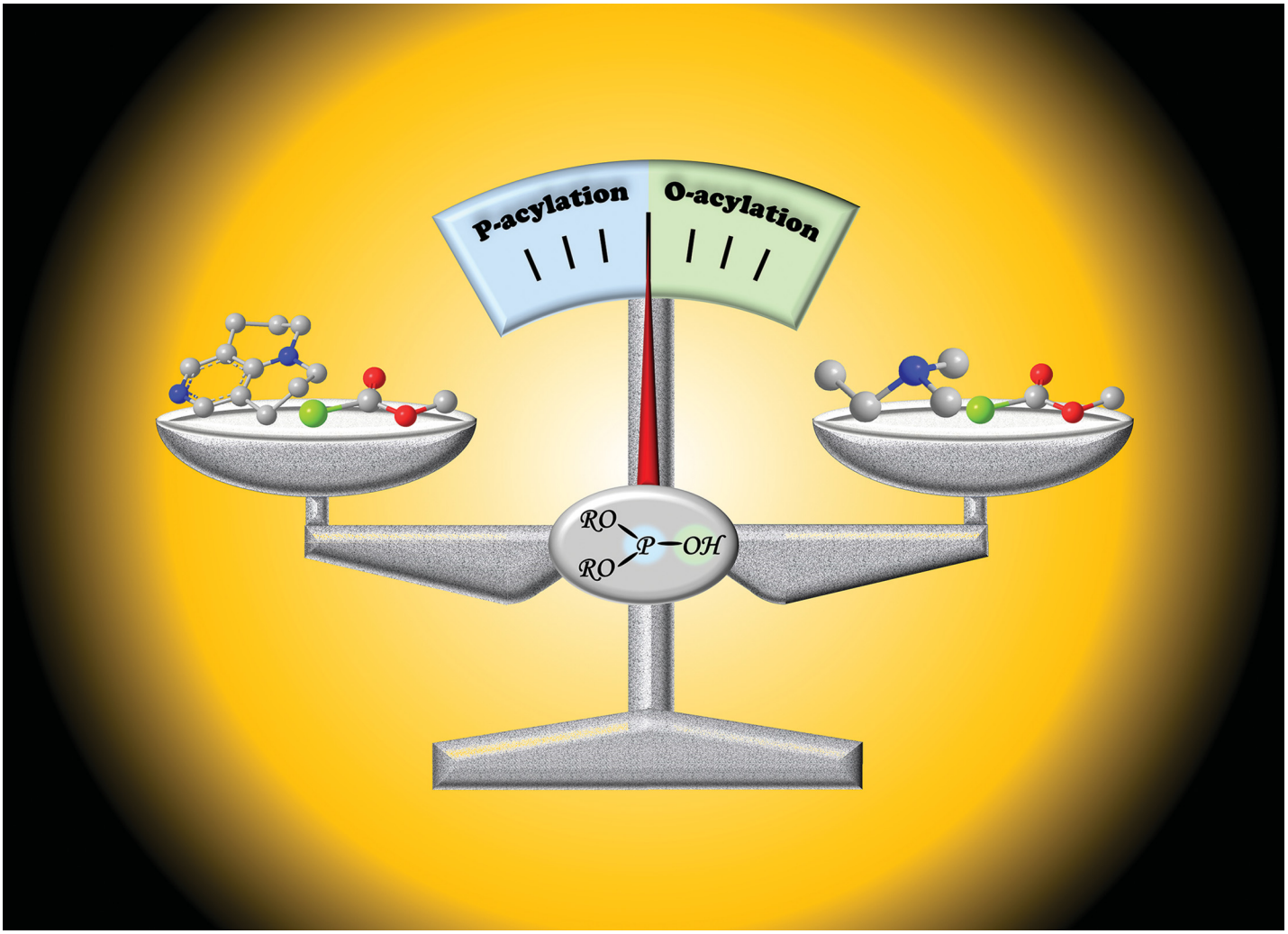
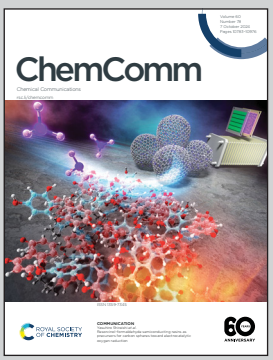


