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Rapid Entry into Biologically Relevant α,α-Difluoroalkylphosphonates Bearing Allyl Protection−Deblocking under Ru(II)/(IV)-Catalysis

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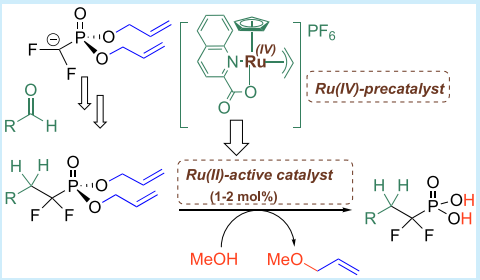
Supporting Information

ABSTRACT: A convenient synthetic route to α,α-difluoroalkylphosphonates is described. Structurally diverse aldehydes are condensed with $LiF_2CP(O)(OCH_2CH{=}CH_2)_2$. The resultant alcohols are captured as the pentafluorophenyl thionocarbonates and efficiently deoxygenated with $HSnBu_3$, BEt_3, and O_2, and then smoothly deblocked with CpRu(IV)(π-allyl)quinoline-2-carboxylate (1−2 mol %) in methanol as an allyl cation scavenger. These mild deprotection conditions provide access to free α,α-difluoroalkylphosphonates in nearly quantitative yield. This methodology is used to rapidly construct new bis-α,α-difluoroalkyl phosphonate inhibitors of PTPIB (protein phosphotyrosine phosphatase-1B).



Phosphate esters are ubiquitous in Nature, as they provide binding handles and partitioning mechanisms for metabolites, as well as the backbone for nucleic acids and phospholipids.[1] The kinetic stability, yet thermodynamic lability, of phosphate esters allows them to serve as on/off-signals for protein regulation and signal transduction and amplification. Since the pioneering work of Blackburn[2] and McKenna,[3] there has been great interest in α,α-difluorinated phosphonates as isopolar mimics of biological phosphates, which are both hydrolytically stable and resistant to phosphatase enzymes. Prior studies on difluorinated phosphonates support the notion of the isopolarity,[4] reduced pK_a,[5] and yet added hydrophobicity[6] of these phosphate mimics.

These postulates have gained significant experimental support, for example, as illustrated in Figure 1. **A** is an effective bisubstrate analogue inhibitor of purine nucleoside phosphorylase (PNP),[7] a target for gout, and **B** acts as an analogue of phosphoenolpyruvate inactivating EPSP synthase,[8] a key target for herbicide development. The β,γ-CF_2-bridged analogues of dATP (**C**) and ATP (**C′**) act as TS probes for DNA polymerase[9] and kinase enzymes,[10] respectively. The α,α-difluorinated phosphonate mimics of L-phosphoserine (**D**),[11] L-phosphothreonine (**D′**),[12] and L-phosphotyrosine (**E**) serve as useful tools for chemical biology.[13] These fluorinated phosphononates behave as "Teflon-phosphates" being inert to biological phosphatase enzymes; when site-specifically incorporated in peptides and proteins, they allow for the study of kinase-mediated signal transduction pathways of great interest to drug development.[14] When incorporated into cyclic peptides, the pTyr analogue **F** leads to effective, cell permeable inhibitors of T-cell PTPase.[15] The difluorinated phosphonate mimic of PLP, **F**, has been shown to serve as a useful proble of vitamin B_6-active sites.[16] Fluorinated phosphonate mimics of dTMP (**G**)[17] and UMP (**G′**)[18] are useful building blocks for phosphonate nucleic acids,[19] an area of burgeoning contemporary interest, particularly for antisense applications. Fluorophosphonate analogues of phospho-sugars are useful tools in chemical biology as substrate mimics,[20] mechanistic probes,[21] or enzyme inhibitors.[22] Glucose 6-phosphate mimic **H** serves as both an alternate substrate for G6PDH[23] and as a mechansistic probe for phosphoglucomutase by NMR.[24] Finally, fluorinated phosphonate analogues of phospholipids[25] such as LPA (**I**)[26] open up new avenues to investigate and modulate phospholipid signaling mechanisms.

