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Synthesis of Fluorinated β-Aminophosphonates and γ-Lactams

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Supporting Information

ABSTRACT: The functionalized polyfluorophosphorylated 1-azadienes **I** have been prepared by a Wittig reaction of ethyl glyoxalate and perfluorophosphorylated conjugated phosphoranes, obtained by reaction of phosphazenes and fluorinated acetylenic phosphonates. Subsequent reduction of both carbon−carbon and carbon−nitrogen double bonds of these 1-azadienes **I** affords the fluorine-containing β-aminophosphonates **II**, with the *syn* β-aminophosphonate being obtained as the major diastereoisomer. Base-mediated cyclocondensation of a diastereomeric mixture of aminophosphonates **II** leads exclusively to a new type of functionalized *trans*-γ-lactams **III** in a diastereoselective way. A computational study has also been used to explain the observed diastereoselectivity of these reactions.

INTRODUCTION

Organophosphorus compounds are important substrates in the study of biochemical processes,[1] and β-aminophosphonates, as they are isosteres of β-amino acids, play an important role as enzyme inhibitors, agrochemicals, and pharmaceuticals[2] as well as reveal diverse and interesting biological and biochemical properties. Some β-aminophosphonic acids and their derivatives have been identified as natural products.[3a,b] The parent acid was first isolated from *Celiata* protozoa,[3c] and subsequently the compound along with its different derivatives was obtained from microorganisms.[3d,e] Other important uses of these compounds are as pesticides[3f] and in the preparation of valuable metal complexes.[3g,h]

Furthermore, the introduction of a fluorine atom or a fluorinated moiety can modulate the properties of a bioactive molecule, since this may lead to changes in solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, or chemical reactivity.[4] Due to the unique properties of the fluorine atom, fluorinated molecules occupy a significant place[5] in pharmaceutical/medicinal,[6] agrochemical,[7] and materials sciences.[8] Fluorine incorporation into a chemical structure has been used in pharmaceutical development and drug design to prevent molecules from being metabolized too quickly, thereby allowing a drug to act before it is cleared from the body.[9] In this respect, particular interest has focused on developing synthetic methods for the preparation of fluorinated building blocks,[6,10] among them fluorinated aminophosphonates.[11] Efficient examples of aminophosphonates containing fluoroalkyl groups as ligands for phosphoglycerate kinase[12a] or antibacterials,[12b] inhibitors of serine esterases, alanine racemase, and pyrimidine phosphorylases,[12c] and also the preparation of fluorinated peptidomimetics[13] have been demonstrated. However, the literature contains very few preparative methods for the preparation of fluorinated β-aminophosphonates, such as by the addition of amines to unsaturated phosphonates,[12b,14] by the addition of fluorinated phosphonate carbanions to N-protected haloamines[12a] or imines,[15] or by ring opening of fluoroalkyl aziridine-2-phosphonates.[16]

On the other hand, γ-lactams have important applications in the drug-discovery process, as key intermediates in the preparation of biologically and pharmaceutically relevant molecules in the treatment of cancer,[17a] fungal infections,[17b] epilepsy,[17c,d] HIV,[17e,f] neurodegenerative diseases,[17g] and depression.[17h] The γ-lactam core showed a better fit than the larger δ-lactam core into the narrow hydrophobic pocket of histone deacetylase (HDAC) active site and showed better inhibition profiles of HDACs and cancer cell growth inhibitory activities.[18a] γ-Lactams are also viable glycinamide replacements within a series of cyclohexane-based CCR2 antagonists which could find additional use in the design and development of future antagonists.[18b]

Continuing with our interest in the chemistry of fluorinated aminophosphorus derivatives as well as of electron-rich,[19] fluorinated,[20] and functionalized 1-azadienes,[21] here we report the diastereolective preparation of novel fluoroalkyl- and phosphorus-substituted γ-lactams **I** and fluorine-containing β-aminophosphonates **II** from functionalized 1-azadienes **III**, easily prepared from phosphazenes **IV**, polyfluoroacetylenephosphonates **V**, and ethyl glyoxalate **VI** (Scheme 1).

RESULTS AND DISCUSSION

The formation of conjugated phosphoranes by the reaction of phosphazenes and acetylenic esters has been reported.[22] Therefore, a convenient method for the synthesis of some diethoxyphosphinyl perfluoroalkylidene phosphoranes based on a [2 + 2] cycloaddition reaction between phosphazenes **1** and polyfluoroacetylenephosphonates **2** has been developed (Scheme 2).

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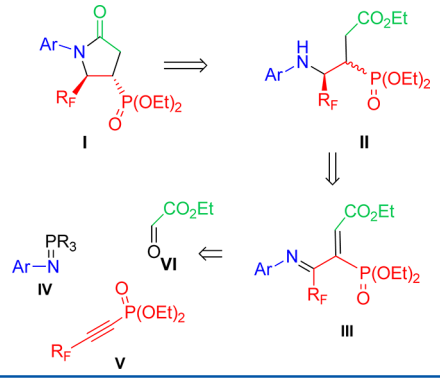
Scheme 1



Phosphazenes **1** were readily prepared by addition of the corresponding phosphines to azides through the Staudinger reaction.[23] Given the instability of *P*-alkylphosphazene species,[24] they were allowed to react in situ with polyfluoroacetylenephosphonates **2** prepared according to the established procedure.[25] Reaction progress for the formation of ylides **4** was monitored by ^{31}P NMR spectroscopy. Signals for the phosphazenes (δ 2−10 ppm) and the yne phosphonates (δ −9 to −11 ppm)[25] disappear, and resonances corresponding to polyfluorophosphorylated ylides **4** appear in the range δ 15−26 ppm. ^{19}F NMR could be applied similarly, with the loss of **2** (δ −53 to −112 ppm) and the appearance of **4** (δ −60 to −70 ppm). The results are summarized in Table 1.

The structure of isolated ylide **4g** (R = Ph) was determined by NMR spectroscopy and mass spectrometry. The ^{31}P NMR spectrum of ylide **4g** presents two doublets for phosphonate and phosphorane phosphorus atoms, observed respectively at δ 24.2 and 25.7 ppm with the coupling constant $^{2}J_{PP}$ = 51.1 Hz. The formation of phosphoranes **4** could be explained by [2 + 2] cycloaddition between phosphazenes **1** and polyfluoroacetylenephosphonates **2**, via intermediates **3** followed by ring opening, affording polyfluoroalkylated diethoxyphosphinyl phosphoranes **4** (Scheme 2) in a way similar to that reported for phosphazenes and phosphorus ylides with acetylenic esters.[22] With the exception of trifluoromethylphosphorylated ylide **4g** (R = Ph), which could be isolated and purified by recrystallization in hexane (68% yield, Table 1, entry 7), in general polyfluorophosphorylated ylides **4** were unstable and were used in situ without purification in further reactions. In fact, water-assisted hydrolysis of trifluoromethyl diethoxyphosphorylated ylide **4a** (R_F = CF_3, Ar = *p*-$MeOC_6H_4$) rapidly yielded the corresponding hydrolyzed product as a mixture of imine-enamine tautomers **5**/**5′** (Scheme 2).

Subsequently, the Wittig reaction of ylides **4** with carbonyl compounds was explored. The perfluoroalkylated conjugated

Table 1. Polyfluorophosphorylated Ylides 4 Obtained

entry	compd	PR_3	R_F	Ar	reaction conditions
1	**4a**	PMe_3	CF_3	*p*-MeO-C_6H_4	$CHCl_3$/30 min/room temp
2	**4b**	PMe_3	CF_3	*p*-Me-C_6H_4	$CHCl_3$/30 min/room temp
3	**4c**	PMe_3	CF_3	*p*-NO_2-C_6H_4	$CHCl_3$/30 min/room temp
4	**4d**	PMe_2Ph	CF_3	*p*-MeO-C_6H_4	$CHCl_3$/30 min/room temp
5	**4e**	PMe_2Ph	CF_3	*p*-Me-C_6H_4	$CHCl_3$/1 h/room temp
6	**4f**	PMe_2Ph	CF_3	*p*-NO_2-C_6H_4	$CHCl_3$/15 h/room temp
7	**4g**[a]	PPh_3	CF_3	*p*-Me-C_6H_4	$CHCl_3$/21.5 h/Δ toluene/17.5h/Δ
8	**4h**	PMe_3	C_2F_5	*p*-MeO-C_6H_4	$CHCl_3$/3 h/room temp
9	**4i**	PMe_3	C_2F_5	*p*-NO_2-C_6H_4	$CHCl_3$/30 h/Δ
10	**4j**	PMe_3	CF_2H	*p*-NO_2-C_6H_4	toluene/4 h/Δ

