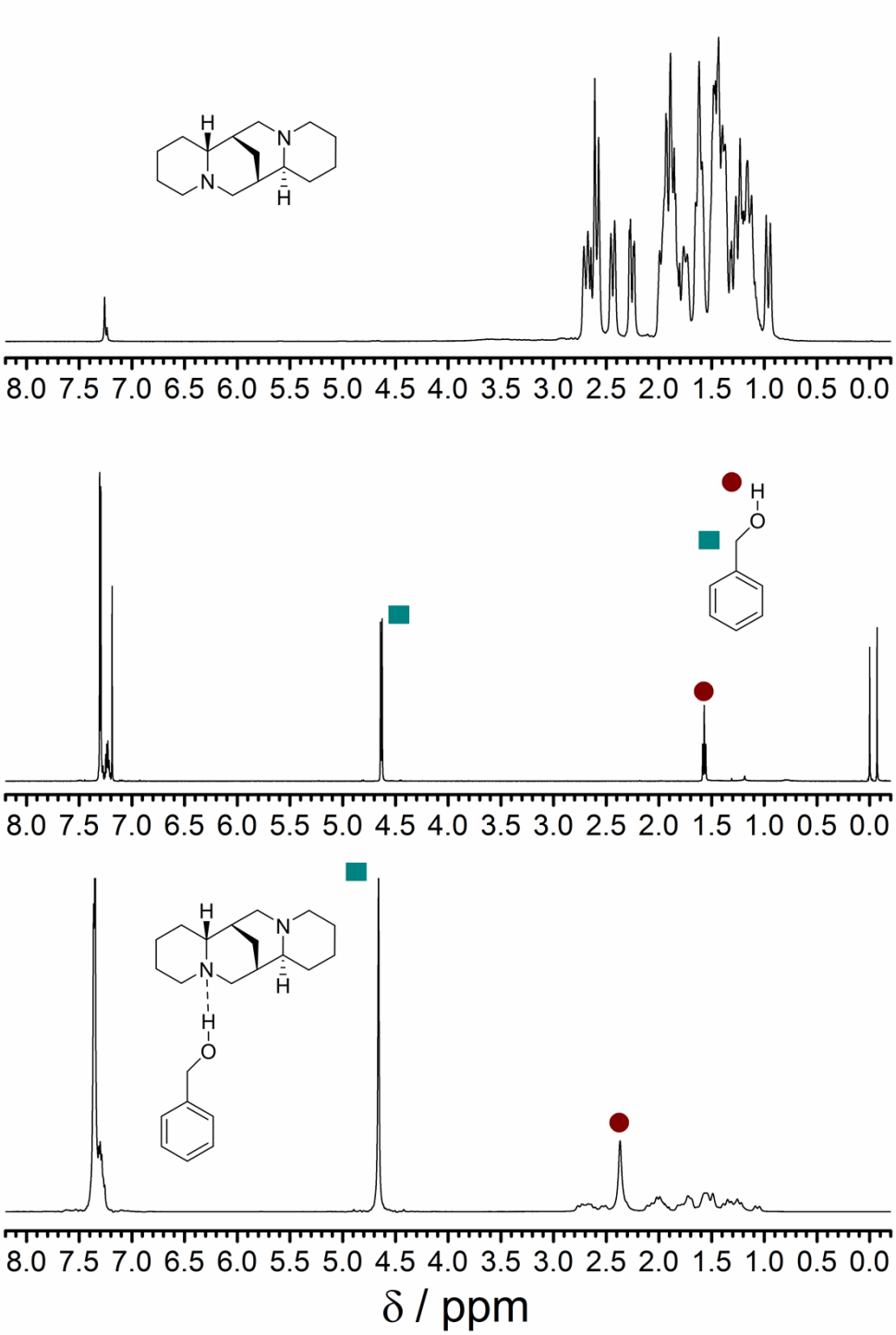
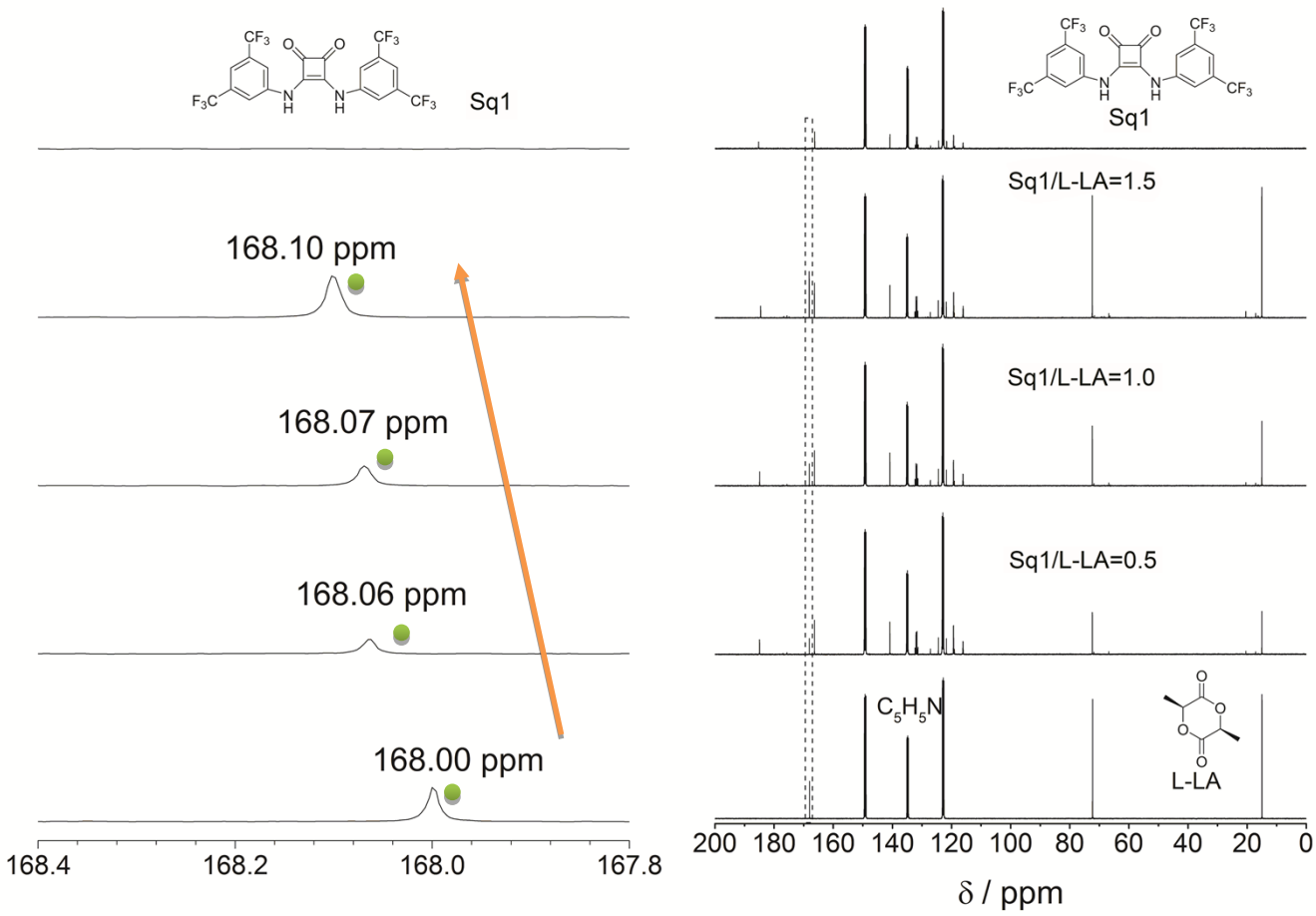
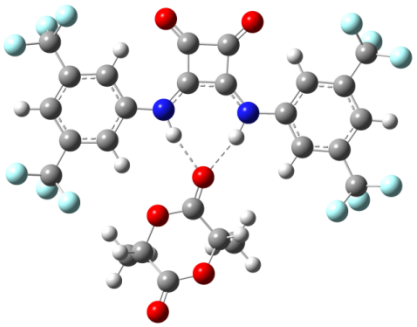


