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Overcoming Barriers in Polycarbonate Synthesis: A Streamlined Approach for the Synthesis of Cyclic Carbonate Monomers

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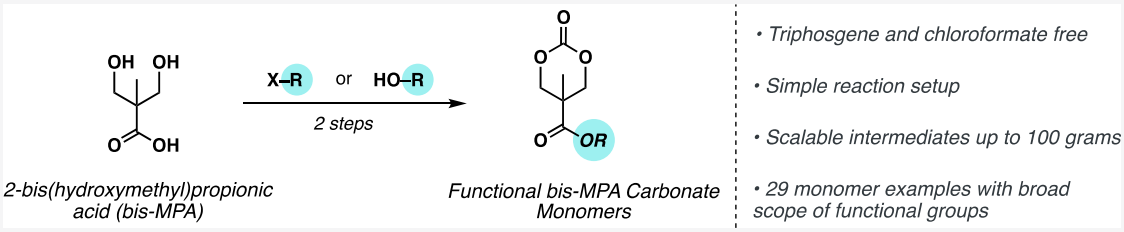

ABSTRACT: Accessing cyclic carbonate monomers on a large scale is critical for the development of any new carbonate-based materials platform. The synthesis of carbonate monomers can be a challenging and tedious endeavor requiring multiple synthetic steps and purifications. To address this, we report a drastically improved process for the synthesis of carbonate monomers via a two-step route that avoids the use of hazardous triphosgene or chloroformate reagents. This process enables rapid access to a broad array of functional groups on the carbonate monomer and the monomers generated from the procedure can readily be polymerized via ring-opening polymerization.

INTRODUCTION

Aliphatic cyclic carbonates are a versatile and widely used monomer scaffold for the preparation of polycarbonates, copolymers, and non-isocyanate polyurethanes.[1−3] These materials find application in a variety of domains including drug-delivery vehicles,[4−6] antimicrobial materials,[7−9] macromolecular chemotherapeutics,[10,11] covalent adaptable networks,[12] materials for three-dimensional (3D) printing,[13] surface patterning,[14,15] heavy-metal sequestration,[16] magnetic resonance imaging contrast agents,[17] computed tomography imaging,[18] solid-phase electrolytes for ion transport,[19,20] and luminescent polymers for white light generation.[21] One of the most commonly used monomer precursors is 2,2-bis-(hydroxymethyl)propionic acid (bis-MPA; Figure 1A) as the installment of various functional groups via esterification enables fine-tuning of the properties of the derived polymers. Despite the low monetary cost of bis-MPA and the breadth of materials utilizing cyclic bis-MPA-based carbonate monomers, their synthesis usually requires multiple steps, the use of toxic reagents, and tedious purifications.[22−27] These factors result in high labor and process costs, creating a barrier to further discovery of new functionalized polycarbonate materials and the commercialization thereof. This is in stark contrast to other monomer platforms, such as methacrylates, where diversification is typically accessible in one step from commercially available precursors. Thus, the development of improved methods for the synthesis and purification of carbonate monomers would greatly accelerate the overall research and development of future polycarbonate-based materials.

Currently, there are several published routes (two to five steps) employed to obtain carbonate monomers from bis-MPA (Figure S1).[22−27] The primary challenges for many of these approaches is the installment of the functional group **R** via esterification and the cyclization of the 1,3-diol to the carbonate (Figure 1A). Some routes rely on protection−deprotection schemes leading to additional synthetic steps (Figure S1A and S1B).[25,27] In addition, these methods rely 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 low concentrations of impurities in the final synthetic step can initiate the oligomerization of the carbonate monomer upon storage or affect the molecular weight distribution for an otherwise well-controlled polymerization.[15,23]

To avoid some of the aforementioned challenges, our group had published the use of bis(pentafluorophenyl) carbonate to simultaneously cyclize bis-MPA and install an activated pentafluorophenyl ester handle for further functionalization

