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Effective Phosphorylation of 2,2′-Methylene-bis(4,6-di-*tert*-butyl) Phenol in Continuous Flow Reactors

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ABSTRACT: Nucleating agent intermediate 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride was synthesized successfully in a continuous flow by the phosphorylation reaction for the first time. After evaluating several different continuous flow reactors, the continuous Coflore agitated cell reactor (ACR) designed based on the continuous stirred-tank reactor (CSTR) principle was proved capable of overcoming the severe channel clogging caused by the precipitation product triethylamine hydrochloride. This can be attributed to the violent agitation and particle size control by the moving agitators. The yield in continuous flow after optimization reached nearly 98% at 100 °C within the residence time of only 4 min and the optimal equivalents of triethylamine and POCl₃ are 2.8 and 1.1, respectively. In contrast to the batch operation, the yield has been increased through continuous operation. This is an effective method for the synthesis of the desired product and exhibits the merits of short residence time, easy operation, and straightforward scale-up.

KEYWORDS: *phosphorylation reaction, continuous flow synthesis, precipitation clogging, process optimization, reactor analysis*

1. INTRODUCTION

2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride is the synthetic intermediate of a series of plastic nucleating agents such as NA-40, NA-45, and NA-71, which are widely used in the modification for mechanical and thermal properties of polypropylene (PP).[1,2] Generally, 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride (**2**) can be prepared by the phosphorylation reaction of 2,2′-methylene-bis(4,6-di-*tert*-butyl) phenol (**1**) and POCl₃ with triethylamine as the acid-binding agent base, as shown in Scheme 1, along with the formation of precipitation product triethylamine hydrochloride (**3**).[3−5] Furthermore, 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride (**2**) can be hydrolyzed to produce 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate (**4**) (Scheme 1), which is the synthetic precursor of nucleating agents and is also considered as a very important chemical in the fine chemical industry.[6−8] A number of synthetic processes for the preparation of **2** in batch reactors have been reported (Table 1). Svara[3] used the reactant POCl₃ as the solvent and *N,N*-dimethylformamide in catalytic amounts as the catalyst and obtained the product only in low yields. Tajima et al.[4] and Nakahara et al.[8] employed triethylamine in catalytic amounts as the acid-binding agent, but the yield obtained was unsatisfactory. Lately, Xin[9] and Gong et al.[10] reported that on increasing the amount of triethylamine in the reaction the yields reached 90%.

Although the preparation of **2** has achieved a satisfactory yield after optimization in a batch reactor,[9,10] the drawbacks of batch operation are still obvious, for example (a) insufficient capability of heat transfer, (b) decrease in production efficiency due to auxiliary operation,[11] (c) consumption of nitrogen to prevent the oxidation of **1**, and (d) dropwise addition of POCl₃, which significantly extends the reaction time. If the

POCl₃ is added too quickly, a conspicuous thermal effect and large masses of HCl acid mist will occur due to the fast reaction rate.

The continuous flow technology has emerged as an excellent choice for setting up a highly efficient and safe process and has been widely used in the coal chemical industry, fine chemical industry, and pharmacy fields.[12−14] The continuous flow reactor has been demonstrated as a strong platform for the continuous synthesis of high-value fine chemicals, functional materials, and pharmaceuticals owing to their larger surface-to-volume ratios, higher mixing efficiency, enhanced heat and mass transfer, tolerance to harsh reaction conditions, precise control over the whole process, excellent process safety, and great airtightness.[15−17] Therefore, the continuous operation mode provides great opportunities for the process intensification of the phosphorylation reaction. However, product **3** is almost insoluble in toluene (the most common solvent in this reaction) and appeared as precipitates. In fact, the manipulation of precipitation reactions in continuous flow reactors is still a huge challenge that persistently hinders the application of continuous flow in fields ranging from fine chemical synthesis to advanced materials manufacturing.[18,19] Accumulation of precipitation products (like halide salts) often results in the sharp increase of system pressure, and then leads to clogging and compelled process shutdown.[20−23] A few methods have been proposed to handle solids in continuous

A

Scheme 1. Reaction for Preparing 2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) Phosphate Chloride (2) and Corresponding Hydrolysis Product 2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) Phosphate (4)
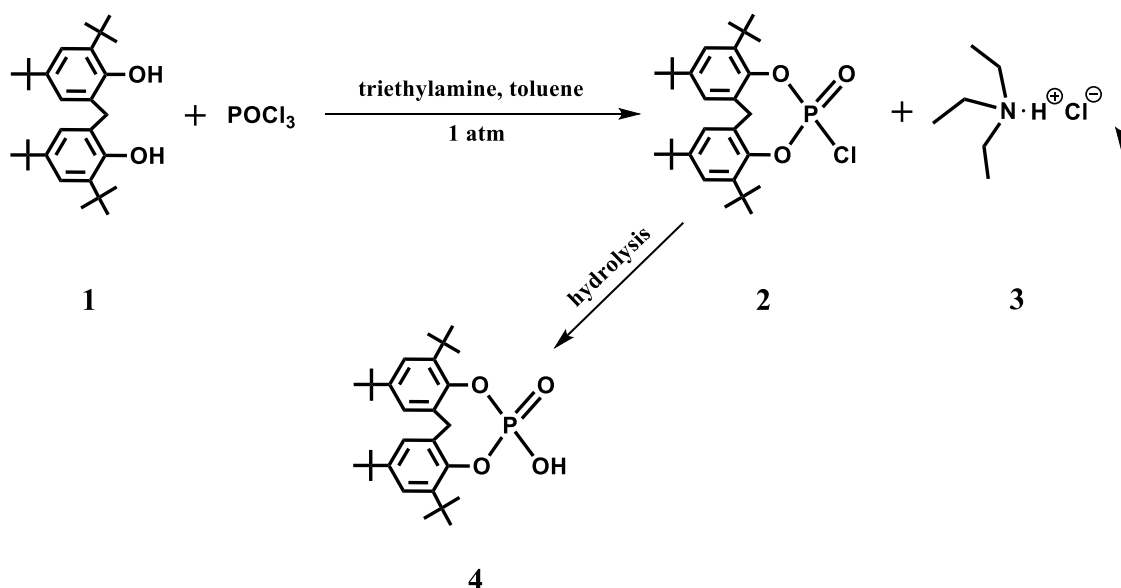

