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Defluorophosphorylation of Fluoroalkyl Peroxides for the Synthesis of Highly Substituted Furans

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Transformation of multifunctional materials with control over site-selectivity and chemical diversity remains challenging. Herein, we present a metal-free, one-pot strategy for the defluorophosphorylation of polyfluoroalkyl peroxides that enables expedient construction of structurally diverse phosphoryl-containing heterocyclic libraries. By judicious choice of reaction conditions, *C*3,4-diphosphoryl furans and *C*4-monophosphoryl furans can be easily accessed. In addition, synthetic derivatization of the obtained organophosphorus heteroarenes to value-added monodentate and bidentate phosphines has been demonstrated. Mechanistic studies revealed that regioselective defluorophosphorylation allows divergent product formations in two reaction modes.

Introduction

Phosphoryl-containing heteroarenes constitute an important class of structurally diverse skeletons that are widely found in natural products, pharmaceuticals, bioactive molecules, and functional materials (Figure 1, A, right).[1-3] These organophosphorus compounds are universal precursors to trivalent phosphine ligands, which are a cornerstone of organometallic chemistry.[4,5] P=O bonds are also found in nucleic acids and the backbone of DNA and RNA.[6]

While the incorporation of phosphoryl moieties into heterocycles has experienced significant advances, their selective installation onto furan derivatives can be challenging (Figure 1, A, left).[7,8] The conventional C2/C5-phosphorylation of furans through metalation or electrophilic aromatic substitution is well known (Figure 1, B, a).[9] These methods rely on air- and moisture-sensitive organometallics and/or toxic phosphorus reagents. During the past decade, Hirao-type[10] or dehydrogenative C(sp^2)–P bond cross-coupling reactions of (hetero)aryl electrophiles with H-phosphine oxides catalyzed by Pd,[11-15] Cu,[16,17] Ni,[18-20] and others[21] have been well documented (Figure 1, B, b). The necessity of harsh reaction conditions, expensive noble metal catalysts, utilization of pre-existing (hetero)arenes, and directing groups hinder the efficient synthesis of phosphorylated heterocycles. Another route to phosphorylated furans is through radical processes based on stoichiometric oxidants (Figure 1, B, c).[22-24] In related studies, Lei's group recently reported the Mn-catalyzed electrooxidative phosphorylation and diphosphorylation of furans.[25] In this study, the site-selectivity is predominantly dictated by the inherent reactivity of the substrate (C2/C5 positions). Another route involves the cyclization of acyclic phosphorylated building blocks (Figure 1, C, d),[26-29] or reaction of unsaturated alkenes or alkynes[30,31] with phosphorus nucleophiles (Figure 1, C, e). These strategies exhibit limited flexibility in the installation of functional groups, especially fluorinated moieties, which generally confer desirable properties to the products.[32] Considering the importance of phosphorus-containing furans, and the difficulty in the formation of C3/C4-substituted derivatives, the development of concise C–P bond-forming methods leading to formation of multisubstituted furans[33-36] is highly desirable.

The defluorofunctionalization of organofluorides has shown promise, as it confers synthetic versatility to normally unreactive C–F bonds.[37-43] One of the most straightforward routes to access a C(sp^3)–P bond is *via* the Michaelis–Arbuzov reaction (Figure 2, A).[22] Recent research in transition metal-free defluorophosphorylation of aryl fluorides[44,45] and *gem*-difluoroalkenes[46] by the groups of Sawamura, Li, Huang, and others add to the available methods for C–P bond formation (Figure 2, B–C). Our laboratory has recently leveraged selective

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Electronic Supplementary Information (ESI) available: General information, experimental details, optimization of reaction conditions, mechanistic studies, characterization data for products, and NMR spectra of products. See DOI: 10.1039/x0xx00000x

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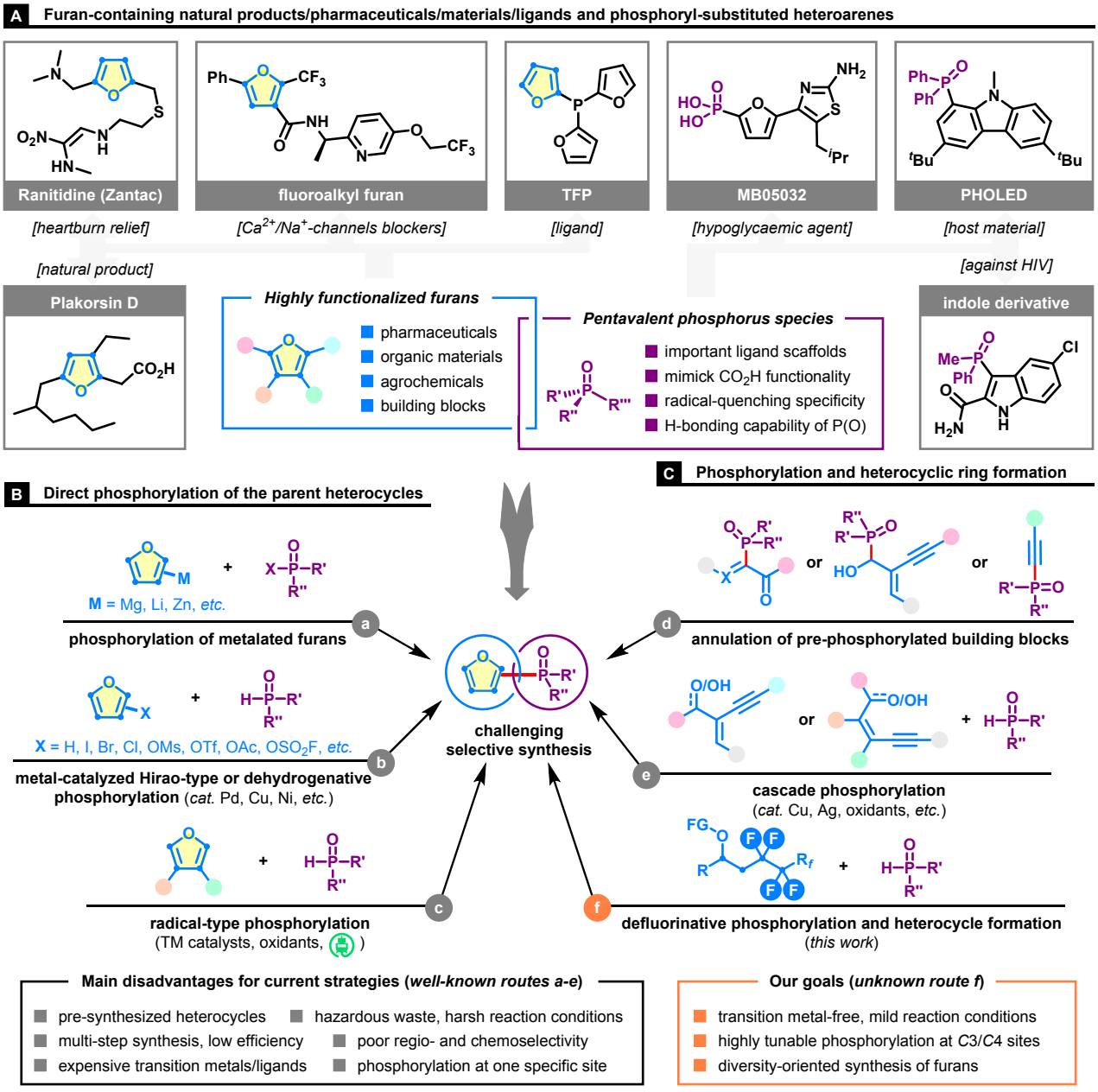

