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Perspective

Poison to promise: The resurgence of organophosphorus fluoride chemistry

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SUMMARY

Organophosphorus(V) fluorides have a long and tumultuous history, with early applications as toxins and nerve agents reflecting their poisonous past. Behind these very real safety considerations, there is also growing potential in a wide range of fields, from chemical biology to drug development. The recent inclusion of organophosphorus(V) fluorides in click chemistry exemplifies the promise these compounds possess and brings these molecules to the brink of a resurgence. In this perspective, we delve into the history of phosphorus(V) fluoride (P(V)–F) compounds, discuss the precautions needed to work with them safely, and explore recent advancements in their synthesis and application. We conclude by discussing how this field can continue on a path toward innovation.

INTRODUCTION

Phosphorus is a ubiquitous element in nature. Notably, pentavalent phosphorus centers are present in essential biomolecules, including nucleic acids, coenzymes, nucleoside triphosphates (ATP/ADP), and several metabolic intermediates.[1] In the 1930s, English and German scientists synthesized organophosphorus(V) fluorides that are not commonly found in nature, akin to other fluorinated motifs (Figure 1). Like other organophosphorus(V) compounds, organophosphorus(V) fluorides are biologically active, with early applications heavily focusing on their use as acetylcholinesterase (AChE) inhibitors.[1,2] As a result, phosphorus(V) fluorides (P(V)–Fs) are most known for their role as toxins for chemical warfare and insecticides.[3] The past decade has witnessed a revival of interest in organophosphorus(V) fluorides, with new applications as positron emission tomography (PET) imaging agents, mechanistic probes in chemical biology, and, very recently, as click reagents in phosphorus fluoride exchange (PFEx) reactions.[4] Despite these recent applications, organophosphorus(V) fluoride chemistry is still underdeveloped.

Recent synthetic innovations involving organophosphorus(V) fluorides, such as electrophilic fluorination, deoxyfluorination, and PFEx, have reignited interest in the promise of these compounds.[5–16] Organophosphorus(V) fluoride chemistry is currently in the same position that sulfur(VI) fluoride (S(VI)–F) chemistry was 10 years ago. At the time, Sharpless and coworkers reinvigorated this field through their foundational sulfur fluoride exchange (SuFEx) study, demonstrating both innovations in the synthesis of S(VI)–Fs and their potential as click chemistry "hubs."[17–20] Since then, S(VI)–F chemistry has exploded, enabling considerable innovations in synthesis, chemical biology, and materials chemistry. Although the toxicity concerns for S(VI)–Fs are not nearly the same as P(V)–Fs, we believe that a similar renaissance for P(V)–F chemistry is on the horizon.

THE BIGGER PICTURE

Challenges and opportunities:

- Historically, compounds built around the phosphorus(V) fluoride (P(V)–F) motif have been employed with nefarious intent. Their role in chemical warfare has largely overshadowed their potential in other sectors, and the associated safety precautions have limited their study.
- Recent advancements have shown organophosphorus(V) fluorides to be competent inhibitors, probes, imaging agents, and more. Recently, phosphorus fluoride exchange (PFEx) has become the latest addition to the pantheon of Nobel Prize click chemistry, likely expanding the applications available to P(V)–F molecules.
- The resurgence of organophosphorus(V) fluorides is currently mitigated by their synthesis. To fully allow this field to blossom, synthetic improvements are needed.