Table 1. Various Synthetic Processes for the Preparation of 2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) Phosphate Chloride (2) in a Batch Reactor

entry	author	solvent	conditions	yield (%)[a]	refs
1	Svara	POCl$_3$	10 h, 105 °C	34	3
2	Tajima	cyclohexane	1.5 h, 20 °C	34	4
3	Nakahara	toluene	2 h, 20 °C	45	8
4	Xin	toluene	6 h, 20 °C	90	9
5	Gong	acetonitrile	2.5 h, 60 °C	90	10

[a]Isolated yields.

flow reactors, such as acoustic power,[24,25] oil drop coating,[26] mechanical energy input (continuous stirring tank and oscillating flow),[27,28] and solvent dissolvable for the precipitation.[29] Noël et al. have overcome the clogging challenges of palladium-catalyzed amination reactions in flow via acoustic irradiation and achieved stable operation of the process.[25] Pomberger et al. developed a small continuous stirred-tank reactor (CSTR) cascade to handle solid-containing photoreactions and realized gram-scale synthesis in 13 h of stable operation, offering a strategy for solid-containing heterogeneous photoflow chemistry.[30] Mao et al. achieved the continuous flow synthesis of antioxidant 168 with chloroform

as the solvent rather than toluene (also the most common solvent in this reaction) due to the excellent solubility of the same product 3 in chloroform.[29]

In this work, we successfully overcame the clogging problem caused by precipitation product 3 and optimized the reaction process conditions in the continuous Coflore agitated cell reactor (ACR). The performances of different continuous flow reactors were also compared. To the best of our knowledge, this is the first time that the complex phosphorylation precipitation reaction of 1 with POCl$_3$ was successfully achieved in a continuous flow, which provided reference-worthy solutions for continuous flow synthesis of similar chemical reactions.

2. RESULTS AND DISCUSSION

To eliminate the precipitates produced, several reaction conditions have been investigated in the batch reactor first. The clogging risk is minimal in the continuous flow reactors if the reaction mixture maintains homogeneous phase rather than gradually becoming a liquid−solid heterogeneous phase. First, the phosphorylation reaction was carried out under different temperatures since the solubility of salt in the solvent generally increases with the temperature. However, the solid content of the reaction mixture did not decrease on increasing the
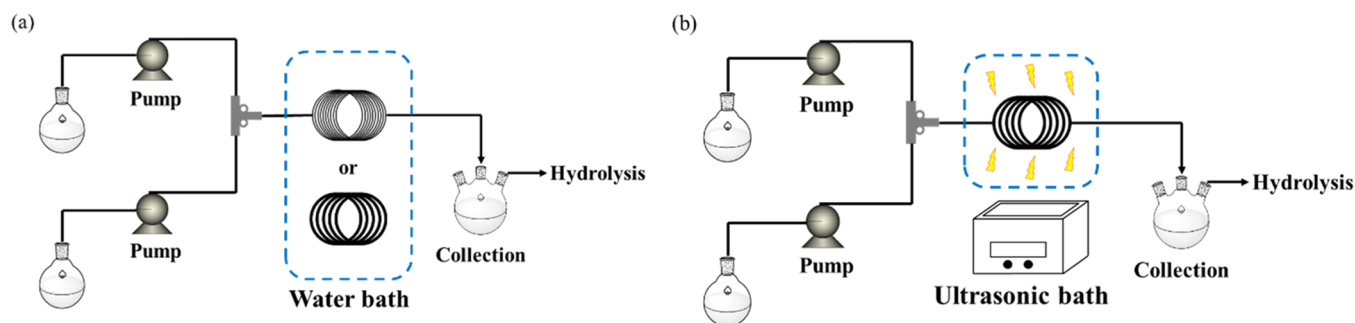

Figure 1. Continuous flow synthesis processes of 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride with a (a) PFA coil-tube reactor and (b) a PFA coil-tube reactor in an ultrasonic bath.
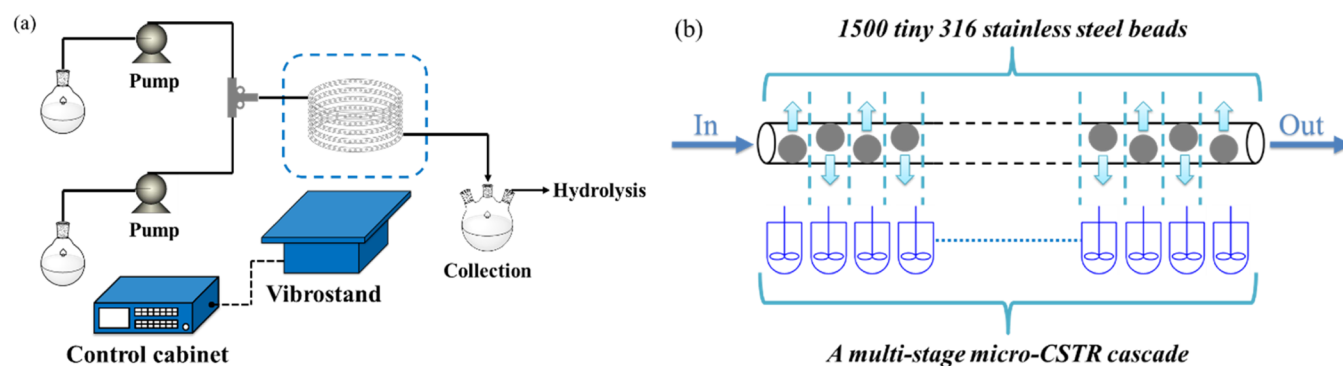
Figure 2. (a) Continuous flow synthesis process of 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride with the continuous vibrating tubular reactor (CVTR) and (b) model of the multistage micro-CSTR cascade.

reaction temperature and was maintained at more than 10 wt % when toluene was used as the solvent. Next, although dichloromethane and 1,2-dichloroethane could slightly decrease the solid content to less than 10 wt % and chloroform can even completely dissolve **3**, high volatility and toxicity limit their applications in production on the industrial scale. Hence, in this work, the tested chloralkanes were not considered as solvents in the development of a continuous flow process. Moreover, other tested solvents could only increase the solid content and especially when using methyl *tert*-butyl ether and chlorobenzene, the solid content reached up to more than 60 wt % and the fluidity of the reaction mixture was greatly reduced. Unfortunately, no other suitable solvent, acid-binding agent, or catalyst screened can achieve the expected process objective. The details of the experimental results and explanations are shown in Section 3 of the Supporting Information.