Showcasing research from Professor Fuse's laboratory at the Graduate School of Pharmaceutical Sciences, Nagoya University, Nagoya, Japan

Switching between P-acylation and O-acylation of *H*-phosphonates with chloroformates by changing acyl pyridinium and acyl ammonium ions in a microflow reactor

The "balance" between the softness and hardness of *in situ* generated acyl pyridinium/ammonium electrophiles is the key to the switching. Structurally diverse phosphotriesters and phosphonoformate esters were synthesized in microflow reactors.

As featured in:



See Shinichiro Fuse *et al.*, *Chem. Commun.*, 2024, **60**, 10874.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Registered charity number: 207890

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2024, **60**, 10874

Received 13th June 2024,
Accepted 12th August 2024

DOI: 10.1039/d4cc02871f

rsc.li/chemcomm

Switching between P-acylation and O-acylation of *H*-phosphonates with chloroformates by changing acyl pyridinium and acyl ammonium ions in a microflow reactor†

Hiroshi Kitamura, Yuma Tanaka and Shinichiro Fuse *

We report the first switchable acylation of *H*-phosphonate with chloroformate. The acylation site (P *vs.* O) in *H*-phosphonate was switched by changing the acyl pyridinium/ammonium ions. Unexpected phosphite formation was observed during the O-acylation of *H*-phosphonate. Twenty-six structurally diverse phosphotriesters and phosphonoformate esters were synthesized in microflow reactors.

Organic transformations in which the reaction sites (X and Y) of substrate **A** can be switched by changing the reaction conditions (Scheme 1a) are useful for synthesizing structurally diverse compounds.[1] Although various types of switching of reaction sites have been reported, developing novel and unique switching methods is important because it enables facile access to structurally diverse molecules, leading to the discovery of new functional molecules.

H-Phosphonate **E** has been used as a building block in the synthesis of organophosphorus compounds.[2] Various organic transformations of **E** have been developed;[3] however, the acylation of **E** remains mostly unexplored. There are six reports for P-acylation of **E**[4a,b] and its silylated derivative **G**[4c–f] with acyl chlorides **F** (Scheme 1b(i)), and there are only two reports by Wada *et al.* that achieved the challenging O-acylation of *H*-phosphonate equivalent **I** (Scheme 1b(ii)).[5] The acylation using chloroformates **K** has been even less explored. Only two reports are available on the P-acylation of **E** and **G** (Scheme 1b(iii)),[6] and no O-acylation reactions have been reported to date (Scheme 1b(iv)). Although modified nucleophiles, such as **G** and **I**, have been used in the previously reported acylations to control the reaction sites, no previous acylation approaches have been used to modify electrophiles. Realizing the unachieved switching between the P-acylation and O-acylation of **E** affords various novel organophosphorus compounds.

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Nagoya, 464-8601, Japan.
E-mail: fuse.shinichiro.z3@f.mail.nagoya-u.ac.jp

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4cc02871f

We have developed efficient microflow processes[7] using highly electrophilic acyl ammonium, acyl pyridinium, and acyl imidazolium ions in the synthesis of peptides and urethane-protected amino acids such as *N*-carboxy anhydrides.[8] A significant change in reactivity has been observed by changing the electrophiles. We also developed the microflow synthesis of acyclic and cyclic phosphotriesters, as well as *H*-phosphonates.[9] Herein, we report the switching of the acylation site (P *vs.* O) of *H*-phosphonate **E** that is in equilibrium with **E′** by changing the acyl pyridinium ion **N** and acyl ammonium ion **O** in a microflow reactor (Scheme 1c). Various phosphonoformate esters **L** and phosphotriesters derived from phosphite **P** were synthesized.

