Towards Automated Monomer Synthesis: A Streamlined Approach for the Synthesis of Cyclic Carbonates

Eddy W. P. Tan¹, James L. Hedrick², Pedro L. Arrechea², Tim Erdmann², Vivien Kiyek^{2,†}, Simon Lottier^{2,††}, Yi Yan Yang¹ and Nathaniel H. Park^{2,}*

¹Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, Singapore 138669, Singapore.

²IBM Research–Almaden, 650 Harry Rd. San Jose, CA 95120

Keywords: Monomer Synthesis, Carbonate Synthesis, Polycarbonates, Automation, Flow Chemistry.

ABSTRACT: Accessing cyclic carbonate monomers on large scales is critical for development of any new carbonate-based material platform. This is particularly important in the context of using automated experimental systems for materials synthesis, which can often require large inputs of starting materials. However, the synthesis of carbonate monomers can be a challenging and tedious endeavor, requiring multiple synthetic steps and purifications. To address this, we report a drastically improved and scalable process for the synthesis of carbonate monomers via a two-step

route that avoids the use of hazardous phosgene or chloroformate reagents. The cyclic carbonate monomers can be obtained in high yields and with minimal need for chromatographic purification. This process enables rapid access to a broad array of functional groups on the carbonate monomer and monomers generated from procedure can readily be polymerized via ring-opening polymerization.

Introduction

Automated materials synthesis offers a promising approach to accelerate the development of new high-performance materials with tailored properties. Recently, our group and others have developed automated platforms that enable programmatic access to a diverse array of polymers and polymer compositions.¹⁻⁴ However, these platforms can consume large quantities of monomer feedstock, even for relatively short, small-scale runs.¹ This requirement becomes a significant production bottleneck when using these platforms, especially for custom monomers. Given our interest in using automated synthetic platforms (Figure 1A) for the development of aliphatic polycarbonate materials sourced from 2,2-bis(hydroxymethyl)propionic acid (bis-MPA, Fig. 1B) for biomedical applications,⁵⁻⁷ the issue of monomer supply has become an impediment for the discovery and development of new material candidates using automated material synthesis.

While there are many examples of aliphatic cyclic carbonate monomers reported,⁸⁻¹¹ bis-MPA sourced carbonates^{8,12} are highly versatile platforms given the breadth of functional groups that may be appended to the monomer scaffold and relative ease of enchainment via ring-opening polymerization (ROP).^{5,13,14} Beyond our own interest in ROP of bis-MPA carbonates, these cyclic carbonates are widely used in a variety of materials in addition to polycarbonates, including non-isocyanate polyurethanes,^{15,16} reagents to functionalize polyethylene imine,¹⁷ and as important

intermediates in dendrimer synthesis.¹² Despite the low monetary cost of bis-MPA and the breadth of materials utilizing cyclic bis-MPA carbonates, the labor-cost of their syntheses is a barrier to further discovery and future commercialization of bis-MPA based materials. In contrast to other monomer scaffolds such as methacrylates—where diversification is often accessible in one step from commercially available materials—bis-MPA based carbonates usually require multi-step syntheses and tedious purification to access a comparable set of monomers. Thus, the development of shorter, more scalable routes to cyclic bis-MPA based carbonate monomers would vastly accelerate downstream developments employing automated experimentation platforms.

A Materials development with automated synthetic platforms

B Comparison of different routes to carbonate monomers

C New routes to bis-MPA carbonates

Figure 1. Advantages of automated materials development and approaches to carbonate monomer synthesis. A) Materials development using automated synthetic platforms, B) Previous synthetic routes to cyclic carbonates (see Figure S1 for details on previous routes). B) Advantages of this work on acid-promoted carbonate formation. See references ^{5,18}, and Figure S1a for information on previous routes to **3c**. C). Routes to cyclic carbonate monomers using acid-promoted carbonate formation. Abbreviations: CDI = carbonyldiimidazole, EDC•HCl = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.

