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Regioselective Synthesis of Fluoroalkylated β-Aminophosphorus Derivatives and Aziridines from Phosphorylated Oximes and Nucleophilic Reagents

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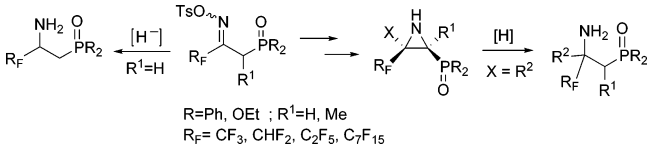

A simple and efficient stereoselective synthesis of fluoroalkyl substituted aziridine-2-phosphine oxides and -phosphonates by diastereoselective addition of methoxide, imidazole, benzenethiol, and Grignard reagents to functionalized ketoxime-phosphine oxides and -phosphonates is described. Aziridines are used as intermediates for the regioselective synthesis of fluorine containing β-amino phosphine oxides and β-amino phosphonates. Amino phosphorus derivatives can also be obtained from ketoximes derived from phosphine oxides and phosphonates with sodium borohydride.

Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes, and β-aminophosphonates, as isosteres of β-amino acids, occupy an important place and reveal diverse and interesting biological and biochemical properties in their role as enzyme inhibitors, agrochemicals, or pharmaceuticals.[1] On the other hand, in the field of bioactive molecules, fluoroorganic compounds have received a great deal of attention since the incorporation of a fluorine containing group into an organic molecule dramatically alters its physical, chemical, and biological properties.[2] These changes in properties make them suitable for diverse applications in synthetic, agricultural and medicinal chemistry as well as in material science.[3] Special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks since they can be used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[4] For these reason, the development of new methods for the preparation of fluorine substituted aminophosphonates is an interesting goal in synthetic organic chemistry, not only because of their use in medicinal chemistry as ligands for phosphoglycerate kinase[5a] or antibacterials,[5b] but also for the preparation of fluorinated peptidomimetics.[6] However, only the addition of amines to unsaturated phosphonates[5b] or the addition of fluorinated phosphonate carbanions to *N*-protected α-haloamines[5a] or imines[7] for the synthesis of fluorine substituted aminophosphonates have been described.

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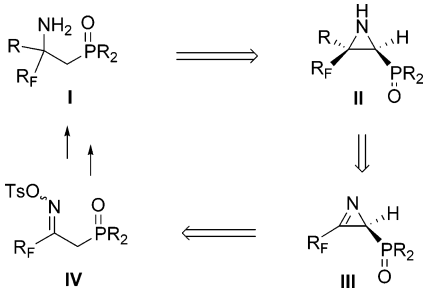
SCHEME 1. Retrosynthetical Pathway for Fluoroalkyl Substituted β-Aminophosphorus Derivatives



Phosphorylated heterocycles have been acquiring increasing interest,[8] and we described new methods for the preparation of acyclic compounds[9] and phosphorylated nitrogen heterocycles.[10] Likewise, we reported the preparation[11] of 2*H*-azirine-phosphine oxides and -phosphonates from *p*-toluenesulfonyl-oximes[12] and their use for the synthesis of aminophosphorus derivatives[13] and phosphorylated pyrazines,[14a] or oxazoles.[14b,c] Continuing with our interest in the chemistry of aminophosphorus derivatives[1] and of small strained nitrogen heterocycles,[11−14] here we report the regioselective preparation of fluorine containing β-aminophosphorus derivatives **I** (R = Ph, OEt; Scheme 1) and fluoroalkyl substituted aziridines **II** from fluorinated *p*-toluenesulfonyl oximes **IV**, probably by means of the nonisolated fluorine containing 2*H*-azirines **III** generated in situ (Scheme 1).

Results and Discussion

Synthesis of Fluoroalkyl Substituted Aziridines. The synthesis of 2*H*-azirine-phosphine oxides and -phosphonates has been described using the modified Neber reaction[15] of *p*-toluenesulfonyl oximes derived from phosphine oxides and phosphonates with alkaloids and solid supported amines.[11] Now we wish to extend the process to the preparation of azirines **III** (Scheme 1) and aziridines derived from phosphine oxides and phosphonates **II** (Scheme 1). With this objective, we first explored the synthesis of β-keto-phosphine oxides and -phosphonates required for the preparation of the *p*-toluenesulfonyl oximes. The reaction of methyldiphenyl-phosphine oxide **1a** (R^1 = H) with ethyl trifluoromethyl acetate **2a** ($R_F = CF_3$) or ethyl 2,2-difluoromethyl acetate **2b** ($R_F = CHF_2$) in the presence of LDA in an inert atmosphere gave, after workup, fluorine-substituted enol-phosphine oxides **4a** and **4b** in good yield (Scheme 2, Table 1, entries 1 and 2). Whereas, when ethyl perfluoroalkyl octanoate **2c** ($R_F = C_7F_{15}$) was used, a mixture of both keto **3c** and enol **4c** tautomers (Table 1, entry 3) was obtained. Formation of compound **4** could be explained by initial formation of β-ketophosphine oxide **3** followed by prototropic tautometization to enol **4**.

However, when ethyldiphenylphosphine oxide **1b** (R^1 = Me) was used, fluorinated β-keto-phosphine oxide **3d**, initially formed, can undergo addition of water to provide the hydrate form **5d**, and therefore a mixture of β-keto-phosphine oxide **3d** and its hydrate **5d** (Scheme 2, Table 1, entry 4) was obtained. The use of high vacuum allows one to dehydrate *gem*-diol **5d** (R = Ph) to obtain β-keto-phosphine oxides **3d**. The electrophic

SCHEME 2. Synthesis of Ketones 3 and 7, and Oximes 9−12

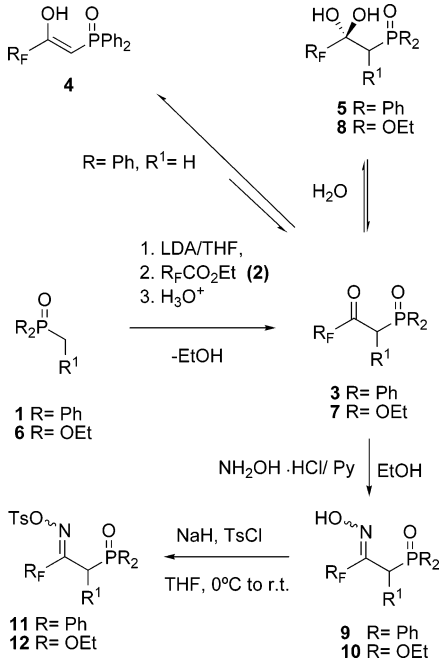


TABLE 1. β-Phosphorylated Ketones 3/7, *gem*-Diols 5/8, and Enols 4

entry	compd	R	R^1	R_F	yield(%)[a]
1	**4a**	Ph	H	CF_3	74
2	**4b**	Ph	H	CHF_2	75
3	**3c/4c**	Ph	H	C_7F_{15}	58[b]
4	**3d/5d**	Ph	CH_3	CF_3	75[c]
5	**7a/8a**	OEt	H	CF_3	78[d]
6	**7b/8b**	OEt	H	C_2F_5	75[d]
7	**7c/8c**	OEt	CH_3	CF_3	73[d]

[a] Yield of isolated purified compounds. [b] Obtained as mixture of derivatives **3/4**. [c] Obtained as a mixture of derivatives **3/5**. [d] Obtained as a variable mixture of derivatives **7/8**.

