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Selective, Green Synthesis of Six-Membered Cyclic Carbonates by Lipase-Catalyzed Chemospecific Transesterification of Diols with Dimethyl Carbonate

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Abstract: A facile and green synthesis of six-membered cyclic carbonates, the potential monomers for isocyanate-free polyurethanes and polycarbonates, was achieved by transesterification of diols with dimethyl carbonate catalyzed by immobilized *Candida antarctica* lipase B, Novozym®435, followed by thermal cyclization in a solvent-free medium. The difference in the chemospecificity of the lipase for the primary, secondary and tertiary alcohols as acyl acceptors was utilized to obtain a highly chemoselective synthesis of the cyclic carbonate in high yield. In the lipase-catalyzed reaction with diols, the product contained almost equal proportions of mono- and di-carbonates with 1,3-propanediol having two primary alcohols, a higher proportion of mono-carbonate with 1,3-butanediol having a primary and a secondary alcohol, and mainly mono-carbonate with 3-methyl-1,3-butanediol having a primary and a tertiary alcohol. The chemospecificity of cyclic carbonates formed by thermal treatment at 90 °C was closely related to the proportion of mono-carbonate. The yield of cyclic carbonate was 99.3% with 3-methyl-1,3-butanediol, 85.5% with 1,3-butanediol, and 43.2% with 1,3-propanediol.

Keywords: 1,3-butanediol; chemoselectivity; 3-methyl-1,3-butanediol transesterification; 1,3-propanediol; thermal cyclization

Cyclic carbonates have attracted attention in recent years as potential monomers for the production of polyurethanes and polycarbonates through a non-toxic, phosgene-free route.[1–6] These aliphatic polymers have a broad range of traditional applications, for example, in engineering, optical devices, seatings, seals, coatings and high performance adhesives, and are even expected to find use in biomedicine due to their features of biocompatibility and low toxicity.[7–10] Carbon dioxide, dialkyl carbonates, diphenyl carbonate, and phosgene derivatives have usually been used as sources of carbonate groups in the cyclic carbonates. One of the commonly reported routes for the synthesis of cyclic carbonates is the transesterification of polyols with a dialkyl carbonate in a metal-[11] or enzyme (lipase)-catalyzed reaction.[12,13] The majority of the studies so far report on the synthesis of five-membered carbonates,[1–4,14] while the six-membered cyclic carbonate is the preferred structure for use in the ring opening polymerization (ROP) process.[11,15,16]

The lipase-catalyzed synthesis of the six-membered cyclic trimethylene carbonate from 1,3-diol and dimethyl or diethyl carbonate has been achieved earlier in a solvent system of acetonitrile and toluene (4:1, v/v) using a very high concentration (900% w/w of the diol) of the immobilized *Candida antarctica* lipase B (Novozym®435, N435), however with only moderate yield (53%) and low productivity.[13] We have recently reported the synthesis of six-membered cyclic carbonates with functional groups using the lipase B-mediated reaction between trimethylolpropane (TMP) and dialkyl carbonate in a solvent-free medium.[17] It was shown that the lipase catalyzes mainly the formation of linear carbonates and their conversion to cyclic carbonates is promoted by increased temperature. It was also shown that the use of hydrophobic solvents in the reaction medium increased the proportion of cyclic carbonates formed.[18] The equal reactivity of the lipase for the primary alcohol groups in the diols and polyols investigated so far poses a limitation in terms of the formation of unwanted side products (e.g., di- and higher carbonates), hence resulting in lower product yield and atom efficiency.

