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Phosphorus fluoride exchange: Multidimensional catalytic click chemistry from phosphorus connective hubs

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SUMMARY

Phosphorus Fluoride Exchange (PFEx) represents a cutting-edge advancement in catalytic click-reaction technology. Drawing inspiration from Nature's phosphate connectors, PFEx facilitates the reliable coupling of P(V)–F loaded hubs with aryl alcohols, alkyl alcohols, and amines to produce stable, multidimensional P(V)–O and P(V)–N linked products. The rate of P–F exchange is significantly enhanced by Lewis amine base catalysis, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). PFEx substrates containing multiple P–F bonds are capable of selective, serial exchange reactions via judicious catalyst selection. In fewer than four synthetic steps, controlled projections can be deliberately incorporated along three of the four tetrahedral axes departing from the P(V) central hub, thus taking full advantage of the potential for generating three-dimensional diversity. Furthermore, late-stage functionalization of drugs and drug fragments can be achieved with the polyvalent PFEx hub, hexafluorocyclotriphosphazene (HFP), as has been demonstrated in prior research.

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AUTHOR CONTRIBUTIONS

Conceptualization, J.E.M. and K.B.S.; Methodology, J.E.M., K.B.S, S.S., J.A.H., C.J.S., and Q.-Q.C.; Investigation, S.S., J.A.H., C.J.S., and Q.-Q.C.; Supervision, J.E.M., K.B.S., and J.A.H; Writing – Original Draft, J.E.M., K.B.S, S.S., J.A.H., and C.J.S.; Funding Acquisition, J.E.M. and K.B.S.; Project Administration, J.E.M., K.B.S., and J.A.H.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online.

A Note on Safety:

The work described in this manuscript involves the synthesis and handling of organophosphorus compounds, including organofluorophosphates. The authors strongly advise colleagues to acquaint themselves with the extensive literature[36] on the toxicological properties of known representative compounds and to adhere to strict safety protocols. See supporting information for more details.

INTRODUCTION

Click chemistry is a versatile and powerful synthesis-based discovery method that relies on the formation of stable molecular connections. At its core, click chemistry encompasses a diverse and expanding set of robust and reliable reactions that enable the precise connection of discrete molecular modules. This approach mirrors the biogenesis of Nature's essential biopolymers, such as DNA, RNA, proteins, and carbohydrates[1,2]. In fact, several of the processes scoring click status[1] can be traced back to reversible chemistries commonly found in Nature, such as Michael additions, Diels–Alder cycloadditions, and condensation reactions. However, it was the advent of the CuAAC (copper-catalyzed azide-alkyne cycloaddition)[2–5] reaction that solidified click chemistry as a leading paradigm for the rapid discovery of functional molecules. This unrivaled and irreversible process lacks a natural counterpart and has earned the reputation as the "cream of the crop" within the click chemistry toolbox.

The world of sulfur-based connective click chemistry was launched in 2014 with the development of Sulfur Fluoride Exchange (SuFEx) by Sharpless and co-workers[8]. SuFEx capitalizes on the latent reactivity of high oxidation state sulfur-fluoride bonds, which can be triggered by catalyst activation, to facilitate nearly perfect exchange[8] with diverse nucleophiles including aryl and alkyl alcohols[9], amines[10–12], and carbanions[13–15]. This ground-breaking technique has opened new possibilities for chemical synthesis and holds tremendous potential for the development of novel functional materials and therapeutic agents.

SuFEx reactions classically occur between sulfur-centered hubs[16] — sulfuryl fluoride (SO_2F_2)[8], thionyl tetrafluoride (SOF_4)[17,18], ethenesulfonyl fluoride (ESF)[8,19,20], and 2-substituted-alkynyl-1-sulfonyl fluorides (SASFs)[21] — and aryl silyl ether nucleophiles. These reactions are typically activated by a suitable Lewis base amine (e.g., DBU)[22,23], bifluoride ion[14,24], or other catalysts[12,23,25]. While the direct S–F exchange between sulfur-containing hubs and aryl and alkyl alcohols is more challenging, modified SuFEx conditions reported by Moses and co-workers have made it possible by employing BTMG catalyst with HMDS additive, termed "Accelerated SuFEx Click Chemistry (ASCC)"[9,26,27].

Among Nature's most essential connectors are the phosphate esters and anhydrides. These unions are important in the makeup of nucleic acids, nucleotide coenzymes, nucleoside triphosphates (i.e., ATP), metabolic intermediates, and intermediates in many biochemical processes[28]. While phosphorus reagents are ubiquitous in synthetic organic chemistry, carbon[5] and sulfur[1,8,29] are more prevalent as synthetic connectors, a sentiment expressed in Westheimer's thesis on *Why Nature Chose Phosphates*: *"We can understand the choices made both by chemists and by the process of natural selection. They are both correct"*[28,30].

The first synthetic phosphate esters were prepared in France over 200 years ago[31–34], laying the foundation for the rich body of chemistry that followed[35–52]. Today, organophosphates are indispensable molecules, with several notable examples including the lifesaving antiviral drug (e.g., (–)-remdesivir (**1**)), anticancer chemotherapy agents (e.g., (±)-cyclophosphamide (**2**)), and pesticides (e.g., terbufos (**3**)). The chemical, physical, and biological properties are

modulated by the three other substituents projecting out along tetrahedral exit vectors from the phosphorus core.

The laboratory synthesis of phosphorus linkages typically hinges on the nucleophilic exchange of P(V) electrophiles. For example, the reaction between phosphoryl chloride ($POCl_3$) with both primary and secondary amines to afford the P(V)–N linked products. However, this halide substitution event is not always optimal; preventing unwanted degradation or over-substitution can be difficult.

At this point, one can take direction from the genesis of SuFEx chemistry. In their seminal work, Sharpless and co-workers revisited early reports on the exceptional stability of sulfonyl fluorides to aqueous conditions by Steinkopf[53,54], Davies and Dick[55,56], and others. Analogous to the P–Cl substitution chemistry, S–Cl exchange often leads to poor outcomes. However, the staggering reactivity gap offered by switching from S–Cl bonds to S–F bonds opened the door to SuFEx – a second near-perfect click reaction alongside CuAAC.

