Fluorinated Phosphonates: Synthesis and Biomedical Application

Vadim D. Romanenko and Valery P. Kukhar*

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of the Ukraine, 1 Murmanska Street, Kyiv-94 02660, Ukraine

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* Corresponding author. Tel: + 38 044 558 53 88. Fax: + 38 044 558 25 52. E-mail: kukhar@bpci.kiev.ua. Postal address: Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of the Ukraine, 1 Murmanska Str., Kyiv-94 02660, Ukraine.

1. Introduction

The phosphate moiety (PO_4^{-2}) is the common structural motif of a wide range of natural phosphorus-based biologically active compounds, which play important roles as metabolic intermediates, as common regulatory switches for proteins, and as a backbone for the genetic information.[1] However, aside from prodrug applications, phosphate esters are normally considered impractical functional groups for drug design because they are subject to cleavage by digestive phosphatases.

The potential of phosphonates as phosphate mimics has been recognized for many years.[2] Unlike a phosphate group, the phosphonate linkage is not readily hydrolyzed in a biological environment, and this unique property has made these compounds attractive as phosphate analogues in numerous applications. Stated differently, the structural correspondence of C−C−P bonds with C−O−P bonds, although significantly dissimilar in their chemical characteristics, has provided an avenue to systematic chemical and biomedical studies of phosphonic acids and their derivatives.[3−5]

The chemistry of fluorinated alkylphosphonates is a relatively new area of research, which has developed mostly during the past two decades. Interest in fluorine substitution of organic groups attached to phosphorus stems from the possible effect of such substitution on physical, chemical, and biological properties of the resulting phosphonates. In

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Vadim D. Romanenko was born in Alchevsk, Ukraine, in 1946. He studied at Dnepropetrovsk Institute of Chemical Technology and received his Ph.D. degree there under the supervision of Professor S. I. Burmistrov. Since 1975, he has been working at the National Academy of Sciences of Ukraine from which he earned his Doctor of Chemistry degree in 1988. He was promoted to full professorship in 1991. From 1992 to 2005, he has been a visiting scientist at the Centre of Molecular and Macromolecular Studies in Lodz (Poland), the Shanghai Institute of Organic Chemistry (China), the University Paul Sabatier (France), the University California, Riverside (USA), and the University of Pau & des Pays de l'Adour (France), Besides organophosphorus and medicinal chemistry, his research interests include synthetic aspects of heavy main group elements. He has published more than 300 papers, book chapters, and review articles and coauthored 3 books. Among his publications are several chapters of *Comprehensive Functional Group Transformations*, first and second editions, and *Comprehensive Heterocyclic Chemistry*, third edition.

Valery Kukhar was born in Kiev, Ukraine, in 1942. He graduated from Dnepropetrovsk Institute of Chemical Technology in 1963, and received his Cand. Chem. Sci. degree in 1967 under the supervision of Professor Alexander Kirsanov from Institute of Organic Chemistry of National Academy of Sciences of Ukraine. He received his Doctor of Chemistry degree in 1974 from Institute of Organic chemistry. In 1978–1988, he was the Chief of Chemical Department of National Academy of Sciences of Ukraine (NASU). Since 1987, he has been Director of Institute of Bioorganic Chemistry and Petrochemistry of NASU. Professor Valery Kukhar is a member of National Academy of Sciences (1985), and he was President of Ukrainian Chemical Society from 1992 to 2002. His research interests concentrated mainly on organophosphorus and organofluorine chemistry. He is the author and editor of 6 books, including *Chemistry of Fluorine-Containing Amino Acids* (1994) and *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity* (2000). He was recipient of the GLOBAL – 500 Prize (UNEP, 1993), San-Valentino Award (World Federation of Scientists, 1999), and Ukrainian State Award in Science & Technology (1999). Valery Kukhar is a member of the OPCW Scientific Advisory Board and International Advisory Group for Chernobyl Shelter Fund, EBRD.

general, incorporating fluorine as either a bioisosteric replacement for hydrogen or an isoelectronic replacement for the hydroxyl group has profound consequences on metabolic degradation, lipophilicity, hydrogen bonding, and reactivity of organic molecules.[6]

A particular refinement of bioisostere strategy in phosphonate chemistry has been developed by Blackburn and coworkers[7] and McKenna and Shen.[8] They suggested that superior bioisosteres might be obtained by the introduction of halogen and, in particular, fluorine on the α-carbon of alkylphosphonates since these surrogates should more accurately mimic the steric and polar character of the phosphate function (Chart 1). In fact, α-monofluoro- and α,α-difluoroalkylphosphonates were found to be more effective analogues of phosphonates compared with the nonfluorinated congeners because the CHF and CF_2 groups can both sterically and electronically mimic an oxygen, enabling the second dissociation constant, pK_{a^2}, to more closely mirror those of the phosphates due to the electron-withdrawing effect of fluorine. For example, the pK_a of the second deprotonation of a phosphate group is ca. 6.4. The CH_2−phosphonate has a corresponding pK_a of ca. 7.6 and is less acidic. The electron-withdrawing effect of the two fluorine atoms on the CF_2−phosphonate significantly lowers the pK_a to ca. 5.4, and the presence of only one fluorine atom in the CHF−phosphonate results in a pK_a of ca. 6.5, almost identical to that of the natural phosphate.[9−11] Theoretical study also indicates that the electrostatic profile of a CHF−phosphonate is close in magnitude to that of a phosphate.[12] Among other parameters that potentially favor α-fluorinated phosphonates over their nonfluorinated analogues are (a) increased C−CF_2−P dihedral angle, (b) increased polarity of the bridging group, (c) the possibility for C−F···H−X hydrogen bonding, and (d) increased hydrolytic stability, as well as oxygen stability.[13] Finally, recent reports from several groups suggest not only that α-monofluoromethylenephosphonates can make excellent bioisosteres but that the CHF stereocenter may serve as an additional tunable parameter within the phosphonate series.[11,14−17] Blackburn's pioneering idea induced a massive amount of work aiming at the rational design of new phosphate mimics and resulted in a conceptually new approach to the metabolic exploration and enzyme regulation. However, whereas the field of simple phosphonates is covered by a considerable number of monographs and reviews, the chemistry of fluorinated phosphonates has never been reviewed systematically. Several brief overviews and review articles on special aspects are available and cover part of the literature. A discussion of the findings on α-monofluoroalkylphosphonates has been presented by Berkowitz and Bose.[13] The chemistry of selected analogues of

Chart 1. Naturally Occurring Phosphates (A) and Their Fluorinated Phosphonate Analogues (B−D)

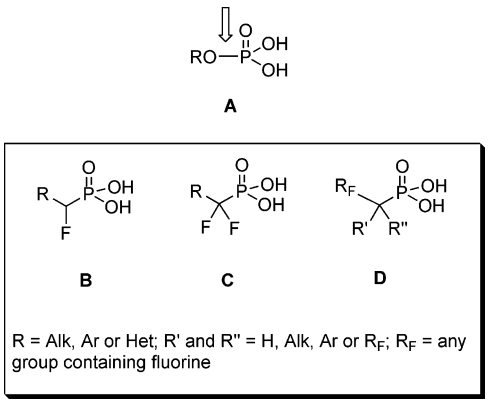


Table 1. Reactions of Fluorohalomethanes with Phosphites

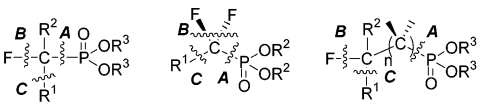
fluorohalomethane	phosphite	conditions	product	yield (%)	ref
CH_2ClF	$(EtO)_2P(O)Na$	toluene, refl.	$(EtO)_2P(O)CH_2F$		25
CH_2ClF	$(^iPrO)_2P(O)Na$	toluene, refl.	$(^iPrO)_2P(O)CH_2F$	50	25
CH_2ClF	$(^sBuO)_2P(O)Na$	toluene, refl.	$(^sBuO)_2P(O)CH_2F$	36	25
$CHCl_2F$	$(EtO)_2P(O)Na$	toluene, 0 °C	$(EtO)_2P(O)CHClF$		31,33
$CHCl_2F$	$(^iPrO)_2P(O)Na$	toluene, 0 °C	$(^iPrO)_2P(O)CHClF$	38	30
$CHBrFCO_2Et$	$(EtO)_3P$	140 °C	$(EtO)_2P(O)CHFCO_2Et$	71	36
CBr_3F	$(EtO)_3P$	hexane, rt	$(EtO)_2P(O)CFBr_2$	90−97	37,35
CBr_3F	$(EtO)_3P$	ether, refl.	$(EtO)_2P(O)CFBr_2$	78	28,26
CBr_3F	$(^iPrO)_3P$	ether, refl.	$(^iPrO)_2P(O)CFBr_2$	22	28,26
$CHClF_2$	$(EtO)_2P(O)Na$	THF, 30−35 °C	$(EtO)_2P(O)CHF_2$	54−77	32,34,29
$CHClF_2$	$(^iPrO)_2P(O)Na$	pentane, 30 °C	$(^iPrO)_2P(O)CHF_2$	49	24
$CHClF_2$	$(BuO)_2P(O)Na$	pentane, 30 °C	$(BuO)_2P(O)CHF_2$	68	24
CCl_2F_2	$(EtO)_2P(O)Na$	toluene, 0 °C	$(EtO)_2P(O)CF_2Cl$		33
CCl_2F_2	$(EtO)_2P(O)Na$	toluene, 0 °C	$[(EtO)_2P(O)]_2CF_2$		33
CBr_2F_2	$(MeO)_3P$	ether, refl.	$(MeO)_2P(O)CF_2Br$	55	26
CBr_2F_2	$(EtO)_3P$	ether, refl.	$(EtO)_2P(O)CF_2Br$	95	26
CBr_2F_2	$(EtO)_3P$	THF, 60 °C	$(EtO)_2P(O)CF_2Br$	96	38
CBr_2F_2	$(^iPrO)_3P$	triglyme	$(^iPrO)_2P(O)CF_2Br$	42	26
CBr_2F_2	$(BuO)_3P$	ether, refl.	$(BuO)_2P(O)CF_2Br$	65−100	26,28,40
CI_2F_2	$(EtO)_3P$	ether, refl.	$(EtO)_2P(O)CF_2I$	96	39
CF_3I	$(EtO)_3P$	UV, rt	$(EtO)_2P(O)CF_3$	51−100	40,27

nucleotides and oligonucleotides featuring difluoromethylenephosphonate and difluoromethylenethiophosphonate groups was discussed by Piettre et al.[18] Synthesis of fluorine-containing bioisosters corresponding to phosphoamino acids and dipeptide units was reviewed by Otaka et al.[19] Some of the fluorine-containing phosphonates are discussed in books by Kukhar and Hudson[3] and Savignac and Iorga.[20] Fluorinated phosphonates have also received some comments within reviews with wider scope.[21,22]

The synthesis, fundamental chemical properties, and biomedical uses of the phosphonic acid derivatives *that bear at least one fluorine substituent on the organyl moiety* are the subject of this review, which is organized as follows. The first part is a survey of synthetic methods used for the preparation of fluorinated phosphonates. The second part consists of a presentation of the different types of fluorophosphonates having significant biological importance. The third part describes the use of fluorinated phosphonates in biomedical studies. Discussion of basic aspects of phosphonate and organofluorine chemistry is reduced to minimum to avoid redundancy to the long series of papers already published in journals and books. Also no particular attention will be paid to subjects that have been recently reviewed in detail. In such cases, only the most important trends are briefly summarized. Literature coverage for the review extends up to April 2006.

2. General Synthetic Methods

Fluorinated phosphonates can be prepared in a number of different ways depending on the nature of organyl moiety (Figure 1). The most common methods are (a) direct



A: syntheses via Arbuzov and Michaelis-Becker reactions, transition metal catalyzed and radical reactions;

B: nucleophilic or electrophilic fluorination of phosphonate substrates;

C: syntheses via fluorinated phosphonate carbanions and radical additions

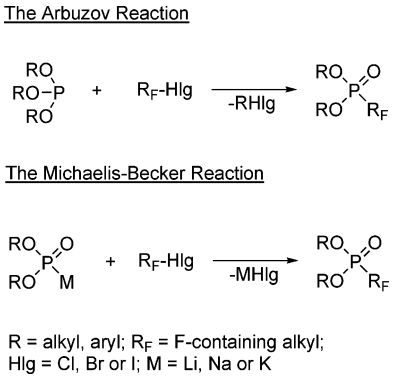
Figure 1. Schematic drawings of possible synthetic approaches to fluorinated phosphonates.

synthesis from trivalent phosphorus derivatives and fluorohaloalkanes, (b) electrophilic fluorination of phosphonate carbanions, (c) nucleophilic fluorination of functionalized phosphonate substrates, (d) syntheses via fluorinated phosphonate carbanions, (e) transition metal catalyzed addition reactions, and (f) radical approaches. Each of these methods is treated in detail in the next five sections.

2.1. The Arbuzov and Michaelis–Becker Reactions

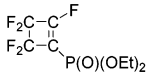
The high binding energy of the C−F bonds makes perfluoroalkanes poor electrophiles. Indeed, inactivated C−F bonds are generally unreactive toward typical phosphorus nucleophiles, such as trialkyl phosphites or dialkyl phosphite anions. As a consequence, mixed fluorohaloalkanes, R_FHlg, react with trivalent phosphorus compounds exclusively via a C−Hlg (Hlg = Cl, Br, or I) bond cleavage, thus providing a route to various fluorine-substituted phosphonates (Scheme 1). For instance, Arbuzov reactions of the fluorous primary

Scheme 1



iodides $R_{F_n}(CH_2)_mI$ [$R_{F_n} = CF_3(CF_2)_{n-1}$; $n/m = 6/2$, 8/2, 8/3, 10/2] and $P(OEt)_3$ (excess, 160 °C) give rise to the fluorinated phosphonates $R_{F_n}(CH_2)_mP(O)(OEt)_2$ in good yield (56−59%).[23] For the synthesis of certain simple phosphonates, such as fluorohalomethylphosphonates, $(RO)_2P(O)CX_nF_{3-n}$

Table 2. Reactions of Fluoroalkenes with Trialkyl Phosphites[52]

fluoroalkene	phosphite	conditions	product	yield (%)
$CF_2=CF_2$	$(EtO)_3P$	160-170 °C, 8 h[a]	$F_2C=CFP(O)(OEt)_2$	15
$CF_2=CF_2$	$(^iPrO)_3P$	160 °C, 7 h	$F_2C=CFP(O)(O^iPr)_2$	26
$CF_2=CFCl$	$(EtO)_3P$	170-180 °C, 8 h	$ClFC=CFP(O)(OEt)_2$	10
$CF_2=CFI$	$(^iPrO)_3P$	80 °C, 60 h	$IFC=CFP(O)(O^iPr)_2$	67
$CF_3CF=CF_2$	$(EtO)_3P$	130-140 °C, 8 h	$CF_3CF=CFP(O)(OEt)_2$	39
$CF_3CF=CF_2$	$(^iPrO)_3P$	125-130 °C, 8 h	$CF_3CF=CFP(O)(O^iPr)_2$	48
$(CF_3)_2C=CHF$	$(EtO)_3P$	20 °C, 16 h	$(CF_3)_2C=CHP(O)(OEt)_2$	40
$(CF_3)_2C=CF_2$	$(EtO)_3P$	90-100 °C, 8 h	$(CF_3)_2C=CFP(O)(OEt)_2$	66
$(CF_3)_2C=CF_2$	$(^iPrO)_3P$	80 °C, 6 h[b]	$(CF_3)_2C=CFP(O)(O^iPr)_2$	50
$(CF_3)_2C=CF_2$	$(BuO)_3P$	90-100 °C, 8 h	$(CF_3)_2C=CFP(O)(OBu)_2$	35
	$(EtO)_3P$	0-5 °C, 10 h		21

[a] In the presence of Et_3N. [b] The fluoroalkene was added to the phosphite at 80 °C with subsequent cooling to 20 °C.

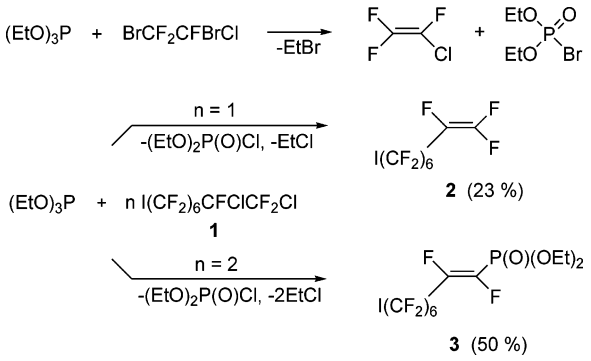
(X = H or Hlg; n = 1 or 2), the reaction between a fluorohalomethane and trialkyl phosphite or a dialkyl phosphite anion is the method of choice (Table 1).[24−40] Fluoromethylphosphonates of the type $(RO)_2P(O)CH_2F$ can be obtained from the reaction of CH_2ClF or CH_2BrF (which has restricted application due to its high mutagenicity) with $(RO)_2P(O)Na$.[25,33] The reaction of $CHClF_2$ with dialkyl sodio phosphites leads to the difluoromethyl analogues, $(RO)_2P(O)CHF_2$.[24,29,32,34] Dibromofluoromethylphosphonates, $(RO)_2P(O)CBr_2F$, are prepared by the reaction between trialkyl phosphites and CBr_3F.[41] The diethyl derivative was obtained in 97% yield when $(EtO)_3P$ in hexane was treated with CBr_3F in sunlight at room temperature.[35,37]

Bromodifluoromethylphosphonate, $(EtO)_2P(O)CF_2Br$, was first prepared by Burton and Flynn via the Arbuzov reaction from CBr_2F_2 and $(EtO)_3P$ in refluxing ether.[26] Yields of the phosphonate are usually high, very often over 90%.[42−47] Nevertheless the same process was reported as "a violent reaction which blew out the addition funnel, nitrogen inlet and stopper".[34] Further investigation showed that the synthesis of $(EtO)_2P(O)CF_2Br$ could be achieved on a molar scale and in safe conditions by slow addition of pure $(EtO)_3P$ to a solution of CBr_2F_2 in refluxing tetrahydrofuran.[38] It was also observed that the reaction of phosphonium bromide, $[Ph_3P^+CF_2Br]Br^-$, with $(EtO)_3P$ results in the formation of $(EtO)_2P(O)CF_2Br$ in 92% yield.[48]

Diisopropyl trifluoromethylphosphonate, $(^iPrO)_2P(O)CF_3$, was detected by ^{31}P NMR in a mixture obtained from reaction between $(^iPrO)_2P(O)Na$ and CF_3Br, but was not isolated.[49] Unlike CF_2Br_2 and CF_2I_2, trifluorohalomethanes themselves are totally inert to trialkyl phosphites. Under photolytic conditions, however, CF_3I reacts cleanly with $(EtO)_3P$ according to Arbuzov to give diethyl trifluoromethylphosphonate, $(EtO)_2P(O)CF_3$, in nearly quantitative yield.[27,40] It may be noted in passing that an elegant photo-Arbuzov rearrangement methodology is now available for the conversion of benzyl phosphites, $(AlkO)_2P(OCHRPh)$, into benzylphosphonates, $(AlkO)_2P(O)CHRPh$.[50] This reaction, a kind of intramolecular photo-Arbuzov process, represents a potentially effective route to fluorous species containing phosphonic acid functionality.

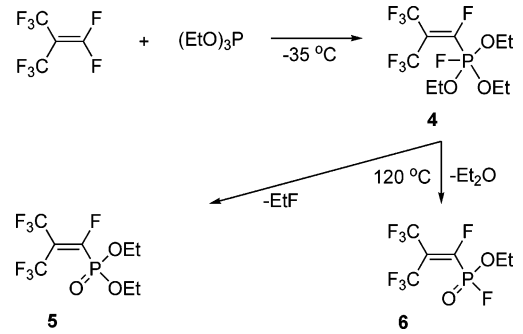
The synthetic utility of the reactions between trialkyl phosphites and fluoropolyhaloethanes and their higher homologues has some limitations since they are usually complicated by 1,2-dehalogenation reactions. Yields of the products depend both on the nature of reagents and on the reaction conditions. For example, treatment of $BrCF_2CFBrCl$ with $(EtO)_3P$ results in the formation of diethyl bromophosphate, $BrP(O)(OEt)_2$, as the only phosphorus-containing product. On the other hand, α,β-dichloro-ω-iodoperfluorooctane, **1**, is reported to react with $(EtO)_3P$ to produce a mixture of ω-iodoperfluorooct-1-ene, **2**, and diethyl alkenylphosphonate, **3** (Scheme 2).[51] Whether the alkenylphosphonate **3** is formed via the reaction of the initially generated perhaloalkene **2** with trialkyl phosphite is disputed. The reader is encouraged to consult refs 52 and 53 describing other similar examples.

Scheme 2

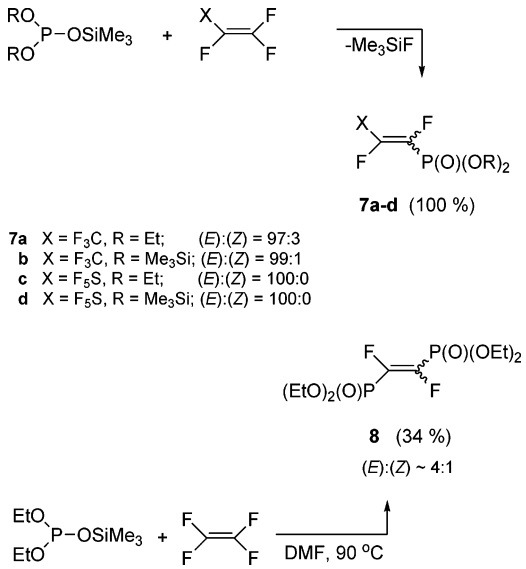


Perfluorinated alkenes undergo a facile Arbuzov-type reaction with trialkyl phosphites to give the corresponding alkenylphosphonates (Table 2). Again, these reactions occur by a multistage process, and yields of the desired phosphonates are often low.[52] For example, treatment of $(EtO)_3P$ with perfluoroisobutylene at −35 °C was reported to yield phosphorane **4**, which decomposes under rather drastic conditions (120 °C) to give dialkyl phosphonate **5** along with alkyl fluorophosphonate **6** (Scheme 3). The O-dealkylation process can be, however, suppressed by using a silyl phosphite instead of a trialkyl phosphite. This can be exemplified by the regioselective synthesis of the phosphonates **7** and bis-phosphonate **8** (Scheme 4).[54]

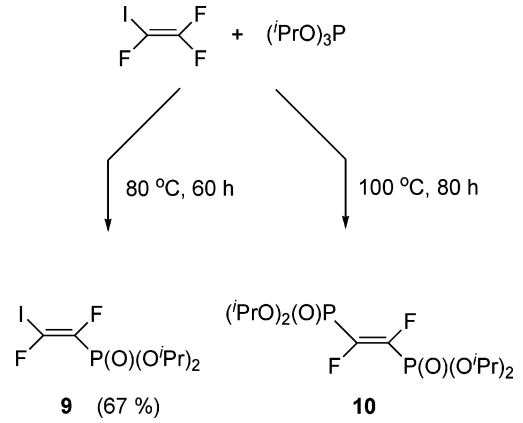
Scheme 3



Scheme 4



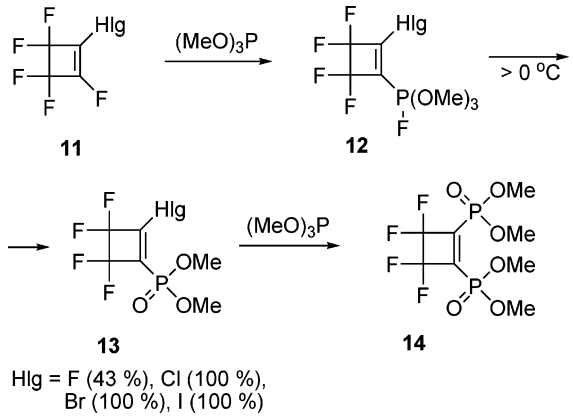
Scheme 5



When the perfluorohaloethene species of the type $F_2C{=}C(Hlg)F$ (Hlg = Cl, Br, or I) are substrates, they tend to react with participation of the C−F but not the C−Hlg bond, as in the synthesis of 2-iodoperfluorovinylphosphonate **9** shown in Scheme 5.[55] This result is explicable in terms of labilizing influence of the iodine substituent on the β-C−F bond. Reaction of perfluoroiodoethene with excess $(^{i}PrO)_3P$ resulted in diphosphonation and the formation of bis-phosphonate **10**.

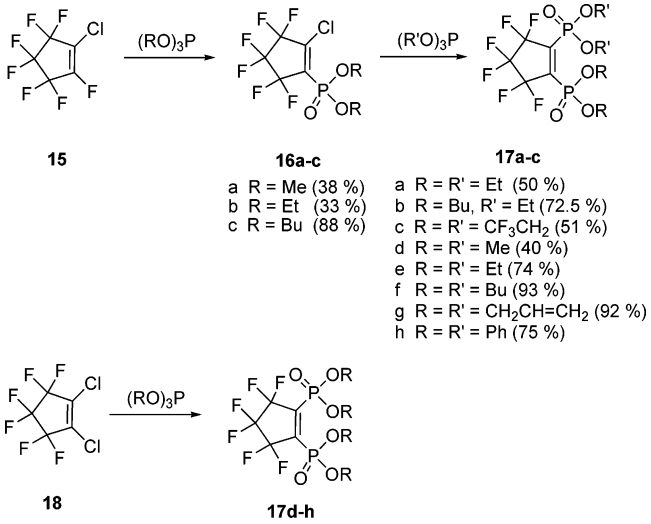
Perfluorocycloalkenes are generally more reactive than their acyclic analogues toward trialkyl phosphites. The earliest example in this area was reported by Knunyants and co-workers in 1959.[52] Treatment of 1-halopentafluorocyclobut-1-enes **11** with $(MeO)_3P$ generated phosphoranes **12**,

Scheme 6



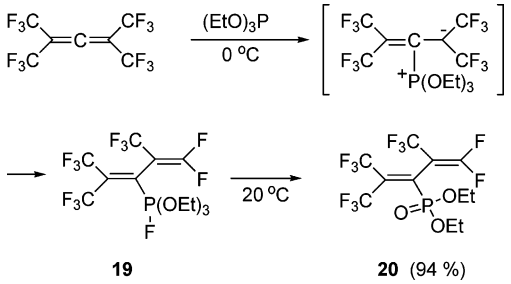
which were found to undergo decomposition to produce phosphonates **13**. As with all compounds containing a Hlg−C=C−F grouping, the nucleophilic attack occurred on the CF-carbon atom (Scheme 6).[56] In the presence of excess trimethyl phosphite, bis-phosphonate **14** was isolated as the major product.[57] A similar chemistry was performed with 1-chloro-2,3,4,5-heptafluorocyclopentene **15** and 1,2-dichloro-3,4,5-hexafluorocyclopentene **18** (Scheme 7).[58−60]

Scheme 7



The formal Arbuzov rearrangement has also been performed with tetrakis(trifluoromethyl)allene. The reaction proceeds via initial formation of the fluorophosphorane **19**, followed by intramolecular rearrangement leading to the phosphonate **20** (Scheme 8).[61] The only products that are

Scheme 8



formed from the reaction of perfluoroazapropene with trialkyl phosphites at room temperature are the corresponding

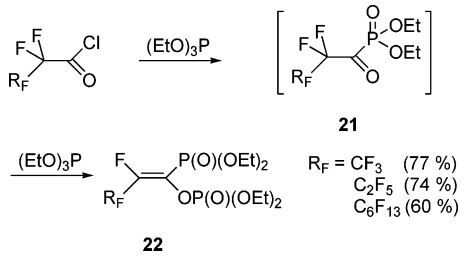
fluorophosphoranes, $CF_3N{=}CFPF(OR)_3$. On heating, these species produce $FP(O)(OR)_2$ and CF_3NC rather than $CF_3N{=}CFP(O)(OR)_2$.[62]

Application of the Arbuzov rearrangement for the synthesis of perfluoroaryl- and perfluoroheterylphosphonates has been reviewed earlier by Furin.[52] In a photolytic reaction analogous to the synthesis of $CF_3P(O)(OR)_2$ described above, treatment of pentafluoroiodobenzene with triethyl phosphite afforded the corresponding phosphonate in 32% yield.[27] Several examples of the thermal Arbuzov reactions have been reported with Ar_FF (Ar_F = 4-$NO_2C_6F_4$, 4-$CF_3C_6F_4$, 4-$C_6F_5C_6F_4$, and 4-HC_6F_4); the best result was obtained in the reaction of pentafluorobenzene with triethyl phosphite to produce the phosphonate 4-$HC_6F_4P(O)(OR)_2$ in 44% yield.[63,64] The main side reactions were reduction of Ar_FF to Ar_FH and the formation of alkylated product Ar_FEt in the case of pentafluorobenzene. The 4-perfluoropyridylphosphonate was prepared (30%) from perfluoropyridine and triethyl phosphite (140−150 °C, 16 h).[63] Later, modification of this procedure utilizing the reaction of perfluoropyridine with triethyl phosphite at lower (60−90 °C) temperatures resulted in the formation of 4-$Py_FP(O)(OR)_2$ in improved (R = Et, 50%; R = ^{i}Pr, 90%) yields. Fluorophosphoranes are formed as intermediates in this reaction.[65]

Phosphonylation of arenes Ar_FF (Ar_F = 4-HC_6F_4, 4-CNC_6F_4, and 4-$CF_3C_6F_4$) with $(RO)_2P(O)Na$ in a THF solution at 60 °C has been shown to give variable yields (10−65%) of $Ar_FP(O)(OR)_2$. By the same protocol, perfluoropyridine was converted to the desired phosphonate in 53% yield.[66] Souzy et al. has recently utilized the Arbuzov and Michaelis−Becker reactions to prepare dialkyl 4-(perfluorovinyloxy)-phenylphosphonates starting from 4-(perfluorovinyloxy)-bromobenzene.[67]

Finally, only brief mention can be made here to the possibility of Arbuzov-type reactions of fluorine-substituted acyl chlorides with trialkyl phosphites to give fluorous α-ketophosphonates. Fluorine-substituted imidoyl chlorides and their analogues are also known to be very popular reagents in the Arbuzov and Michaelis−Becker reactions. The synthetic potential of these reactions will be disclosed in a later sections dealing with fluorinated hydroxy- and aminophosphonic acids, but there are two important examples that need to be noted here. In attempts to prepare α-ketophosphonates **21** by reaction of perfluoroalkanoyl chlorides with triethyl phosphite, Ishihara et al. actually obtained compounds **22** (Scheme 9).[68] On the other hand, in the

Scheme 9

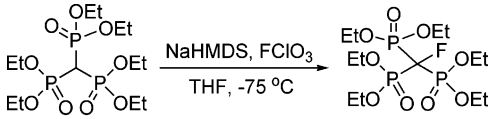


presence of CuI−BuLi, the perfluoroalkanoyl chlorides, $R_FCF_2C(O)Cl$, react with $(EtO)_3P$ to form the vinylphosphonates, $R_FCF{=}CHP(O)(OR)_2$.[69]

2.2. Electrophilic Fluorination of Phosphonate Carbanions

Direct electrophilic fluorination of phosphonate carbanions has proved to be a versatile technique for the synthesis of α-monofluoro- and α,α-difluoroalkylphosphonates. This methodology has been applied successfully for the preparation of HO-, NC-, RC(O)-, RCO_2-, $(RO)_2P(O)$-, RSO_2-, and O_2N-functionalized fluoroalkylphosphonic acids, which are otherwise difficult to prepare (Table 3).[70−79] Perchloryl fluoride, $FClO_3$, and acetyl hypofluorite, $CH_3C(O)OF$, were among the first reagent sources of positive fluorine employed for this purpose.[80] In particular, diethyl methylphosphonate,[31] methylenediphosphonates,[8,71,81] α-ketophosphonates,[82] phosphonoacetates,[83,84] and phenylsulfonylmethanephosphonates[85] have been fluorinated by the reaction with $FClO_3$ in the presence of a base, which is most commonly NaHMDS, LDA, or KO^{t}Bu. These reactions usually give a mixture of mono- and difluorinated alkylphosphonates, although, by suitable adjustment of the proportion of starting material, either product can be made to predominate. For example, when equimolar amounts of $[(^iPrO)_2P(O)]_2CH_2$ and KO^{t}Bu were combined and treated with 1 equiv of $FClO_3$, the yields of mono- and difluorinated phosphonates were, correspondingly, 48% and 13%. With 2 equiv of KO^{t}Bu, the corresponding difluoro derivative could be prepared directly in 43% yield, an increase to 73% being possible on further reaction of the monofluoro derivative.[8] Certainly the general scope of application of $FClO_3$ and $CH_3C(O)OF$ is restricted by the availability of the reagents, difficulties in handling, and danger associated with their use. There are, however, situations where the OF-fluorinating compounds are the reagents of choice; for example, tris(diethylphosphono)-fluoromethane **24** was prepared from **23** in 77% yield using $FClO_3$ at −78 °C in the presence of NaHMDS (Scheme 10).

Scheme 10

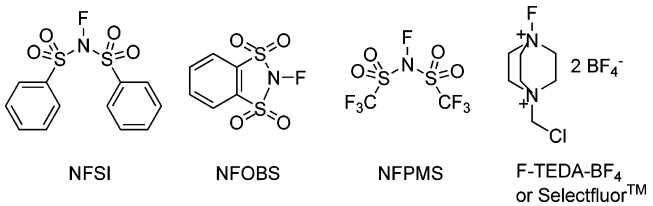


23 **24** (77 %)

Substituting commercially available $(PhSO_2)_2NF$ for $FClO_3$ gave no product even at room temperature. Presumably this is a consequence of the extreme steric hindrance preventing electrophilic substitution at the central carbon atom in **23**.[86−88]

In recent years, the NF electrophilic reagents such as *N*-fluorobenzenesulfonimide (NFSI), *N*-fluoro-*o*-benzenedisulfonimide (NFOBS), *N*-fluoroperfluoromethanesulfonimide (NFPMS), and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) have been used extensively as sources of positive fluorine (Chart 2).[89−93] These reagents are generally less reactive than

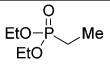
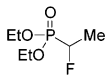
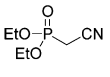
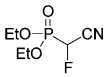
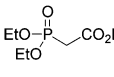
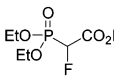
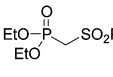
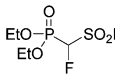
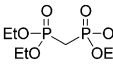
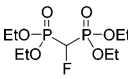
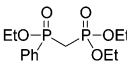
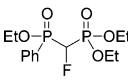
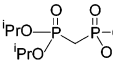
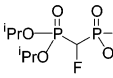
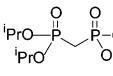
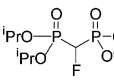
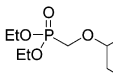
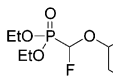
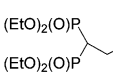
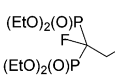
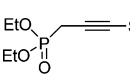
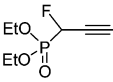
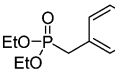
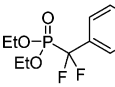
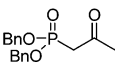
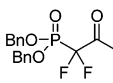
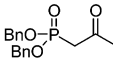
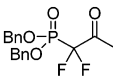
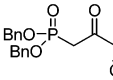
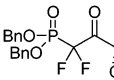
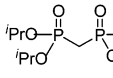
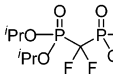
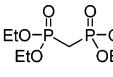
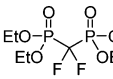
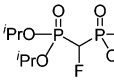
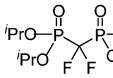
Chart 2



the compounds incorporating the O−F bond but appreciably more selective for the fluorination of carbanionic species.

Differding and co-workers reported the first synthesis of α-fluorinated alkylphosphonates by reactions of the corresponding carbanions with NFSI (Scheme 11).[94] Both mono-

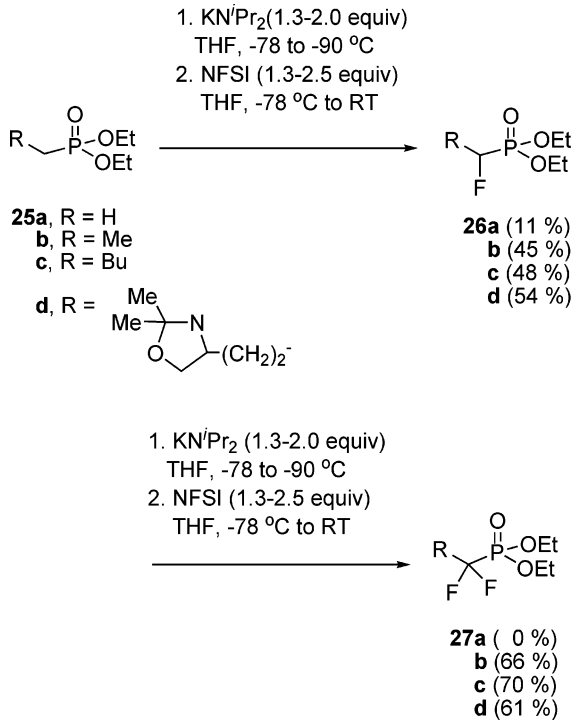
Table 3. Preparation of α-Monofluoro- and α,α-Difluoromethylenephosphonates by Electrophilic Fluorination of Alkylphosphonate Carbanions

substrate	base	fluorinating reagent	product	yield (%)	ref.
	BuLi	$FClO_3$		46	31
	BuLi	$(CF_3SO_2)_2NF$		51	72
	NaHMDS	NFOBS		78	74
	NaH	F-TEDA-BF_4		61	73
	^{t}BuOK	$FClO_3$		34[a]	8
	^{t}BuOK	$FClO_3$		-	71
	^{t}BuOK	$FClO_3$		42[a]	8
	NaH	AcOF		66	70
	^{s}BuLi	$(PhSO_2)_2NF$		29	75
	KH	F-TEDA-BF_4		83	79
	NaHMDS	$(PhSO_2)_2NF$		63	76
	NaHMDS	$(PhSO_2)_2NF$		80	78
	NaH	F-TEDA-BF_4		55	77
	NaH	F-TEDA-BF_4		48	77
	NaH	F-TEDA-BF_4		52[b] 50[c]	77
	KO^tBu	$FClO_3$		73[a]	8
	KO^tBu	$FClO_3$		21[a]	8
	NaH	AcOF		52	8

[a] By ^{19}F NMR analysis. [b] R = tetrahydro-2*H*-2-pyranyl. [c] R = 1-ethoxyethyl.

and difluorinated phosphonates are accessible according to this procedure. However, to obtain the difluorinated product, a two-step process was found to work best in which the monofluorinated phosphonate was first isolated and then subjected to deprotonation at −90 °C followed by fluorination. The yields of the reaction strongly depend on the nature

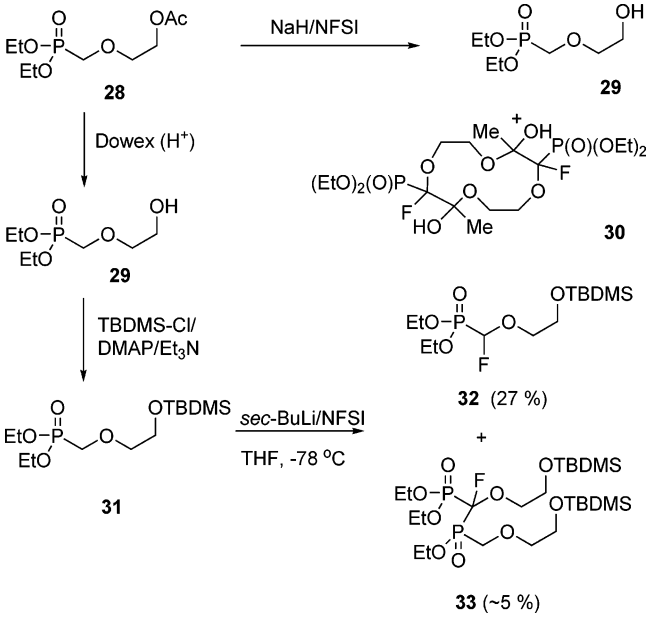
Scheme 11



of the base and counterion, especially when difluorinated product is wanted. KDA appears to be the base of choice since deprotonation of α-fluoroethylphosphonate **26b** with LDA and reaction of the resulting anion with NFSI gave only about 20% of the required difluorinated product, whereas the use of KDA, generated in situ from LDA and KO^{t}Bu, gave 66% of **27b**.

Chen et al. utilized NFSI for the preparation of more sophisticated 2-hydroxyethoxy-functionalized fluoromethylphosphonates (Scheme 12).[75,95] Electrophilic fluorination

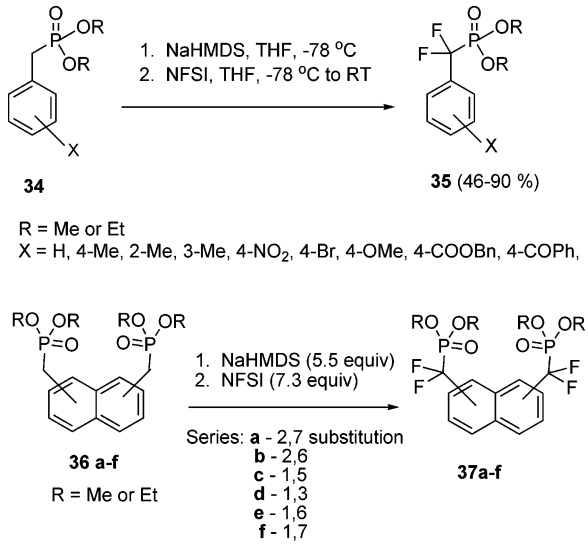
Scheme 12



of diethyl (2-acetoxyethoxy)-methylphosphonate **28** was initially attempted using NFSI in the presence of NaH as a base. Instead of the desired product, the hydrolyzed alcohol **29** and the dimeric fluorine-substituted cyclic hemiketal **30** were obtained. Changing the base from NaH to LDA, LHMDS, KHMDS, or ^{s}BuLi did not affect the course of the reaction. Meanwhile, it was demonstrated that the alcohol **29** can be fluorinated via *tert*-butyldimethylsilyl (TBDMS)-protected phosphonate **31** by using NFSI as the fluorinating reagent and *sec*-butyl lithium as the base. The key phosphonate **32** was formed in 27% yield, along with a small amount of dimer **33**.

There has been much interest in α-monofluoro- and α,α-difluorobenzylphosphonate esters because of their ability to act as potent inhibitors of protein tyrosine phosphatases and kinases. NFSI has proven to be a particularly effective reagent for the preparation of such species.[96] Thus, the successful preparation of difluorinated benzylphosphonates **35** has been achieved in a single step using 2.2 equiv of NaHMDS and 2.5 equiv of NFSI at −78 °C. Although α-monofluorobenzylphosphonates can also be prepared in reasonable yields using equimolar amounts of reagents, the reaction inevitably produces a mixture of mono- and difluorinated products that must be separated. Access to the naphthalene derivatives **37**, bis-functionalized with a methyl- or ethyl-protected $(RO)_2P(O)$ group, is also possible by using NaHMDS/NFSI in THF at −78 °C (Scheme 13).[97,98]

Scheme 13



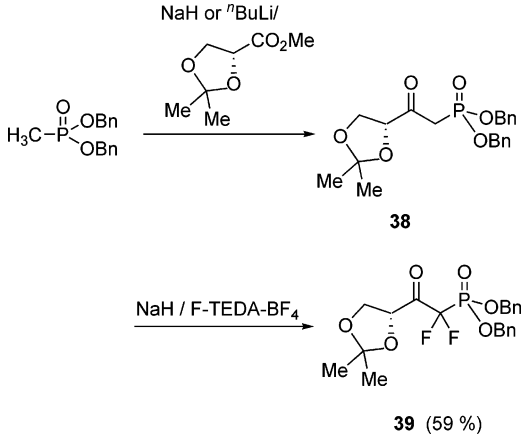
A similar chemistry was performed with NFOBS; for example, fluorination of $(EtO)_2P(O)CH_2CO_2Et$ with NFOBS gave good yield of the corresponding monofluorinated phosphonate.[74] The major difference between NFSI and NFOBS appears to be that the latter is slightly more reactive and being water soluble can be removed during the aqueous workup. By contrast, fluorinations using NFSI require an alkaline wash to remove the dibenzenesulfonimide byproduct.

The search for other NF-fluorinating agents useful for the synthesis of α-fluorophosphonates has not, so far, brought spectacular improvements.[99] Although F-TEDA-BF_4 (Selectfluor) appears to offer some advantages in terms of both yields and reaction rate as compared to NFSI, low mono-/diselectivity of fluorination reactions dogged the acidic alkylphosphonates. Thus, the reaction of $(EtO)_2P(O)CH_2SO_2$-Ph with NaH/F-TEDA-BF_4 afforded a mixture of monofluorinated derivative (60%), difluorophosphonate (15%), and unreacted starting material (25%).[73,92] Fluorination of the sodium enolate of $(EtO)_2P(O)CH_2CO_2Et$ using F-TEDA-BF_4 in a THF−DMF solvent mixture gave a quite poor yield

(17%) of monofluorinated product.[100] However, when 1 equiv of NaH and 1.0−1.5 equiv of F-TEDA-BF_4 were used in THF, triethyl fluorophosphonoacetate, $(EtO)_2P(O)CHFCO_2$-Et, was clearly formed (40−50%).[84] Tetraethyl fluoromethylenebisphosphonate, $(EtO)_2P(O)CHFP(O)(OEt)_2$, was prepared in the same way in 52% yield.[101]

Using fluorination reaction with F-TEDA-BF_4 as a key step, Willson and co-workers recently succeeded in preparing a series of functionalized dibenzyl α,α-difluoromethylene-β-ketophosphonates.[77] A representative example is shown in Scheme 14. Nonfluorinated β-ketophosphonate **38** is easily

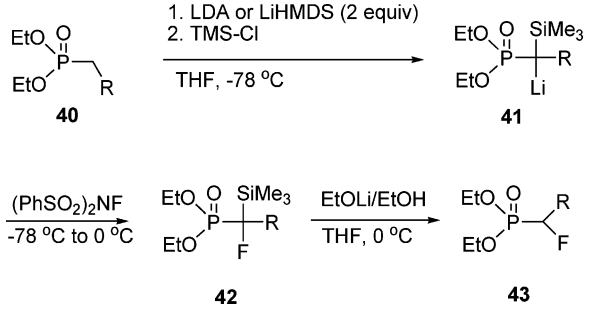
Scheme 14



formed by condensation of $(BnO)_2P(O)CH_2Na$ with the corresponding methyl ester. In the second step, fluorination of the methylene group of the β-ketophosphonate framework was carried out with F-TEDA-BF_4 in THF at room temperature. The fluorination process consists of initial deprotonation of the α-methylene group of β-ketophosphonate with NaH (2 equiv) at 0 °C, followed by treatment with the F-TEDA-BF_4 reagent (2 equiv). A variety of new α,α-difluoromethylene-β-ketophosphonates were thus obtained in moderate to good yields (up to 60%) and after an easy cleavage of the benzyloxy protecting groups transformed into functionalized α,α-difluoromethylene-β-ketophosphonic acids. These syntheses always generated minor amounts of monofluorinated phosphonates (5−10%) as side products. No fluorination of dibenzyl β-ketophosphonates was observed under neutral conditions. On the other hand, the fluorination reaction does not seem to depend on the amount of base, since α,α-difluoro-β-ketophosphonate is always the main product whatever the quantity of NaH added, varying from 0.5 to 3 equiv relative to β-ketophosphonate. It was assumed that this predominant difluorination reaction occurs through an initial addition of F-TEDA-BF_4 to the enolate tautomer, followed by a fast *gem*-fluorination of the more stable enolate resulting from the monofluoro derivative. For the latter, as in the case of β-diketones, the enol form is able to exist in the absence of base and can therefore give rise to the difluoro derivative despite the use of less than 1 equiv of base.