Currently, there are several routes employed to access carbonate monomers from bis-MPA ranging from 2 to 5 steps (Fig. S1).^{12,19–23} The main challenges for many of the approaches to a bis-MPA carbonates are the installment of the ester functional group (**R**, Figure 1) and the cyclization

of the 1,3-diol into the carbonate. Some routes rely on protection–deprotection schemes leading to additional synthetic steps (Figure S1a and Figure S1b).^{22,23} Additionally, these approaches relied on the use of triphosgene or chloroformate reagents to cyclize the diol intermediate to the carbonate. Finally, the resulting monomers often require repeated purification since small impurities from the final step can initiate oligomerization of the carbonate monomer upon storage or affect the molecular weight distribution for an otherwise well-controlled polymerization.^{21,24}

To find an improved synthesis, our group has previously published the use of bis(pentafluorophenyl) carbonate to simultaneously cyclize bis-MPA and install an activated pentafluorophenyl ester handle for further functionalization (Figure S1c).¹⁹ Although this approach proved to be highly amenable to accessing a broad variety of functional carbonate monomers, the transesterification step provided 50–90% yields, needed extended reaction times, and required chromatographic purification to remove unreacted starting materials and byproducts.^{19,25} To improve on this process, Malkoch and coworkers developed an alternative process using *N,N'*-carbonyldiimidazole (CDI) to generate a isolable imidazole ester intermediate that is converted to the carbonate monomer in a separate esterification–cyclization step (Figure S1d).²¹ Although it was demonstrated successfully on a multigram scales, the overall yields were between 23–43% and required purification by chromatography. Dimethyl carbonate was also investigated as a reagent for carbonate formation from diols.²⁰ In the case of a bis-MPA ester diol, however, an extended reaction time was required and the product was contaminated with substantial amounts of a linear bis-carbonate byproduct (Figure S1f). Finally, carbon dioxide has been reported as a reagent capable of synthesizing cyclic carbonates of different ring-sizes (Figure S1g). However, the yields were modest (21–80%), produced a significant amounts oligomeric side-products, and required a complex reaction setup.^{26,27}

Results

Despite advances towards a more direct route for carbonate monomer synthesis, there remains a significant need for improved protocols. Here, we identified two potential short synthetic sequences to access bis-MPA carbonate monomers: 1) selective alkylation (or Fischer esterification) of the bis-MPA carboxylic acid to afford **I** followed by cyclization to the carbonate (Route A, Figure 1C) and 2) selective cyclization of bis-MPA to the corresponding carbonate carboxylic acid (**II**, Figure 1C) followed by EDC•HCl esterification to afford the monomer (Fig. 2).

The advantage of *Route A* is that the alkylation of the carboxylic acid has been frequently performed and is typically accomplished using inexpensive hydroxide (KOH) or carbonate (K_2CO_3 or Cs_2CO_3) bases at elevated temperatures.^{28–30} There are also reports of successful room temperature alkylations employing organic bases.³¹ In both cases, the use of dimethyl formamide (DMF), with its high-boiling point and miscibility in aqueous and organic solvents, complicates the purification of the product. Instead, we found that the combination of triethylamine (Et_3N) or *N,N*-diisopropylethylamine (DIEA) in acetonitrile or ethyl acetate facilitated the transformation with a variety of alkyl halides (Figure S2). In most cases, the isolated material following workup of the reaction mixture was sufficiently pure to use directly in the subsequent cyclization step. In other cases, the diol could be purified via crystallization or filtration through a short silica gel plug (see Supporting Information). In the case of TMC-Et (**2e**), synthesis of the corresponding bis-MPA ethyl ester is best accomplished via a Fischer esterification using standard literature protocols (see Supporting Information).³²