Previously, our lab and others have reported convergent routes into the title compounds via PCF_2−C bond formation. Such routes include the following: (i) triflate displacement chemistry with lithio difluoromethylphosphonate anion;[27] (ii) condensation of such $(RO)_2P(O)CF_2M$ species with the corresponding aldehydes[28] and esters;[12a,29] (iii) Pd(0)-mediated addition of $(RO)_2P(O)CF_2I$ to monosubstituted alkenes followed by reductive deiodination;[30] (iv) conjugate addition of $(RO)_2P(O)CF_2M$ reagents to (*E*)-nitroalkenes in the presence of Ce(III);[31] and (v) a series of radical-mediated alkene addition approaches.[32] Several other elegant routes are specific for generating PCF_2−C(sp^2) bonds[33] or directed at allylic systems.[34] Also, Piettre and co-workers have recently described a convergent approach into the corresponding fluorinated phosphinates.[19a] However, nearly all of these studies lead to diethyl ester protected difluoroalkylphosphonates. To date, these esters are typically deprotected with TMSX reagents that combine both nucleophilic and

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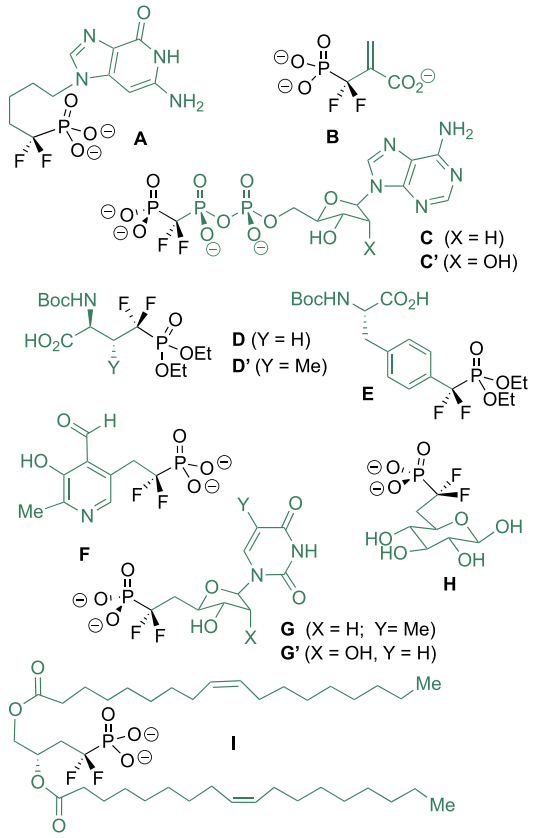

Figure 1. Bio-relevant α,α-difluorinated phosphonates.

Lewis acidic elements in the reagent itself or when generating the reagent in situ from TMSX and NaBr of KI, for example.[35] That said, the TMSX reagent of choice is TMSBr, as delineated in a careful comparative study by McKenna and co-workers,[36] as is discussed in more detail below.

Early on, our lab reported the synthesis of biologically relevant (α,α-difluoroalkyl)phosphonates bearing allyl ester protecting groups[35] by triflate displacement.[27a] In that study, the fluorinated phosphonate esters thereby obtained were deallylated under Pd(0)-catalysis in the presence of the organic-soluble 2-methylhexanoate anion nucleophile as an allyl cation scavenger. The unblocked phosphonates were obtained with moderate to excellent (56−91%) yields, depending on the case. While these results were promising, there still were a couple of limitations to the chemistry reported here. On the one hand, while triflate displacement with $(RO)_2P(O)CF_2Li$ provides for convergency, this approach does have limitations: namely, (i) triflates are generally not stable over long periods of time; (ii) molecules containing highly acid sensitive functionalities may not withstand triflate synthesis conditions; and (iii) triflates may be incompatible with certain internal functionalities/protecting groups (see the *N-para*-methoxybenzyl oxazolidinone case in our early efforts to access the pCF_2Ser-phosphonate mimic).[27c] Therefore, there was a need for new methodology to synthesize CF_2-phosphonate analogues of biological phosphates under milder conditions, and ideally also with ester deblocking conditions that would be exceptionally gentle to streamline access to these chemical biological tools.