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TABLE 2. Phosphorus Substituted Ketoximes 9−12

entry	compd	R	R^1	R_F	*E*/*Z* (%)[a]	yield (%)[b]
1	**9a**	Ph	H	CF_3	0/100	73
2	**9b**	Ph	H	CHF_2	0/100	77
3	**9c**	Ph	H	C_7F_{15}	0/100	84
4	**9d**	Ph	CH_3	CF_3	58/42	60
5	**10a**	OEt	H	CF_3	0/100	45
6	**10b**	OEt	H	C_2F_5	5/95	46
7	**10c**	OEt	CH_3	CF_3	100/0	40
8	**11a**	Ph	H	CF_3	0/100	84
9	**11b**	Ph	H	CHF_2	0/100	59
10	**11c**	Ph	H	C_7F_{15}	0/100	64
11	**12a**	OEt	H	CF_3	0/100	48
12	**12b**	OEt	H	C_2F_5	5/95	43
13	**12c**	OEt	CH_3	CF_3	100/0	45

[a] Ratio of *E*/*Z* isomers determined by ^{31}P NMR. [a] Yield of isolated purified compounds **9**−**12**.

character of the carbonyl group of **3d** is increased[16] because of the high electronegativity of the fluorine atoms, and then water was easily added with the formation of hydrate **5**, in a similar way to that previously reported for fluorine containing carbonyl compounds.[17] The process was extended to alkyl phosphonates **6** (R = OEt), and their reaction with fluoroalkylesters **2** in the presence of LDA gave, after workup, fluorine-substituted mixtures of *β*-keto-phosphonates **7** and their hydrates **8** (Scheme 2, Table 1, entries 5−7). As before, the dehydration of *gem*-diols **8** (R = OEt) to obtain *β*-keto-phosphonates **7** can be performed by using high vacuum. Moreover, enols **4** can be used directly for further synthetic purposes, and it is not necessary to separate ketones **3** and **7** and enol **4** or hydrates **5** and **8** for further synthetic purposes.

Next we accomplished the synthesis of oximes **9** (R = Ph) and **10** (R = OEt) by condensation of hydroxylamine with *β*-keto-phosphine oxides **3** and -phosphonates **7**. *β*-Ketoximes **9** (R = Ph) and **10** (R= OEt) were isolated as a varible mixture of *E* and *Z* isomers (Scheme 2, Table 2, entries 1−7). The *E*/*Z* assigment of derivatives **9** (R = Ph) and **10** (R = OEt) was based on NOE experiments. Irradiating the methylene protons (C**H**$_2$) at δ = 3.63 ppm of oxime **9a** showed an enhancement (0.12%) of the hydroxyl −O−**H** proton at δ = 12.90 ppm, and this result is consistent with the *Z* configuration of oxime **9a**. Subsequent tosylation of *β*-ketoxime-phosphine oxides **9** and -phosphonates **10** gave functionalized *β*-*p*-toluenesulfonyloxime phosphine oxides **11** and phosphonates **12** (Scheme 2, Table 2, entries 8−13) in the same proportion of *E* and *Z* isomers as the *β*-ketoxime-precursors **9** (R = Ph) and **10** (R = OEt).

The base-mediated Neber reaction[15] of fluoroalkyl *p*-toluenesulfonyl oximes **11** (R = Ph) and **12** (R = OEt) was then explored. Reaction of *p*-toluenesulfonyl oxime phosphine oxide **11a** (R = Ph, R^1 = H, R_F = CF_3) with a base such as pyridine did not give 2*H*-azirine **13** (R_F = CF_3, R^1 = H, R = Ph) and starting material was recovered (Scheme 3). On the other hand, the use of bases such as DBU, NaH, or MeLi did not lead to the formation of fluoroalkyl 2*H*-azirine phosphine oxide **13** (R_F = CF_3, R^1 = H, R = Ph), but a complex mixture of products was obtained instead. Therefore, the use of alkoxides as bases was studied; *p*-toluenesulfonyl oxime phosphine oxide **11a** (R = Ph, R^1 = H, R_F = CF_3) was treated with NaOMe/MeOH

SCHEME 3. Preparation of Aziridines 14−17

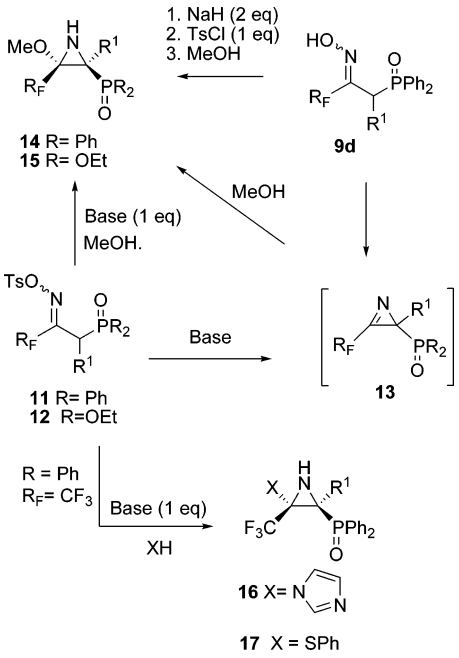

TABLE 3. Functionalized Aziridines 14−17 Obtained

entry	compd	R	R^1	R_F	yield(%)[a]
1	**14a**	Ph	H	CF_3	52[b] (85)[c]
2	**14b**	Ph	H	CHF_2	74[c]
3	**14c**	Ph	H	C_7F_{15}	70[c]
4	**14d**	Ph	CH_3	CF_3	44[d]
5	**15a**	OEt	H	CF_3	47 [b]
6	**16**	Ph	H	CF_3	45[e]
7	**17**	Ph	H	CF_3	69[c]

[a] Yield of isolated purified compounds. [b] Yield obtained by using NaOMe as base. [c] Yield obtained by using Et_3N as base. [d] Yield obtained by using NaH as base from oxime **9d**. [e] Yield obtained by using imidazole as base.

leading exclusively to the formation of *trans*-3-methoxy-3-trifluoromethylaziridin-2-yl diphenylphosphine oxide **14a** (R = Ph, R^1 = H, R_F = CF_3) (Scheme 3, Table 3, entry 1). No trace of the *cis*-aziridine could be observed by ^{31}P NMR. Spectroscopic data were in agreement with the assigned structure of compound **14a.** Well-resolved doublets at δ_H = 2.62 ppm ($^2J_{PH}$ = 17.4 Hz) for H2 in the ^1H NMR spectrum as well as at δ_C = 40.5 ppm ($^1J_{PC}$ = 84.1 Hz), and at δ_C = 72.4 ppm ($^2J_{FC}$ = 42.3 Hz) for C2 and C3 in the ^{13}C NMR spectrum were observed. The stereochemical assignment was based on NOESY 1D experiments. Irradiating the methoxy protons (C**H**$_3$−O−) at δ = 3.52 ppm showed an enhancement (0.20%) of −C2−**H** proton of the azirine ring at δ = 2.80 ppm. Moreover irradiating the −C2−**H** proton of the azirine ring at δ = 2.80 ppm showed an enhancement (0.41%) of the (C**H**$_3$−O−) proton signal at δ = 3.52 ppm.