In the second step for *Route A*, we focused on optimizing the cyclization using CDI. The reagent CDI was chosen for its ease of handling, low toxicity, low cost, and improved reactivity compared to alternatives such as dimethyl- or diphenylcarbonate, which typically require higher temperatures and prolonged reaction times.^{20,33} The phenolic carbonate alternatives also necessitate the removal of super-stoichiometric amounts of a phenol byproduct, significantly complicating purification procedures. In contrast, the imidazole byproducts from CDI are easily removed via acidic aqueous extraction. CDI has been widely used for cyclization of 1,3-diols into carbonates, however, typical conditions often require slow or portion-wise addition of CDI and lengthy reaction times.^{34,35}

Table 1: Optimization of 1,3-Diol Cyclization

Entry	Acid	Acid Equiv.	Temp (°C)	Conversion (%) ^a	2a	I
1 ^b	None	—	20	78	9	60
2	None	—	75	91	49	34
3	MsOH	0.1 ^c	75	98	43	55
4	<i>p</i> -TsOH	0.1 ^c	75	96	50	46
5	TFA	0.1 ^c	75	96	45	51
6	AcOH	0.1	75	100	28	72
7	PPTS	1	75	97	48	49
8	BzOH	1	75	97	54	43
9	AcOH	1	75	96	49	48
10	AcOH	4	75	97	73	27
11	AcOH	16	75	98	96	2

Reagents and conditions: **1a** (1.0 equiv), CDI (1.5 equiv), EtOAc, rt, 5–10 min, then acid (1–16 equiv), rt–75 °C, 2–6 h. ^aConversion and product distribution determined by ¹H NMR of the crude reaction mixture in CDCl₃. ^bReaction time is 5 min. ^c1 eq of acid resulted in degradation. MsOH = methanesulfonic acid, TFA = trifluoroacetic acid, *p*-TsOH = *p*-toluenesulfonic acid; AcOH = acetic acid; PPTS = pyridinium *p*-toluenesulfonic acid; BzOH = benzoic acid.

For our optimization efforts, we investigated the cyclization of the bis-MPA benzyl ester (**S1a**, Table S1, Supporting Information) with CDI (Table 1). Upon addition of CDI to a solution of **S1a** in acetonitrile, the formation of two distinct products was observed by ¹H NMR of the crude reaction mixture after 5 minutes (entry 1, Table 1). The minor product was the cyclic carbonate monomer (**2a**) and the major product was the bis-imidazole carbamate **I** (Table 1, see also Figure S3A). Previously, Malkoch and co-workers isolated an analogous bis-imidazole carbamate from treatment of bis-MPA with excess CDI and converted it to a carbonate in a subsequent step (Figure S1d). Brønsted acid activation of imidazole carbamates has been investigated for the synthesis of esters and oxazolidinones,^{36–38} but has not been utilized to promote cyclic carbonate synthesis. To facilitate a one-pot procedure, we hypothesized that **I** could undergo selective *in situ* cyclization with a Brønsted acid.

To test our hypothesis, we examined a variety of acids following the reaction of **S1a** with CDI (Table 1). Using only 0.1 equivalents acid (Entries 3–6, Table 1) provided similar product ratios as compared to heating of the reaction mixture in the absence of acid (Entry 2, Table 1). Increasing the equivalents of AcOH (Entries 9–11, Table 1) afforded increased conversion to the desired carbonate product, with 16 equivalents affording near 96% conversion to **2a** within one hour of reaction time (entries 7–11, Table 1). Based on these results, we selected AcOH as the acid promoter for cyclic carbonate synthesis. In addition to rate enhancements, the use of AcOH has additional advantages such as (1) low-cost, (2) ease of removal during workup via azeotropic distillation using toluene or heptane, (3) tolerance of acid-labile protecting groups, and (4) a

significantly lower propensity to catalyze the polymerization of cyclic carbonate monomers as compared to stronger acids.³⁹

A Acid-promoted cyclization of bis-MPA (*Route B*)

B Potential mechanism for acid-promoted cyclization

Figure 2. Development of new conditions for the cyclization of bis-MPA diols to their corresponding carbonates. A) Conditions for direct cyclization of bis-MPA to afford **2i**. B) Potential mechanism for acid-promoted cyclization.