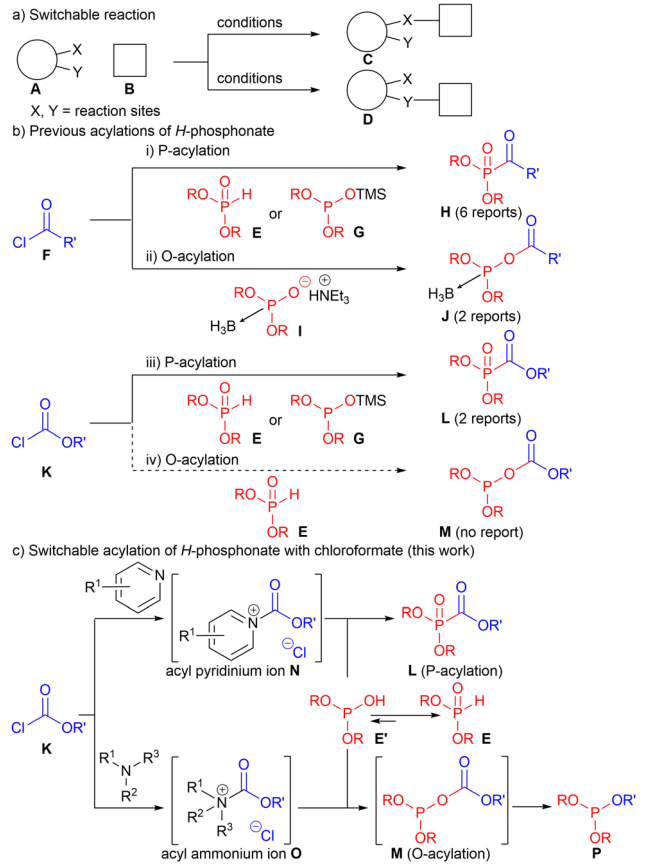
Ethyl chloroformate (**1a**) and diphenyl *H*-phosphonate (**2a**) were employed to examine the switchable acylation of *H*-phosphonate (Table 1). A microflow reactor was used to precisely control the short reaction times and temperatures of the exothermic processes. Two T-shaped mixers were connected with Teflon® (PTFE: polytetrafluoroethylene; ∅ = 0.80 mm) tubing and were immersed in a water bath. Solutions of **1a** in CH_2Cl_2 and **2a** in CH_2Cl_2 were introduced into the first T-shaped mixer using syringe pumps A and B, respectively. A solution of the nucleophilic amines and i-Pr_2NEt was introduced into the second T-shaped mixer using syringe pump C to activate **1a**. The resultant mixture was collected in a test tube and stirred for 50 s.[10] The reaction was quenched by adding 1 M aqueous HCl.

The reaction did not proceed in the absence of a nucleophilic amine (entry 1). Neither P-acylation nor O-acylation occurred, and aminophosphonates were obtained in the presence of pyridine (entry 2). These undesired products were generated *via* the nucleophilic attack of *H*-phosphonate on the *in situ* generated acyl pyridinium ion.[11] The use of heterocyclic aromatic amines, including NMI, DMAP, 4-pyrrolidinopyridine, and 9-azajulolidine, afforded **3a** (entries 3–6). The highest yield was obtained using 9-azajulolidine (entry 6) and its amount can be reduced to 0.6 equiv (Table S2, ESI,† entry 2) without a decrease in yield. In the presence of aliphatic amines, phosphite **5a** was unexpectedly obtained instead of the *O*-acyl product **4a** (entries 7–12). The use

Open Access Article. Published on 27 August 2024. Downloaded on 2/12/2026 9:58:19 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

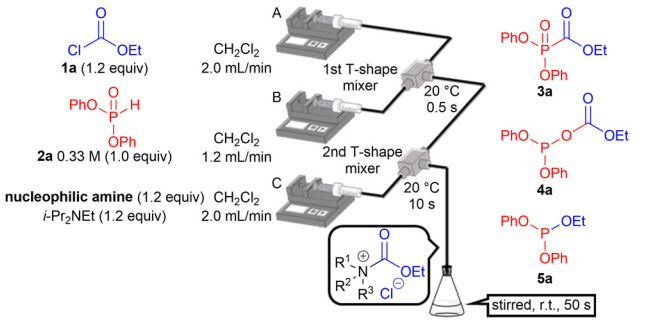
This journal is © The Royal Society of Chemistry 2024

Open Access Article. Published on 27 August 2024. Downloaded on 2/12/2026 9:58:19 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 1 Concept of site-switchable reactions and acylations of *H*-phosphonates reported previously and in this manuscript. (a) Switching the reaction site by changing the reaction conditions. (b) P-Acylation and O-acylation of *H*-phosphonates with acyl chloride or chloroformates (previous reports). (c) Switching between P-acylation and O-acylation of *H*-phosphonates with chloroformates (this work).