The exclusive formation of *trans*-aziridine phosphine oxide **14a** (R = Ph, R^1 = H, R_F = CF_3) could be explained by base-mediated (NaOMe) ring-closure of *p*-toluenesulfonyl oxime phosphine oxide **11a** to azirine **13** (R = Ph, R^1 = H, R_F = CF_3). This 2*H*-azirine **13** is probably unstable owing to the effect of the high electron withdrawing trifluoromethyl group. Then, azirine **13** readily undergoes addition of methoxide to the C=N bond from the least hindered face (see Figure 1) to give *trans*-aziridine **14a**, in a similar way to that observed in the case of other nucleophiles such as hydride.[11b]

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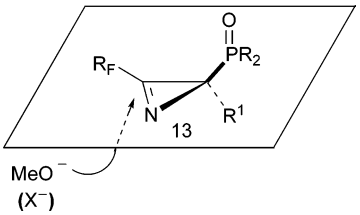


FIGURE 1. Nucleophilic attack of MeO^- (X^-) to azirine **13**.

The use of NEt_3 as base in MeOH as a solvent, gave the same adduct **14a** (R = Ph, R^1 = H, R_F = CF_3) (Scheme 3, Table 3, entry 1) and supported the proposed reaction mechanism. Likewise, fluoroalkyl *trans*-aziridine phosphine oxide **14b** (R = Ph, R^1 = H, R_F = CHF_2) and **14c** (R = Ph, R^1 = H, R_F = C_7F_{15}) (Scheme 3, Table 3, entries 2 and 3) were prepared. Aziridines **14** can also be obtained in a "one pot" reaction from ketoximes. Thus, when oxime **9d** was treated with 2 equiv of base (NaH), followed by addition of *p*-toluenesulfonyl chloride (1 equiv) and subsequent addition of MeOH, *trans*-aziridine phosphine oxide **14d** (R = Ph, R^1 = CH_3, R_F = CF_3, Scheme 3, Table 3, entry 4) was obtained in a stereoselective fashion. This process could also be extended to *p*-toluenesulfonyl oxime phosphonate **12a** (R = OEt, R^1 = H, R_F = CF_3). In this case, formation of aziridine phosphonate **15a** (R = OEt, R^1 = H, R_F = CF_3) was achieved employing NaOMe/MeOH as base (Scheme 3, Table 3, entry 5).

Subsequently, the use of some nitrogen and sulfur nucleophiles to trap generated trifluoroalkyl substituted 2***H***-azirine **13** and thus to prepare new functionalized aziridines was studied. Reaction of *p*-toluenesulfonyl oxime phosphine oxide **11a** (R^1 = H, R_F = CF_3) with imidazole (XH = imidazole, Scheme 3) led exclusively to the formation of *trans*-3-imidazolyl-3-trifluoromethylaziridin-2-yl diphenylphosphine oxide **16** (Scheme 3, Table 3, entry 6). No trace of the *cis*-aziridine was observed by ^{31}P NMR. In this case imidazole acts not only as a nucleophile reagents but also as base. The exclusive formation of *trans*-aziridine phosphine oxide **16** could be explained by the base-mediated (imidazole) ring-closure of *p*-toluenesulfonyl oxime phosphine oxide **11a**, and the subsequent addition of the second molecule of imidazole from the least hindered face of the reactive trifluoromethyl substituted 2*H*-azirine intermediate **13a** (R = Ph, R^1 = H, R_F = CF_3, Figure 1). A similar behavior was observed when benzenethiol (X= SPh, Scheme 3) reacted with *p*-toluenesulfonyl oxime phosphine oxide **11a** in the presence of triethylamine as base to give exclusively *trans*-3-benzothio-3-trifluoromethylaziridin-2-yl diphenylphosphine oxide **17** (Scheme 3, Table 3, entry 7).

These results prompted us to explore whether Grignard reagents could produce a similar effect to that observed in the case of imidazole. If so, the reaction of Grignard reagents with fluoroalkyl substituted ketoximes **11** and **12** could afford functionalized aziridines containing phosphorus and fluorine substituents. Treatment of *p*-toluenesulfonyl oxime phosphine oxide **11a** (R = Ph, R^1 = H, R_F = CF_3) with methylmagnesium bromide **18a** (R^2 = CH_3) in THF at −78 °C led to the formation of a mixture of *cis*-3-methyl-3-trifluoromethylaziridin-2-yl diphenyl phosphine oxide **19a** (R = Ph, R^1 = H, R_F = CF_3, R^2 = CH_3) as the major component along with the corresponding *trans*-isomer **20a** (R = Ph, R^1 = H, R_F = CF_3, R^2 = CH_3) in a 75:25 ratio of both isomers (Scheme 4, Table 4, entry 1). Spectroscopic data were in agreement with the assigned structure of compounds **19/20a**. In the ^{31}P NMR spectrum the phosphine oxide group of these aziridines **19** and **20a** resonated at δ_P = 24.2 and 23.2 ppm, while ^{19}F NMR spectrum showed singlets for trifluoromethyl group at δ_F = −68.8 and −70.6 ppm. The stereochemical assignment was based on HOESY ($^{19}F-^1H$) 2D experiments, which showed for compound **19a** (cis configuration) a correlation between the signal of the trifluoromethyl group (δ_F = −70.6 ppm) with the aromatic protons (^1H) of the diphenylphosphine oxide group.