The perfluoroalkoxy copolymer (PFA) coil-tube reactor is one of the most common and simple continuous flow reactors and its tolerance to the precipitation reaction in the liquid phase is worth exploring. The schematic overview of continuous flow synthetic processes is shown in Figure 1 (see Section 4.3 for details). The upper pressure limits of the plunger pumps were set at 1.5 MPa so that the plunger pumps would stop working automatically if the system pressure exceeded the upper limit, which denotes severe clogging. The experimental results showed that a higher flow rate sped up clogging. This can be explained by a faster growth rate and denser structure of precipitate clusters resulting from the increase in collision frequency and faster wall adhesion.[31] On the other hand, a higher flow rate in continuous flow reactors enhances turbulent contact and leads to a higher mass transfer rate.[32] Thus, the reaction rate could be increased and then the clogging was accelerated. Reducing the reaction concentration and temperature can delay the clogging by decreasing the reaction rate. On the premise of ensuring a satisfying mass and heat transfer effect, a modest increase of the pipe inner diameter from 0.8 to 2.5 mm is certainly conducive to prolonging the stable operation time. However, it turned out that clogging would eventually occur under the tested process conditions and the stable operation time is rarely more than 20 min (see Section 5 in the SI for details).

Ultrasonic wave (UW) irradiation has been regarded as one of the potential methods to handle precipitation reactions in continuous flow reactors.[24,25,27] The sound wave can impose a force on the particles. In cases of the standing wave, the primary radiation force exerted on a particle in flow, F_r, has been given as[24,33,34]

$$F_r = -\left(\frac{2\pi^2 p_0^2 r^3 \beta_S}{3\lambda}\right) \cdot \varphi \cdot \sin\left(\frac{4\pi x}{\lambda}\right) \tag{1}$$

$$\varphi = \left(\frac{5\rho_P - 2\rho_S}{2\rho_P + \rho_S}\right) - \frac{\beta_P}{\beta_S} \tag{2}$$

where p_0 is the acoustic pressure amplitude dependent on the voltage and frequency under which piezoceramic operated, r is the particle radius, β is the compressibility, ρ is the density, φ is the contrast factor, and subscripts S and P refer to the solvent and particle, respectively. Therefore, larger particles are more likely to break up into smaller ones that are less likely to cause clogging. However, though ultrasonic wave irradiation can reduce the particle size according to eq 4 and mitigate particle aggregation and the particle-to-wall interaction to some degree, it was still difficult to dispose of the precipitates accumulated in the continuous flow reactor. As a result, the clogging eventually happened and stable operation could not even be maintained for more than 30 min. The details of experimental results are shown in Section 5 of the Supporting Information.

However, the use of ultrasonic wave irradiation offered a new possible way, namely external force field (mechanical energy input) to handle precipitation reactions in continuous flow reactors. The stirring disturbance has always been regarded as an effective way to deal with the chemical reaction systems containing solids. Based on the continuous stirred-tank reactor (CSTR) principle which has been considered as one of the most widely used and effective methods for handling solid-containing reactions in a continuous flow,[27,30] a new type of continuous vibrating tubular reactor (CVTR) was designed and evaluated. The schematic overview of the synthesis process is shown in Figure 2a. The reactor was made of a coiled 316 stainless steel tube (6.35 mm OD and 4.35 mm ID, 4.5 m length), in which 1500 tiny 316 stainless steel beads (3 mm diameter) were loaded to serve as agitators. The reaction volume V is about 45 mL, calculated according to the following equation

$$V = \pi R^2 L - \frac{4}{3}\pi r^3 \cdot \frac{L}{2r} \tag{3}$$

where R is the pipe inner radius, L is the pipe length, and r is the radius of the bead. The reactor was fixed on a vibrostand connected with a control cabinet. The vibrostand provided an
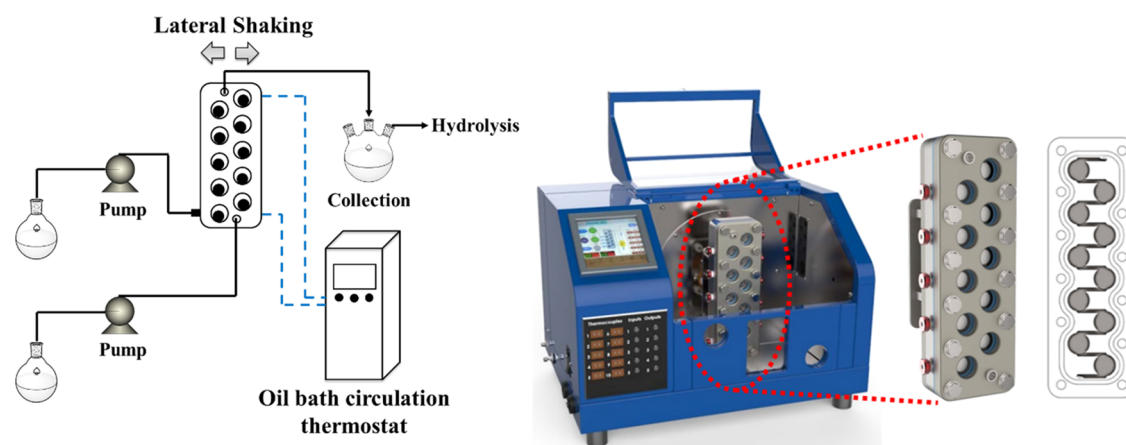
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Figure 3. Continuous flow synthesis process of 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride with Coflore ACR.

intense and effective vertical vibration at a fixed frequency of 50 Hz and amplitude of 5 mm to drive the bead agitators to stir and shear the liquid−solid mixture in flow. Therefore, the reactor is equivalent to a multistage micro-CSTR cascade, as shown in Figure 2b. Herein, we proposed a concept of average equivalent radius R_e, the inner radius of the hollow pipe with the same length and reaction volume as above, which is given as follows

$$V = \pi R_e^2 L \tag{4}$$

Substituting eq 4 in eq 3 gives eq 5 as follows

$$\pi R_e^2 L = \pi R^2 L - \frac{4}{3}\pi r^3 \cdot \frac{L}{2r} \tag{5}$$

As R = 2.175 mm, L = 4.5 m and r = 1.5 mm, the R_e calculated by eq 5 is approximately 1.8 mm. Therefore, the CVTR was compared with a coiled hollow tubular reactor (316 stainless steel, 6 mm OD, and 4 mm ID, 4.5 m length) in terms of the effectiveness of handling the phosphorylation precipitation reaction. The operation conditions were as follows: the residence time was 4 min, the POCl$_3$ equivalent was 1.1, the triethylamine equivalent was 3, the feed concentrations of **1** and POCl$_3$ were 0.36 and 1.77 mol/L, and the feed flow ratio of **1** to POCl$_3$ was 4.5:1. The results showed that a stable operation has been achieved in the CVTR, while the hollow tubular reactor got clogged in 30 min as expected. Hence, it has been demonstrated that the CVTR is capable of handling the phosphorylation precipitation reaction. However, clogging occurred soon once the vertical vibration stopped. Moreover, higher vibration frequencies tended to cause mechanical looseness and wear to the reactor. As a result, it was difficult to set the outer heat exchange jacket. Thus the reaction was carried out only at room temperature (30 °C) and the yield was only 75.9%, less than satisfactory. Perhaps the increase of residence time could increase the yield, but also decrease the throughput significantly.