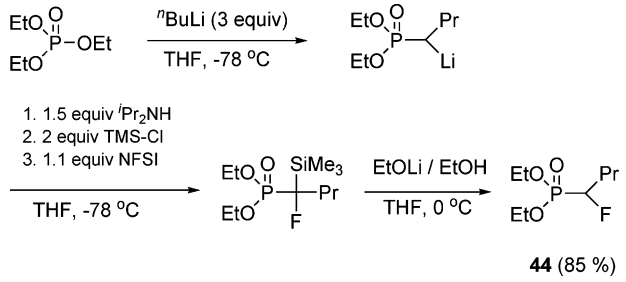
Returning to the synthesis of α-monofluorophosphonates, it should be noted that the direct controlled monofluorination of alkylphosphonates, using the OF- and NF-fluorinating reagents, is a preparative challenge. Still the synthesis of α-monofluorophosphonates could be made more controlled by using a specific protective group at a carbanionic phosphonate center. Such methodology, based on controlled reactivity of phosphonates, was indeed worked out by Savignac and co-workers.[102] Transformation of alkylphosphonates to the pure α-monofluoro derivatives has been accomplished in three steps (Scheme 15).[103−105] Diethyl lithio

Scheme 15



1-(trimethylsilyl)alkylphosphonates **41**, the key intermediates in the synthesis of α-monofluorophosphonates, are easily formed from **40** and TMSCl by using LDA or LiHMDS as metalating agent. The fluorination step takes place at low temperature using a slight excess of NFSI. The TMS group from **42** is removed with EtOLi in EtOH in the third step. This mild and versatile one-pot procedure results in overall yields of 68−97% of the pure α-monofluoroalkylphosphonates **43**. The same workers combine the selective electrophilic fluorination reaction with phosphate−phosphonate conversion to prepare directly α-fluorinated alkylphosphonates from triethyl phosphate. This approach was exemplified by conversion of triethyl phosphate into diethyl α-fluorobutylphosphonate **44** (Scheme 16).[103]

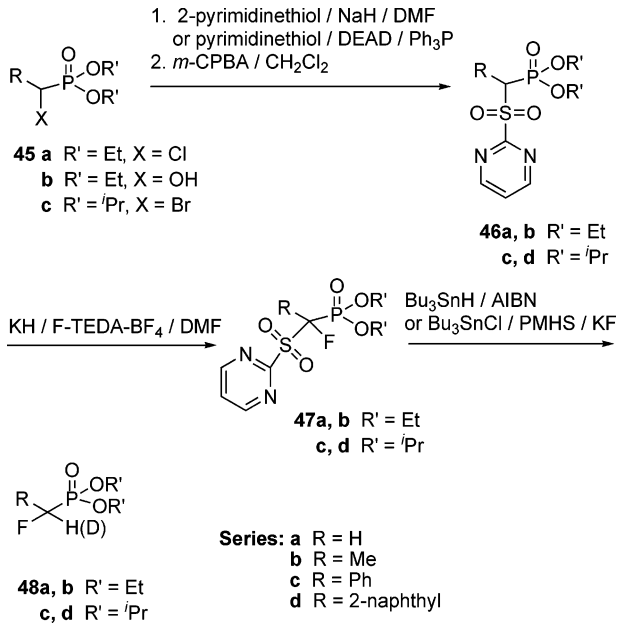
Scheme 16



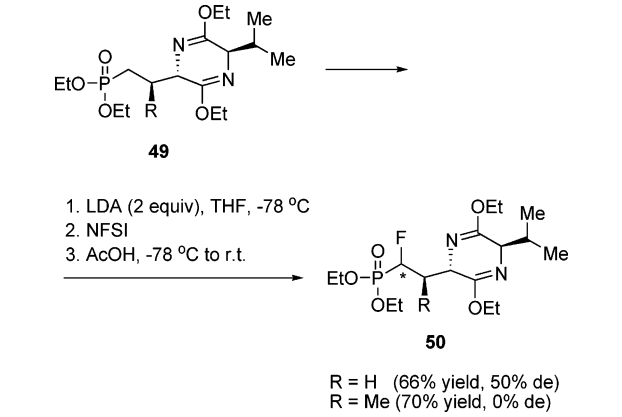
Another variant of protective methodology has been developed by Wnuk, Bergolla, and Garcia.[106] Treatment of α-carbanions generated from α-(pyrimidin-2-ylsulfonyl)-alkylphosphonates **46** with F-TEDA-BF_4 followed by radical desulfonylation of the formed α-fluoro-α-(pyrimidin-2-ylsulfonyl)alkylphosphonates **47** with Bu_3SnH or a "catalytic" tin equivalent gives rise to pure α-monofluoroalkylphosphonates **48** (Scheme 17). In general, removal of the π-deficient pyrimidin-2-ylsulfonyl group from the α-carbon of the benzylic-type phosphonates (c, d series; 78−80% yield) gave better results than those with the alkyl analogues (a, b series; 45−61% yield). Substitution of Bu_3SnD for Bu_3-SnH gave access to α-deuterium-labeled phosphonates.

Stereoselective synthesis of α-fluoroalkylphosphonates using the electrophilic fluorination reactions is so far undeveloped in comparison with the asymmetric synthesis of α-fluoroketones and related compounds.[107] Ruiz et al. exploited Schöllkopf's bislactim ethers **49** as the chiral starting materials, which were fluorinated with NFSI in the presence of LDA to produce the diastereomeric phosphonates **50**. The best result did not exceed 50% de for 66% yield (Scheme 18).[108]

Scheme 17

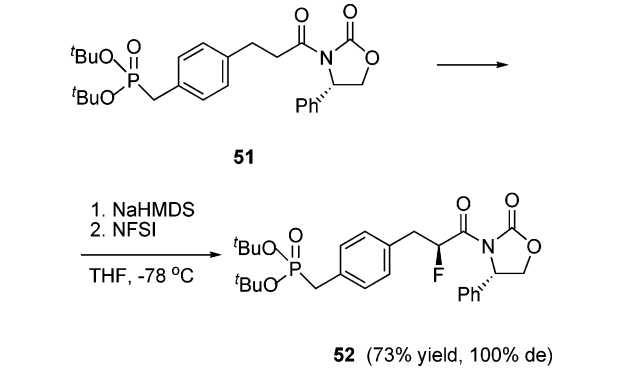


Scheme 18



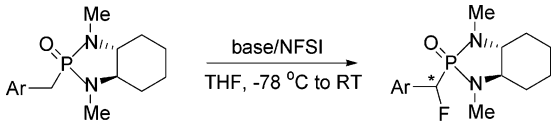
For the synthesis of an α-fluoro-phosphotyrosyl mimetic, Burke et al. have used the diastereoselective electrophilic fluorination of an imide enolate derived from an appropriate Evans chiral oxazolidinone auxiliary.[109] Treatment of **51** with NaHMDS in THF at −78 °C followed by reaction with NFSI gave the (*S*)-α-fluoro derivative **52** in 73% yield without any evidence of the diastereomeric (*R*)-fluoro analogue (Scheme 19).

Scheme 19



Diastereoselective electrophilic fluorination of the chiral phosphonamides bearing *trans*-(*R*,*R*)-1,2-bis(*N*-methylamino)cyclohexane or (−)-ephedrine as a chiral auxiliary has been reported by Taylor and co-workers.[110] The diastereoselectivity was strongly dependent on the nature of the base and counterion with de's ranging from 2% to 72%. Thus, fluorination of **53** to give the fluorinated phosphonamides **54** was achieved by treating **53** with 0.95 equiv of base at −78 °C, followed by the addition of 1.1 equiv of NFSI. Bases with lithium counterions (BuLi and LiHMDS) gave better de's (68−70%) as compared to NaHMDS and KHMDS (Table 4). In contrast, NaHMDS gave the highest de's in

Table 4. Effect of Base and Counterion on the Electrophilic Fluorination of Phosphonamide 53 with NFSI[110]



53 **54**

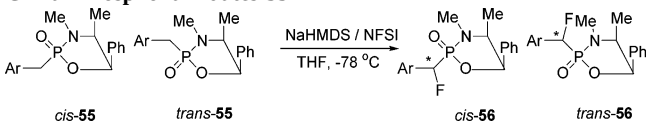
Ar = 2-naphthyl

base	yield (%)	de (%)[a,b]
^{n}BuLi	68	68
LiHMDS	81	70
NaHMDS	69	18
KHMDS	71	37

[a] Performed using 0.95 equiv base and 1.1 equiv NFSI. [b] Absolute stereochemistry was not determined.

the case of the isomeric phosphonamidates **55** (Table 5). The

Table 5. Selected Results for the Electrophilic Fluorination of Chiral Phosphonamidates 55[110]



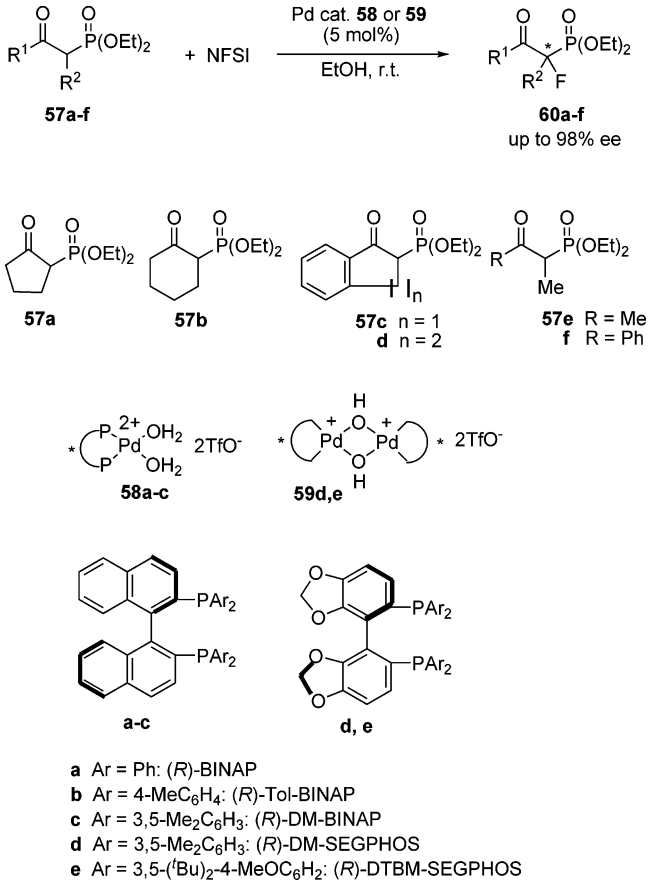
cis-**55** *trans*-**55** *cis*-**56** *trans*-**56**

substrate	Ar	product	yield (%)	de (%)
trans-**55**	2-naphthyl	*trans*-**56**	62	72
cis-**55**	2-naphthyl	*cis*-**56**	54	58
trans-**55**	3-(Ph)Ph	*trans*-**56**	85	25
cis-**55**	3-(Ph)Ph	*cis*-**56**	68	26
trans-**55**	Ph	*trans*-**56**	47	29
cis-**55**	Ph	*cis*-**56**	44	33

diastereomerically pure α-fluorophosphonamidates **56** were isolated by column chromatography. Removal of the ephedrine auxiliary using MeOH−TFA, followed by treatment with TMS−Br, afforded the corresponding α-monofluoroalkylphosphonic acids in greater than 97% ee.

Recently, an efficient catalytic enantioselective fluorination of *β*-ketophosphonates has been reported.[111,112] In the presence of chiral Pd complexes **58** or **59** (1−10%), various cyclic and acyclic *β*-ketophosphonates **57a**−**f** underwent the reaction with NFSI in EtOH to give the corresponding fluorinated products in a highly enantioselective manner (Scheme 20). The substituents at the *meta* positions of the aryl groups of BINAP complexes were found to be important for high asymmetric induction. The reaction of **57a** using a catalytic amount of the Pd complex **58a** (5 mol %) gave the desired fluorinated product **60a** in 81% yield with 75% ee. By use of the Pd complex **58c** consisting of (*R*)-DM-BINAP, enantioselectivity was greatly improved, and the corresponding product was obtained in 91% yield with 95% ee. When the complex **59d** containing the bulkier DTBM-SEGPHOS ligand was used, a higher enantioselectivity of 98% was

Scheme 20



achieved, but the chemical yield was not satisfactory (46%), probably due to the severe steric repulsion. The mechanism postulated for the reactions includes formation of configurationally stable chiral palladium enolates. Also efficient enantioselective fluorination of β-ketophosphonates proceeds using NFSI in the presence of chiral Lewis acids.[113]

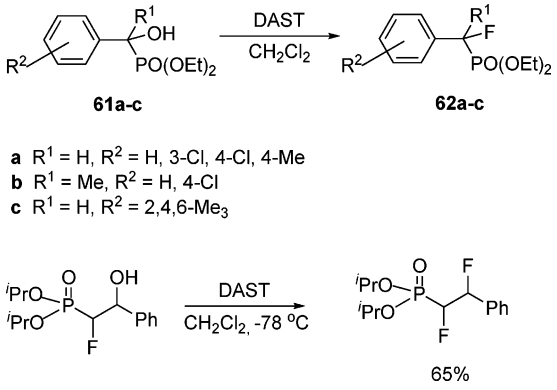
2.3. Nucleophilic Fluorination

2.3.1. Monofluorination Reactions

Introduction of fluorine via nucleophilic substitution reactions in phosphonate derivatives constitutes a valuable synthetic alternative to the electrophilic substitution strategy. However, due to the generally poor nucleophilic character of fluoride-containing reagents, only phosphonate substrates containing leaving groups with high nucleofugicity (such as trifluoromethanesulfonates, imidazolesulfonates, tosylates, and others) meet the requirements for a preparative useful transformation.[114] In practice, one of the most successful procedures for monofluorination of alkylphosphonate derivatives has been the C−OH → C−F transformation of α-hydroxyphosphonates with DAST (Et_2NSF_3, diethylaminosulfur trifluoride), a commercially available reagent that frequently permits less forcing conditions than SF_4 and standard laboratory equipment. The key features common to all these DAST-promoted reactions are the formation of the activated intermediates of the $XYCH-OSF_2NEt_2$ type, which tend to react via S_N-displacement rather than dehydratation or skeletal rearrangement reactions.[21,115,116]

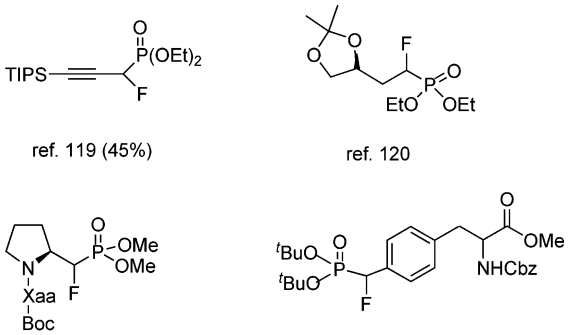
Blackburn and co-workers were the first to demonstrate the utility of the method by studying the DAST fluorodehydroxylation of α-hydroxybenzylphosphonates.[30,117,118] The conversion of the hydroxy into the fluoro function was achieved by the action of 1 equiv of DAST in dichloromethane solution at 0 °C (Scheme 21). There was no sign

Scheme 21



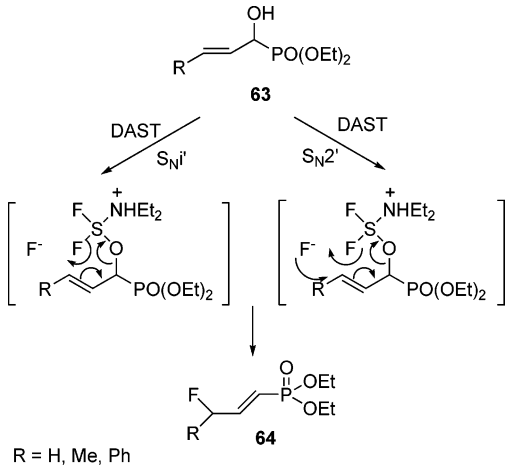
of steric hindrance in the transformation. Thus, the tertiary alcohols **61b** and the highly crowded mesitylene derivative **61c** are readily fluorinated under standard conditions. In recent years, the reaction has been extended to the preparation of nonbenzylic secondary α-fluorophosphonates.[17] Most common organic functional groups (e.g., methyl, halide, ester, amide, TBS, and TIPS) can be present during the DAST-promoted fluorination. This excellent functional group tolerance opened a simple access to a series of highly functionalized α-fluorophosphonate esters capable of further chemical manipulations (Chart 3).[119−122]

Chart 3

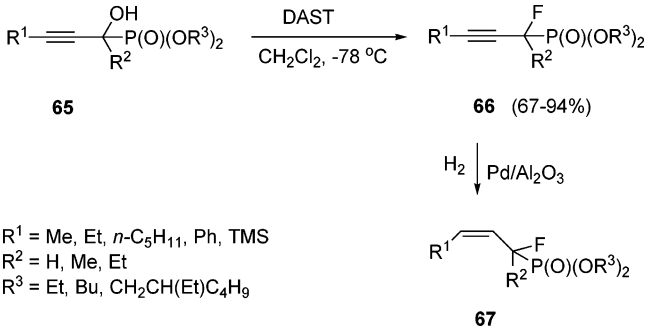


Interestingly, in allylic phosphonate systems **63**, the replacement of the hydroxy group by fluorine proceeds via an S_N2' or a cyclic S_Ni' mechanism producing exclusively the γ-fluoro isomers **64** (Scheme 22).[117,118] Extending Blackburn's work on the fluorination of α-hydroxyallylphosphonates, Hammond and co-workers hypothesized that DAST fluorination of (α-hydroxypropargyl)phosphonate esters **65** should favor the regiospecific formation of the α-fluoro isomers, because the linearity of the alkyne system is expected to hinder intramolecular fluorine transfer via a cyclic S_Ni' mechanism. In addition, triple bond migration through a S_N2' mechanism would be more difficult on **65** because it involved a more energetically unfavorable allene intermediate. In fact, DAST-promoted fluorination of **65** in CH_2Cl_2 led to the exclusive formation of α-fluorophosphonates **66**. Finally, partial catalytic hydrogenation of the triple bond in **66** yielded the desired 1-fluoro-2-butenylphosphonates **67** (Scheme 23).[123,124]

Scheme 22

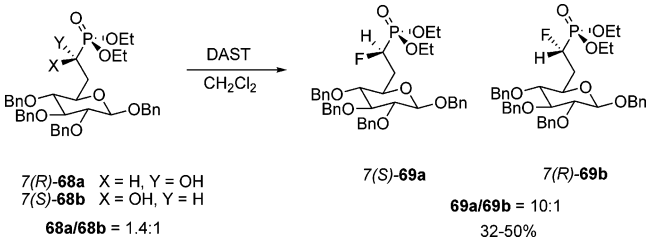


Scheme 23



Especially interesting for synthetic applications is the stereocontrolled fluorodehydroxylation of readily available, enantiomerically pure α-hydroxyphosphonates.[5a,22,125] It is known that the reaction of DAST with secondary alcohols typically proceeds with inversion of configuration.[126] When α-hydroxyphosphonates are employed, striking discrepancies in the stereochemical course of the fluorodehydroxylation reaction were observed. Shibuya and co-workers have shown that, in general, benzylic α-hydroxyphosphonates give scrambling of the α-stereochemistry upon treatment with DAST.[127] This is suggestive of an S_N1-like mechanism, and indeed, there has been speculation that the phosphoryl group may stabilize an adjacent carbocation through the $C^+-{}^-P\equiv O^+$ type resonance structures. Also consistent with the S_N1-like mechanism is the fact that diethyl α-hydroxymethylphosphonate, $(EtO)_2P(O)CH_2OH$, is unreactive toward DAST. Activation of the alcohol by first forming the triflate, $(EtO)_2P(O)CH_2OTf$, followed by nucleophilic displacement with tetrabutylammonium fluoride (TBAF) in THF afforded the corresponding α-fluorophosphonate in good yield.[100] In a related example, treatment of $Ph_2P(O)CH_2OH$ with DAST resulted in the formation of the dimeric sulfite $[Ph_2P(O)CH_2O]_2SO$ instead of the expected $Ph_2P(O)CH_2F$. Here too, when $Ph_2P(O)CH_2OTs$ was treated with KF in triethylene glycol at 160 °C nucleophilic substitution occurred to afford $Ph_2P(O)CH_2F$ in 70−80% yields.[128] These results appear to indicate that stabilization of a carbocation at the α-position by a hydrocarbon substituent is a necessary condition for the successful completion of fluorodehydroxylation. On the other hand, Berkowitz and co-workers have recently observed the inversion of configuration in DAST-mediated fluorination of the nonbenzylic phosphonate **68** (Scheme 24).[17] The diastereomeric mixture (7*R*)-**68a**/(7*S*)-**68b** (ratio 1.4/1) reacted with DAST to give predominantly one diastereomer

Scheme 24

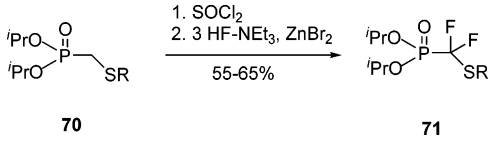


(10/1 selectivity) of the corresponding α-fluorophosphonate **69a** in modest yield. The crystal structure of **69a** established the (7*S*) stereochemistry at the α center to phosphorus. When the DAST reaction was repeated under exactly the same conditions with individual diastereomers, **68a** afforded **69a** in yields comparable to those observed with the diastereomeric mixture, but **68b** decomposed under the reaction conditions. No mechanistic implications have been proposed for the difference in reactivity between (7*S*) and (7*R*) diastereomers **68** toward DAST.

2.3.2. gem-Difluorination Reactions

The direct Hlg/F or TfO/F exchange has only limited utility in *gem*-difluorination of phosphonate esters.[129] The first practical synthesis of the α,α-difluorophosphonates based on the Halex reaction was reported by Lequeux and co-workers, who reacted the phosphonates **70** with $SOCl_2$ followed by treatment with $Et_3N{\cdot}HF$ in the presence of $ZnBr_2$.[130] This finding implies that α,α-dichlorophosphonates are reactive intermediates (Scheme 25). The same type of

Scheme 25

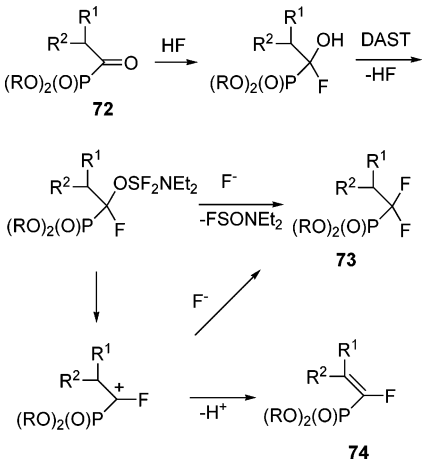


reactivity is observed with the thiodichloroacetate derivatives.[131]

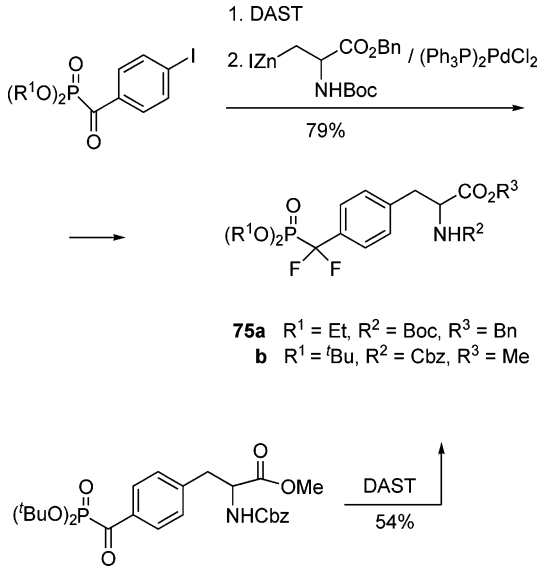
DAST is a singularly important reagent for transformation of α-ketophosphonates **72** into α,α-difluoromethylenephosphonates **73**. The reaction is catalyzed by trace amounts of hydrogen fluoride. Difluoride is formed via DAST-activated alcohol or fluorocarbocation, which can also be susceptible to α-proton loss leading to α-fluorovinylphosphonate **74** (Scheme 26). The proportion of *gem*-difluoride **73** and vinyl fluoride **74** can be strongly influenced by solvent: *gem*-difluorides are usually the major products in nonpolar solvents (CH_2Cl_2), but in polar solvents (*N*-methyl pyrrolidone), vinyl fluorides can predominate. Thus, the essentials of the method are the same as those for making the α,α-difluoro esters from α-keto esters.[22]

DAST-promoted difluorination reactions are typically conducted at or below 0 °C in chlorinated solvents, and yields of α,α-difluorophosphonates are modest to good. The reactions tolerate such functional groups as esters and amides. Probably the best example is the preparation of 4-(phosphonodifluoromethyl)-D,L-phenylalanines **75**, hydrolytically stable analogues of *O*-phosphotyrosine (Scheme 27).[122,132] Other examples can be found describing syntheses of functionalized α,α-difluoromethylenephosphonates, which can serve as useful synthetic blocks for the preparation of peptides

Scheme 26



Scheme 27

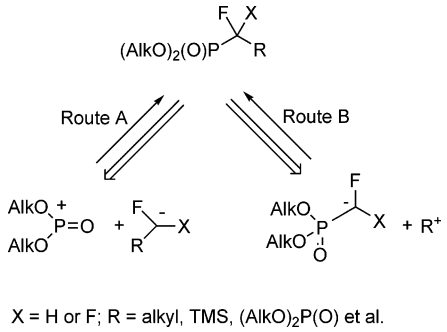


containing non-hydrolyzable analogues of phosphotyrosyl residues.[18,133−136]

2.4. Methodology Employing Fluorinated Phosphonate Carbanions

Most bioactive fluorinated phosphonates are multifunctional molecules often requiring, in a retrosynthetic analysis, the reaction between either an electrophilic phosphorus and a nucleophilic, fluorinated carbon or an electrophilic carbon and a nucleophilic, fluorinated phosphonate derivative (typically an anion of phosphonate). The first route (A) represents the carbon−phosphorus bond-forming strategy, and the second route (B) represents the carbon−carbon bond-forming reactions based on α-fluoroalkylphosphonate carbanion and functionalized carbon electrophile (Scheme 28). In principle, these two strategies complement each other. However, difficulties encountered in the design of the carbanions derived from highly functionalized species hinder a wider use of the reactions proceeding via attack of the fluorinated carbanion at the P^V center. In practice, the carbon−phosphorus bond-forming reactions are only useful for the preparation of simple fluorinated phosphonates. A typical example is represented by the efficient synthesis of $(EtO)_2P(O)CHFSO_2Ph$ from $ClP(O)(OEt)_2$ and $[PhSO_2CHF]^-Li^+$ in THF at −65 °C.[137] The anion of FCH_2CN works equally

Scheme 28



X = H or F; R = alkyl, TMS, $(AlkO)_2P(O)$ et al.

well with $ClP(O)(OEt)_2$ under similar conditions.[138] Only a few other reactions using dialkyl chlorophosphate and fluoroalkyl organometallics have been reported.[139]

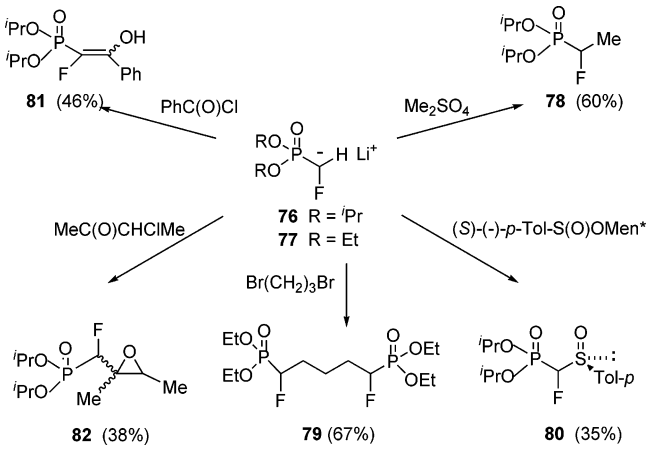
In the last decade, the carbon−carbon bond-forming strategy based on the use of α-fluorophosphonate carbanions has been widely recognized as a versatile approach to $(RO)_2P(O)CHF$- and $(RO)_2P(O)CF_2$-functionalized molecules.[20−22,140,141] The anions $[(RO)_2P(O)CXF]^-$, where X = H, F or any suitable functional group, can be readily generated starting from the corresponding phosphonate esters by standard deprotonation or halogen/metal exchange reactions and attached to a range of organic electrophiles. Many of the α-fluorophosphonate carbanions show enhanced stability compared to the corresponding nonphosphorylated carbanions and thus are easily handled and studied. Last, α-fluorophosphonate carbanions allow shorter synthetic routes by avoiding, for example, the use of protection−deprotection steps, as well as functional group interconversions.

2.4.1. Synthesis via α-Monofluoroalkylphosphonate Carbanions

In 1983, Blackburn and Parratt demonstrated that the α-hydrogen of diisopropyl fluoromethylphosphonate, $(^iPrO)_2P(O)CH_2F$, was sufficiently acidic to undergo metalation with LDA in THF at low temperature.[30,142] The lithiated carbanion $[(^iPrO)_2P(O)CHF]^-\ Li^+$ (**76**) was found to be rather stable and could be used in reactions at temperatures ranging from −78 to 0 °C. The diethyl analogue $[(EtO)_2P(O)CHF]^-Li^+$ (**77**) has proven to be even less thermally stable. When a sample of **77** was kept at −78 °C for 60 min before quenching with a saturated solution of KH_2PO_4, only 49% of starting material was recovered. For the diisopropyl ester **76**, 70% of the starting compound was recovered after stirring at 20 °C for 60 min.[100] Thus, the presence of branched alkyl chains strongly enhances the stability of dialkyl lithiofluoromethylphosphonates. Generation of the lithiated anion **77** was also successfully accomplished with PhLi and LiHMDS, but the reaction did not proceed well with ^{n}BuLi and gave products resulting from P−C bond fragmentation.[143]

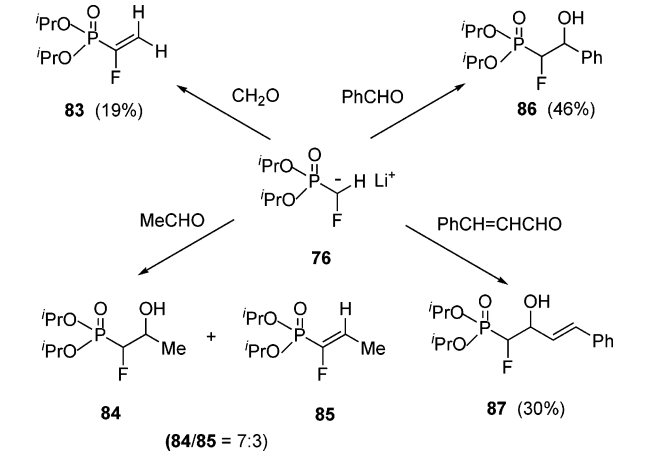
The lithiated carbanions **76** and **77** behave as typical organometallic reagents and can participate in various substitution reactions (Scheme 29).[30,142,143] Methylation of the anion **76** with dimethyl sulfate gives the phosphonate **78** and alkylation of **77** with 1,3-dibromopropane provides the bisphosphonate **79**. Reaction between **76** and (*S*)-(−)-menthyl toluenesulfinate occurred with complete inversion of configuration to give the corresponding (S_s)-fluoro-(*p*-tolylsulfinyl)methylphosphonate **80** as a mixture of diastereomers.[144] Acylation of **76** using benzoyl chloride occurred smoothly to give α-fluoro-β-oxoalkylphosphonate **81**, which exists exclusively as an *E*/*Z* mixture of enol form. The

Scheme 29



reaction of **76** with 3-chlorobutan-2-one provides the β,γ-epoxy-α-fluoroalkylphosphonate **82** by a Darzens-type reaction.[30] Treatment of **76** or **77** with chloro- or bromotrimethylsilane gives a mixture of mono- and bis-silylated derivatives because of facile proton transfer.[142] The carbanion **76** adds to a variety of aldehydes and ketones leading to α-fluoro-β-hydroxyalkylphosphonates, which sometimes spontaneously undergo dehydration to α-fluorovinylphosphonates (Scheme 30).[30] Since no dehydration was observed to

Scheme 30

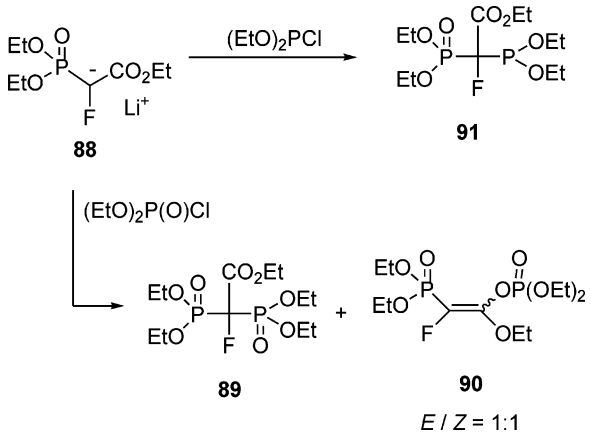


accompany the formation of products **86** and **87**, where a conjugated double bond could be formed, the stereochemical factors appear to determine whether dehydration occurs.

Metalation of α-fluorophosphonate esters of the type $(RO)_2P(O)CH(EWG)F$ bearing an electron-withdrawing functional group (EWG) on the α-carbon atom (e.g., CN, CO_2R, S(O)Ar, SO_2Ph, PO_3R_2, or $SiMe_3$) smoothly proceeds in polar solvents (THF, DME, or DMF) with bases such as ^{n}BuLi, LDA, or LiHMDS (Table 6).[36,37,72,119,138,143−152] Reactivity of these highly stabilized carbanions has been the focus of many studies.[21,153] The main points of interest here are (i) the elaboration of the phosphonate skeleton using alkylation reactions and (ii) the use of fluorinated phosphonate carbanions as Horner−Wadsworth−Emmons (HWE) or Peterson olefination reagents.

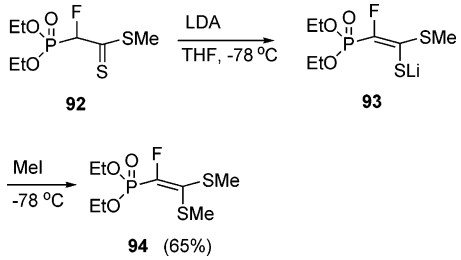
2.4.1.1. Alkylation and Related Reactions. The lithiated anion $[(EtO)_2P(O)CF(CO_2Et)]^-Li^+$ **(88)** can be clearly alkylated with reactive alkyl halides, in particular methyl iodide and allyl and benzyl bromide to give the corresponding C-alkylated products in 60−85% yields.[154] The same type of reactivity was observed with acyl halides.[155] Unlike alkylation and acylation, silylation of **88** with Me_3SiBr proceeded predominantly at oxygen to form the silyl ketene acetal phosphonate, $(EtO)_2P(O)CF{=}C(OSiMe_3)OEt$, as a mixture of *E*/*Z*-isomers.[21] Diethyl chlorophosphate reacting with **88** produces a mixture of carbon- and oxygen-phosphorylated products **89** and **90** in a ratio of 2:3. However, treatment of **88** with $(EtO)_2PCl$ led exclusively to the C-phosphorylated product **91** (Scheme 31).[155]

Scheme 31



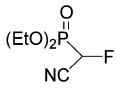
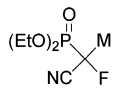
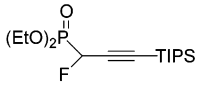
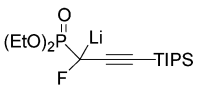
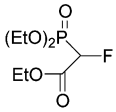
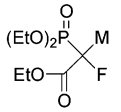
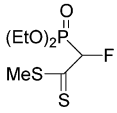
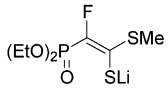
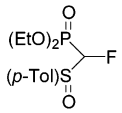
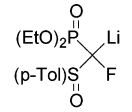
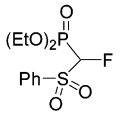
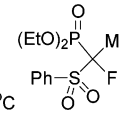
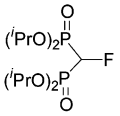
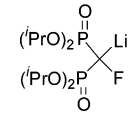
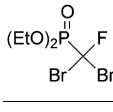
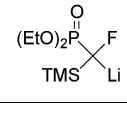
Interestingly, the NMR spectra of a THF solution of **88** indicated that the phosphonate carbanion had the negative charge localized on carbon exclusively rather than on oxygen.[21] By contrast, the metalated anion **93** generated from α-fluoro(phosphono)dithioacetate **92** by deprotonation with LDA, ^{n}BuLi, or ^{t}BuOK features the high stability of its enethiolate form. This anion reacted smoothly at −78 °C with iodomethane to give the ketene dithioacetal **94** (Scheme 32).[152]

Scheme 32

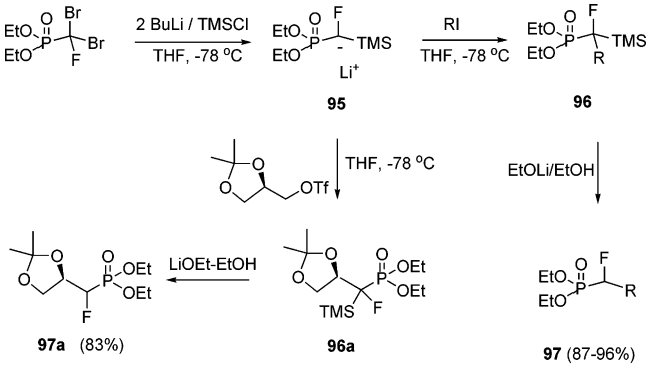


Patois and Savignac have described the generation of the lithiated carbanion $[(EtO)_2P(O)CF(SiMe_3)]^-Li^+$ (**95**) from readily accessible phosphonate $(EtO)_2P(O)CBr_2F$ by a double halogen−metal exchange reaction with ^{n}BuLi in the presence of trimethylsilyl chloride as the trapping agent.[156] The trimethylsilyl group has been shown to be useful as a protecting group for further elaboration of the phosphonate skeleton and as a directing group for a Peterson-type olefination (vide infra).[5,102] Carbanion **95** safely undergoes alkylation with alkyl iodides or triflates leading to the corresponding C-alkylated α-fluoroalkylphosphonate esters. Owing to the presence of an activating fluorine substituent, the C−Si bond in the phosphonates **96** is very sensitive, and the Me_3Si group was easily eliminated with EtOLi in EtOH to produce the α-monofluoroalkylphosphonates **97** in high yields and free of byproducts (Scheme 33).[11,143] Another illustration of the advantages of this methodology is provided

Table 6. In Situ Generation of Functionalized α-Metallo-α-monofluoromethylphosphonates

substrate	reagent	conditions	product	ref(s)
	^{n}BuLi NaH	THF, -78 °C DME, 20 °C		138 72
	LDA	THF, -80 °C		119
	^{n}BuLi NaHMDS	THF, -78 °C		36,148,149 151
	LDA	THF, -78 °C		152
	LDA	THF, -75 °C		144
	LiHMDS LDA KHMDS	THF THF, -60 °C THF-HMPA, -78 °C		146 147 150
	^{n}BuLi	THF, -78 °C		145
	^{n}BuLi (2 equiv) TMSCl	THF, -78 °C		37,143

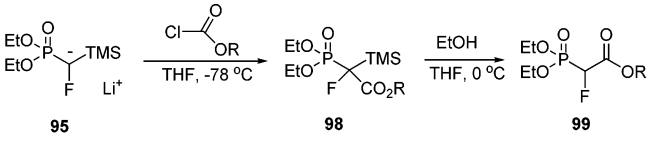
Scheme 33



R = Me, Et, Pr, Bu, H_2C=CH, MeCH=$CHCH_2$, C_5H_{11}, $Cl(CH_2)_3$, $C_{12}H_{25}$

by the synthesis of diethyl α-fluorophosphonocarboxylates **99** shown in Scheme 34. In the case of **98**, anhydrous ethanol was the preferred reagent to cleave the C−Si bond, whereas

Scheme 34

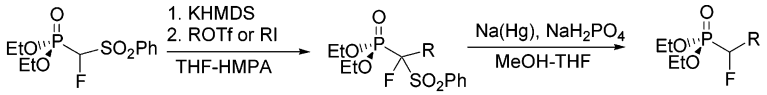


R = Me, CH_2Cl, Et, $(CH_2)_2Cl$, ^{i}Pr, ^{i}Bu, $CH=CH_2$, Ph

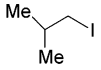
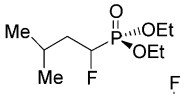
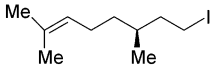
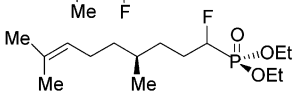
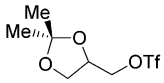
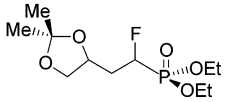
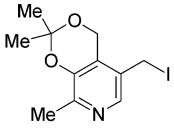
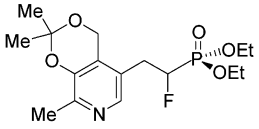
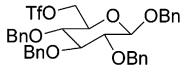
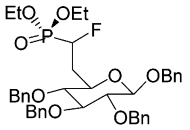
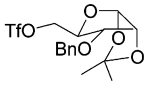
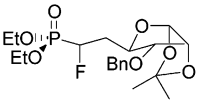
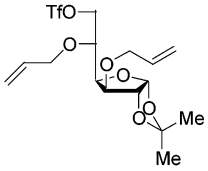
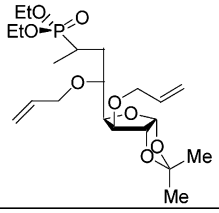
the use of alcoholic lithium ethoxide results in exclusive cleavage of the C−P bond.[35,157] The principle of masking of a proton of the methylene group by the Me_3Si group has also been applied to the preparation of functionalized tetraethyl methylenediphosphonates.[158] Deuteriolysis of the lithiated carbanions $[(EtO)_2P(O)C(SiMe_3)R]^-Li^+$ (R = alkyl, CH=CHMe, aryl, F, Cl, SEt) with heavy water followed by desilylation with LiOD is an excellent method for the incorporation of deuterium into functionalized phosphonates.[159,160] Two trimethylsilyl groups could be also attached without difficulty at low temperature to the carbanion **95** to give diethyl α-fluorobis(trimethylsilyl)methylphosphonate. On hydrolysis in THF using EtOLi−EtOH, the latter easily generates diethyl fluoromethylphosphonate, $(EtO)_2P(O)$-CH_2F.[143]

More recently, Berkowitz and co-workers have reported a convergent triflate displacement approach to α-monofluoroalkylphosphonates using alkylation of the phosphonate salt $[(EtO)_2P(O)CF(SO_2Ph)]^-K^+$ (Table 7).[150] Treatment of primary alkyl triflates or iodides with the carbanion derived from **100** yielded the corresponding α-fluoro-α-phenylsulfonylalkylphosphonates **101** in good yields. The elaborated phosphonates bearing terpenoid, glyceryl, furanose, and pyranose backbones could be efficiently constructed. To evaluate the counterion dependence of the nucleophilic displacement, several bases were examined, the isopropylidene-protected glyceryl triflate serving as the model electrophile. KHMDS provided the best results, lower yields

Table 7. Triflate Displacement Approach to α-Monofluoroalkylphosphonates[150]

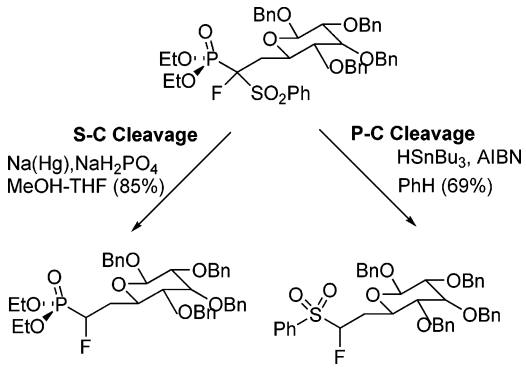


100 101 102

entry	triflate/iodide	**101**, % yield	product	**102**, % yield
a		71		79
b		69		80
c		68		89
d		50		71
e		60		85
f		78		80
g		66		78

being obtained with LiHMDS, NaHMDS, LDA, and Schwesinger's P1-^{t}Bu phosphazene base. No product was observed with ^{n}BuLi. The targeted α-fluoroalkylphosphonates **102** may be accessed with ease via Na(Hg)-mediated desulfonation. Other potential desulfonation methods including Al(Hg)/10% aqueous THF, Mg, $HgCl_2$/EtOH−THF, and SmI_2/HMPA−THF proved far less successful. Interestingly, $HSnBu_3$ under free radical conditions produces dephosphonylation of **101**, thereby providing a route to α-fluoroalkyl sulfones. An example provided in Scheme 35 illustrates the application of this manifold strategy.[150]

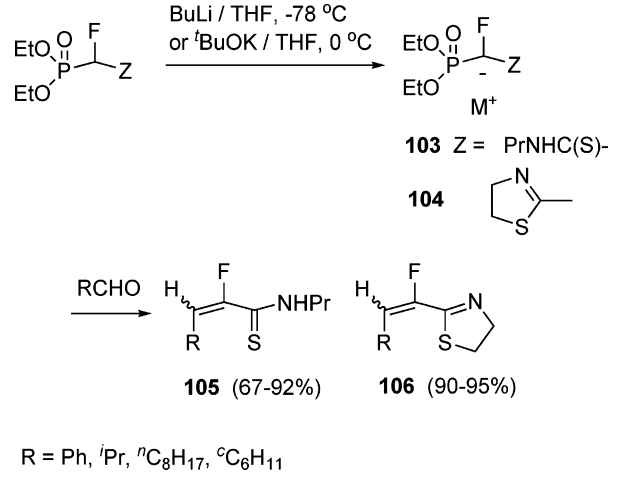
Scheme 35



2.4.1.2. The Use of Monofluorinated Phosphonate Carbanions as Olefination Reagents. α-Fluorocarbanions $[(RO)_2P(O)CF(EWG)]^-$ due to the relatively weak C−P bond are some of the most effective participants in the Horner−Wadsworth−Emmons (HWE) reaction.[21,153] Indeed, in contrast to the mildly stabilized $[(RO)_2P(O)CHF]^-$ anions, which commonly add to aldehydes and ketones to deliver α-fluoro-β-hydroxyphosphonates (vide supra), the carbanions $[(RO)_2P(O)CF(EWG)]^-$ react with carbonyl compounds to form various types of functionalized fluoroalkenes. For example, the lithiated anion $[(EtO)_2P(O)CF(CO_2Et)]^-$ (**88**) affords α-fluoro-α,β-unsaturated esters $R^1R^2C{=}C(F)CO_2Et$ by the HWE reaction with aldehydes and ketones.[148,161−164] Although the carbanion derived from phenylsulfonylmethylphosphonate **100** could in principle react with carbonyl substrates to yield either vinylphosphonates $R^1R^2C{=}C(F)P(O)(OEt)_2$ or vinyl sulfones $R^1R^2C{=}C(F)SO_2Ph$, these reactions uniformly create α-fluorovinyl sulfones. Subsequent reductive removal of the phenylsulfonyl group provides a facile two-step route to vinyl fluorides.[146,147,165−167] The HWE condensation of the lithiated carbanion $\{[(RO)_2P(O)]_2CF\}^-$ with aldehydes and ketones is a general route to α-fluorovinylphosphonates $R^1R^2C{=}C(F)P(O)(OR)_2$.[101,145,168,169] In the case of unsymmetrical diphosphonate, the reaction is accompanied by the elimination of the more electrophilic phosphorus moiety. No reaction

occurred when the phosphonodithioacetate anion **93** was treated with benzaldehyde or nonanal. Nevertheless, as shown in Scheme 36, the α-fluoro-α,*β*-unsaturated thioamides **105**

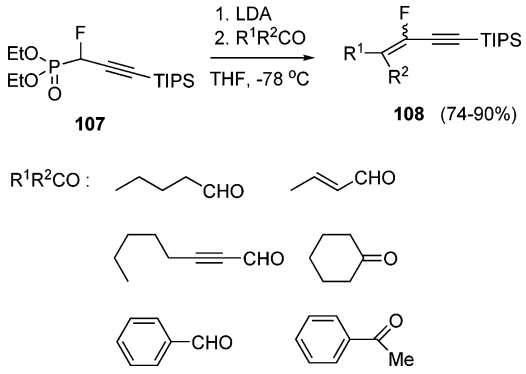
Scheme 36



R = Ph, ^{i}Pr, $^{n}C_8H_{17}$, $^{c}C_6H_{11}$

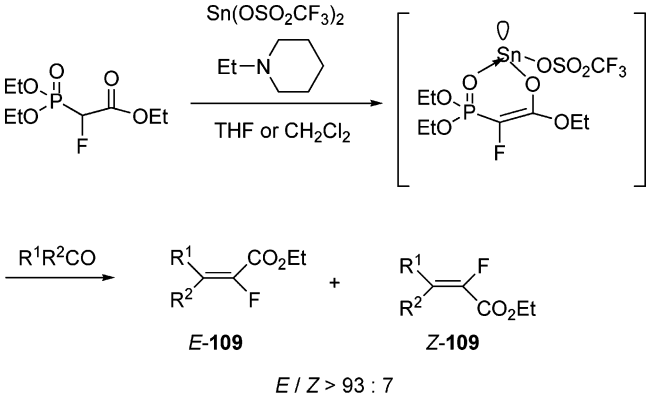
or α-fluorovinylthiazolines **106** have been successfully prepared via the corresponding phosphonothioacetamide or phosphonomethylthiazoline anions. The potential of this method for the synthesis of modified peptides and glycosides was illustrated through the preparation of the vinylogous dipeptide Ser-Phe precursor from Garner's aldehydes and modified glycosides from galactosaldehyde.[152] A new entry into the conjugated fluoro-1,3-enynes and fluoroenediynes using reaction of carbonyl compounds with the lithiated carbanion derived from **107** has been explored by Hammond and co-workers (Scheme 37).[119]

Scheme 37



The *E*/*Z* ratio of fluoroalkenes formed in the reactions of α-fluorophosphonate carbanions with carbonyl substrates varies with the nature of reagents and reaction conditions. Normally, the lithiated anions $[(RO)_2P(O)CF(CO_2Et)]^-$ supply mainly the less hindered *E*-fluoroalkenes in HWE reactions with aldehydes;[148,149,151,161,170] however, there are some notable exceptions. For example, the stereoselective HWE reaction of aromatic and α,*β*-unsaturated aldehydes with $(EtO)_2P(O)CHFCO_2H$ utilizing ^{n}BuLi or ^{i}PrMgBr afforded (*Z*)-α-fluoro-α,*β*-unsaturated carboxylic acids as the major products.[164,171] With ketones, a lower stereoselectivity was observed, and the major isomer appears to have the phosphoryl group trans to the more bulky ketone substituent. Excellent *E*-selectivity was observed in the $Sn(OSO_2CF_3)_2$-mediated HWE reaction of $(EtO)_2P(O)CHF(CO_2Et)$ with alkyl aryl ketones using *N*-ethylpiperidine as base.[172,173] The stereochemical outcome with high *E*-selectivity in this reaction can be rationalized in terms of a six-membered transition state involving Sn^{II} chelation as shown in Scheme 38. Subsequently, this methodology was extended to the

Scheme 38

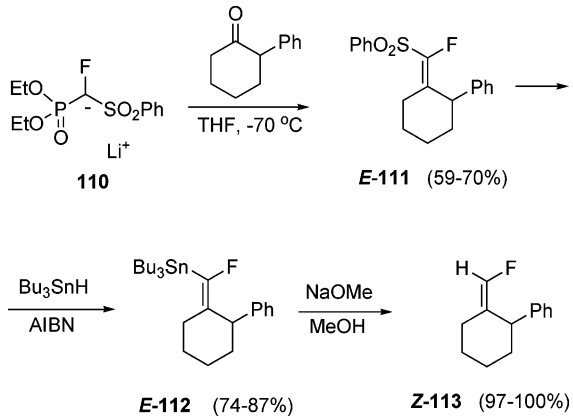


R^1 = Ph, 2-naphthyl, R^2 = Me, Et, ^{i}Pr, ^{t}Bu

reaction of 2-fluoro-2-diethylphosphonoacetates with *σ*-symmetric prochiral 2-substituted-1,3-dioxan-5-ones and 4-substituted-cyclohexanones employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in the presence of an external chiral ligand, (*S*)-(−)-1-methyl-2-(1-piperidinomethyl)pyrrolidine. A chiral α-fluoro α,*β*-unsaturated ester was obtained in up to 80% ee.[174]