Figure 1. **Synthesis and application of phosphorus-substituted furan scaffolds. A** Furan and phosphorylated furans in natural products, pharmaceuticals, materials, and ligands. **B** Direct phosphorylation of furans. **C** Ring formation involving acyclic organophosphorus compounds and cyclization with P–C bond formation.

C(sp^3)–F bond cleavage manifolds of activated polyfluoroalkyl substrates[47] or fluoroalkyl peroxides to give products featuring fluoroalkyl substituents (Figure 2, D–E).[48,35] In this context, developing a tunable strategy for the production of fluoroalkylated heterocycles with control over the number of phosphine oxide moieties would be useful (Figure 1, C, f). Herein we report the synthesis of two types of phosphorylated heterocycles, *C*3,4-diphosphoryl furans and *C*4-monophosphoryl furans, can be selectively synthesized by a divergent defluorophosphorylation of fluoroalkyl peroxides with *H*-phosphine oxides.

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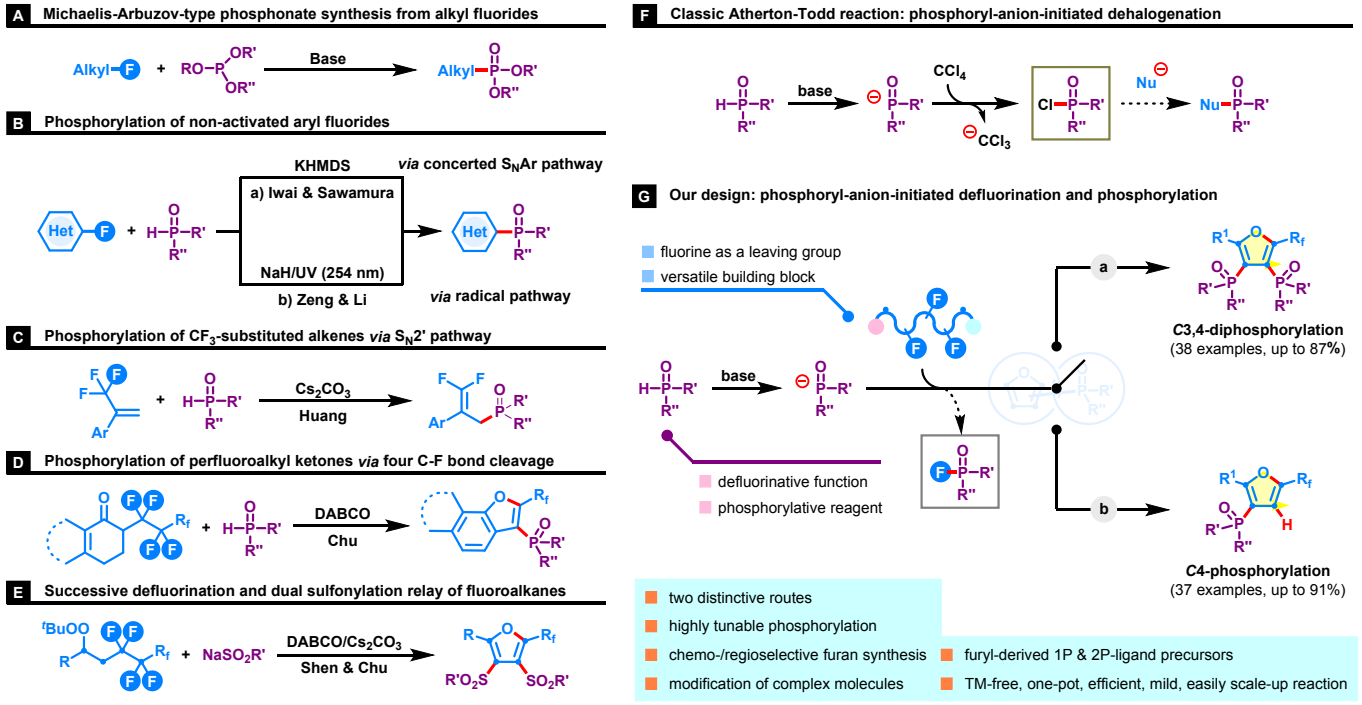
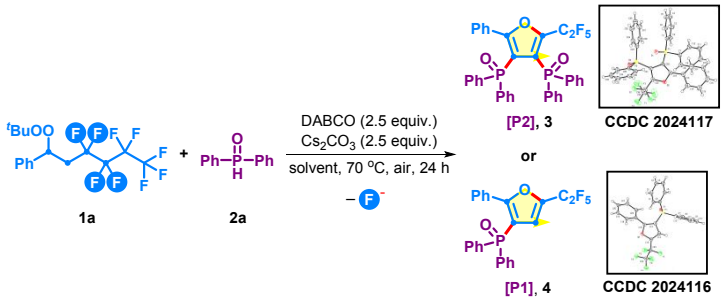