The continuous Coflore ACR is a continuous flow device that is also designed based on the CSTR principle and provides huge potential for operating the reactions containing solids.[35−37] Figure 3 shows the schematic overview of the continuous flow synthetic process with Coflore ACR. The reactor block (manufactured from Hastelloy C276) contains 10 cells (10 mL for each) with agitators loaded inside. The 10 cells are connected in series by square channels (4 mm in width). The agitators used in this work were spring-like high

shear agitators (0.8 cm^3 for each), as shown in Figure 4a. The total available reaction volume is 92 mL. The reactor was
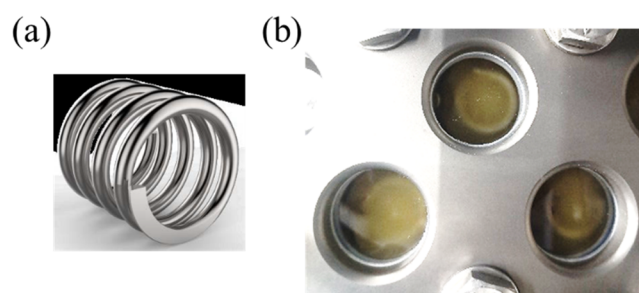

Figure 4. (a) High shear agitator and (b) stirring effect of the agitators on the solid-containing heterogeneous mixture of the phosphorylation reaction.

equipped with an air compressor power system that provides power for the effective lateral shaking of the reactor plate with an adjustable operating frequency of 2−9 Hz. More importantly, besides adjusting the reaction volume, the agitators provide strong shear and agitation on the liquid−solid mixture in flow with drastic shaking of the reactor block. Hence, the heterogeneous mixture could achieve excellent mixing and disturbance, in particular, the sedimentation of solids during the phosphorylation reaction process was avoided (Figure 4b). An oil bath circulation thermostat was used to maintain the predetermined reaction temperature. Two feeds were delivered into the reactor respectively through two inlets set at the bottom of the reactor block and the product was delivered through an outlet set on the upper part. The residence time in the reactor was altered by changing the feed flow rates of plunger pumps.

First, the effect of shaking frequency as a key parameter was studied. The results in Figure 5a show that the variation of the shaking frequency had little effect on the yield. However, the system pressures at frequencies of 4 and 5 Hz increased slowly and indicated a potential risk of clogging. Therefore, the major benefits of the agitator movement were to produce disturbances and prevent sedimentation to ensure steady flow, while the contribution to the mass transfer of the phosphorylation reaction was sufficient. Taking into account the power consumption, 6 Hz should be chosen for further process optimization. It turned out that the ACR has the excellent capability of handling precipitation reactions at
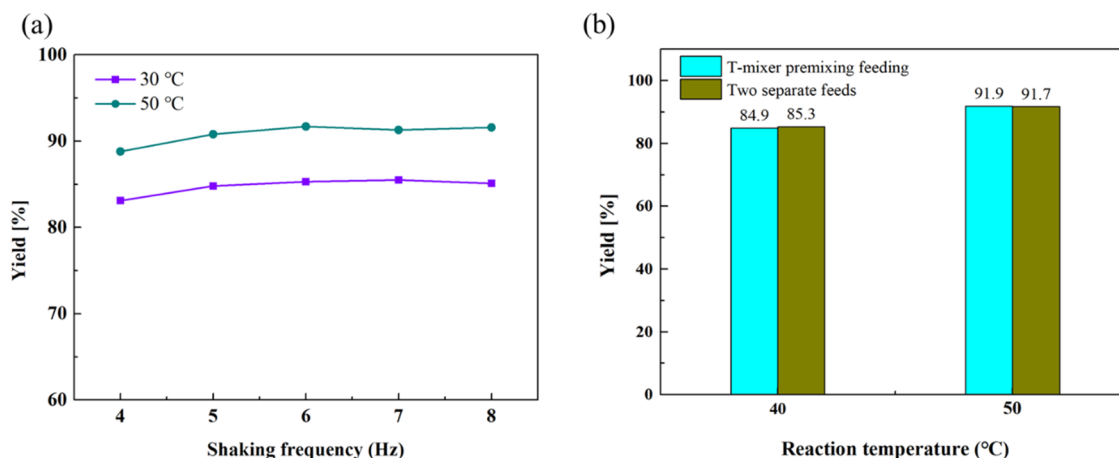
Figure 5. Effects of (a) shaking frequency and (b) feeding methods (at 6 Hz) in the yield. Residence time: 16 min, POCl$_3$: 1.1 equiv, triethylamine: 3 equiv, feed concentration of **1**: 0.36 mol/L and of POCl$_3$: 1.77 mol/L, feed flow ratio of **1** to POCl$_3$: 4.5:1, yield: isolated yields.

appropriate shaking frequencies and no clogging or even pressure increase occurred during the process.

Next, the T-mixer was applied before feeding to examine whether premixing would be beneficial to increase the yield. The results shown in Figure 5b indicate that there was nearly no difference on the yield when comparing T-mixer premixing feeding versus two separate feeds. This indicates that the drastic shaking of agitators in the reactor block provided sufficiently intense and fast mixing of the two reagent feed solutions. In addition, a very short section of the PFA pipe (2.5 mm ID) was employed to connect the T-mixer and reactor inlet. Clogging occurred in the short connecting pipe since the reaction would start as soon as the two feeds contacted. As a result, the precipitates accumulated quickly and then filled the connecting pipe. Hence, premixing was proven unnecessary in this process, and the setup with two separate feeds was adopted for further process optimization.