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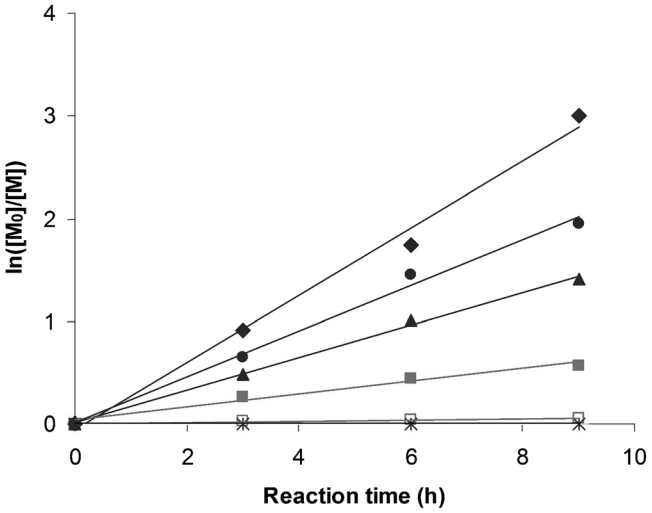


Figure 1. First order plot of the rate of the lipase-catalyzed reaction of DMC with 1-butanol (◆), 2-butanol (■) and *tert*-butanol (∗), respectively; and of the reaction with 1-butanol (▲) and 2-butanol (□) in a mixture of 1-/2-butanol; and 1-butanol (●) in a mixture of 1-/*tert*-butanol.

In the present study, we demonstrate that the differential specificity of the lipase for primary, secondary and tertiary alcohol groups in the substrate can be used to increase the chemoselectivity of the production and yield of six-membered cyclic carbonates from diols and dimethyl carbonate.

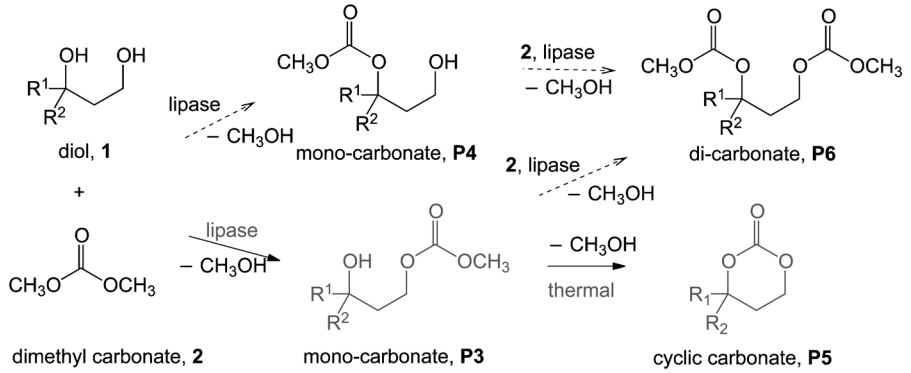
Reaction kinetics of lipase-catalyzed reactions of 1-, 2- and tert-butanol with dimethyl carbonate (DMC): To start with, the rate of lipase-catalyzed reaction between DMC and primary, secondary, and tertiary mono-ols (1-, 2- and *tert*-butanol), individually and in mixture, was determined. Figure 1 shows a 1st order plot of rate for the different reactions. As expected, the rates of the reactions with individual alcohols were in the order: primary > secondary > tertiary alcohol, and in accordance with the earlier reports on the transesterification of various alcohols with acyl donors like fatty acids.[19,20] The rate constant, k_d for 1-butanol was 0.29, which was about 4 times higher than that of 2-butanol (0.075) (Table 1), while no reaction was observed between *tert*-butanol and DMC. In the reaction with a mixture of two alcohols, the reaction rate for 1-butanol was decreased to 0.168, possibly due to inhibition by increased total substrate concentration and the competing reaction, that for 2-butanol was reduced ten-fold as a result of which the difference in the reaction rate between the primary and secondary alcohols was increased to 24 -old. In the reaction with a mixture of 1- and *tert*-butanol, the k_d for the primary alcohol was only slightly reduced which could be attributed only to the substrate inhibition effect since there was no competing reaction.