We set out to synthesize α,α-difluorinated phosphonates bearing allyl blocking groups via condensation of diallyl lithio(difluoromethyl)phosphonate with a series of aldehydes. Earlier, Martin and co-workers had reported the aldehyde condensation route with diethyl lithio(difluoromethyl) phosphonate followed by deoxygenation.[28b] However, the most significant limitation of the Martin route to (α,α-difluoroalkyl)-phosphonate analogues is the need to carry ethyl phosphonate ester protecting groups through the sequence. In order to best mimic a natural phosphorus(V)-based biologically active compound, these ethyl groups need to be removed, typically using TMSX reagents. While Rabinowitz and co-workers had reported the use of TMSCl[37] for this purpose early on, the groups of Olah,[38] Jung,[39] and Blackburn[40] had described the use of TMSI for such purposes. TMSCl only performs well at elevated temperature, and TMSI is more effective for carboxylate ester deprotection than for phosphonate ester deprotection. This latter result was concretely evidenced in an important study by Schmidhauser and McKenna,[36a] in which it was shown that the TMSBr[36b,41] is the TMSX agent of choice for phosphonate ester deprotection.

While there are many examples of the successful use of TMSBr for the deblocking of diethyl phosphonate protecting groups, particularly for simple phosphonate esters, but also for α,α-difluorinated congeners, we and others have encountered deprotection problems with diethyl/dimethyl/dibutyl-phosphonate moieties by TMSBr/I when they are appended to certain lactone, pyranose, or amino acid frameworks.[42] To expand the repertoire of existing deblocking conditions, the corresponding dibenzyl-protected phosphonate reagents were explored, and these proved to be useful in the sugar phosphonate arena.[43] However, due to a lack of stability, the $(BnO)_2P(O)CF_2Li$ reagent has not been used extensively for fluorinated phosphonate synthesis. Therefore, we set out to examine a new route into α,α-difluoroalkyl phosphonates that utilizes the $(H_2C{=}CHCH_2O)_2P(O)CF_2Li$ reagent and that, if successful, would offer medicinal chemists and chemical biologists a streamlined, alternative synthetic entry in this important class of phosphate mimics.

In this new approach, the diallyl (difluoromethyl)-phosphonate anion is first added to a target aldehyde at low temperature. The resulting β-hydroxy-α,α-difluoroalkyl phosphonates are then converted to the corresponding arylthionocarbonate esters. While this can be done in situ, if desired, we chose to perform these operations in two steps, as it was felt that the intermediate β-hydroxy-α,α-difluoroalkyl phosphonates might be of real interest for some chemical biology applications, and so these were fully characterized. Unfortunately, in model studies with benzaldehyde, deoxygenation of the aryl thionocarbonate ester so obtained using typical Barton conditions was largely unsuccessful (Scheme 1).[44] The very low yield of the desired product obtained led us to make a crucial modification in the synthetic approach. In order to prevent undesired side reactions, it was discovered that one could lower the reaction temperature from 80 °C to ambient temperature by replacing the usual AIBN initiator with BEt_3/air. The modified Barton conditions[45] were found to be successful. Under these conditions, the allyl phosphonate ester protecting groups are stable to the radical tin chemistry and the pentafluorophenyl thionocarbonate esters are cleanly reduced off.