This disparity in reactivity of sulfur-halide bond-containing species can be accounted for by considering the unique properties of the S(VI)–F bond. The shorter S–F bond (1.54 Å vs. S–Cl = 1.99 Å[57,58]) has a predicted bond dissociation energy (BDE) almost double that of the chloride[6] (Figure 1A) and exclusively cleaves heterolytically due to the strongly electronegative fluorine[8]. This makes S(VI)–F groups stable toward nucleophilic addition (i.e., hydrolysis)[59], thermolysis, oxidation[55], and reduction[53]. Crucially, however, S(VI)–F bonds can be reliably activated for nucleophilic exchange when the correct catalyst-reagent combination is employed[8].

A similar pre-disposition exists when phosphorus is considered instead of sulfur. The shorter P–F bond (1.52 Å vs. P–Cl = 2.01 Å in CH_3POFCl[60], Figure 1A) has a higher predicted BDE of 602 kJ/mol[7]. Consequentially, in compounds bearing both P–Cl and P–F bonds, it is the P–Cl bond (BDE = 331 kJ/mol[61]) that preferentially reacts with incoming nucleophiles (i.e., amines and alkoxides) and hydrolyzes with KOH at 0 °C[62], leaving the P–F bond untouched. Further, P–F bonds are found to be more thermally stable than P–Cl compounds[63], survive refluxing in aniline[64], and remain intact under reductive conditions[64] (see Scheme 1C). However, activation of P–F bonds toward exchange with nucleophiles can be facilitated in a similar fashion to S–F compounds (i.e., trifluoromethylation with $TMSCF_3$ mediated by KF)[14,65,66]. This pattern of reactivity is then, of course, sufficient to entice curiosity for the amenability of the P–F bond for click chemistry reaction development.

Organo(fluoro)phosphates are highly versatile molecules, but their historic association as toxic nerve agents[67,68] has overshadowed their more favorable applications. For example, the resistance of P–F bonds to hydrolysis under biological conditions has been exploited to develop nucleoside phosphate prodrugs that selectively activate upon enzymatic cleavage[69]. P–F bonds have also found application in ^{19}F NMR-based probes (**4**)[70], therapeutics (e.g., isofluorophate (**5**)[71]), and probes used in protein profiling (e.g., Cravatt's probe (6)[72,73]).

Exploiting the innate tunability of the P–F bond environment, we now bring phosphorus into the click chemistry fold and report catalyst-accelerated Phosphorus Fluoride Exchange

(PFEx), a new click technology emulating Nature's exemplary use of phosphate connectors (Figure 1C). PFEx is characterized by the Lewis base-catalyzed exchange of P(V)–F bonds with incoming nucleophiles to afford stable, tetrahedral P(V)–O and P(V)–N linked products with defined multidimensional projections departing from the tetrahedral phosphorus core. The reactivity profile of P–F hubs surpasses that of their P–Cl counterparts in terms of both reaction rate and performance, qualifying PFEx as a promising click reaction. Further, the controlled and sequential decoration of the central phosphorus atom achieved through PFEx, allows for the rapid construction of multidimensional connections under mild conditions, making PFEx an ideal biomimetic candidate for Diversity Oriented Clicking (DOC)[21] and function-driven discovery projects.

RESULTS AND DISCUSSION

Synthesis of PFEx Substrates

Phosphoryl fluoride (POF_3)[74,75] and thiophosphoryl fluoride (PSF_3) are conceptually ideal PFEx hubs with multiple P–F offerings[76,77], but as highly toxic gases (b.p. −39.4 °C[78] and, b.p. −52.3 °C[79], respectively), are impractical for routine click chemistry[80]. We elected to use the widely available and bench-stable $POCl_3$ (b.p. 103 °C)[81] as a convenient starting point for PFEx substrate synthesis.

A selection of phosphoramidic difluorides[82] (**9a–9g**) was prepared by the addition of secondary amines to $POCl_3$ and Et_3N, followed by fluoride-chloride halogen exchange using an optimized protocol [KF (8.0 equiv) in acetone at room temperature (see supplementary information Table S1)] (Scheme 1A)[83]. The cyclic fluoridates **10a–10g** were prepared following an identical sequence using the corresponding 2-(aminomethyl)phenol. The solid cyclic fluoridates were bench stable for at least 2 months, whereas the liquid phosphoramidic difluoride substrates (**9a–9g**) were found to decompose over several hours at room temperature[84]. However, **9a–9g** were perfectly useable substrates if freshly prepared and delivered to the next step crude following simple Celite® filtration. The phosphoramidofluoridates **12a–12l** were prepared from $POCl_3$ or $PSCl_3$ by the sequential treatment with an aryl alcohol followed by an amine to yield the corresponding phosphoramidochloridates or thiophosphoramidochloridates, respectively. These chloridates were readily converted to the corresponding fluoridates in the presence of KF (8.0 equiv) and tetrabutylammonium chloride (10 mol%) as a phase transfer catalyst (Scheme 1B).

The resistance of 'FExable' substrates to hydrolysis under biological conditions is necessary for application in covalent drugs and 'Sleeping Beauty'-type probes. Hence, we evaluated the stability of representative P(V)–F and P(V)–Cl substrates in phosphate buffer solutions at room temperature (see Scheme 1C and supplementary information Table S2–S7 for full experimental details). The phosphoramidofluoridate **12a** was stable for over 24 hours when exposed to buffers with pH values of 4.8, 7.4, and 8.8, whereas the chloridate **11a** was not (refer to Scheme 3B for structures). A similar trend was observed for the cyclic phosphoramidofluoridates; **10c** hydrolyzed only in the basic buffer after an extended reaction time, while the analogous chloridate **8c** hydrolyzed across the range of buffer systems tested. Even the least stable PFEx substrates prepared (i.e., **12c**) — phosphoramidofluoridates derived from primary amines — demonstrated superior stability

to hydrolytic decomposition when contrasted to their chloride equivalent (Table S4). Each P–F substrate tested was stable when stirred in anhydrous ethanol, while the P–Cl analogs completely degraded after 24 hours[85].