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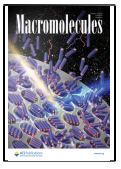

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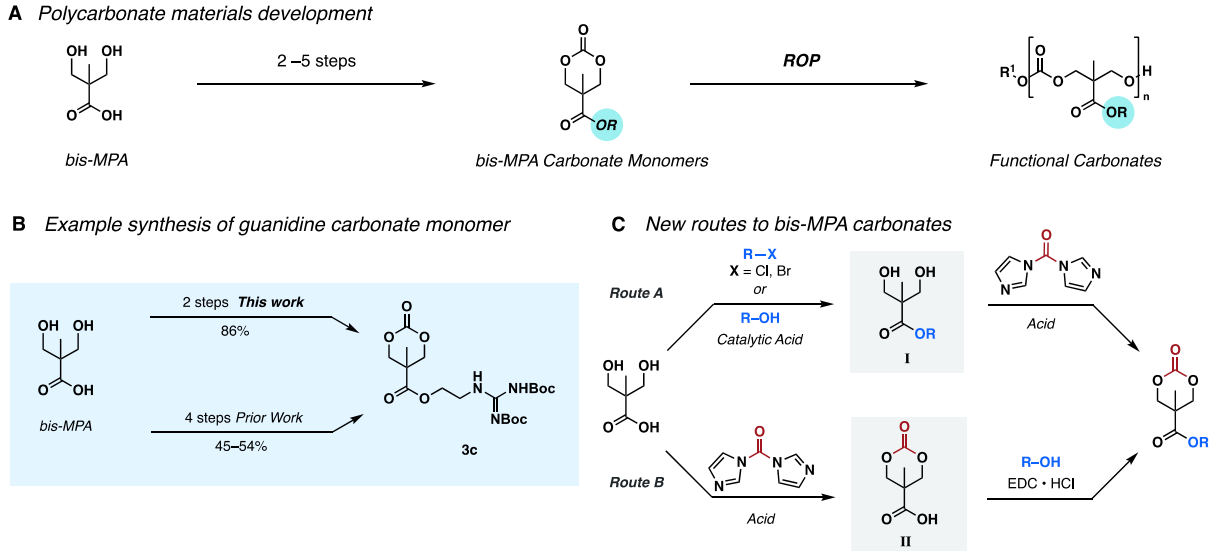

Figure 1. Polycarbonate materials development via bis-MPA-based monomers: state-of-the-art versus new routes from this work. (A) Material development using automated synthetic platforms, (B) comparison of synthetic efforts for cyclic guanidine-functionalized carbonate. See refs 7, 28 and Figure S1A for information on previous routes to **3c**. (C) New routes from this work to cyclic carbonate monomers using acid-promoted carbonate formation. Abbreviations: ROP = ring-opening polymerization, CDI = carbonyldiimidazole, and EDC·HCl = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride.

(Figure S1C).[24] Although this approach was effective in accessing a broad variety of functional carbonate monomers, the transesterification step provided 50−90% yields, required extended reaction times, and necessitated chromatographic purification, which can be inconvenient at a larger scale.[24,29] To improve on this process, Malkoch and co-workers developed an alternative process using *N*,*N*′-carbonyldiimidazole (CDI) to generate an isolable imidazole ester intermediate that is converted to the carbonate monomer in separate esterification−cyclization step (Figure S1D).[23] Although demonstrated successfully on a multigram scales, the yields varied between 23 and 43% and required purification by chromatography.

Dimethyl carbonate has also been investigated as a reagent for carbonate formation from diols.[26] 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). 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%) and produced significant amounts of oligomeric side products.[30,31] To overcome the limitations of these previous methodologies, we report two complementary strategies for accessing a broad scope of bis-MPA carbonate monomers in a two-step synthetic sequence.