The overall streamlined entry into these fluorinated phosphosphonates, featuring these mild deoxygenation conditions, is summarized in Scheme 2. In the first step, the diallyl lithio-α,α-difluoromethylphosphonate anion cleanly adds into a range of aldehydes including those appended to protected

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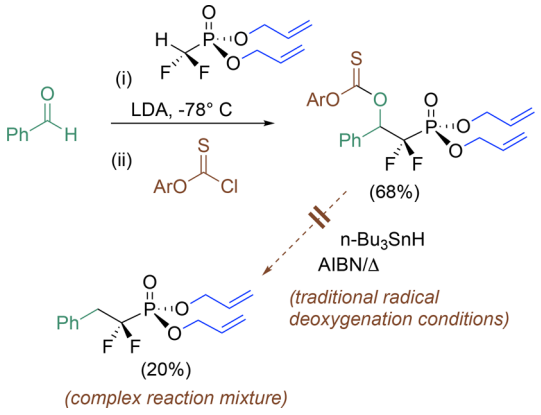
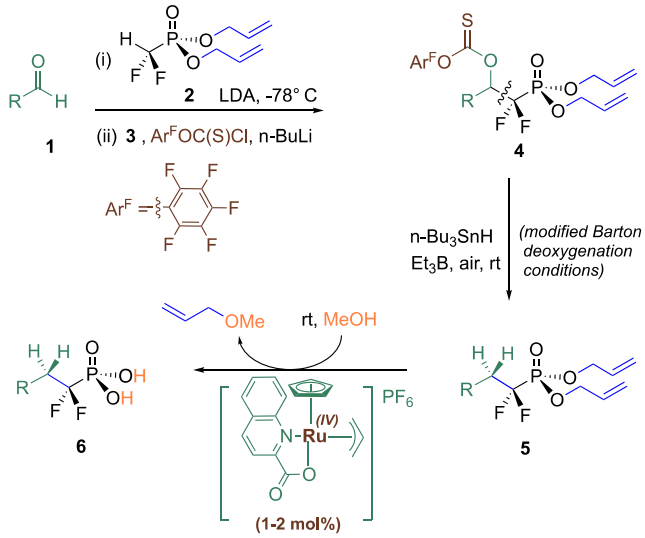
Scheme 1. Standard Deoxygenation Conditions Fail



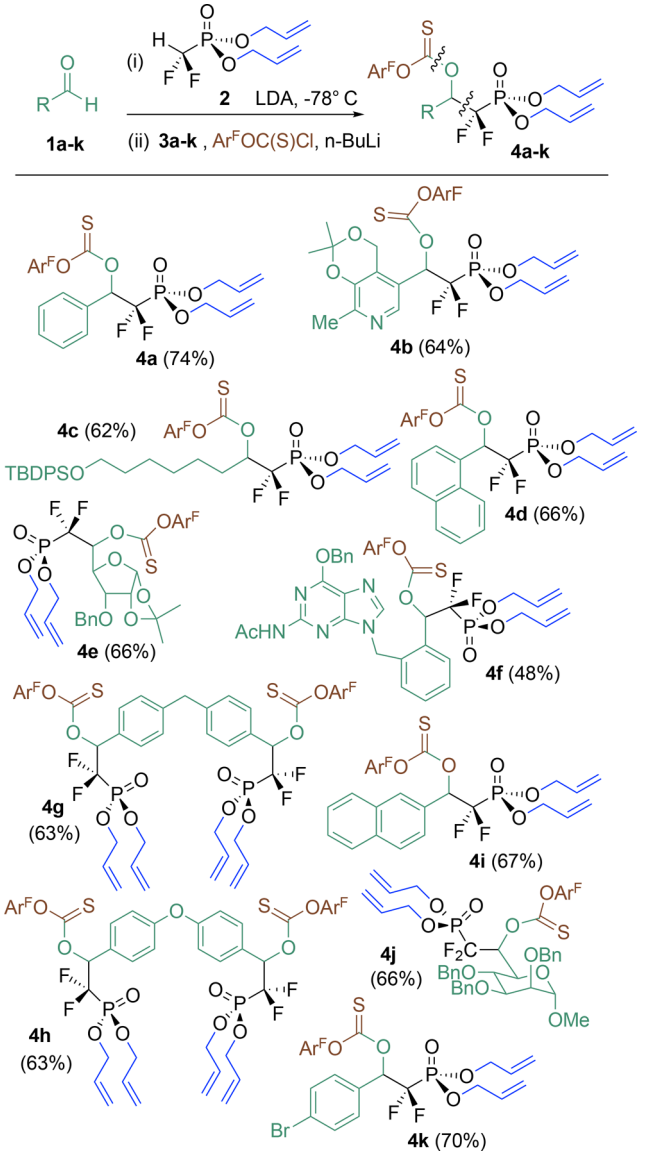
Scheme 2. Streamlined Route into α,α-Difluorinated Phosphonates