Collectively, the stability of P(V)–F bonds over P(V)–Cl bonds to both hydrolysis[86] and uncatalyzed nucleophilic displacement by alcohols, supports a window of reactivity akin to SuFEx, positioning PFEx as a standout candidate for a click reaction.

PFEx Reaction Development

To investigate catalyst-accelerated Phosphorus Fluoride Exchange, we drew inspiration from lessons learned in SuFEx click chemistry[8]. A test reaction was first performed with freshly prepared phosphoramidic difluoride **9b** and the TBS-ether of 4-methoxyphenol in the presence of 20 mol% DBU catalyst at room temperature, which gave the P(V)–O linked PFEx product **12m** in 81% isolated yield in just 1 hour (see Table S9 in the SI for full optimization). No reaction was observed in the absence of the DBU catalyst (entry 6, Table S9). The same catalyst-activated PFEx conditions worked well with a range of electron-rich and electron-deficient aromatic and heteroaromatic aryl silyl ethers, giving the products **12m–12u** in good conversion (Scheme S1).

To streamline the new PFEx protocol and eliminate the need for prerequisite aryl silyl ether synthesis, we adopted the same accelerated conditions developed for SuFEx[9,26]. Phosphoramidates **12m–12u** were prepared directly from the corresponding phenols using a synergistic combination of 20 mol% BTMG (2-*tert*-butyl-1,1,3,3-tetramethylguanidine, Barton's base) and 1 equivalent of HMDS (Scheme 2); a 15-minute reaction time afforded the PFEx products in good to excellent yields. Of note is the preference for PFEx reaction with the difluoride substrates over the corresponding mono-fluoride products, mirroring the reactivity trend observed with the multidimensional iminosulfur oxydifluorides derived from thionyl tetrafluoride (SOF_4)[18]. In each instance, the PFEx reaction stopped following the first substitution, leaving the remaining P(V)–F bond untouched. This impressive selectivity can be explained by considering the attenuation of the phosphorus's electrophilicity after replacing an electron-withdrawing fluoride with an aryl alcohol. Control reactions with analogous dichlorides gave complex product mixtures.

The cyclic phosphoramidofluoridate **10c** was next reacted with 3,5-xylenol (**14a**) in the presence of BTMG and HMDS (Scheme 3A). In just 2 hours at room temperature, full consumption of the substrate **10c** was observed, with the phosphoramidate product **15a** isolated in 89% yield. The reaction with the analogous chloride **8c** required 22 hours under similar conditions to reach a yield of just 70%. The PFEx substrate **12a** was found to be less reactive under BTMG catalysis, requiring 12 hours at room temperature to achieve complete conversion to phosphoramidate **16a**. In contrast, chloride **11a** failed to yield any discernable product and degraded over the 22-hour reaction period (Scheme 3B). The enhanced reactivity of selected cyclic phosphates over their acyclic counterparts is well known[87–92]; with rates of hydrolysis and solvolysis up to a million times faster for cyclic species. The stability of phosphoramidic difluorides (**9**) relative to phosphoramidofluoridates (**10** and **12**) can be explained using an electronic rationale; having two highly electronegative

fluorine atoms bonded to the phosphorus atom creates a substantially more positive P(V) core, leading to increased rates of hydrolysis and decomposition[93]. Replacing one fluorine atom with a less electronegative amino or phenoxy substituent stabilizes the phosphorus core toward hydrolysis/solvolysis.

PFEx Reaction Optimization and Scope

We next investigated a selection of catalysts to optimize the rate of the PFEx reaction. Due to their slow exchange reaction, the phosphoramidofluoridate **12a** and 3,5-xylenol (**14a**) were chosen as model PFEx substrates. The catalyst screen revealed that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and the phosphazene bases P_4-^{t}Bu and P_2-^{t}Bu were the superior catalysts, delivering quantitative yields of the PFEx product **16a** in under 2 hours at room temperature (see Table 1, Tables S10–S12, and Figure S4 for full optimization, catalyst structures, and associated pK_aH values in MeCN).

In the absence of the HMDS additive, none of the catalysts performed well, suggesting that synergism between the silicon reagent and catalyst is crucial for PFEx (*cf.* accelerated SuFEx)[9]. TBD was chosen as the preferred catalyst for further studies due to its relatively lower cost, tolerability of a wide selection of functional groups, and its position in a 'sweet spot' in terms of pK_aH (TBD = 26.2 in MeCN) between the phosphazene superbases (pK_aH 26.0 to 42.7) and guanidine/amidine bases (pK_aH 18.8 to 25.0)[99].

Monitoring the TBD-accelerated PFEx reaction between **12c** and 3,5-xylenol (**14a**) by ^{1}H NMR revealed a clean conversion to the phosphoramidate product **16c** in just 60 minutes (Figure S6 and S7). No intermediates were identified on the NMR time scale[9,27]. Conversely, the reaction between **14a** and chloridate **11c** failed to deliver significant product over 24 hours, as determined by ^{1}H NMR analysis (Figure S8–S10). Unreacted chloridate **11c** instead decomposed to phosphorodiamidate **S4**, likely arising from competing P–Cl exchange with the stoichiometric HMDS reagent and subsequent N–Si bond cleavage (Figure S11). These results demonstrate the superior performance of catalyst-accelerated PFEx over P–Cl equivalents.

The optimized TBD-catalyzed PFEx conditions were successful with a range of P(V)–F substrates, affording P(V)–O linked products in excellent yield (Scheme 4). Reactions involving thiophosphoramidofluoridates required longer reaction times (i.e., 6 h required to form product **15b** compared to 15 min for **15a**)[95]. PFEx is tolerant to a range of functional groups, including aldehydes (**15n**), ketones (**15p** and **16g**), esters (**16h**), and amides (**16f**). Aryl alcohols react chemoselectively as PFEx nucleophiles in the presence of secondary alcohols (**15o**) and anilines (**15e**). Noteworthy are the PFEx products incorporating natural products, including (+)-estrone (**15j**, dr = 1:1), (+)-estriol (**15o**, dr = 1:1), (+)-totarol (**15f**, dr = 1:1), and (–)-cholesterol (**16e**, dr = 2:1).