Then, the effects of reaction temperature and residence time on the yield were researched. As shown in Figure 6, the reaction temperature has a distinct positive effect on the yield at the same residence time, which indicated that the increase of
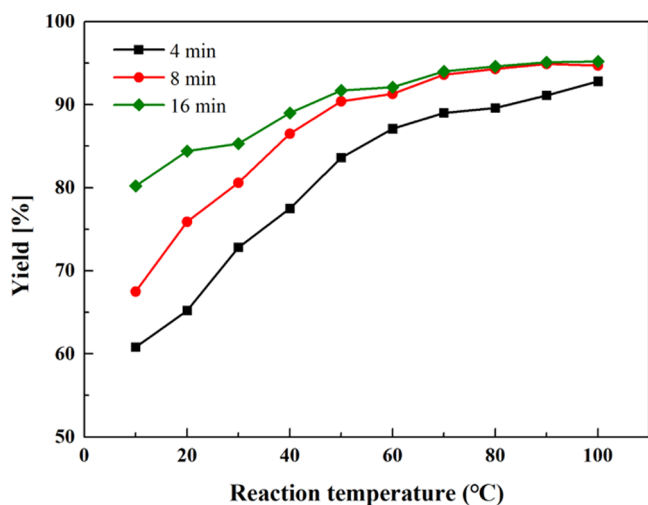

Figure 6. Effects of reaction temperature and residence time on the yield. POCl$_3$: 1.1 equiv, triethylamine: 3 equiv, feed concentration of **1**: 0.36 mol/L and of POCl$_3$: 1.77 mol/L, feed flow ratio of **1** to POCl$_3$: 4.5:1, f: 6 Hz, yield: isolated yields.

reaction temperature significantly accelerated the reaction. Although generally continuous flow reactors can be easily operated at elevated temperatures and pressures, and that is one of the main reasons for choosing continuous flow instead of batch in general, it was difficult to explore the yield at reaction temperature higher than 100 °C in this process. The gasification of the reaction mixture gradually became obvious at temperatures above 100 °C, while the commercially available back pressure regulator (BPR, X-Tec Fluid Technology Co., Ltd.) we used did not tolerate the solid precipitates. The severe clogging in the BPR always led to the shutdown of the process. Furthermore, the residence time also has a distinct positive effect on the yield at the same reaction temperature. But as the reaction temperature gradually increased to 100 °C, the effect of residence time on the yield became less and the yields reached around 95%. Therefore, the decrease in yield caused by the reduction of residence time can be compensated by increasing the reaction temperature. No side reaction occurred when the residence time was extended after the nearly complete conversion of **1**.

To obtain both high yield and high throughput in the ACR reactor before scale-up, a series of further process optimization experiments were carried out based on a residence time of 4 min and reaction temperature of 100 °C. The molar ratio of reactants generally has an obvious effect on the reaction results, thus it is critical to find a proper molar ratio of the other reactants to **1**. The effect of the molar ratio of triethylamine to **1** on the yield was investigated first (Figure 7a). It can be seen that when the equivalents of triethylamine were decreased from 2.8 to 2.1, the yield reduced from 97.6 to 71.0% and the pH of the reaction mixture decreased from about 7.0 to 3.0. This indicated that the phosphorylation reaction of **1** with POCl$_3$ is highly sensitive to the quantity of acid-binding agent base. Based on the experiments in batch, bases weaker than triethylamine led to a decreased yield, and no yield was obtained in the absence of a base (see Section 3 in the SI for details), which demonstrated the high sensibility of the phosphorylation reaction to the alkalinity of the base. Identical conclusions could also be obtained from the phosphorylation reaction mechanism shown in Scheme 2. Triethylamine initiated and participated in the reaction,[38] which also explains the high sensibility of the phosphorylation reaction to the quantity and alkalinity of the base. When the triethylamine equivalent increased from 2.8 to 3.0 and then to 3.2, the pH
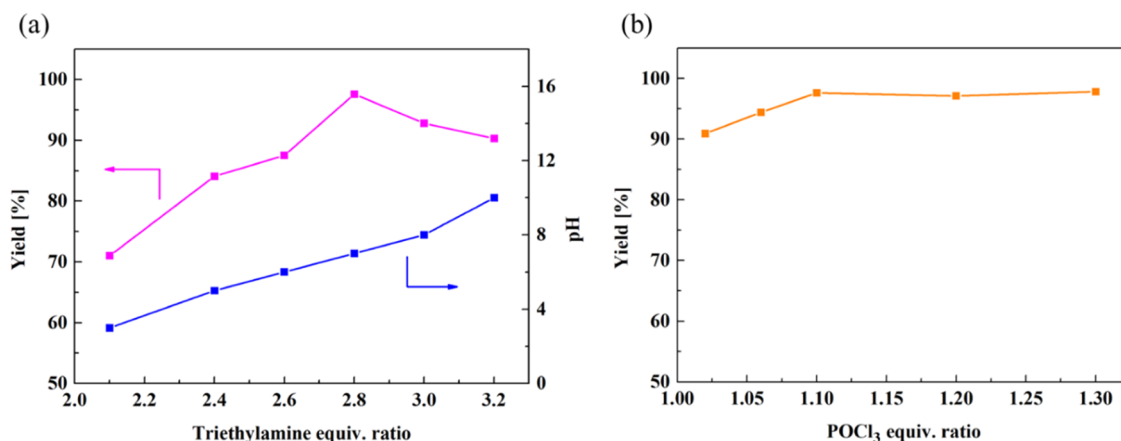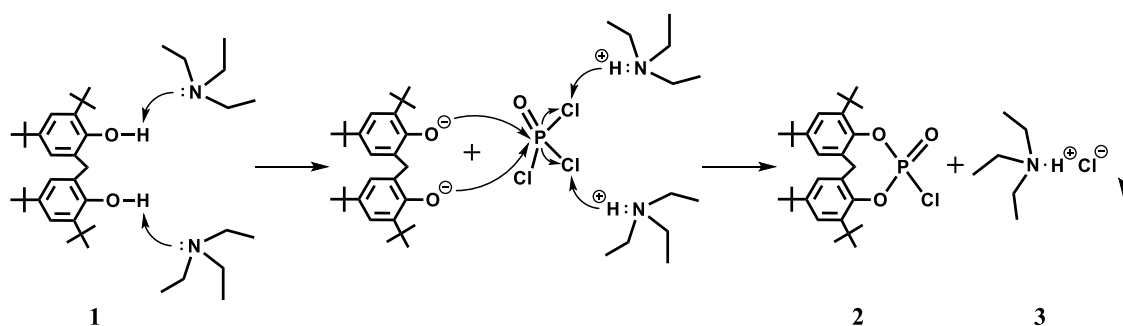
Figure 7. Effects of equivalents of (a) triethylamine (POCl$_3$: 1.1 equiv) and (b) POCl$_3$ (triethylamine: 2.8 equiv) on the yield. T: 100 °C, residence time: 4 min, feed concentration of **1**: 0.36 mol/L and of POCl$_3$: 1.77 mol/L, feed flow ratio of **1** to POCl$_3$: 4.5:1, f: 6 Hz, yield: isolated yields.