[a]Isolated by recrystallization (68%).

phoshorus ylides were found to react with ethyl glyoxalate. Treatment of a chloroform solution of ylide **4** with 1 equiv of ethyl glyoxalate gave corresponding 1-azadienes **6** in moderate to good yields (Scheme 2, Table 2). Formation of 1-azadienes **6**

Table 2. Polyfluorophosphorylated Derivatives 6 Obtained

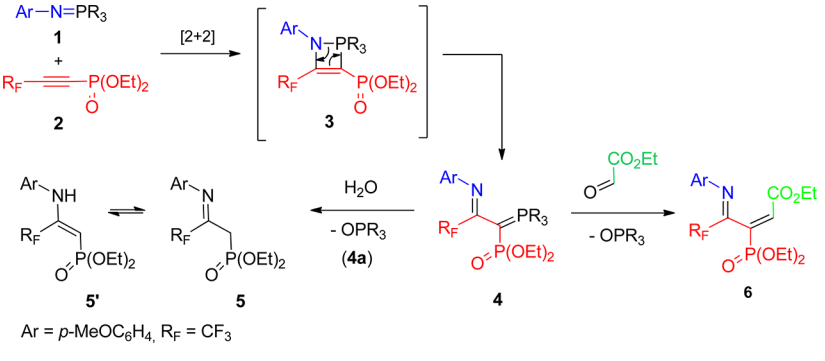
entry	compd	R_F	Ar	reaction conditions	yield, %[a]
1	**6a**	CF_3	*p*-MeO-C_6H_4	15 h/room temp	76
2	**6b**	CF_3	*p*-Me-C_6H_4	12 h/room temp	65
3	**6c**	CF_3	*p*-NO_2-C_6H_4	20 h/room temp	80
4	**6d**	C_2F_5	*p*-NO_2-C_6H_4	24 h/reflux	68
5	**6e**	CF_2H	*p*-NO_2-C_6H_4	15 h/room temp	76

[a]Isolated by flash chromatography.

could be explained by a Wittig reaction between the ylide and the carbonyl group affording stereoselectively the corresponding *E* isomer of 1-azadiene and the corresponding phosphine oxide (Scheme 2).

Polyfluorophosphorylated 1-azadienes **6** were fully characterized by 1D and 2D NMR spectroscopy and MS spectrometry. One characteristic signal for azadiene **6a** (R_F = CF_3, Ar = *p*-$MeOC_6H_4$) in the ^1H NMR spectrum is the doublet at δ 6.96 ppm, with the coupling constant $^{3}J_{HP}$ = 22.7 Hz, corresponding to the vinylic CH proton of the azadiene. The ^{13}C NMR spectrum shows a characteristic doublet signal at δ 139.7 ppm with the coupling constant $^{2}J_{CP}$ = 7.6 Hz for the vinylic CH carbon and a doublet at δ 163.1 ppm with the coupling constant $^{3}J_{CP}$ = 26.0 Hz for the carboxyl carbon. Coupling

Scheme 2. Formation of Fluorinated Phosphorus Ylides 4 and 1-Azadienes 6



Ar = *p*-$MeOC_6H_4$, R_F = CF_3

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constants in this range are consistent with an *E* configuration of the vinylic double bond.

The potential conversion of functionalized azadienes **6** to fluorinated *β*-aminophosphonates was explored. Treatment of **6** with $NaBH_4$ at 0 °C afforded *β*-aminophosphonates **7**/**7′** in good yields as *syn*/*anti* mixtures of diastereoisomers (Scheme 3, Table 3),

Scheme 3. Formation of Diastereomeric Mixture of Fluorinated *β*-Aminophosphonates by 1-Azadiene Reduction with $NaBH_4$

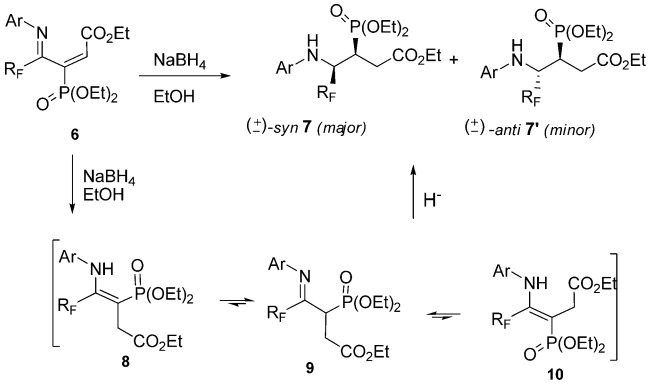


Table 3. Polyfluorophosphorylated Derivatives 7 Obtained

entry	compd	R_F	Ar	reaction conditions	yield, %[a]
1	**7a**/**7′a**	CF_3	*p*-MeO-C_6H_4	2 h/room temp	60[b]
2	**7b**/**7′b**	CF_3	*p*-Me-C_6H_4	1 h/room temp	50[b]
3	**7c**/**7′c**	CF_3	*p*-NO_2-C_6H_4	1 h/room temp	82[b]
4	**7d**/**7′d**	C_2F_5	*p*-NO_2-C_6H_4	1 h/room temp	60[c]
5	**7e**/**7′e**	CF_2H	*p*-NO_2-C_6H_4	2 h/room temp	35[c]

[a]Isolated by flash chromatography. [b]Obtained as a diastereomeric mixture 60/40. [c]Obtained as a diastereomeric mixture 95/5.

in different proportions for the *syn* and *anti* isomers, determined by NMR spectroscopy and mass spectrometry.

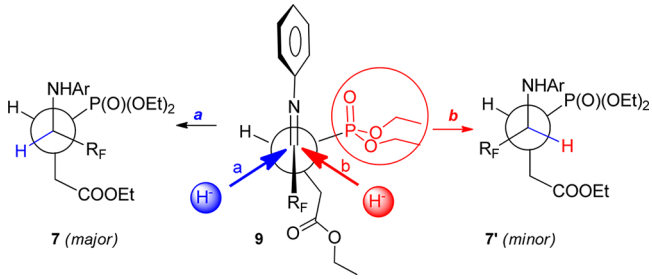
For example, the ^{31}P NMR spectrum of *β*-aminophosphonates **7b**/**7′b** (R_F = CF_3, Ar = *p*-Me-C_6H_4) shows two singlets at *δ* 27.4 and 27.0 ppm, for the major and minor diastereomers (ratio 60/40), respectively, and in the ^{19}F NMR spectrum two doublets appear at *δ* −75.6 ppm ($^3J_{FH}$ = 6.1 Hz) and at *δ* −72.4 ppm ($^3J_{FH}$ = 7.6 Hz), for the major and minor diastereomers, respectively. The ^1H NMR spectrum shows as characteristic signals two methyl singlets at *δ* 2.15 ppm (major) and *δ* 2.14 ppm (minor) and two differentiated multiplets at 4.46−4.56 ppm (major) and 4.26−4.38 ppm (minor) for the proton *α* to the CF_3 group. The ^{13}C NMR spectrum shows two characteristic double quadruplets at *δ* 55.9 ppm with the two coupling constants $^2J_{CF}$ = 29.5 Hz and $^2J_{CP}$ = 2.5 Hz for the major isomer and at *δ* 56.2 ppm with the two coupling constants $^2J_{CF}$ = 30.5 Hz and $^2J_{CP}$ = 4.3 Hz for the minor isomer, corresponding to carbons bonded to the CF_3 group. The *anti* or *syn* configuration assignment for *β*-aminophosphonates **7** and **7′** was difficult to determine by NMR spectroscopy. Small differences in chemical shift, the overlap of signals, and complex splitting patterns due to the presence of nuclei such as phosphorus and fluorine in the structure precluded measurement of accurate coupling constants for each diastereoisomer.

Fortunately, in the case of *β*-aminophosphonate **7b** (R_F = CF_3, Ar = *p*-Me-C_6H_4), the isolation of the major *syn* diastereoisomer was possible in 46% yield by recrystallization from heptane (the minor diastereoisomer has significantly higher solubility), its structure being unequivocally determined by X-ray analysis (see the Supporting Information).