SCHEME 4. Preparation of Aziridines 19−22

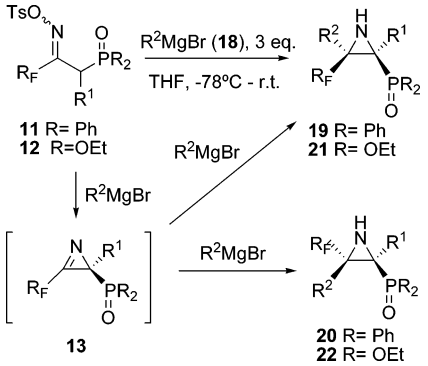


TABLE 4. Aziridines 19−22 Obtained

entry	compd	R	R^1	R_F	R^2	cis/trans[a]	yield (%)[b]
1	**19/20a**	Ph	H	CF_3	CH_3	75/25	58
2	**19/20b**	Ph	H	CF_3	C_2H_5	84/16	69
3	**19/20c**	Ph	H	CF_3	$CH_2-CH=CH_2$	66/34	63 (44)[c]
4	**19/20d**	Ph	H	CF_3	C_6H_5	95/5	73
5	**19/20e**	Ph	H	CHF_2	C_6H_5	76/24	55
6	**21/22a**	OEt	H	CF_3	C_2H_5	71/29	57
7	**21/22b**	OEt	H	CF_3	$C_6H_5-CH_2$	55/45	56
8	**21/22c**	OEt	H	CF_3	C_6H_5	100/0	60
9	**21/22d**	OEt	CH_3	CF_3	$CH_2-CH=CH_2$	60/40	59

[a] The ratio of cis/trans isomers was determined by ^{31}P NMR. [b] Yield of isolated purified compounds. [c] Yield of isolated purified compounds from oxime **9a**.

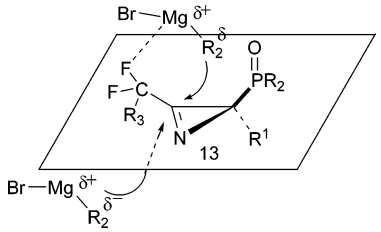


FIGURE 2. Nucleophilic attack of Grignard reagents to azirine **13**.

The formation of the major isomer *cis*-aziridine **19a** suggests that the approach of the methylmagnesium bromide **18a** to azirine **13** from the opposite position to the bulky phosphine oxide group is more favorable. However, in this case *trans*-aziridine **20a**, corresponding to the approach of the methylmagnesium bromide **18a** to the most hindered face of the azirine **13**, is also obtained as the minor isomer. Formation of this *trans*-aziridine **20a** could be explained (see Figure 2) as a consequence of prechelation of the Grignard reagent with the fluorine atoms of the fluoroalkyl substituents of azirine **13**. A prechelation of the Grignard reagent with the carboxyl ester group has been previously observed by Davis et al when azirine-carboxylates were treated with Grignard reagent.[18]

The scope of the reaction was not limited to methylmagnesium bromide **18a** (R^2 = CH_3), but ethylmagnesium bromide **18b** (R^2 = C_2H_5), allylmagnesium bromide **18c** (R^2 = CH_2-

$CH{=}CH_2$), or phenylmagnesium bromide **18d** ($R^2 = C_6H_5$) reacted with *p*-toluenesulfonyl oxime phosphine oxide **11** (R = Ph) to give mixtures of *cis*-**19** (major component) and the corresponding fluoroalkyl substituted *trans*-aziridin-2-yl diphenyl phosphine oxide **20** (minor isomer) (Scheme 4, Table 4, entries 2−5).

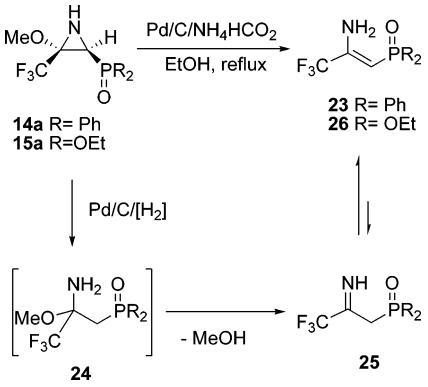
Aziridines **19/20c** can also be obtained in one pot reaction from ketoxime **9a**. When oxime **9a** was heated with 3 equiv of allylmagnesium bromide **18c** ($R^2 = CH_2{-}CH{=}CH_2$), a mixture (66/34 ratio) of *cis*-**19c** (major component) and the corresponding fluorine substituted *trans*-aziridin-2-yl diphenyl phosphine oxide **20c** (minor isomer) (Table 4, entry 3) was obtained.

This process could also be extended to *p*-toluenesulfonyl oximes derived from phosphonates **12** (R = OEt). Treatment of these ketoximes **12** (Scheme 4) with ethylmagnesium bromide **18b** ($R^2 = C_2H_5$), allylmagnesium bromide **18c** ($R^2 = CH_2{-}CH{=}CH_2$), phenylmagnesium bromide **18d** ($R^2 = C_6H_5$), and benzylmagnesium bromide **18e** ($R^2 = CH_2{-}C_6H_5$) gave mixtures of *cis*-**21** (major component) and the corresponding fluoroalkyl substituted *trans*-aziridin-2-yl diphenyl phosphine oxide **22** (minor isomer) (Scheme 4, Table 3, entries 6−9). This strategy describes the first synthesis of aziridine-phosphorus derivatives containing fluoroalkyl substituents.

Ring Opening of Aziridines. Synthesis of *β*-Aminophosphorus Derivatives. Amino phosphorus derivatives[19] in general, and *β*-amino compounds in particular,[1,20] have acquired increased interest in recent years because of their application in organic and medicinal chemistry. For this reason we tried to study if phosphorylated aziridines containing fluoroalkyl substituents could be used for the preparation of *β*-aminophosphorus derivatives. Catalytic hydrogenation of aziridines bearing phosphorus functional groups produces the corresponding amino phosphorus derivatives with highly controlled regioselectivity.[13a,21] Therefore, we explored the regioselective ring opening of phosphorylated aziridines obtained here, to obtain fluoroalkyl substituted *N*-unprotected *β*-amino phosphine oxides or -phosphonates.

However, in this case, when the reaction of 3-methoxy-3-trifluoromethyl aziridine-2-phosphine oxides **14a** with ammonium formate and palladium on carbon in refluxing ethanol was performed, primary enamine **23** (R = Ph) was obtained in 50% yield, instead of the expected *β*-amino phosphine oxides **24** (Scheme 5). The formation of this compound **23** (R = Ph) could be explained by regioselective ring opening of the N−C2 single bond of the ring followed by *β*-elimination of MeOH to form imine **25** (R = Ph) followed by tautomerization to enamine **23** (R = Ph). The presence of a methoxy group in the α-position to the amino group seems to favor the *β*-elimination of MeOH. This reduction could also be extended to the ring opening of 3-methoxy-3-trifluoromethyl aziridine-2-phosphonate **15a** with ammonium formate and palladium on carbon in refluxing ethanol to give a mixture of imine **25** (R = OEt) and tautomeric primary enamine **26** (R = OEt) with 65% yield (ratio 1:1).