RESULTS

We identified two potential synthetic strategies to access bis-MPA carbonate monomers: *Route A*, alkylation (or Fischer esterification) of the bis-MPA carboxylic acid to afford **I**, followed by cyclization to the carbonate (Figure 1C), and *Route B*, selective cyclization of bis-MPA to the corresponding carbonate carboxylic acid **II** (Figure 1C), followed by *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) facilitating the esterification to afford the monomer. The preference of route is dictated by the availability of the appropriate precursors. In some cases, the functional group precursor is commercially available as the alkyl (or benzyl/allyl) halide, which favors *Route A*. In other cases, the functional group precursor is available as alcohol and, therefore, *Route B* is better suited (Figure 1C).

The critical step in both routes is the cyclization of the 1,3-diol to the carbonate and hinges on the successful employment of CDI as the carbonyl source. CDI was chosen for its ease of handling, low cost, and diminished toxicity compared to triphosgene or ethyl chloroformate. Furthermore, CDI exhibits improved reactivity compared to dimethyl- or diphenylcarbonate, which typically requires higher temperatures and prolonged reaction times.[3,26] The phenolic carbonate alternatives also necessitate the removal of super-stochiometric amounts of a phenol byproduct, significantly complicating the purification procedures. In contrast, the imidazole byproducts from CDI are easily removed via acidic aqueous extraction. Previous reports of the CDI facilitated cyclization 1,3-diols required lengthy reaction times, undesirable chlorinated solvents, and portion-wise addition of the reagent.[20,32] Here, we felt an improved protocol for CDI cyclizations could be achieved through a judicious choice of reaction conditions and a careful analysis of the reaction intermediates.

We began our investigation of the identified two-step synthetic routes to carbonate monomers with *Route A*. The first-step of alkylation in *Route A* of the bis-MPA carboxylic acid has been performed using hydroxide (KOH), carbonate (K_2CO_3 or Cs_2CO_3), and organic bases.[4,33−35] The common use of dimethyl formamide (DMF) in these procedures complicates the workup and purification of the bis-MPA ester diol product due to its high-boiling point and miscibility in aqueous and organic solvents. To avoid DMF, we found that the combination of triethylamine (Et_3N) or *N*,*N*-diisopropylethylamine (DIEA) in acetonitrile facilitated the alkylation with a variety of alkyl halides, cleanly affording the bis-MPA ester diols after an aqueous workup or following crystallization (Figure S2).

Moving on to the second synthetic step of *Route A*, we examined a series of cyclization conditions using CDI with the bis-MPA benzyl ester (**S1a**; Figure S2, Supporting Informa-

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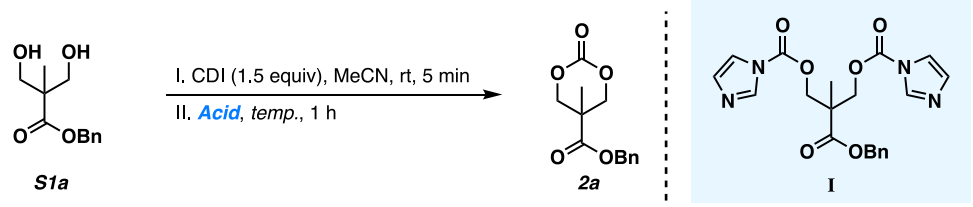
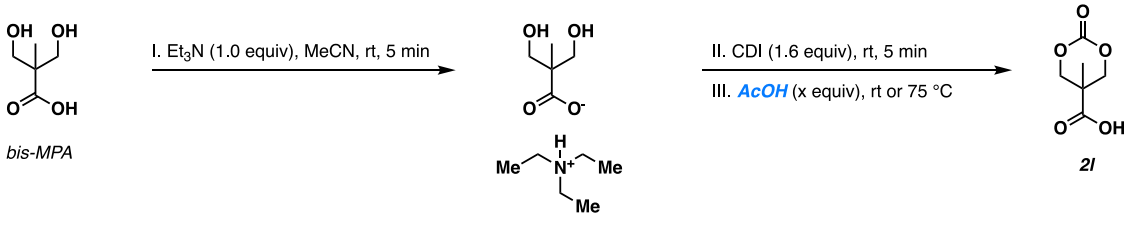
Table 1. Optimization of 1,3-Diol Cyclization for Route A[a]