H The selectivity of *C*3,4-diphosphorylation and *C*4-phosphorylation[a]



entry	solvent	NMR yield of 3 (%)[b]	NMR yield of 4 (%)[b]
1	toluene	40	trace
2	1,4-dioxane	29	trace
3	DME	42	trace
4	THF	11	trace
5	$CHCl_3$	9	trace
6	MeCN	41	trace
7	**DCE**	**94 (87)[c]**	**trace**
8	DMF	trace	18 (16)[c]
9	DMSO	--	73
10	**DMSO**	--[c,d]	**81 (78)[c,d]**

Figure 2. **Defluorophosphorylation protocols**. **A** Michaelis-Arbuzov-type phosphonate synthesis starting from alkyl fluorides. **B** Phosphorylation of non-activated aryl fluorides via concerted S_NAr pathway or radical pathway. **C** Phosphorylation of CF_3-substituted alkenes via an S_N2' pathway. **D** Defluorophosphorylation of perfluoroalkyl ketones. **E** Successive defluorination and dual sulfonylation relay of fluoroalkyl peroxides. **F** Classic Atherton-Todd reaction through phosphoryl-anion-initiated dehalogenation. **G** New design for the synthesis of *C*3,4-diphosphorylated and *C*4-phosphorylated furan derivatives through selective defluorophosphorylation. **H** Key results in reaction optimization. [a] Reaction conditions: (1-(*tert*-butylperoxy)-3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene (**1a**, 0.36 mmol), diphenylphosphine oxide (**2a**, 0.3 mmol), DABCO (0.75 mmol), and Cs_2CO_3 (0.75 mmol) in solvent (2.0 mL) at 70 °C for 24 h under air. [b] Yields were determined by NMR analysis with 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield. [d] **1a** (0.3 mmol), **2a** (0.9 mmol), DABCO (1.05 mmol), and Cs_2CO_3 (1.05 mmol) were used.

Reaction Design and Optimization

At the outset of our studies, we were drawn to the Atherton-Todd reaction, which involves the dehalogenation of tetrachloromethane by strongly nucleophilic anionic phosphorus species (Figure 2, F).[49] This unusual reaction involves nucleophilic attack at the chloride of the Cl–C bond, generating a carbanion and P–Cl bond. The resulting electrophilic P–Cl center can react with nucleophiles. We desired to adapt this mode of reactivity to fluorocarbons (Figure 2, G). There are few reports describing phosphorus species-promoted defluorination, probably due to the inert nature of C–F bonds toward nucleophiles.[50,51]

With the challenges associated with the cleavage of strong C–F bonds in mind, we commenced our investigation by treating

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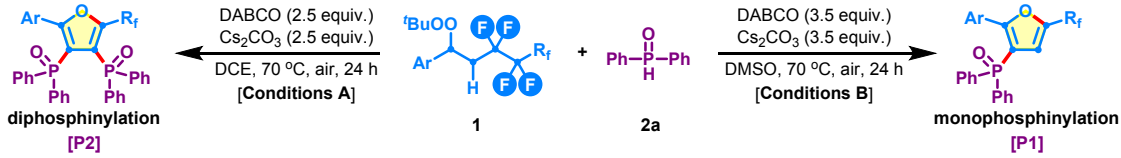
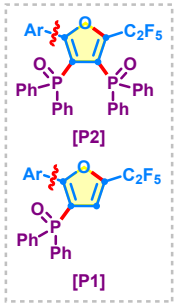
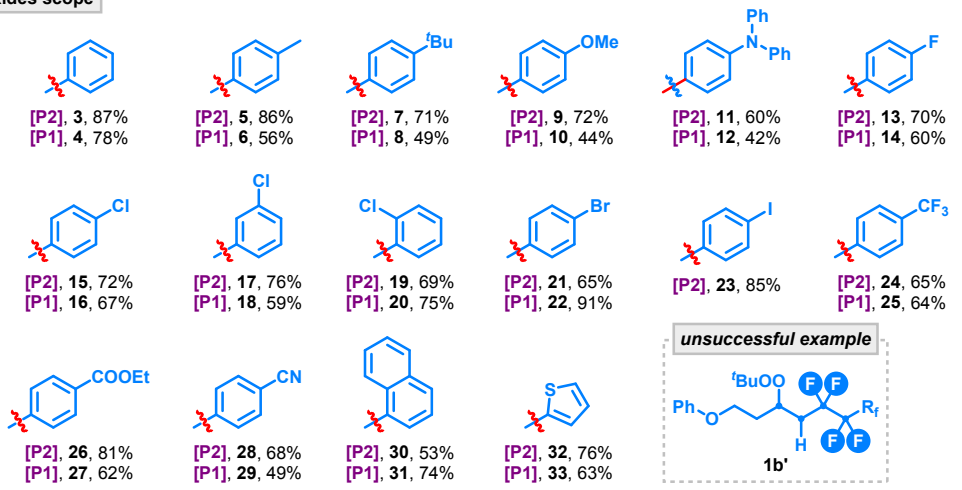
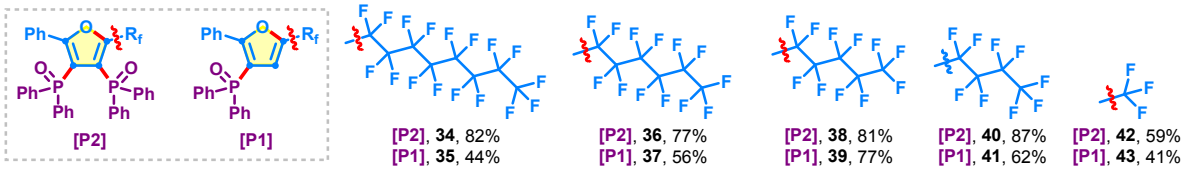
Table 1. Substrate scope of fluoroalkyl peroxides[a]