Kinetics of the lipase-catalyzed reactions of 1,3-propanediol (1,3-PDO), 1,3-butanediol (1,3-BDO), and 3-methyl-1,3-butanediol (3-Me-1,3-BDO) with DMC: Scheme 1 shows the various intermediates and

Table 1. Kinetics of the reaction of 1-, 2-, and *tert*-butanol with DMC catalyzed by Novozym®435 at 60 °C.

Run	Substrate	k_d	$t_{1/2}$ [h]	In mixture of 1- and 2-butanol		In mixture of 1- and *tert*-butanol	
				k_d	$t_{1/2}$	k_d	$t_{1/2}$
1	1-butanol	0.290	2.4	0.168	4.1	0.243	2.9
2	2-butanol	0.075	9.3	0.0071	98.1	NA[a]	NA
3	*tert*-butanol	0	NA	NA	NA	0	NA

[a] NA: not applicable.



1,3-PDO (R^1, R^2 = H), 1,3-BDO (R^1 = H, R^2 = CH_3), 3-Me-1,3-BDO (R^1, R^2 = CH_3)

Scheme 1. Reaction pathway for production of cyclic carbonates by lipase-catalyzed reaction and thermal cyclization.

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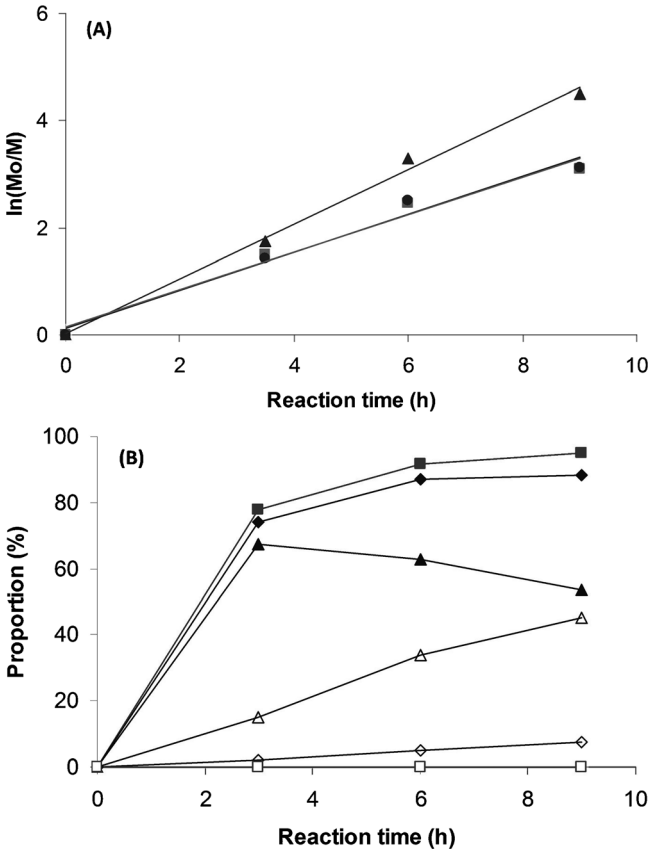

Figure 2. (**A**) First order plot of the reaction rate of 1,3-PDO (▲), 1,3-BDO (●), and 3-Me-1,3-BDO (■) with DMC catalyzed by N435 at 60 °C. (**B**) Proportion of products formed, **P3**+**P5** (▲) and **P6** (△) from 1,3-PDO; **P3**+**P5** (◆) and **P6** (◇) from 1,3-BDO; **P3**+**P5** (■) and P6 (□) from 3-Me-1,3-BDO in the reactions.

products formed in a reaction between a diol and dimethyl carbonate. The desired cyclic carbonate product (**P5**) can be produced only *via* mono-carbonate (**P3**); formation of di-carbonate (**P6**) prevents the formation of **P5**, and hence should be minimized for producing the cyclic carbonate at high yield. From the results obtained with mono-ols, it could be expected that the selectivity for mono-carbonate formation from a diol could be enhanced by introducing substitutes on one of the two alcohol groups. As a next step, the reaction rates for N435-catalyszd esterification of the diols 1,3-PDO, 1,3-BDO and 3-Me-1,3-BDO, respectively, with DMC were compared

Table 2. Kinetics of the reaction of 1,3-diols with DMC catalyzed by Novozym®435 at 60 °C.