					product distribution (%)[b]	
entry	acid	acid equiv	temp (°C)	conversion (%)[b]	2a	I
1[c]	none		20	78	9	60
2	none		75	91	49	34
3	MsOH	0.1[d]	75	98	43	55
4	*p*-TsOH	0.1[d]	75	96	50	46
5	TFA	0.1[d]	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***

[a]Reagents and conditions: **1a** (1.0 equiv), CDI (1.5 equiv), EtOAc, rt, 5−10 min, then acid (1−16 equiv), rt−75 °C, and 1 h. [b]Conversion and product distribution determined by ^{1}H NMR of the crude reaction mixture in $CDCl_3$. [c]Reaction time is 5 min. [d]1.0 equiv 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, and MeCN = acetonitrile.

Table 2. Optimization of Bis-MPA Cyclization for Route B[a]



				conversion at different time points (%)[b]			
entry	acid	acid equiv	temp (°C)	0.5 h	1 h	1.5 h	2 h
1	none		25	17	17	17[c]	18[c]
2	AcOH	1	75	65	93	91	92[c]
3	AcOH	4	75	96	>99	>99	>99[c]
4	AcOH	16	75	98	>99	>99[c]	>99[c]

[a]Reagents and conditions: bis-MPA (1.0 equiv), Et_3N (1.0 equiv), MeCN, rt, 5 min, then CDI (1.6 equiv), rt, 5 min, followed by AcOH (1−16 equiv), rt−75 °C, 2 h. [b]Conversion as determined by ^{1}H NMR in $CDCl_3$. [c]Presence of trace ring-opened byproduct detected by ^{1}H NMR. AcOH = acetic acid, MeCN = acetonitrile, Et_3N = triethylamine, and EtOAc = ethyl acetate.

tion). Here, the addition of CDI to a solution of **S1a** in acetonitrile leads to the formation of two distinct products within 5 min as observed by ^{1}H NMR analysis of the crude reaction mixture (entry 1, Table 1). The minor product was identified as the cyclic carbonate monomer **2a** and the major product was believed to be the bis-imidazole carbamate **I** (Table 1). By employing excess CDI, the exclusive formation of **I** allowed for its isolation and characterization (Figure S3A) to confirm its identity.

Prior work has demonstrated that the Brønsted acid activation of imidazole carbamates can be utilized for the synthesis of esters and oxazolidinones.[36−38] As using Brønsted acids to promote cyclization of bis-imidazole carbamates to carbonates has not been reported, we hypothesized that **I** could be activated with an acid to afford the carbonate product **2a** (Table 1). To test this hypothesis, we investigated the effect of a variety of different acids on the product distribution (Table 1). Substoichiometric amounts of acid (entries 3−6, Table 1) provided similar product ratios as compared to the 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 the increased conversion to the desired carbonate product, with 16 equiv affording nearly 96% conversion to **2a** within 1 h (entries 7−11, Table 1). Subjecting the isolated bis-imidazole carbamate **I** to the same reaction conditions afforded nearly identical results (Figure S3B). Interestingly, an equivalent amount of *N*-acyl imidazole was observed to form in the reaction mixture (Figures S3B and S6). The presence of the *N*-acyl imidazole byproduct, in combination with the observed CO_2 gas evolution, suggests the formation of an anhydride intermediate (**D**, Figure S4). Subsequent reaction of the anhydride intermediate (**D**, Figure