Table 1 Examination of nucleophilic amines[a]



Entry	Nucleophilic amine	**2a** (%)	**3a** (%)	**5a** (%)
1	—	90	Trace	n.d.
2	Pyridine	n.d.	Trace	n.d.
3	NMI	36	57	n.d.
4	DMAP	19	57	n.d.
5	4-Pyrrolidinopyridine	12	55	n.d.
6	9-Azajulolidine	16	74	n.d.
7	NMM	38	Trace	45
8	Me_2NBn	27	Trace	38
9	*N*-Methylpiperidine	7	Trace	83
10	*N*-Methylpyrrolidine	2	Trace	90
11	Me_2NEt	3	Trace	90
12	NMe_3[b]	1	Trace	90

[a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2-trichloroethane as the internal standard. [b] THF solution of NMe_3 (2 M) was used. NMI = *N*-methylimidazole; DMAP = 4-dimethylaminopyridine; NMM = *N*-methylmorpholine; i-Pr = isopropyl; Et = ethyl; Me = methyl; Bn = benzyl.

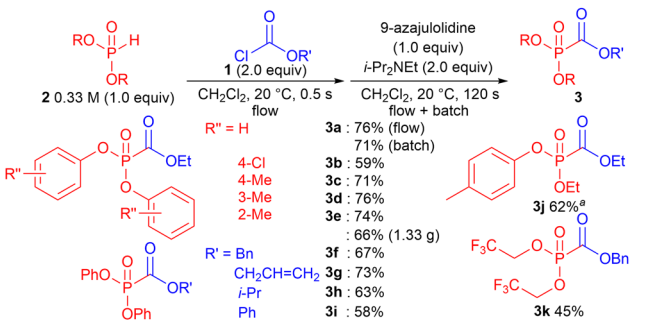


Fig. 1 Substrate scope for the synthesis of phosphonoformate ester **3**. [a] MTBD was used instead of i-Pr_2NEt. The reaction time was extended to 180 s from 120 s. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

of less sterically hindered aliphatic amines including *N*-methylpyrrolidine, Me_2NEt, and NMe_3 afforded **5a** in higher yields (entries 10–12). We speculated that the *in situ* generated acyl pyridinium ions or acyl ammonium ions served as electrophiles and their difference in the chemical hardness was the key to the switching of the acylation. The chemical hardness of the electrophiles was estimated using DFT calculations, and the results indicated that the former ions have a lower chemical hardness than the latter ions (for details, see the ESI†). Therefore, it is conceivable that the soft phosphorus atom preferentially reacts with the carbonyl group in the relatively soft acyl pyridinium ions. Reportedly, 9-azajulolidine has a higher electron-donating ability than DMAP.[12] We presumed that this delocalizes the positive charge of the acyl pyridinium leading to an increase in the chemical softness. Thus the highest yield was observed. By contrast, the more negatively charged oxygen atom preferentially reacts with localized acyl ammonium ions.

We examined the substrate scope employing optimized conditions.[13] In P-acylation (Fig. 1), the electron-withdrawing group on the aromatic ring of *H*-phosphonate decreased the yield in the synthesis of **3b**, whereas the electron-donating group on the aromatic ring of *H*-phosphonate did not affect the yield in the synthesis of **3c**. The desired products were obtained in good yield, regardless of the position of the methyl substituent on the aromatic ring, during the synthesis of **3c–3e**. The desired **3f–3i** with different sizes of the R′ substituent were obtained in acceptable to good yields. The use of i-Pr_2NEt did not result in the acylation of the *H*-phosphonate **3j** containing both alkyloxy and aryloxy groups; therefore, a more basic MTBD was used. Desired **3j** was obtained in an acceptable yield. Desired **3k** containing two trifluoroethyl groups was also obtained, albeit in a moderate yield. Comparable batch conditions were used to synthesize **3a**. (Although a similar yield was

Open Access Article. Published on 27 August 2024. Downloaded on 2/12/2026 9:58:19 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

observed, gas evolved during the reaction. The batch reaction should be performed with caution. Especially in scale-up synthesis, the use of batch synthesis should be avoided because the reaction is exothermic and is accompanied by the generation of HCl.) The scaled-up synthesis (1.33 g) of **3e** was safely performed under flow conditions without a severe decrease in the yield (66%).