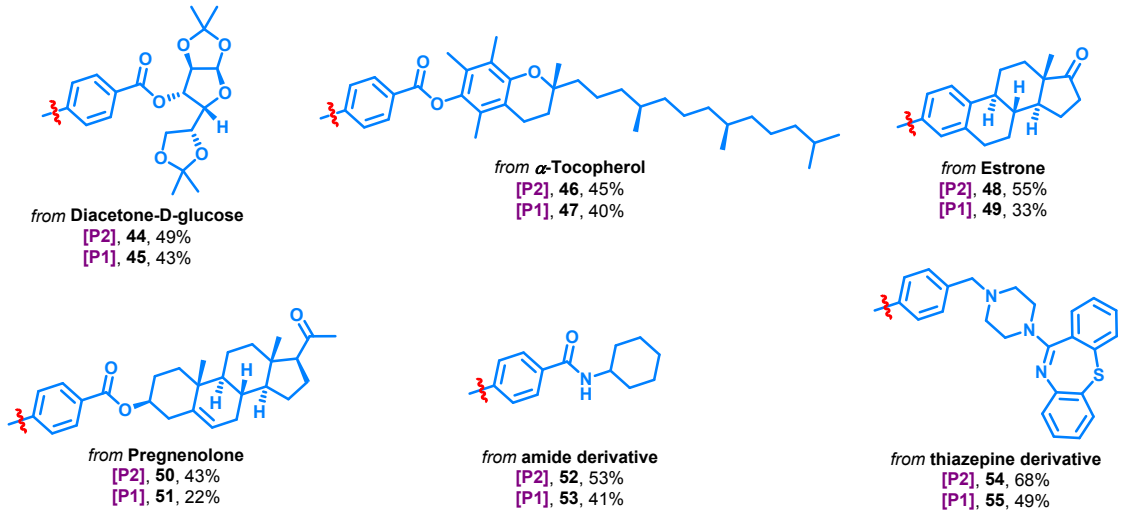
multifluoroalkyl peroxides scope







complex molecules (varying Ar)



[a] [**Conditions A**]: **1** (1.2 equiv.), **2a** (0.3–0.6 mmol), Cs_2CO_3 (2.5 equiv.), DABCO (2.5 equiv.) in DCE (2 mL) at 70 °C for 24 h; [**Conditions B**]: **1** (0.3 mmol), **2a** (0.9 mmol), Cs_2CO_3 (3.5 equiv.), DABCO (3.5 equiv.) in DMSO (2 mL) at 70 °C for 24 h.

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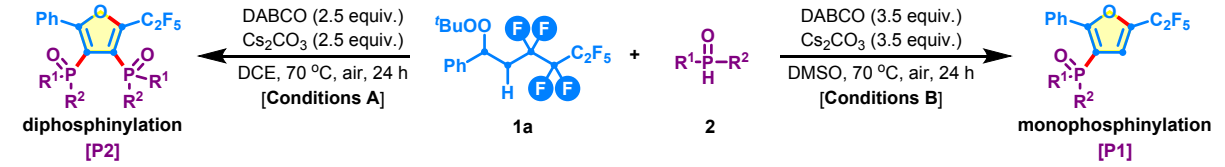
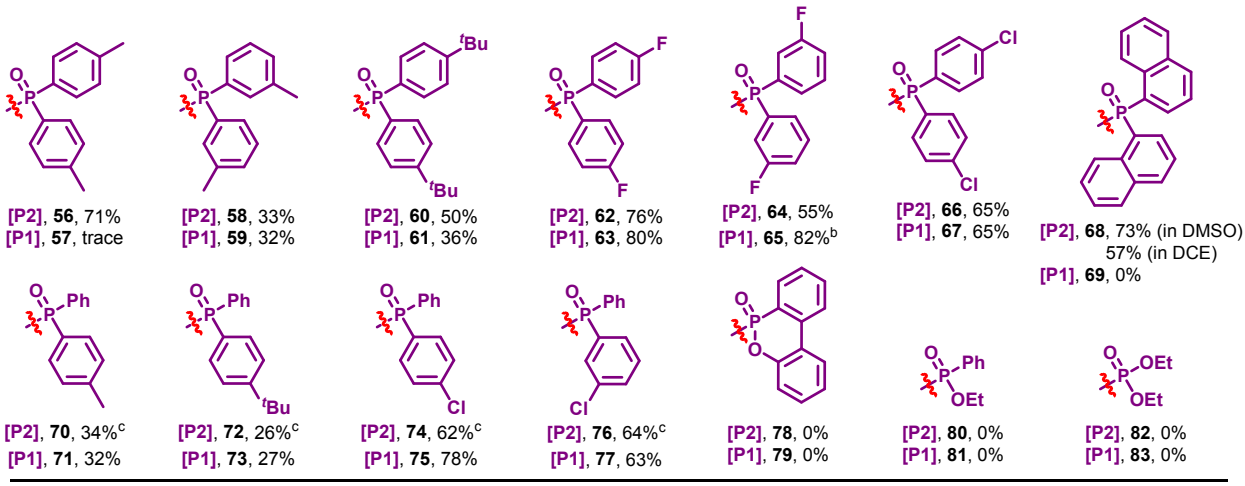
Table 2. Substrate scope of *H*-phosphine oxides[a]





[a] [**Conditions A**]: **1a** (1.2 equiv.), **2** (0.3-0.6 mmol), Cs_2CO_3 (2.5 equiv.), DABCO (2.5 equiv.) in DCE (2-4 mL) at 70 °C for 24 h; [**Conditions B**]: **1a** (0.3 mmol), **2** (3 equiv.), Cs_2CO_3 (3.5 equiv.), DABCO (3.5 equiv.) in DMSO (2 mL) at 70 °C for 24 h. [b] 0.2 mmol scale. [c] 1:1 dr was determined by ^{31}P NMR analysis.