Run	Substrate	k_d	$t_{1/2}$ [h]
1	1,3-propanediol	0.550	1.3
2	1,3-butanediol	0.417	1.7
3	3-methyl-1,3-butanediol	0.409	1.7

(Figure 2 and Table 2). All the reaction rates were higher than that for the mono-ol, and over 80% conversion took place within the initial 3 h for all the substrates. The highest rate of $k_d = 0.550$ was obtained in the reaction with 1,3-PDO, with 99% conversion in 7 h. The reaction profile showed the formation of over 60% mono-carbonate **P3** within 3 h, which decreased with time while the proportion of the undesired di-carbonate increased to about 40% at 9 h (Figure 2, **B**). The other possible mono-carbonate **P4** was not observed in the chromatogram [Figure 3, (**B1**)]. In the case of 1,3-BDO, 96% substrate conversion was obtained at 9 h ($k_d = 0.417$) and the product contained only 9.5% of di-carbonate. On the other hand, the reaction rate was only slightly lower with 3-Me-1,3-BDO with 95% conversion at 9 h ($k_d = 0.409$) but without any di-carbonate formation. These results showing slow and no reaction with secondary and tertiary alcohols, respectively, using N435, were in agreement with the reactions with the mono-ols.

Synthesis of cyclic carbonates by lipase-catalyzed transesterification reaction and thermal cyclization of mono-carbonate: As in our earlier reports,[17,18] the lipase-catalyzed reaction was followed by a thermal treatment step in the presence of molecular sieves only to promote the cyclization of mono-carbonates. Table 3 summarizes the results of reactions between 1 g substrates (1,3-PDO, 1,3-BDO and 3-Me-1,3-BDO, respectively) and 10 mL DMC using 10% (w/w) N435 for 7 h reaction at 60 °C, and the thermal reaction at 90 °C. It is clear from Table 3 and Figure 3 (**B**) that the resulting content of cyclic carbonate in the final product was dependent on the proportion of mono-carbonate formed in the enzymatic reaction.

In the case of the 1,3-PDO, the di-carbonate (**P6**) content remained almost unchanged at about 43% during the thermal step, while the cyclic carbonate (**P5**) content increased from 5% to 43% after 40 h of thermal treatment [Table 3 (Run 1), Figure 3 (**A2**)]. In the 1,3-BDO reaction, 85.5% cyclic carbonate was obtained from the product of the lipase reaction containing 86.3% mono- and 3.3% cyclic carbonate [Table 3b (Run 2)]. A highly selective synthesis of cyclic carbonate (99.3%, **P5**) with a small amount of residual mono-carbonate (<1%, **P3**) was achieved from 3-Me-1,3-BDO having primary and tertiary alcohols through lipase-mediated and thermal reaction [Table 3 (Run 3), Figure 3 (**C2**)]. The thermal reaction was focused on an equilibrium shift to cyclic carbonate, **P5**, which has minimum content of ester ($-CO-OCH_3$), and this was achieved by continuous removal of the resulting methanol by free evaporation, which prevented the reverse reaction from taking place. The rate of cyclization decreased in the order of primary > secondary > tertiary alcohol.