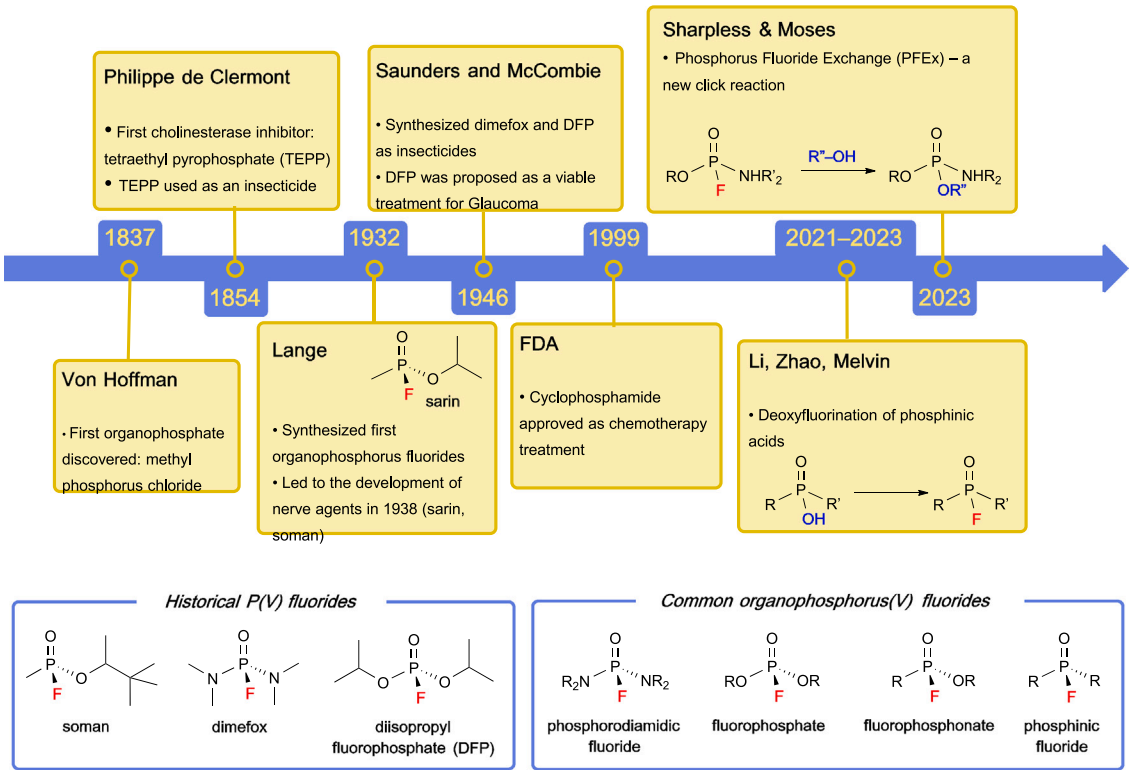

Figure 1. Timeline of organophosphorus(V) fluoride's development, with historical and common examples

Research surrounding organophosphorus(V) fluorides has largely focused on modulating the toxicity of these compounds for use as poisons, with particular interest in four key classes: phosphinic fluorides [$R_2P(O)F$], fluorophosphonates [$R(OR)P(O)F$], fluorophosphates [$(OR)_2P(O)F$], and phosphorodiamidic fluorides [$(NR_2)_2P(O)F$]. Understandably, chemists have been cautious in approaching organophosphorus(V) fluoride chemistry; however, chemists have the tools to understand how to mitigate and address the toxicity challenges to unlock their *promise*. Although hesitation toward organophosphorus(V) fluorides is rooted in real safety concerns, this perspective aims to encourage researchers to look past their reputation as poisons and begin to think creatively about their promise. We will provide a brief historical background into these important molecules, including safety considerations and current applications, to show their potential, followed by synthetic challenges that serve as bottlenecks toward further innovation. The perspective will end with possible future directions for this exciting area.

HISTORY AND SAFETY

Early history of organophosphorus(V) fluorides

In 1932, Lange and coworkers synthesized the first reported organophosphorus(V) fluorides: diethyl and dimethyl fluorophosphates. Notably, the scientists noticed constriction of the larynx and light dizziness upon inhalation.[2] During World War II, organophosphorus(V) fluorides were investigated by German and British scientists as alternatives to mustard gas, chlorine, and phosgene as chemical warfare agents. This led to the discovery of fluorophosphonates like sarin and soman (Figure 1). These compounds were followed by the discovery of Novichok agents by Russian chemists in the 1970s, which have eight to ten times increased potency compared with soman.[2]

