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Flash production of organophosphorus compounds in flow

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ABSTRACT

Flow synthesis techniques have received a significant amount of attention due to their high productivity. However, when reaction condition is heterogeneous, it is usually difficult to adapt it to flow synthesis. Herein, by selecting appropriate reagents, the synthesis of phosphate esters, which is commonly heterogeneous, was made homogeneous, enabling synthesis in flow systems. In addition, reaction rate was accelerated compared to the batch system. It was demonstrated that not only can the high productivity of flow synthesis be achieved in flow, but also high productivity can be achieved by accelerating the reaction. Finally, we demonstrated the synthesis of the Akiyama–Terada catalyst, a chiral organocatalysts, in a short period.

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Introduction

Flow synthesis technology has attracted increasing attention in recent years for the production of chemicals because it is highly productive, safe, and reproducible [1–3]. In particular, the flow can help achieve fast reactions that can be completed in a few seconds or less [4,5], because flow microreactors realize highly efficient heat removal compared to batch-type reactors with poor heat transport efficiency. Therefore, productivity can be improved by continuous production, rapid production can be expected by high-rate reactions, and a significant improvement in the production of chemicals can be expected.

Phosphate esters and phosphite esters are not only important skeletons of biomolecules, but also one of the most important industrial compounds that are applied as catalysts [6–9] and flame retardants [10,11]. A general procedure for the synthesis of phosphoric acid triesters involves the reaction of phosphoryl chloride with an alcohol [12]. Since hydrochloric acid is released in this reaction, triethylamine is added to trap it, resulting in salt formation and precipitation [13–16]. Thus, this reaction condition is heterogeneous and cannot be easily applied in a flow system.

In this paper, we report the synthesis of phosphate esters and phosphite esters in a homogeneous system and the achievement of their continuous production in flow. Particularly, the synthesis of triaryl phosphite was demonstrated via continuous operation and high productivity was achieved by using a high-rate reaction. Additionally, the Akiyama–Terada catalyst [6,7], which is one of

the most important organic chiral catalysts, was synthesized in a short period.

Results and discussions

First, phosphoryl chloride was added dropwise to an alcohol in dichloromethane (DCM) in the presence of triethylamine (TEA) as a base and 4-dimethylaminopyridine (DMAP) as a catalyst, similar to the protocol widely used in batch reactors. Consequently, a considerable amount of white solid was precipitated (Fig. 1a). In contrast, no precipitation was observed when tributylamine (TBA) (having a longer alkyl chain) was used as the base instead of TEA (Fig. 1b). This may be because of the improved solubility of the TBA salt of hydrochloric acid owing to its long alkyl chain. Therefore, the synthesis of phosphate esters (usually heterogeneous systems in batch reactions) can be achieved in a homogeneous system by changing the amine.

For the synthesis of phosphate esters, we compared the batch system with the flow system (Table 1). 2-Phenylethylalcohol, an aliphatic alcohol bearing an aromatic group to facilitate detection by UV–vis spectroscopy, was selected as the alcohol (Scheme 1). As mentioned above, phosphoryl chloride was added dropwise to the alcohol at 0 °C and stirred at room temperature in the batch system. To confirm the progress of the reaction, HPLC yields were determined immediately after the addition of phosphoryl chloride and 1 h after the addition. When a catalytic amount of DMAP (0.1 eq.) was added, as in the general conditions (entry 1), the yield was 63% immediately after the addition of phosphoryl chloride, and it decreased slightly as the reaction was carried out further at room temperature. When 1 eq. of DMAP was used, the yield

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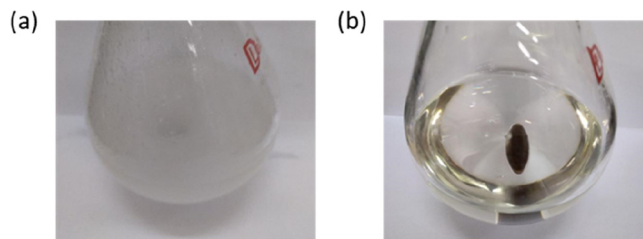


Fig. 1. The synthesis of phosphate triester in a flask. (a) When triethylamine was used as a base, white solids were observed to precipitate. (b) When tributylamine was used, no precipitation was observed.