Scheme 2. Phosphorylation Reaction Mechanism

increased but the yield decreased from 97.6 to 92.8% and then to 90.3%. This could be due to the increased consumption of POCl$_3$ by redundant triethylamine. Therefore, the optimal molar ratio of triethylamine to **1** was 2.8 at 4 min residence time and 100 °C.

Finally, the molar ratio of POCl$_3$ to **1** was evaluated using 2.8 equivalents of triethylamine (Figure 7b). The yield decreased from 97.6 to 90.9% when the equivalents of POCl$_3$ decreased from 1.1 to 1.02, while a continuous increase in the equivalents of POCl$_3$ from 1.1 to 1.3 resulted in no further distinct change in the yield. Hence, it can be demonstrated that appropriate excess POCl$_3$ contributed to the high conversion of **1**. In consideration of the reactant cost, the POCl$_3$ equivalent should be 1.1.

In the batch reactor, the limited mass transfer effect was detrimental to the mixing of reactants **1** and POCl$_3$ and then the decrease of the reaction rate resulted in incomplete conversion, thus the yield was reduced. However, the enhanced mass and heat transfer efficiencies in the ACR improved the mixing effects and increased the reaction rate. Therefore, the yield achieved by continuous flow (up to 97.6%) was higher than that achieved by batch (90%). In addition, nitrogen which was used to prevent the oxidation of **1** was not required because of the great air tightness of the continuous flow reactor. Moreover, compared to the running time of less of than 30 min in the PFA coil-tube reactors, the continuous synthesis reaction has been achieved in the ACR with more than 8 h of stable operation. Adopting the optimized process conditions in terms of maximizing the yield, the space–time yield (STY) of **2** obtained from continuous operation is more than 40 times higher than that

obtained from the batch operation. The superiority of continuous flow over batch for the phosphorylation reaction is shown in Table 2.

Table 2. Comparison between Continuous Operation and Batch Operation for the Phosphorylation Reaction

	continuous operation	batch operation
yield (%)[a]	97.6	90
STY (kg/m^3·s)	0.529	0.013
triethylamine equivalent	2.8	3.0
nitrogen demand	not required	large masses

[a]Isolated yields.

Relying on external mechanical energy, the ACR ensured that the precipitates could flow along with the liquid phase. Compared to the ultrasonic wave irradiation with high frequency and low amplitude, the shaking with low frequency and high amplitude showed more excellent effectiveness on the handling of the precipitation flow. The stirring is pretty sufficient in every stage of the 10 serial cells and the reactor is equivalent to a 10-stage CSTR cascade, as illustrated in Figure 8. According to the multistage completely mixed flow model, the variance σ^2 can be expressed as the inverse of the total series N, given by the following equation[11,39]

$$\sigma^2 = \frac{1}{N} \tag{6}$$

The axial diffusion model of a closed–closed system describes the relationship between the variance and the dimensionless Pe_m number, given by the following equation[11,39]
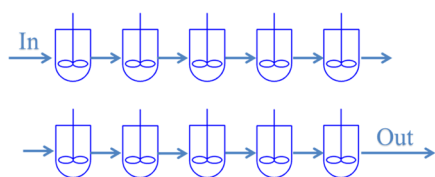
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Figure 8. 10-stage CSTR cascade model of Coflore ACR.

$$\sigma^2 = \frac{2}{Pe_m} - 2\left(\frac{1}{Pe_m}\right)^2\left(1 - e^{-Pe_m}\right) \tag{7}$$

Therein, Pe_m was given as[11,39]

$$Pe_m = \frac{vL_m}{D_{ea}} \tag{8}$$

where v is the average linear velocity of the flow, L_m is the length of a certain fluid section in an infinite straight pipe, and D_{ea} is the axial effective diffusion coefficient. Hence, the total series N can be associated with the axial diffusion model and presented as eq 9

$$\frac{1}{N} = \frac{2}{Pe_m} - 2\left(\frac{1}{Pe_m}\right)^2\left(1 - e^{-Pe_m}\right) \tag{9}$$

When $N = 10$, eq 9 was iteratively computed and the numerical solution of Pe_m is approximately 18.94. This calculated result indicated that the flow in ACR has deviated from the state of fully mixed flow ($Pe_m \rightarrow 0$). However, the flow pattern was still far from the plug flow ($Pe_m \rightarrow +\infty$).[11,39]

The size distributions and morphology features of precipitation particles in the PFA coil-tube reactor with ultrasonic bath, ACR and batch reactor are characterized to study the characteristics of precipitation particles produced from the phosphorylation reaction (Figures 9 and 10 and Table 3). As can be seen from the results, the precipitation particles in the PFA coil-tube reactor, ACR, and batch reactor all consist of a small portion of nanoparticles and the majority are in the micrometer range, including some aggregates. Aggregation may occur during the reaction process among tiny
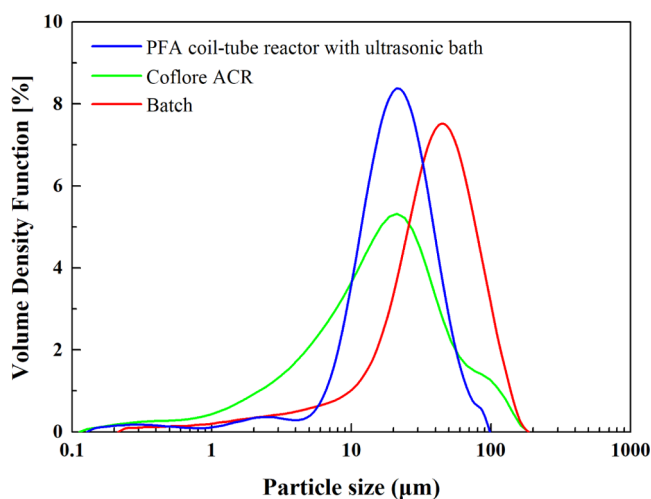