(1-(*tert*-butylperoxy)-3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene (**1a**) with diphenylphosphine oxide (**2a**) in the presence of the base combination Cs_2CO_3 and DABCO in toluene at 70 °C under air for 24 h (Figure 2, H). We were pleased to find that the target *C*3,4-diphosphoryl furan **3** was obtained in 40% assay yield (entry 1, determined by ^1H NMR integration against an internal standard). Systematic evaluation of different solvents (entries 2–7) led to the discovery of DCE as the best solvent for the defluorinative annulation, affording the corresponding product **3** in 94% NMR yield and 87% isolated yield (entry 7, Conditions A). In addition, by switching the reaction solvent from DCE to DMF or DMSO a monophosphoryl furan derivative **4** was also furnished in 18% or 73% NMR yield, respectively (entries 8–9). Further adjustment of the substrate ratio and the loading of bases gave rise to product **4** in 81% NMR yield and 78% isolated yield (entry 10, Conditions B). It was found that these reactions proceeded with high regioselectivity. Moreover, the structures of products **3** and **4** were unambiguously assigned by X-ray crystallographic analysis.[52]

Controllable monophosphorylation and diphosphorylation reactions

The substrate scope of the mono- and diphosphorylation protocols was subsequently examined using Conditions A to generate the diphosphorylation and Conditions B to form the monophosphorylation products. As shown in Table 1, using $Ph_2P(O)H$, polyfluorinated benzylic peroxides **1** bearing a variety of electronically and sterically varied aryl groups reacted smoothly to give the corresponding [**P2**] and [**P1**] products in 42–91% yields. Substituents on the aryl ring, including alkyl (**5**–**8**), methoxy (**9**–**10**), amino (**11**–**12**), halogens (**13**–**23**), trifluoromethyl (**24**–**25**), carbalkoxy (**26**–**27**), and cyano (**28**–**29**), were tolerated under the mild reaction conditions. As for substrates with a naphthalene or thiophene motif, products **30**–**33** were generated in acceptable yields. However, alkyl substituted substrate **1b'** was not a suitable candidate for the titled reactions. In particular, this method was applicable to the modification of biologically active molecules. For example, diacetone-D-glucose, α-tocopherol, estrone, pregnenolone, amide, and thiazepine derivatives were successfully transformed to the furan products **44**–**55**. An attractive feature of the present procedure is the highly selective cleavage of C–F bonds (**34**–**43**) and ability to incorporate fluoroalkyl groups in furan skeletons.

We subsequently probed the use of commercially available *H*-phosphine oxides (**2**) as coupling partners for the assembly of

[**P2**] and [**P1**] products (Table 2). Surprisingly, varying electronic (**57**) and steric character (**58** and **69**) on the P-Ar groups dramatically affected the reaction efficiency. Similarly, the utility of unsymmetrical phosphine oxide components led to the production of tri(hetero)arylphosphorus products **70**–**77** in moderate yields and as mixtures of diastereomers. Less reactive phosphinate oxide derivatives, unfortunately, were not converted into the desired products **78**–**83** under our current reaction conditions.

Synthetic Applications

Scale-up reactions of (1-(*tert*-butylperoxy)-3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene (**1a**) with diphenylphosphine oxide (**2a**) toward [**P2**] (5 mmol scale) or [**P1**] (4 mmol scale) were conducted and the corresponding products **3** and **4** were isolated in 84% and 69% yields, respectively (Figure 3, A). We next subjected bis-polyfluoroalkyl-substituted arene **84** to multi-phosphorylation-heteroannulation (Figure 3, B). The π-conjugated heterocycles **85** and **86**,[53] which are potential structural constituents of optoelectronic materials, were produced in workable yields (38–44%). In addition, the resulting monophosphorylated and diphosphorylated products were transformed into trivalent phosphines (**87**-**93**) under reductive conditions in 47–99% yields (Figure 3, C).[54] These phosphines are potentially useful in catalysis, which will be a subject of future research in our group.