SCHEME 5. Ring Opening of Aziridines 14 and 15



SCHEME 6. Synthesis of Fluorine Containing *β*-Aminophosphorus Derivatives 27 and 28

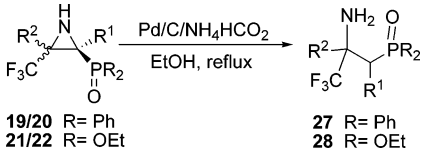


TABLE 5. *β*-Amino Phosphine Oxides 27 and 29 and *β*-Amino Phosphonates 28 and 30 Obtained

entry	compd	R	R^1	R_F	R^2	yield (%)[a]
1	**27a**	Ph	H		CH_3	73
2	**27b**	Ph	H		C_2H_5	59
3	**27c**	Ph	H		*n*-C_3H_7	53
4	**27d**	Ph	H		C_6H_5	65
5	**28a**	OEt	H		C_2H_5	64
6	**28b**	OEt	CH_3		*n*-C_3H_7	57[b]
7	**29**	Ph		CF_3		74
8	**30a**	OEt		CF_3		72
9	**30b**	OEt		C_2F_5		45

[a] Yield of isolated purified compounds. [b] Obtained as a mixture of two diastereoisomers (50:50) and determined by ^{31}P NMR.

Afterward, we explored the regioselective ring opening of 3-alkyl or 3-aryl substituted phosphorylated aziridines **19**−**22**, because the absence of a methoxy group could avoid the *β*-elimination and therefore *N*-unprotected *β*-amino phosphine oxides or -phosphonates could be obtained. Ring opening of the mixture of both isomers *cis*- and *trans*-aziridine-2-phosphine oxides **19**/**20** (R = Ph) was accomplished by catalytic transfer hydrogenation with palladium. Reduction of 3-alkyl- and 3-aryl-aziridine-2-phosphine oxides **19/20** with ammonium formate and palladium on carbon in refluxing ethanol gave *β*-amino phosphine oxides **27** (Scheme 6, Table 5, entries 1−4). The formation of these compounds **27** (R = Ph) could be explained by regioselective ring opening of the N−C2 single bond of the ring. Reaction conditions are strong enough to achieve also the hydrogenation of the allyl group ($R^2 = CH_2{-}CH{=}CH_2$) to *n*-propyl substituent ($R^2 = n\text{-}C_3H_7$) (Scheme 6, Table 4, entry 3).

This process could be extended to aziridines derived from phosphonates **21**/**22**. Catalytic transfer hydrogenation in the presence of Pd(0)/C and ammonium formate of diethyl *cis*- and *trans*-3-ethyl-3-trifluoromethylaziridin-2-ylphosphonate **21/22a** (R = OEt, R^1 = H, $R^2 = C_2H_5$) gave *β*-amino phosphonate **28a** (R = OEt, $R^2 = C_2H_5$) (Scheme 6, Table 5, entry 5) by regioselective ring opening of the N−C2 single bond of the

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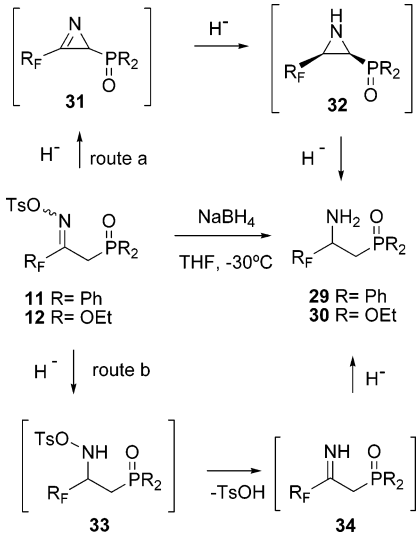
SCHEME 7. Preparation of β-Aminophosphorus Derivatives 29 and 30 from Oximes 11 and 12



ring. Likewise, ring opening of 2-methyl substituted diethyl *cis*- and *trans*-3-ethyl-3-trifluoromethylaziridin-2-ylphosphonate **21**/**22d** (R = OEt, $R^1 = CH_3$, $R^2 = CH_2{-}CH{=}CH_2$), by hydrogenolysis with ammonium formate and palladium on carbon, gave β-amino phosphonate **28b** (R = OEt, $R^1 = CH_3$, $R^2 = n\text{-}C_3H_7$) as a mixture of syn/anti isomers in 50:50 proportion (Scheme 6, Table 5, entry 6). The formation of these compounds could be explained, as before, by regioselective ring opening of the N−C2 single bond of the ring.[13,21b] As far as we know, this strategy reports the first synthesis of fluorine containing β-disubstituted β-aminophosphorus derivatives, and allowed us to prepare β-fluoroalkyl β-amino phosphine oxides **27**, and β-fluoroalkyl β-amino phosphonates **28** from readily available aziridine-phosphine oxides and -phosphonates.

Finally, we explored the preparation of fluorine containing β-amino phosphine oxides or -phosphonates with only a substituent in position β directly from phosphorylated ketoximes. For this objective, we thought that the use of hydrides could be appropriate, because hydrides could act as base and nucleophilic reagents in a similar behavior to that observed in organometallic reagents (vide supra). Oximes[22a,b] and *p*-toluenesulfonyl oximes[22c] have been reduced by lithium aluminum hydride, and the reduction of oximes with sodium borohydride in the presence of transition metal compounds has been reported.[22d] Treatment of fluorine containing *p*-toluenesulfonyl oxime phosphine oxide **11a** (R = Ph, $R_F = CF_3$) and *p*-toluenesulfonyl oxime phosphonates **12a** (R = OEt, $R_F = CF_3$) or **12b** (R = OEt, $R_F = C_2F_5$) with $NaBH_4$ at low temperature (−30 °C) gave fluorine containing β-amino phosphine oxide **29** (R = Ph, $R_F = CF_3$) and β-amino phosphonates **30a** (R = OEt, $R_F = CF_3$) and **30b** (R = OEt, $R_F = C_2F_5$) (Scheme 7, Table 5, entries 7−9) in a regioselective fashion.

Formation of these β-amino phosphorus derivatives **29** and **30** could be explained (route a, Scheme 7) by the initial formation of azirine **31** followed by nucleophilic addition of hydride and subsequent regioselective ring opening of the aziridine **32**. However, a direct reduction of the oxime group (route b, Scheme 7) with formation of *p*-toluelesulfonyl amino derivative **33** followed by β-elimination of *p*-toluelesulfonic acid and subsequent reduction of imine **34** cannot be discounted.

Conclusion

In conclusion, this account describes a simple, mild and convenient strategy for the stereoselective addition of nucleophile reagents such as alkoxides, imidazole, benzenethiol, Grignard reagents, and hydrides to fluoroalkyl substituted ketoxime phosphine oxides and phosphonates to give functionalized aziridine phosphine oxides and phosphonates containing fluorine**.** Fluoroalkyl substituted β-amino phosphine oxides and β-amino phosphonates were obtained by catalytic hydrogenation of aziridines, while the reaction of ketoximes derived from phosphine oxides and phosphonates with sodium borohydride gives directly fluoroalkyl substituted β-amino phosphine oxides and β-amino phosphonates. Substituted azirines[12] and aziridines,[23] as well as β-amino phosphorus derivatives,[1,20] are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest in medicinal chemistry.