Figure S11. Chemical shifts of carbonyl carbon in the ^{13}C NMR spectrum observed by titration of L-LA with squaramide **Sq1** in C_5D_5N.



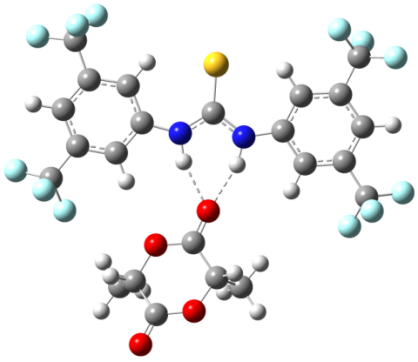
Details of computational studies

Calculations were carried out with the Gaussian ’09 [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 ε = 8.93 (dichloromethane) using IEF-PCM as implemented in Gaussian 09.



H-bonding complex between **Sq1** and L-lactide

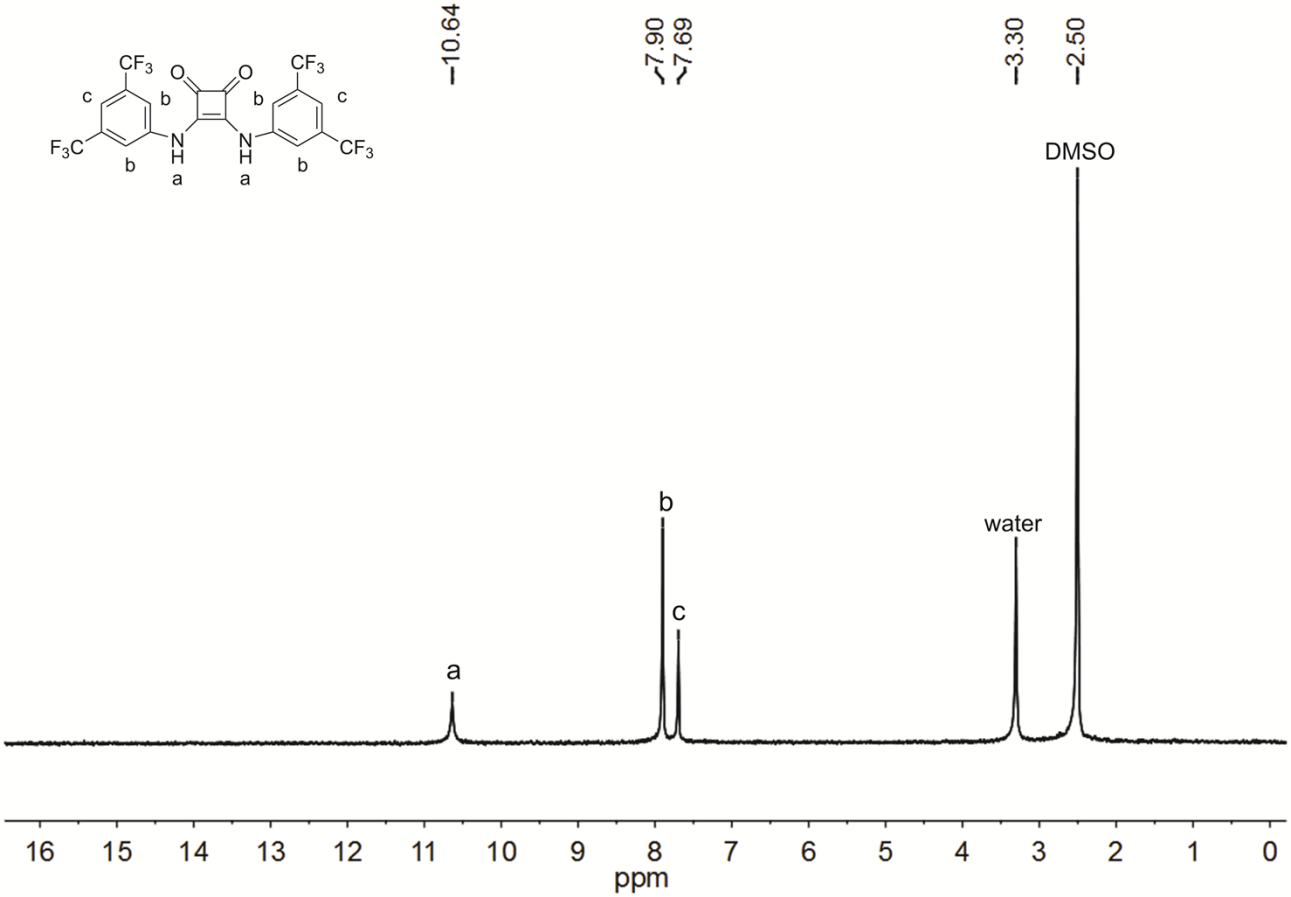
Distance N-H…O=C in **Sq1**• L-lactide = 1.945 Å and 1.977 Å .