In conclusion, the syntheses of various six-membered cyclic carbonates were achieved at high yields

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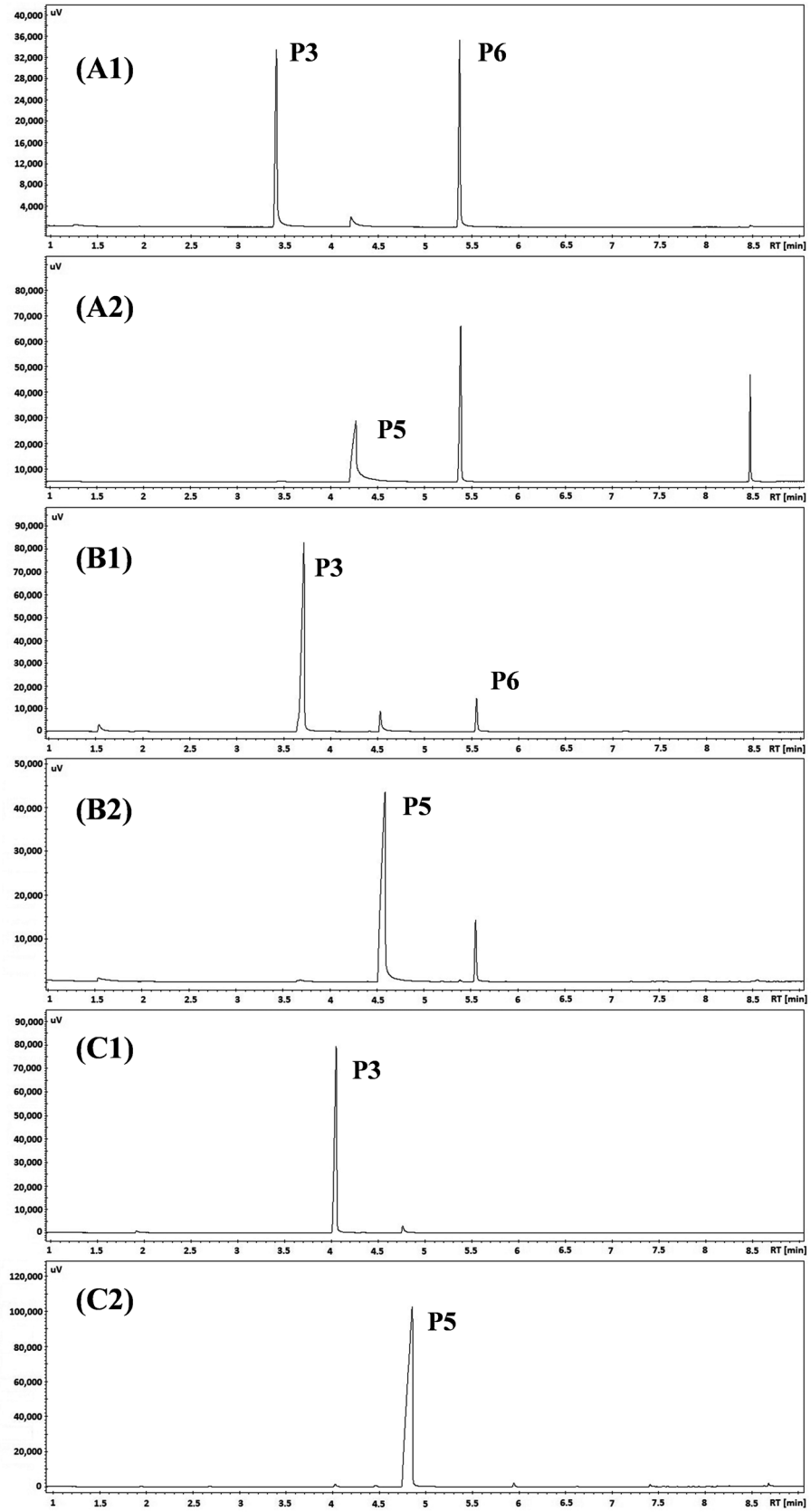

Figure 3. Chromatograms showing products in Table 3 obtained from (1) lipase-catalyzed reaction of (**A**) 1,3-PDO, (**B**) 1,3-BDO, and (**C**) 3-Me-1,3-BDO, respectively, with DMC and (2) thermal cyclization.