α-Fluoro-α-cyanomethylphosphonate anions, $[(RO)_2P(O)CF(CN)]^-$, are anomalous compared to their carbalkoxy counterparts in that they produce mixtures of *Z* and *E* isomers in the range of 4:1 to 1:2.[72,138] The HWE reaction between deprotonated diethyl (S_s)-fluoro-(4-tolylsulfinyl)methylphosphonate, $(EtO)_2P(O)CHF[S^*(O)Tol\text{-}4]$, and aldehydes was found to occur with complete conversion, showing only moderate but consistent *E*-selectivity for butyraldehyde (*E*/*Z* = 70:30), crotonaldehyde (*E*/*Z* = 70:30), and benzaldehyde (*E*/*Z* = 83:17).[144] Addition of fluorinated phenylsulfonylmethylphosphonate and methylenebisphosphonate anions to aldehydes typically results in *E*-fluoroalkenes, although a number of significant nuances have arisen.[147,166,167] The reaction in Scheme 39 constitutes a procedure from *Organic*

Scheme 39

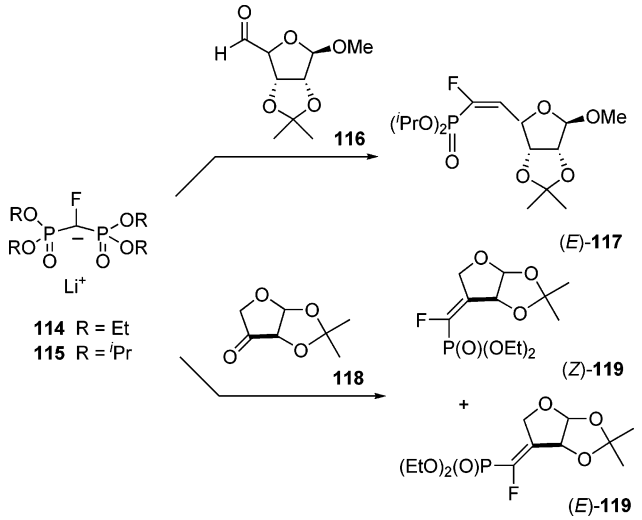


Syntheses that illustrates the application of the lithiated carbanion **110** for stereoselective synthesis of 2,2-disubstituted 1-fluoroalkenes. In the example described, only *E*-fluorovinyl sulfone **111** is formed, which is converted into

Z-fluoroalkene **113** with complete retention of configuration.[146] This reaction sequence has been used for the stereospecific synthesis of fluoroalkene nucleosides.[165]

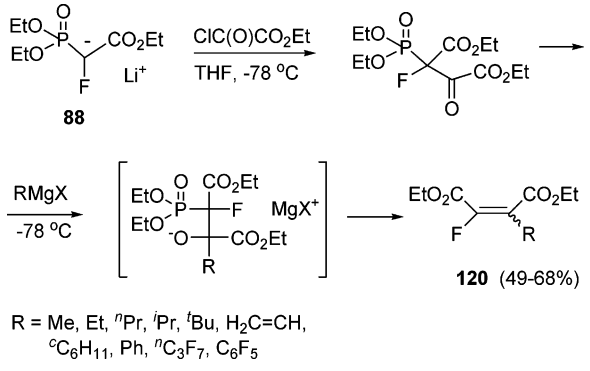
The anion of tetraisopropyl or tetraethyl fluoromethylene bisphosphonate condensed with aldehydes to give fluorovinylphosphonate consisted predominantly of the *E*-alkene. Thus, *E*-fluorovinylphosphonate **117** was obtained exclusively upon reaction of **115** with methyl 2,3-*O*-isopropylidene-β-D-ribo-pentodialdehydo-1,4-furanoside **116**.[145,169] A lower product stereoselectivity was observed for ketones. With ketone **118**, the α-fluorovinylphosphonate **119** was isolated as mixture of *Z*- and *E*-isomers in a 2:3 ratio (Scheme 40).[168]

Scheme 40



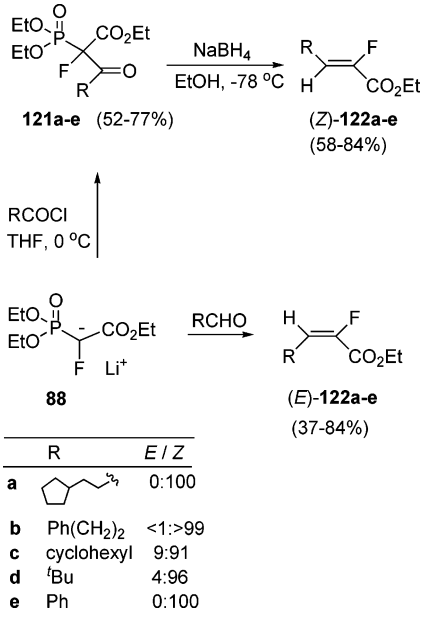
As mentioned above, acylation of **88** is conveniently achieved by using acid chlorides or anhydrides.[155] Hydrolytic cleavage of the formed bis-acylated phosphonates offers an attractive possibility of synthesizing α-fluoro-β-keto esters,[175] α-fluoro-β-keto phosphonates,[176] and α-fluoromalonates.[177,178] Also the carbonyl group of the acylated products derived from acyl chloride was subjected to a nucleophilic attack to form betain-type intermediates, which then underwent intramolecular HWE processes to give α-fluoro-α,β-unsaturated esters. For instance, acylation of **88** ethyl oxalyl chloride followed by in situ reaction with Grignard reagents provides a direct entry to potentially useful α-fluoro-α,β-unsaturated diesters **120** (Scheme 41). The method is applicable to

Scheme 41



primary, secondary, and tertiary alkyl, alkenyl, alkynyl, aryl, cyclohexyl, and perfluorinated Grignard reagents. A high degree of *E*-stereoselectivity was observed in most of the reactions reported. Thus the *E*-isomer is the exclusive product when R = Me, ^{i}Pr, ^{t}Bu, and cyclohexyl. The *E*-isomer also predominates (96%) when R = Me and ^{n}Pr. However, *Z*-stereoselectivity increases when R = Ph and H_2C=CH. If R = C_3F_7 (*E*/*Z* = 0:100) or C_6F_5 (*E*/*Z* = 90:10), the *Z*-isomers were defined when R_F and F were at the same side of the double bond in products **120**.[36,179] Sodium borohydride was also used as a nucleophile in these reactions. When $NaBH_4$ was added to the solution of phosphonate **121e** in EtOH at −78 °C, (*Z*)-α-fluoro-α,β-unsaturated ester **122e** was obtained in 83% yield as the sole product. All the other tandem reduction−olefination reactions of α-acylphosphonates **121** afforded (*Z*)-**122** with excellent *Z*-selectivity in a range of *E*/*Z* ratio of 9:91 to 0:100 in 58−84% yields. A plausible mechanism involving a diastereoselective reduction predicted by the Felkin−Anh model, followed by olefination similar to the HWE reaction, has been proposed. It is noteworthy that the direct HWE reaction of **88** with the corresponding aldehydes resulted in *E*-fluoro-α,β-unsaturated esters **122** (Scheme 42).[180]

Scheme 42



When the phosphonate carbanion $[(EtO)_2P(O)CF(TMS)]^-$ reacted with carbonyl compounds in THF at −78 °C, an unambiguous preference for the Peterson over the HWE reaction was observed (Scheme 43).[30,37,181,182] In this case, the trimethylsilyl group acts as a directing substituent. By analogy to the HWE process, the reaction pathway is assumed to involve a four-membered transition state. Of the two configurations (**A** and **B**) of β-oxidosilanes that have the syn alignment of alkoxide and silicon, **A** with R^1 = H or R^1 smaller than R^2 is preferable on steric grounds. As shown in Table 8, aliphatic aldehydes give a mixture of *E*- and *Z*-isomers in nearly equal amounts. With aromatic or heteroaromatic aldehydes, the *E*-isomers were produced as main products (**124e**−**k**) corresponding to a preference for the configuration **123A**. When the reaction of **95** was extended to ketones, the product composition seemed to be dependent on steric factors, and the respective *Z*-isomers were produced as main products (**124l**−**t**) corresponding to a preference for the configuration **123B**.[37]

Scheme 43

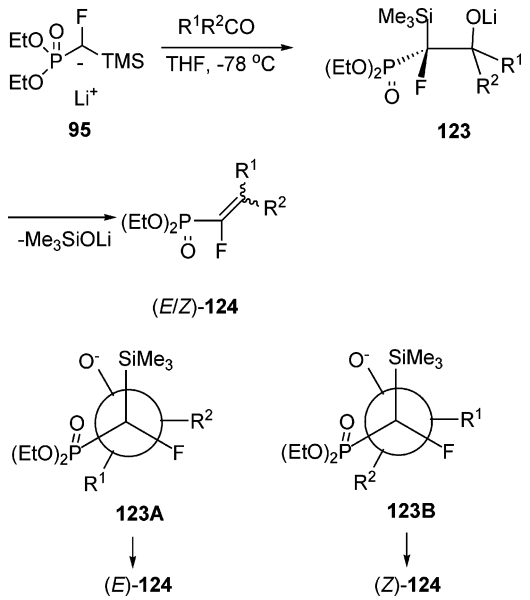


Table 8. α-Fluorovinylphosphonates 124 Obtained by the Reaction of the Lithiated α-Fluoro-α-trimethylsilylmethylphosphonate 95 with Aldehydes and Ketones[37]

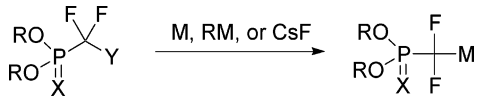
carbonyl compound	product **124**	yield (%)	*E* (%)	*Z* (%)
$PhCH_2CH_2CHO$	**a**	86	49	51
PhCH(Me)CHO	**b**	87	49	51
Et(Me)CHCHO	**c**	80	50	50
^{t}BuCHO	**d**	77	36	64
PhCHO	**e**	82	74	26
p-$MeOC_6H_4CHO$	**f**	91	70	30
p-$Me_2NC_6H_4CHO$	**g**	90	76	24
furan-2-carboxaldehyde	**h**	92	80	20
1-methylpyrrole-2-carboxaldehyde	**i**	67	76	24
thiophene-2-carboxaldehyde	**j**	93	78	22
pyridine-2-carboxaldehyde	**k**	52	85	15
p-$BrC_6H_4(Me)CO$	**l**	90	24	76
cyclo-Pr(Me)CO	**m**	75	62	38
cyclo-Pr(Ph)CO	**n**	67	31	69
$Me_2CH(Me)CO$	**o**	39	40	60
(−)-carvone	**p**	87	0	100
isophorone	**q**	84	0	100
α-tetralone	**r**	52	0	100
2-methylcyclohexan-2-one	**s**	62	0	100
2-methoxycyclohexan-2-one	**t**	80	24	76

2.4.2. Synthesis via α,α-Difluoromethylphosphonate Carbanions

The focus of discussion here will be on reactions in which the $(RO)_2P(O)CF_2M$ species, where M = Li, MgCl, ZnBr, CdBr, and Cu (Table 9), act as a masked $[(RO)_2P(O)CF_2]^-$ carbanionic equivalent. These can be prepared by a variety of methods of which the main ones are (i) deprotonation of $(RO)_2P(O)CF_2H$ with a suitable organometallic base,[29,183] (ii) halogen−metal exchange between $(RO)_2P(O)CF_2Br$ and alkyl lithium or Grignard reagent,[38,184−186] (iii) direct insertion of metal (Zn or Cd) into the carbon−halide bond of $(RO)_2P(O)CF_2Br$ or $(RO)_2P(O)CF_2I$,[187,188] (iv) thiophilic reaction of $(RO)_2P(O)CF_2SMe$ with *tert*-butyl lithium,[130,189] and (v) desilylation of $(RO)_2P(O)CF_2SiMe_3$ initiated by means of fluoride ion.[102,190]

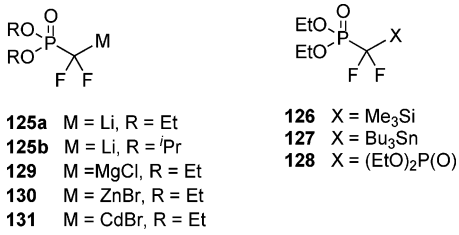
Diethyl lithiodifluoromethylphosphonate (**125a**) was first prepared more than 20 years ago by addition of LDA to $(EtO)_2P(O)CF_2H$ in THF at −78 °C.[29] The phosphonodifluoromethyl anion is thermally unstable and at 0 °C rapidly dissociates to form lithio diethyl phosphite and difluorocarbene. As a consequence, the successful preparation of **125a** requires low reaction temperatures and the use of THF as a solvent either on its own or admixed with other solvents. When **125a** is treated with reactive halides such as Me_3SiCl, Bu_3SnCl, and $(EtO)_2P(O)Cl$, the expected functionalized phosphonates **126**−**128** are produced in good yields.[184,190] The silicon derivative **126** was also prepared by electrochemical reaction of $(EtO)_2P(O)CF_2Br$ in DMF and Me_3SiCl using a zinc anode at a current density of 10 $mA\cdot cm^{-2}$ (Chart 4).[191] When **125a** was treated with $B(OMe)_3$, the boron-stabilized carbanion $(EtO)_2P(O)CF_2B(OMe)_3^-$ Li^+ is formed in almost quantitative yield.[192]

Table 9. Reagents and Reaction Conditions for the Preparation of Metallodifluoromethylphosphonates



X	Y	reagent	conditions	M	ref(s)
O	H	LDA	THF, −78 °C	Li	29,48
O	Br	^{n}BuLi	THF, −78 °C	Li	38,184
O	SMe	^{t}BuLi	THF, −78 °C	Li	189
O	$SiMe_3$	CsF	THF, −78 °C	Cs	102,190
O	Br	^{i}PrMgCl	THF, rt	MgCl	38,184
O	Br	Zn	monoglyme, rt	ZnBr	187,194
O	Br	Cd	triglyme, 70 °C	CdBr	188
O	ZnBr	PhHgCl	THF, rt	HgPh	46
O	ZnBr	CuBr	DMF, rt	$CuZnBr_2$	20
O	CdBr	CuBr	DMF, rt	$CuCdBr_2$	20
S	H	LDA	THF, −78 °C	Li	183
S	Br	^{t}BuLi	THF, −78 °C	Li	185
S	Br	^{i}PrMgCl	THF, rt	MgCl	186

Chart 4



125a M = Li, R = Et
125b M = Li, R = ^{i}Pr
129 M =MgCl, R = Et
130 M = ZnBr, R = Et
131 M = CdBr, R = Et

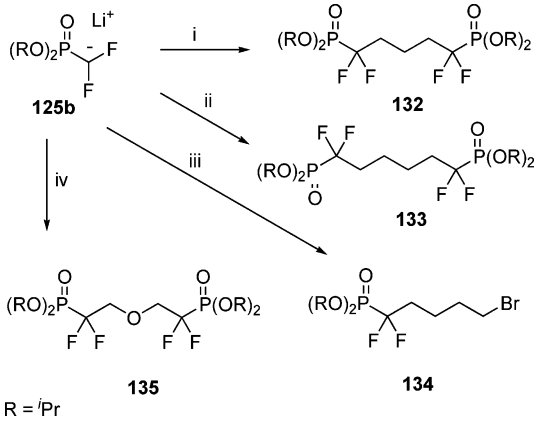
126 X = Me_3Si
127 X = Bu_3Sn
128 X = $(EtO)_2P(O)$

In view of the instability of the lithium reagent, the easily handled magnesium, zinc, and cadmium derivatives **129**−**131** offer better potential as $(RO)_2P(O)CF_2$ transfer agents. The Grignard reagent **129** has been prepared by metal−halogen exchange between $(EtO)_2P(O)CF_2Br$ and ^{i}PrMgCl.[184] This organomagnesium compound is stable for several days at low temperature. Attempts to directly generate **129** from $(EtO)_2P(O)CF_2Br$ and activated magnesium resulted in red-black solutions of unpredictable behavior.[186] The zinc and cadmium reagents **130** and **131** have been studied extensively by Burton and co-workers.[20−22] Both compounds may be synthesized by treatment of $(EtO)_2P(O)CF_2Br$ with acid-washed zinc[187] or cadmium[188] powder in ethereal solvents such as THF, dioxane, monoglyme, or triglyme at room temperature to 60 °C. Organozinc **130** can be stored in ethereal solvents at room temperature for several months without change. Cadmium derivative **131** can be heated at 70−100 °C for a few hours without significant decomposition. As expected, the zinc and cadmium reagents are not as reactive as the lithium reagent, but their low reactivity presents a potential advantage for the preparation of phos-

phonates bearing sensitive functionalities. Moreover, the excellent transmetalation ability of organozinc compounds permits the conversion of these species into a variety of new organometallics. In fact, the reactivity of the C−Zn and C−Cd bonds toward electrophilic substrates can be improved by transmetalation of **130** or **131** to copper derivatives, which react with various classes of alkyl halides or acid chlorides.[42,193−196] Some of these cross-coupling reactions can be performed using catalytic amounts of copper(I) salts.

2.4.2.1. Coupling with Organyl Halides and Triflates. Obayashi and co-workers first reported that ethyl bromide and butyl bromide, as well as alkyl chlorides, undergo displacement reactions with lithiated carbanion **125a** to give the desired α,α-difluoroalkylphosphonates.[29] However, subsequent workers have found that alkyl halides do not always readily undergo displacement reactions with $[(RO)_2P(O)CF_2]^-$ anions and that some of Obayashi's work is not reproducible at the published yields. The reported yields vary from 0% to 43% with simple primary alkyl iodides and bromides.[34,197−203]A recent work brings an example of the good-yielding reaction between $[(^iPrO)_2P(O)CF_2]^-$ anion and 1,3-dibromopropane (63%), but when 1,4-dibromobutane and bis-chloromethyl ether were allowed to react in similar conditions, the corresponding phosphonates **133**−**135** were obtained in poor yields (Scheme 44).[204] The problem seems to

Scheme 44[a]

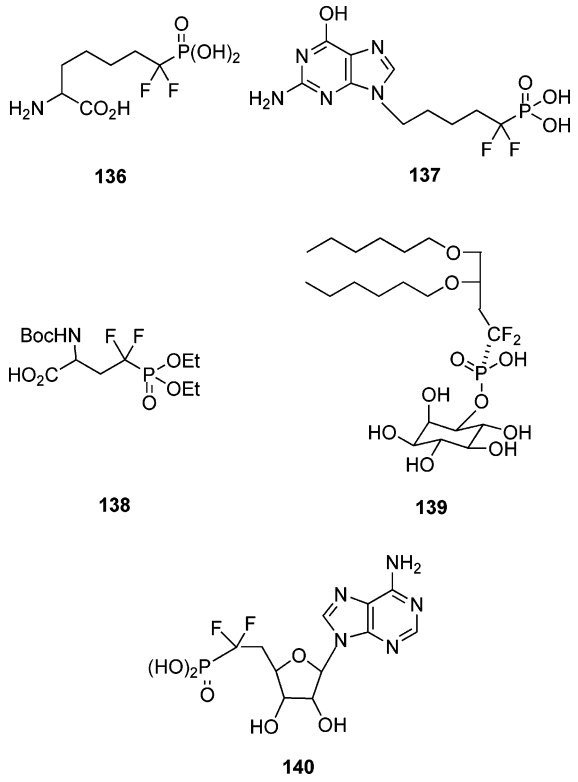


[a] Reagents: (i) 1,3-dibromopropane, 63%; (ii) 1,4-dibromobutane (0.5 equiv), 13%; (iii) 1,4-dibromobutane (1 equiv), 26%; (iv) bis-chloromethyl ether, 16%.

lie in the relatively weak nucleophilicity and thermal instability of the difluoromethylphosphonate anion.[194] Nevertheless, the nucleophilic substitution of primary alkyl bromides and iodides with lithiodifluoromethylphosphonates has been used in the preparation of several analogues of naturally occurring phosphates such as the amino acid derivative **136**[34] and the nucleoside phosphorylase inhibitor **137**[201] (Chart 5).

A much better synthesis of α,α-difluoroalkylphosphonates is based on the triflate displacement methodology.[198,205] Primary alkyl triflates and those derived from nucleosides and carbohydrates are cleanly displaced by $[(RO)_2P(O)CF_2]^-$ anions at −78 °C in THF−HMPA to provide the corresponding products in good yields (Table 10).[206] This procedure served as the key step in the synthesis of α,α-difluoroalkylphosphonate analogues of L-phosphoserine **138**,[207] phosphatidylinositol **139**,[208] and ribonucleoside monophosphates, for example, **140**.[209] The highly acidic hydrolytic reaction medium required for the deprotection of the alkyl esters commonly used for these syntheses may be overcome by the use of specific ester groups. For example, under appropriate conditions, the lithiated carbanions $[(RO)_2P(O)CF_2]^-$ (R = All or Bn) displace alkyl triflates to form the corresponding phosphonates carrying allyl or benzyl ester groups. Diallyl phosphonates can be smoothly deprotected under Pd^0 catalysis,[210] and deprotection of dibenzyl derivatives may be achieved by simple hydrogenolysis.[206]

Chart 5



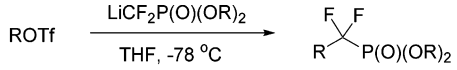
Both the zinc and cadmium reagents **130** and **131** are too weak nucleophiles to react directly with nonactivated alkyl halide substrates. However, they do react with allyl and benzyl halides to give the corresponding difluoromethylenephosphonate derivatives.[45,194,211] For example, the reaction of **131** with allyl bromide affords a versatile synthetic intermediate, $(EtO)_2P(O)CF_2CH_2CH{=}CH_2$ (62%), which is a key compound in the preparation of difluoromethylenephosphonate analogues of glycolytic phosphates.[212] With 2-bromomethylacrylic acid and methyl 2-(bromomethyl)-acrylate as substrates, similar reactions proceed in the presence of copper(I) bromide.[211]

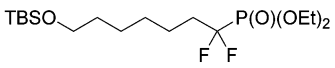
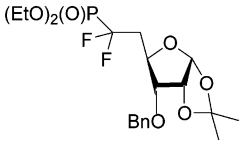
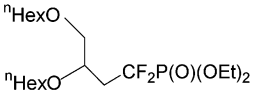
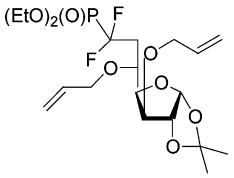
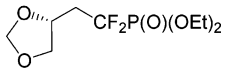
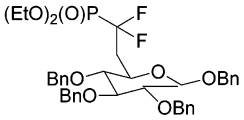
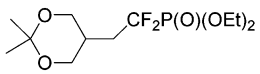
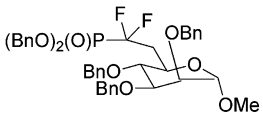
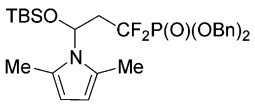
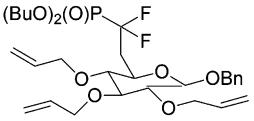
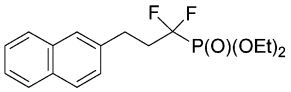
As a further development of the nucleophilic displacement methodology, the synthesis of the chiral building block **144** on a large scale has been achieved as shown in Scheme 45.[213] The coupling reaction of the copper species, generated from zinc reagent **130** and copper(I) bromide, with allylic phosphate **142** leads to the functionalized 1,1-difluoro-but-3-enylphosphonate **143** in 79% yield. The same authors used cyclohex-2-enyl-1-phosphates as precursors to highly oxygenated cyclohexene derivatives having $(EtO)_2P(O)CF_2$ functionality.[214]

Synthesis of allenic α,α-difluoromethylenephosphonates from propargylic tosylates and acetates using the organocopper species, generated from **130** and stoichiometric amounts of copper(I) bromide, has been recently described by Shibuya and co-workers.[215] Conditions of the reactions are disclosed in Table 11.

2.4.2.2. Coupling with Alkenyl and Alkynyl Halides. The presumed organometallic $(EtO)_2P(O)CF_2Cu{\cdot}ZnBr_2$, gen-

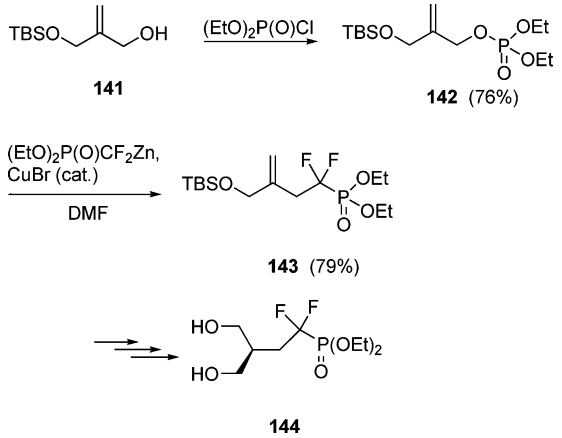
Table 10. Preparation of α,α-Difluoromethylenephosphonates by Displacement of Primary Triflates



phosphonate	yield (%)	ref.	phosphonate	yield (%)	ref.
	60	198		83	198
	88	208		65	198
	63	207		79	198[a]
	-	213		47	206
	55	206		50	206
	59	198			

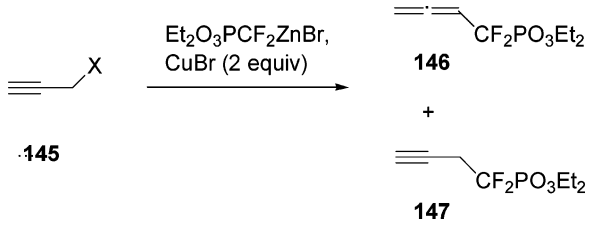
[a] See numerous examples of displacements with D-glucopyranose triflates in ref 198.

Scheme 45



erated by the transmetalation of the zinc reagent **130** with copper(I) bromide in DMF or DMA, readily undergoes cross-coupling under sonification conditions with a variety of iodoalkenes and iodoarenes to give α,α-difluoroallyl- or α,α-difluorobenzyl-phosphonate derivatives in high yield (Shibuya−Yokomatsu coupling).[141,216−219] Some typical examples are listed in Table 12. Both *E*- and *Z*-alkenyl halides possessing aliphatic substituents at the *β*-position were found to react with complete retention of the starting geometry. Based on the experimental results, the following mechanism

Table 11. Copper(I) Bromide-Promoted Reactions of $(EtO)_2P(O)CF_2ZnBr$ (130) with Propargylic Substrates[215]

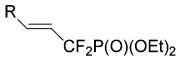
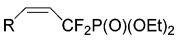
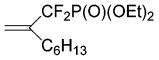
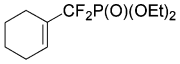


145 (X)	conditions	**146**/**147**[a]	yield (%)
Br	THF, rt	98/2	53
Br	DMF, rt	>99/<1	89
OTs	THF, rt	85/15	80
OTs	DMF, rt	>99/<1	80
OCO_2Me	DMA,[b] rt	>99/<1	26

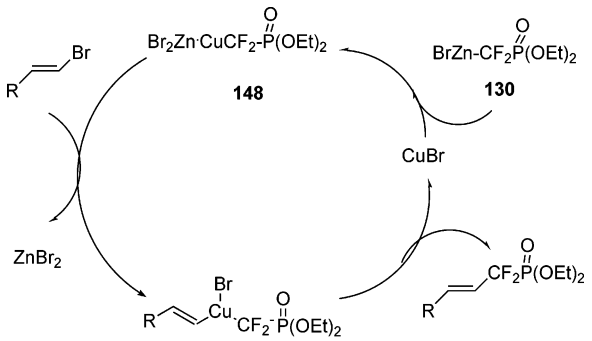
[a] The ratio was determined by ^1H NMR analysis. [b] The reaction was carried out under ultrasound irradiation.

has been proposed: transmetalation of **130** to **148**, followed by oxidative addition to alkenyl halide, gives presumed intermediate **149**, which reductively eliminates CuBr to give the coupling product with retention of stereochemistry (Scheme 46).[216] Remarkably, the reaction tolerates the presence of a broad range of functional groups (Cl, Br, RO, CH_2OAc, NO_2, and CO_2Me). Perfluoroalkanesulfonyl groups (e.g., TfO or $C_4F_9SO_3$) are also accepted as functional groups

Table 12. Shibuya−Yokomatsu Coupling Reactions with Alkenyl Halides

substrate	product	yield (%)	ref(s)
			
R = 4-MeOC$_6$H$_4$	X = Br	49	216
^{n}Bu	I	81	216
THPOCH$_2$	I	76	216,219
THPOCH$_2$CH$_2$	I	93	218
THPO(CH$_2$)$_4$	I	90	216
H$_2$C=CHOCH$_2$	I	84	219
			
R = THPOCH$_2$	X = I	86	216
CO$_2$H	Cl	20	211
		62	216
			
X = I		76	216
OTf		0	216

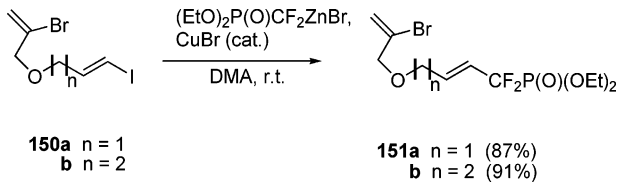
Scheme 46



149

in this repertoire of reactions; in other words, triflates and nonaflates are inefficient substrates for the Shibuya−Yokomatsu coupling. However, reaction conditions are critical for inducing a good yield. All these reactions proceed much faster in DMA or DMF as the solvent than in THF, but they are especially accelerated by ultrasound irradiation. For example, a CuBr-mediated reaction of alkenyl iodides **150a**,**b** with the zinc reagent **130** in DMA proceeded selectively at the iodo-carbon to give the phosphonates **151a**,**b** in 87% and 91% yield, respectively (Scheme 47). However, the yield of

Scheme 47



these compounds was low (ca. 15%) and a substantial amount of starting material was recovered upon conducting the cross-coupling reaction in DMF without sonification.[220,221] Another example demonstrates the key cross-coupling step in the synthesis of 4′-phosphonodifluoromethyl-phenylalanine (F_2-Pmp) derivative **152** (82%). Presumably, the observed regiochemistry derives from the capacity of the benzoate ester to chelate and direct delivery of the organometallic species as well as the *ortho* directing effect of the ester on the incoming nucleophile (Scheme 48).[222]

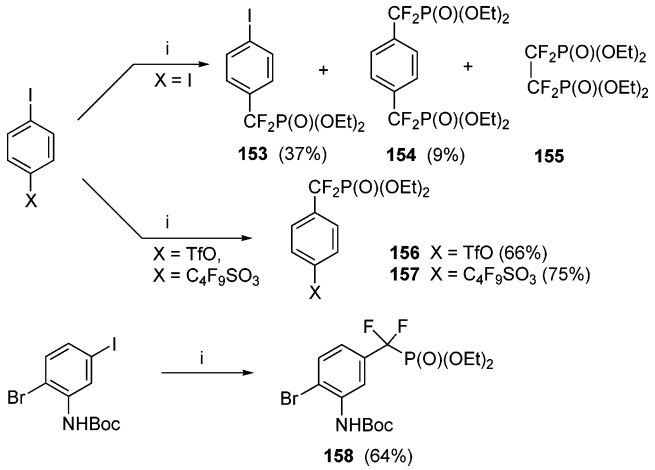
Scheme 48

152 (82%)

Cross-coupling of (EtO)$_2$P(O)CF$_2$ZnBr with 1-haloalkynes is an extremely slow reaction. However, the zinc reagent **130** reacts smoothly with 1-alkynyl halides Hlg−C≡CR (Hlg = Br or I) in the presence of CuBr to give good yields of α,α-difluoropropargylphosphonates, (EtO)$_2$P(O)CF$_2$C≡CR (R = Ph, C$_4$H$_9$, C$_5$H$_{11}$, C$_6$H$_{13}$, and C$_7$H$_{15}$). 1-Bromoalkynes generally gave higher yields of the products compared to 1-iodoalkynes, presumably due to minimum metal/halogen exchange.[223] Hammond and co-workers reported a similar successful coupling of (EtO)$_2$P(O)CF$_2$CdBr with TIPSC≡CI.[76]

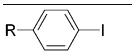
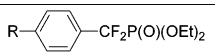
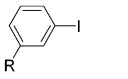
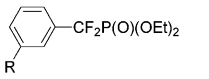
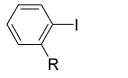
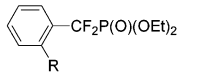
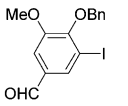
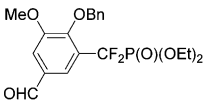
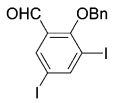
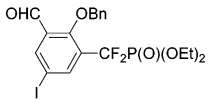
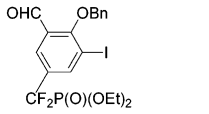
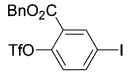
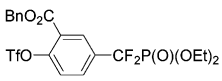
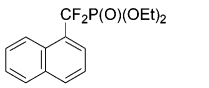
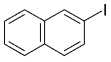
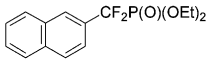
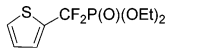
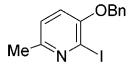
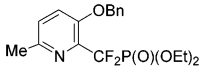
In a series of papers, Shibuya and co-workers[217,224−226] and others[196,222,227] adapted the copper(I) halide-mediated cross-coupling reactions for the production of α,α-difluorobenzylphosphonates and related heteroaromatic templates. The reaction of iodobenzene with the zinc reagent **130** in the presence of copper(I) bromide in DMA for 24 h under ultrasound irradiation leads to a good yield of (EtO)$_2$P(O)-CF$_2$Ph.[217] 1,4-Diiodobenzene underwent the CuBr-mediated cross-coupling with **130** to afford mono-coupled phosphonate **153** and bis-coupled **154**, which could be separated from each other and from homo-coupled **155** by simple column chromatography.[217] Higher yielding reactions were run with 4-(trifluoromethylsulfonyloxy)- and 4-(nonafluorobutylsulfonyloxy)-iodobenzenes **156** and **157**.[225,227] In a similar way, the polyfunctionalized phosphonate **158**, an excellent substrate for the synthesis of small molecular inhibitors of protein-tyrosine phosphatase 1B, has been synthesized in 64% yield (Scheme 49).[225] Table 13 summarizes additional

Scheme 49[a]



[a] Reagents and conditions: (i) (EtO)$_2$P(O)CF$_2$ZnBr (**130**), CuBr, DMA, rt, sonification.

Table 13. The Shibuya Cross-Coupling Reactions with Functionalized Benzenoid and Heteroaromatic Substrates

substrate	conditions[a]	product	yield (%)	ref.
				
R = Me	A		17	217
	B		64	217
R = MeO	C		17	227
R = Cl	A		42	217
R = CO_2Me	A		51	217
				
R = CH_2OAc	A		37	217
	B		54	217
R = MeO	C		32	227
R = CO_2Me	A		52	217
				
R = CH_2OAc	A		42	217
	B		51	217
R = CO_2Me	A		99	217
	C		25	227
	C		21	227
			19	227
	C		67	227
	C		85	217
	C		79	217
	C		62	227
	C		0	227

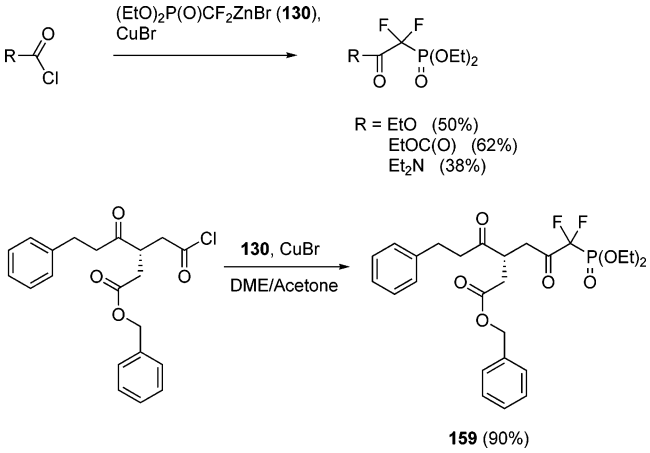
[a] All reactions were carried out at room temperature. Condition A: $(EtO)_2P(O)CF_2ZnBr$ (2 equiv), CuBr (2 equiv), DMF, ultrasound. Condition B: $(EtO)_2P(O)CF_2ZnBr$ (2 equiv), CuBr (2 equiv), DMA, ultrasound. Condition C: $(EtO)_2P(O)CF_2ZnBr$ (1.5 equiv), CuBr (1.5 equiv), DMA, ultrasound.

results with a range of aromatic templates.[227] Significantly, these reactions require a stoichiometric amount of copper bromide in contrast to the related coupling reactions with alkenyl halides, which proceed with a catalytic amount of copper(I) salt. This implies that the mechanism of the coupling reactions with aryl halides differs from that with alkenyl halides.

Last, the coupling reaction of the cadmium reagent **131** proceeds readily with aryl iodides in the presence of a stoichiometric amount of CuCl in DMF or triglyme to give good yields (65−88%) of α,α-difluorobenzylic phosphonates. A variety of functional groups, such as nitro, ether, ester, and halides, could be tolerated in the reaction. With halo-substituted aryl iodides, the reaction selectively gave products coupled at the iodine.[196]

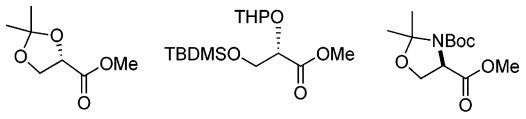
2.4.2.3. Coupling with Acyl Chlorides and Esters. The pioneering work by Burton and co-workers demonstrated that a wide range of α,α-difluoro-*β*-ketophosphonates, $(EtO)_2P(O)CF_2C(O)R$, can be synthesized via acylation of the zinc reagent **130** with acyl chlorides.[187] Ethyl chloroformate and diethylcarbamoyl chloride, however, do not react with **130**. Nevertheless, it was subsequently found that the reactivity of the zinc reagent can be augmented by cuprous bromide catalysis and that such catalysis allowed an efficient reaction to proceed with previously unreactive acyl halides.[42,193] The remarkable aspect of this coupling reaction is its high functional group tolerance, as exemplified by the synthesis of a difluoromethylene analogue of *β*-aspartyl phosphate **159** (Scheme 50).[228]

Scheme 50



An exceptionally useful variant of the $PCF_2-C(O)R$ bond formation was introduced by Berkowitz and co-workers, who found that the lithium reagent **130** is a sufficiently strong nucleophile to react with functionalized but inactivated methyl esters affording the corresponding α,α-difluoro-*β*-ketoalkylphosphonates in very good yield.[229] The synthetic potential of the method was illustrated by the simple synthesis of α,α-difluoro-*β*-ketophosphonates from methyl (*S*)-isopropylideneglycerate **160**, methyl (*S*)-3-*O*-(*tert*-butyldimethylsilyl)-2-*O*-tetrahydropyranylglycerate **161**, and the Garner ester derived from D-serine **162** (Chart 6).

Chart 6



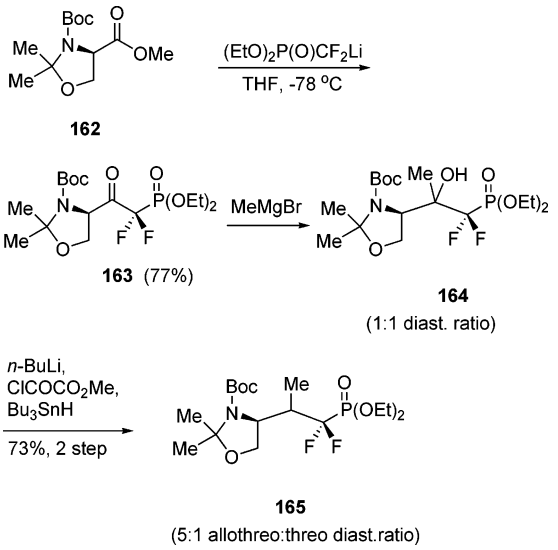
160 **161** **162**

In contrast to methyl esters, ethyl esters generally give at best moderate yields of the desired α,α-difluoro-*β*-keto phosphonates, even with very simple electrophiles such as ethyl benzoate, but Percy and co-workers were able to obtain high yield of the coupling products using a cerium-mediated method.[230] Addition of $(EtO)_2P(O)CF_2H$ to LDA containing cerium(III) chloride in THF at −78 °C generates an organometallic nucleophile that reacts efficiently with ethyl ester affording good yield of ketophosphonate. The reaction accepts a range of substrates, including simple aliphatic and aromatic ethyl esters. Among other advantages of the cerium-

mediated method are short reaction times and reproducibly high yields of the desired ketophosphonates uncontaminated by side products.[230,231]

Significantly, this chemistry opens access to fluorinated phosphonate mimics of secondary phosphates, which cannot be prepared by direct triflate displacement. Scheme 51 clearly

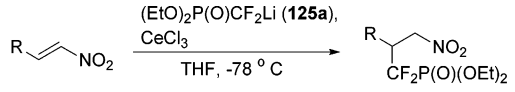
Scheme 51

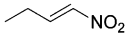
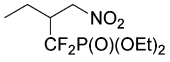
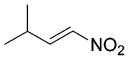
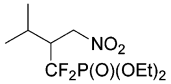
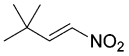
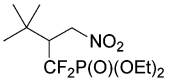
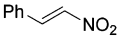
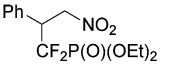


demonstrates this strategy. Thus, interception of the α,α-difluoro-*β*-ketophosphonate **163** with an alkylmetal species, followed by deoxygenation of the tertiary alcohol **164** provides the secondary phosphate analogue **165**.[229]

2.4.2.4. Michael Additions to Activated Olefins. Lithiodifluoromethylphosphonate salt **125a** is able to undergo conjugate addition to nitrostyrene derivatives.[232] However, the reaction required a 3-fold excess of **125a** and no desired adducts were obtained with nitroolefins. Subsequently Lequeux and Percy has shown that the organocerium(III) reagent, prepared by the addition of **125a** to a THF solution of LDA containing freshly dried $CeCl_3$ at −78 °C, reacted with a range of nitroolefins to afford the desired adducts in good yields (Table 14).[233] Further elegant work by Lequeux

Table 14. Cerium-Mediated Additions to Nitroalkenes[233]

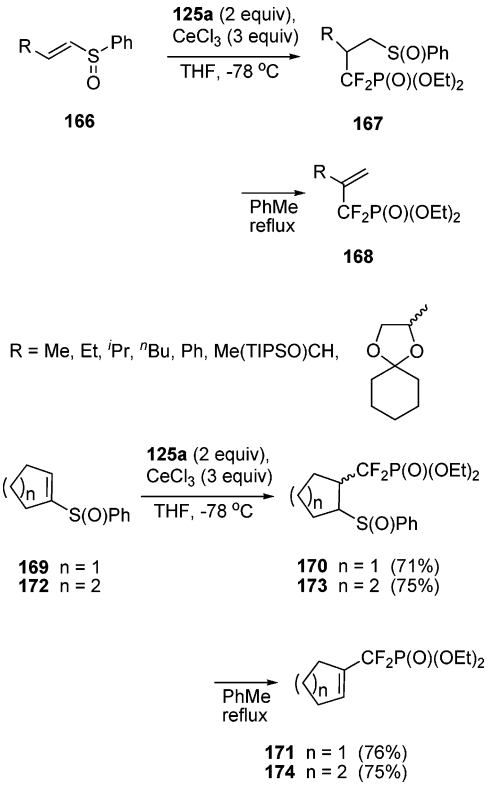


nitroalkene	product	yield (%)
		62
		47
		25
		49

using $[(^{i}PrO)_2P(O)CF_2]^-$ carbanion, generated from $(^{i}PrO)_2P(O)CF_2SMe$ and $^{t}BuLi$, led him to suggest that the influence of the medium is enough to modify the reactivity of the phosphonodifluoromethyl carbanion. In fact, the conjugate addition of the lithiophosphonate prepared from $(^{i}PrO)_2P(O)CF_2SMe$ to nitroolefins was successful, affording secondary difluoromethylphosphonates in the absence of cerium(III) chloride.[189]

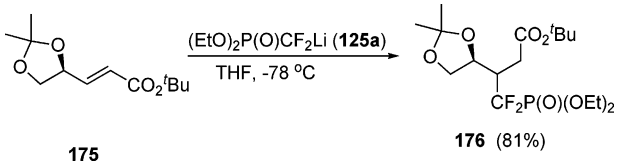
With acyclic vinyl sulfoxides **166**, cerium-mediated addition of **125a** occurred in moderate to poor yields. However, additions to cyclic vinyl sulfoxides **169** and **172** gave the corresponding adducts **170** and **173** in yields up to 75%. Addition failed completely in the absence of cerium(III) chloride. On the other hand, reaction yields only increased when the third equivalent of lanthanide reagent was present, suggesting that the first two equivalents are complexed tightly to the lithiophosphonate nucleophile. On heating to about 110 °C, the compounds **167**, **170**, and **173** decompose to yield the products of formal vinylation (Scheme 52).[234]

Scheme 52



Similarly, the conjugate addition reactions of **125a** to cyclic vinyl sulfones afforded the products of formal alkylation, attaching the difluoromethylenephosphonate group to a secondary carbon atom. With acyclic vinyl sulfones, the addition was considerably less efficient and deprotonation competed with addition.[235] Last, reaction between **125a** and α,*β*-unsaturated ester **175** at −78 °C in THF gave the Michael adduct **176** in 81% yield as a 1:1 mixture of diastereomers (Scheme 53).[236,237]

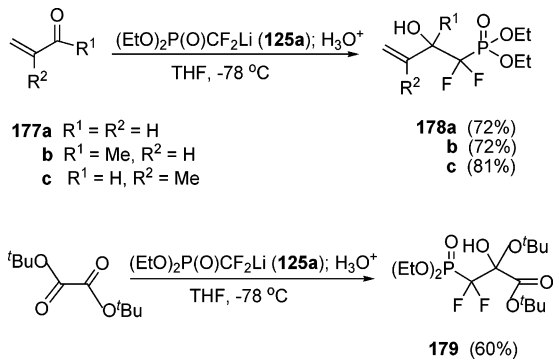
Scheme 53



2.4.2.5. Addition to Aldehydes, Ketones, and Related Compounds. The direct addition of the lithiated carbanion

125a to aldehydes and ketones leads to the corresponding adducts, which can be carefully neutralized to diethyl α,α-difluoro-β-hydroxyalkylphosphonates. Heating the THF solution of the intermediate alkoxide induces the HWE reaction to give 1,1-difluoroalkene. In the case of activated aldehydes, such as 4-nitrobenzaldehyde or 4-pyridinecarbaldehyde, the intermediate adduct easily undergoes rearrangement into fluorinated phosphate.[190] With α,β-unsaturated aldehydes and ketones **177**, only 1,2-adducts **178** were obtained and no 1,4-adducts could be detected in the crude reaction mixture.[238] Condensation of **125a** with di-*tert*-butyl oxalate at −78 °C in THF followed by neutralization produced the unusually stable *tert*-butyl hemiketal **179**, which was further used in the synthesis of the difluoromethylene analogue of phosphoenolpyruvate (Scheme 54).[239] Another significant observation is that *N*,*N*-dimethylformamide could also be used as a substrate in the cerium-mediated reaction. After workup, dihydroxy phosphonate $(EtO)_2P(O)CF_2CH(OH)_2$ was obtained in 80% yield.[240,241]

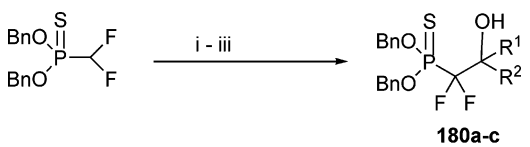
Scheme 54



Interestingly, the interaction of **125a** with carbon dioxide gave the fluorinated phosphonoacetic acid $(EtO)_2P(O)CF_2CO_2H$, which in turn has been used for the synthesis of the aspartate transcarbamoylase (ATC) inhibitor.[240,242] The reaction of **125a** with carbon disulfide followed by alkylation allows access to the phosphonodifluorodithioacetate $(EtO)_2P(O)CF_2C(S)SMe$.[240] The yield was optimized up to 80% when the reaction was performed in the presence of 5 equiv of CS_2 and MeI.[243]

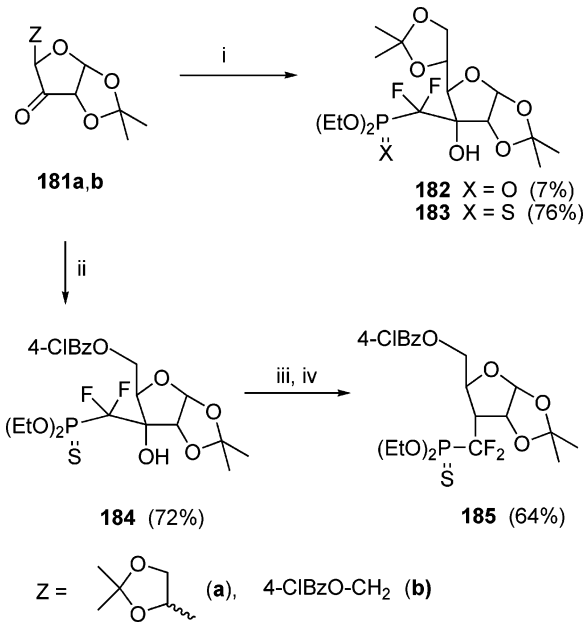
Lithioderivative $(BnO)_2P(S)CF_2Li$ reacted with aldehydes and ketones to furnish the adducts that after quenching at low temperature with glacial acetic acid, delivered the expected alcohols **180** in isolated yields ranging from 63% to 85% (Scheme 55).[183] Sulfur was shown to play a crucial role in the introduction of the $(EtO)_2P(S)$ unit onto the furanose ring.[185,186] For example, addition of **125a** to ketone **181a** produced a mixture of products. Purification led to the isolation of the adduct **182** in only 7% yield. In contrast, reaction of the sulfur reagent $(EtO)_2P(S)CF_2Li$ with ketone **181a** led in perfectly reproducible fashion to the adduct **183** in 76% yield.[185] Even more spectacular is the reaction of **181b** with $(EtO)_2P(S)CF_2MgCl$, which afforded the adduct **184** (65−72%) in a total regio- and stereoselective manner. Deoxygenation furnished ribofuranose derivative **185** as a single adduct possessing the depicted stereochemistry. The procedure resulted in a clean and complete stereochemical inversion of the $(EtO)_2P(S)$ unit from the convex face to the concave one (Scheme 56).[186]

Scheme 55[a]



[a] Reagents and conditions: (i)LDA, THF, −78 °C; (ii) R^1R^2CO, THF, −78 °C; (iii) AcOH, −78 °C.