O-Acylation was also examined (Fig. 2).[13] The phosphite **5** was oxidized to the corresponding phosphotriester **6** using H_2O_2 as an oxidant. As in the case of P-acylation, an electron-withdrawing group on the aromatic ring of *H*-phosphonate decreased the yield of **6b**, whereas an electron-donating group on the aromatic ring of *H*-phosphonate did not affect the yields of **6c** and **6d**. However, unlike P-acylation, a decrease in the yield was observed in the synthesis of **6e** containing two 2-methyl phenoxy groups. The steric bulkiness of OR significantly influenced the product yield. Although **6f** with a sterically less hindered methoxy group was obtained in a high yield, **6g** with a sterically hindered isopropoxy group was obtained in a low yield, presumably because of the bulky isopropoxy group. Compound **6h** with a phenoxy group was obtained in a high yield. The acylation of *H*-phosphonates containing both alkyloxy and aryloxy groups in the presence of MTBD instead of i-Pr_2NEt afforded **6i** in a moderate yield. Desired **6j** containing two trifluoroethyl groups was also obtained in a moderate yield. Comparable batch conditions were employed for the synthesis of **6a**. A slightly lower yield was obtained under batch conditions. (Although a similar yield was observed, the batch reaction should be performed with caution as previously described. Moreover, generation of CO_2 is also problematic for O-acylation.) The scaled-up synthesis (1.26 g) of **6a** was safely performed under flow conditions without a severe decrease in the yield (75%).

Since commercially available chloroformates are limited, we prepared chloroformate equivalent **9** from triphosgene (**7**) and alcohol **8** using a modified procedure based on our previous report[8g] in a microflow reactor, which was used for subsequent O-acylation (Fig. 3). Three T-shaped mixers were connected with Teflon tubing and were immersed in a water bath. A solution of triphosgene (**7**) in CH_2Cl_2 and a solution of alcohol **8** and Me_2NEt in CH_2Cl_2 were introduced into the first

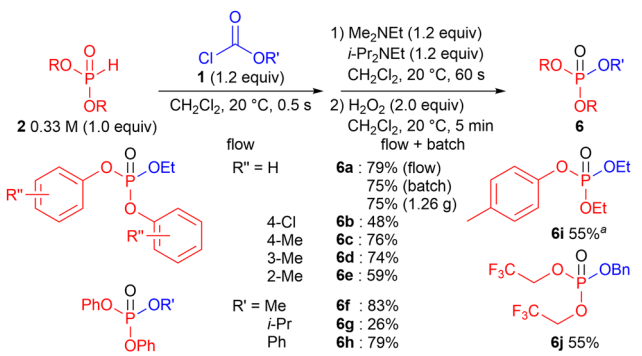


Fig. 2 Substrate scope for the synthesis of phosphotriester **6**. [a] MTBD was used instead of i-Pr_2NEt. The reaction time was extended to 240 s from 60 s.

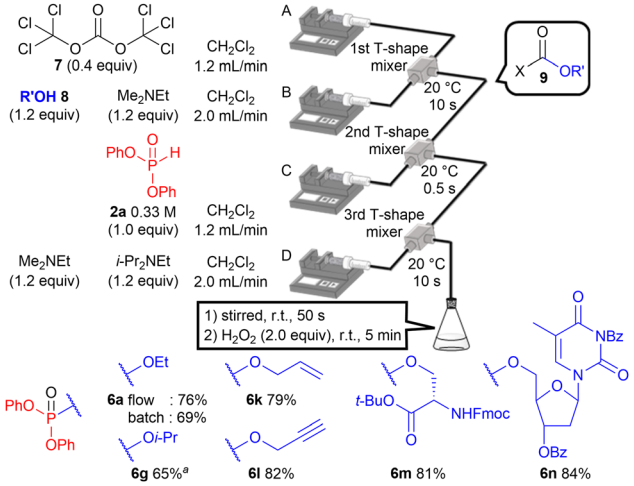


Fig. 3 One-flow synthesis of phosphotriester **6** from alcohol **8** *via* O-acylation. [a] 1.5 equiv of isopropanol (**8a**) was used. The reaction time was extended to 120 s from 60 s.