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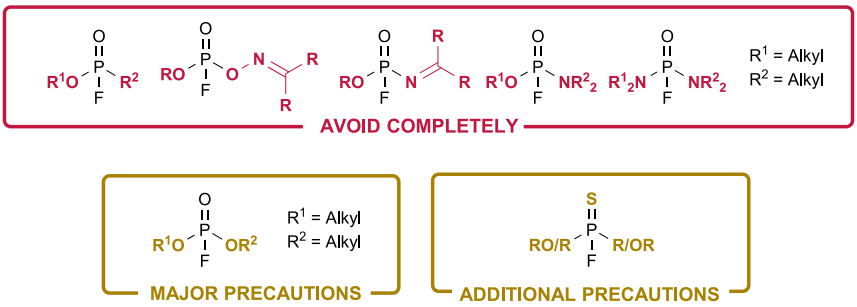

Figure 2. Generalized structures of organophosphorus(V) fluorides that should be avoided or handled with particular precautions

The mode of toxicity of organophosphorus(V) fluorides was elucidated in the early 20th century. It was discovered that P(V)–F compounds, such as sarin gas, act as nerve agents by irreversibly binding to the AChE enzyme. A serine residue in AChE is key to its activity.[2] In the presence of organophosphorus(V) fluorides, the OH group of serine undergoes phosphorylation, effectively inhibiting enzymatic activity. Acetylcholine cannot be broken down in the synapses of neurons, causing overstimulation of the acetylcholine receptors and prolonged depolarization of the postsynaptic neuron. This causes death by asphyxia due to muscle paralysis.

In parallel with their development as nerve agents, organophosphorus(V) fluorides also found a role in agriculture as pesticides, with the discovery of tetramethylphosphorodiamidic fluoride (dimefox) by Schrader and diisopropyl fluorophosphate (DFP) by Saunders and McCombie (Figure 1).[21,22] By the 2000s, organophosphorus(V) fluorides had been discontinued as commercial pesticides in many countries due to demonstrated toxicity in humans.[3]

Methods to attenuate toxicity

When exploring new methods and applications of organophosphorus(V) fluorides, it is imperative to know which subtypes are highly toxic and should be avoided. Fortunately, the safety profiles of these molecules are well known, as much of phosphorus fluoride research has focused on their use as toxins. P(V)–Fs that fall within the Organization for the Prohibition of Chemical Weapons (OPCW) Schedule 1 should be avoided completely.[23] They include phosphonofluoridates bearing an alkyl group (e.g., Me, Et, *n*-Pr, or *i*-Pr) and an O-alkyl group with a carbon count ≤ 10 (Figure 2). Similarly, derivatives that replace the alkyl or O-alkyl group with an oxime or imine moiety should also be avoided as these fall within the general structure of the Novichok nerve agents. Although not listed in the OPCW Schedule 1, compounds with the general formula of [$(NR_2)(OR)P(O)F$] and [$(NR_2)_2P(O)F$]—where R is an alkyl group—should also be avoided or handled with great care as these can still be powerful nerve agents (Figure 2).[24–26]

Structural modification of organophosphorus(V) fluorides can have a marked effect on their toxicity. Fluorophosphates [$(OR)_2P(O)F$] show reduced AChE inhibition compared with fluorophosphonates [$R(OR)P(O)F$] by at least 100-fold.[27] For instance, DFP can be used as a medication to treat glaucoma,[28] though it can still have high *in vivo* toxicity (Figure 2).[29] Compounds with a P=S instead of a P=O are much less toxic, with at least a 5,000-fold reduction in AChE inhibition.[27] As the P=S can hydrolyze back to the P=O, they should still be avoided if they are direct analogs of known nerve agents. Chirality can also influence toxicity. The different stereoisomers of certain nerve agents have

large variations—as much as 3–4 orders of magnitude—in AChE inhibition/metabolism, making one stereoisomer substantially less toxic.[30,31] Any other combinations not so far discussed have not been reported to serve as nerve compounds. Regardless, any work with organophosphorus(V) fluorides should be conducted with caution as they may be lower-level AChE inhibitors. As with other fluorinated compounds, organophosphorus(V) fluorides are also potential hydrogen fluoride (HF)-releasers and should be handled with proper safeguards.