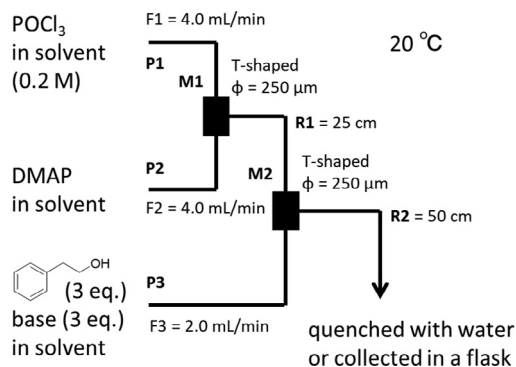


Fig. 2. Schematic diagram of a flow microreactor system for phosphate ester. Microtube precooling units: P1, P2, P3; micromixers: M1, M2; microtube reactors: R1, R2.

was ~50%. Although the reaction was accelerated by increasing the amount of DMAP added, heat removal was insufficient in the batch system, resulting in reduced yield.

The synthesis was investigated using a flow microreactor. DMAP probably forms a 1:1 complex with phosphoryl chloride and activates it. Therefore, in microflow synthesis, where high heat transfer efficiency can be achieved, the use of an equivalent amount of DMAP to that of phosphoryl chloride was expected to activate it effectively and enhance the reaction rate. The procedure

for phosphate ester synthesis was as follows: a solution of phosphoryl chloride (0.2 M in DCM, flow rate: 4.0 mL min⁻¹) and a solution of DMAP (0.2 M in DCM, flow rate: 4.0 mL min⁻¹) were introduced into M1 (T-shaped, $\phi = 250 \mu\text{m}$) and R1 ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$ ($t^{\text{R1}} = 2.9 \text{ s}$)) at $T = 20^\circ\text{C}$ by using syringe pumps to produce the activated species. A reaction with 2-phenylethanol (0.6 M in DCM, flow rate: 2.0 mL min⁻¹) was carried out in M2 ($\phi = 250 \mu\text{m}$) and R2 ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$ ($t^{\text{R2}} = 2.4 \text{ s}$)) at the same temperature (Fig. 2). After steady state was reached, the resulting solution was quenched with water or collected in a dry flask. The collected solution was stirred at room temperature for 1 h.

As shown in entry 4 of Table 1, in the flow system, phosphoric acid triester was obtained in 81% yield within a few seconds (2.4 s). The reaction proceeded quantitatively (HPLC yield of 104%) for 1 h with additional stirring, and the isolated yield was found to be 88%. In this way, a high-rate synthesis was achieved in the flow system compared to that in the batch system, where the reaction time was several hours. On the contrary, when DMAP (0.5 eq.) was used, the yield decreased to 25%. This suggests that the use of a microreactor enabled efficient activation of phosphoryl chloride and DMAP in a ratio of 1:1 and enhanced the reaction rate. Furthermore, even when acetone was used as the solvent, phosphate triester was achieved in good yield, although the reaction was slower than when dichloromethane was used. Acetone availability is valuable for industrial production.

The synthesis of phosphates and phosphites was also studied under the same conditions. When phosphoryl chloride was reacted with phenol (an aromatic alcohol) in the flow, the reaction rate was similar to that in the batch system. In contrast, the reaction proceeded quantitatively for 1 h after the flow synthesis (Table 2, entries 1–2). When phosphorus trichloride was reacted with ethanol (an aliphatic alcohol), the reaction rates were same in both the batch and flow systems, and excellent yields were achieved in a short period (Table 2, entries 3–4). When phosphorus trichloride reacted with phenol, the reaction rate in the flow system was higher than that in the batch system, and triaryl phosphite was achieved in excellent yields (Table 2, entries 5–6) within a few seconds.

We focused on the fast synthesis of triaryl phosphite in the flow system and phosphorus trichloride was reacted with other

Table 1

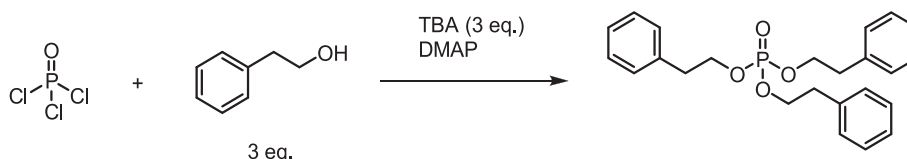
Comparison of macro batch and microflow systems.

