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$TiCl_4$ and Grignard reagent-promoted ring-opening reactions of various epoxides: synthesis of γ-hydroxy-α,α-difluoromethylenephosphonates

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ABSTRACT

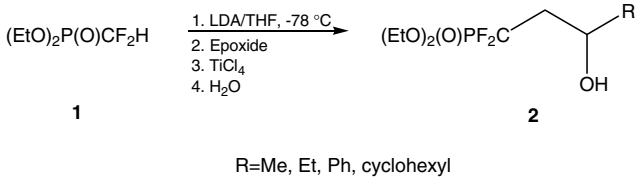
A straightforward methodology for the synthesis of diethyl γ-hydroxy-α,α-difluoromethylenephosphonates is reported. In the presence of titanium tetrachloride, epoxide ring-opening reactions occurred upon treatment with lithium diethyl difluoromethylenephosphonate. When diethyl 3,4-epoxy-1,1-difluorobutylphosphonate was reacted with $TiCl_4$ and Grignard reagents, the corresponding halohydrins were obtained in very good yields.

Lewis acid-mediated cleavage of epoxides with various nucleophiles is an important transformation in organic synthesis.[1] The popularity of oxiranes as versatile intermediates in organic preparations generally emanates from their accessibility, reactivity, and the stereochemical predictability of their reactions. Despite, however, the numerous transformations already reviewed, little attention has been given to the opening of epoxides containing a difluoromethylenephosphonate moiety.[2] Moreover, very few examples are known in the literature, where a phosphorus and fluorine-containing nucleophile has been utilized in these reactions.[3]

Interest in the synthesis of γ-hydroxy-α,α-difluoromethylenephosphonates results mostly from their potential in the design of non-hydrolyzable analogues of biologically active phosphate esters. More recently, they have been described as substrates for NADH-linked *sn*-glycerol 3-phosphate dehydrogenase or as key intermediates in the synthesis of various phosphatase-resistant phosphonolipids.[4] In contrast to non-fluorinated hydroxyl-methylenephosphonates, the preparation of which has been studied largely by oxirane ring-opening reactions with phosphonomethyl organometallic reagents,[5] this methodology has rarely been applied in the synthesis of fluorinated analogues.[2] Hence, we report our results on the Lewis acid-promoted ring-opening reactions of epoxides with lithium diethyl difluoromethylenephosphonate. The reactivity of diethyl 3,4-epoxy-1,1-difluorobutylphosphonate toward Lewis acids and Grignard reagents is also presented.

Our first attempt involved the reaction of propylene oxide with a phosphonodifluoromethyl carbanion (Scheme 1).

In this reaction, $(EtO)_2P(O)CF_2Li$ **1a** was generated by deprotonation of **1** with LDA in dry THF at −78 °C.[6] Propylene oxide was added dropwise, followed by the careful addition of a stoichiometric amount of titanium tetrachloride. An exothermic and vigorous reaction occurred on addition of the first drop of catalyst, but the temperature of the reaction mixture was controlled so as to not exceed −78 °C, which is required for reactions of lithium difluoromethylenephosphonate. After stirring for 2 h at −78 °C, the reaction mixture was quenched with distilled water, and the temperature was allowed to rise to ambient. The reaction was successful and propylene oxide was opened regioselectively at the unsubstituted carbon, affording diethyl 1,1-difluoro-3-hydroxybutylphosphonate **2** in 72% yield. It should be noted that



Scheme 1. Synthesis of γ-hydroxy-α,α-difluoromethylenephosphonates.

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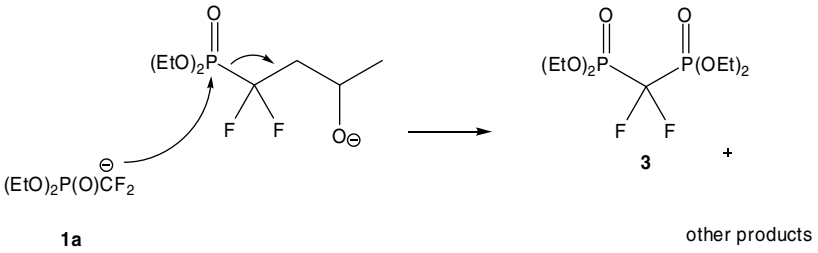


Scheme 2. Formation of tetraethyl difluoromethylenebisphosphonate **3**.

compound **2** was accompanied by a small amount of the corresponding chlorohydrin, which is due to the known ability of metal halides to open simple epoxides.[7] Another byproduct appearing in this reaction was tetraethyl difluoromethylenebisphosphonate **3**. Its formation was probably the consequence of the subsequent slow reaction that product **2** experiences at the P=O center with lithium diethyl difluoromethylenephosphonate **1a** (Scheme 2). All byproducts and unreacted starting materials were removed successfully during work-up, and flash column chromatography afforded pure **2** in 62% yield.