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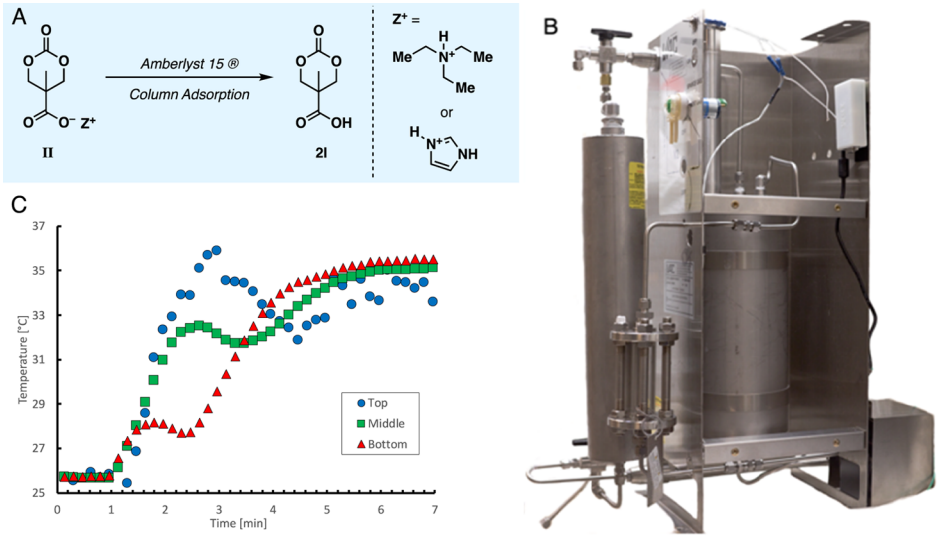

Figure 2. Scale-up purification of **2l**. (A) Scheme of the purification reaction. (B) Photograph of the engineered packed-column setup modified from a commercially available apparatus (for details, see Figure S8, Supporting Information). (C) Temperature traces observed during the purification process. Top, middle, and bottom in the figure key refer to the external thermocouple placement on a packed column. Impure liquid is introduced from the bottom of the column and purified liquid is collected at the top of the column.

S4) with imidazole would produce the observed byproducts and lead to the cyclic carbonate product (Figure S4). While this is not the only possible mechanism, similar ones have been proposed for other acid-promoted reactions with imidazole carbamates in the literature.[37]

Based on the results in Table 1, AcOH was selected as the promoter for cyclization. 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 many acid-labile protecting groups, and (4) a significantly lower propensity to catalyze the polymerization of cyclic carbonate monomers as compared to stronger acids.[39]

We next sought to apply these conditions in *Route B* for the one-pot synthesis of **2l** (Table 2) from bis-MPA, a key intermediate requiring three steps to prepare via the published literature protocols (Figure S1, Route A).[25] The primary obstacle in extending the conditions identified in *Route A* to the direct cyclization of bis-MPA is that carboxylic acids are reactive toward CDI, leading to the formation of acyl imidazoles.[23,36] To mitigate this difficulty, we hypothesized that the treatment of bis-MPA with an amine base such as (Et_3N or DIEA) would deactivate the carboxylic acid[37] and improve the solubility of bis-MPA. To evaluate this hypothesis, we first treated bis-MPA with Et_3N in acetonitrile, followed by the addition of CDI. Analysis of the reaction mixture by ^1H NMR indicated a mixture of products similar to ones identified in *Route A* (Table S1). The distribution of these intermediates was dependent on the amount of CDI used, with the formation of the acyl imidazole intermediate (**III**, Table S1) observed only in small amounts by ^1H NMR when a significant excess of CDI was used (Table S1, entries 1 and 2).[23] Addition of excess AcOH facilitated the cyclization of the imidazole carbamate intermediate (**II**, Table S1) to the corresponding cyclic carbonate **2l** within a reaction time of 1 h (Table 2, entries 3 and 4). We attempted to isolate **II** as its salt (Figure S5A), although a complex mixture of products was obtained. Subjecting this mixture to the reaction conditions did afford smooth conversion to the carbonate **2l** (Figures S5B and S7).