Entry		DMAP eq.	Base	Solvent	HPLC yield (%)	
					0 min ^{*1}	60 min
1	batch reactor	0.1	TBA	DCM	63	57
2		1	TBA	DCM	53	55
3 ^{*2}			TEA	DCM	35	44
4	Microreactor	1	TBA	DCM	81	104 (88) ^{*3}
5		0.5		DCM	25	–
6		1		acetone	46	75

^{*1} In a batch system, reaction mixture was collected and quenched immediately after an addition of phosphoryl chloride. When microreactor was used, reaction (residence) time was 2.4 s.

^{*2} White solids were observed.

^{*3} Isolated yield.



Scheme 1. Synthesis of 2-phenylethyl phosphate.

Table 2

HPLC yields of a phosphate and phosphites using a batch reactor and a microreactor.

Entry	Phosphorous source	Alcohol		HPLC yield (%)	
				0 min	60 min
1	POCl ₃	PhOH	Batch reactor	66	63
2			Microreactor	52	98
3	PCl ₃	EtOH	Batch reactor	85 ^{*1}	90 ^{*1}
4			Microreactor	85 ^{*1}	71 ^{*1}
5	PCl ₃	PhOH	Batch reactor	67	85
6			Microreactor	92	90

^{*1} GC yield.**Table 3**

HPLC yields of BINOL-derived phosphoric acid using a batch reactor and a microreactor.

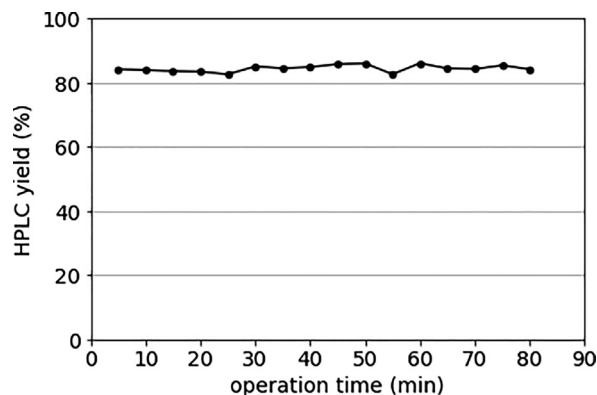
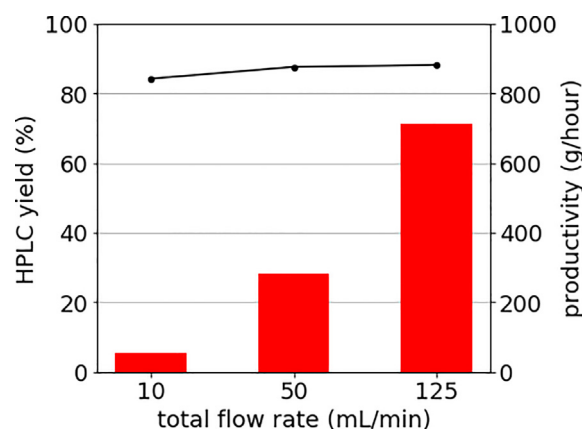
	HPLC yield (%)	
	0 min	60 min
Batch reactor	35	26
Microreactor	78 (74) ^{*2}	–

^{*2} Isolated yield.

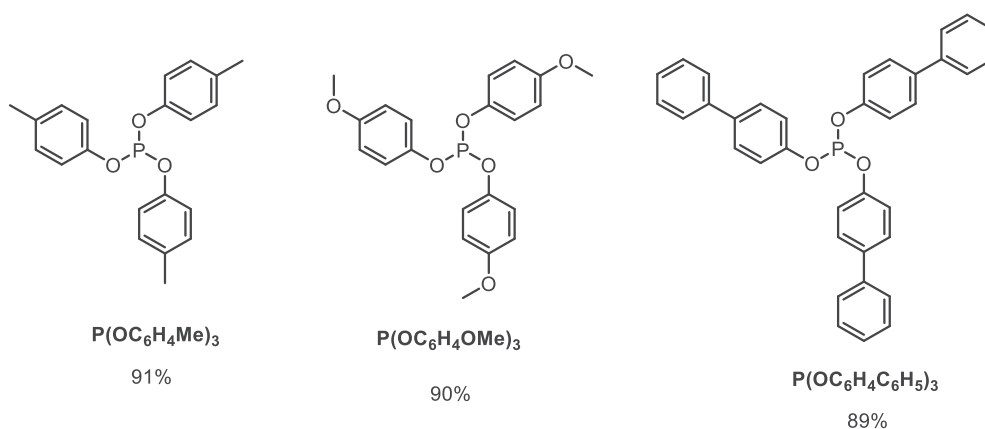
aromatic alcohols, as summarized in Scheme 2. The reaction proceeded in excellent yields with phenols bearing methyl, methoxy, or phenyl group. In addition, the dependence of the yield on residence time indicated that the reaction was very fast and was completed in at least 1.2 s for all substrates (Fig. S1).