Sequential PFEx Click Chemistry

Polyfluorinated organophosphorus compounds offer significant potential in Diversity Oriented Clicking (DOC) strategies centered around PFEx[21]. Having demonstrated the robust mono-PFEx reaction of phosphoramidic difluorides (Scheme 2), we next explored the

serial decoration of hexafluorocyclotriphosphazene (**HFP**) — a hub bearing six P–F bonds. Early studies by Shreeve and co-workers on the substitution of **HFP** by silyl-protected diols and dithiols found catalytic cesium fluoride facilitated this transformation[96], while Chandrasekhar and Nagendran utilized phosphazenes to prepare a collection of multi-site coordinating ligands[97]. We discovered that diols could also be reacted with **HFP** in the presence of 2 equivalents of Et_3N, affording the spirocyclophosphazene products (i.e., **17a**) in good conversions without the need for silyl-protection (Scheme 5A). Alkyl alcohols and amines, such as 2-phenylethanol, benzylamine, azidothymidine (AZT), and cholesterol, behaved similarly with 1 equivalent of Et_3N as a base, delivering compounds **17b**–**17e**, respectively. Phenols underwent selective mono-PFEx with **HFP** when reacted in the presence of DMAP (10 mol%) and HMDS (1.0 equiv) (i.e., **17f**) but generated intractable mixtures of PFEx products with **HFP** in the presence of stoichiometric Et_3N or under TBD-catalyzed conditions.

The multifunctional AZT-containing PFEx substrate **17d** was further reacted with both ethylene glycol (**17g,** Scheme 5B) and ethylene diamine (**17j**, see SI). Substitution of the last remaining P–F bonds of **17g** required more forcing conditions. Adding phenol to **17g** required 10 mol% BTMG in the presence of HMDS. In contrast, 2 equivalents of cesium carbonate were required to react the geminal P–F bond of **17h** with 4-methylphenol to give **17i**[98] — the product of 5 successive PFEx reactions.

The serial functionalization of **HFP** highlights that judicious catalyst selection is crucial to obtain selective reactivity, especially when employing substrates with multiple P–F bonds. Tabulated below (Table 2) are the optimized reaction conditions for each substrate pair explored, which we believe will serve as a helpful resource when designing PFEx strategies.

Orthogonal Click Chemistry

A key criterion of click reactions — and perhaps the most challenging to meet — is a requirement for chemoselective reactivity that allows connections to be made with control, ideally perfect control. To explore the resilience of PFEx as a click-compatible reaction, we prepared **18** as a model hub that is primed for three consecutive click reactions via i) a terminal alkyne for CuAAC, ii) a ‘SuFExable’ fluorosulfate, and iii) a ‘PFExable’ phosphoramidofluoridate (Scheme 6). First, under accelerated SuFEx conditions[9] [BTMG (20 mol%), HMDS (1.0 equiv) in acetonitrile at room temperature, 30 min], the reaction of **18** with 4-phenylphenol afforded compound **19**, exclusively; the incoming nucleophile reacting selectively with the fluorosulfate group. Next, **19** was subjected to TBD-accelerated PFEx conditions in the presence of allyl 4-hydroxybenzoate, giving the expected phosphoramidate **20** in an excellent 91% yield after 5 h. Finally, **20** was reacted with benzyl azide under standard CuAAC conditions [$CuSO_4$•$5H_2O$ (10 mol%), sodium ascorbate (40 mol%) in DMF at room temperature, 3 h] yielding the ‘multi-clicked’ product **21**. The sequential reaction of the click hub **18** under controlled conditions exemplifies the exquisite precision of chemoselective click transformations; the striking difference in reactivity between P–F and S–F clickable moieties creates a window of opportunity for orthogonal connective chemistry.

Conclusion

In this work, we present PFEx (Phosphorus Fluoride Exchange) as a potent click reaction for discovering functional molecules. PFEx transformations proceed smoothly under Lewis nitrogen base catalysis, giving P–O and P–N linked products in high yield and in the absence of unwanted side-products. The superior reactivity of P(V)–F-containing compounds relative to their P(V)–Cl counterparts provides a unique compound class that can be selectively activated by appropriate catalysts, akin to SuFEx click reactions. Substrates with multiple P–F bonds offer an opportunity for Diversity Oriented Clicking, allowing for up to 5 successive steps of serial exchange reactions to create “multi-clickable” hubs, enabling selective PFEx reactions in the presence of SuFExable functional groups. This innovation in P(V)–F chemistry will undoubtedly spark new research and developments in the field.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact—Further information and requests for resources should be directed to, and will be fulfilled by, the lead contact, John E. Moses (moses@cshl.edu).

Materials availability—Full experimental details and characterization data can be found in the supplemental information.

Data and code availability—All data supporting this study are available in the manuscript or supplemental information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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98. Products 17g–17i were obtained as diastereomeric mixtures that were inseparable by either flash column chromatography or LC-MS (refer to Figure S12 for representative 31P NMR spectra).
99. In multi-click sequences, SuFEx reactions must often be conducted prior to PFEx reactions.