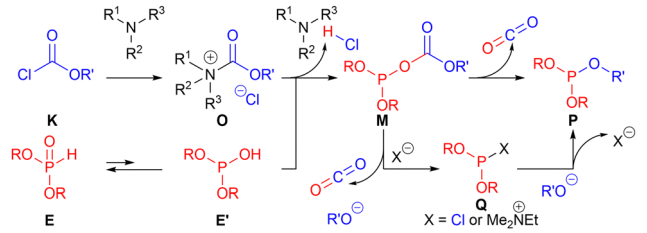
T-shaped mixer using syringe pumps A and B, respectively. A solution of **2a** in CH_2Cl_2 was introduced into the second mixer using syringe pump C. A solution of Me_2NEt and i-Pr_2NEt was introduced into the third T-shaped mixer using syringe pump D to activate **9**. The resultant mixture was collected in a test tube and stirred for 50 s. The phosphite **5** was oxidized to the corresponding phosphotriester **6** by using H_2O_2. The reaction was quenched by the addition of 1 M aqueous HCl. The obtained mixtures were purified using column chromatography, preparative TLC, or gel permeation chromatography (GPC).

The desired products **6a** and **6k–6n** derived from primary alcohol **8** were obtained in good yields. Notably, acid-labile allyl, propargyl, *t*-butoxycarbonyl, base-labile Fmoc, and alpha-phosphoryl oxy groups were tolerated under the developed conditions. The desired phosphotriester (**6g**) was obtained in good yield when 1.5 equivalents of the secondary alcohol isopropanol (**8a**) was added. Comparable batch conditions were used to synthesize **6a**. A slightly lower yield was obtained under batch conditions. (The batch reaction should be performed with extreme caution as previously described because the reaction is exothermic and is accompanied by the generation of phosgene, HCl, and CO_2.)

We investigated the reaction mechanism for the unexpected formation of phosphite **5a** from *H*-phosphonate **2a** and chloroformate **1a** by performing several control experiments (for details, see the ESI†). The plausible reaction mechanism for the formation of phosphite **P** is shown in Scheme 2. The acyl ammonium ion **O** generated from chloroformate **K** and aliphatic amine was reacted with tautomerized trivalent *H*-phosphonate **E′** (ref. 14) affording **M**. Then, intramolecular and intermolecular attacks of the OR′ group concomitant with a decarboxylation of **M** affords phosphite **P**. We experimentally confirmed that the externally added ethanol occurred nucleophilic attack instead of the alkoxide (OR′ = OMe) affording **P** {$(RO)_2POEt$} and this ethanol attack was influenced by the concentration of the reaction mixture (for details, see the ESI†). Thus, we presumed that both intra- and

This journal is © The Royal Society of Chemistry 2024

Open Access Article. Published on 27 August 2024. Downloaded on 2/12/2026 9:58:19 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 2 Plausible reaction mechanism for the formation of phosphite.

intermolecular attacks of the OR′ group affording phosphite **P** are possible.

In summary, we have achieved the first site-switchable acylation of *H*-phosphonate using chloroformates. In contrast to previously reported approaches, our approach is based on the modification of electrophiles. Acyl pyridinium ions preferentially induced P-acylation, whereas acyl ammonium ions preferentially induced O-acylation. Unexpected and unknown phosphite formation was observed during O-acylation. We suggested that O-acylation and subsequent intra- and intermolecular nucleophilic substitutions afforded phosphite. We also demonstrated the *in situ* preparation of chloroformates and their use in subsequent O-acylation in a microflow reactor. Twenty-six structurally diverse phosphotriesters and phosphonoformate esters were successfully synthesized. Our developed approach rapidly produced organophosphorus compounds, including unique phosphonoformate esters. This will contribute to library synthesis, leading to the creation of new organophosphorus-based functional materials in the future.