Scheme 56[a]

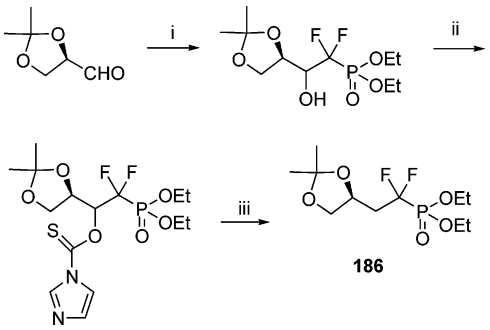


[a] Reagents and conditions: (i) $(EtO)_2P(S)CF_2Li$ (X = O or S), THF, −78 °C, then H_3O^+; (ii) $(EtO)_2P(S)CF_2Br$, ^{i}PrMgCl, THF, −45 °C; (iii) ^{i}PrMgCl, THF, 0 °C, then $ClCOCO_2Me$; (iv) Bu_3SnH, AIBN, toluene, reflux.

The generation of difluoromethylenephosphonate carbanion $[(EtO)_2P(O)CF_2]^-$ by fluoride ion from silicon species $(EtO)_2P(O)CF_2SiMe_3$ (**126**) constitutes a promising extension of the carbanionic approach to α,α-difluoroalkylphosphonates. Several groups have demonstrated that desilylation of phosphonate **126** initiated by CsF, KF, or TBAF is an effective way to transfer the phosphonate carbanion to electrophilic carbonyl centers.[102] Thus, the reaction of **126** with aromatic or heteroaromatic aldehydes in the presence of CsF proceeds easily at room temperature in THF to give the silylated adducts, which are readily hydrolyzed to diethyl α,α-difluoro-β-hydroxyphosphonates in 57−87% yields.[190] Scheme 57 demonstrates the utility of this route in preparing the difluoromethylene phosphonate analogue of *sn*-glycerol-3-phosphate (**186**).[11,184] Another example is synthesis of [1-^{14}C]-2,2-difluoroethene, $F_2C{=}{}^{14}CH_2$. The ^{14}C-radiolabeled formaldehyde adds to **126** in the presence of a catalytic amount of anhydrous CsF producing the phosphonate $(EtO)_2P(O)CF_2{}^{14}CH_2OSiMe_3$. On heating, the latter undergoes a HWE reaction to give the ^{14}C-radiolabeled difluoroethene.[244]

2.4.2.6. Oxacycle Ring-Opening Reactions. In these transformations, three factors have to be considered. One is the source of the $[(RO)_2P(O)CF_2]^-$ carbanion, another is the nature of the oxacycle, and last is the character of the Lewis acid, which is used as catalyst. Generally, difluoromethyl-

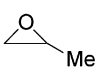
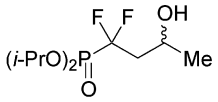
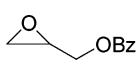
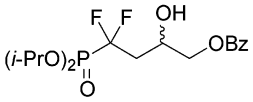
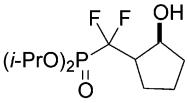
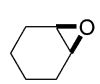
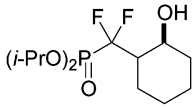
Scheme 57[a]



[a] Reagents and conditions: (i) $(EtO)_2P(O)CF_2SiMe_3$ (**126**), Bu_4NF (0.05 equiv), 3 Å molecular sieves, THF, rt, 24 h, then sat. aq $NaHCO_3$, 36%; (ii) $Im_2C{=}S$, THF, reflux, 81%; (iii) Bu_3SnH, AIBN, toluene, reflux, 66%.

enephosphonate carbanions are not reactive toward oxacycles.[234] It was reported that epoxide ring-opening reactions could be accomplished using the lithium reagent **125a** in the presence of $TiCl_4$.[192] However, when the lithiated carbanion **125a** obtained by deprotonation of $(EtO)_2P(O)CF_2H$ with LDA was reacted with propylene oxide in the presence of $BF_3{-}Et_2O$ (even with 3 equiv), only traces of alcohol $(EtO)_2P(O)CF_2CH_2CH(OH)Me$ were detected. The reaction was practically unsuccessful (<5% yield) with **125a** prepared from $(EtO)_2P(O)CF_2Br$ and ^{t}BuLi. In striking contrast, using the phosphonate salt prepared by addition of $(^i PrO)_2P(O)$-CF_2SMe to a cooled solution of *tert*-butyl lithium in diethyl ether, afforded the desired alcohol in good yield. This straightforward strategy opens access to a variety of primary and secondary ω-hydroxy-α,α-difluorophosphonates (Table 15).[245] The stereochemical outcome of the ring-opening

Table 15. Epoxide Ring-Opening Reactions from $(^i PrO)_2P(O)CF_2SMe/^t$BuLi Source of Carbanion[245]

epoxide	product	yield (%)
		61[a]
		69[b]
		54[b]
		60[b]

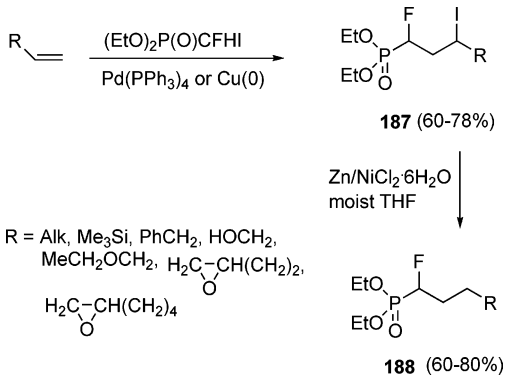
[a] Epoxide/sulfide/$BF_3{\cdot}Et_2O$ ratio = 3:1:2. [b] Epoxide/sulfide/$BF_3{\cdot}Et_2O$ ratio = 1 :2 :2

reactions is due to the phosphonate carbanion attack from the least hindered site of the oxirane ring. The rigid cyclopentene and cyclohexene oxides gave trans products as single diastereomers. The same workers reported that the exothermic reaction with trimethylene oxide afforded α,α-difluoro-γ-hydroxyphosphonate in 63% yield. With borane complex of tetrahydrofuran, the $(^i PrO)_2P(O)CF_2SMe/^t$BuLi system reacts readily to give ϵ-hydroxy-α,α-difluoro phosphonate (71%). However, no ring-opening reaction with tetrahydropyran occurred, and phosphonate $(^i PrO)_2P(O)CF_2H$ was the exclusive product.[245]

2.5. Transition Metal Catalyzed Addition Reactions

A combination of transition metal catalyzed addition of fluoroiodomethylphosphonates to alkenes and reduction of the formed α-fluoro-γ-iodoalkylphosphonates provides an efficient procedure for the incorporation of the fluorinated phosphonate ester moiety into organic substrates, which complements the copper(I) halide mediated coupling reactions of fluorinated phosphonate carbanions with organyl halides and triflates. Thus, the addition of $(EtO)_2P(O)CFHI$ to alkenes is readily accomplished with tetrakis(triphenylphosphine)palladium or copper metal producing α-fluoro-γ-iodoalkylphosphonates **187**. With 1-alkenes, vinyl trimethylsilane, allyl acetates, allyl phosphonates, unsaturated diols, and epoxides, the yields were moderate to good. Reduction of the addition adducts **187** with $Zn/NiCl_2{\cdot}6H_2O$ in moist THF gives the corresponding α-fluoroalkylphosphonates **188** in 60−80% yield (Scheme 58).[246]

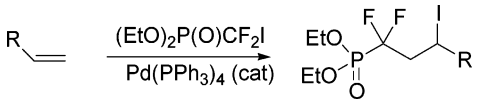
Scheme 58



The addition reaction of $(EtO)_2P(O)CF_2I$ with alkenes is catalyzed by $Pd(PPh_3)_4$ or Cu^0 under mild conditions.[247,248] For example, upon reaction of $(EtO)_2P(O)CF_2I$ with 1-hexene in the presence of 2 mol % of palladium catalyst at room temperature, the corresponding α,α-difluoro-γ-iodophosphonate $(EtO)_2P(O)CF_2CH_2CHI^n$Bu was isolated in 91% yield. Similarly, alkenes containing functional groups, such as trimethylsilyl, epoxy, ester, ketone, and hydroxy, also gave the corresponding adducts in good yields (Table 16).[248] The reactions presumably proceed via a single electron transfer mechanism. This conclusion is corroborated by the fact that the additions are inhibited by both electron transfer and radical inhibitors.

When neat 5-hexene-1,2-diol and 7-octene-1,2-diol were treated with $(EtO)_2P(O)CF_2I$ in the presence of palladium catalyst, the phosphonates **189** and **190** were isolated in high yields (Scheme 59). Addition of $(EtO)_2P(O)CF_2I$ to dienes affords bis-phosphonates. Thus, upon reaction of 1,5-hexadiene with 2 equiv of $(EtO)_2P(O)CF_2I$ and 30 mol % of copper metal at 85 °C, the corresponding bis-phosphonate was isolated in 92% yield.[248]

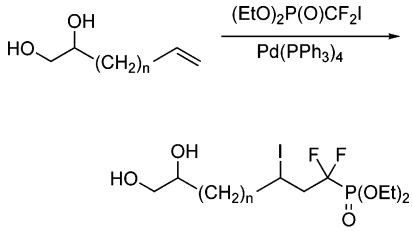
Table 16. Palladium-Initiated Addition of $(EtO)_2P(O)CF_2I$ to Alkenes[248]



R	yield (%)
$^nC_3H_7$	85
$^nC_5H_{11}$	81 (75)[a]
$^nC_6H_{13}$	80
Me_3Si	88 (75)[a]
$HOCH_2$	81
$HO(CH_2)_3$	79
$HO(CH_2)_8$	76
$AcO(CH_2)_3$	68
$MeC(O)CH_2CH_2$	81 (80)[a]
$EtO_2CCHMeCH_2$	65
$HOC(O)CH_2CH_2$	79
$HOCH_2CH(OH)CH_2CH_2$	79
$HOCH_2CH(OH)(CH_2)_4$	76

[a] Copper(0)-catalyzed addition at 75−90 °C.

Scheme 59



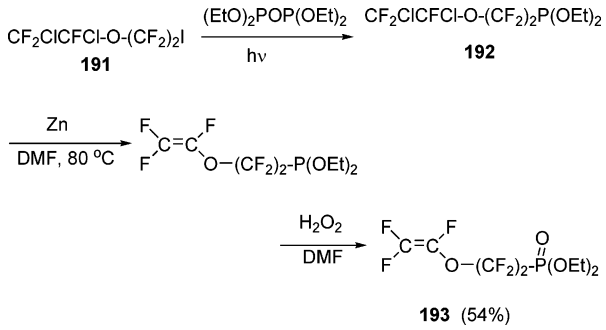
189 n = 2 (79%)
190 n = 4 (76%)

2.6. Radical Approaches

Perfluoroalkyl iodides (R_FI) are representative perfluoroalkylating reagents for various organic compounds and can work not only as electrophiles toward P(III)-derivatives (see section 2.1) but also as perfluoroalkyl radical precursors.[249] In fact, as early as in 1981, Kato and Yamabe reported the synthesis of perfluoroalkylphosphonates from the corresponding perfluoroalkyl iodides via the phosphonites.[250] Thus, thermal decomposition of di-*tert*-butyl peroxide in the presence of perfluoroalkyl iodide leads to the abstraction of an iodine atom from R_FI to produce the reactive perfluoroalkyl radical ($^{\bullet}R_F$). The latter reacts with tetraethyl pyrophosphite, $(EtO)_2POP(OEt)_2$, resulting in perfluoroalkylphosphonite, $R_FP(OEt)_2$. Simple oxidation with *tert*-butyl hydroperoxide provides the desired perfluoroalkylphosphonates, $R_FP(O)(OEt)_2$. Subsequently, Nair and Burton reported that perfluoroalkyl iodides, including 1,3-, 1,4-, and 1,6-diiodides, reacted with tetraethyl pyrophosphate under ultraviolet irradiation to afford the corresponding perfluoroalkylphosphonites and bis-phosphonites, which could be oxidized to the perfluoroalkylphosphonates.[251] Scheme 60 illustrates application of this strategy for the synthesis of fluorinated vinyl ethers containing phosphonate ester groups. The interaction of the fluorinated iodide **191** with tetraethyl pyrophosphite upon irradiation at 254 nm, afforded the phosphonite **192**, which was dechlorinated using zinc dust in DMF and then oxidized yielding the desired heptafluoro-3-oxa-4-pentenylphosphonate **193**.[252]

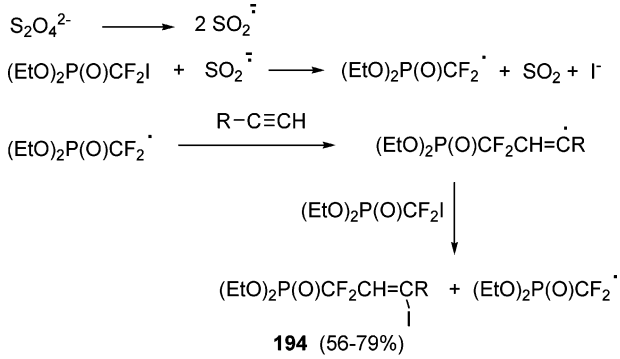
It is well-known that the addition reactions of perfluoroalkyl iodides with alkenes or alkynes initiated by sodium dithionite proceed through an electron-transfer process.[253] Iododifluoromethylphosphonate, $(EtO)_2P(O)CF_2I$, like perfluoroalkyl iodides, can be initiated by a sulfinatodehalogenation system in the reaction with alkynes.[39] The reaction proceeds well in the presence of sodium dithionite and sodium bicarbonate in acetonitrile and water at 0 °C (Scheme 61). Interestingly, the addition reaction afforded adducts **194**

Scheme 60



193 (54%)

Scheme 61

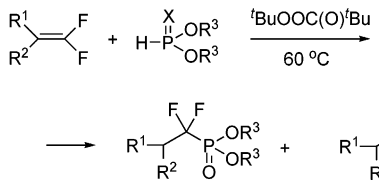


R = $Me(CH_2)_3$, $HOCH_2$, $MeCO_2$, $EtCO_2$, $MeOCH_2$, Ph, $EtOCH_2$, $Me_2NC(O)$

exclusively in *E*-form when the substituent group (R) was electron-deficient, such as ester and amide.

Simple and efficient synthesis of α,α-difluoro-β,β-disubstituted phosphonates and phosphonothioates is possible through an addition of phosphonyl and phosphonothioyl radicals onto readily available 1,1-difluoroolefins (Scheme 62).[254] Good yield of the desired regioadduct **195** or **196** is

Scheme 62



195

Phosphonates **195**			
R^1	R^2	R^3	yield (%)
-$(CH_2)_5$-		Me	66
-$(CH_2)_5$-		Et	60
C_9H_{19}	Me	Me	65
C_9H_{19}	Me	Et	72
C_6H_5	Me	Et	0
-$(CH_2)_5$-		Ph	0
-$(CH_2)_5$-		Bn	8

196

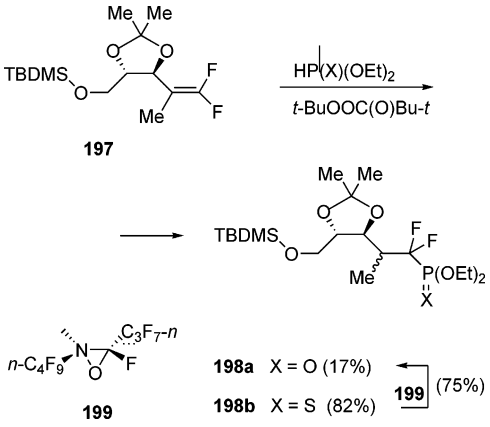
Phosphonothioates **196**			
R^1	R^2	R^3	yield (%)
C_9H_{19}	Me	Et	95
C_6H_5	Me	Et	30
C_9H_{19}	Me	Bn	65

obtained when a degassed benzene solution of difluoroolefin and diethyl phosphite or thiophosphite was heated in the

presence of *tert*-butylperoxypivalate. The higher yields observed for the phosphonothioates are presumably a consequence of greatly increased efficiency in the hydrogen atom abstraction step of the propagation sequence, since the lower electronegativity of the sulfur atom will make a substantial contribution toward weakening the phosphorus−hydrogen bond in the thiophosphite. For example, in the case of 1,1-difluoro-2-methylstyrene, no addition product with diethyl phosphite was isolated; however the corresponding thiophosphonyl compound was obtained in fair yield.

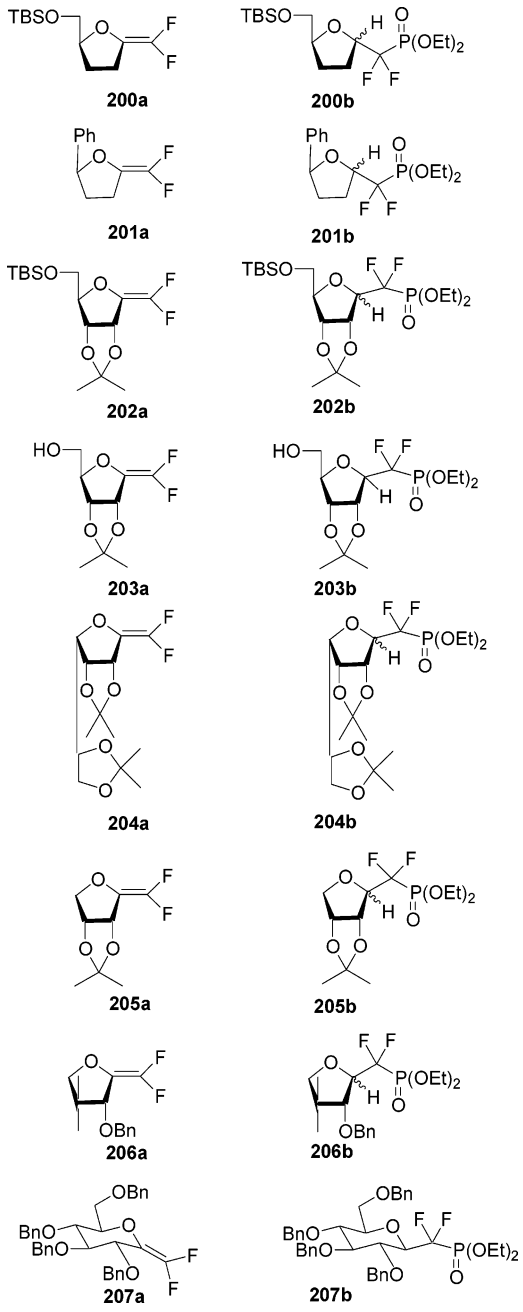
The easy interconversion of α,α-difluoroalkylphosphonates **195** and α,α-difluoroalkylphosphonothioates **196** provides a flexibility in the access to potentially bioactive compounds with manipulatable functionality. Thus for example, phosphonates **195** can be nicely converted to the corresponding phosphonothioates **196** by the treatment with Lawesson's reagent. The reversed transformation (i.e., converting phosphonothioates into phosphonates) is most conveniently carried out with an oxidizing agent such as a perfluorinated oxaziridine, dioxirane, or, more simply, *meta*-chloroperoxybenzoic acid. Moreover, in some cases, the use of the two-step procedure, that is, preparation of the α,α-difluorophosphonothioate and conversion of the P═S bond into the P═O bond, resulted in the isolation of the desired α,α-difluoroalkylphosphonate in much higher yield than the direct, one-step synthesis. For instance, addition of diethyl phosphonyl radical onto 1,1-difluoroolefin **197** gave **198a** in 17% isolated yield, while diethyl thiophosphonyl radical afforded the corresponding thioderivative **198b** in 82% yield. Conversion of **198b** to **198a** using oxaziridine **199** was achieved in 75% yield (Scheme 63).[255]

Scheme 63



Preparation of some anomeric carbohydrate difluoromethylenephosphonates via phosphonyl radical addition to *gem*-difluoroenol ethers has been developed by Motherwell and co-workers.[256,257] These reactions were carried out by addition of a solution of di-*tert*-butyl peroxide in octane to a refluxing solution of diethyl phosphite and the *gem*-difluoroenol ether in the same solvent (method A) or addition of a solution of tributyltin hydride containing AIBN as initiator to a refluxing benzene solution of the carbohydrate *gem*-difluoroenol ether and diethyl (phenylselenyl)phosphonate (method B). The results for a series of carbohydrate *gem*-difluoroenol ethers are shown in Table 17. In the course of these reactions, some unusual stereochemical effects were observed. Thus for the furanose derivatives, the β-stereochemistry of the major isomer at the anomeric center was apparently indicative of hydrogen atom capture from the more hindered face of the molecule. This situation was especially highlighted by the excellent selectivity observed

Table 17. Preparation of Anomeric Carbohydrate Difluoromethylenephosphonates via Phosphonyl Radical Addition to *gem*-Difluoroenol Ethers[256,257]



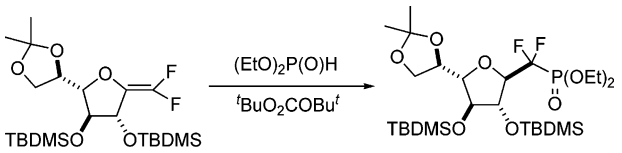
entry	substrate	phosphonate (yield, ratio) method A[a]	phosphonate (yield, ratio) method B[b]
1	**200a**	**200b** (5%, α/β 6:4)	**200b** (52%, α/β 45:55)
2	**201a**	*c*	**201b** (31%, α/β 1:1)
3	**202a**	**202b** (47%, α/β 0:1)	**202b** (73%, α/β 1:6)
4	**203a**	*c*	**203b** (44%)
5	**204a**	**204b** (23%)	**204b** (29%, α/β 0:1)
6	**205a**	**205b** (8%)	**205b** (36%, α/β 0:1)
7	**206a**	*c*	**206b** (28%)
8	**207a**	*c*	**207b** (14%)

[a] Reaction of **200a**−**207a** (1 equiv) and diethyl phosphite (3 equiv) in refluxing octane in the presence of di-*tert*-butyl peroxide (0.5 equiv). [b] Reaction of **200a**−**207a** (1 equiv) and $(EtO)_2P(O)SePh$ (3 equiv) in refluxing benzene with Bu_3SnH (4 equiv) and AIBN (0.5 equiv). [c] No addition products observed.

for the 2,3-isopropylidene derivatives **204b** and **205b** (entries 5 and 6). The absence of a functional group at position 2 leads to an essentially equimolar mixture of both possible anomeric derivatives (entries 1 and 2), while the introduction of a 4-β-substituent appears to diminish the inherent preference for formation of the β-substituted anomeric derivative (cf. entries 3 and 5). The authors explained this stereochemistry by a hyperconjugative interaction forcing the single occupied orbital and CF_2-P bond into an eclipsed conformation and by steric hindrance of the phosphonyl group. Within the pyranose series, the stereochemical outcome is consistent with operation of the "radical anomeric effect".[256]

Radical reaction of **208** with diethyl phosphite and *tert*-butylperoxypivalate afforded **209** in 56% yield (Scheme 64).[258] The anomeric β-configuration of **209** was assigned

Scheme 64



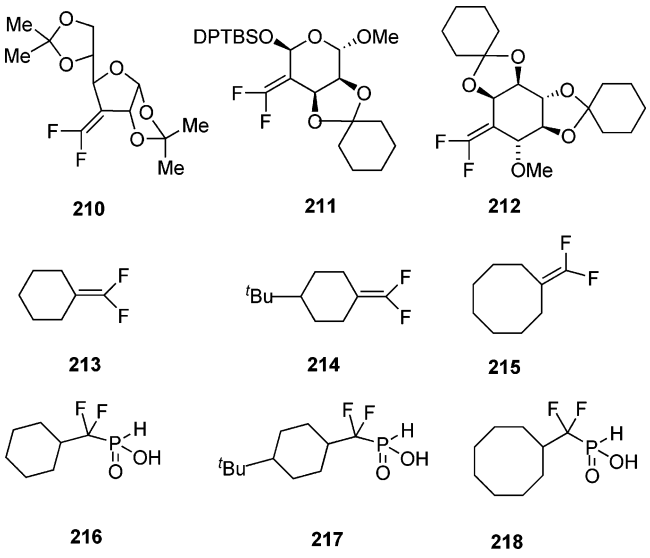
208 **209** (56%)

through a NOESY spectrum, where a coupling between H-1 and H-3 indicated that these hydrogen atoms are in a cis relationship.

The preparation of carbohydrate α,α-difluorophosphonothioates by free radical chain reaction has also been studied.[256] The required thiophosphites were prepared from phosphites by exchange using Lawesson's reag,ent and addition reactions were carried out by slow addition of a solution of di-*tert*-butyl peroxide in octane to thiophosphite and the appropriate difluoroenol ether. Here too, phosphonothioyl radicals show a clear synthetic advantage over their oxygenated counterparts, in view of both their greater ease to undergo homolytic substitution and the higher yield in which the expected adducts are formed. In marked contrast to the reactions of phosphonyl and phosphonothioyl radicals with *gem*-difluorinated enol ethers, other functionalized cyclic molecules bearing an exocyclic difluoromethylene unit failed to yield any adducts under a variety of conditions (e.g., compounds **210**−**212**).[18,185] Since the nonfluorinated analogue of **210** undergoes efficient addition of both phosphonyl and phosphonothioyl radicals,[259] one can conclude that the ether group has a strong effect on the course of the reaction by overcoming the electronic and steric action of the fluorine atoms.

Extending Nifant'ev's work on the synthesis of phosphinates through a radical chain mechanism,[260] Piettre and coworkers found that substrates **213**−**215** react with hypophosphorous acid, $H_2P(O)OH$, and its sodium salt, $H_2P(O)ONa$, in the presence of a catalytic amount of *tert*-butylperoxypivalate as radical initiator to give the expected adducts **216**−**218** in 75−83% isolated yields (Chart 7).[18,261] The α,α-difluoro-*H*-phosphinates thus obtained exhibit the features of typical hydrophosphoryl compounds and can participate in a second radical addition reaction. Thus, the sodium salt of hypophosphorous acid was shown to act as a double radical precursor in a double, sequential radical addition on 3-*exo*-methylenefuranose derivatives. Moreover, α,α-difluoro-*H*-phosphinates are capable of reacting with chlorotrimethylsilane in the presence of pyridine to give the corresponding *O*,*O*-bissilylated phosphites, which in turn

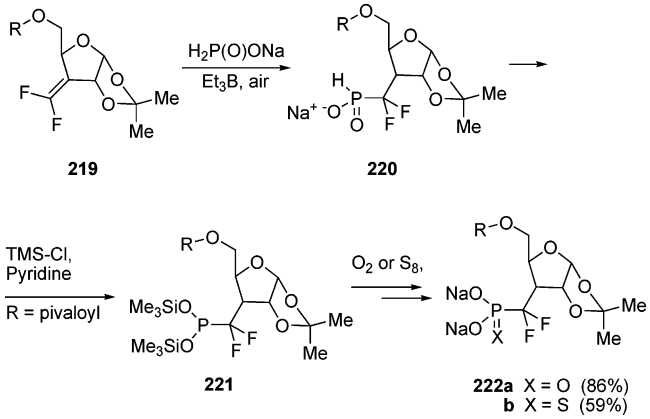
Chart 7



210 **211** **212** **213** **214** **215** **216** **217** **218**

constitute a class of useful intermediates en route to a number of difluorinated functional groups. For instance, when difluoroalkene **219** was reacted with hypophosphorous acid sodium salt in the presence of triethylborane and air, adduct **220** was isolated as a single diastereomer. Treatment of **220** with chlorotrimethylsilane in the presence of pyridine afforded *O*,*O*-bissilylated phosphite **221**, which upon reaction with oxygen and sulfur gave the corresponding phosphonate **222a** and phosphonothioate **222b** in the form of their disodium salts (Scheme 65).[18,261]

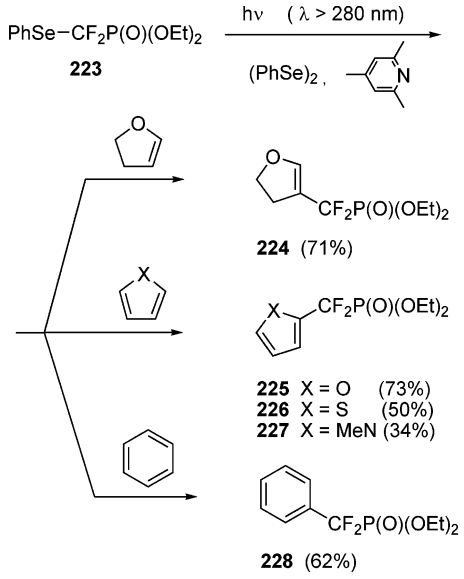
Scheme 65



219 **220** **221** **222a** X = O (86%) **b** X = S (59%)

A potentially very promising method for the synthesis of α-aryl-α,α-difluoromethylphosphonates is the direct photochemical substitution at the unsaturated carbon atom in which hydrogen is substituted by difluoromethyl radical bearing phosphonate group. In fact, the easily accessible α,α-difluoro-α-(phenylseleno)acetates and phosphonates, PhSe−CF_2EWG (EWG = COOEt, $P(O)(OEt)_2$), have been shown to react with alkenes under a photochemical irradiation to give difluoromethylene-substituted unsaturated products.[262] However, the procedure gave poor yields. Efficient and selective substitution with difluoromethylphosphonyl radicals photogenerated from **223** was achieved in the presence of 2,4,6-trimethylpyridine and diphenyldiselenide. This novel photochemical method was successfully extended to aromatic and heteroaromatic substitution to provide the corresponding α,α-difluoromethylphosphonates **224**−**228** in good to moderate yields (Scheme 66).[263]

Scheme 66

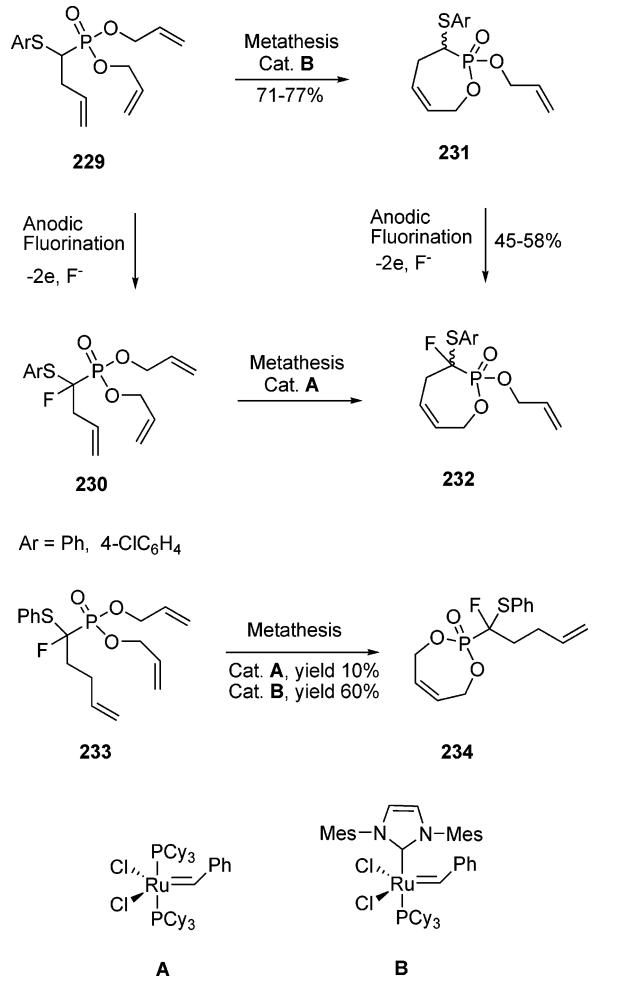


2.7. Miscellaneous Reactions

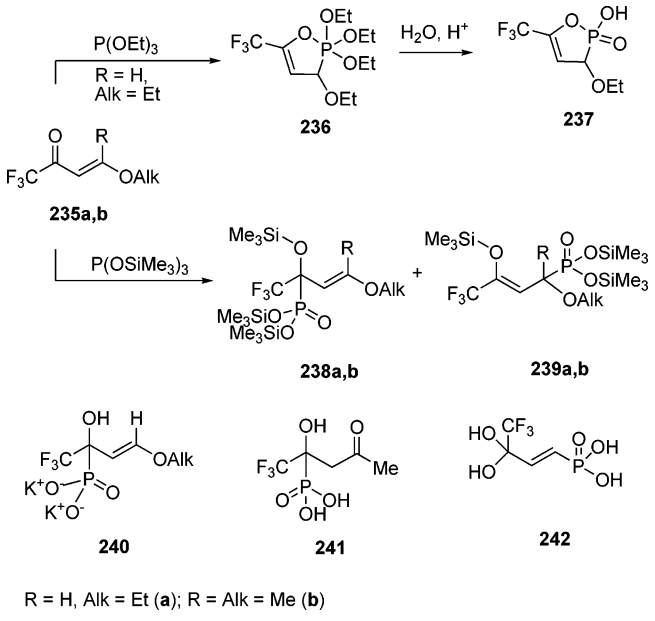
A combination of the ring-closing olefin metathesis (RCM) reaction and anodic fluorination has recently been used for the preparation of cyclic α-arylthio-α-monofluorophosphonate esters.[264] Thus, seven-membered cyclic monofluorophosphonate esters **232** were successfully synthesized from open-chain allyl phosphonates **229** using anodic fluorination, followed by ring-closing metathesis with the first-generation Grubbs' catalyst **A**. Alternatively, allyl phosphonates **229** were transformed to cyclic phosphonates **231** using the second-generation Grubbs' catalyst **B**, and subsequently the cyclic phosphonates **231** were subjected to anodic fluorination to provide the desired cyclic phosphonates **232**. The latter route was found to be more efficient. On the other hand, in an attempt to synthesize an eight-membered cyclic phosphonate starting from the open-chain fluorinated precursor **233**, the RCM reaction took place between two allyloxy chains to give seven-membered cyclic phosphonate ester **234** (Scheme 67).

The reactions between β-alkoxy-α,β-unsaturated trifluoromethyl ketones and phosphites have been used to prepare novel trifluoromethylated α-hydroxyalkylphosphonic acids (Scheme 68). The alkoxyenone **235a** reacts with triethyl phosphite in boiling benzene to form the cyclic 1,2-λ^5-oxaphospholene **236**. Treatment of the latter with a 1 N solution of hydrochloric acid led to the crystalline compound **237**.[265] Under similar conditions, the alkoxyenones **235** react with tris(trimethylsilyl) phosphite to give a mixture of phosphonates **238** and **239**. Decreasing the reaction temperature as low as −30 °C results in the formation of only 1,2-adduct **238**, while increasing the reaction temperature leads to rearrangement of 1,2-adduct **238** to 1,4-adduct **239**. It is assumed that this rearrangement proceeds via tris(trimethylsilyl) phosphite elimination−addition. The presence of the trifluoromethyl group may promote the dissociation of compounds **238** since electron-withdrawing substituents decrease the thermal stability of tris(trimethylsilyl) phosphite adducts with aldehydes and ketones. Treatment of **238a** with

Scheme 67



Scheme 68



methanolic KOH led to the dipotassium salt of the corresponding phosphonic acid **240**. On the other hand, treatment of the phosphonate **238b** with water containing a trace of hydrochloric acid yielded ketophosphonic acid **241**. The hydrolysis of phosphonate **239a** led to phosphonic acid **242**.[266]

3. Fluorinated Phosphonates of Significant Biological Importance

3.1. Fluorinated *gem*-Diphosphonates

Interest in these species stems from biological usefulness of a large number of functionalized geminal methanediphosphonic acid derivatives.[267−270] For example, 1-hydroxyethylidene-, 1-hydroxy-2-(3-pyridyl)ethylidene-, 1-hydroxy-2-(1-imidazolyl)ethylidene-, and 4-amino-1-hydroxybutylidene-1,1-diphosphonic acids (i.e., etidronate, risedronate, zoledronate, and alendronate) have been utilized for bone disease therapy.[271] Dichloromethylene diphosphonic acid, $[(HO)_2(O)P]CCl_2$ (clodronic acid), has been found to be active in bone and calcium phosphate metabolism.[272] Other α-halogenated methylenediphosphonic acids including mono- and difluoromethylene diphosphonates show antiviral activity,[75,273] inhibit bone lysis[274] and mammalian DNA polymerase δ,[275] and find application as ligands in radiopharmaceuticals.[276] More recently, *gem*-diphosphonates have also attracted considerable interest as nucleotide analogues, in which a bridging phosphoanhydride oxygen is replaced by carbon in situations where it is desirable to repress hydrolysis of P−O−P linkages. The major concerns associated with this strategy are differences between reactivities of the diphosphonate analogues and normal pyrophosphate substrates. The lower electronegativity of the methylene group, compared to oxygen, leads to a significant decrease in the acid dissociation constants of the phosphonic analogues, which is often reflected in a reduction of biological activity. A particular refinement of phosphate/phosphonate strategy has been developed by Blackburn and co-workers.[277−280] These authors found that the replacement of bridging methylene by a difluoromethylene unit in diphosphonates restored the pK_a's of analogues to values almost identical with those of the natural phosphate substrates giving compounds that have improved potential as phosphate mimetics. Based on this concept, within the last decade or two, a variety of nucleoside triphosphate analogues featuring the difluoromethylenephosphonate group have been synthesized and successfully employed as substrates in enzymatic processes and as biochemical probes of nucleic acid−protein interactions.[281−284]

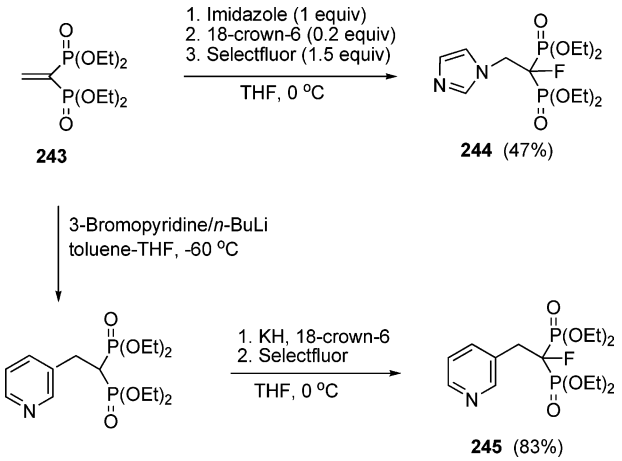
3.1.1. Simple Fluorine-Containing Diphosphonates

Several methods, based either on the Michaelis−Becker reaction or on alternative methodologies, have been developed for the preparation of monofluoromethanediphosphonic acid, $[(HO)_2(O)P]_2CHF$ (FMDPA), and difluoromethanediphosphonic acid, $[(HO)_2(O)P]_2CF_2$ (F_2MDPA), which are F-labeled, hydrolysis-inert isopolar analogues of inorganic pyrophosphoric acid, $[(HO)_2(O)P]_2O$. Direct route to both compounds includes the reaction of methanediphosphonates with perchloryl fluoride or other electrophilic fluorinating reagents.[8,70,145,277] The preparation of $[(EtO)_2P(O)]_2CF_2$ was successfully achieved by treating $(EtO)_2P(O)CF_2Br$ with diethyl phosphite anion.[28,285] The reaction between $(^iPrO)_2P(O)CF_2Br$ and $(^iPrO)_2PONa$ gave the corresponding tetrakis(isopropyl) difluoromethanediphosphonate. The same compound was formed using CBr_2F_2 and $(^iPrO)_2PONa$; the mixed halogen tetraester $[(^iPrO)_2P(O)]_2CFBr$ was obtained from $[(^iPrO)_2P(O)]_2CFH$ upon treatment with bromine in aqueous K_2CO_3.[285] Coupling reactions have also been used; for example, the lithium salt obtained from $(EtO)_2P(O)CF_2H$ and LDA gave, on reaction with $(EtO)_2P(O)Cl$, the corresponding diphosphonate in 74% yield.[29] Treatment of the alkyl esters $[(RO)_2P(O)]_2CHF$ and $[(RO)_2P(O)]_2CF_2$ with bromotrimethylsilane gives the expected trimethylsilyl esters, which then can be hydrolyzed to the free acids.[8]

Taken together with the parent methanediphosphonic acid (MDPA), the monofluoro acid (FMDPA) and the difluoro acid (F_2MDPA) show a smooth trend of decreasing melting point (MDPA, 203 °C; FMDPA, 162 °C; F_2MDPA, 87 °C) and increased nuclear magnetic resonance shielding at phosphorus as the α-hydrogen atoms of MDPA are replaced by fluorine atoms (δ_P relative to H_3PO_4: MDPA, 17.6; FMDPA, 10.5; F_2MDPA, 3.7 ppm). The effect of fluorine substitution on the acidity of MDPA has also been studied. The monofluoro acid (FMDPA) is predicted to have a p$K°_4$ of ∼10.1, or 1 order of magnitude below that of MDPA, while the fourth proton of the difluoro acid (F_2MDPA) is calculated to be 100-fold more acidic than that in the nonfluorinated acid. The enhanced acidity of FMDPA and F_2MDPA was apparent in their derivative chemistry. MDPA forms a bis(dicyclohexylamine) salt, but treatment of FMDPA and F_2MDPA with a small excess of the base led to formation of the tris(dicyclohexylamine) derivatives.[8]

Minami and co-workers reported a convenient synthetic route to new functionalized diphosphonates, which are efficacious in osteoporosis therapy.[79] In this approach, the Michael addition of sodium or potassium imidazole to 1,1-bis(phosphono)ethylene **243** was the key to success. Fluorination of addition product with Selectfluor afforded 1-fluoro-2-(1-imidazolyl)ethyl-1,1-diphosphonate **244** in 47% yield. Similar one-pot synthesis using 3-pyridyl lithium produced only trace amounts of the corresponding fluorinated diphosphonate **245**. However, this problem was overcome by a two-step procedure. Treatment of **243** with KH at 0 °C in THF containing 18-crown-6, followed by addition of Selectfluor, afforded the desired diphosphonate **245** in 83% yield (Scheme 69).

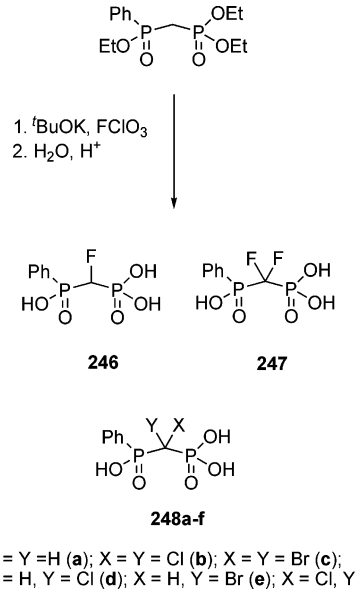
Scheme 69



Fluorinated [(phenylphosphinyl)methyl]phosphonic acids **246** and **247** were prepared via synthesis of the corresponding fluorinated triethyl esters, acid hydrolysis, and isolation of pyridine salts (Scheme 70).[71] The racemic monofluoro derivative **246** was found to be the most effective inhibitor of Na^+-gradient-dependent Na^+-phosphate cotransport across renal brush border membrane (BBM) in the group of compounds tested (**246**−**248**).

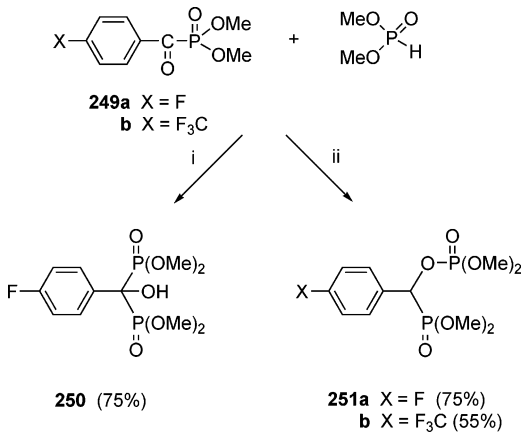
In search of compounds with specific high-density lipoprotein inducing activity, several *gem*-diphosphonate and

Scheme 70



gem-phosphonate−phosphate derivatives containing remotely fluorinated aryl substituents have been investigated.[286] For example, compounds **250** and **251** were prepared from acylphosphonates **249** with dimethyl phosphite in the presence of various amounts of Et_2NH or Bu_2NH in ether at 0 °C (Scheme 71). A catalytic amount of base gave hydroxydiphosphonate **250**, while the use of about 80−100 mol % of the same base yielded the corresponding phosphonate−phosphates **251**. It was found that although compounds of each subclass display significant activity, the effect of increasing plasma α-/β-cholesterol ratio is associated most consistently with the phosphonate−phosphate compounds.

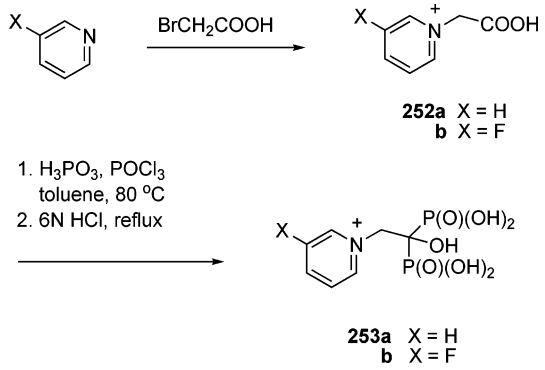
Scheme 71[a]



[a] Reagents and conditions: (i) 5% Et_2NH or Bu_2NH in ether, 0 °C; (ii) 80−100 mol % Et_2NH or Bu_2NH in ether, 0 °C.

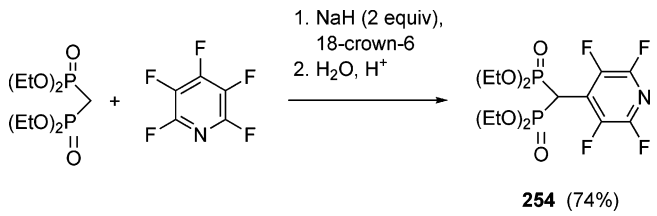
Pyridinium-1-yl-hydroxydiphosphinates are inhibitors of farnesyl diphosphate synthase (FPPS) and bone resorption.[287] In an effort to enhance activity of **253a**, Oldfield and coworkers prepared fluorinated diphosphonate **253b** and tested it in the FPPS assay. Thus, 3-fluoropyridine was alkylated by using bromoacetic acid, and the resulting pyridinium-1-yl acetic acid **252b** was converted to the corresponding diphosphonate by using $H_3PO_3/POCl_3$ (Scheme 72). When tested in the human γδ T cell activation assay, authors found a slight increase in activity on fluorine substitution (from 4.8 μM with **253a** to 2.7 μM with **253b**), and in bone resorption assay, the effect was much larger, with a 75 nM IC_{50} for **253b** to be compared with a 670 nM IC_{50} for **253a**. These results show, therefore, that **253b** is more active in this bone resorption assay than the drugs currently used to treat osteoporosis, alendronate (IC_{50} = 290 nM) and residronate (IC_{50} = 300 nM), although it is less active than zoledronate (IC_{50} = 34 nM).[287]

Scheme 72



The route employing nucleophilic aromatic substitution appeared to be a very general method for synthesizing perfluoroaromatic diethyl methylphosphonates, $(EtO)_2P(O)$-$CH(Ar_F)X$ (X = CN, CO_2Et, PO_3Et_2).[288] An example provided in Scheme 73 illustrates the application of this approach for the synthesis of potentially bioactive diphosphonate **254** containing a perfluorohetaryl substituent.

Scheme 73

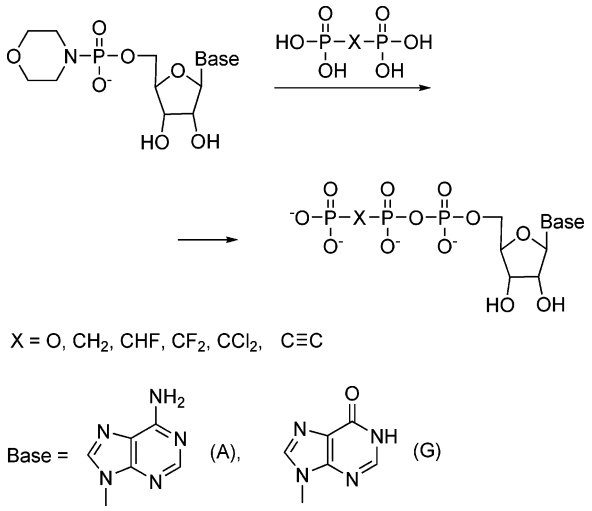


Trifluoroacetylated diphosphonate $[(EtO)_2P(O)]_2C(Me)C$-$(O)CF_3$ may be generated from the diphosphoryl-stabilized carbanion salt $[(EtO)_2P(O)]_2C(Me)Li$ and trifluoroacetic anhydride. This reagent generated in situ is effective for the stereoselective synthesis of trifluoromethylated vinyl- and dienylphosphonates, which are useful building blocks for the synthesis of biologically active hetero- and carbocyclic compounds.[289,290]

3.1.2. Analogues of Nucleoside Triphosphates Featuring Monofluoromethylene- and Difluoromethylenephosphonate Groups

In their pioneering work in this area, Blackburn and coworkers prepared diphosphonate analogues of several nucleotides, including monofluoro- and difluoromethylene-bridged analogues of adenosine triphosphate (ATP) and guanosine triphosphate (GTP).[9,279,280] Diphosphonic acids coupled with 5′-phosphoromorpholidates of adenosine and guanosine provided phosphonate analogues of ATP and GTP. ^{31}P NMR and pK_a data showed that the physical analogy improves in the series $CH_2 < CCl_2 \leq CHF < CF_2 < C{\equiv}C < O$ with respect to the β,γ-bridging function (Scheme 74). NMR and ion-selective electrode measurements on the binding of the divalent metals Mg, Ca, Zn, and Ba suggested that the pattern of metal cation binding to the nucleotide tetra-anion responds both to steric and to electronic features of the phosphonates,

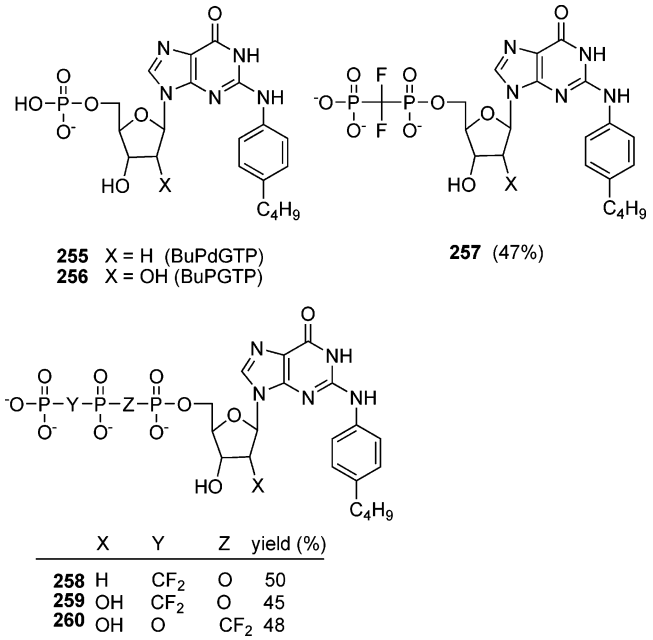
Scheme 74



with the β,γ-difluoromethylene analogue most closely resembling ATP. Noteworthy in this study was the good substrate activity of the ATP analogue with several ATP-utilizing enzymes, including DNA-dependent RNA polymerase, adenylate kinase, and (2′−5′)-oligoadenylate synthetase.