The isolation and purification of **2l** required additional effort as the standard aqueous workup protocol afforded variable yields, presumably due to the increased water solubility of the carbonate. After examining many different workup or extraction protocols, we found that the 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 2A).

To facilitate the purification of the crude reaction mixture on a larger 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 diluted crude reaction solution through the column, facilitating the purification (Figures 2B and S8A). The fluid is introduced at the bottom of the column from a reservoir and the purified solution is collected at the top of the column. In our experiments, we found that a single column was capable of purification of the monomer at the 100 g scale before exhausting the capacity of the charged resin. By the use of Swagelok quick connects incorporating internal valving, the column can be replaced mid-campaign without the use of tools or loss of reaction liquid. This feature allows for the purification of an arbitrary amount of monomer limited by the amount of the available resin. This system simplified the workup and purification procedure on the scale-up and afforded **2l** in 95% yield.

During attempts of purification, it was found that the process generated significant heat as impurities were adsorbed onto the packing material and at these increased scales, adiabatic behavior was 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. As shown in Figure 2C (Figures S9–S12), the temperatures at the top of the column reach a maximum as the liquid is purified. To diminish the temperature change, extra solvent (acetonitrile) was added prior to purification. The slow addition of the reaction contents during the purification in parallel with the ability to replace columns mid-campaign

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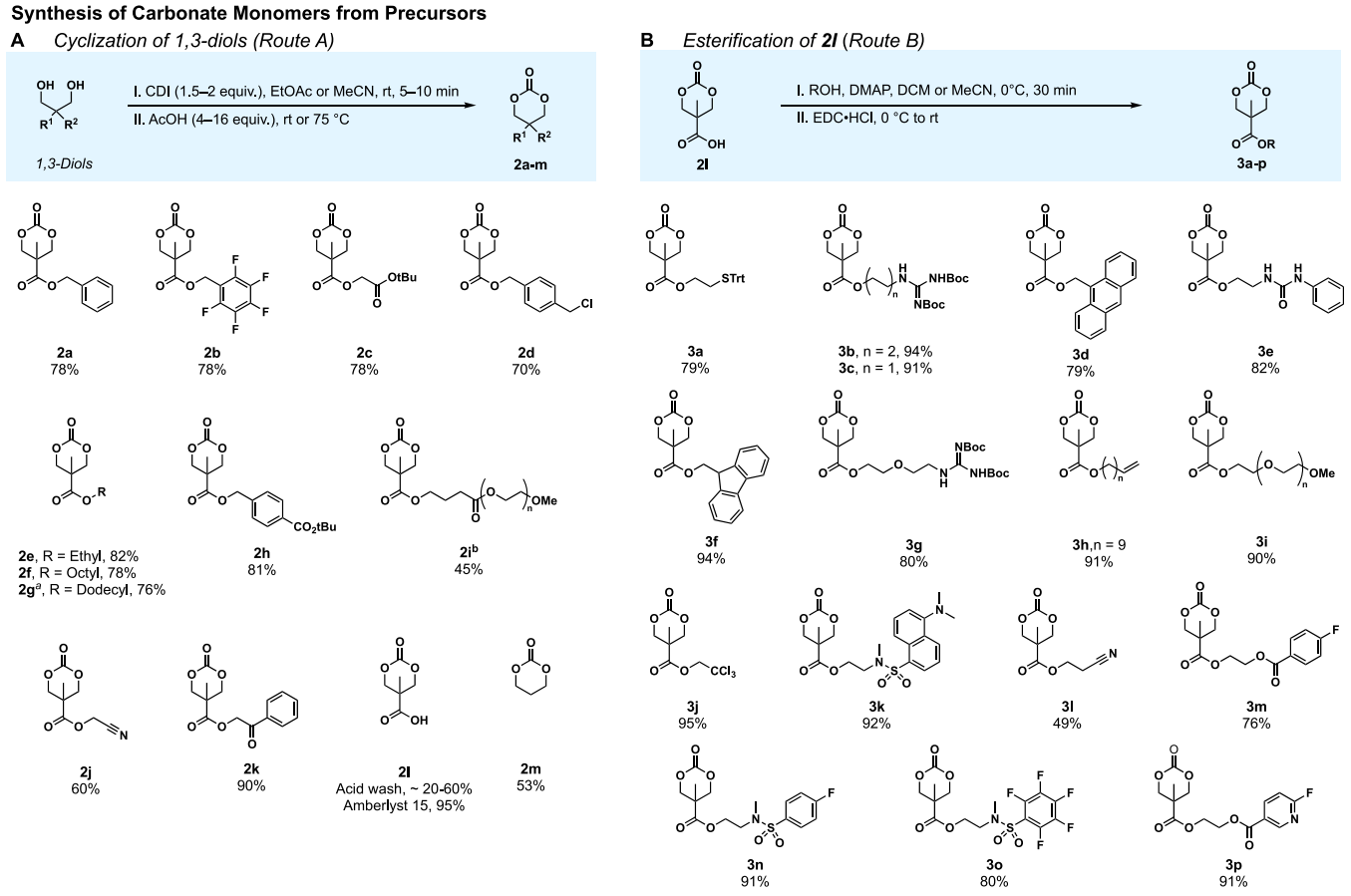