This work was partially supported by the Grant-in-Aid for Scientific Research (B) from JSPS (21H01929), JSPS Fellows (23KJ1102), the Grant-in-Aid for Transformative Research Areas (B) from JSPS (21H05081), JST SPRING (JPMJSP2125), and the Research Support Project for Life Science and Drug Discovery [Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)] from the Japan Agency for Medical Research and Development (AMED) under Grant No. JP23ama121044.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For recent reviews of switchable reactions, see: (*a*) G. Zhan, W. Du and Y.-C. Chen, *Chem. Soc. Rev.*, 2017, **46**, 1675–1692; (*b*) I. P. Beletskaya, C. Nájera and M. Yus, *Chem. Soc. Rev.*, 2020, **49**, 7101–7166; for recent reports on switchable reactions, see: (*c*) Y. Sakakibara and K. Murakami, *ACS Catal.*, 2022, **12**, 1857–1878; (*d*) C. Ma, J. Shen, C. Qu, T. Shao, S. Cao, Y. Yin, X. Zhao and Z. Jiang, *J. Am. Chem. Soc.*, 2023, **145**, 20141–20148; (*e*) J. Jin, C. Li, R. Wang, Z. Xia, Q. Yan, W. Wang, S. Gu, H. Wang and F. Chen, *Org. Lett.*, 2023, **25**, 6012–6017.
2 J. Stawinski and A. Kraszewski, *Acc. Chem. Res.*, 2002, **35**, 952–960.
3 A. Kraszewski and J. Stawinski, *Pure Appl. Chem.*, 2007, **79**, 2217–2227.
4 (*a*) Y. Ogata and H. Tomioka, *J. Org. Chem.*, 1970, **35**, 596–600; (*b*) T. Yano, T. Kawasaki, T. Yuhki, N. Ishida and M. Murakami, *Org. Lett.*, 2018, **20**, 1224–1227; (*c*) E. de Vroom, C. E. Dreef, H. van den Elst, G. A. van der Marel and J. H. van Boom, *Recl. Trav. Chim. Pays-Bas*, 1988, **107**, 592–595; (*d*) T. Johansson and J. Stawinski, *Bioorg. Med. Chem.*, 2001, **9**, 2315–2322; (*e*) N. Ishida, T. Yano, T. Yuhki and M. Murakami, *Chem. – Asian. J.*, 2017, **12**, 1905–1908; (*f*) J.-Q. Zhang and L.-B. Han, *Org. Lett.*, 2020, **22**, 4633–4637.
5 (*a*) K. Sato and T. Wada, *Org. Biomol. Chem.*, 2016, **14**, 11092–11095; (*b*) Y. Takahashi, K. Kakuta, Y. Namioka, A. Igarashi, T. Sakamoto, R. I. Hara, K. Sato and T. Wada, *J. Org. Chem.*, 2023, **88**, 10617–10631. There are two more reports on O-acylation; however, the detailed procedure has not been reported, and acylation is not completely regulated. See: (*c*) A. Kers, I. Kers, J. Stawiński, M. Sobkowski and A. Kraszewski, *Tetrahedron*, 1996, **52**, 9931–9944; (*d*) A. Kers, I. Kers, A. Kraszewski and J. Stawiński, *Collect. Czech. Chem. Commun.*, 1996, **61**, S246–S249.
6 (*a*) R. A. Moss, H. Morales-Rojas, S. Vijayaraghavan and J. Tian, *J. Am. Chem. Soc.*, 2004, **126**, 10923–10936; (*b*) V. Gagnard, A. Leydet, A. Morère, J.-L. Montero, I. Lefèbvre, G. Gosselin, C. Pannecouque and E. D. Clercq, *Bioorg. Med. Chem.*, 2004, **12**, 1393–1402.