APPLICATIONS

P(V)–Fs in drug development

Although much of the initial development of organophosphorus(V) fluoride compounds focused on their toxicity, several early studies found pharmaceutical potential. For example, it has been known since the 1940s that DFP can be used to treat glaucoma. DFP increases synaptic transmission by inhibiting AChE, allowing fluid to drain from the eye via enhanced ciliary muscle contraction.[28,32,33] More recently, Rademann and coworkers have shown that a unique class of P(V)–Fs that contain pentafluorophosphate anions can act as protein tyrosine phosphate (PTP) inhibitors. The compounds were physiologically stable and are an improvement over the classic α,α-fluorobenzylphosphonate phosphotyrosine mimetics, which lack cell membrane permeability. However, the binding affinities of these PF_5 inhibitors were low.[34] In 2022, the same group developed a new synthetic protocol to access pentafluorophosphato amino acids, and these displayed up to 30-fold stronger binding affinity to protein tyrosine phosphatase 1B (PTP1B) than the classic biomimetics (Figure 3).[35]

Another powerful application of P(V)–Fs is biological probes. For example, FP-biotin can detect labeled proteins in sub-nanomolar concentrations (Figure 3).[36] It has also been used for a myriad of other applications, such as quantifying the expression of recombinant serine hydrolases in western blots[37] and mapping endocannabinoid hydrolases.[38] Similar P(V)–F probes have been developed for use in imaging mass spectrometry (IMS) for studying serine hydrolases.[39] Phospholipases are also targets for P(V)–F-containing probes.[40]

Compounds containing P(V)–Fs are also useful in ^{19}F NMR spectroscopy. Nucleotide analogs have been synthesized as reporter molecules in enzyme binding and activity assays.[41] In 2020, oligodeoxyribonucleotides functionalized with fluoromonophosphate and fluorodiphosphate groups were explored as probes for examining nucleic-acid-related processes by ^{19}F NMR spectroscopy studies. The probes are an improvement on standard fluorophore-containing probes for small molecule interactions with secondary structures. Traditional probes suffer from false positives and false negatives, whereas ^{19}F NMR-spectroscopy-based probes allow direct observation by viewing chemical shift perturbation.[42]

P(V)–Fs in synthesis and catalysis

P(V)–F-containing compounds have also impacted catalytic and synthetic methodologies. For example, the Stephan group has taken advantage of the high Lewis acidity of phosphorus-fluorine compounds for sequestering and trapping CO_2. This has potential relevance for carbon capture—an emerging technology for climate change mitigation. The method uses amidophosphorane intermediates, which then react rapidly with CO_2 to form carbamatofluorophosphoranes (Figure 3).[43] Following this work, the same group used a class of phosphonium salts to break an alkyl C–F bond, forming a carbocation. In combination with a hydride source, overall hydrodefluorination (HDF) reactions take place. The researchers suggest that these easily