Experimental Section

General Procedure for the Preparation of β-Phosphorylated Ketones 3/7, *gem*-Diols 5/8, and Enols 4. To a solution of LDA (6 mmol) in THF (25 mL) was added a solution of alkylphosphine oxide **1** or alkylphosphonate **6** (5 mmol) in THF (15 mL) cooled at −78 °C under nitrogen atmosphere. The mixture was stirred for 1 h at −78 °C. Next a solution of the corresponding ester was added (6 mmol) in THF (12 mL) at the same temperature, and then the mixture was allowed to warm at room temperature (15 h). After the reaction was complete, the solvent was evaporated under vacuum. The crude residue was treated with HCl to 10% (5 mL) during 30 min. The crude reaction was extracted three times with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by vacuum distillation or by chromatography using silica gel eluting with 2:1 hexane/ethyl acetate to afford, according to the cases, β-phosphorylated ketones **3**/**7**, *gem*-diols **5**/**8**, or enols **4**.

3,3,3-Trifluoro-2-hydroxypropenyldiphenylphosphine Oxide 4a. The general procedure was followed using diphenylmethylphosphine oxide **1a** (1.01 g, 5 mmol) and ethyl trifluoromethyl acetate **2a** (0.86 g, 6 mmol). Chromatographic purification eluting with 2:1 hexane/ethyl acetate afforded 1.15 g (74%) of compound **4a** as a yellow solid: mp 114−115 °C. ^{1}H NMR ($CDCl_3$): δ 7.79−7.42 (m, 12H) ppm. ^{13}C NMR ($CDCl_3$): δ 134.8−129.3 (m), 125.9 (dq, $^1J_{FC}$ = 289.6 Hz, $^3J_{PC}$ = 11.6 Hz), 210.0 ppm. ^{31}P NMR ($CDCl_3$): δ 36.5 ppm.^{19}F NMR ($CDCl_3$): δ −83.4 ppm. IR (KBr): 3201, 3060, 1568, 1239, 1162, 759 cm^{-1}. MS (EI): *m*/*z* 312 (M^+, 20). Anal. Calcd for $C_{15}H_{12}F_3O_2P$: C, 57.70; H, 3.87. Found: C, 57.90; H, 3.90.

General Procedure for the Preparation of (*Z*) and (*E*)-β-Phosphorylated Ketoximes 9 and 10. To a solution of the β-ketophosphine oxides **3** or -phosphonate **7** (5 mmol) and hydroxylamine hydrochloride (0. 42 g, 6 mmol) in ethanol (15 mL) was added pyridine (0. 75 mL, 9. 3 mmol) at 0 °C. The reaction mixture was kept at reflux for 6 h until the disappearance of the starting material. Solvent was removed under reduced pressure, and the residue was

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diluted in CH_2Cl_2 and washed twice with HCl 2 N (2 × 10 mL) and then with water (10 mL). The organic layer was dried with $MgSO_4$ anhydrous and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography using silica gel eluting with 1:1 hexane/ethyl acetate to afford β-ketoximes **9** or **10** as a variable mixture of *E* and *Z* isomers.

(*Z*)-3,3,3-Trifluoro-2-*N*-hydroxyiminopropyldiphenylphosphine Oxide 9a. The general procedure was followed using the enol **4a** (1.56 g, 5 mmol). Chromatographic purification eluting with 1:1 hexane/ethyl acetate afforded 1.12 g (73%) of compound **9a** as a yellow solid: mp 156−157 °C. ^{1}H NMR ($CDCl_3$): δ 12.9 (s,1H), 7.81−7.40 (m, 10H), 3.63 (d, $^2J_{PH}$ = 13.6 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 140.2 (dq, $^1J_{FC}$ = 33.7 Hz, $^2J_{PC}$ = 9.6 Hz), 132.6−128.6 (m), 119.6 (q, $^1J_{FC}$ = 273.5 Hz, $^3J_{PC}$ = 2.0 Hz), 27.9 (d, $^1J_{PC}$ = 64.5 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ 28.0 ppm. ^{19}F NMR ($CDCl_3$): δ −68.7 ppm. IR (KBr): 3151, 3059, 1590, 1122 cm^{-1}. MS (EI): *m*/*z* 328 (M^+ + 1, 55). Anal. Calcd for $C_{15}H_{13}F_3NO_2P$: C, 55.05; H, 4.00; N: 4.28. Found: C, 54.90; H, 3.90; N: 4.25.

General Procedure for the Preparation of Phosphorylated β-*p*-Toluenesulfonyloximes 11 and 12. To a solution of NaH (5.5 mmol) in THF (15 mL) was added, at 0 °C under nitrogen atmosphere, the oxime **9** or **10**, and the mixture was allowed to react at room temperature during 30 min. Then, to the mixture was added, in portions at 0 °C, tosyl chloride (1. 05 g, 5. 5 mmol) freshly recrystallized from hexane. The mixture was allowed to warm at room temperature, and the reaction mixture was stirred for 2 h. The NaH remainder was neutralized with methanol, and the solvent was evaporated under vacuum. The crude reaction was extracted with CH_2Cl_2 (15 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel eluting with 2:1 hexane/ethyl acetate to yield the compounds **11** as a white solid and **12** as a pale yellow oil.

(*Z*)-3,3,3-Trifluoro-2-(*N*-*p*-toluenesulfonyloxyimino)propyldiphenylphosphine Oxide 11a. The general procedure was followed using the β-ketoxime-phosphine oxide **9a** (1.63 g, 5 mmol). Chromatographic purification eluting with 2:1 hexane/ethyl acetate afforded 2.02 g (84%) of compound **11a** as a white solid: mp 109−110 °C. ^{1}H NMR ($CDCl_3$): δ 7.81−7.20 (m, 14H), 3.64 (d, $^2J_{PH}$ = 14.5 Hz, 2H), 2.38 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ 150.2 (dq, $^2J_{FC}$ = 35.2 Hz, $^2J_{PC}$ = 9.0 Hz), 146.1, 132.7−126.5 (m), 119.0 (q, $^1J_{FC}$ = 277.0 Hz, ^3J_P), 30.5 (d, $^1J_{PC}$ = 57.9 Hz), 21.7 ppm. ^{31}P NMR ($CDCl_3$): δ 24.8 ppm. ^{19}F NMR ($CDCl_3$): δ −68.2 ppm. IR (KBr): 3070, 1590, 1122 cm^{-1}. MS (EI): *m*/*z* 482 (M^+ + 1, 53). Anal. Calcd for $C_{22}H_{19}F_3NO_4PS$: C, 54.89; H, 3.98; N: 2.91; S: 6.66. Found: C, 54.80; H, 3.94; N: 2.93; S: 6.64.

General Procedure for the Preparation of Aziridines 14−17. To a solution of fluorinated *p*-toluenesulfonyl oximes **11** or **12** (5 mmol) in MeOH (15 mL) was added slowly at 0 °C, under nitrogen atmosphere, the corresponding base (5.5 mmol). Then, the mixture was allowed to warm at room temperature until TLC indicated the disappearance of oxime. The solvent was evaporated under reduced pressure, and the mixture was diluted in CH_2Cl_2 (15 mL) and washed with water. The organic phase was dried with anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/AcOEt 1/1) to yield the aziridines **14** or **15**.

