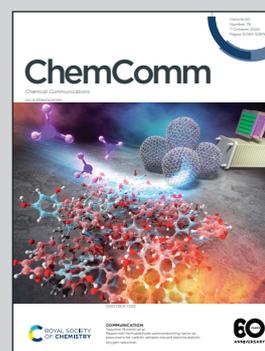


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Switching between P-acylation and O-acylation of *H*-phosphonates with chloroformates by changing acyl pyridinium and acyl ammonium ions in a microflow reactor

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.

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

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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.

We have developed efficient microflow processes⁷ 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; $\varnothing = 0.80$ mm) tubing and were immersed in a water bath. Solutions of **1a** in CH₂Cl₂ and **2a** in CH₂Cl₂ were introduced into the first T-shaped mixer using syringe pumps A and B, respectively. A solution of the nucleophilic amines and *i*-Pr₂NEt 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.

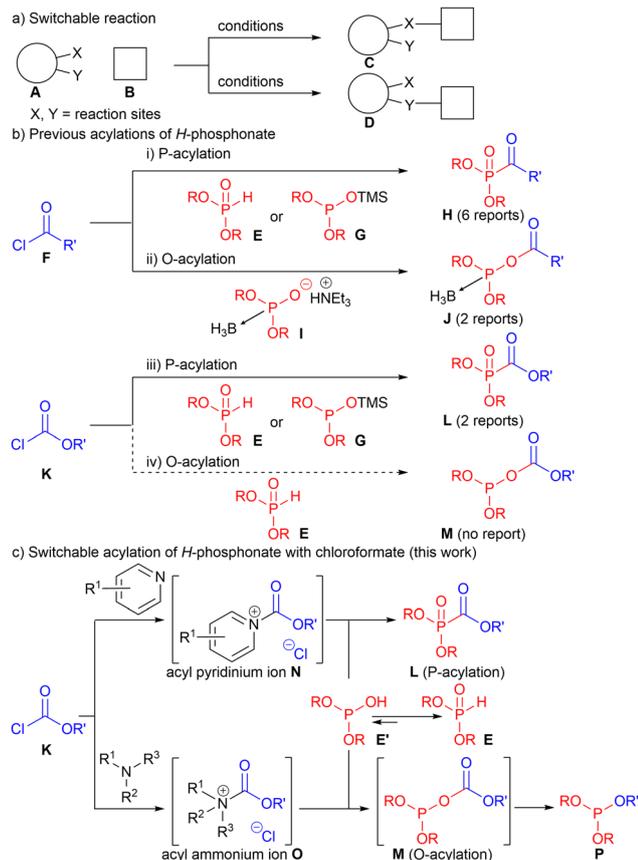
The reaction did not proceed in the absence of a nucleophilic amine (entry 1). Neither P-acylation nor O-acylation occurred, and aminophosphonates were obtained in the presence of pyridine (entry 2). These undesired products were generated *via* the nucleophilic attack of *H*-phosphonate on the *in situ* 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

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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).

of less sterically hindered aliphatic amines including *N*-methylpyrrolidine, Me₂NEt, and NMe₃ 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

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 ₂ NBn	27	Trace	38
9	<i>N</i> -Methylpiperidine	7	Trace	83
10	<i>N</i> -Methylpyrrolidine	2	Trace	90
11	Me ₂ NEt	3	Trace	90
12	NMe ₃ ^b	1	Trace	90

^a Yields were determined by ¹H NMR analysis of the crude reaction mixture using 1,1,2-trichloroethane as the internal standard. ^b THF solution of NMe₃ (2 M) was used. NMI = *N*-methylimidazole; DMAP = 4-dimethylaminopyridine; NMM = *N*-methylmorpholine; *i*-Pr = isopropyl; Et = ethyl; Me = methyl; Bn = benzyl.