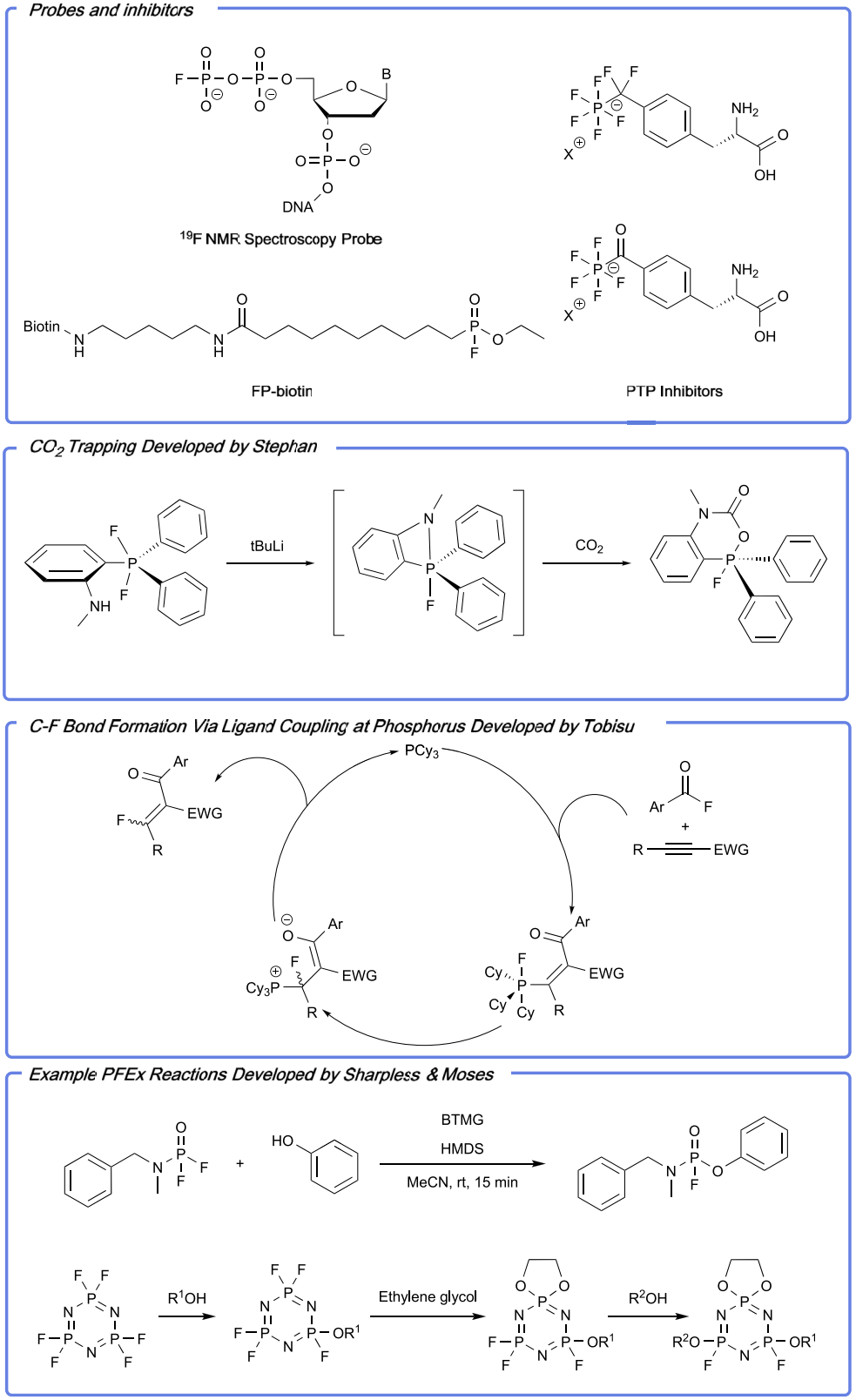

Figure 3. Key applications of organophosphorus(V) fluorides

accessible P–F compounds could be useful for removing potent greenhouse gases from the atmosphere, such as chlorofluorocarbons (CFCs) and hydrofluorocarbons (HFCs).[44] The same group later showed the salt's utility as a catalyst for metal-free hydrogenation of alkenes.[45]

In 2020, Tobisu developed a catalytic intermolecular carbofluorination reaction, where a key fluorophosphorane intermediate effects ligand coupling reactions at the phosphorus center to form a new C–F bond through an alkyne acylfluorination (Figure 3).[46] The same group has also applied a fluorophosphorane intermediate in a three-component coupling between an alkyne, acyl fluoride, and a silyl enol ether,[47] and a solution-stable fluorophosphorane reagent in the synthesis of dibenzophospholes.[48]