With the results from Table 1, we next sought to apply these optimized conditions to the one-pot synthesis of **2i** (Figure 2A) from bis-MPA. Achieving this shorter synthesis would greatly expand the scope of potential monomers that can be accessed, particularly since this intermediate requires three steps to prepare²² (Figure S1, Route A). The primary obstacle in extending the conditions identified to bis-MPA is that carboxylic acids are reactive towards CDI leading to the formation of acyl imidazoles.^{21,36} To mitigate this difficulty, we hypothesized that treatment of bis-MPA first with an amine base such as (Et_3N or DIEA) would deactivate the carboxylic acid³⁷ and

furthermore improve the solubility of bis-MPA. This hypothesis was validated as we were successfully able to generate the desired cyclic carbonate **2l** under similar conditions as **2a** albeit with pretreatment with Et₃N (Figure 2A). As indicated in our optimization efforts, a mixture of intermediate products was observed by ¹H NMR of the crude reaction mixture following addition of CDI. We found that the distribution of these intermediates was dependent on the equivalents of CDI used (Table S2, Supporting Information). The bis-MPA acyl imidazole intermediate isolated by Malkoch and co-workers (Figure S1, Route D) was only observed in small amounts by ¹H NMR when significant excess of CDI was used (Table S2, entries 1 & 2, Supporting Information). Together, these results demonstrate that selective reaction of the primary alcohols of bis-MPA can be achieved in the presence of an unprotected carboxylic acid.

Based on the results summarized in Table 1 and Figure 2A—in addition to prior work in the literature^{36,37}—a possible mechanistic pathway for the acid-promoted cyclization of the 1,3-bis-imidazole carbamate intermediate to the corresponding carbonate is presented in Figure 2B. Here, an imidazole carbamate on intermediate **B** is protonated by acetic acid to afford **C**. The generated acetate can then displace the protonated imidazole to afford the anhydride **D**. Imidazole may then be acylated by the anhydride **D** followed by concomitant decarboxylation to reveal the alcohol **E**, which can then be further activated with AcOH and cyclize to afford the cyclic carbonate **A**. This mechanism is supported by the observation of both generation of CO₂ gas from the reaction in addition to the *N*-acyl imidazole byproduct. Additionally, these byproducts are also generated when the bis-imidazole intermediate (**II**, Figure S4) was isolated and subjected to the reaction conditions, with the *N*-acyl imidazole being formed in stoichiometric quantities (Figure S6). These experiments suggest that the CO₂ and *N*-acyl imidazole byproducts are not formed from the hydrolysis of residual CDI or reaction of residual CDI with AcOH. The same byproducts are

also observed when the benzyl bis-imidazole carbamate intermediate (**I**, Figure 2A and Figure S3) is isolated and subjected to the reaction conditions (Figure S5), implying a similar mechanistic pathway.

Figure 3. A) Synthesis of carbonate monomers from functional diols. *Reagents and conditions:* Bis-MPA Ester Diol (1.0 equiv), CDI (1.5–1.8 equiv), MeCN or EtOAc, rt, 5–10 min, then AcOH (10–16 equiv), reflux 2–16 h. ^aIsolated yield over two steps starting from bis-MPA. ^bIsolated yield over three steps starting from mPEG₃₅₀-OH. ^cSignificant loss in yield occurred in silica plug filtration step. ^dReaction run at room temperature for 24 h. B) Esterification of **2l** to bis-MPA carbonates. *Reagents and conditions:* i) alcohol (1 equiv), DMAP (0.1 equiv), MTC-OH (1.5 equiv), DCM or MeCN, 0 °C, 0.5 h, ii) EDC.HCl (1.5 equiv), 0 °C to rt, 16 h.

Together, the conditions from Tables 1 and Figure 2A were broadly applicable to cyclize a variety of 1,3-diols into carbonate monomers (Figure 1). The carbonate monomers can be readily isolated in high purity following an aqueous workup. However, purification via crystallization or filtration through a silica gel plug is necessary to ensure complete removal of trace impurities that may promote slow decomposition of the carbonate monomer via oligomerization. Once the

monomers are purified, they are quite stable. In some cases, carbonate monomers have been stored on the benchtop in a vacuum desiccator for over 15 months with no observed degradation.