Figure 3. (A) Synthesis of carbonate monomers from functional diols. Reagents and conditions: 1,3-diol (1.0 equiv), CDI (1.5−1.8 equiv), MeCN or EtOAc, rt, 5−10 min, then AcOH (10−16 equiv), reflux 2−16 h. [a]Isolated yield over two steps starting from bis-MPA. [b]Isolated yield over three steps starting from methoxy-terminated polyethylene glycol (M_n = 350). (B) Esterification of **2l** to bis-MPA carbonates. Reagents and conditions: (i) alcohol (1 equiv), DMAP (0.1 equiv), **2l** (1.5 equiv), DCM or MeCN, 0 °C, 0.5 h, (ii) EDC·HCl (1.5 equiv), 0 °C to rt, 16 h. Abbreviations: DMAP = dimethylaminopyridine, DCM = dichloromethane, and EDC·HCl = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride.

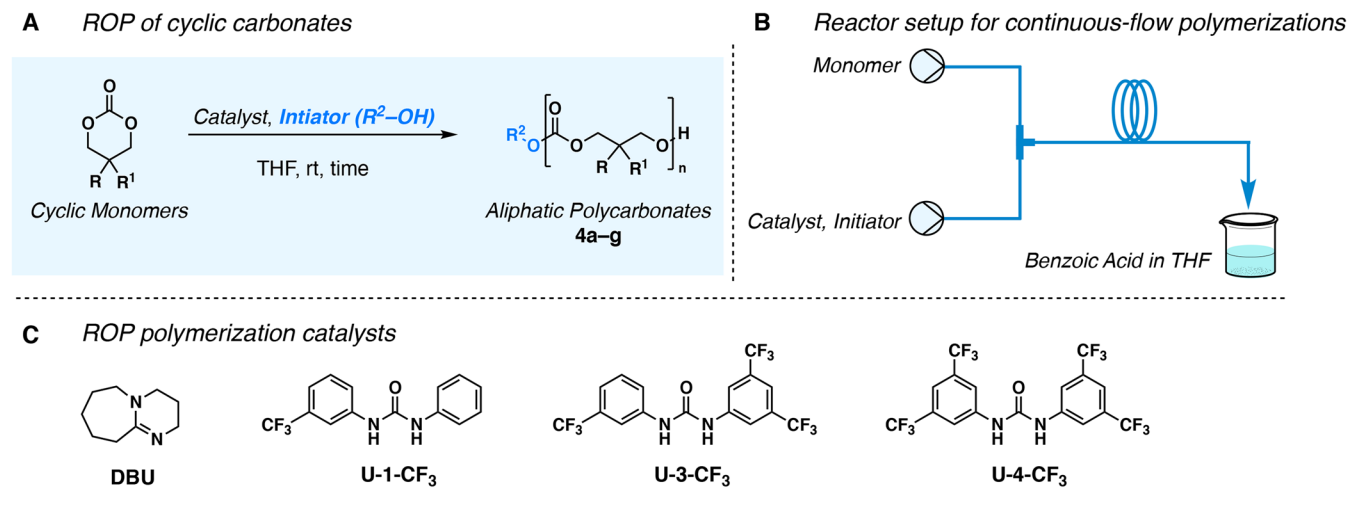

Figure 4. (A) Ring-opening polymerization of cyclic carbonates. (B) Flow reactor setup for polymerization of carbonate monomers. (C) Catalysts used for ring-opening polymerization of carbonates.

would allow for arbitrarily larger scaled reactions (>100 g) without "overheating".

Having addressed the critical cyclization step and developed a scalable purification method for **2l**, we proceeded to evaluate the synthetic scope of both routes in the preparation of a variety of carbonate monomers (Figure 3). In the case of *Route B*, the esterification of **2l** could be accomplished using EDC·HCl to afford the functional carbonate monomer (Figure 3B). Notably, the methodology developed for *Route* A and *Route* B enabled us to prepare carbonate monomers with a variety of pendant functional groups, many of which have been previously reported to be used in a variety of material

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Table 3. ROP Polymerization of Cyclic Carbonate Monomers[a]

entry	monomer	polymer	mode	initiator	catalyst	time[b]	conversion (%)[d]	M_n (GPC)[c]	$Đ$[c]
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

[a]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. [b]Time for flow reaction is the residence time of the reactor. [c]Determined by ^1H NMR of the crude reaction mixture. [d]Measured 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.