5′-Polyphosphates of N^2-(*p*-*n*-butylphenyl)-2′-deoxyguanosine and guanosine that contain a CF_2 group in place of a phosphoanhydride oxygen have been synthesized and studied as probes of DNA polymerases and G proteins (Chart 8).[291]

Chart 8

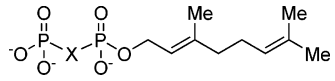


	X	Y	Z	yield (%)
258	H	CF_2	O	50
259	OH	CF_2	O	45
260	OH	O	CF_2	48

Thus, 5′-[β,γ-(difluoromethylene)triphosphates **258** and **259** were prepared by reaction of the corresponding 5′-phosphates **255** and **256**, activated by 1,1′-carbonyldiimidazole, with the soluble tri-*n*-butylammonium salt of difluoromethanediphosphonic acid. Preparation of the α,β-CF_2 derivative of N^2-(*p*-butylphenyl)guanosine 5′-triphosphate (BuPGTP), compound **260**, required first the synthesis of the diphosphonate **257**. The latter was prepared by treatment of a protected 5′-tosyl nucleoside with difluoromethanediphosphonate, followed by deprotection. Condensation of this nucleotide, activated with 1,1′-carbonyldiimidazole, with orthophosphate gave α,β-(difluoromethylene)triphosphate **260**. The phosphonates were tested for their ability to displace [^{3}H]GDP from GTP binding protein cellular (EC) and oncogenic (Leu-61) Ha-*ras* p21 and for their ability to inhibit DNA polymerase from Chinese hamster ovary cells.

Other nucleotide analogues with a CF_2 group in the place of an oxygen next to the first phosphorus atom were prepared from the tris(tetrabutylammonium) salt of difluoromethanediphosphonic acid and the tosylate of the nucleoside; they initially give the CF_2 pyrophosphate analogues, which were converted with orthophosphate into α,β-CF_2-nucleotides.[292,293] Isopentyl and geranyl difluoromethylenephosphonates of general formula **261** were also prepared using this methodology (Chart 9).[43,294]

Chart 9

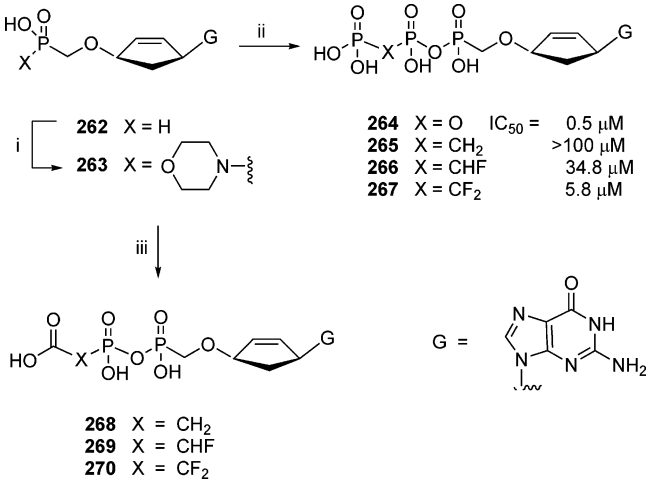


261

X = O, CH_2, CF_2

The search for carbocyclic nucleotides with potent anti-HIV (human immunodeficiency virus) activity led to the synthesis of the pyrophosphoryl phosphonate **264**[295,296] and its diphosphonate analogues **265**−**267**[100,297] with progressive fluoro-substitution within the β,γ-methylene linker group, as described in Scheme 75. Noteworthy features of the

Scheme 75[a]



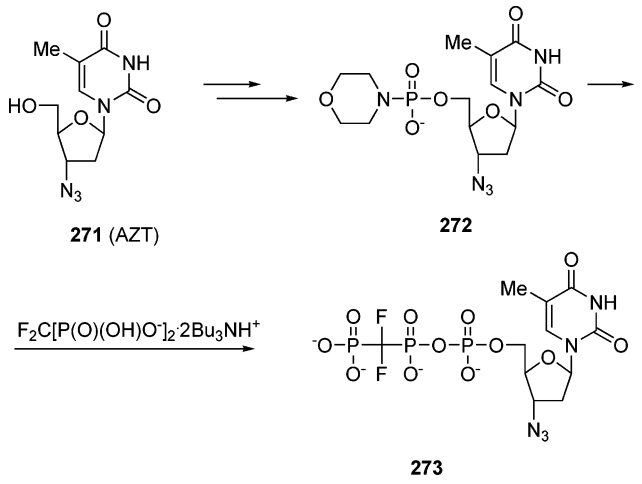
[a] Reagents and conditions: (i) morpholine, DCC, ^{t}BuOH, H_2O; (ii) $[(HO)_2P(O)]_2X{\cdot}Bu_3N$ (X= CH_2, CHF, CF_2), DMSO, rt; (iii) $(HO)_2P(O)XC-O_2H$ (NBu_3 salt), DMSO), rt.

chemical syntheses include the transformation of the nucleoside monophosphate **262** into the activated morpholidate **263**, and the coupling of **263** with the corresponding diphosphonates. Nucleotide **264** was found to be a potent inhibitor of HIV reverse transcriptase. The three nucleotide triphosphate mimics **268**−**270** were also synthesized and tested as inhibitors of HIV RT in an enzyme assay. Both **268** and the monofluorinated analogue **269** showed relatively poor activity, being 3 orders of magnitude less active than the parent compound **264**. The difluorinated analogue **270** was markedly more effective than the monofluorinated substrate but was still two hundred times less potent than **264**. The disappointing activity of **268**−**270** may be because the

carboxy group is a poor mimic of the terminal phosphonate group in compound **267**.[100]

3′-Azido-3′-deoxythymidine (**271**, AZT), used extensively as an approach to the management of HIV infection, is metabolized in cells to the corresponding 5′-triphosphate (AZTTP), the proximate inhibitor of HIV RT.[298] The preparation of the β,γ-difluoromethylene-bridged analogue of AZTTP (**273**) was accomplished by the coupling of difluoromethanediphosphonic acid to 3′-azido-3′-deoxythymidine 5′-monophosphate, activated as the morpholidate **272** (Scheme 76).[70]

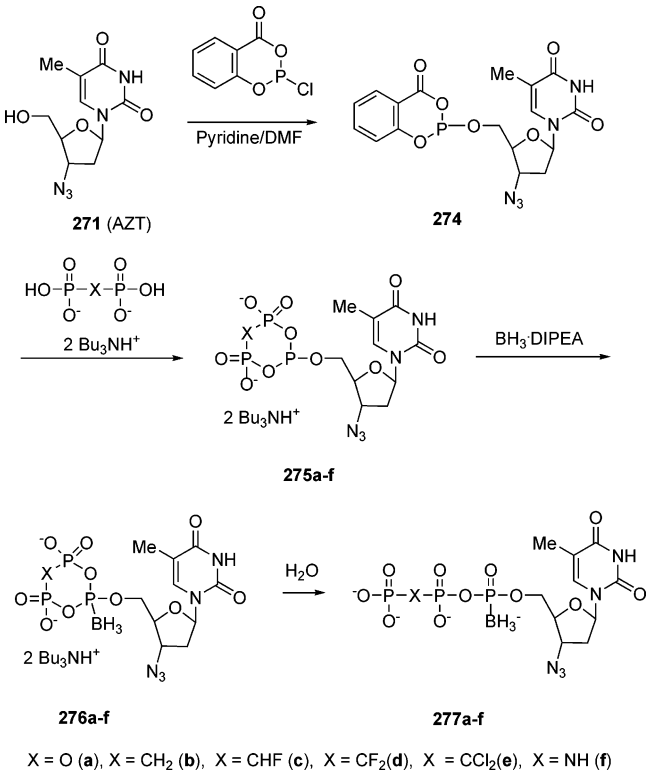
Scheme 76



A very efficient synthetic procedure via an activated phosphite and a cyclized triphosphate intermediate was adopted by Wang and co-workers for the preparation of series of novel AZT triphosphate mimics.[299] Reaction of **271** with 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one, followed by treatment of the phosphite intermediate **274** with pyrophosphate analogues, yielded the cyclic triphosphate intermediates **275**, which were subjected to boronation and subsequent hydrolysis to give AZT 5′-α-borano-β,γ-bridge-modified triphosphates **277** in moderate to good yields (Scheme 77). As in oligonucleotide synthesis, the phosphite intermediate **275d** could be oxidized with iodine and a subsequent treatment with a nucleophile yielded AZT triphosphate mimics having diverse modifications on the triphosphate moiety (Scheme 78). Other types of triphosphate mimics containing α-borano-β,γ-difluoromethylene and γ-*O*-methyl/phenyl (**279a**,**b**), α-*P*-thio (or dithio) and β,γ-difluoromethylene (**280** and **281**), and α,β-difluoromethylene and γ-*P*-methyl/phenyl (**282a**,**b**) were also synthesized (Chart 10). Several new compounds exhibited very potent inhibition of HIV-1 RT.

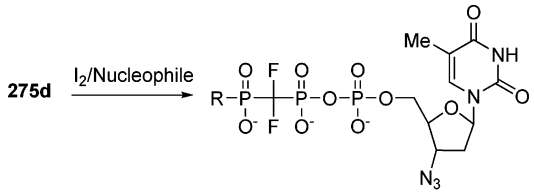
Synthesis of a series of 2′,3′-dideoxynucleoside 5′-α-*P*-borano-β,γ-(difluoromethylene)-triphosphates, ddN5′-αB-β,γ-CF_2TPs, and their inhibitory properties on HIV-1 RT have also been studied (Scheme 79).[300] Compounds **283** were prepared according to a similar procedure for preparation of AZT 5′-αB-β,γ-CF_2TPs (see Scheme 77). However, this synthetic route did not apply well to the nucleosides having an exocyclic amino group; therefore, an alternative synthetic procedure was developed (Scheme 80). The course of the reactions was similar to that in Scheme 77 except that the bis(diisopropylamino)phosphites were the active phosphite intermediates. Treatment of **284** with bis(tributylammonium) difluoromethylenediphosphonate presumably yielded the

Scheme 77



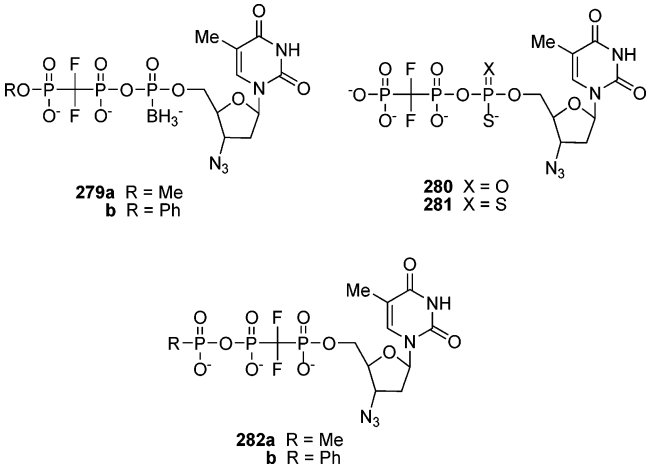
X = O (**a**), X = CH_2 (**b**), X = CHF (**c**), X = CF_2(**d**), X = CCl_2(**e**), X = NH (**f**)

Scheme 78



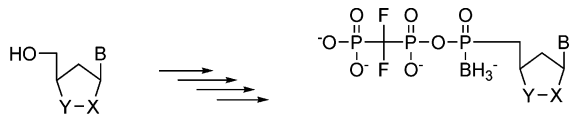
R = OH (**a**), MeNH (**b**), EtNH (**c**), PhNH (**d**), NH_2 (**e**), N_3 (**f**), F (**g**), MeO (**h**), PhO (**i**)

Chart 10



cyclic triphosphates **285**, which were subsequently subjected to boronation and hydrolysis to give **286**. All the resulting ddN5′-αB-β,γ-CF_2TPs demonstrated essentially the same level of inhibition of HIV-1 RT as the corresponding ddNTPs. Given their enhanced biological stability, these compounds represent a new class of potential antiviral agents.

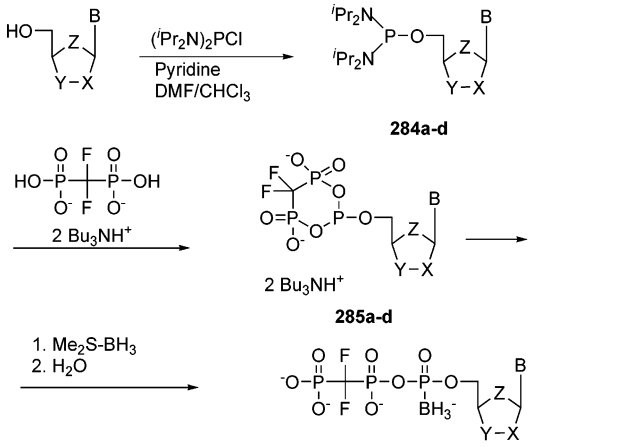
Scheme 79



283a-f

B = thymine, X = Y = CH_2 (**a**); B = thymine, X, Y = CH=CH (**b**); B = 5-F-cytosine, X = CH_2, Y = S (L-ribose) (**c**); B = uracyl, X = Y = CH_2 (**d**); B = adenine, X = Y = CH_2 (**e**); B = 7-deazaguanine, X = Y = CH_2 (**f**)

Scheme 80



284a-d

285a-d

286a-d

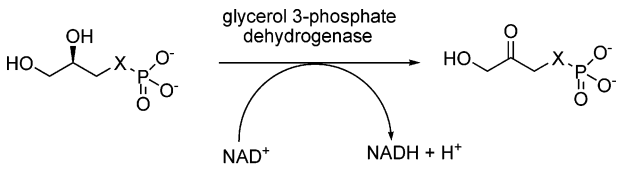
B = cytosine, X = Y = CH_2, Z = O (**a**); B = cytosine, X = CH_2, Y = S (L-ribose), Z = O (**b**); B = thymine, X = CH_2, Y = CHF (F on α-face), Z = O (**c**); B = guanine, X = Y = CH, Z = CH_2 (**d**)

Recently Mohamady and Jakeman have shown that nucleoside monophosphates, when activated by trifluoroacetic anhydride and *N*-methylimidazole, efficiently couple with a variety of electron-deficient diphosphonates (>72% isolated yield). Unlike traditional methods for the preparation of nucleoside 5′-β,γ-methylenetriphosphate analogues, there is no requirement for predrying or conversion to specific salt forms of commercially available nucleoside monophosphate starting materials.[301]

3.2. Analogues of *sn*-Glycerol 3-Phosphate and Phospholipids

3(*S*),4-Dihydroxybutylphosphonate **288** and the corresponding CHF- and CF_2-phosphonates **289** and **270**, the isoelectronic and isosteric analogues of biologically important *sn*-glycerol 3-phosphate **287**, are substrates for NADH linked *sn*-glycerol 3-phosphate dehydrogenase (Scheme 81).[11,184,212]

Scheme 81

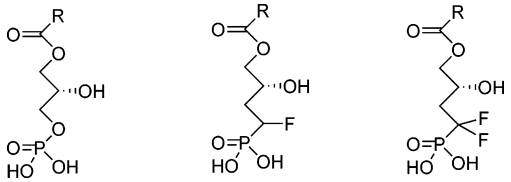


	K_m/mmol dm^{-3}	V_{rel}
287 X = O	0.2	1.0
288 X = CH_2	0.18	0.8
289 X = CHF	0.17	0.9
290 X = CF_2	0.73	0.8

A synthetic approach to 3(*S*),4-dihydroxy-1-(*R*,*S*)-fluorobutylphosphonate **289** exploited methodology employing fluorinated phosphonate carbanions (see Scheme 33). Treatment of the protected monofluorophosphonate **97a** with bromotrimethylsilane and subsequent addition of water provided the α-monofluorophosphonic acid **289** as a diastereomeric mixture (1:1) epimeric at the CHF stereogenic center. Synthesis of the 3(*S*),4-dihydroxy-1,1-difluorobutylphosphonate **290** has been performed by addition of $(EtO)_2P(O)CF_2$-$SiMe_3$ to (*S*)-2,3-*O*-isopropylideneglyceraldehyde under fluoride catalysis followed by dehydroxylation (Scheme 57). The difluorophosphonate **186** formed was deprotected in the mentioned manner and isolated as its biscyclohexylammonium salt. Both fluorinated phosphonates **289** and **290** emerged as good substrates for G-3-P dehydrogenase. The Michaelis constants (K_m) and relative V_{max} values revealed that the CHF-phosphonate **289** is a significantly better substrate for the dehydrogenase than the CF_2-phosphonate **290**. In fact, **289** shows the same K_m value as the CH_2-phosphonate **288**, and both **288** and **289** have lower K_m values than *sn*-glycerol 3-phosphate itself. The study also revealed that the diastereomers of **289** are processed at different rates suggesting that the enzyme can discriminate the CHF stereogenic centers.[184]

Interest in phosphatase-resistant phosphonolipids as phospholipids analogues has grown substantially with the recognition that lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) is an important mitogenic signal in ovarian cancer and in normal cell proliferation and migration.[302,303] In a benchmark series of papers, Prestwich and co-workers have prepared a variety of new phosphonate analogues of natural phospholipids in which the bridging oxygen in the monophosphate was replaced with a CHF or CF_2 moiety (Chart 11).[101,120,304−307]

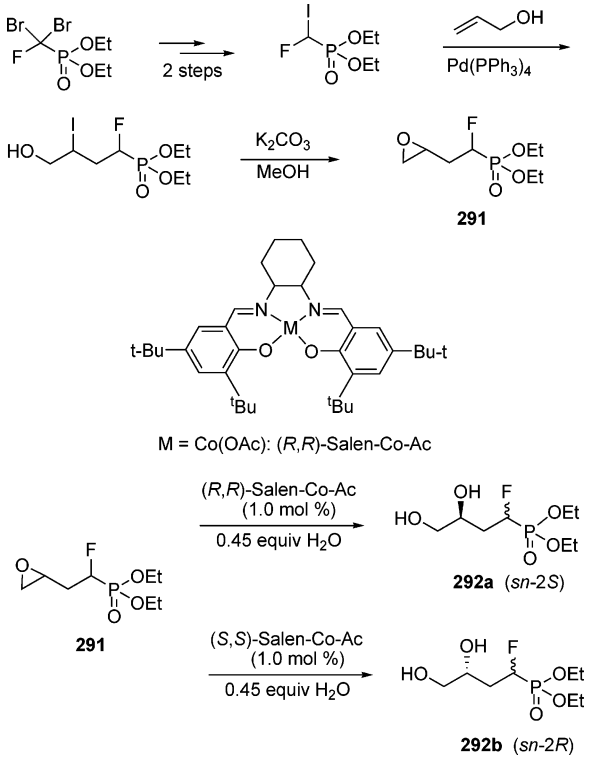
Chart 11. *sn*-1-*O*-Acyl Lysophosphatidic Acid (LPA, left) and Its Fluorinated Phosponate Analogues



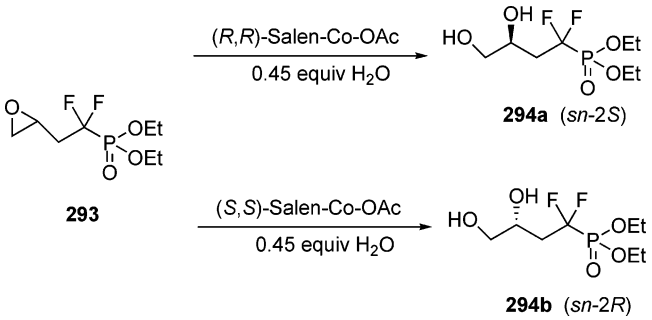
The synthesis of the monofluoromethylene phosphonate analogues **292** by hydrolytic kinetic resolution of the racemic 1-fluoro-3,4-epoxybutylphosphonate **291** is illustrated in Scheme 82.[120] Reaction of **291** with 0.45 equiv of H_2O in a minimum volume of THF, in the presence of 1.0 mol % of enantiomeric cobalt complex (*R*,*R*)-Salen-Co-OAc as catalyst, gave diol **292a** in 73% isolated yield and 90% ee. Similarly, catalyst (*S*,*S*)-Salen-Co-OAc provided the opposite configuration of diol **292b** with 89% ee and in 90% yield. Each diol was isolated as an inseparable equimolar mixture of two diastereomers epimeric at C-1. In analogy to **292**, the hydrolytic kinetic resolution of 1,1-difluoro-3,4-epoxybutylphosphonate **293** using a chiral Salen-Co-OAc complex was employed as a key step to obtain enantiomeric α,α-difluoroalkylphosphonates **294** with 99% ee (Scheme 83).[304]

Regioselective acylation of the primary hydroxy group of diols **292** and **294** was readily accomplished (Scheme 84). For example, treatment of **292a** with 0.95 equiv of oleic acid and 1.2 equiv of DCC and DMAP provided **295aa** in 42% yield. The corresponding palmitate **295ab** and linoleate **295ac** were similarly produced, as were the enantiomeric oleate **295ba** and palmitate **295bb**. Deesterification of these

Scheme 82



Scheme 83

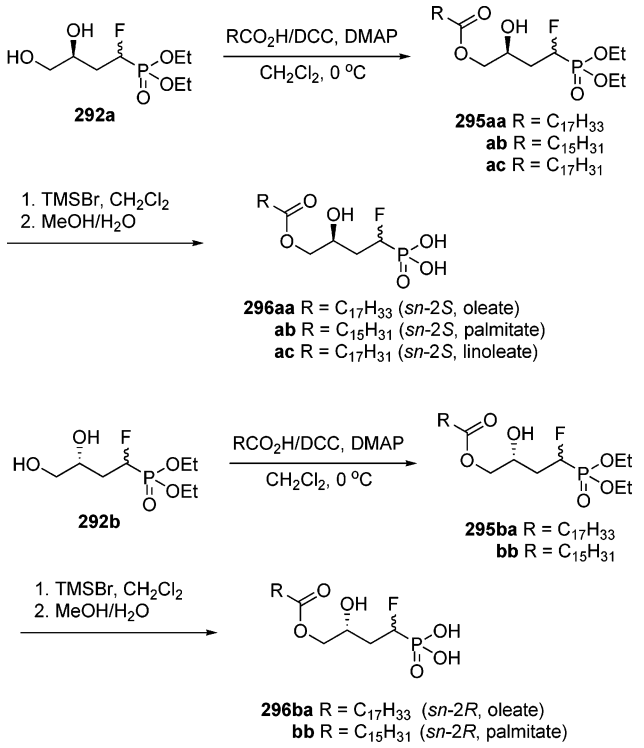


LPA analogues was accomplished by treatment of the diethyl esters with excess bromotrimethylsilane. The diastereomeric 1-fluoro-3-hydroxyl isomers of compounds **292**, **295**, or **296**, however, could not be separated.[120]

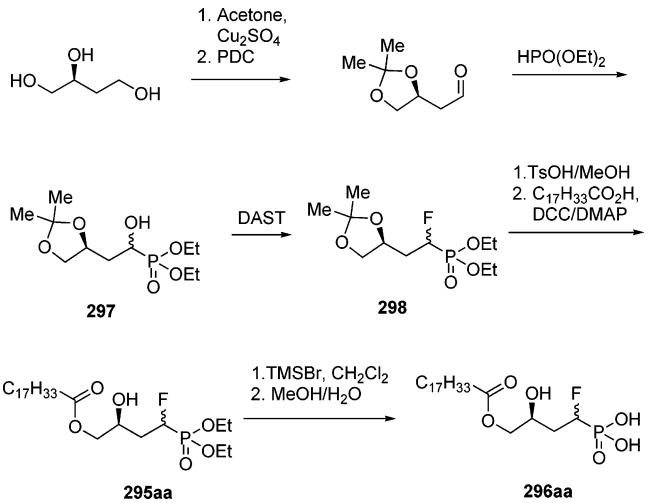
Diastereoselective synthesis of *sn*-1-*O*-acyl fluoromethylenephosphonate LPA analogue **296aa** is shown in Scheme 85. (2*S*)-1,2,4-butantriol was protected as the isopropylidene ketal and oxidized with pyridinium dichromate to give the corresponding aldehyde. The Pudovik reaction was then employed to introduce the C−P bond. This addition reaction occurred without diastereoselectivity. The compound **297** was treated directly with DAST, which gave a pair of diastereomers **298** in a 6.3:1 ratio. After deprotection by acid hydrolysis and selective esterification, phosphonate **295aa** was obtained in >89% de. Finally, TMSBr deprotection gave the phosphonate **296aa** showing >89% de.[120] Remarkably, the monofluoromethylenephosphonate LPA analogue **296aa** was 1000-fold more potent than natural 1-oleoyl LPA for the LPA_3 receptor. This response was enantiospecific, indicating that the α-fluorophosphonates are structurally informative and receptor-selective mimics for phosphate in LPA.[308]

Methods for selective introduction of an *O*-methyl group at the *sn*-2 and *sn*-1 positions were also developed (Scheme 86).[101] Thus, the slow reaction of Meerwein's trimethyloxonium tetrafluoroborate salt with diol **292a** in the presence of non-nucleophilic amine base (e.g., proton sponge, 1,8-bis(dimethylamino)naphthalene) provided a good yield of

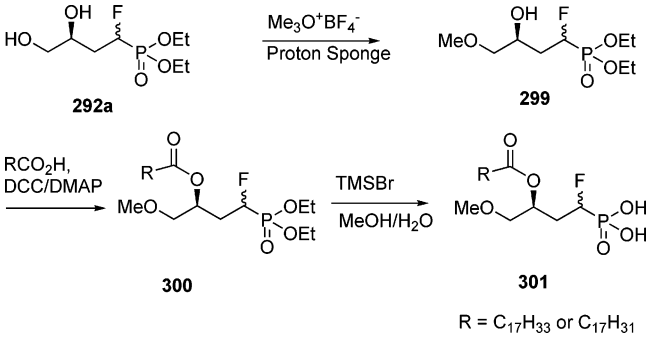
Scheme 84



Scheme 85

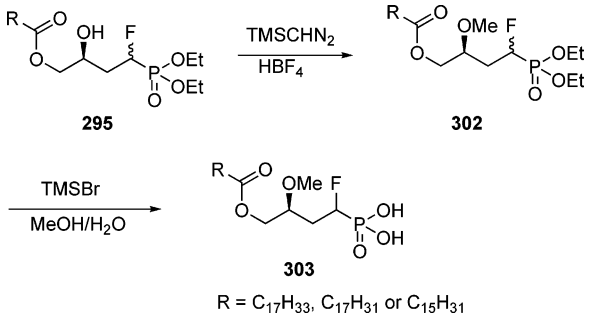


Scheme 86



1-*O*-methylation product **299** after 4 days at room temperature. After esterification at *sn*-2 position and deprotection of diethyl ester, the acyl-chain migration-blocked *sn*-2 LPA analogues **301** were obtained. In turn, 2-*O*-methylated products **303** bearing an acyl group at the *sn*-1 position have been prepared by direct reaction of the compounds **295** with trimethylsilyldiazomethane. This reaction provided good yield of **302** with no acyl migration observed. Treatment of each ester with bromotrimethylsilane and subsequent addition of 5% aq methanol provided the desired *sn*-2-*O*-methylated LPA analogues **303** in nearly quantitative yields (Scheme 87).

Scheme 87



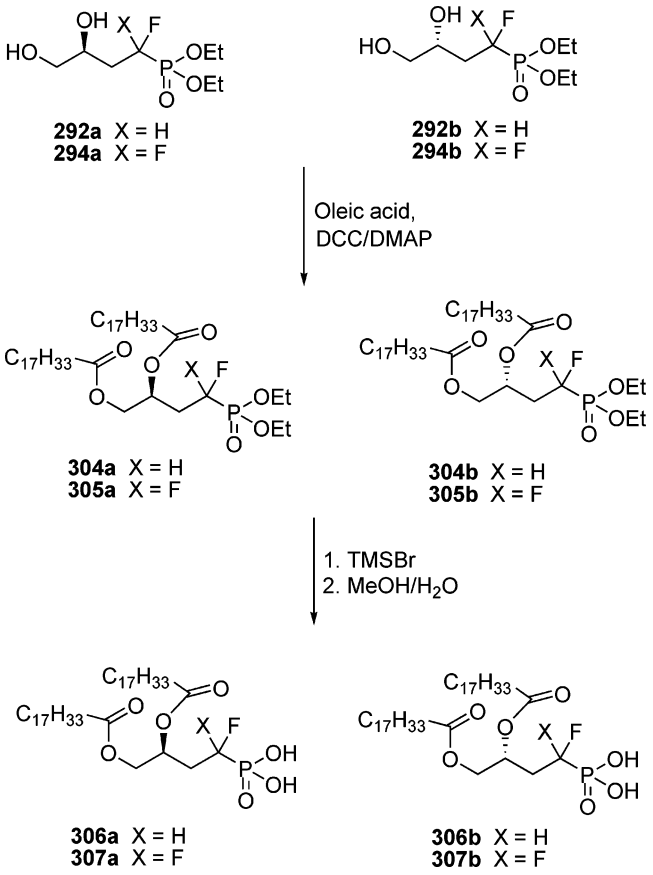
Recently, phosphatidic acid (PA, 1,2-diacyl-*sn*-glycerol 3-phosphate) has been reported to be critically involved in the mammalian target of rapamycin (mTOR) pathway.[309] Therefore, phosphonate analogues of PA were synthesized, in which the bridging oxygen was replaced by a fluoromethylene or difluoromethylene moiety. Thus, treatment of the diols **292** and **294** with 2.2 equiv of oleic acid, 2.4 equiv of DCC, and a catalytic amount of DMAP (0.5 equiv) gave the corresponding diacylated diethyl phosphonates **304** and **305** in good yield. Dealkylation of the esters with excess bromotrimethylsilane and subsequent hydrolysis by addition of 5% aq methanol led to the PA analogues **306** and **307** in essentially quantitative yield (Scheme 88). The biological evaluation indicated that each of the four metabolitically stabilized PA analogues, **306a**,**b** and **307a**,**b**, stimulated S6 kinase, a downstream target of mTOR signaling, to a similar or slightly greater extent relative to PA in quiescent HEK 293 cells. Interestingly, the fluoromethylenephosphonate PA analogues with the unnatural (2*R*) configuration at *sn*-2 (**306b** and **307b**) were more active than those with the natural (2*S*) configuration (**306a** and **307a**).[305]

Toward the objective of preparing a series of optically pure analogues of 1,2-dihexanoyl-*sn*-glycero-3-phosphocholine (**308**) containing different replacements of the phosphate group, Martin and co-workers developed an efficient route to the difluoromethylenephosphonate **311** (Scheme 89).[197] Diacylation of diol **294a** followed by selective deprotection of phosphonate diester **314** provided an intermediate phosphonic acid, which was coupled with choline chloride in the presence of trichloroacetonitrile/pyridine to furnish **311**. Kinetic studies indicated that the phosphatidylcholine analogues tested were competitive inhibitors of the bacterial phospholipase C from *Bacillus cereus* with increasing K_i's as follows: **312** ≈ **313** < **309** < **310** ≈ **311**.

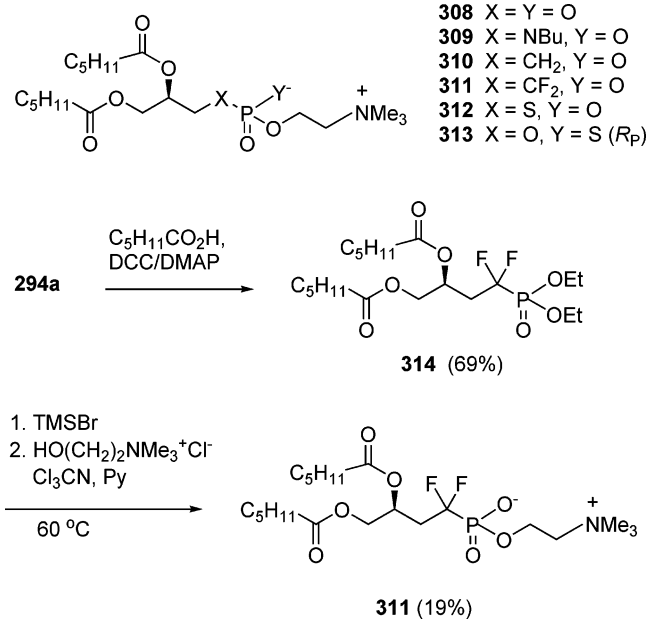
3.3. Analogues of Phosphoenolpyruvate

2-[(Dihydroxyphosphonyl)difluoromethyl]propenoic acid **318** in addition to being isopolar and isosteric with PEP was

Scheme 88

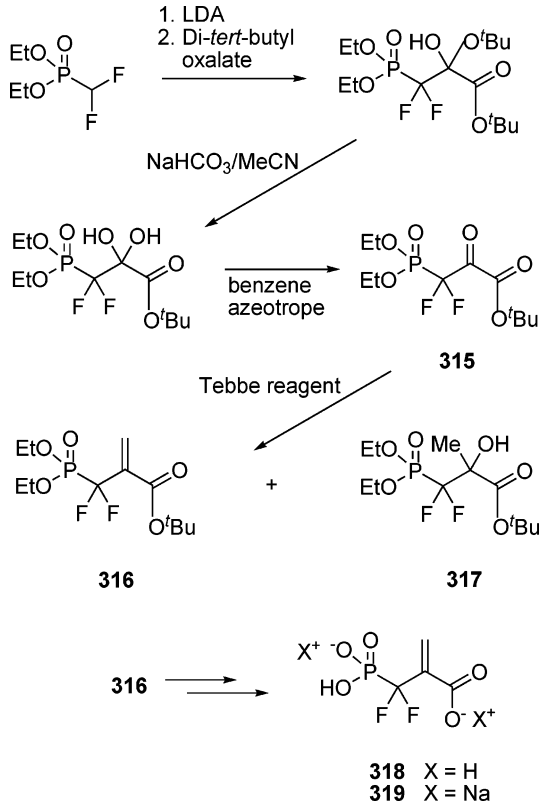


Scheme 89



envisioned to be a potential Michael acceptor that could bind irreversibly to an enzyme site for which PEP is a substrate.[239] The synthesis of disodium salt of **318** is shown in Scheme 90. Keto ester **315** has been synthesized via the reaction of difluoromethylenephosphonate carbanion with di-*tert*-butyl oxalate followed by hydrolysis and azeotropic dehydration with benzene. Attempts to prepare **316** by a traditional Wittig reaction or by a Peterson olefination sequence have not been successful. In contrast, Tebbe reagent (μ-chloro-μ-methylenebis(cyclopentadienyl)titanium-dimethylaluminum) reacted

Scheme 90



with **315** to give an inseparable 3:1 mixture of **316** and **317**. Treatment of the mixture with *N*,*O*-bis(trimethylsilyl)-acetamide and subsequent purification by preparative LC afforded pure **316** in 20% yield. The latter was converted to 2-(phosphonodifluoromethyl)acrylic acid **318** by heating in trifluoroacetic acid. Disodium salt **319** showed irreversible time-dependent inhibition of EPSP synthase, which catalyzes the reaction of shikimate 3-phosphate (S3P) with PEP to produce 5-enolpyruvoylshikimate 3-phosphate as an intermediate in the biosynthesis of essential aromatic amino acids.[239]

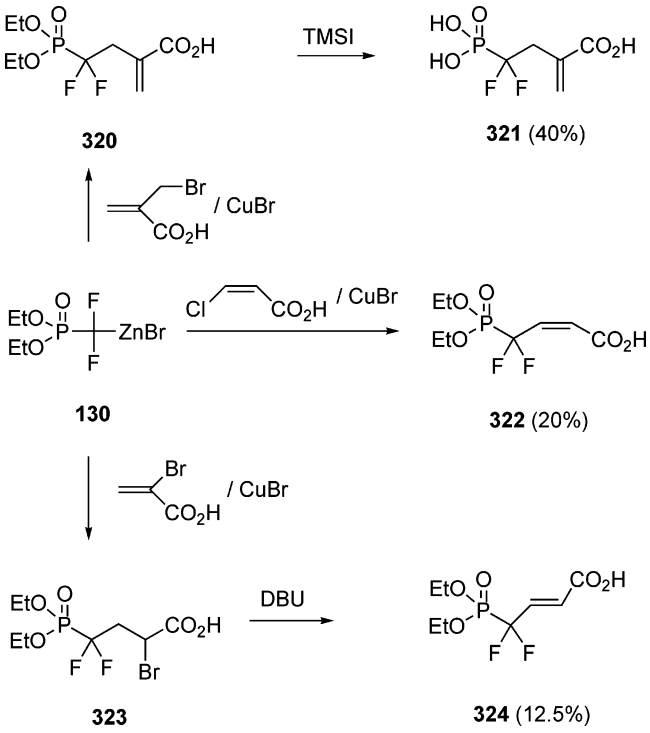
New types of phosphonate analogues of PEP have been developed by Kawamoto and Campbell (Scheme 91).[211] Diethyl 4,4-difluoro-4-(diethoxyphosphonyl)-2-methylenebutanoate **320** was prepared by the reaction of the zinc reagent $(EtO)_2P(O)CF_2ZnBr$ (**130**) with 2-(bromomethyl)acrylic acid in the presence of a catalytic amount of CuBr. Treatment of **320** with excess TMSI provided the corresponding acid **321** in 40% yield. Reaction of **130** with *cis*-3-chloroacrylic acid afforded compound **322** with same *Z*-configuration as starting material. Additionally, *E*-isomer **324** has been prepared by the route involving the reaction of **130** with 2-bromoacrylic acid and subsequent dehydrobromination of **323** with DBU.

Phosphonate **325**, another target substrate because of its potential use in the shikimate pathway, has been prepared from lithio difluoromethylphosphonate and methylpyruvate (Scheme 92).[211] Hydrolysis of **325** at 60 °C over period of 7 days afforded **327** in quantitative yield. The direct dehydration of **325** to the corresponding olefin **326**, which is an analogue of PEP, was unsuccessful.

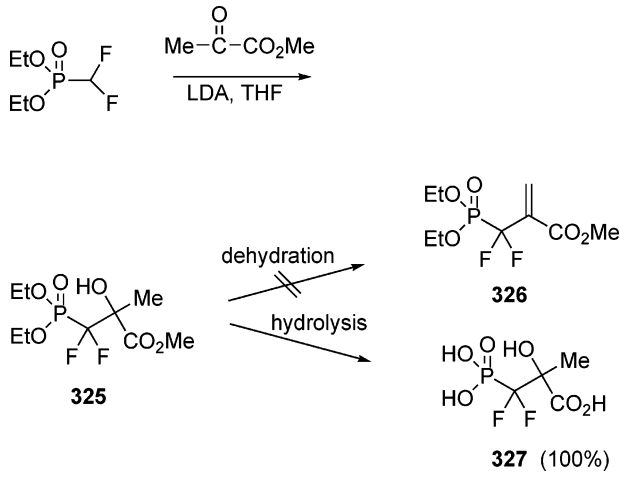
3.4. Carbohydrate- and Related Polyol-Derived Fluorophosphonates

Synthesis of fluorinated phosphonocarbohydrates appears attractive to prepare new classes of phosphate mimics of

Scheme 91



Scheme 92

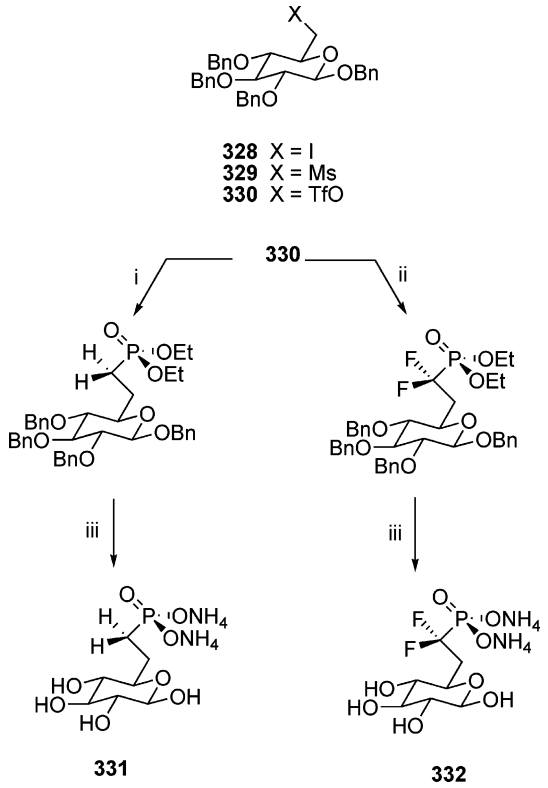


natural metabolites that retain high affinity for targeted enzymatic phosphate binding pockets but are themselves resistant to phosphatase-mediated cleavage. Here, we focus our attention on the carbohydrate structures featuring $CHFP(O)(OH)_2$ and $CF_2P(O)(OH)_2$ groups. Synthesis and transformations of deoxyfluoro sugars and *C*-difluoromethylene-containing *C*-trifluoromethyl and *C*-perfluoroalkyl carbohydrates have been reviewed.[140,310,311]

The most useful methods of grafting a $(RO)_2P(O)CF_2$ group on a carbohydrate are (i) nucleophilic displacement of primary triflates derived from monosaccharides,[17,198,206−210] (ii) nucleophilic addition−deoxygenation sequence,[18,186,259,312] and (iii) radical addition of a dialkyl phosphite to the anomeric difluoromethylene compounds.[255−259]

In search for synthetic approaches to a glucose 6-phosphate (G6P) analogue, Berkowitz and co-workers examined glucopyranose iodide **328** and mesylate **329** and found that neither underwent displacement with $(EtO)_2P(O)CF_2$ anion. Triflate **330**, on the other hand, was stable to an aqueous bicarbonate workup and silica gel chromatography yet

Scheme 93



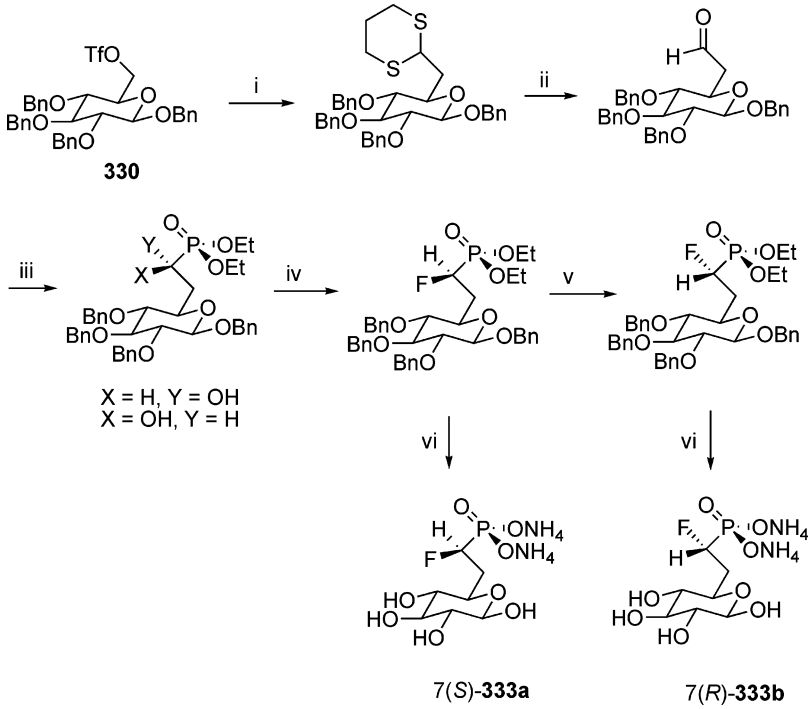
reactive enough to be displaced by difluoromethylenephosphonate anion at −78 °C.[198] Thus, construction of the C6−C7 bond by nucleophilic displacement of glucopyranose triflates with lithiomethylphosphonates was used as the key step in convergent syntheses of both the nonfluorinated phosphonate **331** and its α,α-difluorinated congener **332** (Scheme 93).[17]

For the synthesis of α-monofluoroalkylphosphonate analogues, homologation of **330** was achieved via lithiodithiane-mediated triflate displacement, followed by aldehyde unmasking. The Abramov reaction was then employed to fashion the C7−P bond. Addition of diethyl phosphite anion produces diastereomeric (α-hydroxy)phosphonates, which are transformed into diastereomerically pure phosphonocarbohydrates **333** as shown in Scheme 94. Titration of G6P itself and the free phosphonic acids provides second pK_a values of 6.5 (G6P, bridging O), 5.4 (**332**, bridging CF_2), 6.2 (**333a**, bridging CHF), and 7.6 (**331**, bridging CH_2). Thus, α-monofluorination produces a phosphonate functionality that is most nearly "iso-ionic" (pK_{a^2} = 6.2) with the actual phosphate ester (pK_{a^2} = 6.5). Steady-state enzyme kinetic analysis with glucose 6-phosphate dehydrogenase (G6PDH) from *Leuconostoc mesenteroides* yields normalized k_{cat}/K_m values of 0.043 (**333b**, bridging 7(*R*)-CHF), 0.11 (**332**, bridging CF_2), 0.23 (**331**, bridging CH_2), and 0.46 (**333a**, bridging 7(*S*)-CHF) relative to G6P itself, largely reflecting differences in K_m. Thus, the most striking observation is that the best phosphate mimic, **333a** (K_m = 0.23 mM vs 0.12 mM for G6P) is of the iso-acidic α-monofluorophosphonate class, as is also the worst phosphate mimic, **333b** (K_m = 2.3 mM). These results clearly indicate that close attention must be paid to the effect of CHF stereochemistry upon receptor binding in this type of hydrolytically stable phosphate mimic.[17]

Treatment of difluoroalkene **334** with hypophosphorous acid sodium salt in the presence of triethylborane and oxygen (air) produced adduct **335**, isolated as a single isomer. The latter could be esterified by reaction with alcohol **336** in the presence of DCC and trifluoroacetic acid. α,α-Difluoro-*H*-phosphinic acid monoester **337** was then treated with chlorotrimethylsilane, pyridine, and sulfur to give difluorophosphonothioic acid monoester, isolated as its triethylammonium salt **338** (Scheme 95).[18,261]

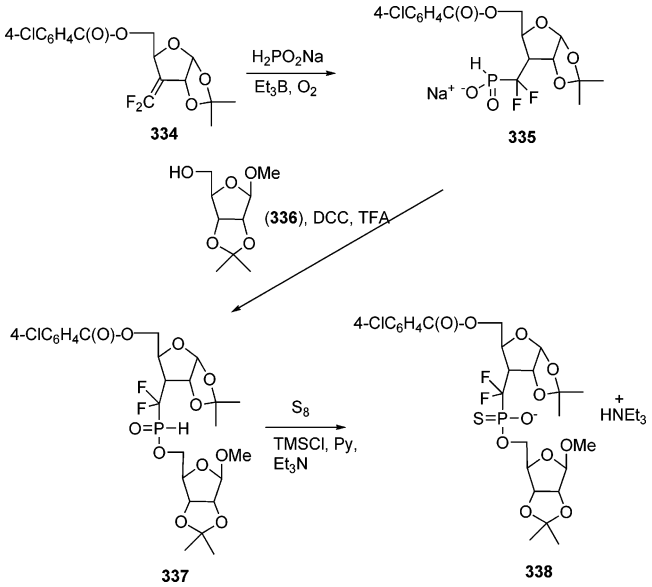
In the last decade, inhibitors of the enzymes involved either in the formation of D-galactofuranosyl (D-Gal*f*) residues (mutases) or in their transfer onto carbohydrate chains

Scheme 94[a]



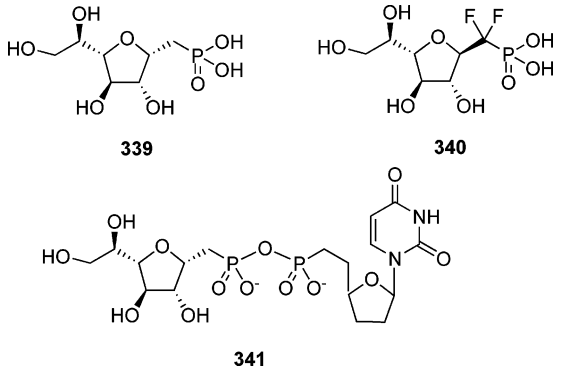
[a] Reagents: (i) dithiane, BuLi (94%); (ii) $Hg(ClO_4)_2$, $CaCO_3$; THF, H_2O (88%); (iii) $(EtO)_2P(O)H$, LiHMDS; THF (93%); (iv) DAST, CH_2Cl_2 (32−50%); (v) LDA, HOAc quench; (vi) TMSBr, CH_2Cl_2; then H_2, $Pd(OH)_2/C$; NH_4HCO_3 (3 steps).