In the case of **2l**, the standard aqueous workup protocol afforded variable yields, presumably due to the increased water solubility of the carbonate (Figure 3). After thoroughly examining many different workup or extraction protocols, we found that simple filtration of the crude reaction mixture through a packed column of Amberlyst® 15 was sufficient to afford the desired product in high yield and purity (Figure 3). Trimethylene carbonate (**2m**, Figure 3) was also found to be sensitive to aqueous workup and was also purified via filtration through Amberlyst® 15 resin.

Figure 4. Scale-up purification of **2l**. A) Scheme of purification reaction. B) Photograph of engineered packed-column setup modified from a commercially available apparatus. C) Traces of heat evolved during purification process, top, middle, and bottom refer to external thermocouple placement on packed column. Liquid is introduced from the bottom of the column and collected at the top of the column.

As **2l** is a key intermediate for *Route B* (Figure 1C), it was imperative to scale-up production and purification of this intermediate to at least 100 grams. To facilitate the purification

of the crude reaction mixture on this scale, we designed an automated apparatus employing a removable packed bed charged with Amberlyst® 15 resin (~1 kg). The design incorporates a positive displacement pump to force the reaction contents through the column thus effecting the purification (Figure 4B, Figure S7A). The process generates significant heat as impurities are adsorbed onto the packing material and at these increased scales adiabatic behavior is a concern. Since elevated temperature encourages polymerization and reduces the yield of the monomer, both modeling efforts and measurements with thermocouples were employed to understand the temperature dynamics during purification (Figure 4C, Figures S9–S12). This system greatly simplified the work-up and purification procedure on scale-up and afforded **2I** in 95% yield.

With a scalable route to **2I**, we could focus on the second step of *Route B* (Figure 1). Here, the EDC coupling of the **2I** with an alcohol to afford the desired cyclic carbonate monomer. Under our optimized protocol, the coupling reaction can be performed at room temperature to afford high yields of the carbonate monomer (Figure 3B). Purification can be achieved through filtration of the crude reaction mixture through a silica gel plug to remove EDC coupling byproducts or an aqueous work-up followed by crystallization (see Supporting Information).

Table 2: ROP polymerization of cyclic carbonate monomers

Entry	Monomer	Polymer	Mode	Initiator	Catalyst	Time ^a	Conversion (%) ^c	M_n (GPC) ^d	$\bar{D}$ ^d
1	2b	4a	Batch	mPEG _{5K} OH	DBU	30 min	94	15.3	1.20
2	2b	4b	Batch	KOMe	U-4-CF ₃	5 s	95	9.6	1.08
3	2c	4c	Batch	mPEG _{5K} OH	DBU	30 min	90	11.4	1.12
4	2e	4d	Flow	4-MBA	U-1-CF ₃	0.5 s	93	10.0	1.13
5	2g	4e	Flow	4-MBA	U-1-CF ₃	0.5 s	92	10.2	1.10
6	3a	4f	Batch	mPEG _{5K} OH	DBU	30 min	90	14.8	1.20
7	3b	4g	Batch	mPEG _{5K} OH	DBU	30 min	89	13.4	1.07

Reagents and conditions: All batch polymerizations using mPEG_{5K}OH as an initiator had a starting [M]₀: [DBU]₀: [I]₀ ratio of 1:3:20 (entries 1, 3, 6, and 7). For entries 1, 3, and 6, [M]₀ = 1 M, for entry 7 [M]₀ = 0.5 M. For entry 2, [M]₀: [Urea]₀: [I]₀ of 50:3:1 and [M]₀ = 1.0. For entries 4 and 5, KH is used as a cocatalyst and [M]₀: [Urea]₀: [I]₀: [KH]₀ is 50:3:1:1 and 30:3:1:1, respectively. ^aTime for flow reaction is the residence time of the reactor. ^bDetermined by ¹H NMR of the crude reaction mixture. ^cMeasured via advanced polymer chromatography (APC) in THF at 25 °C calibrated using polystyrene standards. Abbreviations: KOMe = potassium methoxide, KH = potassium hydride, 4-MBA = 4-methylbenzyl alcohol, and mPEG_{5K}OH = poly(ethylene glycol) methyl ether, 5.0 KDa average M_n .