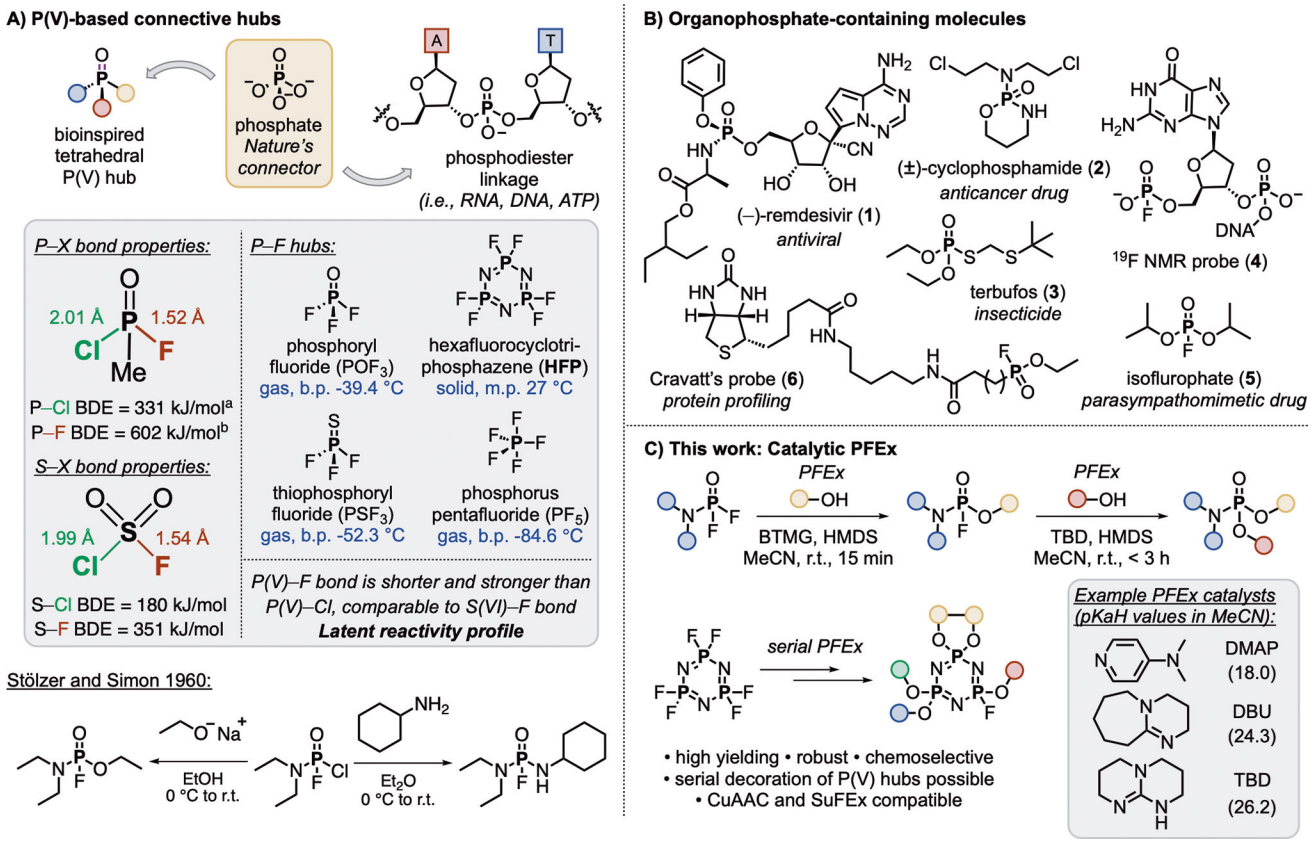


Figure 1. Selected organophosphorus hubs.

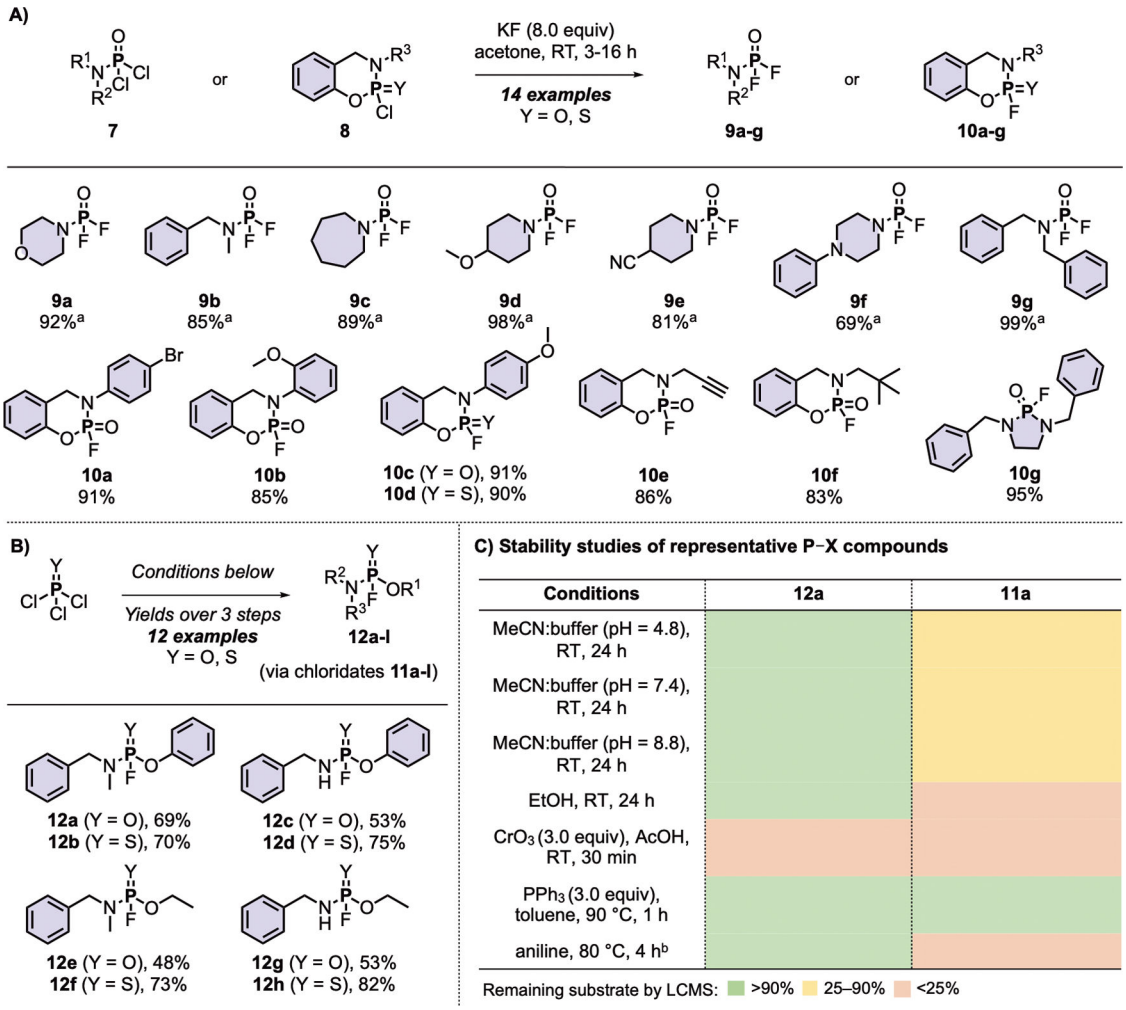
(A) P(V)-based connective hubs and associated physicochemical properties. A = adenine, T = thymine.