P(V)–Fs as PFEx agents

PFEx reactions involving the phosphorylation of alcohols were demonstrated in the 1960s and 1980s, but the reactions were of limited scope and utility.[49–51] PFEx processes have also been fundamental to the function of P–F containing biological probes and P–F nerve agents (*vide supra*). Recently, the Sharpless and Moses groups reported a significant expansion in PFEx chemistry—demonstrating a new click-type reaction.[4] The reaction takes P(V)–F hubs and treats them with a variety of phenolic nucleophiles, forming products in high yield. A broad scope of P(V) compounds with various P–O and P–N links can be accessed, offering a straightforward way to synthesize P(V) compounds with structural diversity (Figure 3). The reactions do not produce complex mixtures of products, which is an issue with analogous P(V)–Cl compounds. P(V)–Cl substances also suffer from rapid hydrolysis and are less thermally stable. The researchers also demonstrate controlled, sequential functionalization of a P(V) center using hexafluorophosphazene. Finally, the versatility of the reaction is shown with a molecule containing "successive clickable hubs," which undergoes consecutive SuFEx, PFEx, and copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions. Each reaction is high-yielding, showing minimal side reactions.

SYNTHESIS OF P(V)–FS

Historical strategies

Throughout the 20th century, synthetic innovations focused on fluorophosphonates [R(OR)P(O)F] due to their use as poisons (*vide supra*). In 1929, Lange and Krueger reported one of the first routes to fluorophosphonates, utilizing phosphorus pentoxide and ammonium fluoride followed by the addition of silver and the requisite alkyl iodide.[52] The poor overall yield of this method led to the exploration of new pathways. One such strategy focused on synthesizing the chlorophosphonate [R(OR)P(O)Cl] precursor first, followed by the addition of a fluoride source to initiate a halogen exchange. In 1946, Saunders and coworkers first demonstrated the feasibility of this method by utilizing several protocols to synthesize the chlorophosphonate precursor, which was then converted to the desired fluorine-containing product using sodium fluoride (NaF).[21,53] Nearly 15 years later, Reesor and coworkers synthesized sarin and several derivatives via a halogen exchange of the P(V)–Cl, although using HF as the fluoride source.[5]

An alternative early strategy made use of P(V) reagents that already had the phosphorus–fluorine bond in place. One such example also comes from Saunders, where gaseous phosphorus oxydichlorofluoride [$P(O)Cl_2F$] was treated with two equivalents of alcohol.[21,22] Substitution of the two chlorides led to the efficient formation of the fluorophosphate. In 1960, Reesor developed a similar method, although the gaseous P(V)–F reagent they selected was methyl phosphonyldifluoride