Scheme 95



(transferases) became important drug targets. Among others, D-galactofuranosylphosphonates **339** and **340** were prepared via the Arbuzov rearrangement and the phosphonyl radical addition, respectively. These are stable substrates, and the α-phosphono analogue **339** has been easily converted into UDP-C-Gal*f* **341**. Preliminary studies of the inhibition of the formation of UDP-Gal*f* from UDPGal*p* were performed (Chart 12).[258]

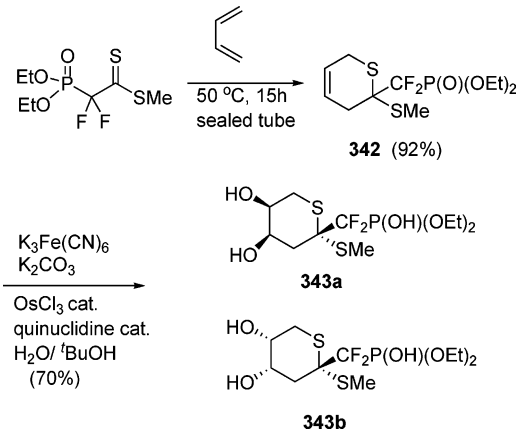
Chart 12



To obtain new potential inhibitors of glycosyltransferases, Lequeux and co-workers investigated the synthesis of fluorinated phosphonodithioacetate, $(EtO)_2P(O)CF_2CS_2Me$ (see section 2.4.2.5), and explored its potential as a new building block to prepare carbohydrate structures.[243] A specific reaction useful for the synthesis of phosphonodifluorothiaglycoside precursor **342** is shown in Scheme 96. By use of the modified Sharpless conditions, thiapyran **342** was selectively dihydroxylated without affecting the sulfur centers. A mixture of the two dihydroxy-tetrahydrothiapyran diastereomers **343a** and **343b** was obtained in 8/2 ratio and isolated in 70% yield.

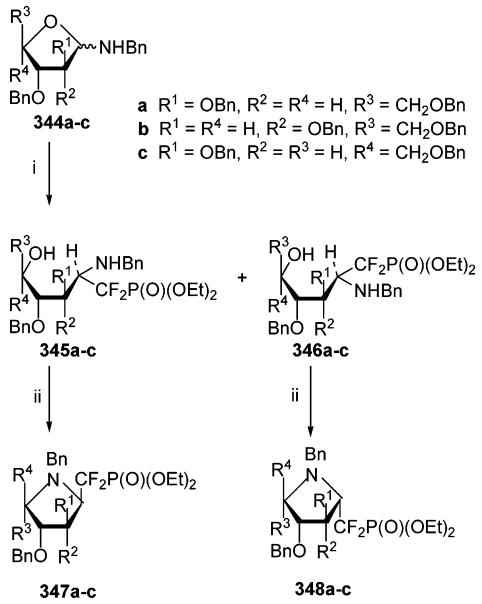
Synthesis of difluoromethylphosphonate azasugars designed as inhibitors for glycosyl transferases was reported by Guillerm and co-workers.[313] It was demonstrated that polyhydroxylated aminofuranoses **344** derived from protected D-arabinose, D-ribose, and L-xylose readily undergo nucleophilic ring opening with $(EtO)_2P(O)CF_2Li$ to give the two possible diastereomers **345** and **346**. In all cases, the

Scheme 96



diastereoselection is moderate. For the final cyclization step, each of the difluorophosphonate derivatives **345** and **346** was esterified with methanesulfonyl chloride to give the corresponding methanesulfonates, which underwent smooth nucleophilic displacement with the amino group to form the expected azasugars **347** and **348** with inversion of configuration at C-5 (Scheme 97).

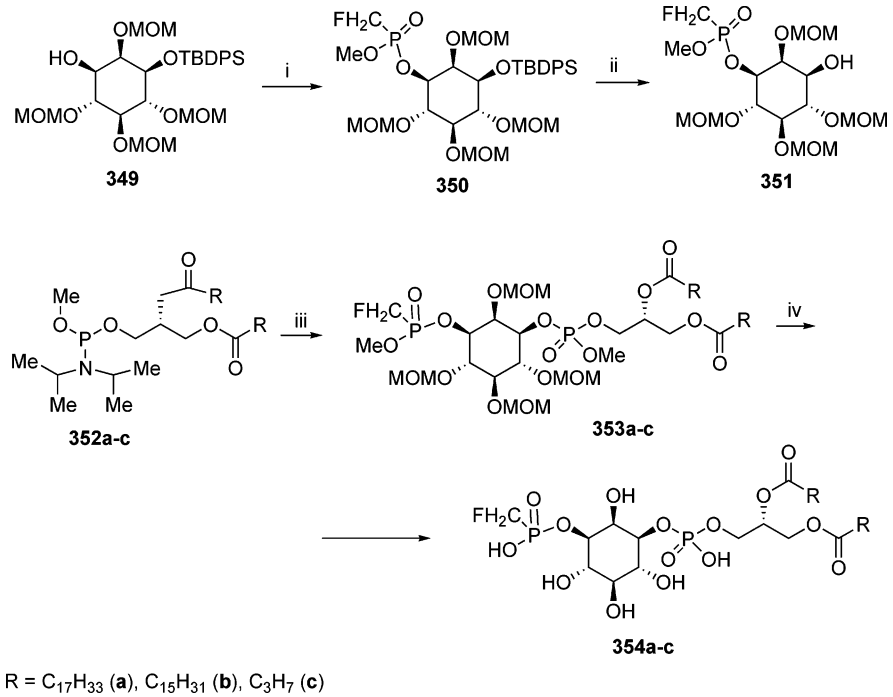
Scheme 97[a]



[a] Reagents and conditions: (i) $(EtO)_2P(O)CF_2H$, LDA, THF−hexane, −78 °C; (ii) MsCl, pyridine.

The chemistry of phosphonates bearing the monofluoromethyl group has been exploited in the synthesis of phosphatase-resistant analogues of phosphatidylinositol-3-phosphate (PtdIns(3)P) (Scheme 98).[314] In the presence of *t*BuOK, reaction of D-*myo*-inositol derivative **349** with methyl (fluoromethyl)phosphonyl chloride, which has general applications for the preparation of "pK_a-matched" monofluorophosphonates, provides a convenient synthesis of phosphonate ester **350**. The silyl group in the 1-position was removed with the neutral reagent TBAF−HOAc, and the resulting alcohol **351** was treated with one of the three diacylglyceryl phosphoramidite reagents **352a**−**c** in the presence of tetrazole followed by mild oxidation with *n*-Bu_4NIO_4 to give the fully protected PtdIns(3)P derivatives **353**. The PtdIns(3)P analogues **354a**,**b** with dioleoyl and dipalmitoyl chains were metabolically stabilized substrates for the 5-kinase enzyme PIKfyve.

Scheme 98[a]



[a] Reagents and conditions: (i) $FCH_2P(O)(OMe)Cl$, ^tBuOK, CH_2Cl_2; (ii) $TBAF\cdot 3H_2O$, HOAc, THF; (iii) **351**, 1H-tetrazole, THF/MeCN; then $^nBu_4NIO_4$, MeCN; (iv) Me_3SiBr, CH_2Cl_2; then $MeOH/H_2O$; then EtSH.

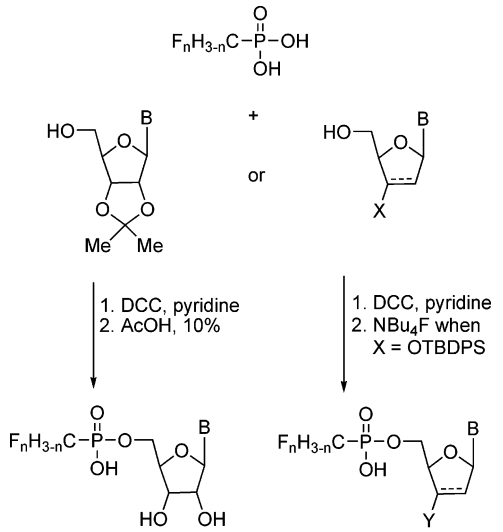
In the field of the acyclic polyol-derived phosphonates it is worth noting a recent synthesis of chiral 1,2-dihydroxy-3,3,3-trifluoropropylphosphonate, $F_3CCH(OH)CH(OH)P(O)(OEt)_2$.[315] Ethyl trifluoroacetate was reacted with anion of methylphosphonate to give 2-oxo-3,3,3-trifluoropropylphosphonate and its hydrate, which are reduced with sodium borohydride affording 2-hydroxy-3,3,3-trifluoropropylphosphonate in almost quantitative yield. This compound undergoes dehydration in the reaction with mesyl chloride in the presence of trimethylamine to provide an propenyl derivative $F_3CCH{=}CHP(O)(OEt)_2$. Treatment of the latter with aqueous potassium permanganate solution gave diethyl 1,2-dihydroxy-3,3,3-trifluoropropylphosphonate in 48% yield. Enzymatic kinetic resolution of the racemic chloroacetyl derivatives by *Candida antarctica* lipase B (CALB) or immobilized *Mucor miehei* (IM) afforded optically active 1,2-dihydroxy-3,3,3-trifluoropropylphosphonate with satisfactory chemical and enantiomeric yield.

3.5. Nucleoside Fluorophosphonates

The preparation of modified oligonucleotides has been the center of interest of many research groups in the two past decades.[13,18,141,316−319] Due to their higher stability toward enzymatic hydrolysis, modified nucleotides featuring fluorophosphonate groups have proven to be valuable as model constructs for designing enzyme inhibitors and as probes in elucidation of mechanisms of enzyme-catalyzed phosphoryl transfer reactions.

Besides replacement of the bridging oxygens in di- and triphosphate moieties (see section 3.1.2), fluoromethylene groups CHF or CF_2 could be either incorporated into nucleotides in place of 3′- or 5′-ribofuranoside oxygens, or incorporated as CH_2F, CHF_2, or CF_3 in place of a hydroxyl unit on the phosphate. In addition, during the past decade, extensive drug-discovery research has been devoted to the design and synthesis of acyclic analogues of nucleoside fluorophosphonates.

Scheme 99



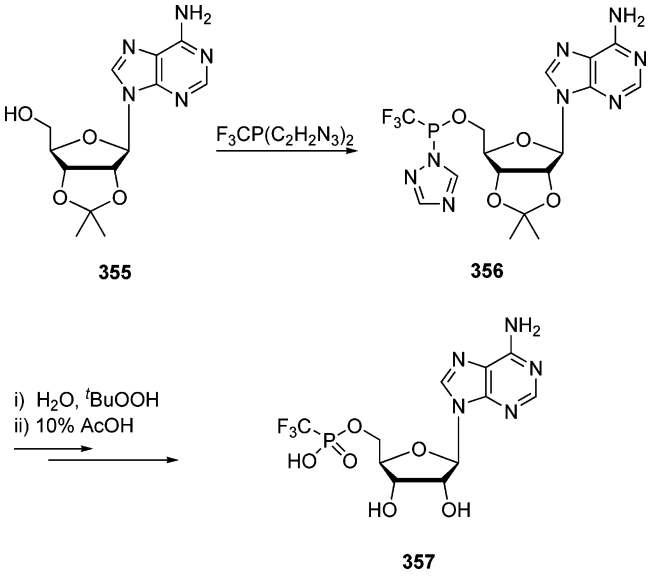
B = Nucleic base (G, A, C, U, T, 5-fluorouracil);
X = N_3, OTBDPS, or H Δ 2'-3'; Y = N_3, OH, or H Δ 2'-3';
n = 1-3

3.5.1. C_5'- and C_3'-Modified Nucleotides Featuring Monofluoro-, Difluoro-, and Trifluoromethyl Phosphonate Groups

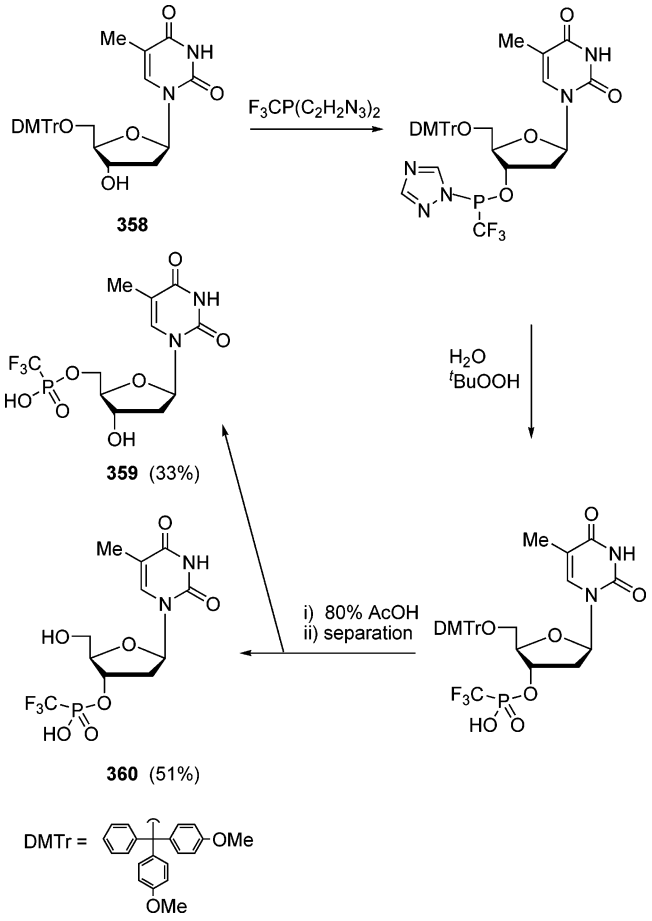
A general and straightforward route to the title compounds, starting from the appropriately protected nucleosides or 2′-deoxynucleosides and from monofluoro-, difluoro-, or trifluoromethylphosphonic acids is shown in Scheme 99. The chemical stability of the synthesized pseudo-nucleotides has been evaluated in various media. For example, no significant hydrolysis was found for the 5′-fluoromethylphosphonate of AZT at pH = 7.35 for 12 days at 50 °C, and only a slight hydrolysis at pH = 1.15 was observed during the same period. Several of the nucleoside fluorophosphonates had some activity against reverse transcriptase.[320]

An approach starting from 2′,3′-*O*-isopropylideneadenosine **355** and trifluoromethylphosphorous bis-triazolide provided the intermediate triazolyltrifluoromethylphosphonite **356**, which on hydrolysis, oxidation with ^{t}BuOOH, and deprotection gave the desired analogue of AMP **357** (Scheme 100).[321] Application of the same methodology to 5′-*O*-dimethoxytrityl thymidine **358** and trifluoromethylphosphorous bis-triazolide allowed Blackburn and Guo to obtain trifluoromethylphosphonate analogues of nucleotides **359** and **360** (Scheme 101).[321] Fluorinated nucleotide analogues such as **357**, **359**, and **360** are anticipated to be more prone to hydrolysis as compared with methylphosphonate analogues and might well be hydrolyzed with P−C cleavage to give phosphate diesters after passage across the cell membrane.

Scheme 100

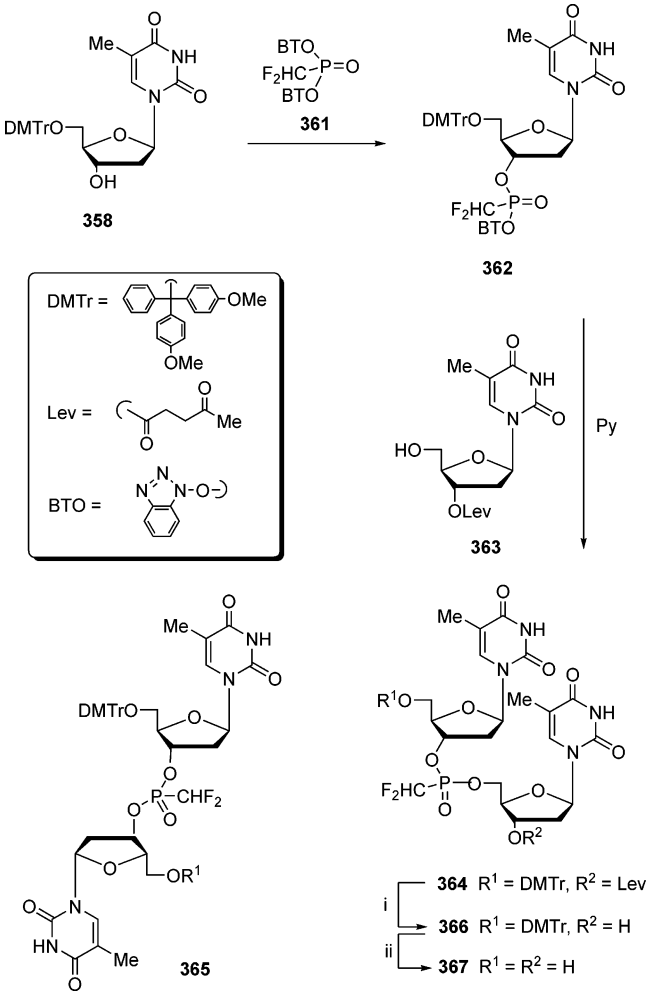


Scheme 101



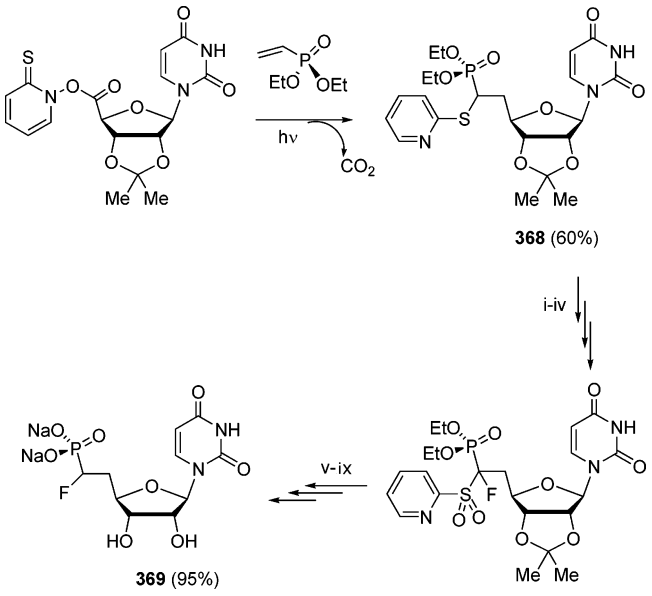
The synthesis of nonionic fluorophosphonate-linked nucleotide analogue **367** is divided into four parts: (a) the preparation of the 5′-*O*-protected thymidine **358**, (b) the preparation of the 3′-*O*-protected thymidine **363**, (c) the preparation of the difluoromethylphosphonate reagent **361**, and (d) the formation of the required 3′−5′ phosphonodiester linkage by employing the block-building method (Scheme 102). During the synthesis, it was found that the bis(1-benzotriazolyl)difluoromethylphosphonate **361** could function as the phosphonylating agent for 2 equiv of nucleoside giving a significant amount of 3′−3′-linked product **365** (35−40%) alongside the compound **362**. The yield of 3′−5′-linked dinucleotide analogue **364** has been improved up to 54% by running the first coupling reaction (formation of **362**) in an ice bath. The two diastereomers of the fully protected 3′−5′-linked thymidine dimer, **364***R*$_P$ and **364***S*$_P$, differing in configuration at phosphorus are formed in nearly equal amounts but were successfully separated by column chromatography.[32]

Scheme 102[a]



[a] Reagents and conditions: (i) hydrazine hydrate, Py/AcOH (3:2); (ii) AcOH/H_2O.

Scheme 103[a]



[a] Reagents and conditions: (i) *m*-CPBA; (ii) BzCl/EtN(ⁱPr)₂/Py; (iii) KH/Selectfluor, THF−DMF; (iv) NH_3/MeOH; (v) Bu_3SnH/AIBN, benzene, reflux; (vi) TFA/H_2O; (vii) TMSBr/DMF; (viii) DEAE, Sephadex; (ix) Dowes 50 × 8(H^+), then (Na^+).

3.5.2. C_5'- and C_3'-Modified Nucleotides Featuring Fluoromethylenephosphonate or Fluoromethylenephosphonothioate Groups

Synthesis of the first homonucleoside α-monofluoromethylenephosphonate has been reported by Wnuk and Robins.[322] They employed Barton's chain-extension method with diethyl vinylphosphonates and a protected uridine 5′-thiohydroxamic ester to obtain the 6′-(pyridine-2-yl) thioether **368**. Treatment of the latter with *m*-CPBA followed by benzoylation (BzCl), fluorination (KH/Selectfluor), desulfonation (Bu_3SnH/AIBN), and deprotection afforded the phosphonate homouridine disodium salt **369** as a mixture of diastereomers (Scheme 103).

The preparation of 5′-difluoromethylphosphonate nucleotide analogues containing difluoromethylene groups in place of their 5′-oxygens was described by Usman and co-workers (Scheme 104).[209,323] Nucleoside analogues **375** were synthesized from **370** and silylated bases under Vorbrüggen conditions ($SnCl_4$ as a catalyst, refluxing acetonitrile). Selective *N*-1 glycosylation took place in the pyrimidine derivative syntheses giving **371a** (B = uracyl) in 62% yield and **371b** (B = cytosine) in 75% yield. Glycosylation of silylated N^6-benzoyladenine yielded a mixture of *N*-9 isomer **372** and *N*-7 isomer **373** in 34% and 15% yield, respectively. The deprotection of **371** and **372** was carried out by a one-pot, two-step procedure with bromotrimethylsilane in acetonitrile followed by debenzoylation with ammonia−methanol. By using the standard procedure for the preparation of nucleoside triphosphates from nucleoside monophosphates, that is, activation of the phosphate (phosphonate) group with 1,1′-carbonyldiimidazole followed by condensation of the intermediate phosphorimidazolidate with tributylammonium pyrophosphate, adenosine analogue **375c** was converted to the 5′-triphosphate analogue **376** in 80% yield. The synthesis of a dinucleotide **378** incorporating the 5′-difluoromethylene functionality was carried out by DDC-promoted condensation of **374a** with a suitably protected cytidine monomer **377** (Scheme 105).

The rational synthesis of isosteric analogues of nucleotides where the 3′-oxygen was replaced with a CF_2 group has been developed by Pietre and co-workers.[185,186,261] The reaction of $(EtO)_2P(S)$-bearing furanoses **379** with protected or unprotected base under Lewis acid catalysis results in the stereoselective formation of nucleotide analogues **380** (Table 18). The use of Vorbrüggen conditions proved especially efficient to introduce the monocyclic bases,[324] while adenine and protected guanine were installed by using the procedure of Saneyoshi and Robins.[325,326] A complete diastereoselectivity can be accommodated by the steric hindrance generated by both the 2-acetoxy group and the 3-phosphonothiodifluoromethyl unit. An alternative explanation, equally possible, is that the longer P═S bond (1.886 Å versus 1.580 Å for the P═O bond) allows the latter group to participate in the stabilization of the intermediate cation. Interconversion between difluorophosphonothioates and difluorophosphonates was discussed earlier (section 2.6). The existing methods are mild enough and tolerant of various functional groups, as demonstrated by transformation of nucleoside-based difluorophosphonothioates **380** into the corresponding nucleoside phosphonates **381** (Scheme 106).[18,185] Interestingly, a conformational analysis of nucleoside-3′-phosphonates reveals that a CH_2 replacement of the 3′-oxygen atom of a 3′-phosphorylated nucleoside results in a conformational change of the furanose ring (C3′-endo to C2′-endo). Potential consequences of this are diminished binding interactions between the modified nucleotide and its target or, in the case of oligonucleotides, a lower stability of the RNA/MON duplex. The difluoromethylenephosphonate (DFM) function was found to be instrumental in governing the conformational behavior of the ribofuranose ring by shifting the N/S equilibrium to the northern position (C3′-endo), which is favorable for the double strand association in RNA and DNA structures.[327] Thus, although the DFM group is considered a close mimic of the phosphate function, there is a conformational discrepancy between the DFM-modified and natural nucleotides.

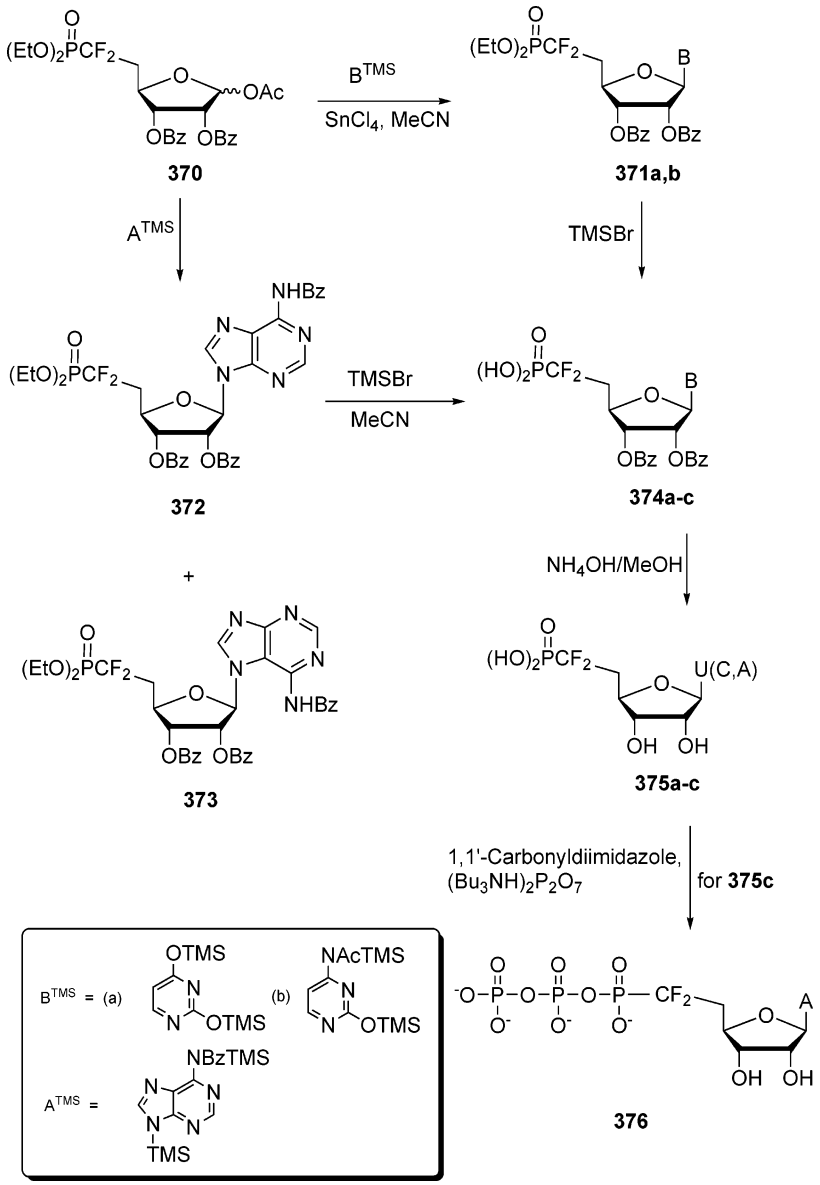
Zard and co-workers demonstrated several years ago the possibility of building difluorophosphonate thionucleotide analogues using a radical xanthate transfer reaction (Scheme 107).[328] Thus, when xanthate **382** and 1,1-difluoro-3-butenylphosphonate in the presence of lauroyl peroxide were heated, the xanthate was produced with reasonable efficiency. Cleavage of **383** with ethylenediamine and exposure of the crude thiol to hot trifluoroacetic acid provided thiolactone **384** in high yield. Reduction of this intermediate with sodium borohydride followed by acylation furnished the desired precursor **385**. Finally, Vorbrüggen coupling of **385** with silylated thymine in the presence of $SnCl_4$ provided the thionucleoside analogue **386** as a 55%:45% mixture of epimers. Although the stereocontrol at the "anomeric" position was not high, these transformations demonstrate the potential of the radical-based xanthate transfer reaction in thionucleoside synthesis.

An original route to some carbocyclic phosphonate analogues of nucleotides is via "purinoselenenylation" starting from $(RO)_2P(O)CF_2$-functionalized cyclopentenyl derivatives.[329]

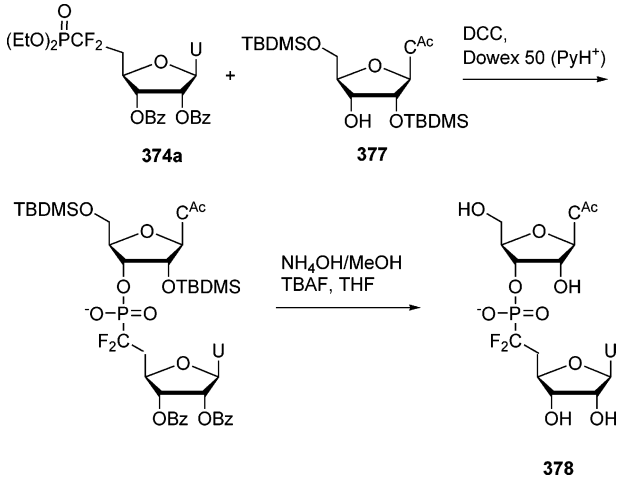
3.5.3. Acyclic Nucleoside Fluorophosphonates

The first series of acyclic nucleoside phosphonates possessing the α-fluoro(phosphonyl)methoxy group were prepared by coupling of the fluoromethyl derivatives **387**, **389**,

Scheme 104



Scheme 105

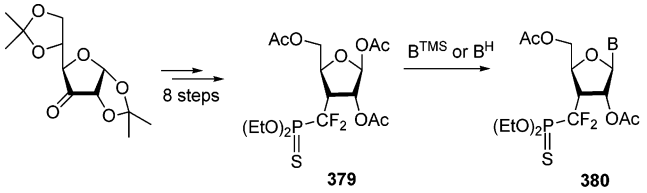


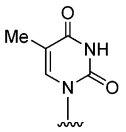
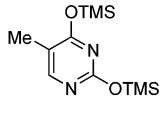
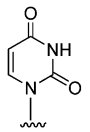
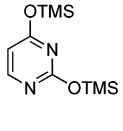
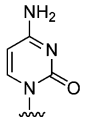
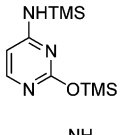
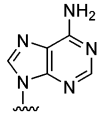
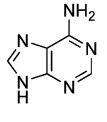
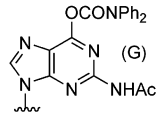
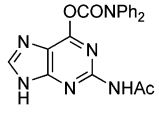
or **391** with the corresponding purine or pyrimidine nucleic bases under either modified Mitsunobu conditions or base-catalyzed alkylation conditions (Scheme 108).[75,95] The synthesized fluorinated acyclic nucleoside phosphonates were tested against herpes viruses, respiratory viruses, hepatitis B virus, and HIV. The monoammonium salt of the monoethylester of [2-(adenine-9-yl)ethoxy]fluoromethylphosphonic acid (prepared from **388a** and concentrated aqueous ammonia) was found to be active against human cytomegalovirus (HCMV), Epstein Barr virus, and measles with EC_{50} values of 5.6, 1.6, and 32 μg mL^{-1}, respectively.

The purine adduct **394** was regioselectively (>95%) obtained by reacting 2-amino-6-chloropurine (a proguanine derivative) with 5-iodo-1,1-difluoro-1-(diethylphosphono)-pentane (**393**) in anhydrous DMF containing potassium carbonate. The transformation of **394** into the final product **137** was achieved through removal of the ester groups and aqueous hydrolysis (Scheme 109).

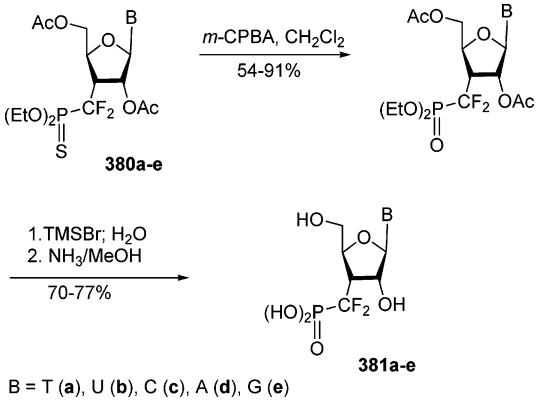
In an attempt to prepare the acyclic phosphonate derivatives of purines, allyl chloride **395** was treated with adenine in the presence of an excess of cesium carbonate. The major product isolated was the dienic monofluorophosphonate derivative **397** (60:22:12:6 mixture of four stereoisomers) resulting from a base-catalyzed dehydrofluorination of the expected nucleophilic substitution product **396**. However, when the reaction was run using 6-chloropurine as a

Table 18. Synthesis of Phosphonothiodifluoromethylene Analogues of Nucleoside 3′-Phosphates

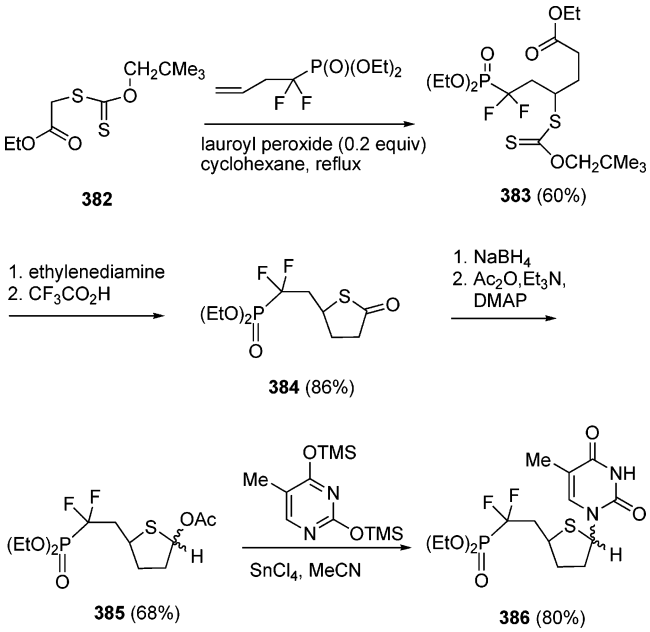


B	B^{TMS} or B^{H}	conditions	yield, %
	(T) 	TMSOTf, DCE	92
	(U) 	TMSOTf, DCE	81
	(C) 	TMSOTf, DCE	95
	(A) 	$SnCl_4$, MeCN	87
	(G) 	TMSOTf, DCE	66

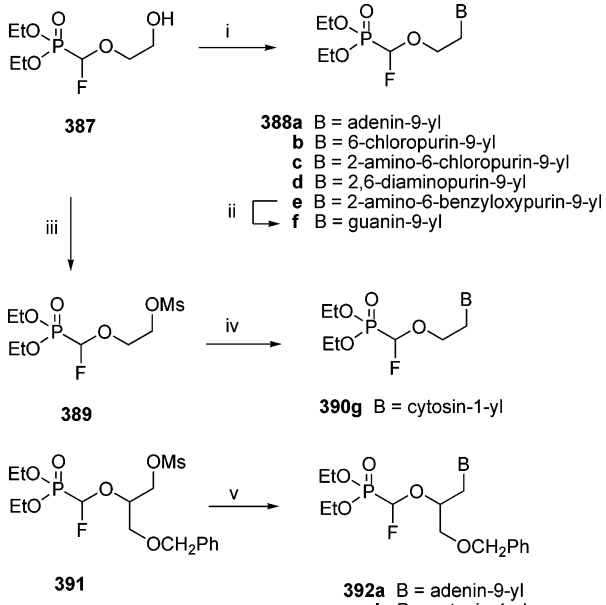
Scheme 106



Scheme 107



Scheme 108[a]



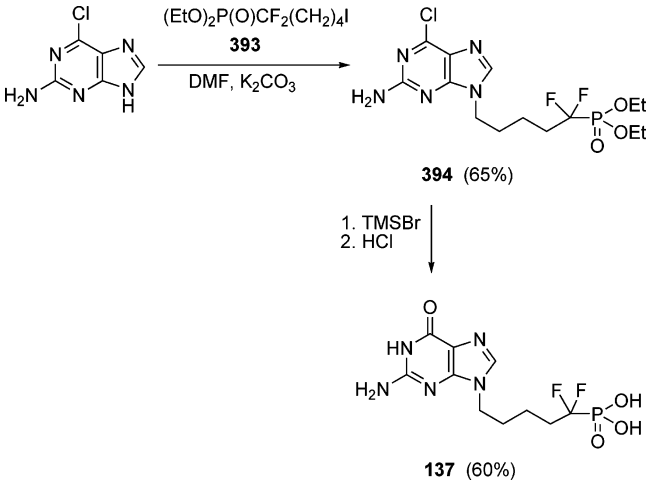
[a] Reagents: (i) nucleic base, DEAD, Ph_3P, DMF; (ii) H_2, Pd/C, EtOH; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) cytosine, $CsCO_3$, DMF; (v) nucleic base, Cs_2CO_3, DMF.

nucleophile and only 1.1 equiv of potassium carbonate, the unsaturated α,α-difluoroallylphosphonate derivative of purine **398a** was prepared in 42% yield. The use of the neutral fluoride ion catalyzed procedure allowed the preparation of the unsaturated difluorophosphonate derivative of guanine **398b** in 55% yield from 2-amino-6-chloropurine. The same conditions used to prepare **398c** were found to be less satisfactory as only 30% of product was obtained after flash-chromatography purification (Scheme 110).[238]

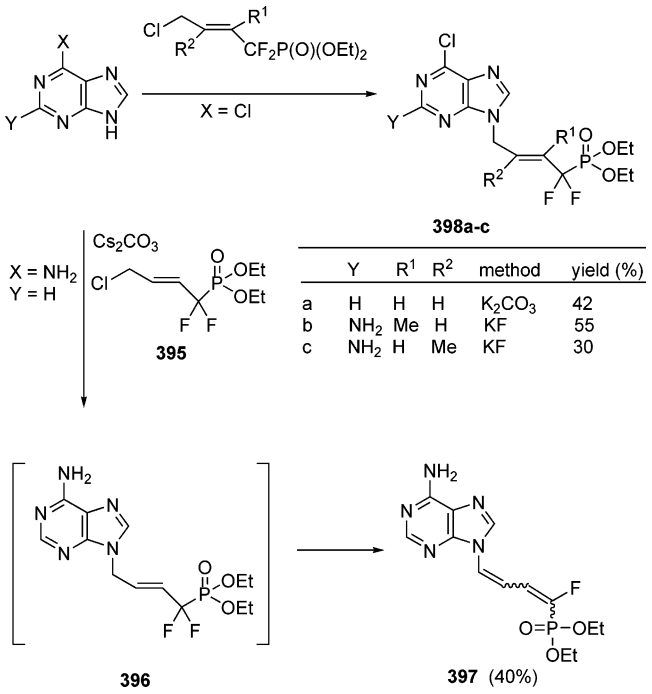
The phosphonate derivatives of N^9-benzylguanine **401** have been obtained by a common strategy from the arylphosphonates **399** (Scheme 111). The key step of the synthesis involves the condensation of the benzyl bromides **400** with 2-amino-6-chloropurine in the presence of potassium carbonate or sodium hydride. This reaction was found to proceed with a high control of N^9 regioselectivity (> 90%). Removal of the ethyl protecting groups was performed by treatment with bromotrimethylsilane in CH_2Cl_2 or CH_3CN followed by acid aqueous hydrolysis. Enzyme inhibition studies with PNP from calf spleen or human erythrocyte showed that compounds **401b** and **401c** are among the best PNP inhibitors ever reported, demonstrating further the importance of fluorine in such inhibitors.[330]

Shibuya and co-workers synthesized a series of nucleotide analogues wherein a nucleobase and a difluoromethylene-phosphonate moiety are linked with an alkyl spacer having either a double bond or a cyclopropane ring.[141,218,331−335] Thus, the tosylate (*E*)-**402** was coupled with either 2-amino-6-chloropurine or 6-chloropurine to give (*E*)-**402a**,**b** in

Scheme 109

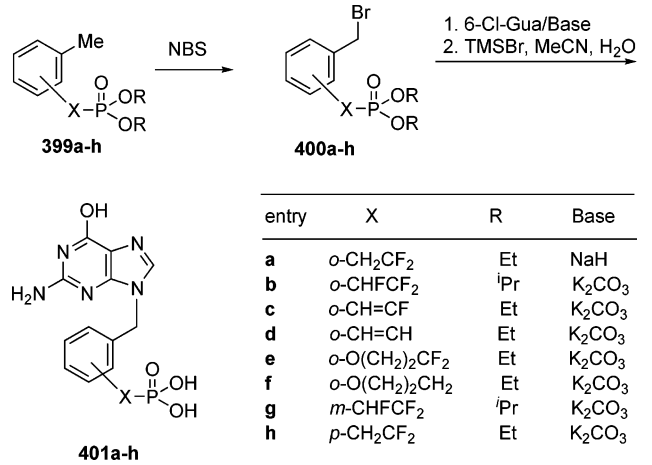


Scheme 110



	Y	R^1	R^2	method	yield (%)
a	H	H	H	K_2CO_3	42
b	NH_2	Me	H	KF	55
c	NH_2	H	Me	KF	30

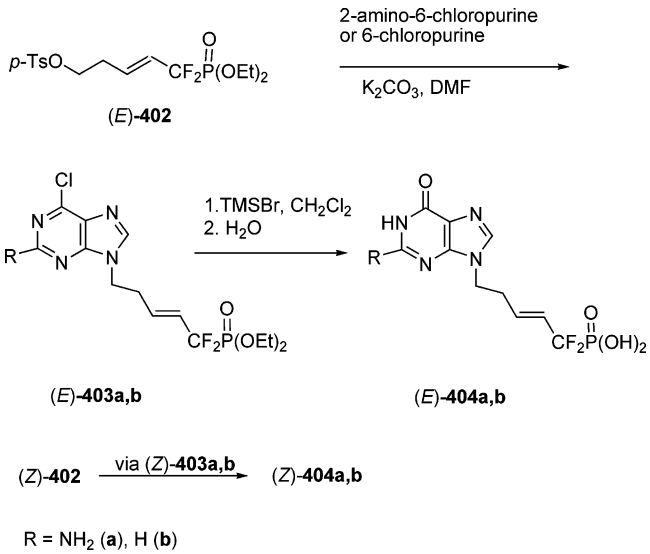
Scheme 111



entry	X	R	Base
a	*o*-CH_2CF_2	Et	NaH
b	*o*-$CHFCF_2$	^{i}Pr	K_2CO_3
c	*o*-CH=CF	Et	K_2CO_3
d	*o*-CH=CH	Et	K_2CO_3
e	*o*-$O(CH_2)_2CF_2$	Et	K_2CO_3
f	*o*-$O(CH_2)_2CH_2$	Et	K_2CO_3
g	*m*-$CHFCF_2$	^{i}Pr	K_2CO_3
h	*p*-CH_2CF_2	Et	K_2CO_3

moderate yields. The corresponding *Z*-isomers **403a**,**b** can be stereoselectively obtained starting from (*Z*)-**402**. Treatment of (*E*)-**403** and (*Z*)-**403** with bromotrimethylsilane, followed by hydrolysis with water in one pot afforded desired (*E*)-**404** and (*Z*)-**404** (Scheme 112).[218] The difluorophospho-

Scheme 112



noalkylpurine derivatives having cyclopropane rings were prepared from the corresponding 2-hydroxycyclopropanes by the same procedure as a series of **404**.[218] The evaluation of PNP inhibitory activities of all compounds synthesized in this study reveals that the cyclopropane ring and the hypoxanthine residue increase the profile of inhibitory activity.

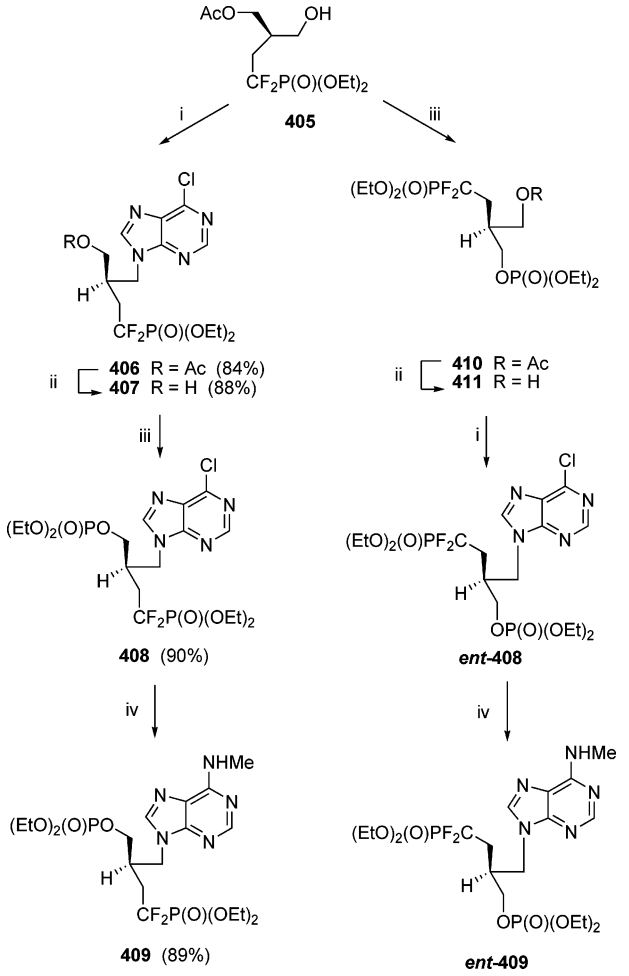
Acyclic nucleotide analogues are also known in which a difluoromethylenephosphonate moiety is incorporated as an isostere for one of two phosphate groups normally present in adenosine bisphosphates. Thus, recent work by Yokomatsu and co-workers utilizes the chiral building block **405** to synthesize the enantiomerically pure nucleoside phosphonate **409** (Scheme 113).[213] During the transformation, no racemization took place, which was confirmed by NMR analysis of the Mosher esters derived from **407**. To obtain the enantiomer (***ent*-409**) of **409**, the monoacetate **405** was phosphorylated with diethyl chlorophosphate to give **410**. Deprotection of the acetyl group with Et_3N in MeOH provided **411** in 42% yield. The latter was condensed with 6-chloropurine under the Mitsunobu conditions to form the enantiomer of **408** and the resulting product was treated with Me_2NH in MeOH to give ***ent*-409** in 72% yield. The acyclic nucleotide analogues **409** and ***ent*-409** would be expected to show antithrombotic activity.

Acyclic nucleoside phosphonates **412** and **413** containing fluorinated ester moieties have been obtained via base-induced alkylation (Scheme 114). The latter was shown to be a HBV-specific antiviral reagent and exhibits high anti-HBV activity in vitro.[336,337] The unprotected nucleoside phosphonate **412** was labeled by [^{11}C]methyl triflates ($^{11}CH_3OTf$) through *O*-[^{11}C]-methylation of the hydroxyphenyl position under basic conditions. This chemistry provides the foundation for further biological evaluation of [^{11}C]-**413** as a novel potential position emission tomography (PET) cancer imaging agent for hepatitis B virus and herpes simplex virus thymidine kinase in vivo.[336]

3.6. Fluorine-Containing Aminophosphonic Acids and Phosphonopeptides

The key role of naturally occurring amino acids in the chemistry of life has led to intense interest in the synthesis

Scheme 113[a]



[a] Reagents: (i) 6-chloropurine, DIAD, PPh_3, THF; (ii) Et_3N, MeOH; (iii) $ClP(O)(OEt)_2$, pyridine; (iv) 2.0 M $MeNH_2$−MeOH.

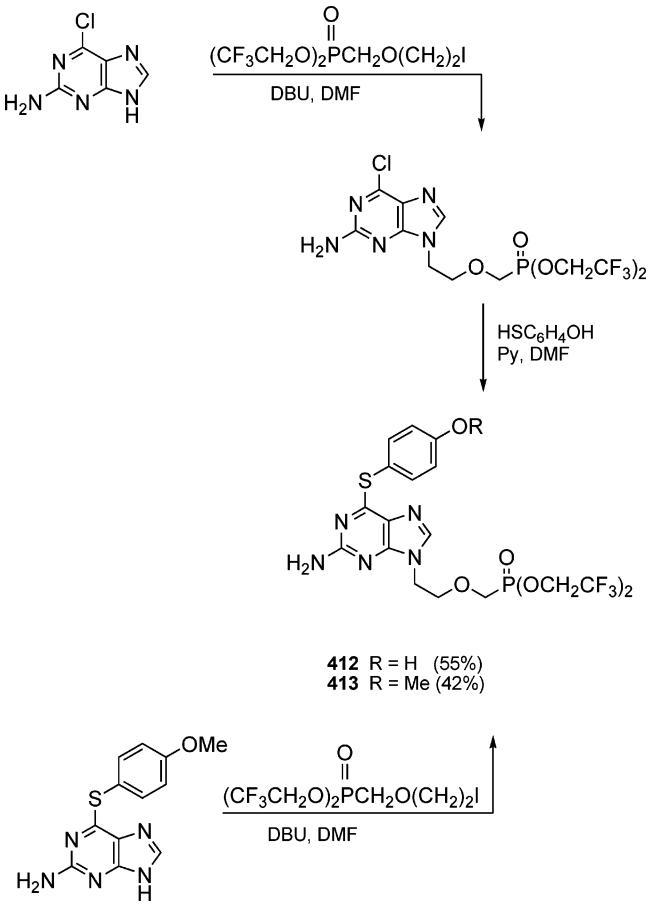
and biological activity of synthetic analogues.[5,338] As such, during the past two decades a large number of phosphonic acid analogues of protein or nonprotein amino acids have been synthesized and investigated. Because of the tetrahedral configuration at phosphorus, aminophosphonic acids serve as stable analogues of the tetrahedral carbon intermediates formed in enzymatic reactions and, therefore, act as enzyme inhibitors. Data concerning the biological activity of the fluorinated aminophosphonates indicate their usefulness as inhibitors of proteases,[339,340] alanine racemase,[341] pyrimidine phosphorylases,[342] glycosyl transferases,[313,343] proline selective depeptidase,[121] sphingomyelinases,[344] and cholinesterases.[345,346] Also cytotoxic and antibacterial activities have been reported for some of the fluorine-containing aminophosphonates.[347,348]

In contrast to the widely investigated nonfluorinated aminophosphonic acids,[349] the synthetic approaches to enantiomeric fluorine-containing analogues are few in number and of limited applicability.