Formation of *β*-aminophosphonates **7** could be explained by reduction of both the carbon−carbon and the iminic carbon−nitrogen double bonds to give both diastereoisomers of saturated *β*-aminophosphonates. The mechanism of this reaction could be explained as follows: first reduction of the carbon−carbon double bond by means of an initial attack of hydride at the most positive carbon of the heterodienic system to afford the corresponding enamine **8** (Scheme 3, vide supra), which is in tautomeric equilibrium with imine **9** and enamine **10**, and subsequent reduction of the second double bond.

The relative energies of structures **8**−**10** (when R_F = CF_3, C_2F_5, CF_2H) were calculated using Gaussian 09[26] within the density functional theory (DFT) framework[27] at the B3LYP-(PCM)/6-31G* and M06-2X(PCM)//6-31G*//B3LYP/6-31G* level using ethanol as solvent (for details see the Supporting Information). Taking into account the results obtained, imines **9** are more stable than enamines **8** or **10** in all cases (R_F = CF_3, C_2F_5, CF_2H; see the Supporting Information for details). Afterward, for the subsequent reduction of the iminic double bond of derivatives **9**, a second hydride entrance to the iminic intermediate could be possible by *a* or *b* face approach (Scheme 4), affording the *syn* (**7**)

Scheme 4. Hydride Attack onto Imine 9



or *anti* (**7′**) diastereoisomer, respectively, of the corresponding *β*-aminophosphonate.

Hydride approaches the face containing the smaller groups, affording the corresponding *syn* *β*-aminophosphonate **7** as the major diastereoisomer. Therefore, experimental and theoretical results may explain that reduction of polyfluorophosphorylated 1-azadienes **6** with $NaBH_4$ in ethanol affords the corresponding *syn* *β*-aminophosphonates **7** as major diastereoisomers. It is noteworthy that these compounds show an interesting structure from a biological point of view,[2,6] and no precedents for the synthesis of this type of polyfluoro *β*-aminophosphonates can be found in the literature.

β-Aminophosphonates **7** were efficiently converted to highly valuable *γ*-lactams[17,18] by ring closure of these acyclic compounds. Base treatment of diastereomeric mixture of fluorinated *β*-aminophosphonates **7**/**7′** with NaH in THF afforded exclusively the cyclic *trans*-*γ*-lactam **11** as a single diastereoisomer (Scheme 5, Table 4).

The exclusive formation of *trans*-*γ*-lactam diastereoisomer **11** may be explained by deprotonation of the amine group with NaH in THF and intramolecular attack of the resulting nitrogen anion on the carbonyl group followed by the loss of ethanol to afford *γ*-lactams **11**/**11′** as a mixture of *trans* and *cis* diastereoisomers. However, due to the basic reaction conditions, isomerization may occur in *γ*-lactams **11**/**11′**, and

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Scheme 5. Cyclization of Fluorinated β-Aminophosphonates 7 toward γ-Lactams

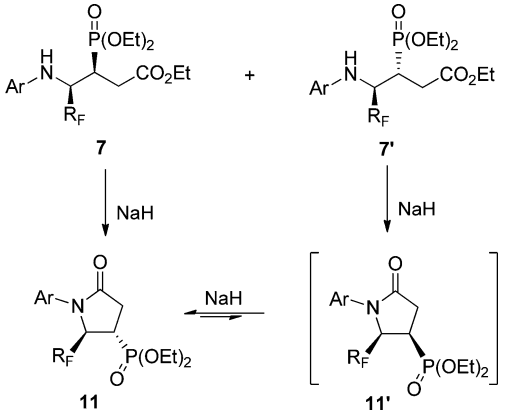


Table 4. Polyfluorophosphorylated γ-Lactams 11 Obtained

entry	compd	R_F	Ar	reaction conditions	yield, %[a]
1	**11a**	CF_3	*p*-MeO-C_6H_4	15 h/room temp	90
2	**11b**	CF_3	*p*-Me-C_6H_4	3 h/room temp	80
3	**11c**	CF_3	*p*-NO_2-C_6H_4	24 h/room temp	90
4	**11d**	C_2F_5	*p*-NO_2-C_6H_4	36 h/room temp	90
5	**11e**	CF_2H	*p*-NO_2-C_6H_4	5 h/room temp	70

[a]Isolated by flash chromatography.

only the most stable *trans* diastereomer of polyfluorophosphorylated-γ-lactam **11** (Scheme 5) is obtained. As far as we know, this strategy appears to represent the first synthesis of polyfluorophosphorylated γ-lactams.[17,18]

The structure of γ-lactams **11** was assigned on the basis of 1D and 2D NMR spectroscopy, including HMQC and HMBC experiments, and mass spectrometric data. The ^{1}H NMR spectrum of compound **11c** (R_F = CF_3, Ar = *p*-NO_2-C_6H_4) shows one double quadruplet at δ 4.90 ppm with the coupling constants $^3J_{HF}$ = 6.4 and $^3J_{HP}$ = 18.4 Hz corresponding to the proton 4-H bonded to the carbon with a CF_3 substituent (Figure 1); also the characteristic absence of carboxylic ethyl

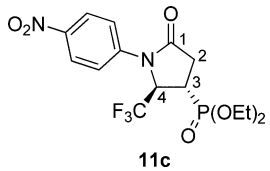
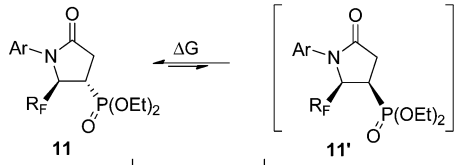


Figure 1. Labeled and numbered carbons for γ-lactam **11c**.

group signals is observed. Moreover, in the ^{31}P NMR spectrum a singlet at δ 26.4 ppm and in the ^{19}F NMR spectrum a doublet at δ −75.9 ppm with the coupling constant $^4J_{PF}$ = 6.1 Hz are observed. The structure of compound **11c** was also confirmed unambiguously by X-ray analysis (see the Supporting Information).

To have a better understanding of factors controlling the stereoselective formation of *trans*-γ-lactam **11**, the relative stabilities of *cis*-γ-lactam **11′** and *trans*-γ-lactam **11** were determined. Calculated free energy differences computed at the B3LYP(PCM)/6-31G* and M06-2X(PCM)//6-31G*//B3LYP/6-31G* level using tetrahydrofuran as solvent indicate that *trans*-γ-lactams **11a−e** are about 3 kcal/mol more stable than *cis*-γ-lactams **11′a−e** (Scheme 6 and the Supporting Information), and these

Scheme 6. Transformation of Compounds 11′ into 11 and Their Calculated Free Energy Differences (in kcal/mol) Computed at the B3LYP(PCM)/6-31G* + ZPVE Level Using Tetrahydrofuran as Solvent[a]



R_F	Ar	ΔG (kcal/mol)
CF_3	*p*-MeO-Ph	- 3.6 (-3.0)
CF_3	*p*-Me-Ph	-3.0 (-2.4)
CF_3	*p*-NO_2-Ph	-3.5 (-2.6)
C_2F_5	*p*-NO_2-Ph	-3.9 (-4.0)
CF_2H	*p*-NO_2-Ph	-1.5 (-2.4)

[a]Numbers in parentheses correspond to calculated free energy differences (in kcal/mol) computed at the M06-2X(PCM)/6-31G*//B3LYP/6-31G* + ZPVE level using tetrahydrofuran as solvent.

results are in agreement with the isomerization of the γ-lactam under the basic reaction conditions.

CONCLUSION

In summary, we report the synthesis of functionalized polyfluorophosphorylated 1-azadienes by Wittig reactions from perfluorophosphorylated conjugated phosphoranes, obtained by the reaction of phosphazenes and fluorinated acetylenic phosphonates. Subsequent reduction of both carbon−carbon and carbon−nitrogen double bonds of 1-azadienes constitute a convenient synthetic route leading to novel fluoroalkyl β-aminophosphonates as a diastereomeric mixture, with the *syn* β-aminophosphonate being obtained as the major diastereoisomer. It was shown that base-mediated cyclocondensation of diastereomeric mixture of aminophosphonates leads exclusively to a new type of functionalized *trans*-γ-lactams. Fluoroalkyl β-aminophosphonates and polyfluorophosphorylated γ-lactams could be interesting, because these new phosphorus- and fluorine-containing compounds show promise for the preparation of novel, biologically active compounds useful in drug design.[2,6,17,18] Theoretical calculations have been used to explain the diastereoselectivity of the 1-azadiene reduction mechanism, and computational studies also show a higher stability for the *trans* γ-lactams than for the *cis* isomers, in concert with the experimental observations.