carbohydrate, purine, and vitamin B_6-cofactor scaffolds. The resultant α,α-difluorinated β-hydroxyphosphonates were derivatized as pentafluorophenyl thionocarbonates. As can be seen from Table 1, the method displays broad substrate scope and provides two-step yields of the corresponding thionocarbonate derivatives that are over 63% (>80% average per step) for all but one densely functionalized protected guanine system **4f**.

The BEt_3/O_2-initiated radical Bu_3SnH-mediated deoxygenation step proceeds particularly efficiently in this sequence. As can be seen from Table 2, for the model system (**4a** →**5a**) described above, one sees a dramatic improvement in yield (86%) over that obtained under traditional AIBN-initiated deoxygenation conditions at elevated temperature (20%). These findings lead us to hypothesize that, at the higher deoxygenation temperature initially employed, the intermediate tributyltin radical reacts with the allyl protecting group centers in competition with Sn−S bond formation, the desired entrée into the deoxygenation reaction manifold. Indeed, the deoxygenation conditions described (ambient temperature, oxygen-triethylborane initiation) are a key cog in the methodology presented herein as they are robustly tolerated across all substrates in our library, giving an average deoxygenation yield of ∼80%.

Table 1. P−CF_2−C Bond Formation/Thionocarbonate Capture



Finally, as is depicted in Table 3, we have deblocked a set of allyl-protected α,α-difluorinated phosphonate mimics of biological phosphates using the novel Cp-Ru(II)-2-quinolinecarboxylate catalyst developed in the Kitamura group.[46] To our knowledge, these are the first examples of the use of this catalyst to provide access to this class of " teflon" phosphate mimics. The deallylation proceeds under exceptionally mild conditions, using the cationic Ru(IV)-PF_6 precatalyst shown, at moderate loading (1−2%). In addition, with this catalyst system, addition of an exogenous allyl cation acceptor is unnecessary, since the reaction solvent, MeOH, fills this role, affording methyl allyl ether as a volatile, readily removable byproduct. By using this methodology we have demonstrated a streamlined synthesis of a variety of "teflon" phosphonates in fully deprotected form.

As shown in Table 3, the deallylation reaction provides essentially quantitative conversion with all the selected substrates. This methodology provides a practical route into analogues of several biologically relevant phosphates, such as **6b**, an analogue of pyridoxal phosphate (PLP) of proven

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Table 2. Deoxygenation with Retention of Allyl PGs