3.6.1. Analogues of 1-Aminoalkanephosphonic Acids

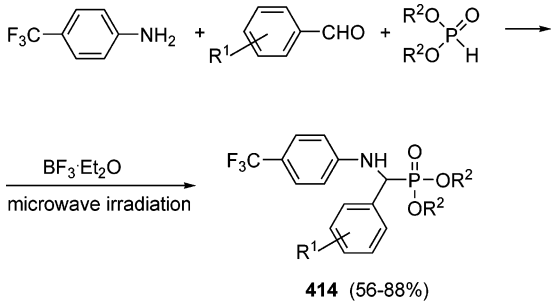
Among the methods that can be employed to prepare α-aminophosphonic acids, the most straightforward one involves a one-pot Mannich-type procedure using the three-component reaction of aldehydes, amines, and dialkyl phosphites.[3] In principle, the synthesis provides a general route to α-aminophosphonates bearing side-chain C−F

Scheme 114



linkages, but the correct choice of conditions is essential if good yields of pure compounds are to be obtained. Experimental details for the preparation of a series of novel dialkyl (4-trifluoromethylphenylamino)-(4-trifluoromethyl or 3-fluorophenyl)methylphosphonates **414** have recently been described by Song and co-workers (Scheme 115).[350] The title

Scheme 115



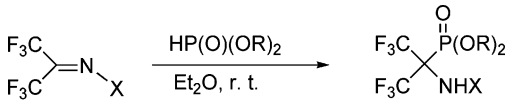
R^1 = 4-CF_3, 3-F; R^2 = Me, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu

compounds were synthesized through the reaction of 4-trifluoromethylbenzaldehyde or 3-fluorobenzaldehyde with dialkyl phosphite by microwave irradiation in the presence of boron trifluoride−ether catalyst.

The nucleophilic addition of dialkyl (or diaryl) phosphite to a C=N double bond, the "Pudovik reaction", is known to be very useful approach for the synthesis of α-aminophosphonic acids.[351] In the syntheses of fluorinated α-aminoalkanephosphonates by this method the Schiff bases derived from hexafluoroacetone were examined first. These reactions proceed at room temperature without catalysts (Scheme

116).[346,352−355] Imines derived from trifluoromethyl ketones

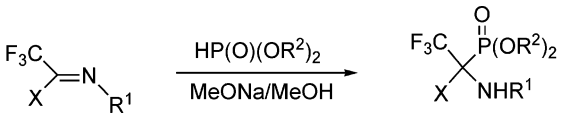
Scheme 116



X = SO_2Ph (ref. 352); CO_2Alk (ref. 346, 353, 354); $C(O)CF_3$ (ref. 346); $P(O)(OAlk)_2$ (ref. 355)

and trifluoropyruvates undergo similar addition in the presence of catalytic amounts of sodium methoxide (Scheme 117).[356] β-Fluorinated aldehydes due to their low stability

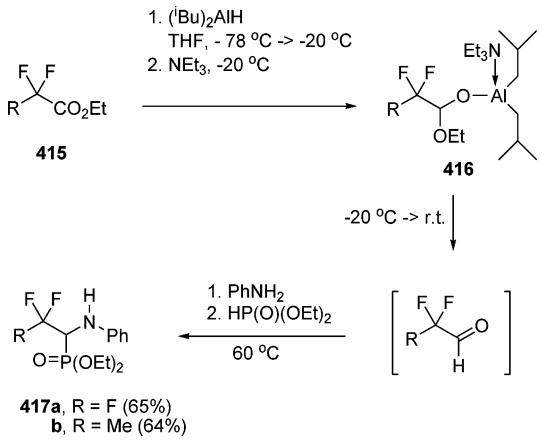
Scheme 117



X = CO_2Me; R^1 = $COCF_3$, SO_2Ph; R^2 = Me, Et, C_5H_{12}, Ph;
X = CO_2Me; R^1 = $P(O)(OEt)_2$; R^2 = Ph;
X = Ph, 4-MeC_6H_4; R^1 = H, $COCF_3$; R^2 = Me, Et, Pr, ^{i}Pr

are poor substrates in such reactions. However, Haas and Hägele reported conditions for in situ generation of aldehydes $RCF_2C(O)H$ (R = F or Me) and their consecutive reactions with N- and P-nucleophiles.[357] Thus treatment of fluorinated carboxylic acid esters **415** with diisobutylaluminum hydride (DIBAL) in the presence of triethylamine at low temperature produces aluminoxy acetals **416**, which undergo subsequent reactions with aniline and diethyl phosphite at higher temperature, presumably via the corresponding aldehydes and imines, giving rise to aminophosphonates **417**. Yields are reasonable for compounds **417a**,**b**, but phosphonates bearing the aryldifluoromethyl fragment are not accessible by simple analogy (Scheme 118).

Scheme 118

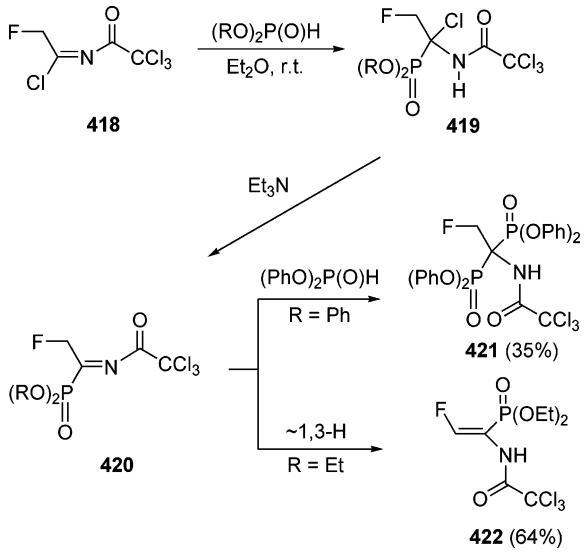


417a, R = F (65%)
b, R = Me (64%)

The reaction between imidoyl chloride **418** and diphenyl phosphite in the presence of triethylamine is reported to give the aminodiphosphonate **421** via intermediate formation of the highly reactive imidoyl phosphonate **420**. If diethyl phosphite is used in this reaction, the phosphonate **420** undergoes isomerization into phosphorylated vinylamide **422** [(*E*)/(*Z*) ~5:1] (Scheme 119).[358]

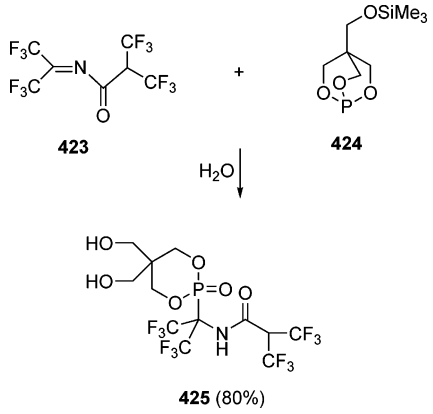
In contrast to dialkyl phosphites, trialkyl phosphites usually react with *N*-acylimines derived from hexafluoroacetone via [4 + 1]-cycloaddition to give oxazaphospholines containing

Scheme 119



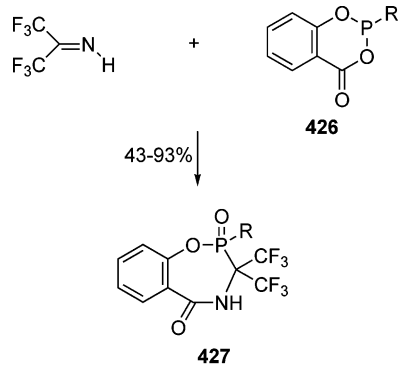
a pentacoordinate phosphorus atom.[359] However, treatment of the *N*-acylimine **423** with sterically restrained tricyclic phosphite **424** gave access, after hydrolysis, to α-acylaminophosphonate **425** (Scheme 120).[342] Treatment of benzo-

Scheme 120



1,3,2-dioxaphosphorin-4-ones **426** with hexafluoroacetone imine in dichloromethane affords benzo-1,4-oxazaphosphepanes **427** (Scheme 121).[360] There is also report in the

Scheme 121

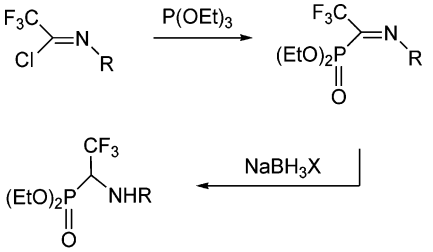


R = MeO, Et_2N, $F_2CHCF_2CH_2O$

literature that *N*-(arylsulfonyl)trifluoroacetimidoyl chloride reacts with triethyl phosphite to form 1-chloro-2,2,2-trifluoro-1-tosylaminoethylphosphonate.[361]

Another reasonably general approach to aminophosphonates bearing fluorinated substituents is a multistep process that involves the interaction of an imidoyl chloride with trialkyl phosphite (or dialkyl phosphites in the presence of organic bases) followed by reduction of the formed imidoyl phosphonate as outlined in Scheme 122.[341,362−364] Reduction

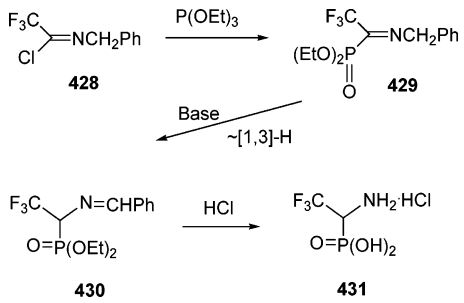
Scheme 122



of imidoyl phosphonates is usually conducted using $NaBH_4$, $NaBH_3CN$, or $NaBH(OAc)_3$.[365] Aminophosphonates $(EtO)_2P(O)CH(R)NH_2$ ($R = CHF_2$, CF_3) with primary amino group are formed via consecutive $NaBH_3CN$ and H_2/Pd−C reduction of *N*-(diphenylmethyl)imidoyl phosphonates prepared from the imidoyl chloride $ClC(CF_3)=NCHPh_2$.[341,366] It should be noted, however, that the "imidoyl chloride" route is not always successful, and other workers have isolated only traces of the products.[357] Moreover, imidoyl chlorides bearing electron-withdrawing substituent at the nitrogen atom give very poor yields of imidoyl phosphonates due to competing processes such as aza-Perkov reaction with participation of the trifluoromethyl group and cycloaddition leading to phosphoranes.[361]

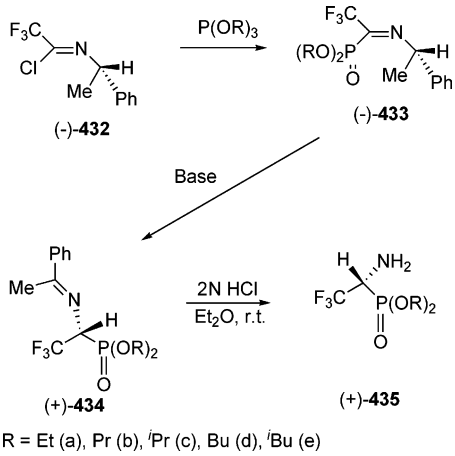
A novel route to fluorinated α-aminophosphonates starting from imidoyl chlorides was demonstrated by reacting the *N*-benzyl-substituted imidoyl chloride **428** with triethyl phosphite followed by a base-catalyzed [1,3]-proton shift reaction of the primary formed imidoyl phosphonate **429**. Azomethine **430** thus formed was then transformed to the corresponding α-aminophosphonic acid **431** by further hydrolysis in concentrated HCl (Scheme 123).[367−370] This

Scheme 123



approach was subsequently applied to the asymmetric synthesis of 1-amino-2,2,2-trifluoroethanephosphonic acids.[371,372] Some examples taken from the studies by Yuan and co-workers are shown in Scheme 124.[373] Detailed investigations revealed the strong influence of solvent, base, and steric nature of dialkyl phosphonate moiety on the stereochemical result of the [1,3]-proton shift reaction.[369,370,373] In particular, when triethylamine was used as a base and solvent, compounds (+)-**435a**−**d** were isolated with moderate enantiomeric purity (42−67% ee). Under the same conditions, the isomerization of (−)-**433e**, bearing an isobutyl

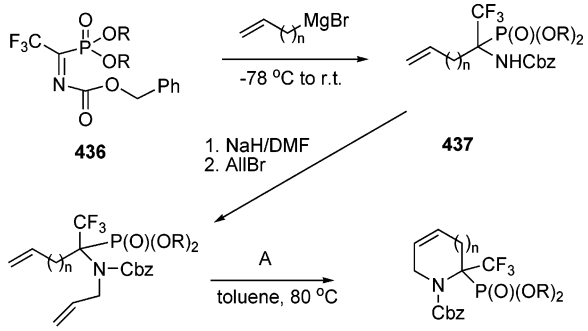
Scheme 124



ester group, gave the isomerization product (+)-**435e** with a relatively good stereochemical result (67% ee).[373]

A specific method for the synthesis of six- and seven-membered α-aminophosphonates via ring closing metathesis (RCM) has recently been developed by Osipov, Dixneuf, and co-workers.[374−377] It is based on the addition of two hydrocarbon chains bearing terminal alkene groups to the electrophilic fluorinated imines $(RO)_2P(O)C(CF_3)=NCbz$, followed by ruthenium-catalyzed RCM reaction. Thus, the imino esters **436** were transformed by nucleophilic and then electrophilic additions into fluorine-containing aminophosphonates **438** with two pendent alkene chains. The ring closing metathesis of the 1,7- and 1,8-heterodienes **438** was performed with the help of 10 mol % of the allenilidene ruthenium catalyst. Complete conversion of the dienes was achieved in toluene at 80 °C within 6 h and the six-membered and seven-membered α-aminophosphonates **439** were obtained in good yields (61−70%) (Scheme 125).[374] Readers

Scheme 125

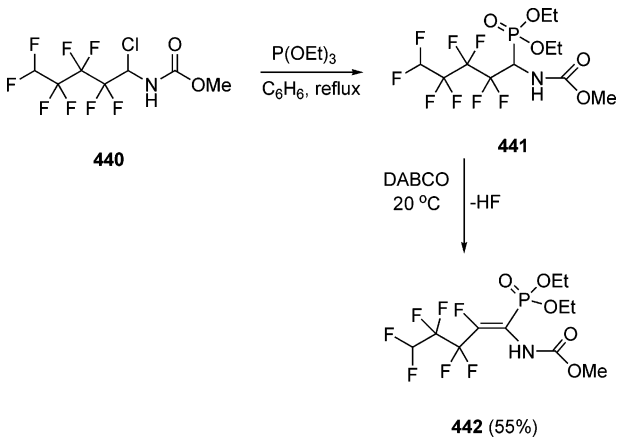


are referred to a review[378] for more detailed information concerning application of RCM methodology in the synthesis of cyclic α-amino acids.

The direct replacement of a chlorine atom in protected α-chloroalkylamines by a phosphonate moiety is rarely used for the preparation of fluorinated aminophosphonates. This method was, however, successfully applied in synthesis of the compound $(MeO)_2P(O)C(CF_3)_2N=CHNMe_2$ when the key step was the conversion of functionalized formamidine $ClC(CF_3)_2N=CHNMe_2$ into the mentioned phosphonate via

the Arbuzov reaction.[379] Another example of this process was uncovered in the reaction of α-chloroalkylamide **440** with triethyl phosphite (Scheme 126). The ready availability

Scheme 126

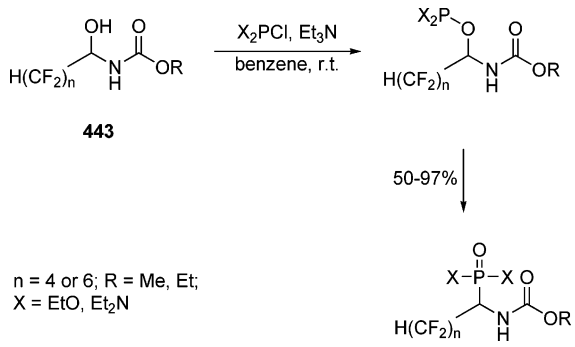


440 **441** **442** (55%)

of fluorinated chloroalkylamides combined with the variety of possible transformations of the products make the reaction potentially useful. Thus, treatment of **441** with organic bases such as DABCO or Et_3N resulted in a dehydrofluorination reaction to give a new type of *C*-phosphorylated secondary enamides **442**.[380] The same authors described the synthesis of phosphorylated isocyanate $F_2CH(CF_2)_3CH[P(O)(OEt)_2]$-NCO using compound **442** as the starting material. This product can serve as building block to prepare the more elaborated α-aminophosphonate derivatives.[381]

There are also several literature reports on the exchange of a hydroxyl group in fluorinated *N*-acyl hemiaminals for the phosphonate moiety via phosphite−phosphonate rearrangement. For example, aminophosphonic acid derivatives were synthesized in good yields by treatment of hemiaminals **443** with diethyl chlorophosphite in the presence of triethylamine (Scheme 127).[382,383] The synthetic potential of the

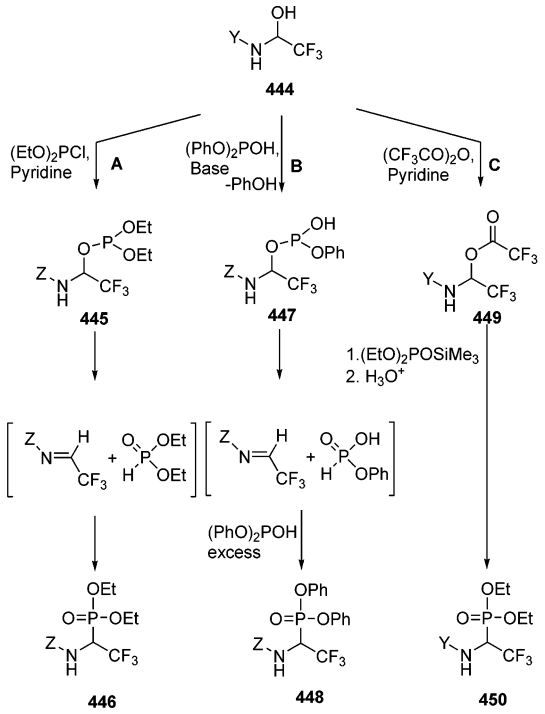
Scheme 127



443

method is nicely illustrated by a recent study by French chemists.[384] Thus, three methods (A−C) were used for the one-pot synthesis of the fully protected fluorinated alanine analogues **446**, **448**, and **450** using the readily accessible N-protected β-fluoroaminals (Scheme 128). The use of diethyl chlorophosphite enabled the instantaneous formation of **445** in the presence of pyridine. The formed phosphite undergoes slow rearrangement into phosphonate **446**, which may result a priori from either an intermolecular or an intramolecular process. The latter path seems unlikely because of the following: (i) addition of dimethyl phosphite, $HP(O)(OMe)_2$, to **445** led to a significant amount of the

Scheme 128



444 **445** **447** **449** **446** **448** **450**

Y = acyl group in particular Benzyloxycarbonyl (Z), Z-Ala, Z-Gly, $(BnO)_2P(O)$

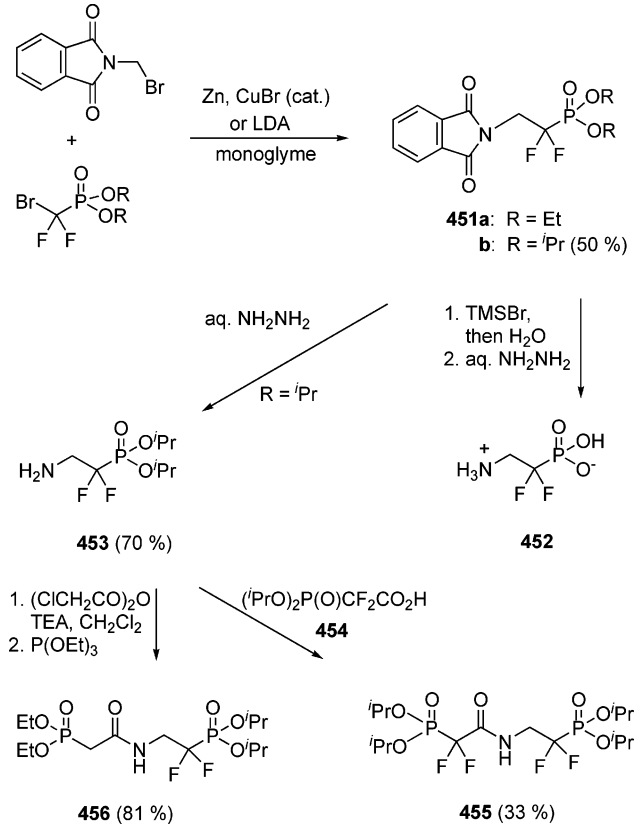
phosphonate dimethyl ester, $ZNHCH(CF_3)P(O)(OMe)_2$, and (ii) the rearrangement was considerably accelerated in the presence of triethylamine. Therefore, the transformation is believed to proceed through a β-elimination, liberation of diethyl phosphite and imine, and a subsequent addition reaction. When diphenyl phosphite was used as reactant with hemiaminals **444**, the phosphonic diphenyl esters of type **448** were easily obtained. Finally, *O*-trifluoroacetyl derivatives of the hemiaminals **444** were shown to react with $(EtO)_2P(OSiMe_3)$ forming the corresponding *N*-trimethylsilylaminophosphonates in quantitative yields. The desilylation reaction readily proceeded during aqueous workup. The complete or partial deprotection of these aminophosphonic esters allowed the synthesis of the free amino acids and racemic β-trifluoromethylphosphonamidic acid $ZNHCH(CF_3)P(O)(OH)NH(CH_2)_4Me$. The latter, which represents a transition state analogue formed by the bacterial transpeptidase, is perfectly stable at pH 4.7, contrary to the nonfluorinated analogues.

Finally, the optically active diethyl *N*-(*p*-toluenesulfonyl)-aziridine 2-phosphonates derived from phosphonoserine enantiomers have been shown to react with tetrabutylammonium fluoride in THF allowing for the rapid production of β-fluoro-substituted α-amino phosphonates in either the (*R*)- or (*S*)-configurations.[385]

3.6.2. Analogues of 2-Aminoalkanephosphonic Acids

The early route to α-fluoro-β-aminophosphonates was the reaction of fluorinated phosphonate carbanions with N-protected α-haloamino derivatives. The simplest example is the synthesis of α,α-difluoro-β-aminoethylphosphonic acid **452** as shown in Scheme 129. On reaction of *N*-(bromomethyl)phthalimide with organozinc reagent $BrZnCF_2P(O)(OEt)_2$ in the presence of CuBr as catalyst, the α,α-difluoro-β-amino phosphonates **451** were isolated in moderate yield. The full deprotection of **451a** could be accomplished by successive treatment with bromotrimethylsilane and aqueous

Scheme 129

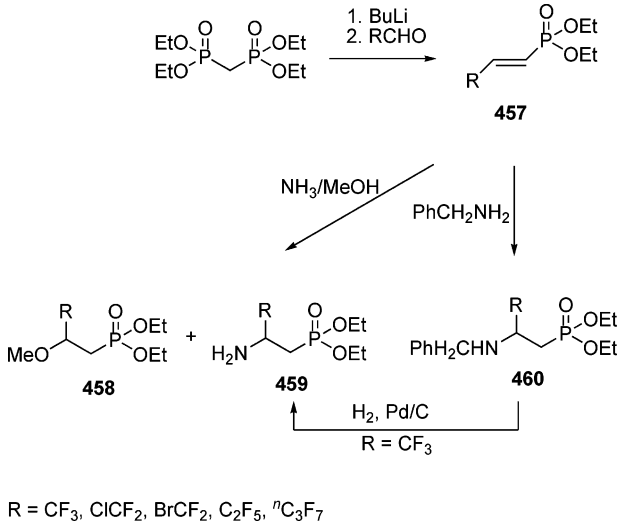


hydrazine. The selective N-deprotection of **451b** was performed using aqueous hydrazine. Reaction of the resulting β-aminophosphonate **453** with fluorinated phosphonoacetate **454** offered a convenient route to diphosphonate **455**. Analogously, a two-step method was developed for the preparation of related diphosphonate **456**. These compounds are highly potent ligands for phosphoglycerate kinase.[204]

Another simple method for the synthesis of fluorinated β-amino phosphonic acids is based on the addition of amines to electrophilic α,β-unsaturated phosphonates. Thus, nucleophilic addition of saturated methanolic ammonia to the vinylphosphonates **457** produced a mixture of 2-methoxy- and 2-amino-2-perfluoroalkylphosphonates **458** and **459**, which could be separated by chromatography. Benzylamine reacted with compounds **457** to give 2-benzylamino derivatives **460**, which were smoothly hydrogenated with Pd/C to afford **459** (Scheme 130).[386] By the same strategy, the diphosphonate derivatives **462a**−**c** of three fluoroquinolone antibacterials, norfloxacin (compound **461a**), enoxacin (compound **461b**), and ciprofloxacin (compound **461c**), were prepared as shown in Scheme 131. De-esterified free-acid species **463a**−**c** have the ability to bind to bone and to inhibit the growth of Gram-negative bacteria.[348]

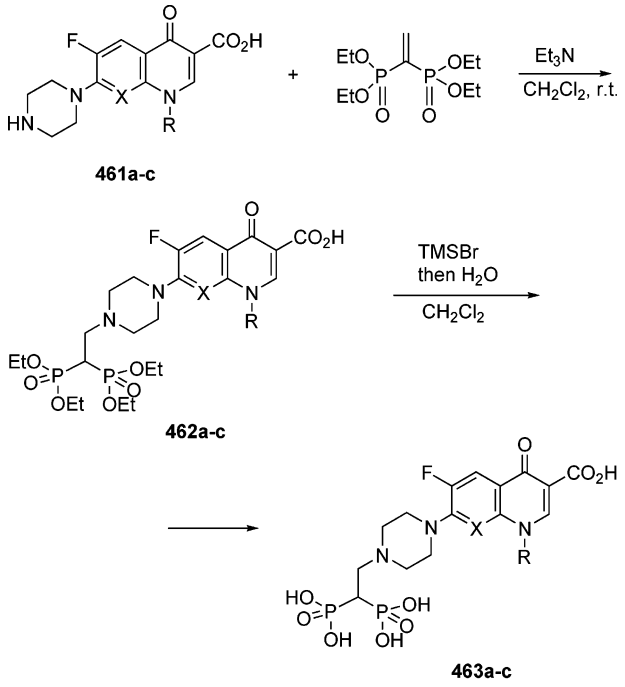
More recent investigations on the synthesis of fluorinated β-aminophosphonates and their derivatives have dealt with the addition of phosphonate carbanions to imines. Several variants of these reactions are known. The initial report describes the condensation of trifluoroacetimidoyl chlorides **464** with carbanions generated from compounds $RCH_2P(O)(OEt)_2$ and NaH or BuLi (Scheme 132).[387] When R is hydrogen or alkyl, butyl lithium was used as the carbanion-generating base, and a mixture of iminophosphonate **465** and enamine **466** was formed in 5:2 molar ratio. When R was a methoxycarbonyl unit, NaH acted first as the base to generate

Scheme 130



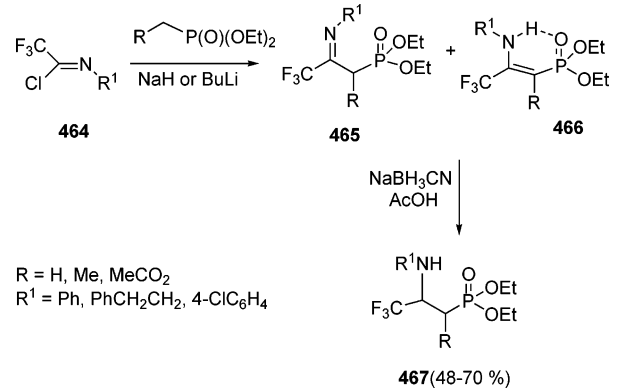
R = CF_3, $ClCF_2$, $BrCF_2$, C_2F_5, $^nC_3F_7$

Scheme 131



X = CH, R = Et (**a**); X = N, R = Et (**b**); X = CH, R = cyclopropyl (**c**)

Scheme 132

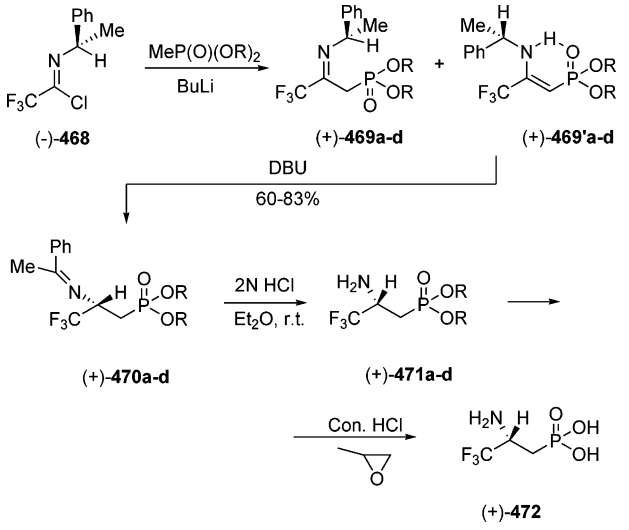


a mixture of imine and enamine (4:1 molar ratio). After 6 h, enamine **466** was the only product of the reaction due to its greater thermodynamic stability. The mixture was treated

without purification with $NaBH_3CN$ to give esters of β-amino alkanephosphonic acids **467** in 48−70% yields.

Phosphonate carbanions have been employed to prepare nonracemic β-aminophosphonates through base-induced [1,3]-proton shift reaction of the intermediate *N*-benzyl-substituted 2-imino-3,3,3-trifluoropropanephosphonates. In particular, upon reactions of *N*-(−)-α-methylbenzyl trifluoroacetimidoyl chloride **468** with carbanions derived from methanephosphonates, the mixture of iminophosphonates (+)-**469** and their isomeric enamines (+)-**469′** are formed in 42−59% yield. A subsequent DBU-induced [1,3]-proton shift reaction afforded the Schiff bases (+)-**470** with good stereochemical outcome. For example, the compounds (+)-**469b**/(+)-**469′**b undergo a proton shift to produce **470b** in 72% yield and 83% ee value. Schiff bases (+)-**470** were hydrolyzed under mild conditions to give β-amino phosphonates (+)-**471**, which were transformed to the corresponding amino acids (+)-**472** by further hydrolysis in concentrated hydrochloric acid (Scheme 133).[388]

Scheme 133

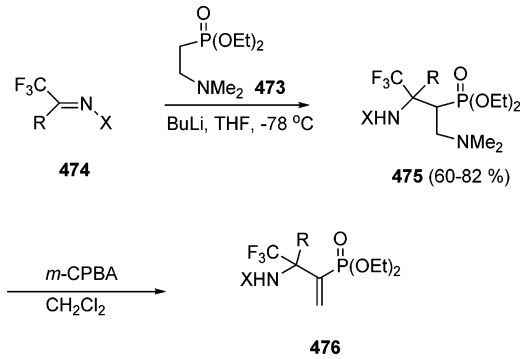


R = Et (**a**), ^{n}Pr (**b**), ^{i}Pr (**c**), ^{n}Bu (**d**)

The base-catalyzed aldol-like addition of alkylphosphonates to trifluoromethylated *N*-benzoyl and *N*-carbalkoxy imines is also known. In some cases, this approach opens the route to compounds that are difficult to prepare by other methods. Thus, after nucleophilic addition of the carbanions generated from phosphonate **473** to imines **474** and preparation of the corresponding β-aminophosphonates **475**, their reaction with *m*-chloroperbenzoic acid in dichloromethane at elevated temperatures provides the desired compounds **476** via *N*-oxide intermediates (Scheme 134).[389] Phosphonates **476** represent a special type of β-aminophosphonic acids because of the sp^2-hybridized α-carbon atom, which imposes rigidity to the phosphonate backbone.

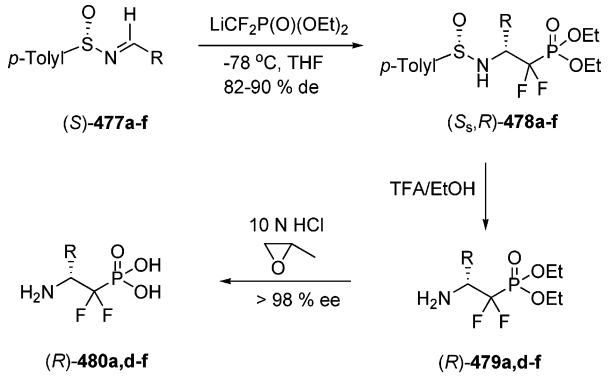
Chiral enantiopure imines, such as sulfinimines, have been successfully used in the asymmetric synthesis of α,α-difluoro-β-aminophosphonic acids (Scheme 135). Enantiomerically pure sulfinimine (*S*)-**477a** was easily reacted with 1.3 equiv of diethyl lithiodifluoromethyl phosphonate in THF at −78 °C to give after quenching with aqueous NH_4Cl the crude product **478a** in a diastereomeric ratio of 95:5. The major diastereomer could be readily obtained in optically pure form by crystallization, and its absolute stereochemistry was determined to be (S_s, *R*) by X-ray analysis. This result is consistent with a transition-state in which the sulfinimine

Scheme 134



X = PhCO, ^{t}BuOCO; R = F_3C, MeOCO

Scheme 135



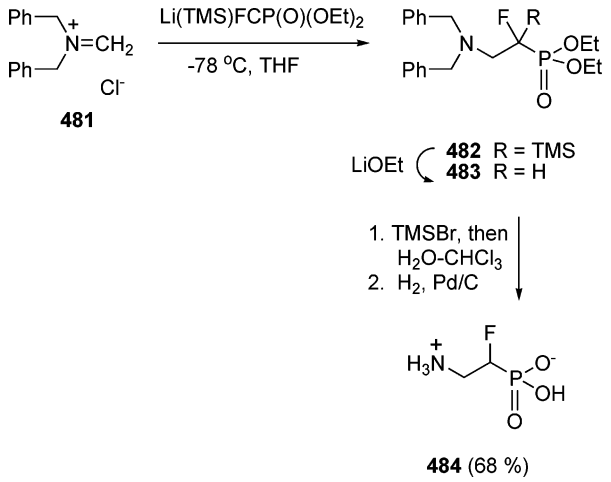
R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-$CF_3C_6H_4$ (**c**), 2-thienyl (**d**), $^nC_5H_{11}$ (**e**), ^{i}Pr (**f**)

is in the stereochemically favorable *E*-configuration and the organometallic reagent preferably attacks the C═N double bond from opposite to the *p*-tolylsulfinyl group direction. The diastereoselectivity of additions was independent of electronic factors, and adducts **478b**,**c** were obtained with a stereochemical outcome comparable with that observed for **478a**. The size of alkyl group (R) had no effect on the (S_s, *R*)/(S_s, *S*) diastereoselectivity as illustrated by sulfinimines **478e** (92:8) and **478f** (91:9), where R = pentyl and isopropyl, respectively. The *N*-sulfinyl group was selectively removed by treatment with trifluoroacetic acid in ethanol at 0 °C. Subsequent hydrolysis of (*R*)-**479a**,**d**−**f** was carried out by heating under reflux in 10 N HCl to deliver enantiopure α,α-difluoro-β-amino phosphonic acids (*R*)-**480a**,**d**−**f** in 67−92% yield. In contrast, hydrolysis of fully protected (S_s,*R*)-**478a**,**d**−**f** in one step using 10 N HCl under reflux was a low yielding procedure, with typical yields of 30−35%.[390−392]

Addition of carbanions derived from α-fluorinated alkylphosphonates to iminium salts can also be used for the preparation of β-amino phosphonates. The first demonstration of this strategy employed *N*,*N*-dibenzyl methyleneiminium chloride **481** as the substrate and Li(TMS)FCP(O)$(OEt)_2$ as the organometallic reagent and gave fully protected aminophosphonate **482**, which then was transformed into the corresponding free α-monofluoro-β-aminomethylphosphonic acid **484** (Scheme 136). The zwitterionic nature of this compound rendered it crystalline and therefore suitable for X-ray single-crystal structure determination.[184]

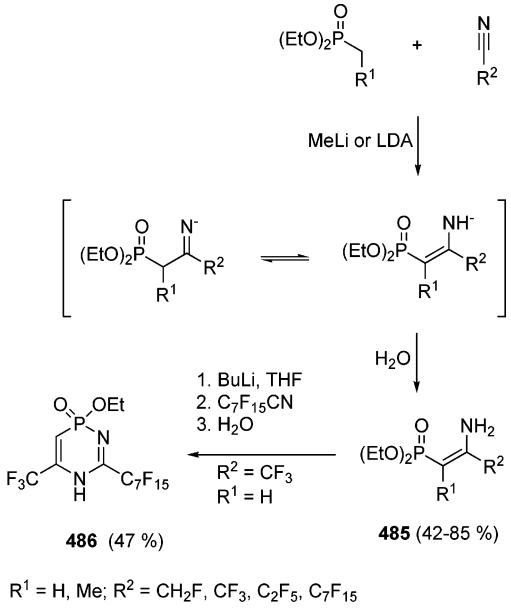
At least conceptually, fluorinated β-amino phosphonates can be prepared through a simple addition of metalated alkylphosphonates to fluoroalkyl nitriles. In fact, as one can

Scheme 136



see from the examples shown in Scheme 137, the reactions

Scheme 137

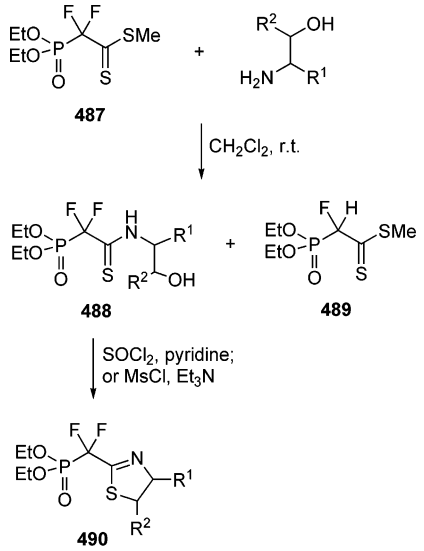


between α-lithiated alkylphosphonates and fluoroalkyl nitriles open an easy route to primary *β*-enamino phosphonates **485**.[393] The latter are apparently highly reactive and have been suggested as reactive substrates in a number of reactions. In particular, treatment of **485** with butyl lithium, followed by the addition of perfluorooctanenitrile, afforded fluorine-containing 2,5-dihydro-1,5,2-diazaphosphine **486** in moderate yield.[394]

Synthesis of phosphonodifluoromethyl azasugars has been reported by Guillerm et al. and is based on nucleophilic opening of arabino-, ribo-, and xylofuranosylamines with diethyl lithiodifluoromethylphosphonate followed by cyclization of the intermediate aminophosphonate products (see Scheme 97).[313] Interaction of lithiodifluoromethylphosphonate with glycosamines **344** led to the formation of a mixture of the two possible diastereomeric α,α-difluoro-*β*-aminophosphonates **345** and **346**. These compounds can be separated by column chromatography. The reaction favors the formation of the *threo* product, suggesting that only the stereocenter at C-2 is controlling the addition process. The configuration at the newly created stereocenter in **345** and **346** was assigned after their conversion to the respective azasugars **347** and **348**. Guillerm et al. also has shown the possibility of reaching *N*-allyl-difluoromethylphosphonopyrrolidines by condensation of $LiCF_2P(O)(OEt)_2$ with *N*-allylglycosylamines.[343]

A new entry into the *β*-aminophosphonate chemistry using a building block approach has recently been explored by Lequeux and co-workers.[395] Methyl difluoro(diethoxyphosphono)dithioacetate **487** is an excellent N-thioacylating reagent and easily reacts with *β*-amino alcohols to give the corresponding *gem*-difluorophosphonothioacetamides **488**, which then can be transformed into thiazolines **490** (Scheme 138).

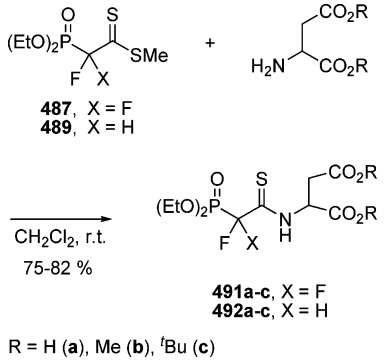
Scheme 138



Interestingly, the yields of **488** (77−85%) were depressed by competing formation of the monofluoro dithioester **489** (5−12%). Formation of this product was explained by initial thiophilic addition of methanethiol (or its anion) liberated during the reaction onto the starting difluorodithioester **487**, followed by elimination of hydrogen fluoride. Subsequent displacement of the methylthio group upon an intermediately formed ketenedithioacetal disulfide with methanethiol would afford monofluorophosphono dithioacetate **489** and dimethyl sulfide. In fact, treatment of **487** with 2 equiv of lithium ethanethiolate afforded monofluorinated dithioacetate **489** in 92% yield. This dithioester also reacted smoothly at room temperature with primary amines, including protected amino acids and amino alcohols. From (*S*)-phenylglycinol, (*S*)-phenylalanine, and (1*R*,2*R*)-norephedrine resulted a 1/1 mixture of two diastereomeric thioamides. The formation of only two diastereomers for (1*R*,2*R*)-norephedrine confirms the absence of epimerization at the stereogenic centers of the norephedrine reagent during the thioacylation.[154] More than likely, the synthesis of fluorophosphonomethylthioacetamides and thiazolines can be extended to the preparation of modified peptides and glycosides.

The biomedical potential of the fluorinated *N*-(phosphonoacetyl)-L-aspartate (PALA) analogues is illustrated by the synthesis of fluorothiosparfosic acid derivatives **491** and **492** (Scheme 139). ThioPALA(FF) **491c** was shown to be

Scheme 139



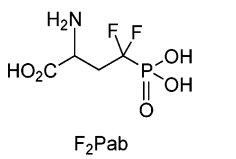
markedly more cytotoxic than PALA toward murine leukemia L1210.[347]

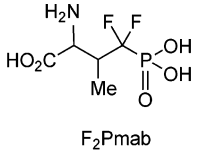
3.6.3. Fluorinated α-Amino Acid Analogues Bearing Side Chain C–P Linkages

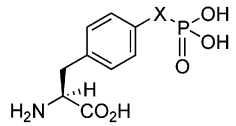
Fluorinated analogues of biological α-amino acids in which the normal α-amino acid functionality remains intact but a C−P linkage is incorporated in one way or another into the side chain have been the focus of much synthetic effort.[19]

Synthetic approaches toward CF_2-substituted phosphoamino acid mimetics by Burke,[396] Berkowitz,[13] Otaka,[19,397] and others[133,134,398,399] have provided 2-amino-4,4-difluoro-4-phosphonobutanoic acid (F_2Pab), 2-amino-4,4-difluoro-3-methyl-4-phosphonobutanoic acids (F_2Pmab), and 4-phosphonodifluoromethyl phenylalanine (F_2Pmp) as CF_2-substituted analogues of L-phosphoserine (pSer), L-phosphothreonine (pThr), and phosphotyrosine (pTyr), respectively (Chart 13).

Chart 13



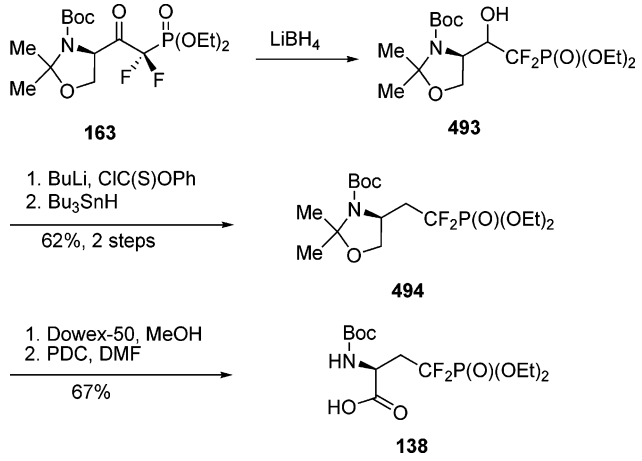




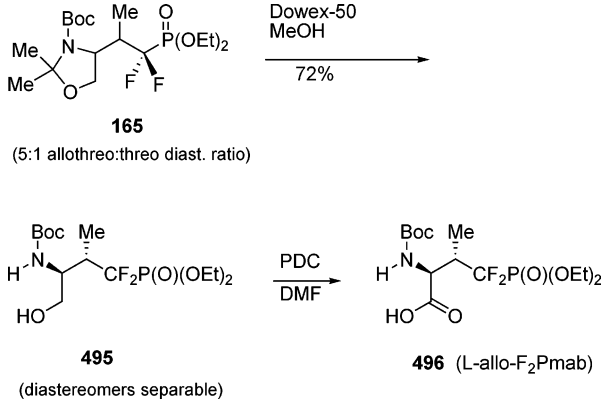
Phosphoaminoacid (pTyr) and its mimetics	X
pTyr	O
Pmp	CH_2
F_2Pmp	CF_2

For a Boc-protected isosteric phosphonic acid analogue of *O*-phosphoserine, several routes were developed starting from D-serine,[207] (*R*)-isopropylideneglycerol,[207,229] and Garner's aldehyde derived from D-serine.[400] The synthesis of the unprotected free chiral difluoro analogue was also reported, but the target material appears to undergo rapid racemization.[399] Subsequently, Berkowitz and co-workers have shown that all three α,α-difluoroalkylphosphonate analogues of L-phosphoserine, L-phosphoallothreonine, and L-phosphothreonine can be obtained from a common precursor, β-keto-α,α-difluorophosphonate **163**. Thus low-temperature reduction of **163** with $LiBH_4$ proceeded chemoselectively to deliver the corresponding diastereomeric alcohols **493**. The remainder of the sequence leading to L-phosphoserine analogue **138** is shown in Scheme 140.[229] Alternatively, β-keto-α,α-difluorophosphonate **163** may be converted to the diastereomeric tertiary alcohols **164** (see Scheme 51) by condensation with MeMgBr in place of hydride reduction. The subsequent deoxygenation step with $ClCOCO_2$-Me/Bu_3SnH proceeds with considerable diastereoselectivity to provide predominantly (allothreo/threo = 5:1) the protected L-allothreoninol-phosphate analogue **165**. Dowex 50-mediated *N*,*O*-acetal cleavage, followed by four-electron Corey−Schmidt oxidation yields the Boc-protected analogue of L-phosphoallothreonine **496** (Scheme 141).[229]

Scheme 140

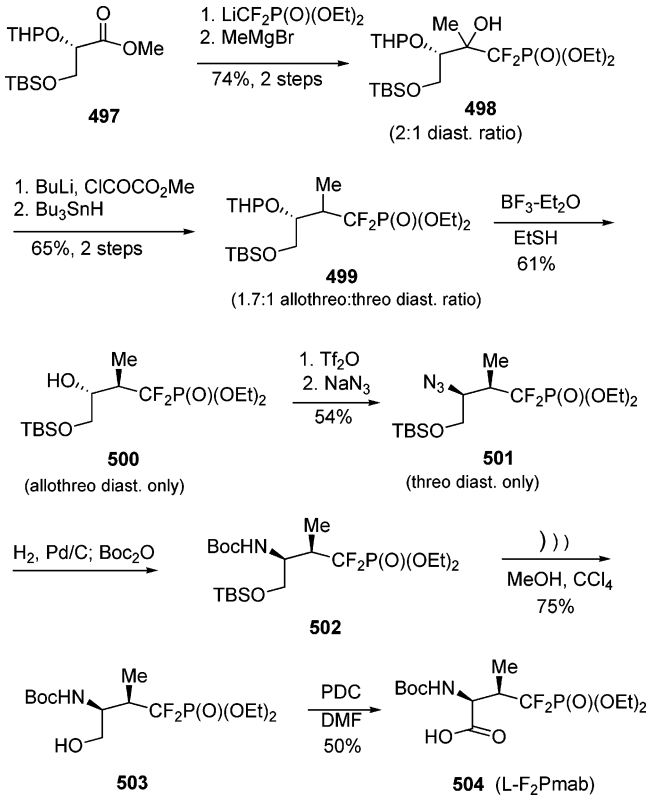


Scheme 141



Synthetic strategy for the L-phosphothreonine analogue **504** is outlined in Scheme 142. Perhaps most interesting in this sequence is the substantial increase in diastereoselectivity upon THP−ether deprotection. Thus, subjection of diastereomers **499** to the THP deprotection conditions of Nambiar and Mitra provides only allothreo alcohol **500**. The secondary alcohol **500** is inverted via triflation and displacement with azide ion to introduce the amino group with the desired L-threo stereochemistry.[229] All four stereoisomers of CF_2-substituted phosphothreonine derivatives (L-allo-F_2Pmab, L-F_2Pmab, and their enantiomers) have also been synthesized via a Cu(I)-mediated cross-coupling reaction of $BrZnCF_2P(O)(OEt)_2$ and β-iodo-α,β-unsaturated ester I(Me)C=$CHCO_2R$ (R = *p*-methoxybenzyl) with stereochemistry of both α- and β-stereocenters being established using bornane-10,2-sultam as a chiral auxiliary.[396] The same authors attempted the conjugated addition of a methyl copper reagent to γ-phosphono-γ,γ-difluoro-α,β-enoate, $(EtO)_2P(O)CF_2CH$=$CHCO_2Et$, to introduce the methyl group on the β-position. The reaction proceeded smoothly not to afford the desired conjugated addition product but to give an organocopper-mediated reduction−elimination product, α-fluorovinylphosphonate,

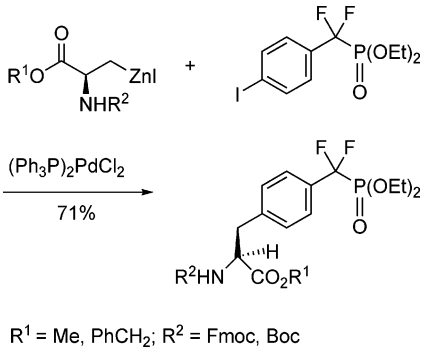
Scheme 142



$(EtO)_2P(O)CF{=}CHCH_2CO_2Et$, instead of the desired conjugate addition product. This newly found reaction was first successfully applied to the synthesis of monofluoromethyl CHF-substituted nonhydrolyzable pSer mimetics.[401]

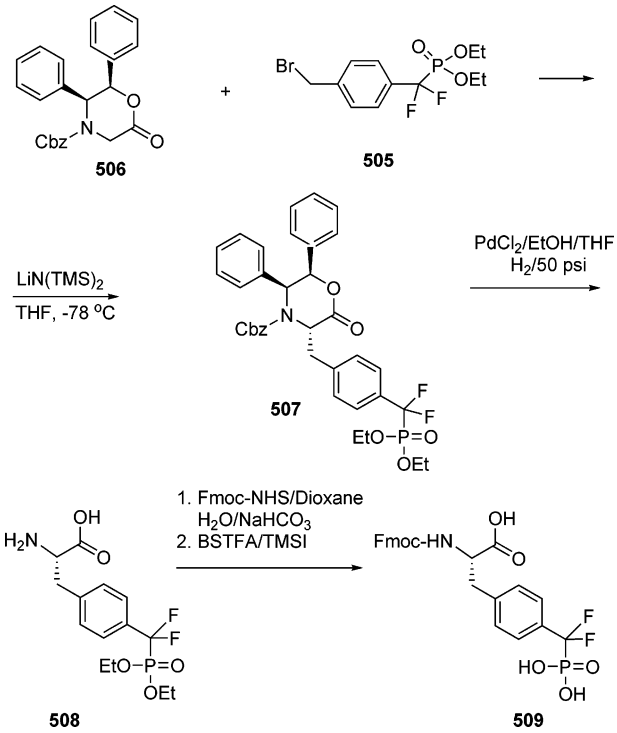
In the field of cellular signal transduction, amino acid analogues of phosphotyrosyl residues (pTyr) have emerged as especially important molecular probes.[396,402] Much of the interest in these pTyr mimetics has centered around nonhydrolyzable phosphonic acids such as (phosphonomethyl)-phenylalanine (Pmp) due to its ability to faithfully replicate several biological interactions of native pTyr residues. Since its original preparation as the racemic, free phosphonic acid, enantioselective synthesis of Pmp in its *N*-α-Fmoc 4-(bis-(*tert*-butyl)phosphonomethyl)-L-phenylalanine form [*N*-α-Fmoc-L-Pmp(tBu)-OH] has allowed facile introduction of Pmp into a variety of peptides using standard Fmoc protocols.[403,404] After 1993, progress focused on the use of the phosphotyrosine isostere F_2Pmp, mainly in its phosphonic ester form, as an efficient inhibitor of protein tyrosine phosphatase because of its lower pK_a value relative to that of Pmp. In addition and contrary to Pmp, the mimetic F_2-Pmp, by virtue of its electronegative fluorine atoms, is still capable of acting as hydrogen-bond acceptor. The methods employed to date have resulted in both racemic and enantioselective syntheses of the difluoromethylene analogue of *O*-phosphotyrosine.[122,132−134,136,398] One convergent synthesis where a modified Fmoc-L-serine ester is used to establish the correct stereochemistry of the final compounds is shown in Scheme 143. In this case, the (phosphonodifluoromethyl)-phenyl block is attached via a palladium-mediated cross-coupling reaction.[132] Another effective synthesis of *N*-α-Fmoc-4-(phosphonodifluoromethyl)-L-phenylalanine **509** utilizes both commercially available α-bromotoluic acid as a ready source for the synthesis of the alkylating agent **505**

Scheme 143



and the commercially available imino lactone **506** as the chiral glycine enolate (Scheme 144). Alkylation of the imino

Scheme 144



lactone **506** with bromide **505**, in the presence of HMPA, afforded a 78% yield of the alkylated product **507**. Hydrogenation of the latter using $H_2/PdCl_2$ gave the amino acid **508** in quantitative yield. The last step in the synthesis involved the protection of the amino group using Fmoc-NHS ester followed by deprotection of the phosphonate with a mixture of iodotrimethylsilane (TMSI) and bis(trimethylsilyl)trifluoroacetamide (BSTFA).[134]

Relying on studies that showed that peptides containing the pTyr mimetic Pmp are effective protein−tyrosine phosphatase (PTP) inhibitors,[404] Burke and co-workers prepared a Pmp-containing hexamer peptide based on the epidermal growth factor receptor-derived sequence ($EGFR_{988-993}$), "D-A-D-E-**X**-L", where X = Tyr, which has been shown to be a good PTP substrate when X = pTyr. The resulting peptide, "Ac-D-A-D−E-**X**-L-amide", where X = Pmp was compared with the same peptide containing (difluorophosphonomethyl)-phenylalanine (F_2Pmp). It was found that the F_2Pmp-containing peptide exhibited a 1000-fold enhancement in PTP binding relative to the CH_2-phosphonate-containing congener.[405] F_2Pmp peptide even reverses the impairment of insulin

receptor function associated with the overexpression of PTP1B in some forms of diabetes.[406]

Finally, it should be mentioned that incorporation of ethyl-protected CF_2-phosphonate derivatives into peptides has recently been achieved using a sequential two-step deprotection protocol involving first 0.3 M *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA)−tetrabutylammonium iodide (TBAI) in CH_2Cl_2, $BF_3{\cdot}Et_2O$, then 1 M trimethylsilyl trifluoromethanesulfonate (TMSOTf)−thioanizole in TFA, *m*-cresol, and ethanedithiol (EDT). This methodology was applied to the synthesis of nonhydrolyzable Cdc2 peptide possessing two phosphoamino acids (F_2Pmp and F_2Pmab) (Scheme 145). Protected peptide resin corresponding to the

Scheme 145

Ac-Lys(ClZ)-Ile-Gly-Glu(OBzl)-Gly-F_2Pmab$(OEt)_2$-F_2Pmp$(OEt)_2$-Gly-Val-Val-Tyr(Cl_2Bzl)-Lys(ClZ)-MBHA resin

Deprotection of ethyl groups

0.3 M BSTFA-TBAI in CH_2Cl_2 (200 eq.) + $BF_3.Et_2O$ (40 eq.) at room temperature for 90 min

Ethyl-deprotected peptide resin

Deprotection of other protecting groups and release of peptide from the resin

1M TMSOTf-thioanizole in TFA, m-cresol, EDT (100:5:5, v/v) at 0 °C for 90 min then at room temperature for 30 min

Ac-Lys-Ile-Gly-Glu-Gly-F_2Pmab-F_2Pmp-Gly-Val-Val-Tyr-Lys-NH_2

Cdc2 peptide was assembled on methylbenzhydrylamine (MBHA) resin using standard Boc solid-phase technique, where the following protecting groups were used: Bzl for glutamate, Cl_2Bzl for tyrosine, ClZ for lysine, and Et for F_2Pmp and F_2Pmab. Treatment of the completed resin with 0.3 M BSTFA−TBAI in CH_2Cl_2 and $BF_3{\cdot}Et_2O$ at room temperature, followed by washing with solvent and exposure to 1 M TMSOTf−thioanisole in TFA, *m*-cresol, and EDT at 4 °C resulted in the release of the completely deprotected peptide. HPLC purification of the crude peptide furnished the purified Cdc2 peptide in 25% yield based on the protected peptide resin.[19]

4. The Use of Fluorinated Phosphonates in Biomedical Studies

In the following discussion, representative applications of fluorinated phosphonates in biomedical studies will be presented. This section is subdivided according to the types of target enzymes or the biological activity.