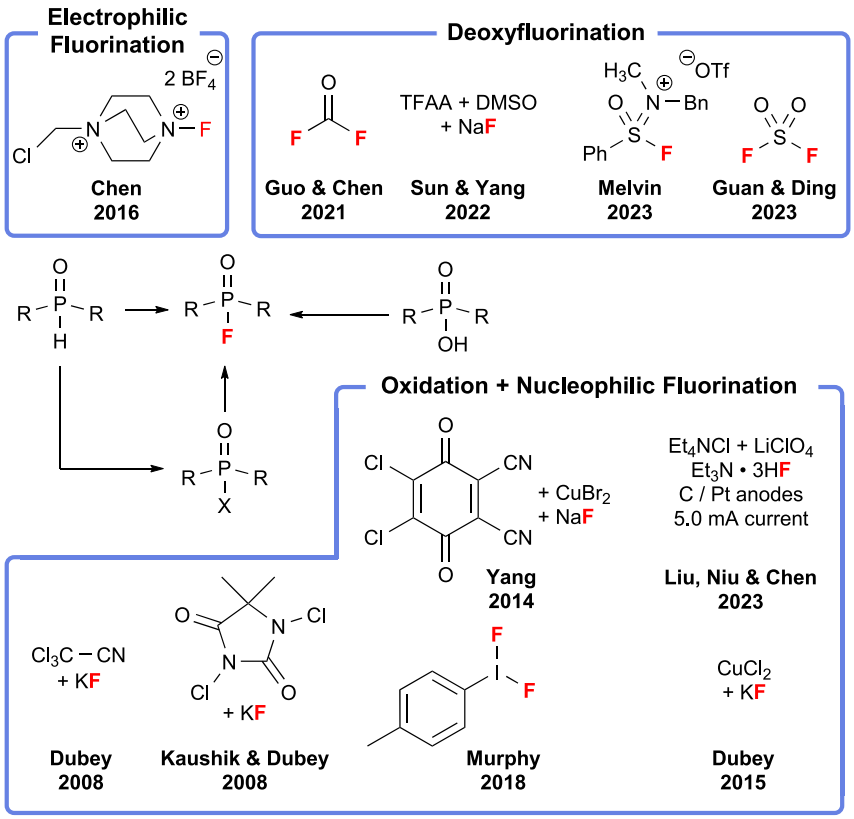

Figure 4. Synthesis approaches to organophosphorus(V) fluorides

[$MeP(O)F_2$].[5] The addition of various alcohols led to the desired sarin product and several derivatives.

Modern advancements

In the last 20 years, synthetic strategies have started to shift away from methodologies that require gaseous P(V)–F reagents or rely heavily on isolating chloride precursors. This is partly due to the safety hazards of working with low molecular weight, gaseous P(V)–F reagents. Modern techniques can be sorted into two categories based on the substrate class employed: direct or indirect conversion of phosphine oxides and deoxyfluorination of phosphinic acids (Figure 4).

Phosphine oxides

The conversion of phosphine oxides, indirectly or directly, to the corresponding phosphinic fluorides has recently surged in popularity. The phosphine oxide starting materials are easy to synthesize, and it is straightforward to vary the R groups. Although various reagents transform P(V)–H to P(V)–F bonds, two mechanistic pathways prevail: (1) oxidation followed by nucleophilic fluorination or (2) electrophilic fluorination.

A strategy involving oxidation followed by nucleophilic fluorination was developed first and remains the most utilized. Dubey and coworkers demonstrated that dialkylphosphites [$(OR)_2P(O)H$] could be converted to dialkyl chlorophosphates using trichloroacetonitrile (TCA), with the halogen exchange initiated by potassium fluoride (Figure 4).[6] Although this method efficiently generated dialkyl fluorophosphates

[$(OR)_2P(O)F$], it required refluxing conditions and the use of TCA as the solvent. Two follow-up reports from Dubey's group made this strategy more practical. When TCA is replaced with 1,3-dichlorodimethylhydantoin/potassium fluoride (DCDMH/KF)[7] or cesium fluoride ($CuCl_2$), lower temperatures can be used.[8] Both reagent combinations facilitate the synthesis of dialkyl fluorophosphates at room temperature in good yields. In 2023, Liu, Niu, and Chen achieved similar transformations through an electrochemical process.[9] Via an electrochemical Atherton-Todd process, the authors successfully generated phosphinic chloride intermediates from phosphine oxides, which were subsequently converted to the fluoride product with triethylamine-HF.

An alternative strategy is the direct oxidation and fluorination of P(V)–H compounds. In 2014, Yang and coworkers demonstrated that a combination of 2,3-dichloro-5,6-dicyano-4-benzoquinone (DDQ), catalytic $CuBr_2$, and NaF produces the desired phosphinic fluorides.[10] This method is most efficient when the R groups are aryl or alkyl. Similarly, Murphy and coworkers showed that hypervalent iodine reagent $TolIF_2$ was also an effective partner in this strategy, producing moderate to good yields of phosphinic fluorides.[11] In 2022, Sun and Yang utilized a mixture of trifluoroacetic anhydride (TFAA) and dimethyl sulfoxide (DMSO) with NaF at 100°C to effectively convert phosphine oxides to phosphinic fluorides.[12] Finally, S(VI)−F reagents, including sulfone iminium fluorides (SIF)[13] and sulfuryl fluoride (SO_2F_2),[14] also effectively exchange P(V)–H bonds for fluorine. In 2016, Chen and colleagues published the only example of electrophilic fluorination of P(V)–H bonds.[15] After finding little success with *N*-fluorobis(benzenesulfonyl)imide (NFSI), Selectfluor was found to be effective for this transformation, successfully synthesizing an array of aryl-substituted phosphinic fluorides.