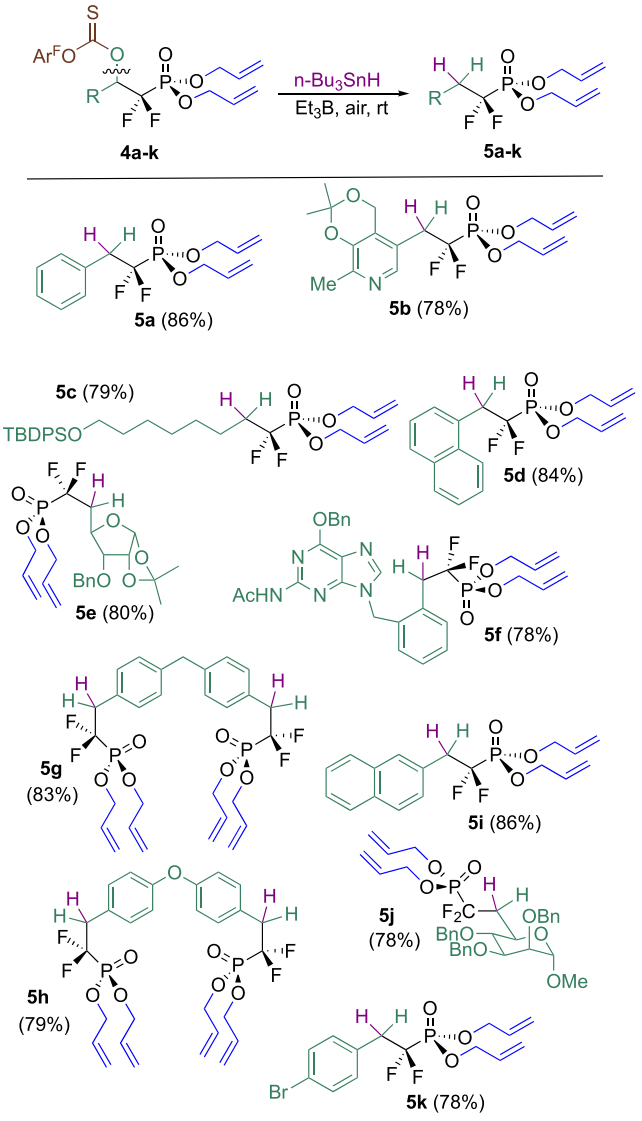
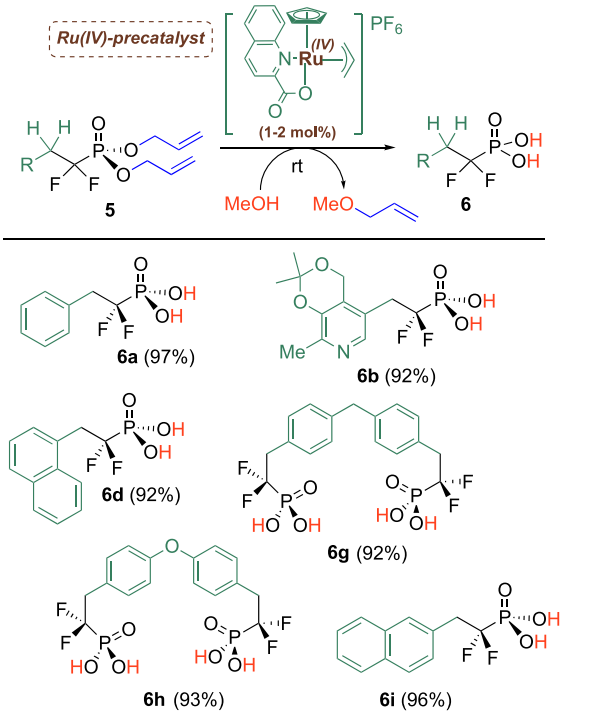


Table 3. Deallylation to the Free α,α-Difluorophosphonates



These results highlight the advantage of the *bis*-phosphonates over their monomeric congeners (Figure 2) in binding to PTP1B.

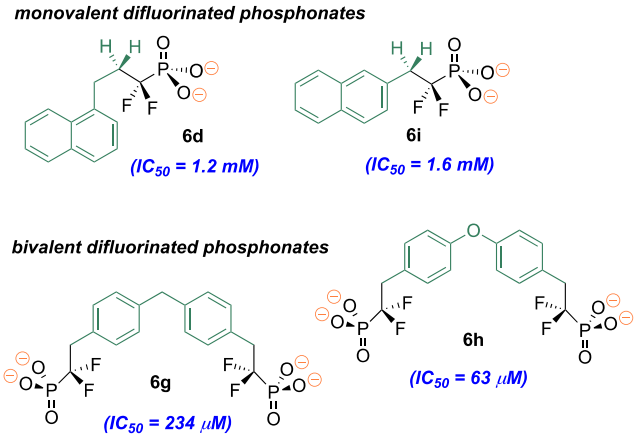


Figure 2. Comparison of rapidly assembled mono- and bivalent fluorinated phosphonate PTP1B inhibitors.