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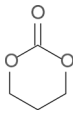
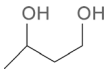
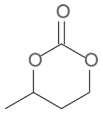
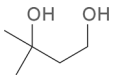
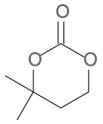
Table 3. Summary of synthesis of cyclic carbonates by a process involving lipase-catalyzed transesterification and thermal cyclization.

Run	Substrate	Lipase reaction[a]					Thermal reaction at 90 °C[b]		
		Time [h]	Product [%]			Conversion [%]	Time [h]	Cyclic carbonate	
			P3	**P5**	**P6**			Structure	**P5** [%]
1		3	57.7	1.4	6.2	65.4	6		8.7
		5	55.8	6.9	34.3	97.0	15		24.2
		7	50.7	5.2	42.9	98.8	40		43.2
2		3	75.7	1.3	2.4	79.4	6		6.8
		5	85.5	2.4	5.5	93.4	30		73.3
		7	86.3	3.3	8.7	98.3	48		85.5
3		3	78.0	1.5	0	79.5	24		10.8
		5	92.2	2.6	0	94.9	48		95.2
		7	94.8	4	0	98.8	65		99.3

[a] 1 g substrates (1,3-PDO, 1,3-BDO and 3-Me-1,3-BDO, respectively) were reacted with 15 mL DMC at 60 °C.
[b] Thermal reactions were carried out using 0.2 g product obtained from lipase catalysed reactions with each substrate.

by a lipase-catalyzed reaction between diols and DMC combined with thermal cyclization without using any catalyst. A strategy to be considered for achieving higher selectivity would be to minimize the proportion of di-carbonate, by utilizing the differences in the specificity of the lipase for primary, secondary and tertiary alcohol groups. The highest chemoselectivity for the synthesis of a cyclic carbonate was obtained from reaction between a diol having primary and tertiary alcohol groups, and DMC followed by intra-molecular reaction of the carbonate with the hydroxy group at high temperature. These results are a significant improvement over the earlier reports on the synthesis of six-membered cyclic carbonate.[12,13,17,21] Furthermore, the reaction did not involve any solvents; the DMC used in excess served also as the solvent, and is easily recovered by distillation and recycled.

Experimental Section

Lipase-Catalyzed Reaction and Thermal Cyclization

Novozym®435 (N435) was a generous gift from Novozymes A/S (Bagsvaerd, Denmark). Dimethyl carbonate (97%, DMC), 1,3-propanediol, (±)-1,3-butanediol (>99%), 3-methyl-1,3-butanediol (>97%), 1-butanol, 2-butanol, *tert*-butanol, chloroform-*d* ($CDCl_3$) and molecular sieves (4 Å) were purchased from Sigma–Aldrich. HPLC grade acetonitrile was purchased from Merck (Germany). All chemicals were used without further treatment. To investigate the reactivity of lipase with different alcohol groups, 1.5 mmol substrates, for example, 111 mg mono-ols (1-, 2- and *tert*-butanol, respectively), and diols (114.2 mg 1,3-PDO, 135.2 mg 1,3-BDO, and 156.23 mg 3-Me-1,3-BDO, respectively) were dissolved in 1.5 mL (17.8 mmol) DMC in a 5 mL vial by shaking in a thermomixer (MKR 13, HLC Biotech, Germany) at 700 rpm and 60 °C. The reactions were started by addition of 10 mg N435 along with 200 mg molecular sieves. Aliquots were withdrawn at different time intervals for analysis of the reaction components.