7 For selected recent reviews on continuous-flow syntheses, see: (*a*) R. Gérardy, N. Emmanuel, T. Toupy, V.-E. Kassin, N. N. Tshibalonza, M. Schmitz and J.-C. M. Monbaliu, *Eur. J. Org. Chem.*, 2018, 2301–2351; (*b*) J. M. De Souza, R. Galaverna, A. A. N. De Souza, T. J. Brocksom, J. C. Pastre, R. O. M. A. De Souza and K. T. De Oliveira, *An. Acad. Bras. Cienc.*, 2018, **90**, 1131–1174; (*c*) B. T. Ramanjaneyulu, N. K. Vishwakarma, S. Vidyacharan, P. R. Adiyala and D.-P. Kim, *Bull. Korean Chem. Soc.*, 2018, **39**, 757–772; (*d*) P. L. Suryawanshi, S. P. Gumfekar, B. A. Bhanvase, S. H. Sonawane and M. S. Pimplapure, *Chem. Eng. Sci.*, 2018, **189**, 431–448; (*e*) M. Guidi, P. H. Seeberger and K. Gilmore, *Chem. Soc. Rev.*, 2020, **49**, 8910–8932; for representative publications on "flash chemistry" enabled by flow micro technologies, as reported by Yoshida *et al.*, see: (*f*) J.-I. Yoshida, *Flash Chemistry – Fast Organic Synthesis in Micro Systems*, Wiley-VCH, Weinheim, 2008; (*g*) J.-I. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896–9904.
8 (*a*) N. Sugisawa, H. Nakamura and S. Fuse, *Chem. Commun.*, 2020, **56**, 4527–4530; (*b*) Y. Otake, Y. Shibata, Y. Hayashi, S. Kawauchi, H. Nakamura and S. Fuse, *Angew. Chem., Int. Ed.*, 2020, **59**, 12925–12930; (*c*) R. Okabe, N. Sugisawa and S. Fuse, *Org. Biomol. Chem.*, 2022, **20**, 3303–3310; (*d*) O. Shamoto, K. Komuro, N. Sugisawa, T.-H. Chen, H. Nakamura and S. Fuse, *Angew. Chem., Int. Ed.*, 2023, **62**, e202300647; (*e*) N. Sugisawa, A. Ando and S. Fuse, *Chem. Sci.*, 2023, **14**, 6986–6991; (*f*) S. Fuse and R. Okabe, *Eur. J. Org. Chem.*, 2023, e202300700; (*g*) K. Miyamoto, R. Okabe and S. Fuse, *Org. Process Res. Dev.*, 2024, **28**, 1971–1978.
9 For recent reviews on the microflow synthesis of organophosphorus compounds, see: (*a*) R. Morodo, P. Bianchi and J.-C. M. Monbaliu, *Eur. J. Org. Chem.*, 2020, 5236–5277; (*b*) H. Kitamura and S. Fuse, *ChemPlusChem*, 2023, **88**, e202300176. For our recent reports on the microflow synthesis of organophosphorus compounds, see: (*c*) H. Kitamura, Y. Otake, N. Sugisawa, H. Sugisawa, T. Ida, H. Nakamura and S. Fuse, *Chem. – Eur. J.*, 2022, **28**, e202200932; (*d*) Y. Tanaka, H. Kitamura and S. Fuse, *J. Org. Chem.*, 2024, **89**, 1777–1783; (*e*) K. Nakabayashi, H. Kitamura and S. Fuse, *Chem. – Asian. J.*, 2024, **19**, e202400256.
10 The shortening of stirring time in the flask to 10 s significantly decreased the yield (Table S10, ESI,† entry 15). Thus, the desired coupling reaction was not complete in the tube.
11 T. Fischer, Q.-N. Duong and O. G. Mancheño, *Chem. – Eur. J.*, 2017, **23**, 5983–5987.
12 I. Held, S. Xu and H. Zipse, *Synthesis*, 2007, 1185–1196.
13 The reaction conditions (reaction times, reaction temperatures, bases, solvents, concentrations, and amounts of reagents) were optimized before the substrate scope. For details, see Tables S2–S4, S6–S10, and S12 (ESI†).
14 J.-L. Montchamp, *Acc. Chem. Res.*, 2014, **47**, 77–87.