***trans*-3-Methoxy-3-trifluoromethylaziridin-2-yldiphenylphosphine Oxide 14a.** The general procedure was followed using (*Z*)-3,3,3-trifluoro-2-(*N*-*p*-toluenesulfonyloxyimino) propyldiphenylphosphine oxide **11a** (2.40 g, 5 mmol) and triethylamine (0.76 mL, 5.5 mmol) or NaOMe (0.28 g, 5.5 mmol). Chromatographic purification eluting with 1:1 hexane/ethyl acetate afforded 1.45 g (85%) (using triethylamine) or 0.88 g (52%) (using NaOMe) of compound **11a** as a white solid: mp 110−111 °C. ^{1}H NMR ($CDCl_3$): δ 7.78−7.30 (m, 10H), 3.37 (s, 3H), 2.62 (d, $^2J_{PH}$= 17.4 Hz, 1H), 2.41 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 132.6−128.6, 122.7 (q, $^1J_{FC}$ = 281.0 Hz), 72.4 (q, $^2J_{FC}$ = 42.3 Hz), 55.2, 40.5 (d, $^1J_{PC}$ = 84.1 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ 22.1 ppm. ^{19}F NMR ($CDCl_3$): δ −70.6 ppm. IR (KBr): 3111, 1434, 1189 cm^{-1}. MS (EI): *m*/*z* 341 (M^+, 10). Anal. Calcd for $C_{16}H_{15}F_3NO_2P$: C, 56.31; H, 4.43; N: 4.10. Found: C, 56.40; H, 4.45; N: 4.07.

Procedure for the Preparation of *trans*-3-Imidazolyl-3-trifluoromethylaziridin-2-yldiphenylphosphine Oxide 16. To a solution of fluorinated *p*-toluenesulfonyl oximes **11a** (2.40 g, 5 mmol) in THF (15 mL) was added slowly at 0 °C, under nitrogen atmosphere, imidazole (0.76 g, 11 mmol). Then, the mixture was allowed to warm at room temperature until TLC indicated the disappearance of oxime. The solvent was evaporated under reduced pressure, and the mixture was diluted in CH_2Cl_2 (15 mL) and washed with water. The organic phase was dried with anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/AcOEt 1/1) to afford 0.85 g (45%) of compound **16** as a white solid: mp 150−151 °C. ^{1}H NMR ($CDCl_3$): δ 7.79−7.20 (m, 11H), 6.77 (d, $^3J_{HH}$ = 7.0 Hz, 2H), 3.29 (s, 1H), 2.88 (t, $^3J_{HH}$ = 12.7 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 137.5, 132.9−128.2 (m), 126.0, 121.7 (q, $^1J_{FC}$ = 279.3 Hz), 119.4, 54.2 (q, $^2J_{FC}$ = 39.3 Hz), 37.2 (d, $^1J_{FC}$ = 98.7 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ 21.8 ppm. ^{19}F NMR ($CDCl_3$): δ −77.1 ppm. IR (KBr): 3116, 3003, 1620, 1491, 1189 cm^{-1}. MS (EI): *m*/*z* 378 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{15}N_3F_3OP$: C, 57.30; H, 4.01; N: 11.14. Found: C, 57.30; H, 4.01; N: 11.14.

General Procedure for the Preparation of Aziridines 19−22. To a solution of fluorinated *p*-toluenesulfonyl oximes **11** or **12** (5 mmol) in THF (15 mL) cooled at −78 °C, was added a solution of Grignard reagent **18** (15 mmol) in diethyl ether under nitrogen atmosphere. The mixture was stirred for 1 h at −78 °C and then was allowed to warm at room temperature (15 h). After the reaction was complete, the mixture was quenched with a saturated NH_4Cl solution (15 mL). The crude reaction was extracted three times with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude residue was then purified by flash chromatography on silica gel (hexane/AcOEt 2/1) affording mixtures of cis and trans isomers: derivatives **19**/**20** as white solids and derivatives **21**/**22** as pale yellow oils.

3-Methyl-3-trifluoromethylaziridin-2-yldiphenylphosphine Oxide 19/20a. The general procedure was followed using (*Z*)-3,3,3-trifluoro-2-(*N*-*p*-toluenesulfonyloxyimino) propyldiphenylphosphine oxide **11a** (2.40 g, 5 mmol) and methylmagnesium bromide **18a** 3 M (5 mL, 15 mmol). Chromatographic purification eluting with 2:1 hexane/ethyl acetate afforded 0.94 g (58%) of a mixture (75/25) of *cis*-**19a** (major component) and *trans*-**20a** (minor component) as a white solid: mp 177−179 °C.

***cis*-19a.** ^{1}H NMR ($CDCl_3$): δ 7.77−7.40 (m, 10H), 2.30 (dd, $^2J_{PH}$ = 17.9 Hz, $^3J_{HH}$ = 8.7 Hz 1H), 2.07 (dd, $^2J_{PH}$ = 17.1 Hz, $^3J_{HH}$ = 9.6 Hz 1H), 1.44 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ 134.4−129.6, 124.9 (q, $^1J_{FC}$ = 277.0 Hz), 43.2 (q, $^2J_{FC}$ = 37.8 Hz), 41.3 (d, $^1J_{PC}$ = 84.6 Hz), 19.5 ppm. ^{31}P NMR ($CDCl_3$): δ 24.2 ppm. ^{19}F NMR ($CDCl_3$): δ −68.8 ppm.

***trans*-20a.** ^{1}H NMR ($CDCl_3$): δ 7.77−7.40 (m, 10H), 2.61 (dd, $^2J_{PH}$ = 15.6 Hz, $^3J_{HH}$ = 8.7 Hz 1H), 2.07 (dd, $^2J_{PH}$ = 17.1 Hz, $^3J_{HH}$ = 9.6 Hz 1H), 1.59 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ 133.1−128.8, 124.4 (q, $^1J_{FC}$ = 277.0 Hz), 40.8 (q, $^2J_{FC}$ = 35.3 Hz), 34.0 (d, $^1J_{PC}$ = 91.6 Hz), 11.9 ppm. ^{31}P NMR ($CDCl_3$): δ 23.2 ppm. ^{19}F NMR ($CDCl_3$): δ −70.7 ppm. IR (KBr): 3184, 3078, 1434, 1387, 1175 cm^{-1}. MS (EI): *m*/*z* 326 (M^+ + 1, 100). Anal. Calcd for $C_{16}H_{15}F_3NOP$: C, 59.08; H, 4.65; N: 4.31. Found: C, 59.17; H, 4.66; N: 4.30.