The rate constant (k_d) of first order reaction was calculated using Eq. (1):

$$\ln([M_0]/[M]) = k_d t \qquad \text{(Eq. 1)}$$

where $[M_0]$ and [M] are the concentrations of the alcohol substrate at time zero and time t (in hours), respectively. The half-life, $t_{1/2}$, that is, the time for the substrate concentration to reach half of the initial concentration, was calculated using Eq. (2):

$$t_{1/2} = \ln(2)/k_d \qquad \text{(Eq. 2)}$$

For studying the thermal cyclization, 1 g each of 1,3-PDO, 1,3-BDO and 3-Me-1,3-BDO, respectively, were reacted with 10 mL DMC using 2 g molecular sieves and 10% (w/w) N435 for 7 h at 60 °C, followed by filtration to remove solids including the immobilized lipase and molecular sieves, and evaporation. The product samples (0.2 g) were then heated with shaking at 90 °C under atmospheric pressure.

Quantitative Analyses and Structure Elucidation

Quantitative analyses of reaction components were performed using gas chromatography (GC, Varian 430-GC, Varian, USA) equipped with a FactorFour Capillary column, VF-1 ms (Varian, 15 m × 0.25 mm) and a flame ionization detector. The initial column oven temperature was increased from 50 to 250 °C at a rate of 20 °C min^{-1}. The samples, diluted with acetonitrile, to a concentration of 0.1–0.5 mg mL^{-1}, were injected in the split injection mode of 10% at 275 °C. The conversion of the substrates and ratio of products formed were calculated by comparison of peak areas on the gas chromatograms.

The structures of the products were then determined by ^1H NMR using a 400 MHz NMR spectrometer (Bruker, UltraShield Plus 400, Germany), from which it was seen that high proportions of mono-carbonates were obtained in the

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initial stages of the lipase-catalyzed reaction, while more dicarbonates were obtained by performing the reaction for a longer time. Cyclic carbonates were prepared from monocarbonate by thermal treatment at 90 °C.

Products of 1,3-PDO Reaction (see Supporting Information, Figure S1): ^{1}H NMR (400 MHz, $CDCl_3$). Mono-carbonate (3-methoxycarbonyloxypropan-1-ol, **P3**): δ = 1.861 (2H, m), 2.535 (1H, t), 3.669 (2H, t), 3.733 (3H, s), 4.237 (2H, t). Cyclic carbonate (trimethylene carbonate, **P5**): δ = 2.068 (2H, m), 4.250 (4H, t). Di-carbonate [1,3-bis(methoxycarbonyloxy)propane, **P6**]: δ = 2.058 (2H, m), 3.792 (3H, s), 3.797 (3H, s), 4.253 (4H, t).

Products of 1,3-BDO reaction (see Supporting Information, Figure S2); ^{1}H NMR (400 MHz, $CDCl_3$). Mono-carbonate (3-methoxycarbonyloxybutan-1-ol, **P3**): δ = 1.246 (3H, d), 1.760 (1Ha, m), 1.848 (1Hb, m), 1.996 (1H, d), 3.955 (1H, m), 3.797 (3H, s), 4.257 (1Ha, m), 4.387 (1Hb, m). Cyclic carbonate (1-methyl-trimethylene carbonate, **P5**): δ = 1.346 (3H, d), 1.957 (2H, m), 4.221 (2H, b), 4.899 (1H, b). Di-carbonate [1,3-bis(methoxycarbonyloxy)butane, **P6**]: δ = 1.341 (3H, d), 1.968 (2H, m), 3.784 (3H, s), 3.789 (3H, s), 4.229 (2H, t), 4.907 (1H, m).

Products of 3-Me-1,3-BDO reaction (see Supporting Information, Figure S3); ^{1}H NMR (400 MHz, $CDCl_3$). Mono-carbonate (3-methoxycarbonyloxy-3-methyl-butan-1-ol, **P3**): δ = 1.267 (6H, s), 1.835 (1H, s), 1.873 (2H, t), 3.776 (3H, s), 4.319 (2H, t). Cyclic carbonate (1,1-dimethyl-trimethylene carbonate, **P5**): δ = 1.507 (6H, s), 2.022 (2H, t), 4.451 (2H, t).

Acknowledgements

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