Phosphinic acids

Although some early reports utilized a deoxyfluorination strategy, only recently has this pathway become a fully viable option in the synthesis of P(V)–F compounds. In 2021, Guo and Chen generated carbonyl fluoride (COF_2) from perfluoroalkyl ether carboxylic acids and showed its competency for the deoxyfluorination of phosphinic acids.[16] To produce the active fluorinating reagent, high temperatures (>100°C) are required as well as an inert atmosphere. Similarly, the TFAA/DMSO/NaF combination described above can achieve the same phosphinic fluoride products through a deoxyfluorination mechanism, also with elevated temperatures.

In 2023, the Melvin group utilized a SIF reagent to effect deoxyfluorination.[13] Employing this highly reactive reagent, symmetrical and unsymmetrical phosphinic fluorides could be synthesized following a 60-s, room temperature reaction. Other S(VI)–F reagents, such as SO_2F_2, can successfully convert phosphinic acids to the corresponding fluorides, albeit requiring higher temperatures and longer reaction times.[14]

SYNTHETIC ADVANCEMENTS ARE ESSENTIAL TO THE FUTURE OF organophosphorus(V) FLUORIDES

The dangerous history of organophosphorus(V) fluorides is well documented; however, there is an untapped promise. 10 years ago, S(VI)–F chemistry was in a similar stage. Synthetic innovations in S(VI)–F chemistry expanded the structural diversity of these compounds, which accelerated advances in application. The potential of organophosphorus(V) fluoride chemistry is currently limited by a synthetic bottleneck, one that can be resolved through pursuits in these three areas: (1) continued

exploration and expansion of electrophilic and deoxyfluorination protocols, (2) the development of methodologies that generate the P(V)–F bond *in situ*, and (3) enantioselective processes that produce chiral organophosphorus(V) fluorides.

The last decade has demonstrated that a multitude of reagents can furnish P(V)–F bonds. Although the vast majority of these protocols have centered on the oxidative or nucleophilic fluorination of phosphine oxides, recent innovations have also demonstrated the viability of both electrophilic fluorination and deoxyfluorination. Both of these methods have shown great promise for synthesizing phosphinic fluorides, although future optimizations should be focused on branching out into other P(V)–F products.

Adding P(V)–Fs to the growing collection of click chemistry hubs will influence how these molecules will be used moving forward. To bring PFEx more to the fore, developing methods that can both effectively generate P–F bonds and then subsequently exchange the fluoride for a desired nucleophile would be desirable. Currently, PFEx chemistry often requires the isolation of organophosphorus(V) fluorides, thereby creating additional synthetic and purification steps. Strategies that allow for both the *in situ* generation and transformation of P(V)–F compounds also help to reduce safety concerns as they obviate the need to isolate and handle potentially hazardous organophosphorus(V) fluorides.

The configuration of the phosphorous center in P(V)–F compounds can lead to markedly different biological activities (*vide supra*). However, there is a dearth of modern techniques that can prepare these compounds enantioselectively, representing a key area for future contributions.[53,54] Inspiration toward this challenge could be gleaned from the approaches used for sulfur, which either use simple chiral sulfur(IV) starting materials[55–58] or induce enantioselectivity via chiral ligands.[59] If enantioselective processes can be developed, chiral organophosphorus(V) fluorides could have wide-reaching applications. Subsequent exchange reactions via PFEx chemistry would likely be stereoretentive, facilitating access to a broader range of chiral P(V)-containing molecules This approach would advance promising P(V) drugs like Remdesivir—a broad spectrum anti-viral recently employed against COVID-19. Also, greater control over the stereochemistry of certain classes of organophosphorus(V) fluorides could help lower the associated dangers of handling these molecules. Overall, the challenge of controlling the configuration of the P(V) center is significant, but the advantages would be immense.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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