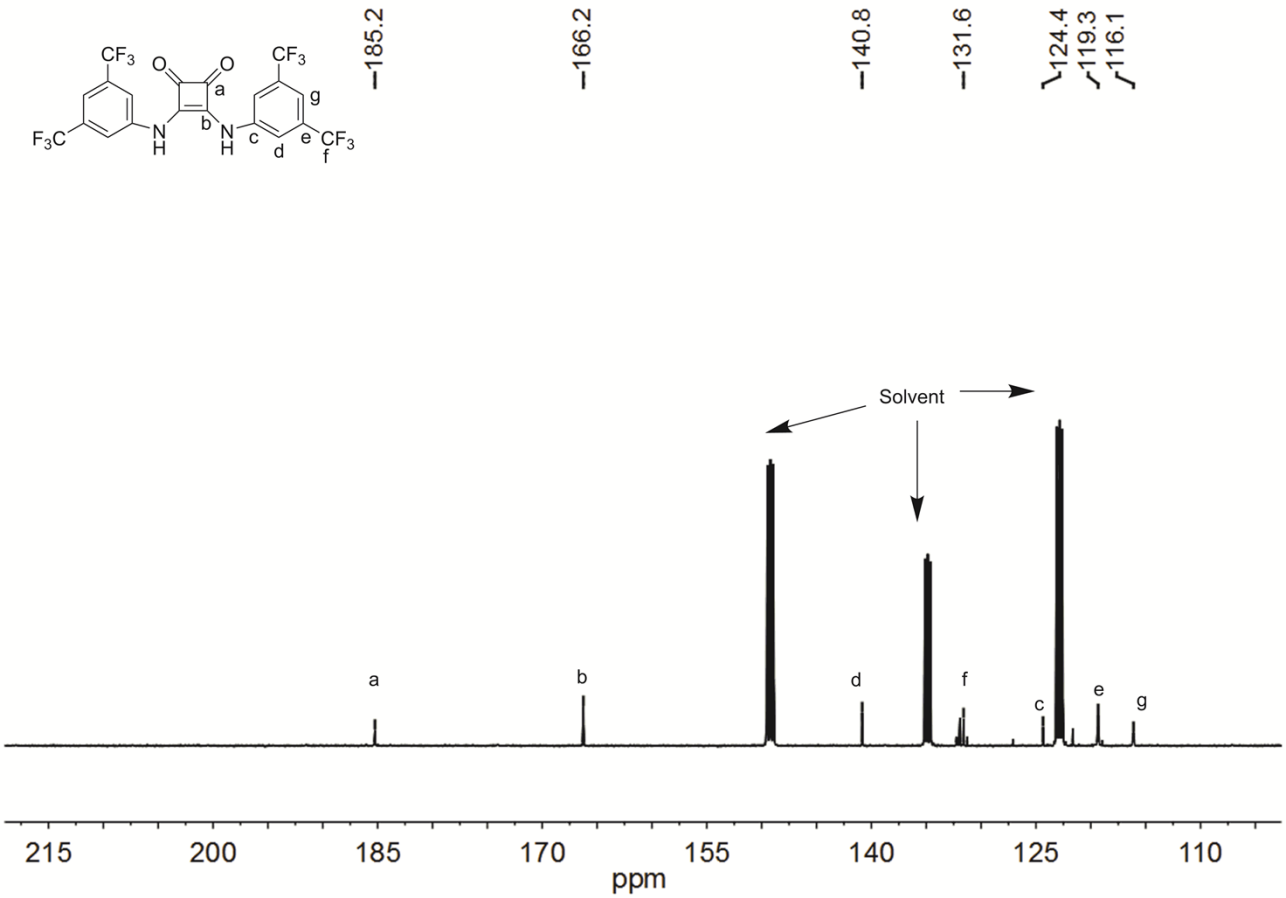


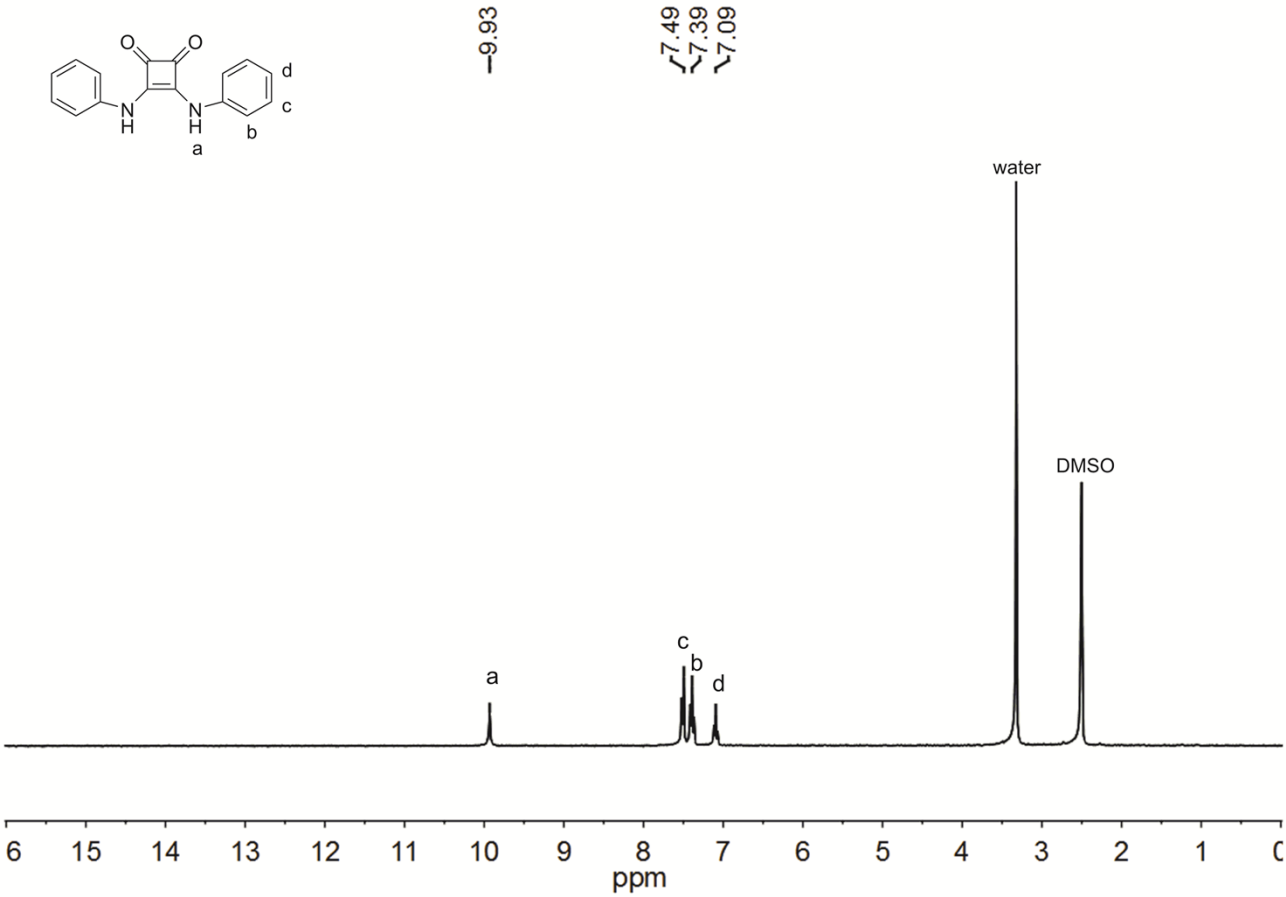
H-bonding complex between **TU** and L-lactide