EXPERIMENTAL SECTION

All reagents from commercial suppliers were used without further purification. All solvents were freshly distilled before use from appropriate drying agents. THF was distilled from sodium/benzophenone and used immediately. All other reagents were recrystallized or distilled when necessary. Reactions were performed under a dry nitrogen atmosphere. Analytical TLCs were performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Column chromatography was carried out using silica gel 60 (230−400 mesh ASTM). Melting points were determined with an electrothermal digital melting point apparatus without correction. NMR spectra were obtained on 300 MHz and 400 MHz spectrometers and recorded at 25 °C. Chemical shifts for ^{1}H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C NMR spectra are recorded in ppm relative to internal chloroform (δ 77.2 ppm for ^{13}C), chemical shifts for ^{19}F NMR are reported in ppm downfield from fluorotrichloromethane ($CFCl_3$), and chemical shifts for ^{31}P NMR are reported in ppm from an aqueous

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solution of H_3PO_4 (33%). Coupling constants (J) are reported in hertz. The terms m, s, d, t, and q refer to multiplet, singlet, doublet, triplet, and quartet, respectively; br refers to a broad signal. ^{13}C NMR, ^{31}P NMR, and ^{19}F NMR were broad-band decoupled from hydrogen nuclei. Infrared spectra (IR) were recorded with an infrared spectrometer; absorbance frequencies are given at maximum intensity in cm^{-1}. MS spectra were obtained on a chromatographic spectrometer, and HRMS spectra were obtained on an instrument at 70 eV with a ionization source.

Perfluoroacetylene phosphonates[26] and azides[23] (*caution!* low-molecular-weight carbon azides used in this study are potentially explosive; appropriate protection measures should always be taken when handling these compounds) were prepared according to literature procedures.

General Procedure for the Preparation of Ylides. To a solution of azide (10 mmol) in $CHCl_3$ (25 mL) at 0 °C under nitrogen atmosphere was added dropwise a solution of phosphine (11 mmol). (*Caution! Low-molecular-weight carbon azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.*) The mixture was stirred at room temperature until N_2 release had finished. Afterward a solution of the corresponding perfluoroacetylenephosphonate (10 mmol) in $CHCl_3$ was added dropwise and stirred at the corresponding temperature until the disappearance of starting materials was observed by ^{31}P NMR spectra.

*[1-Diethoxyphosphinyl-2-(4-tolylimino)-3,3,3-trifluoropropylidene]-triphenylphosphorane (**4g**).* The general procedure was followed using *p*-tolyl azide (1.33 g) and triphenylphosphine (2.62-g) stirred at 20 °C for 30 min followed by addition of trifluoromethylacetylenephosphonate **2a** (2.31 g). (*Caution! Low-molecular-weight carbon azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.*) The mixture was then stirred with refluxing chloroform for 21.5 h. Evaporation of the solvent gave a residue which was recrystallized in hexanes, affording 2.14 g of a yellowish solid (68%), mp 118−120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 2.15 (s, 3H, CH_3), 3.76−3.83 (m, 4H, OCH_2), 5.67 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H_{arom}), 6.77 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H_{arom}), 7.43−7.55 (m, 10H, H_{arom}), 7.83−7.89 (m, 5H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2−16.4 (m, $2CH_3$), 20.6 (CH_3), 60.7 (m, $2OCH_2$), 118.2 (dq, $^1J_{CF}$ = 116.8 Hz, $^3J_{CP}$ = 14.1 Hz, CF_3), 118.3 (HC_{arom}), 118.5 (HC_{arom}), 123.0 (d, $^3J_{CP}$ = 17.1 Hz, C_{arom}), 126.2 (dd, $^1J_{CP}$ = 91.7 Hz, $^1J_{CP}$ = 2.5 Hz, C_{arom}), 128.1 (HC_{arom}), 128.2 (HC_{arom}), 128.3 (HC_{arom}), 128.4 (HC_{arom}), 128.6 (HC_{arom}), 129.1 (HC_{arom}), 130.8 (HC_{arom}), 131.5 (HC_{arom}), 131.6 (HC_{arom}), 131.8 (HC_{arom}), 131.8 (HC_{arom}), 131.9 (HC_{arom}), 132.5 (d, $^1J_{CP}$ = 9.6 Hz, HC_{arom}), 133.8 (d, $^1J_{CP}$ = 9.6 Hz, HC_{arom}), 147.3 (C_{arom}), 146.6 (C_{arom}), 153.4 (dq, $^2J_{CF}$ = 28.4 Hz, $^2J_{CP}$= 9.2 Hz, C=N) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 24.2 (d, $^2J_{PP}$ = 51.1 Hz), 25.7 (d, $^2J_{PP}$ = 51.1 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.3 ppm. MS (EI, 70 eV): m/z (%) 597 (10) $[M]^+$. HRMS for $C_{32}H_{32}F_3NO_3P_2$ $[M]^+$: calcd 597.1810, found 597.1815.

Hydrolysis of Ylides. *Diethyl (3,3,3-Trifluoro-2-((4-methoxyphenyl)imino)propyl)phosphonate (**5**) and Diethyl (3,3,3-Trifluoro-2-((4-methoxyphenyl)amino)prop-1-en-1-yl)phosphonate (**5′**).* To a solution of 4-methoxyphenyl azide (10 mmol, 1.49 g) in $CHCl_3$ (25 mL) at 0 °C under a nitrogen atmosphere was added dropwise a solution of trimethylphosphine (11 mmol, 2.62 g). (*Caution! Low-molecular-weight carbon azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.*) The mixture was then stirred in chloroform at room temperature for 30 min. Afterward a solution of trifluoromethylacetylenephosphonate **2a** (10 mmol, 2.31 g) in $CHCl_3$ was added dropwise and the mixture was stirred at room temperature for 30 min. To the resulting solution was added 1.5 mL of water, and the reaction mixture was stirred at room temperature for 1.5 h until consumption of starting ylide, as monitored by ^{31}P NMR and ^{19}F NMR spectroscopy. Evaporation of the solvent gave a residue which was purified by column chromatography, affording the corresponding mixture of imine **5** and enamine **5′** as a colorless oil (70%), R_f = 0.48 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.29−1.41 (m, 12H, CH_3), 3.14 (d, $^2J_{HP}$ = 23.8 Hz, CH_2−P), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.08−4.21 (m, 8H, OCH_2), 4.68 (d, $^2J_{HP}$ = 6.0 Hz, =CH-P), 6.61 (d, $^3J_{HH}$ = 7.1 Hz, 2H, H_{arom}), 6.79 (d, $^3J_{HH}$ = 7.1 Hz, 2H, H_{arom}), 6.92 (d, $^3J_{HP}$ = 8.8 Hz, 2H, H_{arom}), 7.17 (d, $^3J_{HP}$ = 8.8 Hz, 2H, H_{arom}), 8.78 (s, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8 (CH_3 imine), 16.1 (CH_3 enamine), 28.4 (d, $^1J_{CP}$ = 136.2 Hz, CH_2−P imine), 52.2 (d, $^1J_{CP}$ = 103.3 Hz, =C−P enamine), 55.3 (OCH_3 enamine), 55.4 (OCH_3 imine), 62.6 (d, $^2J_{CP}$ = 6.1 Hz, OCH_2 enamine), 63.2 (d, $^2J_{CP}$ = 6.5 Hz, OCH_2 imine), 113.9 ($2HC_{arom}$ enamine), 114.3 ($2HC_{arom}$ imine), 118.2 (q, $^1J_{CF}$ = 279.4 Hz, CF_3 enamine), 118.5 (q, $^1J_{CF}$ = 278.8 Hz, CF_3 imine), 120.9 ($2HC_{arom}$ imine), 128.1 ($2HC_{arom}$ enamine), 131.9 (d, $^4J_{CP}$ = 9.1 Hz, C_{arom}−N enamine), 139.6 (C_{arom}−N imine), 139.7150.9 (m, C−CF_3 imine), 157.7 (C_{arom}−O imine), 158.1 (C_{arom}−O enamine), 160.5 (N−C= enamine) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.6 (imine), 22.8 (enamine) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.04 (enamine), −71.46 (imine) ppm. HRMS for $C_{14}H_{19}F_3NO_4P$ $[M]^+$: calcd 353.1004, found 353.1009.

General Procedure for the Preparation of 1-Azadienes. To a solution of ylide (10 mmol) in $CHCl_3$ (25 mL) at 0 °C under a nitrogen atmosphere was added dropwise a solution of ethyl glyoxalate (10 mmol, 50% in toluene, 1.0 mL). The reaction mixture was stirred at the corresponding temperature and monitored by ^{31}P NMR and ^{19}F NMR spectroscopy until consumption of starting materials. Evaporation of the solvent gave a residue which was purified by column chromatography, affording the corresponding 1-azadienes.