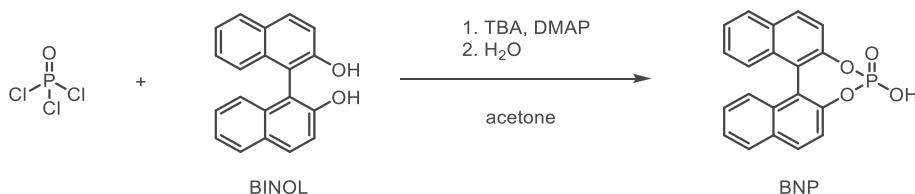
Next, we focused on the productivity of P(OC₆H₄C₆H₅)₃. Using a diaphragm pump [17], P(OC₆H₄C₆H₅)₃ was continuously produced for 80 min, with an average yield of 84%, as shown in Fig. 3. The flow rate and internal pressure were sufficiently stable during 80 min of continuous operation (Fig. S3), suggesting that a longer operation was possible. To achieve even higher productivity, the synthesis was carried out at 5 and 12.5 times the flow rate (Fig. 4). A productivity of 713 g/h with 88% yield was demonstrated when the synthesis was carried out at 12.5 times the flow rate (F1 = F2 = 50 mL/min, F3 = 25 mL/min).

Phosphate ester derivatives bearing a BINOL skeleton (BNPs) are known as Akiyama–Terada catalysts and act as chiral organocatalysts [6,7]. This BNP molecule is usually synthesized by dropping phosphoryl chloride into a suspension of BINOL in pyridine [18]. Alternatively, it can be obtained via long-term reaction in dichloromethane [19]. Under both conditions, the mixture is a heterogeneous system because of the poor solubility of BINOL.

**Fig. 3.** Continuous production in flow using diaphragm pumps.**Fig. 4.** Improving productivity by increasing flow rates. Plots indicate HPLC yield and bars indicate productivity.

BINOL was dissolved in acetone to obtain a homogeneous mixture under the conditions mentioned in entry 6 of Table 1. Thus, we explored the synthesis of BNP using acetone as the solvent (Scheme 3). In the batch system, the yield was 35% immediately after the addition of phosphoryl chloride, and the yield decreased with increasing reaction time. On the other hand, in the flow system, BNP was synthesized in a high yield (78%) within 2.4 s; the isolated yield was 74% (Table 3).

**Scheme 2.** HPLC yields of triaryl phosphite using micro flow system.



Scheme 3. Synthesis of BINOL-derived phosphoric acid.

Conclusions

The synthesis of phosphate esters was performed in a homogeneous manner using TBA as a base, enabling the synthesis in a flow system. The same reaction conditions were applied to various phosphates and phosphites. Furthermore, we succeeded in improving productivity in terms of long-term continuous production and rapid reaction. Finally, BNP, a chiral organocatalyst, was obtained in high yields in a short period.

We showed that a heterogeneous reaction in a batch system can become homogeneous and adaptable to a flow system by selecting appropriate reagents. We also demonstrated that it is possible to increase productivity by increasing the reaction rate. With this approach, the advantages of flow technology over the batch systems will become increasingly significant.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2021.153364>.