(B) Selected organophosphorus-containing molecules.

(C) This work: Catalytic phosphorus(V) fluoride exchange (PFEx).

[a]Calculated BDE of P–Cl bond in $POCl_3$[6].

[b]Calculated BDE of P–F bond in POF_3[7].



Scheme 1. Synthesis of PFEx substrates.

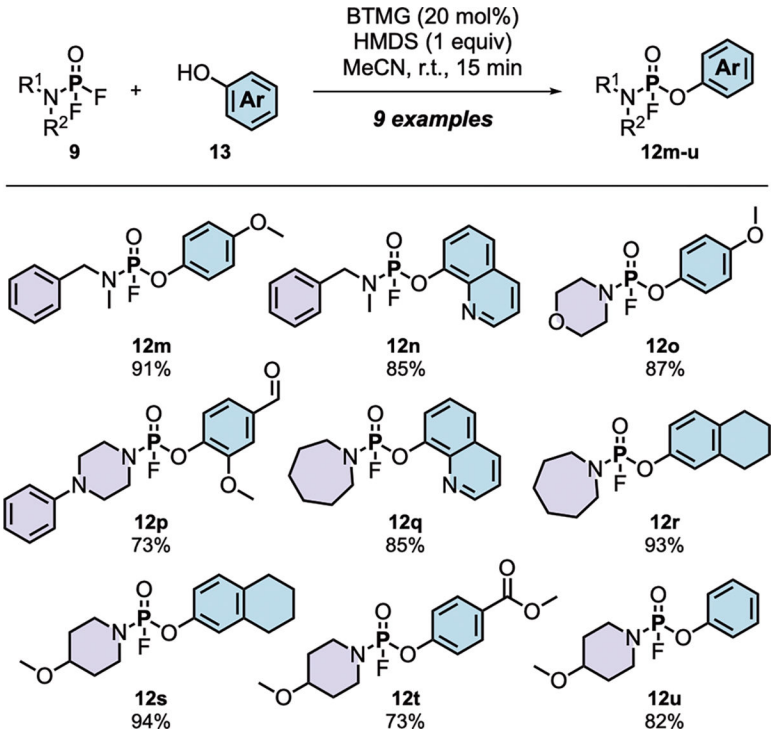
(A) Synthesis of phosphoramidic difluorides, cyclic phosphoramidofluoridates, and cyclic thiophosphoramidofluoridates.

(B) Synthesis of phosphoramidofluoridates and thiophosphoramidofluoridates. *General reaction conditions:* $POCl_3$ or $PSCl_3$ (1.0 equiv) and Et_3N (1.0 equiv) were added to relevant phenol (1.0 equiv) in CH_2Cl_2 (0.25 M) at −78 °C then stirred overnight at room temperature. The required amine (1.0 equiv) was added, followed by Et_3N (1.0 equiv) dropwise at −78 °C. The reaction was stirred at room temperature until complete (^{31}P NMR). The reaction was filtered and concentrated. KF (8.0 equiv) and $^{n}Bu_4NCl$ (0.10 equiv) were added to the crude in acetone (0.25 M). After completion (^{31}P NMR), the reaction was filtered, concentrated, and purified by silica column chromatography. Isolated yields are reported. Reactions were performed on 5.0 mmol following general procedures detailed in the supporting information unless stated otherwise. See supporting information for a complete list of products.

(C) Stability studies of representative P–X compounds.

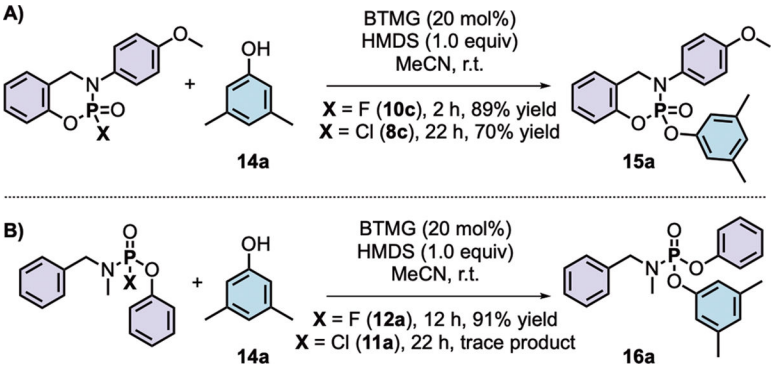
[a]Product had limited stability.

[b]**11a** was completely consumed after 1 h; P–Cl exchange product was identified.



Scheme 2. PFEx reaction of phosphoamidic difluorides with phenols.