applications, in a less toxic and less labor- and time-intensive manner. The monomers were readily isolated in high purity following workup and purification (see Supporting Information). Trimethylene carbonate (**2m**, Figure 3) was also found to be sensitive to aqueous workup and was also purified via filtration through Amberlyst 15 resin (see the Supporting Information).

After demonstrating the effectiveness of both routes in the synthesis of 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 (Figure 4 and Table 3). In all cases, monomers prepared via these methods led to the controlled synthesis of different polycarbonate homopolymers or AB block copolymers with predictable molecular weights and narrow dispersity. The polymers synthesized under continuous flow conditions exhibited very short residence times, consistent with our prior work using flow platforms for polyester and polycarbonate synthesis.[40] The data for the polymerizations and resulting polymers are summarized in Table 3.

CONCLUSIONS

In summary, we have demonstrated a scalable and operationally simple approach for the synthesis of a broad array of functionalized carbonate monomers derived from bis-MPA. This approach (1) obviates the need for toxic chloroformate or phosgene-based reagents, (2) affords byproducts that are easily removed during workup, (3) does not require anhydrous or air-free conditions, (4) replaces the use of high-boiling and/or toxic solvents such as DMF with ethyl acetate or acetonitrile when possible, and (5) minimizes the number of synthetic steps and improves the overall yield of the targeted monomers. Furthermore, this work was motivated in part by the desire to achieve a large-scale and easy monomer synthesis needed for conducting polymerizations in continuous flow. Overall, the time and cost savings of this approach removes barriers in the synthesis and development of polycarbonate materials sourced from bis-MPA.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c02880.

All characterization data for monomers and polymers; experimental procedures; scale-up purification using packed-bed reactor (PBR) adsorption column; trouble-shooting the acid-promoted cyclization of 1,3-diols; polymerization of carbonate monomers; and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

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

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