References

- [1] K. Geyer, J.D.C. Codée, P.H. Seeberger, Microreactors as tools for synthetic chemists—The chemists' round-bottomed flask of the 21st Century?, *Chem. Eur. J.* 12 (33) (2006) 8434–8442.
- [2] R.L. Hartman, J.P. McMullen, K.F. Jensen, Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis, *Angew. Chem. Int. Ed.* 50 (33) (2011) 7502–7519, <https://doi.org/10.1002/anie.201004637>.
- [3] F. Fanelli, G. Parisi, L. Degennaro, R. Luisi, Contribution of microreactor technology and flow chemistry to the development of green and sustainable synthesis, *Beilstein J. Org. Chem.* 13 (2017) 520–542, <https://doi.org/10.3762/bjoc.13.51>.
- [4] H. Kim, K.I. Min, K. Inoue, J. Imdo, D.P. Kim, J. Yoshida, Submillisecond organic synthesis: outpacing fries rearrangement through microfluidic rapid mixing, *Science* 352 (6286) (2016) 691–694, <https://doi.org/10.1126/science.aaf1389>.
- [5] M. Colella, A. Nagaki, R. Luisi, Flow technology for the genesis and use of (highly) reactive organometallic reagents, *Chem. -Eur. J.* 26 (1) (2020) 19–32, <https://doi.org/10.1002/chem.201903353>.
- [6] M. Terada, Chiral phosphoric acids as versatile catalysts for enantioselective transformations, *Synthesis* 2010 (12) (2010) 1929–1982, <https://doi.org/10.1055/s-0029-1218801>.
- [7] M. Rueping, A. Kuenkel, I. Atodiresei, Chiral Brønsted acids in enantioselective carbonyl activations – activation modes and applications, *Chem. Soc. Rev.* 40 (9) (2011) 4539–4549, <https://doi.org/10.1039/C1CS15087A>.
- [8] D.A. Albisson, R.B. Bedford, P. Noelle Scully, S.E. Lawrence, Orthopalladated triaryl phosphite complexes as highly active catalysts in biaryl coupling reactions, *Chem. Commun. (Cambridge, U. K.)* 19 (1998) 2095–2096, <https://doi.org/10.1039/a806041j>.
- [9] A. Zapf, M. Beller, Palladium/phosphite catalyst systems for efficient cross coupling of aryl bromides and chlorides with phenylboronic acid, *Chem. Eur. J.* 6 (10) (2000) 1830–1833.
- [10] I. van der Veen, J. de Boer, Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis, *Chemosphere* 88 (10) (2012) 1119–1153, <https://doi.org/10.1016/j.chemosphere.2012.03.067>.
- [11] S. Hörold, Phosphorus-based and intumescent flame retardants, in: C.D. Papaspyrides, P. Kiliaris (Eds.), *Polymer Green Flame Retardants*, Elsevier, Amsterdam, 2014, pp. 221–254.
- [12] C.R. Noller, G.R. Dutton, Note on the preparation of trialkyl phosphates and their use as alkylating agents, *J. Am. Chem. Soc.* 55 (1) (1933) 424–425, <https://doi.org/10.1021/ja01328a506>.
- [13] K. Täuber, F. Marsico, F.R. Wurm, B. Scharrel, Hyperbranched poly (phosphoester)s as flame retardants for technical and high performance polymers, *Polym. Chem.* 5 (24) (2014) 7042–7053, <https://doi.org/10.1039/C4PY00830H>.
- [14] J.C. Markwart, A. Battig, M.M. Velencoso, D. Pollok, B. Scharrel, F.R. Wurm, Aromatic vs. aliphatic hyperbranched polyphosphoesters as flame retardants in epoxy resins, *Molecules* 24 (21) (2019) 3901, <https://doi.org/10.3390/molecules24213901>.
- [15] M. Patel, S. Mestry, G. Phalak, S. Mhaske, Novel catechol-derived phosphorus-based precursors for coating applications, *Polym. Bull.* 77 (5) (2020) 2183–2203, <https://doi.org/10.1007/s00289-019-02855-3>.
- [16] L. Fang, J. Sun, X. Chen, Y. Tao, J. Zhou, C. Wang, Q. Fang, Phosphorus- and sulfur-containing high-refractive-index polymers with high tg and transparency derived from a bio-based aldehyde, *Macromolecules* 53 (1) (2020) 125–131, <https://doi.org/10.1021/acs.macromol.9b01770>.
- [17] Y. Nakahara, M. Furusawa, Y. Endo, T. Shimazaki, K. Ohtsuka, Y. Takahashi, Y.Y. Jiang, A. Nagaki, Practical continuous-flow controlled/living anionic polymerization, *Chem. Eng. Technol.* 42 (10) (2019) 2154–2163, <https://doi.org/10.1002/ceat.201900160>.
- [18] J. Jacques, C. Fouquey, Enantiomeric (S)-(+)- and (R)-(-)-1,1'-Binaphthyl-2,2'-Diyl Hydrogen Phosphate, *Org. Synth.* 67 (50) (1989), <https://doi.org/10.15227/orgsyn.067.0001>.
- [19] S. Nakamura, N. Matsuda, M. Ohara, Organocatalytic enantioselective azafriedel-crafts reaction of cyclic ketimines with pyrroles using imidazolinephosphoric acid catalysts, *Chem. Eur. J.* 22 (28) (2016) 9478–9482.