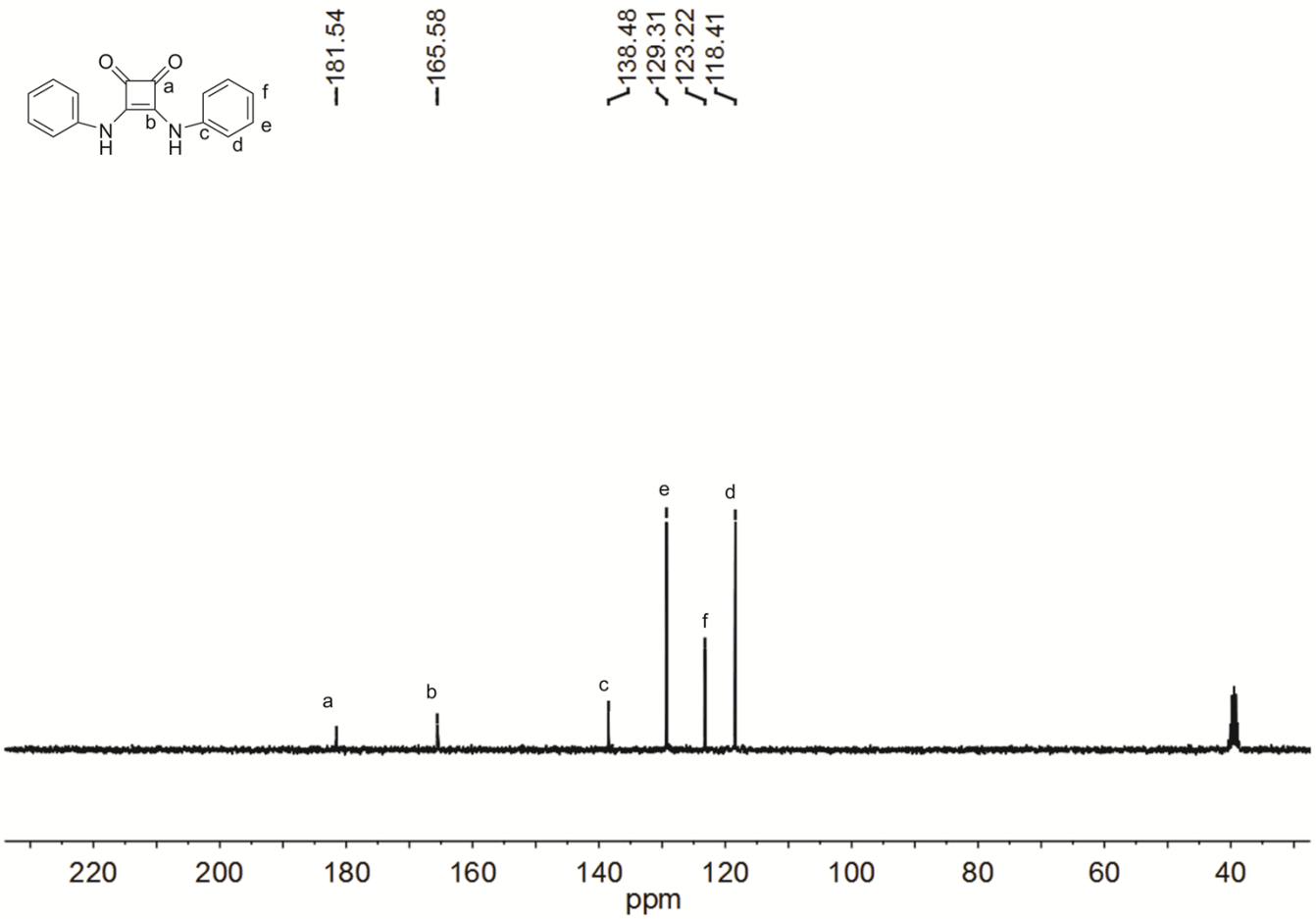
Distance N-H…O=C in **TU**• L-lactide = 2.046 Å and 1.982 Å .