Mechanistic investigations

To elucidate the phosphorylation/cyclization processes, several control experiments were performed (Figure 4). First, treatment of peroxide **1a** with DABCO in DCE in the absence of diphenylphosphine oxide (**2a**) provided defluorinated unsaturated ketone **94** in 43% yield (Figure 4, A). A similar reaction performed in DMSO, however, was more complex and no intermediates were identified. Second, when independently synthesized ketone **94** was used in place of **1a** under otherwise standard conditions, it was converted into the corresponding products **3** and **4** in 91 and 63% yields, respectively (Figure 4, B). These results indicate that the reactions are likely initiated by a base-mediated O-O bond cleavage followed by HF-elimination.[55] Third, when (*E*)-4,4,5,5,6,6,6-heptafluoro-1-phenylhex-2-en-1-one (**95**) was subjected to the standard conditions, no [P2] or [P1] were formed, illustrating the necessity of the β-fluoroenone for realizing these transformations (Figure 4, C). Fourth, the treatment of sterically hindered trifluoromethyl chalcone **96** with $HP(O)Ph_2$ gave hydrodefluorinated product **97**, diphenylphosphinic fluoride **98**, and diphenylphosphinate **99** in 53%, 5%, and 4% yields, respectively (Figure 4, D). The byproduct diphenylphosphinic fluoride (**98**) is presumed to be formed *via* an anionic phosphorus species-promoted defluorination of **96**. Intermediate **98** can react with the enolate of **97** to afford **99**.[49] Four oxidized phosphorus-containing species, namely the phosphoryl fluoride **98**, phosphoric acid **100**, diphosphane 1,2-dioxide **101**, and diphenylphosphinic anhydride **102**, were detected by *in situ* high-resolution electrospray ionization mass spectrometry (ESI-HRMS) analysis of the model reaction under Conditions B (Figure 4, E). Moreover, ^{31}P analysis of the reaction mixture determined the existence of **100**, **101**, and **102**. The lack of detection of **98** could attribute to its instability under basic conditions (see Supporting Information for more details).[56] These results support the fluorinative oxidation of the P–H bond.[Error! Bookmark not defined.] Additionally, the need for excess diphenylphosphine oxide (**2**) in monophosphorylation reactions is consistent with its defluorinating function (Figure 2, H, entry 10). A reaction pathway involving the direct phosphorylation of product **4** or radical intermediates is ruled out, as indicated by the control experiments in Figure 4F and TEMPO-trapping experiment in Figure 4G. Finally, two deuterium-labeling experiments were performed (Figure 4, H). When 20 equiv of D_2O was added to the reaction (Conditions B), a deuterium atom was incorporated into product **4** (73% yield, 78% deuterium). In contrast, the same reaction conducted in DMSO-d_6 afforded product **4** in 74% yield, with no deuterium incorporation. This observation confirmed that water was the hydrogen source for product **4**. Finally, we note that the reaction to produce [P1] proceeds under N_2 and air, suggesting that dioxygen is not an oxidant in this chemistry.

On the basis of the experimental results above, and a literature survey, we propose mechanisms for the formation of [P2] and [P1] in Figure 5. The reaction is initiated by two base-assisted eliminations (Figure 5, top left), first of the O–O bond to form a carbonyl group and subsequent HF elimination to give the pivotal unsaturated ketone **B**, which is supported by the isolation of **94** (Scheme 4, A). The ketone **B** easily undergoes a substitution/elimination sequence with P-nucleophile **2'** and loss of fluoride to form the β-phosphorylated intermediate **C** (Figure 5, left). It is also possible that ketone **B** undergoes further β-F elimination to give an alkyne intermediate **B'**, which could react with **2'** to yield intermediate **C**. Next, the electron-deficient nature of the unsaturated C=C bond of **C** sets the stage for an S_N2' reaction with **2'** with loss of another equivalent of fluoride to furnish diphosphorylated **D**. Deprotonation of the acidic α-C–H gives an enolate that undergoes a 5-*endo*-trig cyclization followed by defluorinative aromatization to provide the furan product.

In the *C*4-monophosphorylation transformation (Figure 5, right), it is likely that P-nucleophile **2'** reacts with the intermediate **B** *via* an S_N2'-type pathway in DMSO, leading to an α-phosphorylated carbonyl compound **H**. The absence of a fluoride in the [P1] compounds, and the incorporation of deuterium on the furan ring, signal that a C–F bond must be reduced. We propose, therefore, that nucleophilic attack by the P-nucleophile **2'** on the most electron poor C–F bond, in analogy to the Atherton-Todd reaction, with loss of an equivalent of fluoride to afford the alkynyl species **M**. This step is supported by detection of phosphinic fluoride **J** as a byproduct. The P(O)-F elimination process may be accelerated by the coordination of the Cs cation with the departing fluoride anion[57] and the strong electronegativity of the R_f group. After deprotonation of the α-