Figure 9. Particle size distribution of precipitation particles in the PFA coil-tube reactor with ultrasonic bath, Coflore ACR, and batch reactor. T: 50 °C, POCl$_3$: 1.1 equiv, triethylamine: 3 equiv, concentration of **1**: 0.36 mol/L and of POCl$_3$: 1.77 mol/L.

particles which adhere to each other for a smaller surface-area-to-volume ratio and thus lower surface tension.[40,41] In batch operation of the phosphorylation reaction, the particles tended to grow freely and formed spherical-like appearances. The particle size in the batch reactor was roughly larger than that in the PFA coil-tube reactor and ACR. The particle size in ACR was close to that in the PFA coil-tube reactor, while had wider distribution. This corresponds with the scanning electron microscopy (SEM) images in which precipitation particles in the PFA coil-tube reactor seem relatively more uniform and regular in columnar appearances, while the shape of those in ACR seems disordered and irregular. It means that the drastic shaking of agitators in the ACR reactor block is capable of controlling particle size, just like the ultrasonic wave irradiation. In addition to this, the movement of agitators exerted violent agitation on precipitates to avoid their sedimentation and adhesion on the reactor wall, which is the key to ensure stable operation of the continuous flow reactor without clogging.

The experiments using the laboratory-scale reactor Coflore ACR demonstrate that a continuous flow sequence for the preparation of intermediate **2** in the manufacturing of a series of plastic nucleating agents is feasible. Despite the excellent performance exhibited by ACR on a small scale, larger quantities of product synthesis have been always desired and can be achieved by a continuous flow reactor with a larger volume. The application of a continuous Coflore agitated tube reactor (ATR) is a favorable strategy for scaling up the process to a larger scale and has become a specially attractive option for heterogeneous reactions, in particular the precipitation reactions.[42−44] Also, the spike-shaped residence time distribution curves measured in this reactor are strong evidence proving that the excellent agitation technology of ATR can reduce back mixing and promote ideal plug flow more efficiently compared to the Coflore ACR.[45] The reaction volume in ATR is 10 L (8 tubes in series and 1.25 L for each) which is 100 times larger than that in ACR. Hence, based on sufficient stirring, mixing, and heat transfer, the corresponding throughput can be increased significantly in contrast to that obtained from ACR when the reaction conditions remain the same. The synthesis process scaled up by ATR is quite promising.

3. CONCLUSIONS

An important intermediate 2,2′-methylene-bis(4,6-di-*tert*-butylphenol) phosphate chloride was synthesized successfully in a continuous flow by the phosphorylation reaction for the first time. Facing the huge challenge of handling the precipitation product triethylamine hydrochloride in a continuous flow, the new type of continuous Coflore ACR designed based on the multistage CSTR cascade principle was demonstrated as a more excellent choice for overcoming the clogging issue and achieve the stable operation compared to the coil-tube reactors. The process was operated steadily for more than 8 h and no pressure increase and clogging were observed. Besides providing intense mixing and controlling particle size, the drastic shaking of the reactor block and agitators were also used to produce violent disturbances, prevent solid sedimentation, and ensure uniformly dispersed steady flow. The shaking frequency had little effect on the yield because of the sufficient mixing in the reactor at the tested frequencies and thus the premixing was not required. An increasing temperature could apparently accelerate the reaction and reduce the residence
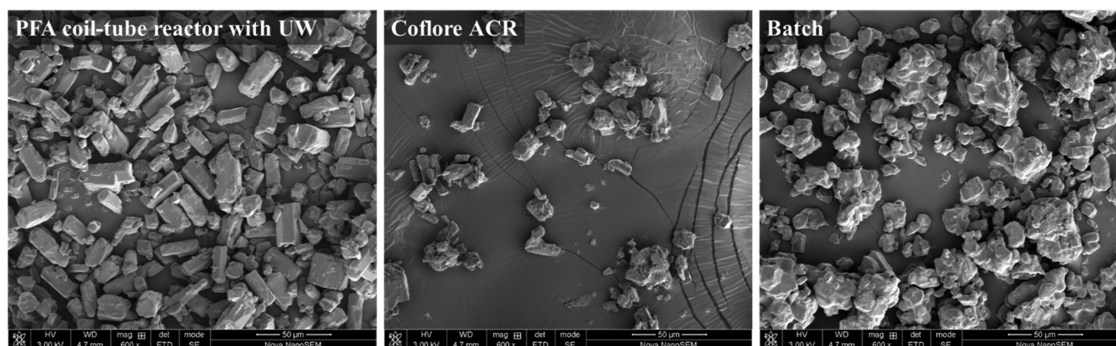
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Figure 10. Morphologies of precipitation particles in the PFA coil-tube reactor with ultrasonic bath, Coflore ACR, and batch reactor. T: 50°C, $POCl_3$: 1.1 equiv, triethylamine: 3 equiv, concentration of **1**: 0.36 mol/L and of $POCl_3$: 1.77 mol/L.

Table 3. Particle Size Distribution Parameters for Precipitation Particles in the PFA Coil-Tube Reactor with Ultrasonic Bath, Coflore ACR, and Batch Reactor

reactor type	particle size[a] (μm)		
	d_{10}	d_{50}	d_{90}
PFA coil-tube reactor with ultrasonic bath	14.08	28.85	58.88
Coflore ACR	12.69	39.14	111.02
batch reactor	27.40	59.07	112.43

[a]d_{10}, 10% of the particle sizes are smaller than this value; d_{50}, 50% of the particle sizes are smaller than this value; d_{90}, 90% of the particle sizes are smaller than this value. T: 50 °C, $POCl_3$: 1.1 equiv, triethylamine: 3 equiv, concentration of **1**: 0.36 mol/L and of $POCl_3$: 1.77 mol/L.

time. With the increasing amount of triethylamine (as an acid-binding agent), the pH of the reaction mixture gradually increased but the yield first increased and then slightly decreased. The yield leveled off with the increasing amount of $POCl_3$. In contrast to the 90% yield obtained within several hours from batch, the yield from continuous flow after optimization reached nearly 98% at 100 °C and 6 Hz within only 4 min and the corresponding optimal equivalents of triethylamine and $POCl_3$ are 2.8 and 1.1, respectively. The continuous agitated technology has provided an available excellent strategy for handling precipitation processes and also offered the basic principles for continuous flow synthesis of similar reactions from laboratory to larger scales.