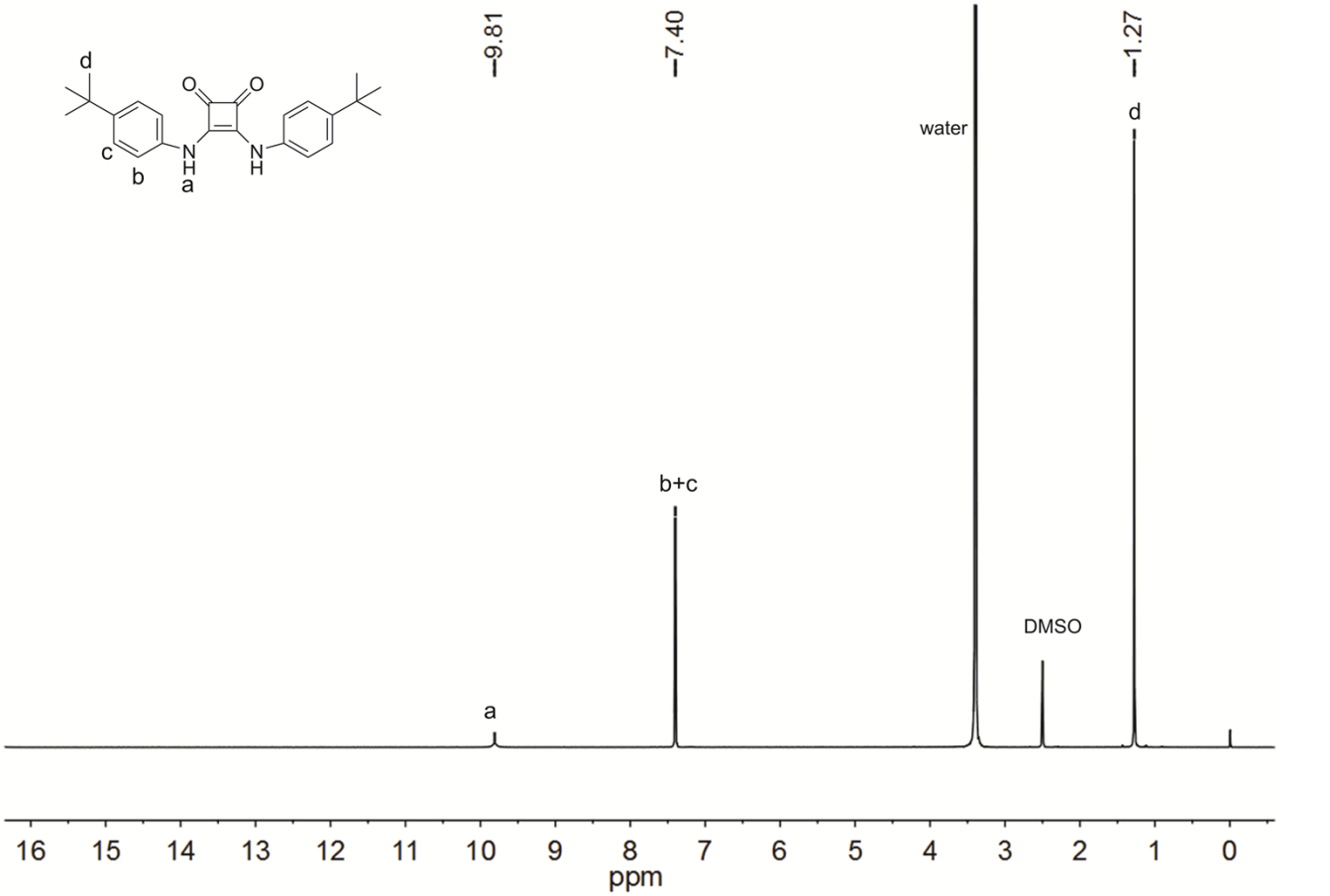
^{1}H and ^{13}C NMR of catalysts

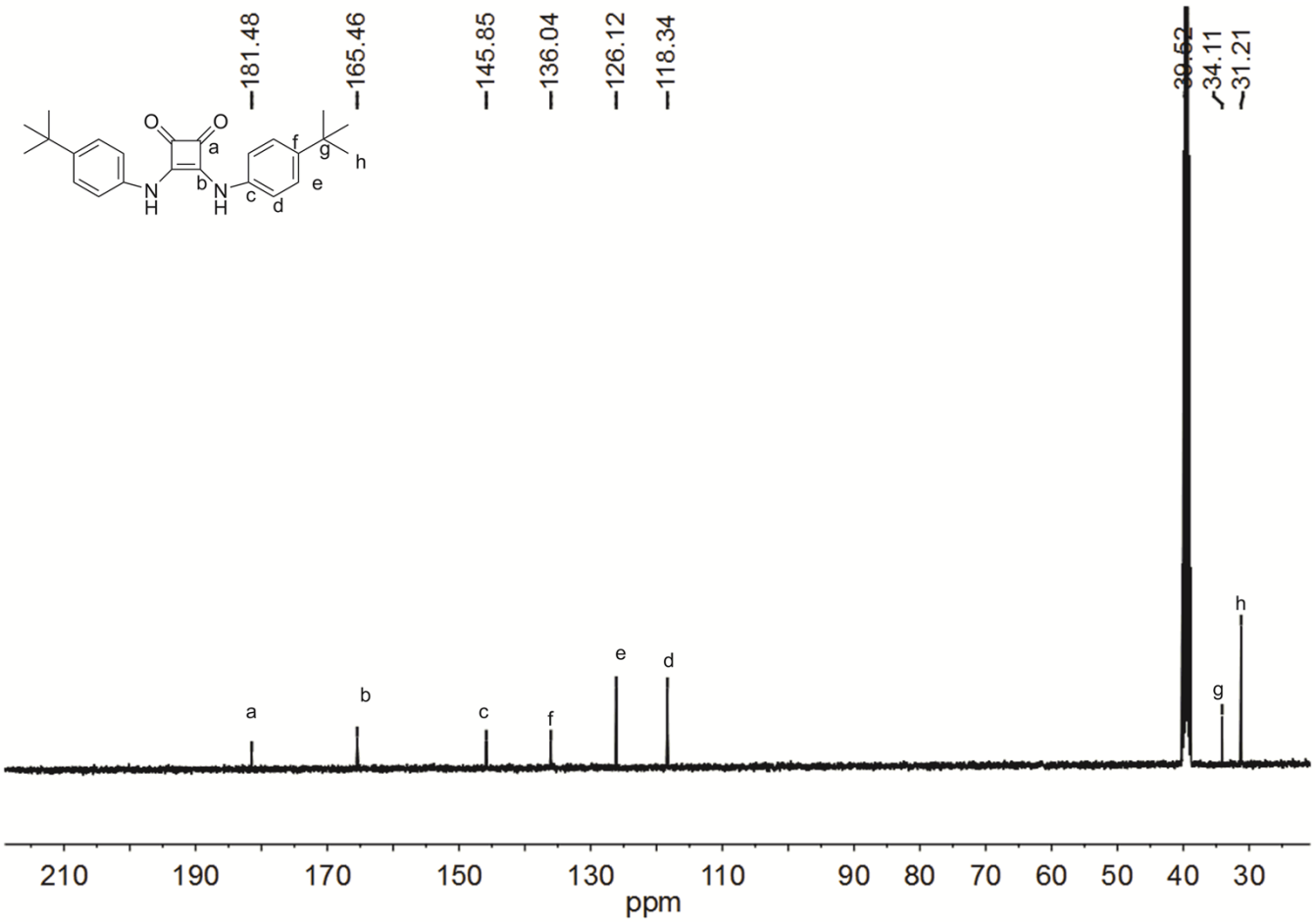


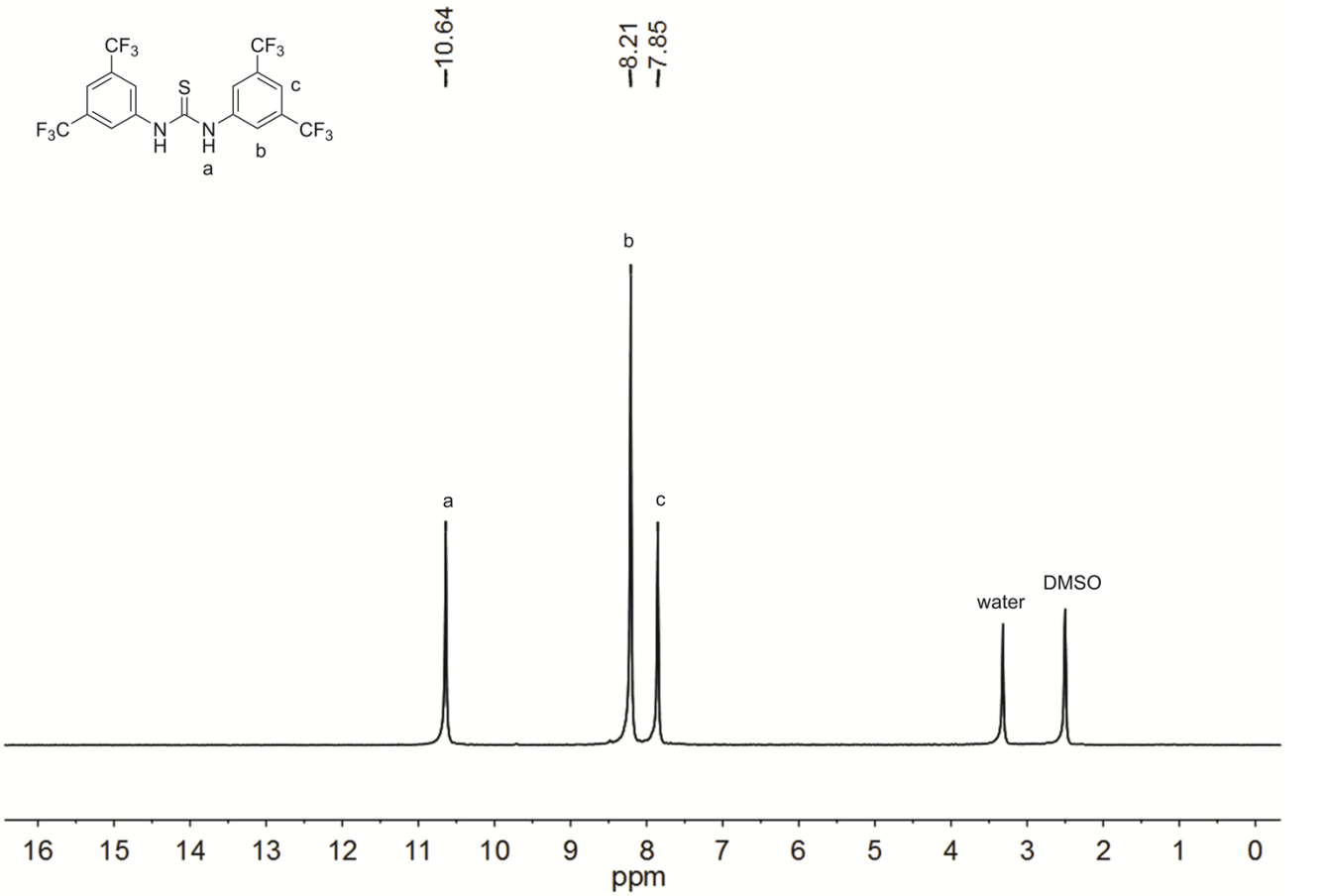


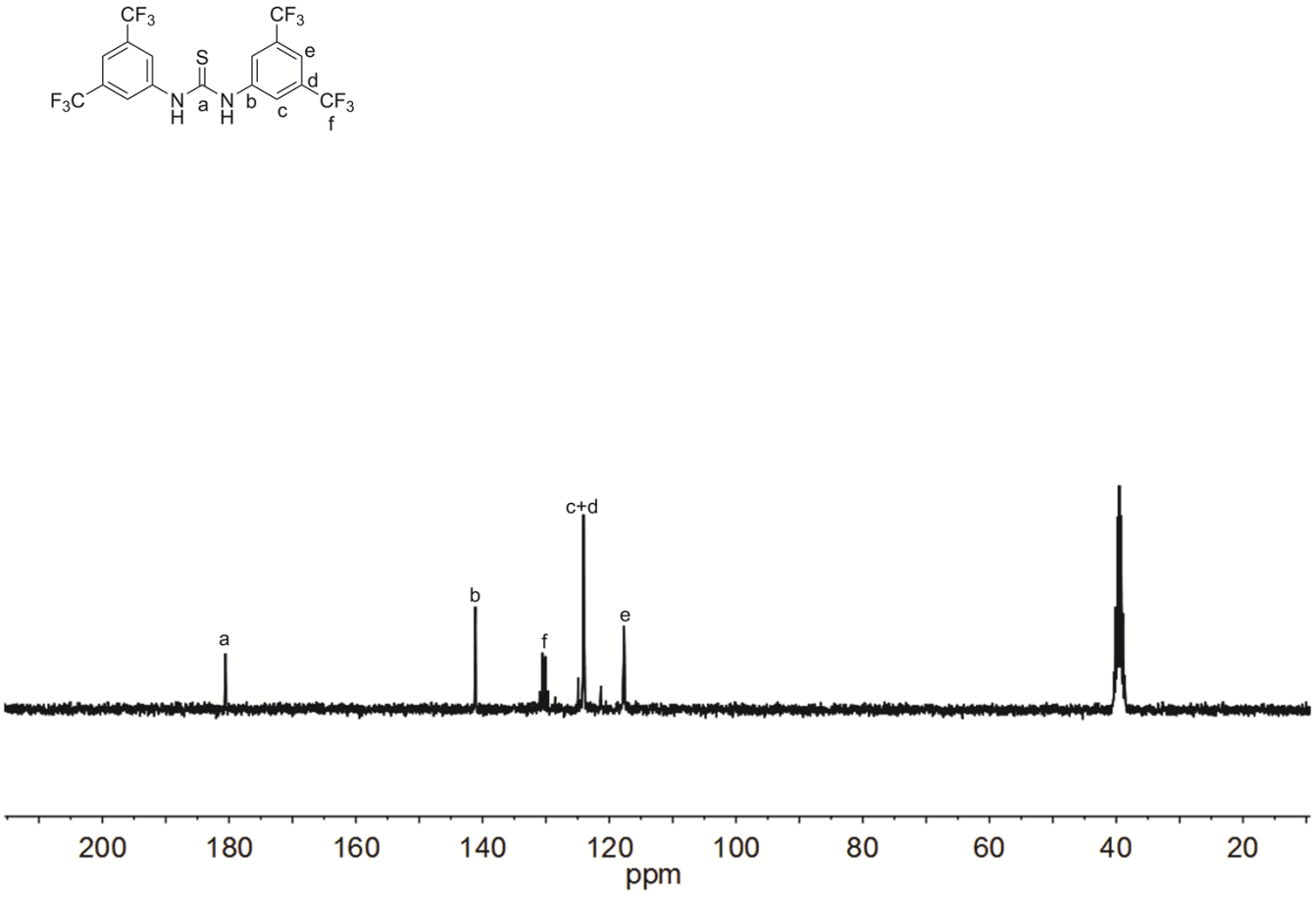

9.93
7.49
7.39
7.09
water
DMSO
a
c
b
d
ppm


181.54
165.58
138.48
129.31
123.22
118.41
a
b
c
d
e
f
ppm


d
O
O
c
N
H
b
a
N
H
9.81
7.40
water
1.27
d
b+c
DMSO
a
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


181.48
165.46
145.85
136.04
126.12
118.34
39.62
34.11
31.21
O
O
a
f
g
h
b
N
H
N
H
c
d
e
a
b
c
f
e
d
g
h
210
190
170
150
130
110
90
80
70
60
50
40
30
ppm


10.64
8.21
7.85
a
b
c
water
DMSO
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
ppm


a
b
c+d
e
f
200 180 160 140 120 100 80 60 40 20
ppm

References

[1] H. LIU, C. Tomooka, S. Xu, B. Yerxa, R. Sullivan, Y. XIONG, H. Moore, *Org. Syn.* **1999**, *76*, 189-198.

[2] A. Rostami, A. Colin, X. Y. Li, M. G. Chudzinski, A. J. Lough, M. S. Taylor, *J. Org. Chem.* **2010**, *75*, 3983-3992.

[3] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. akrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.