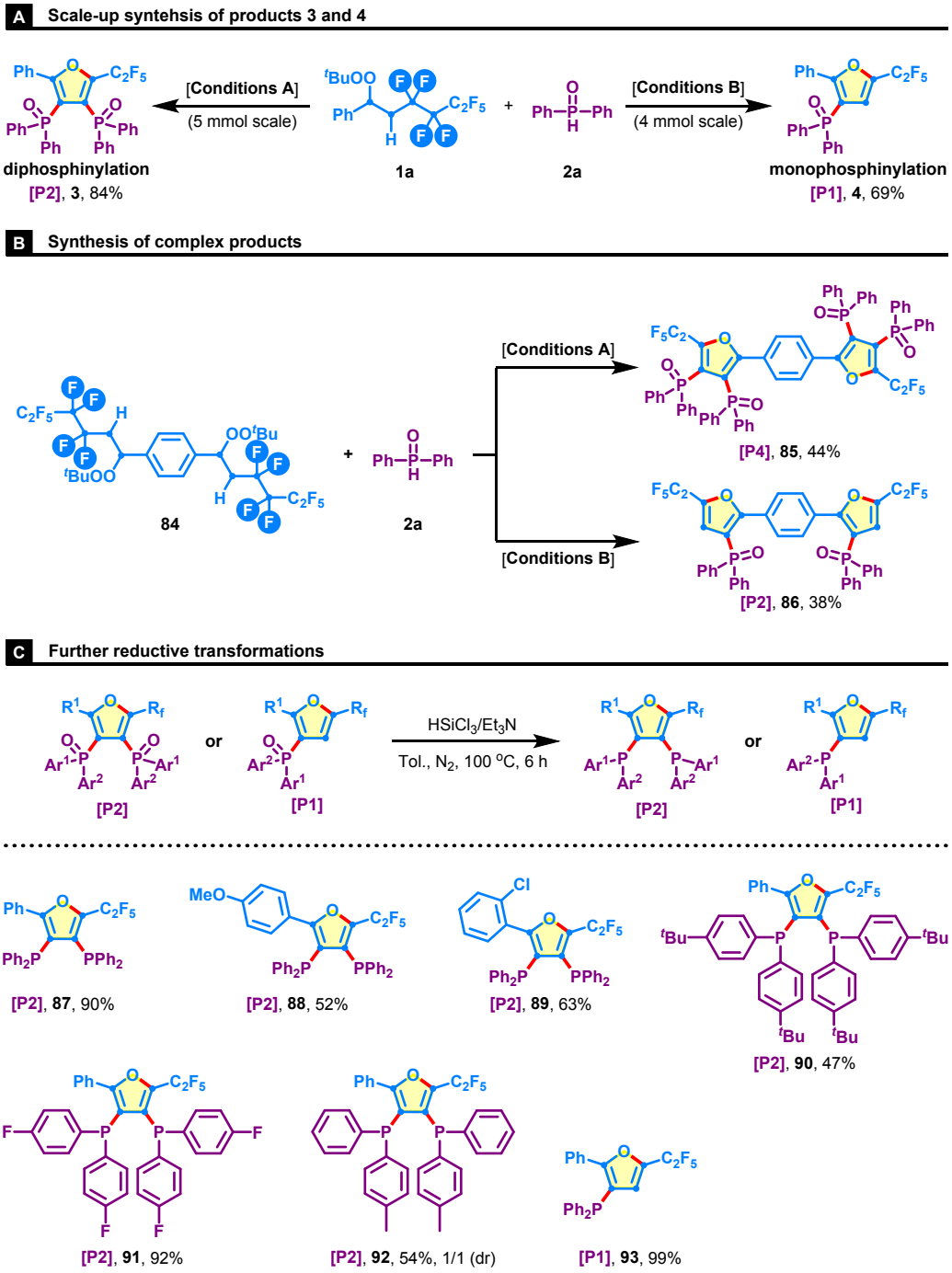


Figure 3. Scale-up synthesis and further transformations. **A** Scale-up synthesis of phosphoryl furans **3** and **4**. **B** Synthesis of complex products. **C** Further reductive transformation of phosphoryl furans to trivalent phosphines.

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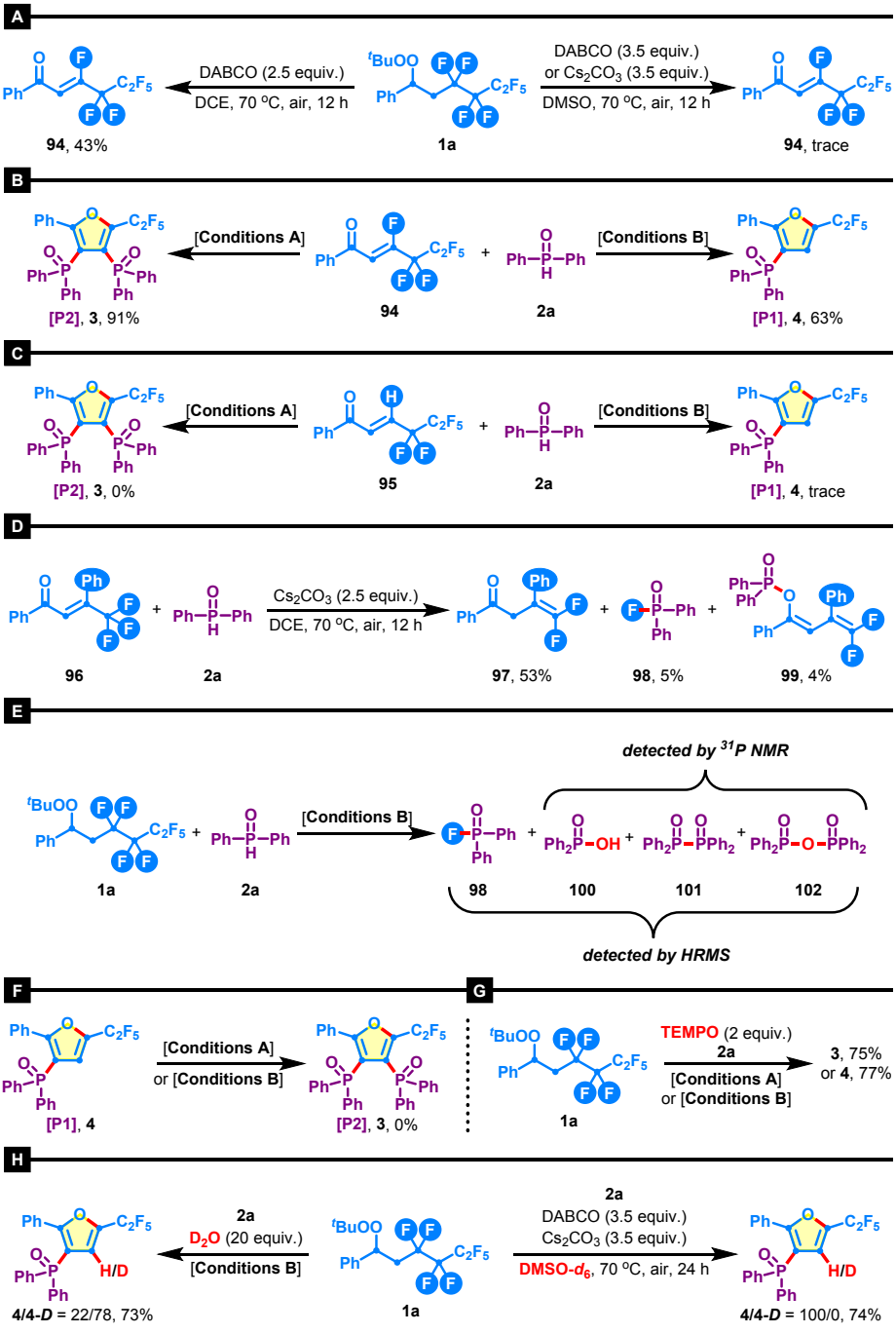

Figure 4. Mechanistic studies. **A** The formation of unsaturated ketone intermediate. **B** The defluorinative transformation of unsaturated ketones to furan products. **C** The necessity of vinyl fluoride for these transformations. **D** The role of $HP(O)Ph_2$ as a defluorinative reagent. **E** HRMS and ^{31}P NMR analysis of the reaction mixture. **F** Direct phosphorylation of monophosphorylated product was unsuccessful. **G** TEMPO-trapping experiment. **H** Deuterium-labeling experiments.