utility,[16] at a time when modified PLP analogues are finding expanded use in chemical biology,[47] and **5e**, an analogue of ribose-5-phosphate that could be used to synthesize non-hydrolyzable RNA mimics as discussed.[17,19b,e,g] Heterocycle **5f** is a precursor to potent bisubstrate analogue inhibitors of purine nucleoside phosphorylase,[7a] and **5j** is a building block for constructing conjugates of the CF_2-phosphonate mannose-6-phosphate (M6P) mimic.[48] This phosphatase-inert M6P-surrogate is of great interest as an unnatural ligand for the insulin-like growth factor-II receptor (IGFIIR). Polyvalent versions of such ligands may promote the dimerization of this receptor and thereby stimulate internalization of circulating IGF-II growth factor, a potential approach to cancer therapy currently under investigation.[49]

Finally, we have rapidly constructed a set of α,α-difluorinated *mono-* and *bis*-phosphonates (**6d**, **6i** and **6g**, **6h**) to demonstrate how this chemistry can be used to assemble targeted libaries, here a set of protein tyrosine phosphatase-1B inhibitor candidates. PTP1B is a high value potential therapeutic target for type II diabetes.[14,15,50] In fact, for such rapidly assembled scaffolds, significant inhibition was observed in the midmicromolar range with **6h**, in particular.

A docked structure of **6h**, bound to the PTP1B active site (from pdb 2B07),[51] is presented in Figure 3 (AutodockVina;[52] best of 25 poses shown). Each difluorinated phosphonate group is seen to engage in favorable electrostatic/H-bonding interactions with R24 and K120, with each arene ring of the inhibitor available for edge-to-face π−π interactions with F182 and Y46, respectively. Thus inhibitor **6h** is expected to be a useful tool for chemical biology; it is a potential lead scaffold for PTP inhibitor development to facilitate the study of signal transduction via protein (de)phosphorylation.[13a]

In conclusion, a practical route for the synthesis of α,α-difluoroalkyl)phosphonates bearing allyl ester protection has been established, by exploiting the favorable low temperature

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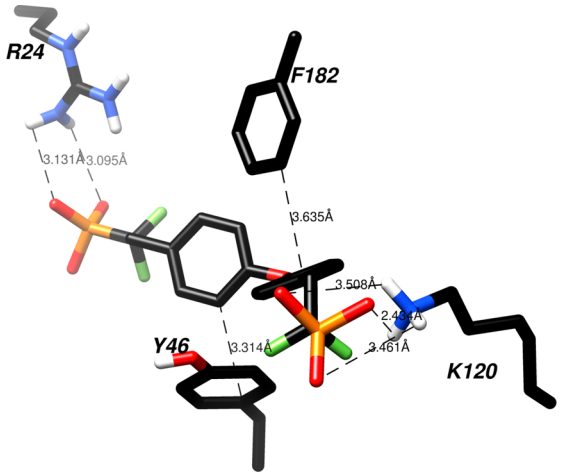

Figure 3. Inhibitor **6h** docked in the PTP1B active site.

condensation of the $(H_2C{=}CHCH_2O)_2P(O)CF_2Li$ reagent with a set of functionalized aldehydes appended to diverse biologically relevant scaffolds. A modified Barton deoxygenation is then employed, compatible with the presence of allyl phosphonate ester functionality. Fluorinated phosphonate deprotection is achieved under exceptionally mild conditions with the Ru(II)-catalyst pioneered in the Kitamura lab. The new method has been applied to the synthesis of CF_2-phosphonate mimics of PLP (vitamin B_6), D-mannopyranosyl and D-ribofuranosyl phosphates, and an established purine-based phosphonate scaffold for PNP inhibition. Finally, this chemistry has been deployed in a parallel, bidirectional fashion using aromatic *bis*-aldehyde substrates to provide rapid access to simple *bis*-α,α-difluoromethylene phosphonates that display midmicromolar inhibitory potency against PTP1B. Indeed, PTP inhibitor **6h** provides an attractive and readily accessible scaffold from which to potentially build out specificity and enhanced affinity across the PTP family of signal-transducing enzymes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03707.

Detailed experimental procedures (synthesis and enzyme kinetics assays) and characterization data (^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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