Having successfully accessed a broad array of cyclic carbonate monomers via two different routes, we investigated their ability to undergo ring-opening polymerization (ROP) under both batch and flow conditions (Table 2). In all cases, monomers prepared via these methods led the controlled synthesis of a different polycarbonate homopolymers or AB diblock copolymers with predictable molecular weights and narrow dispersity. Polymers synthesized under continuous flow conditions exhibited very short residence times, consistent with our prior work using flow platforms for polyester and polycarbonate synthesis.¹ The data for the polymerizations and resulting polymers is summarized in Table 2.

Conclusion

In summary, we have demonstrated a scalable and operationally simple approach for the synthesis of a broad array of carbonate monomers derived from bis-MPA. This approach (1) obviates the need for toxic chloroformates or phosgene-based reagents, (2) affords byproducts that are easily removed during workup, (3) does not require anhydrous or air-free conditions, and (4)

minimizes or eliminates the need for complex chromatographic purification. Additionally, our approach substitutes the use high-boiling and/or toxic solvents such as DMF, for ethyl acetate or acetonitrile. The time and cost savings of this approach removes barriers in the synthesis and development of materials sourced from bis-MPA. This work enables us to generate quantities of monomer that can be used in polymerization campaigns by programmatic, continuous-flow platforms. Going forward, automated purification systems—such as the one we developed here—along with complete automation of the monomer synthesis, will be critical tools in facilitating accelerated materials discovery.

ASSOCIATED CONTENT

Supporting Information. All characterization data for monomers and polymers and supplementary figures.

The following files are available free of charge.

Supporting Information (PDF)

AUTHOR INFORMATION

Corresponding Author

*npark@us.ibm.com

Present Addresses

[†]Peter Grünberg Institute (PGI-9), Forschungszentrum Jülich 52425 Jülich, Germany

^{††}Arts et Métiers ParisTech – PIMM 151 bd de l'Hôpital, 75013 Paris, France

ABBREVIATIONS

bis-MPA, 2-bis(hydroxymethyl)propionic acid; CDI, *N,N'*-carbonyldiimidazole;

REFERENCES

1. Lin, B., Hedrick, J. L., Park, N. H. & Waymouth, R. M. Programmable High-Throughput Platform for the Rapid and Scalable Synthesis of Polyester and Polycarbonate Libraries. *J. Am. Chem. Soc.* **141**, 8921–8927 (2019).
2. Walsh, D. J. & Guironnet, D. Macromolecules with programmable shape, size, and chemistry. *Proc. Natl. Acad. Sci.* **116**, 1538–1542 (2019).
3. Rubens, M., Vrijssen, J. H., Laun, J. & Junkers, T. Precise Polymer Synthesis by Autonomous Self-Optimizing Flow Reactors. *Angew. Chem. Int. Ed.* **58**, 3183–3187 (2019).
4. Zhou, Y., Gu, Y., Jiang, K. & Chen, M. Droplet-Flow Photopolymerization Aided by Computer: Overcoming the Challenges of Viscosity and Facilitating the Generation of Copolymer Libraries. *Macromolecules* **52**, 5611–5617 (2019).
5. Chin, W. *et al.* A macromolecular approach to eradicate multidrug resistant bacterial infections while mitigating drug resistance onset. *Nat. Commun.* **9**, 917 (2018).
6. Park, N. H. *et al.* Addressing Drug Resistance in Cancer with Macromolecular Chemotherapeutic Agents. *J. Am. Chem. Soc.* **140**, 4244–4252 (2018).
7. Zhong, G. *et al.* Polymers with distinctive anticancer mechanism that kills MDR cancer cells and inhibits tumor metastasis. *Biomaterials* **199**, 76–87 (2019).
8. Rokicki, G. Aliphatic cyclic carbonates and spiroorthocarbonates as monomers. *Prog. Polym. Sci.* **25**, 259–342 (2000).
9. Gregory, G. L., Jenisch, L. M., Charles, B., Kociok-Köhn, G. & Buchard, A. Polymers from Sugars and CO₂: Synthesis and Polymerization of a d-Mannose-Based Cyclic Carbonate. *Macromolecules* **49**, 7165–7169 (2016).