*(2E)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-methoxyphenylimino)pent-2-enoate (**6a**).* The general procedure was followed using ylide **4a** and stirring at room temperature for 15 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (5/1) as eluent, affording 3.32 g of a orange oil (76%), R_f = 0.43 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.21−1.42 (m, 6H, CH_3), 3.74 (s, 3H, OCH_3), 3.84−4.17 (m, 4H, OCH_2), 4.20−4.29 (m, 2H, OCH_2), 6.80 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{arom}), 6.93 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{arom}), 6.96 (d, $^3J_{HP}$ = 22.7 Hz, 1H, =CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 ($2CH_3$), 15.7 ($2CH_3$), 55.2 (OCH_3), 62.1 (OCH_2), 62.5 (d, $^2J_{CP}$ = 6.2 Hz, OCH_2), 62.8 (d, $^2J_{CP}$ = 6.2 Hz, OCH_2), 113.8 ($2HC_{arom}$), 119.1 (q, $^1J_{CF}$ = 279.4 Hz, CF_3), 122.4 ($2HC_{arom}$), 138.7 (C_{arom}), 139.7 (d, $^2J_{CP}$ = 7.6 Hz, HC=), 150.0 (dq, $^2J_{CF}$ = 35.9 Hz, $^2J_{CP}$ = 5.5 Hz, C−CF_3), 159.0 (C_{arom}), 163.1 (d, $^3J_{CP}$ = 26.0 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.9 ppm. HRMS for $C_{18}H_{23}F_3NO_6P$ $[M]^+$: calcd 437.1215, found 437.1214.

*(2E)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-tolylimino)-pent-2-enoate (**6b**).* The general procedure was followed using ylide **4b** and stirring at room temperature for 15 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (5/1) as eluent, affording 3.06 g of a yellowish oil (65%), R_f = 0.43 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.21−1.32 (m, 6H, CH_3), 2.27 (s, 3H, CH_3), 3.92−4.10 (m, 4H, OCH_2), 4.23−4.29 (m, 2H, OCH_2), 6.80 (d, $^3J_{HH}$ = 6.5 Hz, 2H, H_{arom}), 6.90 (d, $^3J_{HH}$ = 22.2 Hz, 1H, =CH), 7.07 (d, $^3J_{HH}$ = 6.5 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 15.8 (CH_3), 15.9 (CH_3), 20.7 (CH_3), 62.1 (OCH_2), 63.0 (d, $^2J_{CP}$ = 6.5 Hz, OCH_2), 63.2 (d, $^2J_{CP}$ = 6.0 Hz, OCH_2), 118.4 (q, $^1J_{CF}$ = 279.5 Hz, CF_3), 120.0 ($2HC_{arom}$), 129.1 ($2HC_{arom}$), 135.8 (C_{arom}), 136.2 (d, $^1J_{CP}$ = 156.1 Hz, C−P), 139.6 (d, $^3J_{CP}$ = 7.5 Hz, HC=), 144.3 (C_{arom}), 151.6 (dq, $^2J_{CF}$ = 36.6 Hz, $^2J_{Cp}$ = 5.5 Hz, C−CF_3), 163.2 (d, $^3J_{CP}$ = 25.7 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.1 ppm. HRMS for $C_{18}H_{23}F_3NO_5P$ [M]+: calcd 421.1266, found 421.1268.

*(2E)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-nitrophenylimino)pent-2-enoate (**6c**).* The general procedure was followed using ylide **4c** and stirring at room temperature for 20 h. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 1.82 g of a yellowish oil (80%).

The general procedure was followed using ylide **4f** and stirring at room temperature for 6 days. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 0.68 g of a yellowish oil (30%), R_f = 0.27 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19−1.38 (m, 9H, CH_3), 4.02−4.14 (m, 4H, OCH_2), 4.31−4.38 (m, 2H, OCH_2), 6.80 (d, $^3J_{HP}$ = 21.7 Hz, 1H, =CH), 7.03 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}), 8.22 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{arom})

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ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($2CH_3$), 16.1 (CH_3), 62.6 (OCH_2), 63.5 (d, $^2J_{CP}$ = 17.1 Hz, OCH_2), 63.7 (d, $^2J_{CP}$ = 17.1 Hz, OCH_2), 119.9 ($2HC_{arom}$), 124.7 ($2HC_{arom}$), 130.1 (q, $^1J_{CF}$ = 224.8 Hz, CF_3), 138.8 (d, $^1J_{CP}$ = 174.5 Hz, =C−P), 139.5 (d, $^2J_{CP}$ = 7.1 Hz, HC=), 145.5 (C_{arom}), 152.7 (C_{arom}), 155.2 (dq, $^2J_{CF}$ = 37.4 Hz, $^2J_{CP}$ = 8.9 Hz, C−CF_3), 163.5 (d, $^3J_{CP}$ = 25.2 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.7 ppm. HRMS for $C_{17}H_{20}F_3N_2O_7P$ $[M]^+$: calcd 452.0960, found 452.0980.

*(2E)-Ethyl 3-Diethoxyphosphinyl-3,3,4,4,4-pentafluoro-4-(4-nitrophenylimino)pent-2-enoate (**6d**).* The general procedure was followed using ylide **4i** and stirring in refluxing chloroform for 24 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (5/1) as eluent, affording 3.41 g of an orange oil (68%), R_f = 0.72 (50/50, hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21−1.74 (m, 9H, CH_3), 3.82−4.21 (m, 4H, CH_2), 4.21−4.43 (m, 2H, CH_2), 6.82 (d, $^3J_{HP}$ = 21.7 Hz, 1H, =CH), 7.07 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}), 8.21 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ13.9 ($2CH_3$), 16.1 (CH_3), 62.6 (OCH_2), 63.5 (d, $^2J_{CP}$ = 17.1 Hz, OCH_2), 63.7 (d, $^2J_{CP}$ = 17.1 Hz, OCH_2), 114.0−120.5 (m, C_2F_5), 119.6($2HC_{arom}$), 125.6 ($2HC_{arom}$), 137.6(d, $^1J_{CP}$ = 174.7 Hz, =C−P), 139.6(d, $^2J_{CP}$ = 6.5 Hz, HC=), 145.3 (C_{arom}), 152.4 (C_{arom}), 154.0 (m, C−C_2F_5), 163.1(d, $^3J_{CP}$ = 24.7 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 8.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −80.8 (CF_3), −118.3 (CF_2) ppm. HRMS for $C_{18}H_{20}F_5N_2O_7P$ $[M]^+$: calcd 502.0926, found 502.0928.

*(2E)-Ethyl 3-Diethoxyphosphinyl-5,5-difluoro-4-(4-nitrophenylimino)pent-2-enoate (**6e**).* The general procedure was followed using ylide **4j** and stirring at room temperature for 15 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (5/1) as eluent, affording 1.65 g of a dark orange oil (76%), R_f = 0.61 (50/50, hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19−1.38 (m, 9H, CH_3), 3.87−4.38 (m, 6H, CH_2), 6.32 (t, $^3J_{HH}$ = 52.5 Hz, 1H, CHF_2), 6.78 (d, $^3J_{HP}$ = 24.7 Hz, 1H, =CH), 7.03 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}), 8.20 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 16.3 ($2CH_3$), 62.6 (OCH_2), 63.7 (d, $^2J_{CP}$ = 5.5 Hz, $2OCH_2$), 111.9 (t, $^1J_{CF}$ = 247.3 Hz, CF_2H), 120.0 ($2HC_{arom}$), 124.6 ($2HC_{arom}$), 136.7 (C_{arom}), 138.2 (d, $^1J_{CP}$ = 26.2 Hz, =C−P), 145.2 (d, $^2J_{CP}$ = 7.1 Hz, CH), 153.7 (C_{arom}), 159.8−162.0 (m, C−CF_2H), 163.8 (d, $^3J_{CP}$ = 25.7 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 8.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −120.2 (dq, $^2J_{FF}$ = 306.7 Hz, $^2J_{FH}$ = 27.6 Hz) ppm. HRMS for $C_{17}H_{21}F_2N_2O_7P$ $[M]^+$: calcd 434.1054, found 434.1073.