In the course of our studies to optimize the reaction conditions, we observed that **1a** was not sufficiently reactive to open the oxirane ring without the presence of the Lewis acid (Table 1). This observation is not surprising since anion **1a** is a weak nucleophile, and apparently the formation of the complex: epoxide—Lewis acid is mandatory for the reaction to occur. Furthermore, we found that the use of a stoichiometric amount of $TiCl_4$ gave the best yield. This is probably due to the poor solubility of $TiCl_4$ at the low temperature at which the reaction is carried out. We also found that neither the use of excess starting $(EtO)_2P(O)CF_2H$ (2 equiv) nor lengthening the reaction time improved the conversion yield.

The epoxide-opening reaction with lithium diethyl difluoromethylenephosphonate **1a** was also examined in the presence of other Lewis acids such as Ti(O-*i*Pr)$_4$, Ti(OTf)$_4$, $BF_3{\cdot}Et_2O$ and Cu(OTf)$_2$ (Table 1). Generally, none of these catalysts afforded the desired ring-opened products. Ti(O-*i*Pr)$_4$ and titanium and copper triflates were ineffective, and starting material was recovered. Also, no activation was observed in the presence of LiBr, the use of which was mentioned in the case of epoxide opening with perfluorohexyl lithium.[8]

Surprisingly, the use of boron trifluoride $BF_3{\cdot}Et_2O$, the most common catalyst applied in ether cleavage reactions was unsuitable.[9] $BF_3{\cdot}Et_2O$ has been applied successfully for oxirane ring-opening reactions with fluorinated vinyllithium compounds and non-fluorinated phosphonates, however, in our case it gave only a 5% yield of the expected product **2**. Boron trifluoride under these conditions seems to be less prone to coordinate at the boron center with an epoxide, and to catalyze nucleophilic ring opening. Preferentially, in the case of difluoromethylenephosphonate anion **1a**, $BF_3{\cdot}Et_2O$ undergoes reaction with **1a** to afford $(EtO)_2P(O)CF_2BF_3^-Li^+$ as the main product (87% yield). We envisage this new and very interesting compound as an organoboron reagent for cross-coupling reactions, since the analogous perfluoroorganotrifluoroborate salts have been described recently as highly efficient reagents for reactions of this type.[10]

Table 1
Lewis acids used in ring-opening reactions with $(EtO)_2P(O)CF_2H$ (**1**)

Entry	Catalyst	Reaction conditions	Yield of **2**[a] (%)
1	$TiCl_4$	LDA, THF, −78 °C	72
2	None	LDA, THF, −78 °C	—
3	$BF_3{\cdot}Et_2O$	LDA, THF, −78 °C	5[b]
4	Ti(O*i*-P)$_4$	LDA, THF, −78 °C	—
5	Ti(OTf)$_4$	LDA, THF, −78 °C	—
6	Cu(OTf)$_2$	LDA, THF, −78 °C	—
7	$TiCl_4$	*t*-BuLi, Et_2O, −90 °C	5

[a] ^{19}F NMR yields from starting $(EtO)_2P(O)CF_2H$.
[b] Main product: $(EtO)_2P(O)CF_2BF_3^-Li^+$ (87%).

In an attempt to extend the scope of the above-described reaction, we decided to explore the possibility of opening other oxiranes. All the representative epoxides studied here, 1,2-butene oxide, styrene oxide, and cyclohexene oxide were ring-opened and gave the corresponding products. As originally expected, the reaction is regioselective, which is undoubtedly due to nucleophilic attack at the less hindered site of the oxirane ring. Except for 1,2-butene oxide, in all cases, the formation of analogous chlorohydrins was observed. All impurities were removed easily during work up to afford alcohols **4**–**7** in satisfactory yields (Table 2).