10. Venkataraman, S., Veronica, N., Voo, Z. X., Hedrick, J. L. & Yang, Y. Y. 2-Amino-1,3-propane diols: a versatile platform for the synthesis of aliphatic cyclic carbonate monomers. *Polym. Chem.* **4**, 2945–2948 (2013).
11. Venkataraman, S. *et al.* A Simple and Facile Approach to Aliphatic N-Substituted Functional Eight-Membered Cyclic Carbonates and Their Organocatalytic Polymerization. *J. Am. Chem. Soc.* **137**, 13851–13860 (2015).
12. García-Gallego, S., Nyström, A. M. & Malkoch, M. Chemistry of multifunctional polymers based on bis-MPA and their cutting-edge applications. *Prog. Polym. Sci.* **48**, 85–110 (2015).
13. Ono, R. J. *et al.* Benzyl Chloride-Functionalized Polycarbonates: A Versatile Platform for the Synthesis of Functional Biodegradable Polycarbonates. *Macromolecules* **47**, 7725–7731 (2014).
14. Venkataraman, S. *et al.* Formation of Disk- and Stacked-Disk-like Self-Assembled Morphologies from Cholesterol-Functionalized Amphiphilic Polycarbonate Diblock Copolymers. *Macromolecules* **46**, 4839–4846 (2013).
15. Sardon, H. *et al.* Synthesis of Polyurethanes Using Organocatalysis: A Perspective. *Macromolecules* **48**, 3153–3165 (2015).
16. Yuen, A. *et al.* Room temperature synthesis of non-isocyanate polyurethanes (NIPUs) using highly reactive N-substituted 8-membered cyclic carbonates. *Polym Chem* **7**, 2105–2111 (2016).
17. Ichiyama, K. *et al.* Cooperative Orthogonal Macromolecular Assemblies with Broad Spectrum Antiviral Activity, High Selectivity, and Resistance Mitigation. *Macromolecules* **49**, 2618–2629 (2016).

18. Cooley, C. B. *et al.* Oligocarbonate Molecular Transporters: Oligomerization-Based Syntheses and Cell-Penetrating Studies. *J. Am. Chem. Soc.* **131**, 16401–16403 (2009).
19. Sanders, D. P. *et al.* A Simple and Efficient Synthesis of Functionalized Cyclic Carbonate Monomers Using a Versatile Pentafluorophenyl Ester Intermediate. *J. Am. Chem. Soc.* **132**, 14724–14726 (2010).
20. Pyo, S.-H. & Hatti-Kaul, R. Chlorine-Free Synthesis of Organic Alkyl Carbonates and Five- and Six-Membered Cyclic Carbonates. *Adv. Synth. Catal.* **358**, 834–839 (2016).
21. Olsson, J. V., Hult, D., Cai, Y., García-Gallego, S. & Malkoch, M. Reactive imidazole intermediates: simplified synthetic approach to functional aliphatic cyclic carbonates. *Polym. Chem.* **5**, 6651–6655 (2014).
22. Pratt, R. C., Nederberg, F., Waymouth, R. M. & Hedrick, J. L. Tagging alcohols with cyclic carbonate: a versatile equivalent of (meth)acrylate for ring-opening polymerization. *Chem Commun* 114–116 (2008) doi:10.1039/B713925J.
23. Liu, Z.-L., Zhou, Y. & Zhuo, R.-X. Synthesis and properties of functional aliphatic polycarbonates. *J. Polym. Sci. Part Polym. Chem.* **41**, 4001–4006 (2003).
24. Vora, A. *et al.* Orientation Control of Block Copolymers Using Surface Active, Phase-Preferential Additives. *ACS Appl. Mater. Interfaces* **8**, 29808–29817 (2016).
25. Chan, J. M. W., Sardon, H., Engler, A. C., García, J. M. & Hedrick, J. L. Tetra-n-butylammonium Fluoride as an Efficient Transesterification Catalyst for Functionalizing Cyclic Carbonates and Aliphatic Polycarbonates. *ACS Macro Lett.* **2**, 860–864 (2013).
26. McGuire, T. M., López-Vidal, E. M., Gregory, G. L. & Buchard, A. Synthesis of 5- to 8-membered cyclic carbonates from diols and CO₂: A one-step, atmospheric pressure and ambient temperature procedure. *J. CO₂ Util.* **27**, 283–288 (2018).