General Procedure for the Preparation of β-Aminophosphonates. To a solution of the 1-azadiene (5 mmol) in ethanol (15 mL) cooled to 0 °C under a nitrogen atmosphere was added sodium borohydride portionwise. The reaction mixture was stirred at the corresponding temperature and monitored by ^{31}P NMR and ^{19}F NMR spectroscopy until consumption of starting materials. Then the reaction mixture was diluted with a water/HCl (2 M)/methylene chloride mixture (1/1/3) (3 × 50 mL); the aqueous phase was extracted with methylene chloride and dried over $MgSO_4$, and the crude product was purified by column chromatography to afford the corresponding β-aminophosphonate.

*(3S,4R),(3R,4S)- and (3S,4S),(3R,4R)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-methoxyphenylamino)pentanoate (**7a/7′a**).* The general procedure was followed using 1-azadiene **6a** and 2 equiv of sodium borohydride (0.38 g, 10 mmol). The reaction mixture was stirred at room temperature for 2 h. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 1.27 g of an orange oil (60%) as a 60/40 diastereomeric mixture, R_f = 0.52 (50/50, hexane/ethyl acetate). Data for the major isomer **7a** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12−1.29 (m, 9H, CH_3), 2.59−2.93 (m, 3H, CH_2, P−CH), 3.66 (s, 3H, OCH_3), 3.91−4.52 (m, 8H, OCH_2, CH, NH), 6.67−6.73 (m, 4H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 16.1 (CH_3), 16.2 (CH_3), 31.9 (CH_2), 33.0 (d, $^1J_{CP}$ = 143.7 Hz, CH−P), 55.6 (OCH_3), 55.7 (dq, $^2J_{CF}$ = 30.9 Hz, $^2J_{CP}$ = 4.0 Hz, CH−CF_3), 61.2 (OCH_2), 62.2−62.6 ($2OCH_2$), 114.5−116 ($4HC_{arom}$), 125.2 (dq, $^1J_{CF}$ = 284.8 Hz, $^3J_{CP}$ = 15.6 Hz, CF_3), 139.9 (C_{arom}), 154.0 (C_{arom}), 171.4 (d, $^3J_{CP}$ = 15.3 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.6 (d, $^4J_{FH}$ = 7.6 Hz) ppm. HRMS for $C_{18}H_{27}F_3NO_6P$ $[M]^+$: calcd 441.1532, found 441.1528. Data for the minor isomer **7′a** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12−1.29 (m, 9H, CH_3), 2.59−2.93 (m, 3H, CH_2, P−CH), 3.69 (s, 3H, OCH_3), 3.91−4.52 (m, 7H, OCH_2, CH), 4.76 (d, $^3J_{HH}$ = 10.3 Hz, 1H, NH), 6.57 (d, $^3J_{HH}$ = 9.0 Hz, 2H, CH_{arom}), 6.67−6.73 (m, 2H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 30.5 (CH_2), 33.5 (d, $^1J_{CP}$ = 143.6 Hz, CH−P), 55.6 (OCH_3), 57.1 (dq, $^2J_{CF}$ = 30.3 Hz, $^2J_{CP}$ = 3.9 Hz, CH−CF_3), 61.3 (OCH_2), 62.4−62.8 ($2OCH_2$), 114.5−116 ($4HC_{arom}$), 125.8 (dq, $^1J_{CF}$ = 284.2 Hz, $^3J_{CP}$ = 4.7 Hz, CF_3), 126.5 ($2HC_{arom}$), 140.5 (C_{arom}), 153.0 (C_{arom}), 171.6 (d, $^3J_{CP}$ = 12.8 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.5 (d, $^3J_{FH}$ = 6.1 Hz) ppm. HRMS for $C_{18}H_{27}F_3NO_6P$ $[M]^+$: calcd 441.1532, found 441.1528.

*(3S,4R),(3R,4S)- and (3S,4S),(3R,4R)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-tolylamino)pentanoate (**7b/7′b**).* The general procedure was followed using the 1-azadiene **6b** (5 mmol) and 2 equiv of sodium borohydride (0.38 g, 10 mmol). The reaction mixture was stirred at room temperature for 1 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (50/50) as eluent, affording 1.06 g of a yellow oil (50%) as a 60/40 diastereomeric mixture: R_f = 0.54 (50/50, hexane/ethyl acetate). Data for the major isomer **7b** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10−1.26 (m, 9H, CH_3), 2.15 (s, 3H, CH_3), 2.55−2.92 (m, 3H, CH−P, CH_2), 3.88−4.13 (m, 6H, OCH_2), 4.38 (d, $^3J_{HH}$ = 10.7 Hz, 1H, NH), 4.46−4.56 (m, 1H, CH−CF_3), 6.62 (d, $^3J_{HH}$ = 8.5 Hz, 2H, H_{arom}), 6.88−6.92 (m, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 16.0 (CH_3), 16.2 (CH_3), 20.2 (CH_3), 31.8 (CH_2), 33.4 (d, $^1J_{CP}$ = 143.4 Hz, CH-P), 55.9 (dq, $^2J_{CF}$ = 29.5 Hz, $^2J_{CP}$ = 2.5 Hz, CH−CF_3), 61.0 (d, $^2J_{CP}$ = 3.8 Hz, OCH_2), 62.4 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2), 114.0 ($2CH_{arom}$), 125.5 (dq, $^1J_{CF}$ = 284.8 Hz, $^3J_{CP}$ = 15.5 Hz, CF_3), 128.3 (C_{arom}), 129.6 ($2CH_{arom}$), 143.4 (C_{arom}), 171.1 (d, $^3J_{CP}$ = 15.3 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.6 (d, $^3J_{FH}$ = 6.1 Hz) ppm. HRMS for $C_{18}H_{27}F_3NO_5P$ $[M]^+$: calcd 425.1579, found 425.1590. Data for the minor isomer **7′b** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10−1.26 (m, 9H, CH_3), 2.14 (s, 3H, CH_3), 2.55−2.92 (m, 3H, CH−P, CH_2), 3.88−4.13 (m, 6H, OCH_2), 4.26−4.38 (m, 1H, CH−CF_3), 4.90 (d, $^3J_{HH}$ = 10.4 Hz, 1H, NH), 6.50 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H_{arom}), 7.00−7.17 (m, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 16.1 ($2CH_3$), 20.1 (CH_3), 29.9 (CH_2), 33.3 (d, $^1J_{CP}$ = 143.5 Hz, CH−P), 56.2 (dq, $^2J_{CF}$ = 30.5 Hz, $^2J_{CP}$ = 4.3 Hz, CH−CF_3), 61.2 (d, $^2J_{CP}$ = 6.3 Hz, OCH_2), 62.5 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2), 113.3 ($2CH_{arom}$), 125.1 (dq, $^1J_{CF}$ = 284.3 Hz, $^3J_{CP}$ = 4.3 Hz, CF_3), 127.8 (C_{arom}), 129.6 ($2CH_{arom}$), 143.9 (C_{arom}), 170.9 (d, $^3J_{CP}$ = 12.5 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.4 (d, $^3J_{FH}$ = 7.6 Hz) ppm. HRMS for $C_{18}H_{27}F_3NO_5P$ $[M]^+$: calcd 425.1579, found 425.1590.

*(3S,4R),(3R,4S)- and (3S,4S),(3R,4R)-Ethyl 3-Diethoxyphosphinyl-5,5,5-trifluoro-4-(4-nitrophenylamino)pentanoate (**7c/7′c**).* The general procedure was followed using the 1-azadiene **6c** (5 mmol) and 1 equiv of sodium borohydride (0.19 g, 5 mmol). The reaction mixture was stirred at room temperature for 1 h. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 1.87 g of an orange oil (82%) as a 60/40 diastereomeric mixture: R_f = 0.76 (50/50, hexane/ethyl acetate). Data for the major isomer **7c** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21−1.24 (m, 9H, CH_3), 2.57−3.02 (m, 3H, CH_2, P−CH), 4.04−4.26 (m, 6H, OCH_2), 4.53−4.85 (m, 1H, CH), 6.13 (d, $^3J_{HH}$ = 10.1 Hz, 1H, NH), 6.77 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{arom}), 8.09−8.14 (m, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 16.5 (CH_3), 16.6 (CH_3), 30.5 (CH_2), 33.5 (d, $^1J_{CP}$ = 143.6 Hz, HC-P), 53.4 (dq, $^2J_{CF}$ = 30.5 Hz, $^2J_{CP}$ = 3.3 Hz, HC−CF_3), 61.9 (OCH_2), 61.2−62.5 (m, $2OCH_2$), 112.6 ($2HC_{arom}$), 124.5 (dq, $^1J_{CF}$ = 284.9 Hz, $^3J_{CP}$ = 13.1 Hz, CF_3), 126.5 ($2HC_{arom}$), 139.7 (C_{arom}), 151.6 (C_{arom}), 171.4 (d, $^3J_{CP}$ = 15.6 Hz, C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.5 (d, $^4J_{FH}$ = 7.6 Hz) ppm. HRMS for $C_{17}H_{21}F_2N_2O_7P$ $[M]^+$: calcd 434.1054, found 434.1061. Data for the minor isomer **7′c** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21−1.24 (m, 9H, CH_3), 2.57−3.02 (m, 3H, CH_2, CH), 4.04−4.26 (m, 6H, OCH_2), 4.53−4.85 (m, 1H, CH),