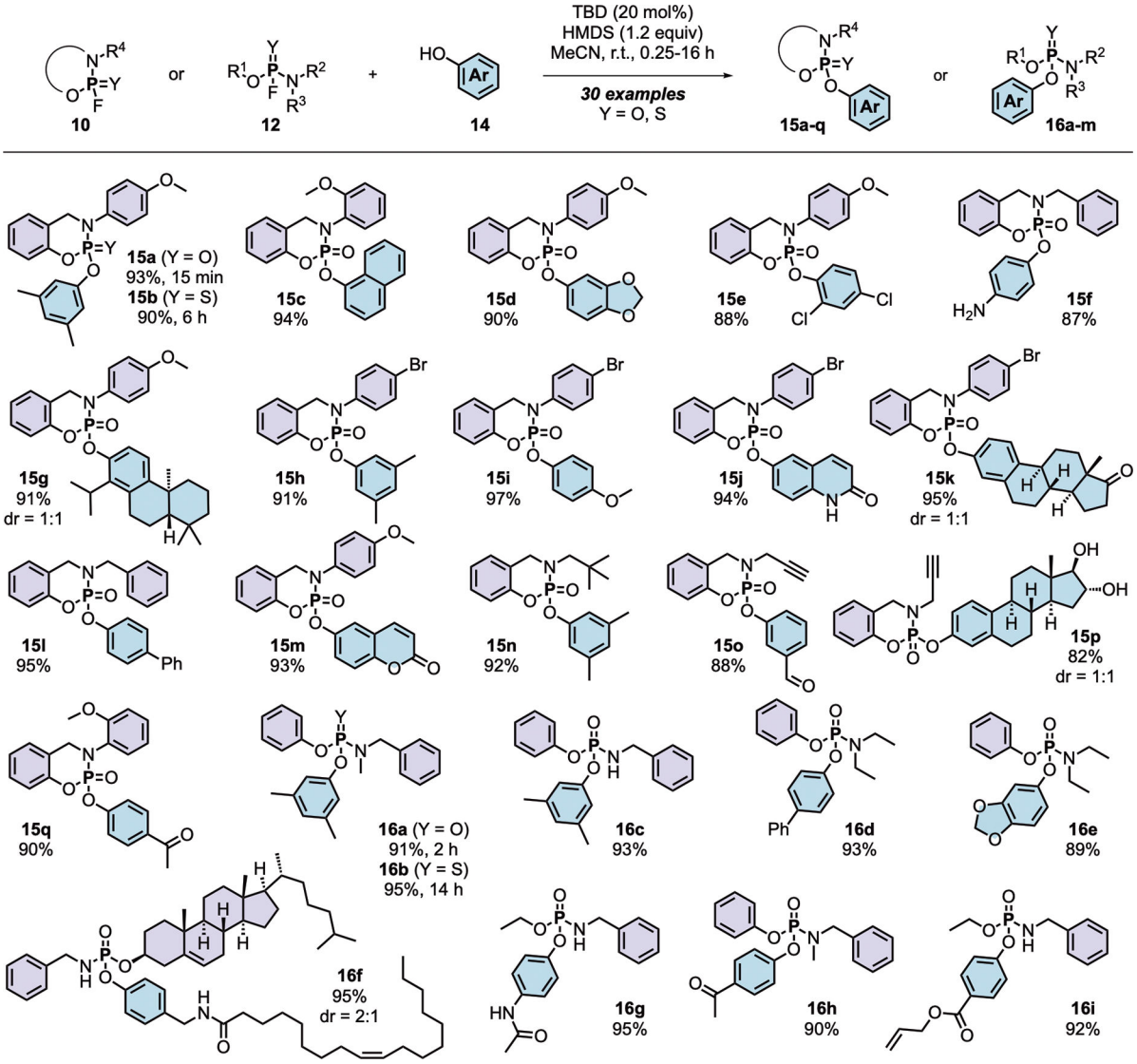
General reaction conditions: P(V)–F derivative (1.2 equiv) and phenol (1.0 equiv) were stirred in acetonitrile (0.4 M) in the presence of BTMG (20 mol%) and HMDS (1.0 equiv) for 15 min at room temperature. Isolated yields are reported. Reactions were conducted on a 1.20 mmol scale unless otherwise stated.



Scheme 3. Comparison of the reactivity of P(V)–F and P(V)–Cl substrates with 3,5-xylenol under catalyst-accelerated PFEx conditions.

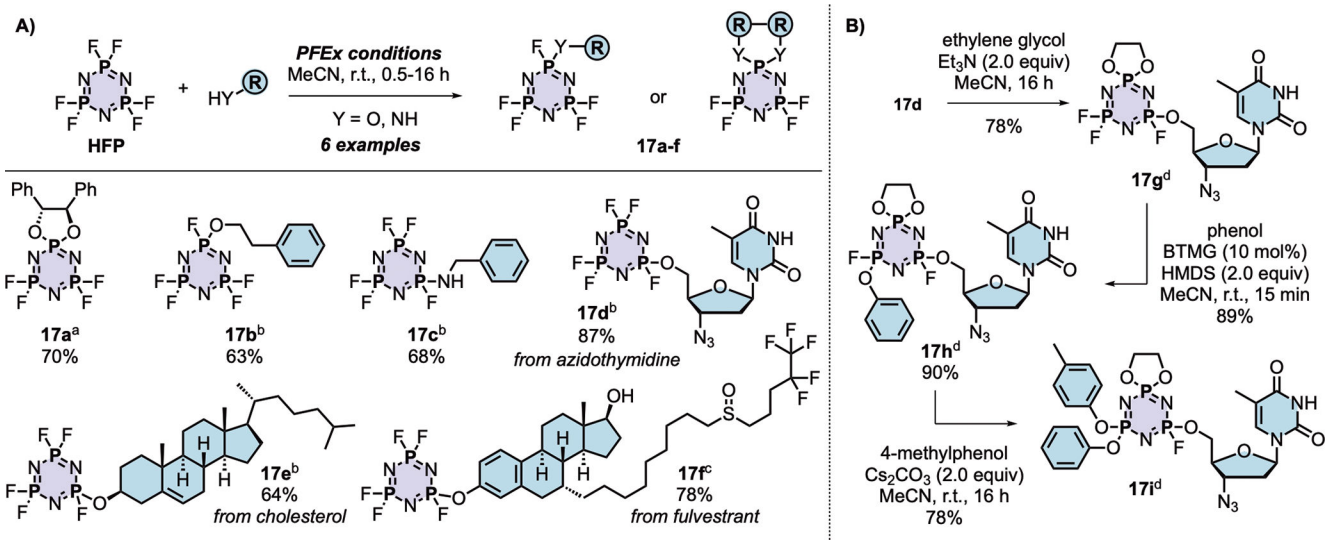
(A) Cyclic PFEx substrates.

(B) PFEx substrates.



Scheme 4. Substrate scope for TBD-catalyzed PFEx reaction.