27. Gregory, G. L., Ulmann, M. & Buchard, A. Synthesis of 6-membered cyclic carbonates from 1,3-diols and low CO₂ pressure: a novel mild strategy to replace phosgene reagents. *RSC Adv.* **5**, 39404–39408 (2015).
28. Fischer, A. M. & Frey, H. Soluble Hyperbranched Poly(glycolide) Copolymers. *Macromolecules* **43**, 8539–8548 (2010).
29. Malhotra, S., Calderón, M., Prasad, A. K., Parmar, V. S. & Haag, R. Novel chemoenzymatic methodology for the regioselective glycine loading on polyhydroxy compounds. *Org. Biomol. Chem.* **8**, 2228–2237 (2010).
30. Wang, H., Wu, Y., Liu, G., Du, Z. & Cheng, X. A Biodegradable and Amphiphilic Linear-Dendritic Copolymer as a Drug Carrier Platform for Intracellular Drug Delivery. *Macromol. Chem. Phys.* **217**, 2004–2012 (2016).
31. Zeng, F.-R. *et al.* Hyperbranched Aliphatic Polyester via Cross-Metathesis Polymerization: Synthesis and Postpolymerization Modification. *Macromol. Rapid Commun.* **39**, 1700658 (2018).
32. Teo, P. Y. *et al.* Hydrophobic modification of low molecular weight polyethylenimine for improved gene transfection. *Biomaterials* **34**, 7971–7979 (2013).
33. Matsukizono, H. & Endo, T. Reworkable Polyhydroxyurethane Films with Reversible Acetal Networks Obtained from Multifunctional Six-Membered Cyclic Carbonates. *J. Am. Chem. Soc.* **140**, 884–887 (2018).
34. Mindemark, J. & Bowden, T. Synthesis and polymerization of alkyl halide-functional cyclic carbonates. *Polymer* **52**, 5716–5722 (2011).

35. Mindemark, J., Imholt, L., Montero, J. & Brandell, D. Allyl ethers as combined plasticizing and crosslinkable side groups in polycarbonate-based polymer electrolytes for solid-state Li batteries. *J. Polym. Sci. Part Polym. Chem.* **54**, 2128–2135 (2016).
36. Heller, S. T. & Sarpong, R. Chemoselective Esterification and Amidation of Carboxylic Acids with Imidazole Carbamates and Ureas. *Org. Lett.* **12**, 4572–4575 (2010).
37. Heller, S. T. & Sarpong, R. On the reactivity of imidazole carbamates and ureas and their use as esterification and amidation reagents. *Tetrahedron* **67**, 8851–8859 (2011).
38. Heller, S. T., Fu, T. & Sarpong, R. Dual Brønsted Acid/Nucleophilic Activation of Carbonylimidazole Derivatives. *Org. Lett.* **14**, 1970–1973 (2012).
39. Coady, D. J. *et al.* Polymerizing Base Sensitive Cyclic Carbonates Using Acid Catalysis. *ACS Macro Lett.* **2**, 306–312 (2013).