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6.22 (d, $^3J_{HH}$ = 10.2 Hz, 1H, NH), 6.67 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{arom}), 8.09−8.14 (m, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 16.3 (CH_3), 16.4 (CH_3), 31.9 (CH_2), 33.0 (d, $^1J_{CP}$ = 143.7 Hz, HC−P), 55.0 (dq, $^2J_{CF}$ = 31.6 Hz, $^2J_{CP}$ = 4.3 Hz, HC−CF_3), 61.8 (OCH_2), 61.2−62.5 (m, 2OCH_2), 112.2 (2HC_{arom}), 124.5 (dq, $^1J_{CF}$ = 288.5 Hz, $^3J_{CP}$ = 4.3 Hz, CF_3), 126.5 (2HC_{arom}), 139.7 (C_{arom}), 152.0 (C_{arom}), 171.6 (d, $^3J_{CP}$ = 13.2 Hz, C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.1 (d, $^4J_{FH}$ = 7.6 Hz) ppm. HRMS for $C_{17}H_{21}F_2N_2O_7P$ $[M]^+$: calcd 434.1054, found 434.1063.

*(3S,4R),(3R,4S)- and (3S,4S),(3R,4R)-Ethyl 3-Diethoxyphosphinyl-5,5,6,6,6-pentafluoro-4-(4-nitrophenylamino)hexanoate (**7d/7′d**).* The general procedure was followed using the 1-azadiene **6d** (5 mmol) and 2 equiv of sodium borohydride (0.38 g, 10 mmol). The reaction mixture was stirred at room temperature for 1 h. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 1.52 g of a yellow oil (60%) as a 95/5 diastereomeric mixture: R_f = 0.52 (50/50, hexane/ethyl acetate). Data for the major isomer **7d** are as follows. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20−1.37 (m, 9H, CH_3), 2.67−2.86 (m, 3H, CH_2, CH), 3.92−4.27 (m, 6H, OCH_2), 4.86−5.01 (m, 1H, CH), 5.71 (d, $^3J_{HH}$ = 11.1 Hz, 1H, NH), 6.74 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{arom}), 8.07 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 16.2 (CH_3), 16.3 (CH_3), 30.3 (CH_2), 33.8 (d, $^1J_{CP}$ = 143.3 Hz, HC−P), 50.4−50.9 (m, HC−C_2F_5), 61.6 (OCH_2), 62.1−62.8 (m, 2OCH_2), 112.4 (HC_{arom}), 121.1−126.3 (m, C_2F_5), 126.2 (HC_{arom}), 139.7 (C_{arom}), 150.7 (C_{arom}), 171.4 (d, $^3J_{CP}$ = 13.6 Hz, C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −82.4 (CF_3), −116.4 (d, F_a, $^2J_{FF}$ = 274.4 Hz), −126.3 (dd, F_b, $^2J_{FF}$ = 274.4 Hz, $^3J_{FH}$ = 24.0 Hz) ppm. HRMS for $C_{18}H_{24}F_5N_2O_7P$ $[M]^+$: calcd 506.1239, found 506.1241. Data for minor isomer **7′d** are as follows. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −82.7 (CF_3), −118.0 (d, F_a, $^2J_{FF}$ = 273.8 Hz), −124.2 (dd, F_b, $^2J_{FF}$ = 273.8 Hz, $^3J_{FH}$ = 22.0 Hz) ppm. HRMS for $C_{18}H_{24}F_5N_2O_7P$ $[M]^+$: calcd 506.1239, found 506.1241.

*(3S,4R),(3R,4S)- and (3S,4S),(3R,4R)-Ethyl 3-Diethoxyphosphinyl-5,5-difluoro-4-(4-nitrophenylamino)pentanoate (**7e/7′e**).* The general procedure was followed using the 1-azadiene **6e** (5 mmol) and 2 equiv of sodium borohydride (0.38 g, 10 mmol). The reaction mixture was stirred at room temperature for 2 h. Evaporation of the solvent gave a residue which was purified by chromatography with ether as eluent, affording 0.77 g of a yellow oil (35%) as a 95/5 diastereomeric mixture,: R_f = 0.24 (50/50, hexane/ethyl acetate). Data for major isomer **7e** are as follows. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17−1.57 (m, 9H, CH_3), 2.45−2.98 (m, 3H, CH_2, CH), 4.10−4.20 (m, 6H, OCH_2), 4.20−4.39 (m, 1H, CH), 5.81 (d, $^3J_{HH}$ = 10.0 Hz, 1H, NH), 6.05 (dt, $^2J_{HF}$ = 57.7 Hz, $^3J_{HH}$ = 6.1 Hz, 1H, CF_2H), 6.45 (d, $^3J_{HH}$ = 10.3 Hz, 2H, CH_{arom}), 8.08 (d, $^3J_{HH}$ = 10.3 Hz, 2H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (CH_3), 16.4−16.2 (m, 2CH_3), 31.0 (CH_2), 32.8 (d, $^1J_{CP}$ = 136.1 Hz, HC−P), 54.7−55.4 (m, HC−CF_2H), 61.5 (OCH_2), 62.9−63.2 (m, 2OCH_2), 111.9 (HC_{arom}), 115.4 (t, $^1J_{CF}$ = 277.0 Hz, CF_2H), 126.2(HC_{arom}), 139.0 (C_{arom}), 152.4(C_{arom}), 170.8 (d, $^3J_{CP}$ = 16.6 Hz, C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −121.0 (ddd, F_a, $^2J_{FF}$ = 285.0 Hz, $^2J_{FH}$ = 55.6 Hz, $^3J_{FH}$ = 6.1 Hz), −124.1 (ddd, F_b, $^2J_{FF}$ = 285.0 Hz, $^2J_{FH}$ = 56.4 Hz, $^3J_{FH}$ = 12.2 Hz) ppm. HRMS for $C_{17}H_{25}F_2N_2O_7P$ $[M]^+$: calcd 438.1367, found 438.1384. Data for minor isomer **7′e** are as follows. ^{31}P NMR (120 MHz, $CDCl_3$): δ 27.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −121.2 (dd, F_a, $^2J_{FF}$ = 284.5 Hz, $^3J_{FH}$ = 6.2 Hz), −124.4 (ddd, F_b, $^2J_{FF}$ = 284.5 Hz, $^2J_{FH}$ = 56.4 Hz, $^3J_{FH}$ = 12.9 Hz) ppm. HRMS for $C_{17}H_{25}F_2N_2O_7P$ $[M]^+$: calcd 438.1367, found 438.1384.

General Procedure for the Preparation of γ-Lactams. To a sodium hydride suspension (0.04 g, 1.5 mmol) in THF (5 mL) cooled to 0 °C under a nitrogen atmosphere was added dropwise a solution of the β-aminophosphonate (1 mmol) in THF. The reaction mixture was stirred at the corresponding temperature and monitored by ^{31}P NMR and ^{19}F NMR spectroscopy until consumption of the starting β-aminophosphonate. Evaporation of the solvent gave a residue which was purified by column chromatography, affording the corresponding γ-lactam.