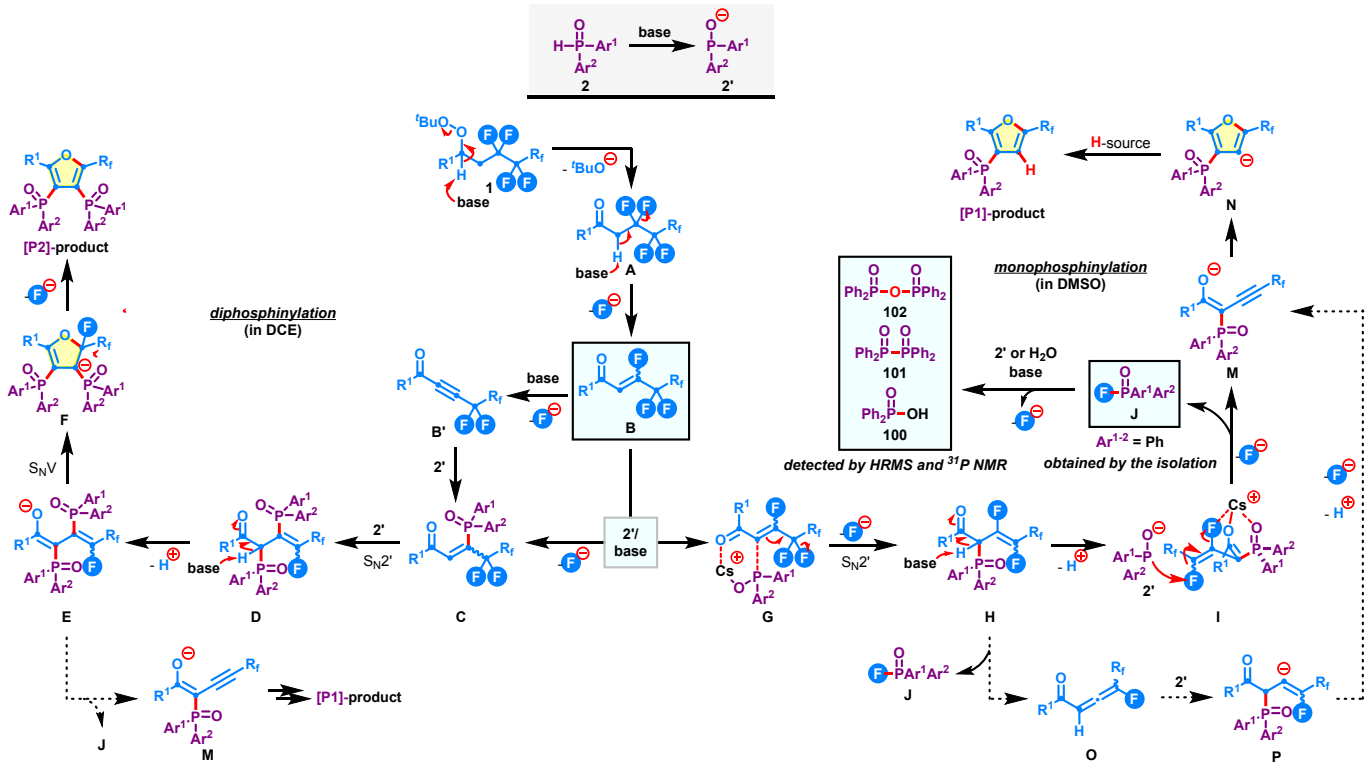

Figure 5. Proposed mechanism.

C–H to give the enolate, cyclization and protonation (or deuteration in the presence of D_2O) is proposed to generate the observed monophosphorylated product. We cannot rule out a pathway where intermediate **E** is directly defluoro dephosphorylated afford to alkynyl intermediate **M**. In addition, there is a possibility of forming an allenyl ketone **O** *via* the removal of a molecule of phosphinic fluoride **J** from intermediate **H**. Such reactive species **O** subsequently undergoes rephosphorylation with **2'** to give the alkyne **M**. We believe that different outcomes of two defluorophosphorylation reactions with the installation of one or two diaryl phosphoryl groups on 3- and 4-site of furan are mainly tuned by the reaction solvent and reactant ratio.

It should be mentioned that DABCO undoubtedly participated in the activation of the perfluoroalkyl substrates. The initial reaction begins with DABCO-promoted Kornblum–DeLaMare reaction to convert the peroxy group to the carbonyl group with simultaneous elimination of a molecule of HF. The base of Cs_2CO_3 contributes to the successive defluorination, C-P bond formation, and ultimate intramolecular cyclization. Sometimes DABCO is considered as a temporary supernucleophile, and this property is manifested depending on the solvents and conditions.[58] Further thorough investigations of the mechanism are ongoing in our laboratory.

Conclusions

A highly tunable defluorophosphorylation of fluorinated peroxides for the preparation of *C*3,4-diphosphoryl furans and *C*4-monophosphoryl furans under conditions with no added transition metals is disclosed. The resulting P(O)-containing products could be readily transformed into useful monodentate and bidentate phosphines. The present approach features broad substrate scope, procedural simplicity, and product diversity. It is easily scalable, and the chemoselectivity between the phosphorylated products can be readily controlled by choice of conditions. Mechanistic investigations reveal that the H–P(O) compound not only serves as a phosphorylating reagent but also can induce defluorination. We envisioned that this finding could enrich the current toolkit of P(O)-containing heteroarene synthesis and provide inspiration for C–F bond functionalizations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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