It should be noted that no product of type **8** resulting from cleavage of the oxolane ring with lithium salt **1a** was observed (Table 2, entry 5), which makes THF a potential solvent for this type of reaction.

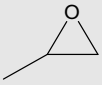
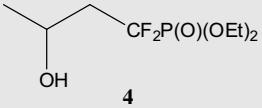
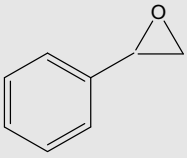
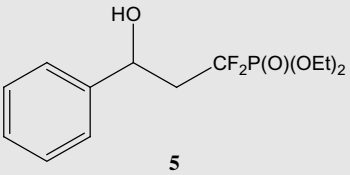
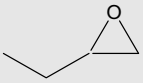
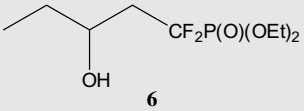
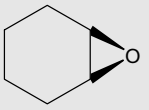
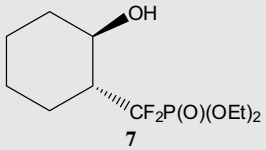
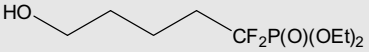
These results prompted us to examine the reactivity of diethyl 3,4-epoxy-1,1-difluorobutylphosphonate **10** toward various Lewis acids and Grignard reagents. We considered that this transformation could represent another route to γ-hydroxy-α,α-difluoromethylenephosphonates.

The synthesis of diethyl 3,4-epoxy-1,1-difluorobutylphosphonate **10**[11] was achieved successfully as shown in Scheme 3 by the reaction of methyl(trifluoromethyl)dioxirane generated in situ with unsaturated phosphonate **9** in a water-acetonitrile mixture as solvent.[12] This new and simple procedure, which is an alternative to previously reported syntheses of this compound, was very efficient and led to the desired product in excellent yield (92%), even when the reaction was conducted on a preparative scale.

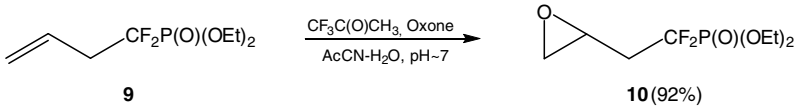
Next, we treated oxirane **10** with titanium tetrachloride (1.1 equiv) in dry THF and after two hours of stirring at room temperature, we observed complete consumption of the starting material (by ^{19}F NMR). After typical work up and column chromatography, the sole product, diethyl 4-chloro-1,1-difluoro-3-hydroxybutylphosphonate, was isolated in 82% yield. Moreover, we found that the reaction occurred with complete regioselectivity via preferential attack on the terminal carbon of epoxyphosphonate **10**. With milder Lewis acids, for example $BF_3{\cdot}Et_2O$ and Me_3Al, no reaction occurred and only starting materials were recovered.

Interestingly, similar behavior was observed when Grignard reagents were used as nucleophiles. In this case, the reaction resulted in the regioselective formation of the corresponding chloro- or bromohydrin (attack on the less hindered side of the epoxide) and no other products were detected in the reaction mixtures (based on ^{19}F NMR analysis). This unexpected behavior of diethyl 3,4-epoxy-1,1-difluoromethylenephosphonate **10** with organomagnesium reagents suggests that these could also act as Lewis acids. Probably, due to the reaction conditions, the Schlenk equilibrium, which occurs in solutions of Grignard reagents,[13] tends to favor the formation of diorganyl magnesium and a

Table 2
Diethyl γ-hydroxy-α,α-difluoromethylenephosphonates produced as shown in Scheme 1

Entry	Epoxide/Oxolane	Product	Yield[a] (%)
1		 **4**	62
2		 **5**	34
3		 **6**	47
4		 **7**	26
5		 **8**	0

[a] Isolated yields after purification by flash column chromatography.



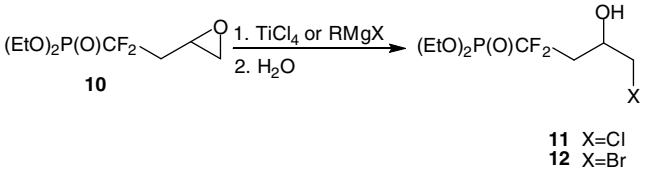
9 **10** (92%)

Scheme 3.

magnesium halide salt (a weak Lewis acid). Complexation of this Lewis acid with epoxide **10** is then possibly preferred over the reaction with the Grignard reagent. As a consequence, halohydrins were obtained in very good yields as sole products, even when the reactions were carried out under different reaction conditions (Scheme 4, Table 3).