*4-Diethoxyphosphinyl-5-trifluoromethyl-1-(4-methoxyphenyl)-pyrrolidin-2-one (**11a**).* The general procedure was followed using a diastereomeric mixture of β-aminophosphonates **7a/7′a** (0.44 g). The reaction mixture was stirred at room temperature for 15 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (1/10) as eluent, affording 0.36 g of an orange oil (90%): R_f = 0.24 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25−1.35 (m, 6H, CH_3), 2.66−3.08 (m, 3H, CH, CH_2), 3.56 (s, 3H, OMe), 4.11−4.22 (m, 4H, OCH_2), 4.55−4.65 (m, 1H, CH−CF_3), 6.87 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}), 7.16 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 (CH_3), 16.4 (CH_3), 29.4 (d, $^1J_{CP}$ = 107 Hz, CH), 30.6 (d, $^2J_{CP}$ = 4.7 Hz, CH_2), 55.4 (OCH_3), 61.0 (q, $^2J_{CF}$ = 28.8 Hz, HC−CF_3), 63.3 (d, $^2J_{CP}$ = 6.8 Hz, 2OCH_2), 114.6 (2HC_{arom}), 124.7 (dq, $^1J_{CF}$ = 268.3 Hz, $^3J_{CP}$ = 15.7 Hz, CF_3), 127.1 (2HC_{arom}), 129.5 (C_{arom}), 158.9 (C_{arom}), 172.6 (C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −76.0 (d, $^4J_{FH}$ = 6.1 Hz) ppm. HRMS for $C_{16}H_{21}F_3NO_5P$ $[M]^+$: calcd 395.1126, found 395.1109.

*4-Diethoxyphosphinyl-5-trifluoromethyl-1-(4-tolyl)pyrrolidin-2-one (**11b**).* The general procedure was followed using a diastereomeric mixture of β-aminophosphonates **7b/7′b** (0.46 g). The reaction mixture was stirred at room temperature for 3 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (10/1) as eluent, affording 0.37 g of an orange oil (80%): R_f = 0.29 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20−1.24 (m, 6H, CH_3), 2.29 (s, 3H, CH_3), 2.70−3.10 (m, 3H, CH, CH_2), 4.11−4.18 (m, 4H, OCH_2), 4.87−4.93 (m, 1H, CH−CF_3), 7.12 (d, $^3J_{HH}$ = 8.7 Hz, 2H, HC_{arom}), 7.16 (d, $^3J_{HH}$ = 8.7 Hz, 2H, HC_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 (CH_3), 16.4 (CH_3), 29.2 (d, $^1J_{CP}$ = 150.6 Hz, CH), 31.0 (d, $^2J_{CP}$ = 4.7 Hz, CH_2), 61.0 (q, $^2J_{CF}$ = 34.2 Hz, C−CF_3), 63.3 (d, $^2J_{CP}$ = 6.6 Hz, 2OCH_2), 124.1 (2HC_{arom}), 124.5 (dq, $^1J_{CF}$ = 284.3 Hz, $^3J_{CP}$ = 16.0 Hz, CF_3), 124.8 (2HC_{arom}), 142.5 (C_{arom}), 145.7 (C_{arom}), 172.0 (C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −76.0 (d, $^4J_{FH}$ = 6.1 Hz) ppm. MS (EI, 70 eV): *m/z* (%) 379 (3) $[M^+]$. HRMS for $C_{16}H_{21}F_3NO_4P$ $[M]^+$: calcd 379.1171, found 379.1160.

*4-Diethoxyphosphinyl-5-trifluoromethyl-1-(4-nitrophenyl)-pyrrolidin-2-one (**11c**).* The general procedure was followed using a diastereomeric mixture of β-aminophosphonates **7c/7′c** (0.46 g). The reaction mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (10/1) as eluent, affording 0.36 g of a yellow solid (90%): mp 115−117 °C (methylene chloride/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (m, 6H, CH_3), 2.70−3.20 (m, 3H, CH, CH_2), 4.11−4.18 (m, 4H, OCH_2), 4.90 (dq, 1H, $^3J_{HF}$ = 6.4 Hz, $^3J_{HP}$ = 18.4 Hz, CH−CF_3), 7.55 (d, $^3J_{HH}$ = 8.7 Hz, 2H, HC_{arom}), 8.23 (d, $^3J_{HH}$ = 8.8 Hz, 2H, HC_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 (CH_3), 16.4 (CH_3), 29.2 (d, $^1J_{CP}$ = 150.6 Hz, CH), 31.0 (d, $^2J_{CP}$ = 4.7 Hz, CH_2), 61.0 (q, $^2J_{CF}$ = 34.2 Hz, C−CF_3), 63.3 (d, $^2J_{CP}$ = 6.6 Hz, 2OCH_2), 124.1 (2HC_{arom}), 124.5 (dq, $^1J_{CF}$ = 284.3 Hz, $^3J_{CP}$ = 16.0 Hz, CF_3), 124.8 (2HC_{arom}), 142.5 (C_{arom}), 145.7 (C_{arom}), 172.0 (C═O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.9 (d, $^4J_{FH}$ = 6.1 Hz) ppm. HRMS for $C_{15}H_{18}F_3N_2O_6P$ $[M]^+$: calcd 410.0855, found 410.0859.

*4-Diethoxyphosphinyl-5-perfluoroethyl-1-(4-nitrophenyl)-pyrrolidin-2-one (**11d**).* The general procedure was followed using a diastereomeric mixture of β-aminophosphonates **7d/7′d** (0.46 g). The reaction mixture was stirred at room temperature for 36 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (10/1) as eluent, affording 0.37 g of an orange oil (90%): R_f = 0.36 (50/50, hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 1.22−1.34 (m, 6H, CH_3), 2.74−3.21 (m, 3H, CH, CH_2), 4.12−4.25 (m, 4H, CH_2), 4.97−5.17 (m, 1H, CH−CF_2), 7.60 (d, $^3J_{HH}$ = 9.0 Hz, 2H, HC_{arom}), 8.29(d, $^3J_{HH}$ = 9.0 Hz, 2H, HC_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 (CH_3), 16.4 (CH_3), 29.2 (d, $^1J_{CP}$ = 143.9 Hz, CH), 31.0 (d, $^2J_{CP}$ = 6.8 Hz, CH_2), 59.5 (m, HC−CF_2), 63.3 (d, $^2J_{CP}$ = 2.0 Hz, 2OCH_2), 111.2−116.7 (m, CF_3), 118.3 (qt, $^1J_{CF}$ = 305.9 Hz, $^2J_{CF}$ = 35.1 Hz, CF_2), 124.1 (2HC_{arom}), 124.6 (2HC_{arom}), 143.1 (C_{arom}), 145.6 (C_{arom}), 172.0 (C═O) ppm.

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^{31}P NMR (120 MHz, $CDCl_3$): δ 25.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −81.9 (CF_3), −123.4 (d, $^2J_{FF}$ = 280.0 Hz, CF_3) ppm. HRMS for $C_{16}H_{18}F_5N_2O_6P$ $[M]^+$: calcd 460.0834, found 460.0823.

*4-Diethoxyphosphinyl-5-difluoromethyl-1-(4-nitrophenyl)-pyrrolidin-2-one (**11e**).* The general procedure was followed using a diastereomeric mixture of β-aminophosphonates **7e**/**7′e** (0.44 g). The reaction mixture was stirred at room temperature for 5 h. Evaporation of the solvent gave a residue which was purified by chromatography with hexane/ethyl acetate (10/1) as eluent, affording 0.27 g of an orange oil (70%): R_f = 0.39 (50/50, hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25−1.74 (m, 6H, CH_3), 2.66−3.12 (m, 3H, CH_2CH_2), 4.12−4.19 (m, 4H, $2OCH_2$), 4.78−4.98 (m, 1H, CH-CF_2H), 5.97 (t, $^2J_{HF}$ =54.5 Hz, 1H, CF_2H), 7.13 (d, $^3J_{HH}$ = 8.9 Hz, 2H, HC_{arom}), 7.21(d, $^3J_{HH}$ = 8.9 Hz, 2H, HC_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 (CH_3), 16.4 (CH_3), 29.9 (d, $^2J_{CP}$ = 5.5 Hz, CH_2), 31.3 (d, $^1J_{CP}$ = 160.8 Hz, CH), 60.8−61.0 (m, HC−CF_2H), 63.3 ($2OCH_2$), 100.8−116.1 (m, CF_2H), 123.3 (HC_{arom}), 125.0 (HC_{arom}), 142.5 (C_{arom}), 145.8 (C_{arom}), 172.3 (C=O) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ −129.2 (dd, $^2J_{FH}$ = 7.6 Hz, $^2J_{FH}$ = 55.0 Hz) ppm. HRMS for $C_{15}H_{19}F_2N_2O_6P$ $[M]^+$: calcd 392.0961, found 392.0949.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and CIF files giving ^{1}H NMR and ^{13}C NMR spectra of compounds **4g**, **5**/**5′**, **6a**−**e**, **7**/**7′a**−**e**, **7b**, and **11a**−**e**, 2D spectra of compounds **6a** and **11c**, ORTEP and X-ray crystallographic data of compounds **7b** and **11c**, and Cartesian coordinates, harmonic analysis data, and energies for all the stationary points discussed in the computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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