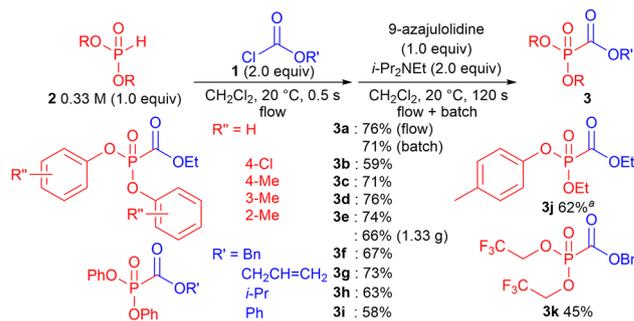


Fig. 1 Substrate scope for the synthesis of phosphonofosphate ester **3**. ^a MTBD was used instead of *i*-Pr₂NEt. The reaction time was extended to 180 s from 120 s. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

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*-Pr₂NEt 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



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 H₂O₂ 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*-Pr₂NET 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 CO₂ 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 CH₂Cl₂ and a solution of alcohol **8** and Me₂NET in CH₂Cl₂ were introduced into the first

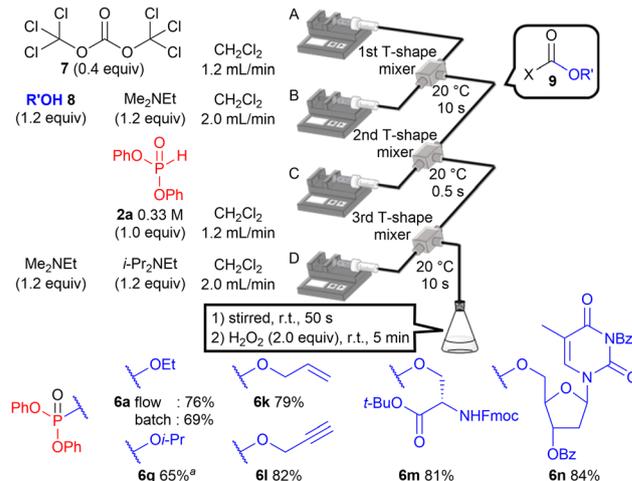


Fig. 3 One-flow synthesis of phosphotriester **6** from alcohol **8** via O-acylation. ^a1.5 equiv of isopropanol (**8a**) was used. The reaction time was extended to 120 s from 60 s.

T-shaped mixer using syringe pumps A and B, respectively. A solution of **2a** in CH₂Cl₂ was introduced into the second mixer using syringe pump C. A solution of Me₂NET and *i*-Pr₂NET 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 H₂O₂. 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 phosphene, HCl, and CO₂.)

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

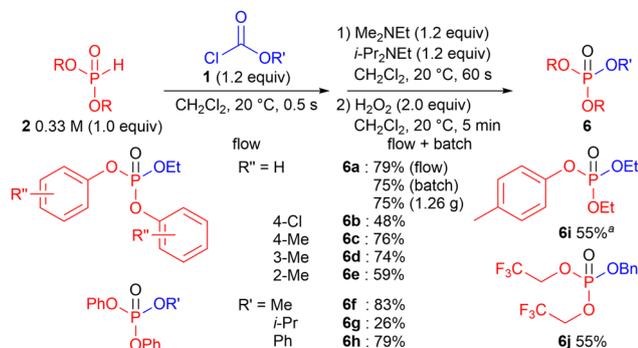
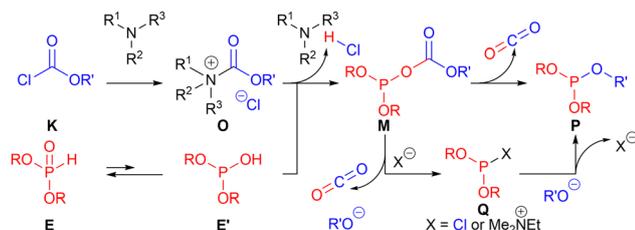


Fig. 2 Substrate scope for the synthesis of phosphotriester **6**. ^aMTBD was used instead of *i*-Pr₂NET. The reaction time was extended to 240 s from 60 s.





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 phosphonofosphate esters were successfully synthesized. Our developed approach rapidly produced organophosphorus compounds, including unique phosphonofosphate esters. This will contribute to library synthesis, leading to the creation of new organophosphorus-based functional materials in the future.

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Data availability

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

Conflicts of interest

There are no conflicts to declare.

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