As has already been mentioned, all of these reactions occured at the less hindered side of the oxirane ring. The predominant regioselectivity can be explained by Coulombic repulsion between the lone pairs of the difluoromethyl group and the negative charge on the nucleophile (Scheme 5).[14]

It is also worth mentioning that all the γ-hydroxy-α,α-difluoromethylenephosphonates show complicated spectra, but particularly significant are the CF_2 fluorine signals in the ^{19}F NMR spectra which exhibit a characteristic AB type pattern. In these molecules, both the fluorine atoms as well as both protons at the β carbon are not equivalent (F_a, F_b, and H_a, H_b), which is due to the stereogenic carbon. The complicated multiplicity of each fluorine atom is a consequence of coexisting couplings between fluorine–fluorine, fluorine–phosphorus, and finally fluorine–proton.



10

11 X=Cl
12 X=Br

Scheme 4.

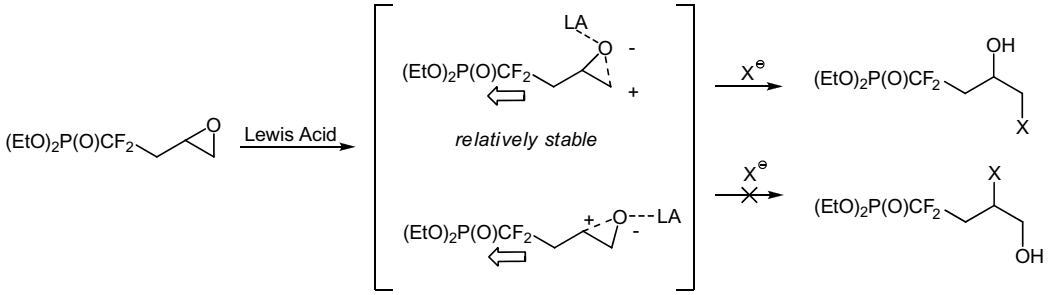
Table 3
Grignard reagents used in the formation of halohydrins produced as shown in Scheme 4

Entry	Grignard reagent	Reaction conditions (product)	Yield[a] (%)
1	CH_3MgCl	−78 °C → rt, THF, 24 h (**11**)	97
2	CH_3MgCl	rt, 12 h (**11**)	97
3	AllylMgCl	−78 °C → rt, THF, 24 h (**11**)	78
4	AllylMgCl	rt, 12 h (**11**)	78
5	PhMgBr	−78 °C → rt, THF, 24 h (**12**)	79
6	PhMgBr	rt, 12 h (**12**)	73
7	$PhCH_2MgCl$	rt, 12 h (**11**)	78

[a] Isolated yields after purification by flash column chromatography.

What is more, the presence of hydroxyl, difluoromethylene, and phosphonyl groups in the same molecule creates the possibility of hydrogen bonding. Parameters such as state (solid or in solution), concentration, temperature and polarity of the solvent will determine the preferred conformation (*synclinal* or *antiperiplanar*) and will be crucial for the formation of either intramolecular or intermolecular hydrogen bonds. Simple NMR experiments at room temperature in solvents of different polarity—$CDCl_3$ and D_2O, have delivered much information already.[15]

In conclusion, a general access to diethyl γ-hydroxy- and δ-halo-γ-hydroxy-α,α-difluoromethylenephosphonates via epoxide



Scheme 5.

ring-opening reactions has been developed. Representative oxiranes underwent the reaction with lithium difluoromethylenephosphonate in the presence of $TiCl_4$ to give the corresponding products in good yields. The successful opening of cyclohexene oxide broadens the utility of the reaction described herein to 1,2-disubstituted epoxides. Moreover, when diethyl 3,4-epoxy-1,1-difluorobutylphosphonate was reacted with $TiCl_4$ or Grignard reagents, the corresponding halohydrins were obtained. Compounds of this type are of synthetic potential and can serve as useful precursors for a variety of derivatives.[4]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.146.

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