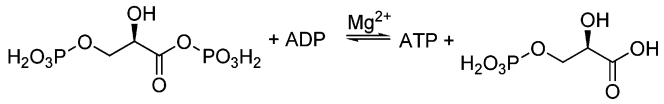
4.1. Fluorophosphonates as Inhibitors of Enzymes

4.1.1. Inhibition of Phosphoglycerate Kinase

Phosphoglycerate kinase (PGK; EC 2.7.2.3) is the enzyme that equilibrates phosphate transfer between position-1 of 1,3-bisphosphoglycerate (1,3-BPG) and the γ-phosphate of ATP. It is an attractive drug design target because trypanosomes rely on glycolysis as their sole source of energy, and hence inhibition of PGK could provide effective treatment for trypanosomal infections. Blackburn and co-workers were the first to demonstrate the superiority of difluoromethylene-phosphonic acids over methylenephosphonic acids as inhibitors of PGK.[407] Scheme 146 depicts selected data for some novel, conformationally restricted diphosphonate analogues of 1,3-BPG. As can be seen, α-hydroxylation of the diphosphonic acids does not essentially enhance their affinity for PGK. By contrast, multiple fluorine substitution for hydrogen improves affinity of the diphosphonic acids for PGK, usually by 1 or 2 orders of magnitude, and it was suggested that this was because of the lower pK_a induced

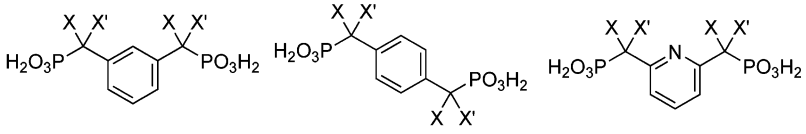
Scheme 146

Phosphate Transfer Catalyzed by PGK:



1,3-BPG 3-PGA

Selected Diphosphonate Inhibitors:



Type A Type B Type C

Type	X	X'	IC_{50}/μM	pK_{a3}	pK_{a4}
A	H	H	200	7.11	7.71
	H	OH	150	6.78	7.23
	H	F	1.3	6.01	6.37
	F	F	0.96	-	-
B	H	H	193	7.03	7.49
	H	OH	181	-	-
	H	F	1.15	6.02	6.37
	F	F	0.98	4.82	5.60
C	H	H	182	6.70	8.49
	H	OH	163	6.57	7.58
	H	F	1.33	-	-
	F	F	1.17	5.18	5.30

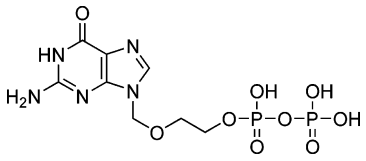
by fluorine. In quantitative terms, there is a modest correlation of IC_{50} with pK_a[3] ($R = 0.87$) and a similarly modest relationship with pK_a[4] ($R = 0.85$) over the range of 22 diphosphonates thus evaluated. This analysis appears to suggest that the enzyme responds to the charge on each phosphonate group independently. In a second paper, Blackburn also looked at diphosphonate ligands for PGK lacking the benzene motif and confirmed the specific preferences for this enzyme.[204] The dominant structural parameters of highly potent diphosphonate ligands for PGK are the separation of the two phosphonyl groups by a four- or five-atom spacer. In ionization terms, there is a clear requirement for pK_a[3] to be not greater than 6 and strong indication that complete ionization of the second phosphonate is not essential. Difluorination at either position adjacent to phosphorus increases binding over 100-fold. Interestingly, replacement of both methylenephosphonate functions by difluoromethylenephosphonate functions does not lead to further increase in affinity, suggesting that only one end of the molecule required the lower pK_a and consequent greater charge density at neutral pH. In fact, by using a novel NMR method for quantifying orientation preference based on relaxation effects, it was shown that the driving force for the orientational preference of the unsymmetrical 1,3-bisphosphoglycerate analogues is to put the difluoromethylenephosphonate group in the "basic patch" (nontransferable phosphate) position.[408]

4.1.2. Purine Nucleoside Phosphorylase Inhibitors

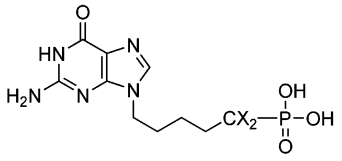
Purine nucleoside phosphorylase (PNP; EC 2.4.2.1) catalyzes the reversible phosphorolysis of guanosine and inosine nucleosides (and their 2′-deoxy forms) to their respective free base and ribose 1-phosphate (or deoxyribose-1-phosphate). Inhibitors of PNP have been suggested to have therapeutic value as immunosuppressive agents as well as in the treatment of T-cell proliferative diseases (such as T-cell leukemia), in the suppression of host-vs-graft response in organ transplant patients, and in the treatment of some parasitic diseases such as malaria. In addition, PNP inhibitors may also prolong the plasma half-lives of some purine nucleosides used as chemotherapeutic agents by preventing the PNP-catalyzed inactivation.[409]

Based on the finding that the diphosphate derivative of acyclovir (**510**) is a potent inhibitor of the human enzyme ($K_i = 8.7$ nM at 1 mM orthophosphate concentration),[410,411] metabolitically stable acyclic nucleotide analogues **511** and **137** containing a guanine and a phosphate-like 9-phosphonoalkyl moiety have been designed as multisubstrate analogue inhibitors of purine nucleoside phosphorylase (Chart 14). Compound **511** was found to inhibit human erythrocyte PNP with a K_i value of 170 nM.[412] At pH 7.4, 9-(5′,5′-difluoro-5′-phosphonopentyl)guanine **137** has a K_i value 5- to 26-fold lower than that of the nonfluorinated analogue **511** regarding PNP from four different origins. The difference between K_i values of **511** and **137** was even more pronounced when the inhibition study was performed at pH 6.2 (K_i **511**/K_i **137** is 96).[201] These data represent clear evidence of the superiority of a difluorophosphonate derivative over a phosphonate as enzyme inhibitor. In addition, the binary complex of the trimeric calf spleen phosphorylase, which is highly homologous to human PNP, and the ground-state analogue inhibitor **137** were cocrystallized and analyzed by high-resolution X-ray diffraction. The crystal structure confirms that **137** acts as a multisubstrate analogue inhibitor

Chart 14



510

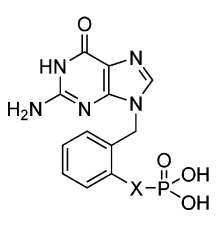


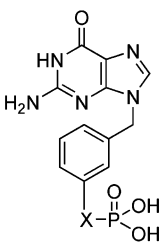
511 X = H
137 X = F (DFPP-G)

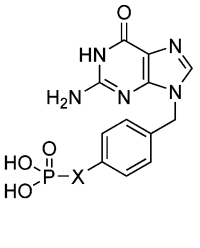
as it binds to both nucleoside- and phosphate-binding sites. The structure also provides the answers to some questions regarding the substrate specificity and molecular mechanism of trimeric PNPs.[335]

In search of motifs effective to inhibit human PNP, Halazy and co-workers synthesized the phosphonate derivatives of ortho-substituted 9-benzylguanine **401a**−**f** and their meta (**401g**) and para (**401h**) isomers (Chart 15).[330] These nucleotide analogues present inhibitor properties closely related to position of their phenyl ring substituent. Compound **401g**, the meta analogue of **401b**, is 100-fold less potent than its isomer as an inhibitor of PNP from human erythrocyte and calf spleen; compound **401h**, the para analogue of **401a**, is 1000-fold less potent than **401a** when tested on the same enzymes. The nucleotide analogues **401b**, **401c**, and **401d** are among the best PNP inhibitors ever reported ($K_i = 1.3$, 1.8, and 3.2 nM, respectively).

Chart 15







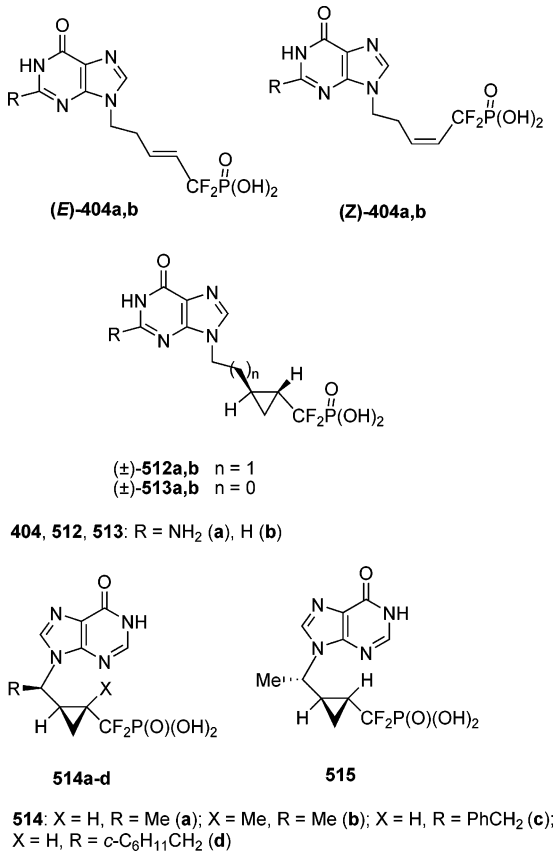
401a X = CH_2CF_2
b X = $CHFCF_2$
c X = (*E*) CH=CF
d X = (*E*) CH=CH
e X = $O(CH_2)_2CF_2$
f X = $O(CH_2)_2CH_2$

401g X = $CHFCF_2$

401h X = CH_2CF_2

The K_i values of a series of guanine derivatives (*E*)-**404a**, (*Z*)-**404a**, and **(**±**)**-**512a** against the PNP from *Cellulomonas* sp. range from 20.4 to 29.1 nM and show that the binding affinities are almost identical to that of **511** (Chart 16). However, the IC_{50} values for this series of inhibitors are 1.4- to 3.2-fold more potent than that of **511**. Inhibition of *Cellulomonas* sp. by hypoxanthine derivatives (*E*)-**404b**, (*Z*)-**404b**, **(**±**)**-**512b**, and **(**±**)**-**513b** resulted in a significant decrease in K_i value compared to the corresponding guanine derivatives. While no significant difference in K_i and IC_{50} values between configurational isomers of alkenylphosphonates (*E*)-**404b** and (*Z*)-**404b** was observed, these compounds ($K_i = 11.4$ and 16.2 nM, respectively) were apparently more

Chart 16



potent than **511** (K_i = 28.7 nM). The K_i and IC_{50} values of the cyclopropane derivative (±)-**512b** having a hypoxanthine nucleobase were determined to be 8.8 and 70 nM, respectively. Finally, inhibition potencies of the diastereomeric nucleotide analogues **514a**−**d** and **515** were evaluated in comparison with the nucleotide analogue **513b**. The result revealed that introduction of a methyl substituent to the side chain of **513b** increases its inhibitory potency for the catalytic reaction of PNP, while the binding affinity for the enzyme protein itself is decreased. The IC_{50} values of **514a** and **515** for PNP (*Cellulomonas* sp.)-catalyzed phosphorylation of inosine were determined to be 70 and 90 nM, respectively. K_i values of **514a** and **515** were 19.6 and 20.4 nM, respectively, and the binding affinities of the two diastereomers were almost the same. The IC_{50} and K_i values of **513b** have been determined to be 190 and 5.4 nM, respectively.[218,332,334]

Experimental details for the synthesis and biological evaluation of the nucleotide analogues (±)-*cis*-**516**, -**517**, and (±)-trans-**516**, -**517** in which a hypoxanthine and a difluoromethylene phosphonic acid are linked by an alkyl spacer composed of a five-membered oxacycle have also been reported (Chart 17).[220,221]

Inhibition constants of **137**, (±)-**512a**, (±)-**512b**, (±)-*cis*-**516**, -**517**, and (±)-trans-**516**, -**517** for human erythrocyte PNP-catalyzed phosphorylation of inosine are presented in Table 19. As can be seen, the stereochemistry of the inhibitors affects significantly the inhibitory potency. The nucleotide analogue (±)-*cis*-**516** with an IC_{50} of 88 nM is about 4-fold more potent than *trans*-**516** with an IC_{50} of 320 nM. Tetrahydropyranyl derivatives (±)-*cis*-**517** and (±)-*trans*-**517** were more potent than the tetrahydrofuranyl derivatives (±)-*cis*-**516** and (±)-*trans*-**516**. From the assessment on human PNP, the most potent compound in this set was identified to be (±)-*cis*-**517** (IC_{50} = 38 nM, K_i = 26.9 nM). Under the same conditions, the reference nucleotide analogue **137** shows modest inhibitory potency (IC_{50} = 380 nM) and binding affinity (K_i = 53.0 nM) toward the PNP.

Chart 17

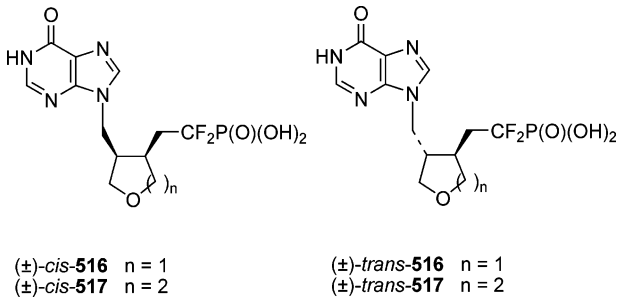


Table 19. Comparison of Inhibitory Constants of 137, (±)-512a, (±)-512b, (±)-*cis*-516, -517 and (±)-*trans*-516, -517 for Human Erythrocyte PNP [220]

compound	IC_{50} (nM)[a]	K_i (nM)[a]
137	380	53.0
(±)-**512a**	330	43.4
(±)-**512b**	340	17.3
(±)-*cis*-**516**	88	15.2
(±)-*trans*-**516**	320	*b*
(±)-*cis*-**517**	38	26.9
(±)-*trans*-**517**	106	*b*

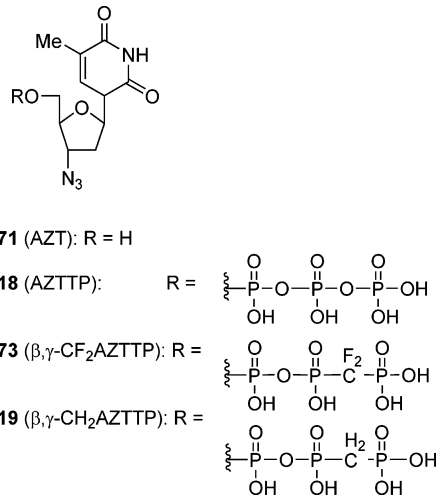
[a] Determined in the presence of 0.1 mM inosine in 100 mM potassium phosphate buffer (pH 7.5). [b] Not determined.

4.1.3. Inhibition of HIV-1 Reverse Transcriptase

The replacement of oxygen in the P−O−P phosphate ester bonds by CF_2 group has been an effective strategy in the development of a number of potent inhibitors of HIV-1 (human immunodeficiency virus, type 1) reverse transcriptase. The HIV RT catalyzes both RNA-directed DNA synthesis and DNA-directed DNA synthesis in cytoplasm shortly after retrovirus infection of a cell. The currently approved agents that target HIV RT are dideoxynucleoside analogues (ddN), which are metabolized in cells to the corresponding ddN 5′-monophosphates, ddN 5′-diphosphates, and ddN 5′-triphosphates (ddNTP). The triphosphates are active chemical species utilized by HIV RT as mimetics of natural substrates for DNA chain polymerization. Overall viral DNA synthesis is inhibited predominantly through incorporation of the ddNTP into the elongation DNA chain and subsequent chain termination.[413] For example, 3′-azido-3′-deoxythymidine (AZT, **271**), used extensively as an approach to the management of HIV infection, is metabolized to the ddNTP **518**, which is strongly inhibitory to HIV RT (IC_{50} = 0.022 μM when tested against HIV-1 peptide derived RT obtained from HIV-1-infected H9 cell culture).[70,298] AZT 5′-β,γ-difluoromethylene analogue **273** and AZT 5′-β,γ-methylene analogue **519** proved to be less inhibitory to HIV-1 RT, having IC_{50} values that were 30-fold and 300-fold higher, respectively. The diminished interaction of **273** and **519** suggests that the β,γ-phosphoanhydride oxygen plays a significant role in binding of AZTTP to HIV-1 reverse transcriptase. In this case, β,γ-CF_2-AZTTP had much greater anti-HIV RT activity than did β,γ-CH_2-AZTTP (Chart 18).[70]

AZT 5′-β,γ-difluoromethylene-γ-substituted analogues **278a**−**h** and other types of AZT 5′-triphosphate mimics

Chart 18



containing either α-borano-*β*,*γ*-difluoromethylene (**277a**−**f**), α-*P*-thio (or dithio) (**280**, **281**), or α,*β*-difluoromethylene (**282a**,**b**) functions were also synthesized (see section 3.1.2) and evaluated as HIV-1 RT inhibitors.[299] The 5′-*γ*-*P*-substituted AZTTP **278a**−**h** exhibited varied inhibitory effects. Except for **278e**, which was a weak inhibitor, the other *γ*-substituted AZTTP mimics containing *γ*-*P*-F, *γ*-*P*-NH_2, *γ*-*P*-OMe, *γ*-*P*-OPh, *γ*-*P*-NHMe, *γ*-*P*-NHEt, and *γ*-*P*-NHPh all showed significant activities with K_i values in a range of 0.04−0.85 *μ*M. Compound **260**, containing α-R_P/S_P-thio showed slightly higher K_i than **273** (0.090 vs 0.041 *μ*M), whereas **281**, containing the α-*P*-dithio, was a much weaker inhibitor. Modification of the *β*,*γ*-bridge of 5′-α-borano-*β*,*γ*-bridge-modified triphosphates resulted in varied activities (K_i from 0.0095 to ≫0.5 *μ*M) for AZTTP mimics **277b**−**f**, while modification at the α,*β*-bridge of triphosphate led to weak AZTTP inhibitors **282a**,**b**. The most active compound, AZT 5′-α-R_P-borano-*β*,*γ*-difluoromethylene triphosphate (**277d-I**), is as potent as AZTTP with a K_i value of 0.0095 *μ*M and is at least 20-fold more stable than AZTTP in the serum and cell extracts. Activity of the diastereomer **277d-II** (containing α-S_P-borano) was decreased compared to that of diastereomer **277d-I**.

Other 2′,3′-dideoxynucleoside 5′-α-*P*-borano-*β*,*γ*-difluoromethylene triphosphates were also studied. For example, compounds **283a**−**f** and **286a**−**d** were evaluated as inhibitors of HIV-1 RT. All ddN's tested exhibited essentially the same level of inhibition as the corresponding ddNTP. A conclusion was made that 5′-α-B-*β*,*γ*-CF_2TP is a generic and promising triphosphate mimic concerning HIV-1 RT inhibition and serum stability.[300]

In addition to nucleoside analogues such as AZT, carbocyclic nucleosides have been shown to possess potent anti-HIV activity. Thus, early work by Roberts and co-workers had demonstrated that the pyrophosphoryl phosphonate **264** is a potent inhibitor of HIV RT (IC_{50} = 0.5 *μ*M; cf. AZTTP IC_{50} = 1.0 *μ*M).[296] Further progress in this area results from structural modification of the diphosphate unit in **264** to enhance its stability in vivo. To this end, the same workers have prepared and tested as inhibitors of HIV RT a series of compounds **265**−**267**. These nucleoside triphosphate mimics showed an expected correlation of increased activity with an increase in fluoro-substitution. Except for **265**, which was a relatively weak inhibitor, **266** and **267** containing *β*,*γ*-CHF and -CF_2 bridge in the triphosphate moiety showed significant activities. Thus, the *β*,*γ*-difluoromethylene derivative **267** is only 1 order of magnitude less active than the parent compound **264**. It also exhibits a greatly enhanced stability to dephosphorylation in fetal blood serum, relative to AZTTP and other nucleoside triphosphates.[297] Nucleoside triphosphate mimics **268**−**270** were also tested as inhibitors of HIV RT. Both **268** and the monofluorinated analogue **269** showed relatively poor activity, being 3 orders of magnitude less active than the parent compound **264**. The difluorinated analogue **270** was markedly more effective than the monofluorinated substrate but was still two hundred times less potent than **264**. The disappointing activity of **268**−**270** may be because the carboxy group is a poor mimic of the terminal phosphonate group in compound **267**.[100]

4.1.4. Implication for the Design of Transition-State Analogue Inhibitors

The similarity between tetracoordinated phosphorus compounds and tetrahedral intermediates of enzyme reactions taking place at the carbonyl carbon atoms was recognized nearly 50 years ago.[414] However, the practical development of this concept for the design of enzyme inhibitors is of much more recent origin. In particular, many attempts have been made to improve the utility of phosphonamides, RP(O)(OH)-NHR′, as inhibitors of peptidases. These species are not used as drugs because they are rather unstable at physiological pHs. For example, Cbz-$NHCH_2$P(O)(OH)Phe, one of the most stable, potent inhibitors of carboxypeptidase A, displays a half-life of 4 h at pH 6.2.[415] Recently, synthesis of stable phosphonamide transition-state analogues of the type *Z*-$NHCH(CF_3)$P(O)(OH)$NH(CH_2)_4$Me including a racemic *β*-trifluorophosphonamidic acid has been described.[384] The latter, which represents a transition-state analogue formed by the bacterial transpeptidase, is perfectly stable at pH 4.7, contrary to the nonfluorinated compounds. This compound and related completely or partially deprotected *β*-fluoroaminophosphonic acids are expected to be antibiotics.

A general strategy for designing phosphonate-based transition-state analogue inhibitors for dipeptidases is to synthesize short peptide sequences containing a phosphonate moiety able to interact with an enzyme-bound nucleophile. Examples are *β*-fluorinated proline derivatives **520**, which are potential transition-state inhibitors for proline selective serine dipeptidases (Chart 19).[121] Since a dipeptide skeleton is necessary

Chart 19

520 **521**

Xaa = Ile or N-cyclohexylgycine
R = H or Me

for recognition by the enzyme, the pyrrolidine ring in **520** is attached to L-isoleucine or cyclohexylglycine, two amino acids that are also present in other inhibitor series for this type of enzymes. Preliminary biochemical evaluation of the compound **520** on dipeptidyl peptidase IV (DPP IV) showed promising activity (IC_{50} = 50 *μ*M).

Considering that the *γ*-glutamylcysteine synthetase (*γ*-GCS; 6.3.2.2) and glutamine synthetase (GS; 6.3.1.2) are important for use as therapeutic and agrochemical agents targeted toward the metabolism of the *γ*-glutamyl peptides, Hiratake and co-workers designed the phosphonofluoridate

521 as a potential transition-state analogue inhibitor.[416] This compound was chosen as a tetrahedral transition-state analogue in the hope that nucleophilic substitution by the substrate amine and phosphorylation by ATP would afford a transition-state mimic. In fact, phosphonofluoridate **521** inhibited GS with a K_i of 59 μM and partially inactivated the enzyme in an NH_3- and ATP-dependent manner. Compound **521** is stable under acidic conditions, and no hydrolysis was observed over a week at 4 °C in an aqueous solution at pH 5. In alkaline to neutral media, however, **521** was susceptible to hydrolysis.

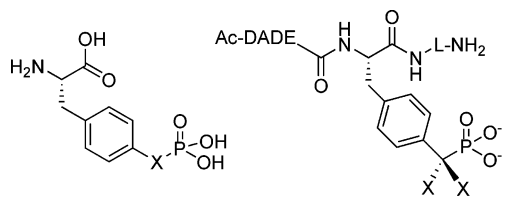
4.1.5. Inhibitors of Phosphotyrosyl-Dependent Signal Transduction

Maintenance of specific levels of protein−tyrosine phosphorylation and dephosphorylation is vital to normal cell functioning. It is controlled by the competing activities of protein−tyrosine kinases and protein−tyrosine phosphatases (PTPs). When these processes are aberrant, they can contribute to a number of diseases including cancers. Consequently, there is tremendous interest in the development of therapeutic agents that target these enzymes.[417]

The most common approach to designing PTP inhibitors has been to replace the labile phosphate group with a stable, nonhydrolyzable phosphate mimetic. The phosphotyrosine isosteres such as phosphonomethyl phenylalanine (Pmp) and its fluorinated analogues FPmp and F_2Pmp, mainly in their phosphonic ester form, have been the focus of much synthetic and biomedical efforts by the groups of Burke,[15,122,406,418−426] Taylor,[98,427−429] and others.[19,127,225,430] The milestones of these studies have been presented in numerous review articles covering the literature up to 2003.[431−433]

α,α-Difluorinated phosphonates are known to be especially effective phosphate isosteres in human protein phosphotyrosine phosphatase 1B (PTP1B) active site. For example, the Burke group found that F_2Pmp, when incorporated into an appropriate hexapeptide **523**, enhances PTP1B-binding affinity 2000-fold relative to the analogous peptide **522** bearing methylenephosphonyl phenylalanine (Chart 20).[405]

Chart 20

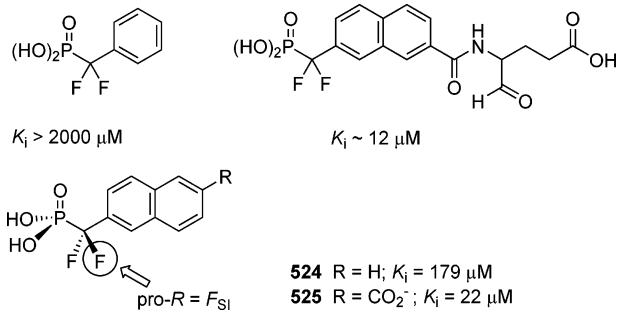


pTyr X = O
Pmp X = CH_2
FPmp X = CHF
F_2Pmp X = CF_2

522 X = H; IC_{50} = 200 μM
523 X = F; IC_{50} = 100 nM

The exceptional affinity of F_2Pmp in PTP1B enzyme active sites has led to its widespread use as structural motif in PTP and SH2 domain antagonist development.[433,434] As a result, several syntheses of F_2Pmp have been developed in both racemic[122,136] and L-forms.[132−134,435] Burke and co-workers[14,135] and Taylor and co-workers[78,98,311,429] later discovered that much simpler low molecular weight arylmethyl difluorophosphonates, lacking the peptide component, retained inhibitory potency (Chart 21). Interestingly, for inhibitors **524** and **525**, Burke and co-workers[14] propose an unconventional C−F_{si}···HN(Phe-182) hydrogen bond between the

Chart 21



pro-*R* fluorine (F_{si}) of the inhibitor and the amide NH of Phe-182. With molecular dynamic simulations, it was shown that at least for the PTP1B−**524** structure this hydrogen bond contributes up to −4.6 kcal/mol to the E−I interaction energy.[14] In support of the hypothesis that binding enhancement is due preferentially to interactions of one fluorine atom, model studies with enantiopure aryl monofluoromethylphosphonic acids have indicated a 10-fold difference in affinity depending on chirality at the α-fluoromethylene center.[110]

The inhibitory activity of aryl α,α-difluoro-β-ketophosphonates against PTP1B was measured using *O*-methyl fluorescein monophosphate (OMFP) as substrate.[231] The simple phenyl α,α-difluoro-β-ketophosphonate, $PhC(O)CF_2$-$PO(OH)_2$, shows competitive inhibition with an IC_{50} of 76 μM and a K_i of 129 μM, respectively. The *N*,*N*-bis[*p*-(2,2-difluoro-1-oxo-1-phosphonoethyl)benzyl] derivatives **526** were found to be considerably more potent inhibitors of PTP1B with IC_{50} values in the range of 0.5−1.3 μM. The best compound from this class, **526d**, has an IC_{50} of 0.6 μM and K_i of 0.17 μM (Chart 22). Presumably introduction of the second α,α-difluoro-β-ketophosphonate group provides additional binding interactions with the second phosphate-binding site or nearby region in PTP1B.

Very recently the inhibition of PTP1B with a series of benzotriazole phenyldifluoromethylphosphonic acids was also reported. The biphenylphosphonic acid **527** was found to be the most potent PTP1B inhibitor with IC_{50} = 0.003 μM. The binding mode was confirmed by X-ray of the PTP1B complexed with the compound.[436] There is also a literature report on the discovery and structure−activity relationships (SAR) of novel sulfonamides containing a single difluoromethylenephosphonate group. Investigation of SAR led to the identification of compound **528** with IC_{50} or K_i values in the low nanomolar range.[437] Similarly, SAR was exploited to design a series of potent deoxybenzoin PTP1B inhibitors such as compound **529**, which was orally bioavailable and active in the animal models of non-insulin-dependent diabetes mellitus (NIDDM).[438]

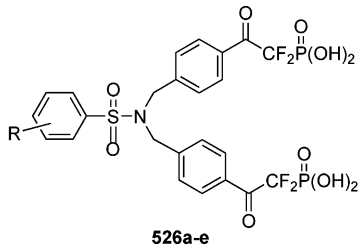
4.1.6. Other Inhibitory Activities

In addition to inhibitory applications described above, fluorinated phosphonates have been evaluated as inhibitors of other types of enzymes. Some selected examples are presented in Table 20.[439−447]

4.2. Catalytic Antibodies

A difluoromethylenephosphonate analogue of phosphoserine, first synthesized in the laboratory of Berkowitz and later incorporated into peptide **530**, served as a useful bioorganic tool, allowing Appella and co-workers to induce otherwise unobtainable antibodies to the Ser^6-phosphorylated

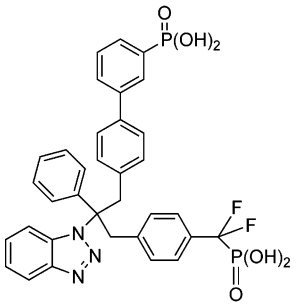
Chart 22



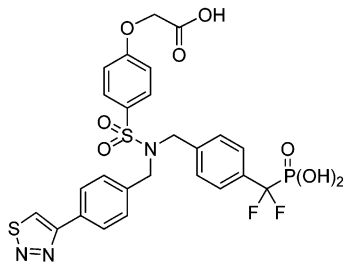
526a-e

Compound	R	IC_{50} (μM)	K_i (μM)
526a	2-Et, 4-Br	1.3	0.57
b	2-OCF_3, 4-Br	0.5	0.28
c	2-F, 5-F	0.7	ND
d	2-Me	0.6	0.17
e	4-Me	1.1	ND

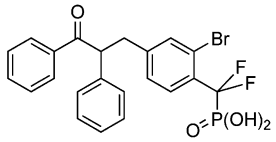
ND: not determined



527 IC_{50} = 0.003 μM



528 IC_{50} = 0.074 μM
K_i = 0.056 μM



529 IC_{50} = 0.120 μM

form of the important human tumor suppressor protein p53, for the study of its regulation (Chart 23).[13,448]

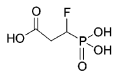
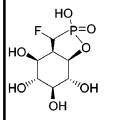
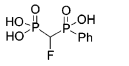
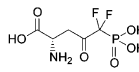
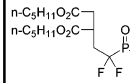
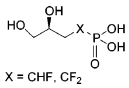
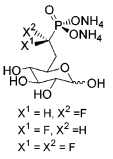
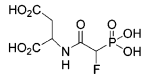
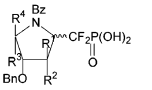
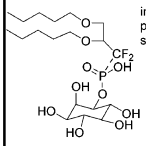
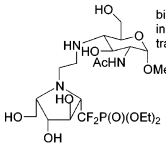
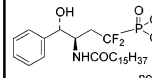
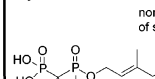
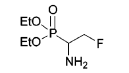
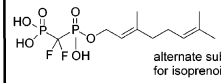
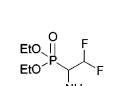
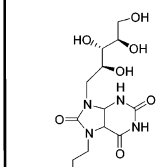
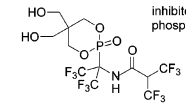
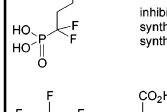
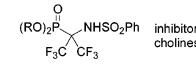
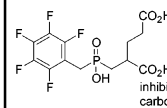
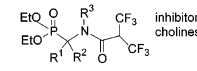
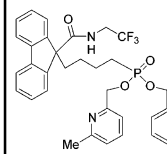
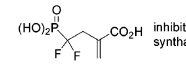
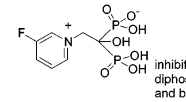
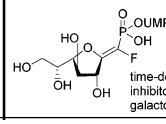
4.3. Miscellaneous Biomedical Applications

4.3.1. Antiviral Activities

The fluorinated acyclic nucleoside phosphonate **531** was found to be active against human cytomegalovirus (HCMV), Epstein Barr virus, and measles with EC_{50} values of 5.6, 1.6, and 32 μg mL^{-1}, respectively (Chart 24). The fact that the corresponding nonfluorinated monoethyl ester has been reported to be antivirally inactive implies that introduction of fluorine into the α-position of the phosphonate plays a key role in maintaining the biological activity of **531**.[75]

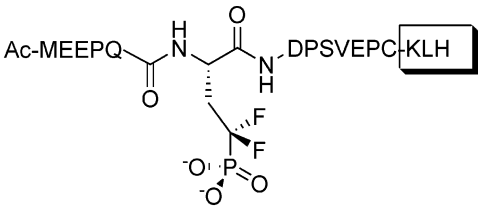
Acyclovir (ACV) is representative of the acyclic nucleoside analogues, which exhibit selective activity against herpes simplex virus types 1 and 2 (HSV-1, HSV-2). Acyclovir is initially phosphorylated at 4-hydroxyl by viral thymidine kinase to monophosphate **532**, which is subsequently converted to a triphosphate by host cell kinases. This triphosphate selectively inhibits viral-specified DNA polymerase and thus virus replication. Analogue **533**, which is a mimic of the phosphate by incorporation of the α,α-difluoro carbon, was ineffective against HSV-1 and HSV-2. These results suggest that the structural requirements of (phosphonomethoxy)ethyl purines for anti-HSV activity appear to be very strict.[200]

Table 20. Selected Fluorinated Phosphonates Designed as Inhibitors and Substrates of Enzymes

compound	activity	ref.	compound	activity	ref.
	inhibitor of mammalian DNA polymerase δ	275		inhibitor of PI-specific phospholipase C	446
	inhibitor of renal BBM Na^+-P_i cotransporter	71			
	inhibitor of L-aspartate-β-semialdehyde dehydrogenase	228 439		inhibitor of bacterial phospholipase C	197
 X = CHF, CF_2	substrates for NADH linked sn-glycerol-3-phosphate	11	 X^1 = H, X^2 =F X^1 = F, X^2 =H X^1 = X^2 = F	substrate for glucose 6-phosphate dehydrogenase	17
	inhibitor of aspartate transcarbamylase	440	ApCF$_2$ppCF$_2$pA AppCHFppA AppCF$_2$ppA	inhibitors of the ADP-induced platelet aggregation	284
	inhibitors of glycosyl transferases	313		inhibitor of phosphatidylinositol-specific phospholipase C	208
	bisubstrate analogue inhibitor for glycosyl-transferases	343			
	inhibitor of mandelate racemase	441		non-competitive inhibitor of sphingomyelinases	344
	inhibitor of alanine rasemase	341		alternate substrate for isoprenoid enzymes	231
	inhibitor of alanine rasemase	341			
	inhibitor of pyrimidine phosphorylases	342		inhibitor of riboflavin synthase and lumazine synthase	443
	inhibitors of cholinesterases	442		inhibitor of glutamate carboxypeptidase	444
	inhibitors of cholinesterases	345		inhibitor for lipoprotein secretion in HepG2 cells	445
	inhibitor of EPSP synthase	211			
	inhibitor of farnesyl diphosphate synthase and bone resorption	287		time-dependent inhibitor of UDP-galactopyranose mutase	447

Quite recently, Zheng and co-workers have synthesized and studied acyclic nucleoside **413** (ABE) as a new hepatitis B virus (HBV) specific antiviral reagent (IC_{50} 0.03 μM). Compound ABE might be suitable for hepatitis B chemotherapy.[336]

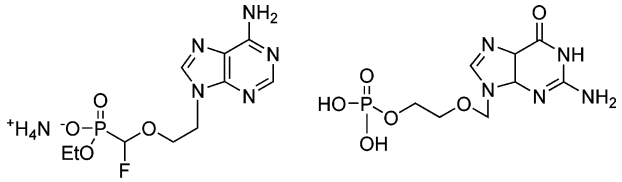
Chart 23



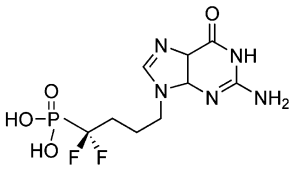
530

hapten for antibodies to Ser-6-phosphorylated p53 tumor suppressor protein

Chart 24



531 **532**

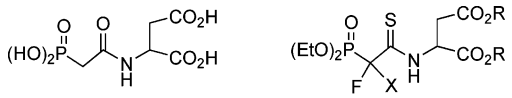


533

4.3.2. Antitumoral Activity

The *N*-(phosphonoacetyl)-L-aspartate (sparfosic acid; PALA) is known to exhibit antitumor activities against cancers such as Lewis lung carcinoma and melanoma, which could not be targeted by other antimetabolites. Nevertheless, in comparison with in vitro results, in vivo inhibition of pyrimidine biosynthesis was less efficient due to the difficult penetration of PALA in the cells under its tetra-anion state. The modification of the structure by replacement of the carboxylic amino acid moiety by phosphonic unit or the peptidic bond by methylene−sulfide, sulfoxide, sulfone, or sulfonamide groups were unsuccessful. However, high cytotoxic activities were recently observed from mono- and difluorophosphonothioacetamides **491** and **492** (Chart 25). These fluorinated

Chart 25



PALA

491a-c X = F
492a-c X = H

R = H (**a**), Me (**b**), ^{t}Bu (**c**)

thioPALA analogues exhibit an activity toward murine leukemia L1210 8−13 times superior to PALA itself. The most active compound was tetraester **491c** ($IC_{50} = 31.4\ \mu M$; cf. PALA $IC_{50} = 421\ \mu M$). The high cytotoxicity of **491c** compared to that of sparfosic acid is probably due to its better lipophilicity, which makes this ester more prone to cross the cell membrane.[336]

Carbon-11 labeled antiviral nucleoside analogue 2-amino-6-(4-[^{11}C]methoxyphenylthio)-9-[2-(phosphonomethoxy)-ethylpurine bis(2,2,2-trifluoroethyl)ester ([^{11}C]-**413**) was proposed as a novel reporter probe for positron emission tomography to image HBV and herpes simplex virus thymidine kinase (HSV-tk) in cancers.[336]

4.3.3. Anti-Platelet-Aggregation Agents

The anti-platelet-aggregation activity and resistance to hydrolysis of the phosphonate analogues of Ap_4A (diadenosine 5′,5‴-P^1,P^4-tetraphosphate) make them potentially useful therapeutic agents, poised at a primary stage in the cascade of reactions leading to thrombosis. In particular, the compound AppCHFppA showed good inhibitory effect on ADP-induced platelet aggregation. This compound may be useful as an antithrombotic agent.[284]

5. Concluding Remarks

The chemistry of fluorinated phosphonates has reached a volume that probably nobody could have predicted 20−30 years ago. Certainly, much impact has been given by the concept of bioisosteres, which has been and is still a very useful fertilizer for new or even novel chemical reactions, mechanistic considerations, and biochemical studies. Monofluoro- and difluoromethylenephosphonates that are isosteric and isoelectronic to organophosphates augmented the range of known phosphate mimics that allowed, through NMR spectroscopic and crystal structure analyses, the investigation of a wide range of bioactive fluorinated phosphonic acid derivatives. There is still room for chemical creativity in approaching new and effective fluorophosphonate mimics. The potential advantage of "isoacidity" and "tenability" in the α-monofluorinated phosphonates has been largely unexplored. More comprehensive studies on individual (*R*)- and (*S*)-stereoisomers in the α-fluoromethylenephosphonate series are clearly warranted to establish the nature of host−guest complexes. As it has been pointed out, the CHF stereochemistry may influence such factors as unfavorable steric effects, favorable van der Waals interactions, dipole−dipole and ion−dipole interactions, and fluorine hydrogen bonding. These effects remain controversial and difficult to evaluate. Finally, the conclusions drawn from discussions about enhancing the hydrogen bond acceptor ability of fluorine through a geminal fluorine anomeric effect highlight the need for a more systematic study of this phenomenon. It appears almost certain that many additional details concerning interactions of fluorinated phosphonate substrates with enzymatic binding partners await future exploration.

And at last, it is worth noting that the union of fluorine and phosphorus has natural origin! Identification of 5-fluoro-5-deoxy-D-ribose-1-phosphate as an intermediate in fluorometabolite biosynthesis was recently reported by O'Hagan and co-workers.[449] Crucial insights into the nature of fluorination enzymes can provide some of the most intriguing chemistry of the next decade. On the other hand, there can be no doubt that the "artificial" introduction of the fluorine into biological systems inspired by biochemical processes will continue to generate new efficient biochemical agents and pharmaceuticals. Thus it seems appropriate to close this article by paraphrasing De la Torre and Sierra:[450] *The purpose of the game is the same for cells as for the people working in the laboratory.*

6. Abbreviations

AIBN 2,2′-azobis(isobutyronitrile)

ATP	adenosine triphosphate
AZT	3′-azido-3′-deoxythymidine
DAST	diethylaminosulfur trifluoride, Et_2NSF_3
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DPTBS	diphenyl-*tert*-butylsilyl
EWG	electron-withdrawing functional group
F_2MDPA	difluoromethanediphosphonic acid, $[(HO)_2(O)P]_2CF_2$
F_2Pmp	4-phosphonodifluoromethylphenylalanine
FMDPA	monofluoromethanediphosphonic acid, $[(HO)_2(O)P]_2CHF$
FPPS	farnesyl diphosphate synthase
F-TEDA-BF_4 or Selectfluor	1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]-octane bis(tetrafluoroborate)
G-3-P	*sn*-glycerol 3-phosphate
G6P	glucose 6-phosphate
GTP	guanosine triphosphate
HIV	human immunodeficiency virus
RT	reverse transcriptase
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner−Wadsworth−Emmons reaction
KDA	potassium diisopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LPA	lysophosphatidic acid, 1- or 2-acyl-*sn*-glycerol 3-phosphate
m-CPBA	*meta*-chloroperbenzoic acid
MDPA	methanediphosphonic acid
Men	menthyl
MOM	methoxymethyl
mTOR	mammalian target of rapamycin
NaHMDS	sodium bis(trimethylsilyl)amide
NFOBS	*N*-fluoro-*o*-benzenedisulfonimide
NFPMS	*N*-fluoroperfluoromethanesulfonimide
NFSI	*N*-fluorobenzenesulfonimide
PA	phosphatidic acid, 1,2-diacyl-*sn*-glycerol 3-phosphate
PDC	pyridinium dichromate
PEP	phosphoenolpyruvate
PGK	phosphoglycerate kinase
PMHS	polymethylhydrosiloxane
Pmp	(phosphonomethyl)phenylalanine

Glossary

PNP	purine nucleoside phosphorylase
PTP	protein−tyrosine phosphatase
pTyr	phosphotyrosyl residue
S3P	shikimate 3-phosphate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	tributylsilyl
TFA	trifluoroacetic acid
Tf	triflate (CF_3SO_2)
THF	tetrahydofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
amino acids	The standard three-letter or one-letter abbreviations for amino acid residues are used

7. Acknowledgments

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