General Procedure for Ring Opening of Aziridines. To a solution of aziridine-2-phosphine oxides **14** or **19**/**20** or aziridine-2-phosphonate **15** or **21**/**22** (5 mmol) in EtOH (15 mL) was added, under nitrogen atmosphere, Pd/C (20%) and then ammonium formate (4.74 g, 75 mmol). The mixture was kept at reflux for 18

h, until TLC indicated the disappearance of azirine. The solvent was evaporated under reduced pressure, and the mixture was diluted in water. Then, NH_4OH solution (25%) was added until pH 8, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated. The crude mixture was purified by flash column chromathography on silica gel (hexane/AcOEt 1/1) to afford amino phosphorus derivatives **23** or **25**−**30** as white solids or colorless oils.

2-Amino-3,3,3-trifluoropropen-1-yldiphenylphosphine Oxide 23. The general procedure was followed using *trans*-3-methoxy-3-trifluoromethylaziridin-2-yldiphenylphosphine oxide **14a** (1.71 g, 5 mmol). Chromatographic purification eluting with 1:1 hexane/ethyl acetate afforded 0.78 g (50%) of compound **23** as a white solid: mp 162−163 °C. ^{1}H NMR ($CDCl_3$): δ 7.70−7.23 (m, 10H), 5.82 (s, 2H), 4.86 (d, $^2J_{PH}$ = 17.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 148.8 (q, $^2J_{FC}$ = 33.2 Hz), 134.6−128.5, 120.4 (dq, $^1J_{FC}$ = 276.5 Hz, $^3J_{PC}$ = 27.7 Hz), 86.2 (dd, $^1J_{PC}$ = 108.8 Hz, $^3J_{FC}$ = 2.5 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ 29.3 ppm. ^{19}F NMR ($CDCl_3$): δ −72.4 ppm. IR (KBr): 3370, 3298, 3056, 1648, 1434, 1259, 1174 cm^{-1}. MS (EI): *m*/*z* 311 (M^+, 10), 310 ($M^+ - 1$, 100). Anal. Calcd for $C_{15}H_{13}F_3NOP$: C, 57.88; H, 4.21; N: 4.50. Found: C, 58.00; H, 4.22; N: 4.48.

2-Amino-2-trifluoromethylpropyldiphenylphosphine Oxide 27a. The general procedure was followed using 3-methyl-3-trifluoromethylaziridin-2-yldiphenylphosphine oxide **19**/**20a** (1.63 g, 5 mmol). Chromatographic purification eluting with 1:1 hexane/ethyl acetate afforded 1.19 g (73%) of compound **27a** as a white solid: mp 65−66 °C. ^{1}H NMR ($CDCl_3$): δ 7.82−7.45 (m, 10H), 2.73 (dd, $^2J_{PH}$ = 11.9 Hz, $^2J_{HHgem}$ = 15.4 Hz, 1H), 2.59 (dd, $^2J_{PH}$ = 11.2 Hz, $^2J_{HHgem}$ = 15.4 Hz, 1H), 1.89 (s, 2H), 1.40 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ 134.7−128.7 (m), 126.9 (dq, $^1J_{FC}$ = 281.7 Hz, $^3J_{PC}$ = 14.2 Hz), 56.8 (dq, $^2J_{FC}$ = 27.7 Hz, $^2J_{PC}$ = 4.0 Hz), 34.5 (d, $^1J_{PC}$ = 73.0 Hz), 23.0 ppm. ^{31}P NMR ($CDCl_3$): δ 28.4 ppm. ^{19}F NMR ($CDCl_3$): δ −84.4 ppm. IR (KBr): 3396, 3371, 3224, 1626, 1434, 1176, 1122 cm^{-1}. MS (EI): *m*/*z* 327 (M^+, 7), 215 ($CH_2P(O)Ph_2^+$, 100). Anal. Calcd for $C_{16}H_{17}F_3NOP$: C, 58.72; H, 5.24; N: 4.28. Found: C, 58.78; H, 5.25; N: 4.29.

Procedure for the Preparation of Fluorine Containing *β*-Aminophosphine Oxide 29 or *β*-Aminophosphonate 30 from *p*-Toluenesulfonyloxime 11 or 12. To a solution of fluorinated *p*-toluenesulfonyloxime phosphine oxide **11** (5 mmol) or *p*-toluenesulfonyloxime phosphate **12** (5 mmol) in THF (15 mL) was added $NaBH_4$ (15 mmol) at −30 °C under nitrogen atmosphere. The mixture was stirred at −30 °C until TLC indicated the disappearance of *p*-toluenesulfonyloxime. After the reaction was complete, the mixture was quenched with a saturated NH_4Cl solution (15 mL). The crude reaction was extracted three times with CH_2Cl_2 (3 × 15 mL). Organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude residue was then purified by flash chromatography on silica gel (hexane/AcOEt 2/1) to yield the compounds **29** and **30** as a pale yellow oil.

2-Amino-3,3,3-trifluoropropyldiphenylphosphine Oxide 29. The general procedure was followed using (*Z*)-3,3,3-trifluoro-2-(*N*-*p*-toluenesulfonyloxyimino) propyldiphenylphosphine oxide **11a** (2.40 g, 5 mmol). Chromatographic purification eluting with 2:1 hexane/ethyl acetate afforded 1.15 g (74%) of compound **29** as a pale yellow oil: R_f = 0.41 (ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.82−7.45 (m, 10H), 3.71 (m, 1H), 2.62 (ddd, $^2J_{PH}$ = 10.4 Hz, $^2J_{HHgem}$ = 15.1 Hz, $^2J_{HH}$ = 2.0 Hz 1H), 2.46 (ddd, $^2J_{PH}$ = 11.4 Hz, $^2J_{HHgem}$ = 15.1 Hz, $^2J_{HH}$ = 12.1 Hz 1H), 1.94 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 134.7−128.7 (m), 127.1 (dq, $^1J_{FC}$ = 280.5 Hz, $^3J_{PC}$ = 17.6 Hz), 49.8 (dq, $^2J_{FC}$ = 30.7 Hz, $^2J_{PC}$ = 3.5 Hz), 30.3 (d, $^1J_{PC}$ = 72.5 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ 30.6 ppm. ^{19}F NMR ($CDCl_3$): δ −80.0 ppm. IR (KBr): 3396, 3306, 3058, 1160, 1122 cm^{-1}. MS (EI): *m*/*z* 313 (M^+, 7), 215 ($CH_2P(O)Ph_2^+$, 100). Anal. Calcd for $C_{15}H_{15}F_3NOP$: C, 57.51; H, 4.83; N: 4.47. Found: C, 57.45; H, 4.82; N: 4.48.

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Supporting Information Available: Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, and elemental analysis) for compounds **4b**, **3c**/**4c**, **3d**/**5d**, **7a**/**8a**, **7b**/**8b**, **7c**/**8c**, **9b**−**d**, **10a**−**c**, **11b**,**c**, **12a**−**c**, **14b**−**d**, **15a**, **17**, **19/20b**, **19/20c**, **19/20d**, **19/20e**, **21/22a**, **21/22c**, **21/22b**, **21/22d**, **25/26**, **27b**−**d**, **28a**,**b**, **30a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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