4. EXPERIMENTAL SECTION

4.1. General Procedures. 2,2′-Methylene-bis(4,6-di-*tert*-butyl) phenol (purity > 99%) was purchased from Shanghai Shengpan New Material Technology Co., Ltd. Ultrapure water was taken from Laboratory Water Purification System purchased from Shanghai Hetai Instrument Co., Ltd. Nitrogen (purity > 99.999%) was purchased from Shanghai Weichuang Standard Gas Analysis Techniques Co., Ltd. All of the other reagents (purity > 99%) were purchased from Shanghai Titan Technology Co., Ltd. All of the reagents were used directly without any further purification. The vibrostand and control cabinet (LS-ZD-50) were purchased from Dongguan LES Test Equipment Co., Ltd. Coflore ACR (ACR-P200) was purchased from AM Technology Co., Ltd., U.K. The air compressor power system (GA-85X) was purchased from Shanghai GREELOY Industrial Co., Ltd. The oil bath circulation thermostat (XT 550) was purchased from LAUDA Technology Co., Ltd., Germany. A melting point meter (WRS-1C,

INESA, Inc., Shanghai) was used to test the melting points. The temperature increased from room temperature at 5 °C/min. The purities of the reactant and product were analyzed using a high-performance liquid chromatography system (HPLC; Agilent 1260, Agilent, Inc.) equipped with a capillary column (Phenomenex Polar-RP C18 4.6 × 150 mm^2). A water/methanol (6:94 v/v) mixture was used as the mobile phase and the elution was carried out at 1 mL/min. The ^{1}H NMR spectrum was recorded on a Bruker Ascend instrument at 500 MHz. Chemical shifts are reported in δ (ppm) referenced to an internal tetramethylsilane (TMS) standard for ^{1}H NMR spectroscopy. The following abbreviations are used to explain multiplicities: s = singlet, d = doublet. A dry laser diffraction particle size analyzer (MASTERSIZER 3000, Malvern, Inc., U.K.) was used to test the particle size distributions of precipitates from the phosphorylation reaction. A scanning electron microscope (SEM, Nova NanoSEM 450, FEI, Inc.) was used to observe the morphological features of precipitation particles from the phosphorylation reaction. An accelerating voltage of 3 kV was used and samples were covered by a 10 nm platinum layer.

4.2. Synthesis Procedure of 2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) Phosphate Chloride in Batch. 2,2′-Methylene-bis(4,6-di-*tert*-butyl) phenol (10.62 g, 25 mmol, 1 equiv), solvent (45 mL), and base (75 mmol, 3 equiv) were added to a 250 mL four-necked flask equipped with condenser and spirit thermometer. After nitrogen was blown slowly into the flask for 10 min, the mixture was stirred and heated to a specific temperature in an oil bath (DF-101S, YUHUA, Inc., Gongyi). Then $POCl_3$ (2.56 mL, 27.5 mmol, 1.1 equiv) was diluted with about 12 mL of the same solvent and dropwise added slowly with a dropping funnel in 30 min. The reaction continued for a few hours before it stopped, and then the nitrogen blow was removed. Due to the great difficulties in separating **2**, the results of the phosphorylation reaction were evaluated using hydrolysis product **4**. The reaction mixture was directly heated to about 95 °C, sufficiently hydrolyzed by steam distillation until all of the solvent has been distilled out. Then, the mixture was naturally cooled to room temperature. The hydrolyzed mixture was filtered, washed with ultrapure water three times, and then dried in a vacuum oven at 80 °C for 6 h to obtain the crude product. Subsequently, the crude product was recrystallized with toluene and dried in a vacuum oven at 80 °C for 6 h to get purified product **4**. The product was weighed to calculate the yield and analyzed with an HPLC system, an NMR spectrometer, and a melting point meter to confirm the purity. To characterize particle size distributions,

particle morphological features, and solid contents, the phosphorylation reaction mixture was filtered and the precipitates obtained were dried in a vacuum oven at 80 °C for 6 h.

4.3. Synthesis Procedure of 2,2′-Methylene-bis(4,6-di-*tert*-butylphenol) Phosphate Chloride in a Continuous Flow. 2,2′-Methylene-bis(4,6-di-*tert*-butyl) phenol and triethylamine were dissolved in toluene at 70 °C and then cooled as solution A. POCl₃ was dissolved in toluene at room temperature as solution B. The two solutions were introduced into the reactor, respectively, at predetermined flow rates via two plunger pumps (MPF0502C, Sanotac, Inc., Shanghai). As shown in Figure 1a, the process was mainly constructed with a PFA T-mixer (2.5 mm ID, Runze Fluid, Inc., Nanjing) and a PFA coil-tube reactor (Runze Fluid, Inc., Nanjing) of 10 m length with two different diameters (1.59 mm OD, 0.8 mm ID, and 3.175 mm OD, 2.5 mm ID) used in the experiments. The reactor was immersed inside the water bath (RCT D S025, IKA, Inc., DER) to maintain a preset temperature. The whole experimental setup was filled with reaction solvent toluene in advance and subsequently flushed with reaction mixture for three residence times under the reaction conditions to achieve steady-state data collection. Then, 90 mL of effluent from the outlet was collected in a 250 mL four-necked flask. The reaction mixture was directly heated to about 95 °C, sufficiently hydrolyzed by steam distillation until all of the solvent has been distilled out. Then the mixture was naturally cooled to room temperature. The hydrolyzed mixture was filtered, washed with ultrapure water three times, and then dried in a vacuum oven at 80 °C for 6 h to obtain the crude product. Then the crude product was recrystallized with toluene and dried in a vacuum oven at 80 °C for 6 h to get purified product **4**. The product was weighed to calculate the yield from the ratio of the actual final dry product mass obtained from the effluent collected in the four-necked flask to the corresponding theoretical product mass after complete conversion and analyzed with an HPLC system, an NMR spectrometer, and a melting point meter to confirm the purity. To characterize the size distribution and morphological features of the precipitation particles, the phosphorylation reaction mixture was filtered and the obtained precipitates were dried in a vacuum oven at 80 °C for 6 h.

The reactor shown in Figure 1b was immersed inside the ultrasonic water bath with a heating function (SK2510LHC, KUDOS, Inc., Shanghai) and the others were identical to those in Figure 1a.

The reactor shown in Figure 2a was the CVTR fixed on a vibrostand connected with a control cabinet and the others were identical to those in Figure 1a.

The reactor shown in Figure 3 was the Coflore ACR and the others were identical to those in Figure 1a.

ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00105.

> Descriptions of experimental procedures, further details of experimental results, data of HPLC spectra, ¹H NMR spectrum, and melting points (PDF)

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Notes

The authors declare no competing financial interest.

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