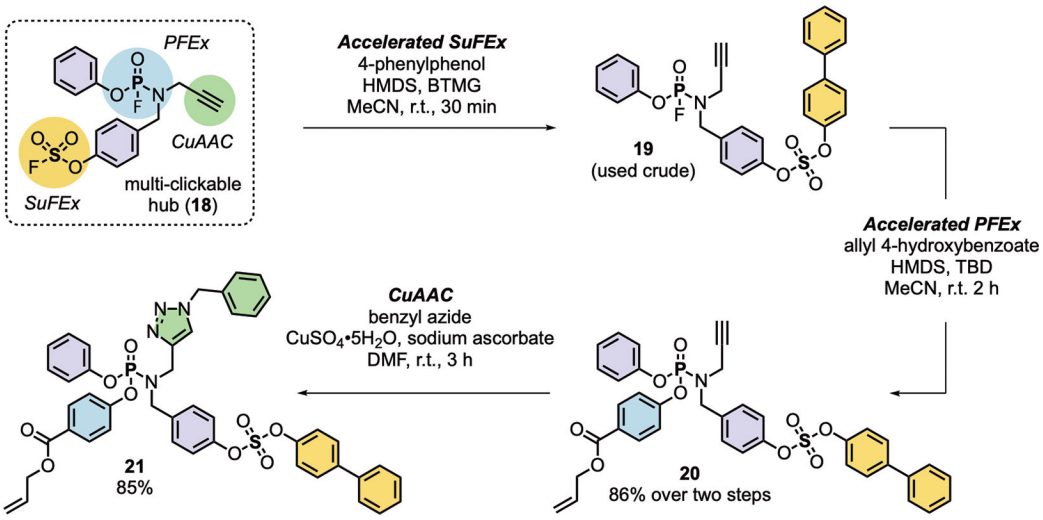
General reaction conditions: P(V)–F derivative (1.0 equiv) and phenol (1.2 equiv) were stirred in acetonitrile (0.4 M) in the presence of TBD (20 mol%) and HMDS (1.2 equiv) until completed as determined by TLC and both ^{19}F and ^{31}P NMR. Isolated yields are reported. See supporting information for a complete list of products.



Scheme 5. PFEx reactions of hexafluorocyclotriphosphazene (HFP).

(A) Reaction with alcohols and phenols. PFEx conditions = [a]Et_3N (2.0 equiv); [b]Et_3N (1.0 equiv); [c]DMAP (10 mol%), HMDS (1.0 equiv).

(B) Sequential PFEx functionalization of **HFP**. [d]Inseparable, unquantifiable mixture of diastereoisomers obtained.

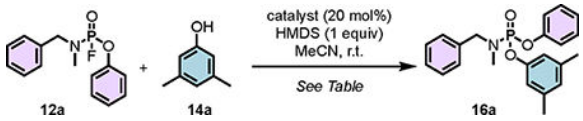


Scheme 6. The orthogonal reactivity between PFEx, SuFEx, and CuAAC catalysis.

Accelerated SuFEx conditions: HMDS (1.0 equiv), BTMG (20 mol%), MeCN, r.t., 30 min. Accelerated PFEx conditions: HMDS (1.2 equiv), TBD (20 mol%), MeCN, r.t., 2 h. CuAAC conditions: $CuSO_4•5H_2O$ (10 mol%), sodium ascorbate (40 mol%), DMF, r.t., 3 h.

Table 1.

PFEx catalyst screen.



Entry	Catalyst	pK_aH (MeCN)	Time (h)	Conversion (%)[a]
1	P_4-^{t}Bu	42.7	1	>99
2	P_2-^{t}Bu	33.5	1.5	>99
3	TBD	26.2	5	>99
4	BTMG	~26	14	91
5	DBU	24.3	14	80
6	P_1-^{t}Bu	26.9	14	10
7	TMG	23.7	14	9
8	DPG	18.8	14	Trace
9	BEMP	27.5	14	66
10	MTBD	25.0	14	64
11	DMAP	18.0	14	0
12 [b]	**TBD**	**26.2**	**2**	**>99**
13[c]	TBD	26.2	7	16
14[d]	TBD	26.2	7	20

Reactions were conducted on a 0.10 mmol scale in acetonitrile (0.25 M). Refer to supplementary information Figure S4 for a list of catalyst structures.

[a] Conversions were determined by ^{31}P NMR and ^{19}F NMR.

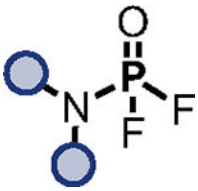
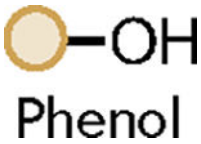
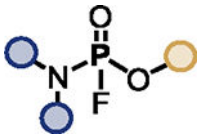
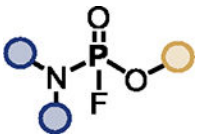
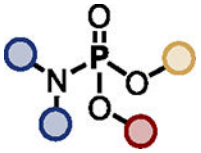
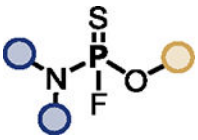
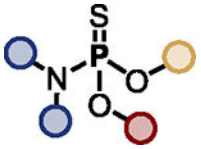
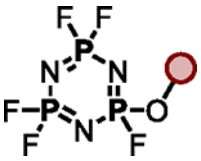
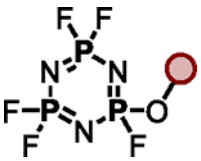
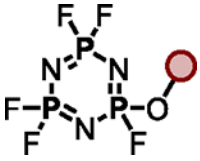
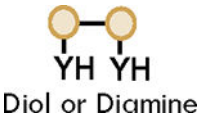
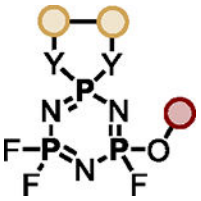
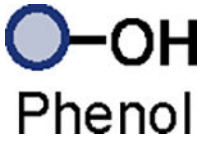
[b] 1.20 equiv HMDS and 3, 5-dimethyphenol in MeCN (0.5 M) were employed.

[c] HMDS was replaced with Et_3N (1.0 equiv).

[d] Without HMDS.

Table 2.

Optimized PFEx conditions.

Entry	Phosphate	Substrate	Catalyst	Additive	Product
1			BTMG (20%)	HMDS (1.0 eq.)	
2			TBD (20%)	HMDS (1.2 eq.)	
3			TBD (20%)	HMDS (1.2 eq.)	
4			DMAP (10%)	HMDS (1.0 eq.)	
5			–	Et_3N (1.0 eq.)	
6			–	Et_3N (2.0 eq.)	
7			BTMG (20%)	HMDS (1.0 eq.)	

Entry	Phosphate	Substrate	Catalyst	Additive	Product
8			–	Cs_2CO_3 (2.0 eq.)