Attempts at asymmetric electrosynthesis of α-fluorinated cyclopropylphosphonamides

Sophie Goumain,[a] Hassan Oulyadi,[b] Philippe Jubault,[a] Christian Feasson[a] and Jean-Charles Quirion[a]

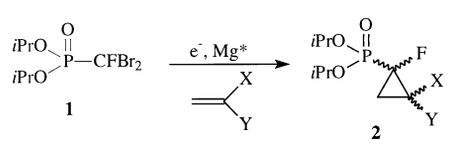
[a] *Laboratoire d'Hétérochimie Organique, INSA de Rouen, IRCOF, 1 rue Tesnière, 76130 Mont-Saint-Aignan Cedex, France*
[b] *Laboratoire de Chimie Organique et Biologie Structurale de l'IRCOF, Université de Rouen, 1 rue Tesnière, 76130 Mont-Saint-Aignan Cedex, France*

Received (in Cambridge, UK) 6th November 2000, Accepted 19th February 2001
First published as an Advance Article on the web 14th March 2001

Variously *N*,*N*-disubstituted chiral dibromofluoromethylphosphonamides **3** were easily prepared and used for the asymmetric electrosynthesis, in the presence of *tert*-butyl acrylate, of α-fluorinated cyclopropylphosphonamides **7**. The diastereoisomeric excesses are moderate (up to 40%). Moreover, the identification of the *trans* and *cis* stereoisomers has been deduced from analysis of 2D ^{1}H–^{19}F HOESY spectra.

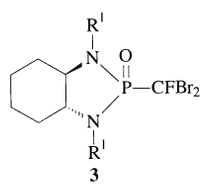
The cyclopropane moiety can be found in a number of natural and unnatural substances, and some of these have received particular attention due to their biological properties.[1,2] Hence, this group continues to attract a lot of attention in synthetic organic chemistry as well as in medicinal and agricultural chemistry. Furthermore, it is known for biologically active compounds that the replacement of a C–H bond with a C–F bond can lead to dramatic effects on their physiological properties.[3] Therefore, the development of new synthetic approaches to fluorinated compounds is an important field of research.[4] Moreover, phosphonic acids exhibit important biological properties because of their similarity to phosphates.[5] The carbon–phosphorus bond in phosphonates, unlike that in phosphates, is not susceptible to the hydrolytic action of phosphatases, thereby imparting greater stability under physiological conditions. In pioneering work, Blackburn *et al*. established that α-fluorination of phosphonates is a successful strategy for the design of phosphonate analogues of phosphate esters.[6]

We recently described the first synthesis[7] of α-fluorinated cyclopropylphosphonates **2** from the readily available[8] diisopropyl dibromofluoromethylphosphonate **1** (Scheme 1). A



Scheme 1 Electrosynthesis of α-fluorinated cyclopropylphosphonates.

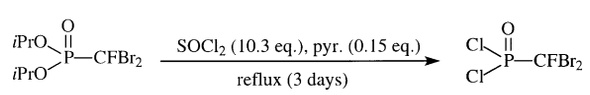
novel method for the asymmetric synthesis of fully functionalized cyclopropanes has been found based on Hanessian's phosphonamide technology[9] using C_2-symmetric diamines. This process has been also applied, for example, to the asymmetric synthesis of aziridines[10] and to asymmetric alkylations.[11] With a good methodology to achieve the synthesis of **2** in hand, we became interested in the asymmetric version of these electrosyntheses using chiral dibromofluoromethylphosphonamides of type **3**, the synthesis of which can be easily achieved from the corresponding diamine and phosphonic dichloride **5**.



Results and discussion

Synthesis of dibromofluoromethylphosphonamides 3 derived from (*R*,*R*)-1,2-bis(*N*-alkylamino)cyclohexanes 4

Firstly, in this study, we investigated the synthesis of dibromofluoromethylphosphonic dichloride **5**. Several methods have been described for the synthesis of such phosphonic dichlorides. In our case, none of the previously reported methods [PCl_3, $AlCl_3$, $CFBr_3$, H_2O);[12] (iPrO)$_2$P(O)CFBr$_2$, PCl_5, P(O)Cl$_3$);[13] (iPrO)$_2$P(O)CFBr$_2$, $SOCl_2$, DMF[14]] allowed the preparation of the expected compound. Finally we successfully applied the methodology developed by Bergstrom[15] based on the reaction between diisopropyl dibromofluoromethylphosphonate **1**, thionyl chloride (10.3 eq.) and pyridine (0.15 eq.). We then obtained in quantitative yield dibromofluoromethylphosphonic dichloride **5** (Scheme 2). The (*R*,*R*)-1,2-



Scheme 2 Synthesis of dibromofluoromethylphosphonic dichloride **5**.

bis(*N*-alkylamino)cyclohexanes **4a–e** have been prepared by known procedures[9c] from the readily available (*R*,*R*)-1,2-diaminocyclohexane.[16] The coupling reaction between **4a–e** and **5** was carried out in toluene using triethylamine (Scheme 3). The results for the synthesized phosphonamides **3a–e** and their characteristics are collected in Table 1. These chiral phosphonamides are generally obtained in good yields (except for **3c**, probably because of the steric hindrance of the two neopentyl substituents).

DOI: 10.1039/b008906k

Table 1 Synthesis and physical and analytical data of phosphonamides **3**

Product	R^1	Yield (%)[a]	^{31}P ($CDCl_3$)[b] δ (ppm) [$^2J_{PF}$/Hz]	^{19}F ($CDCl_3$)[b] δ (ppm)	Mp/°C
3a	CH_2Ph	52	23.1 [67.2]	−68.5	133
3b	CH_3	47	24.2 [67.9]	−69.4	84
3c	$CH_2C(CH_3)_3$	24	21.2 [61.6]	−62.8	112
3d	$(CH_2)_2C(CH_3)_3$	55	22.7 [68.4]	−69.2	122
3e	$CH_2CH_2OCH_3$	41	22.7 [69.3]	−69.1	118

[a] Product purified by flash chromatography over silica gel (see Experimental for eluents) and characterized by ^1H and ^{13}C NMR spectroscopy. Satisfactory microanalyses were obtained. [b] Each signal appeared as a doublet.

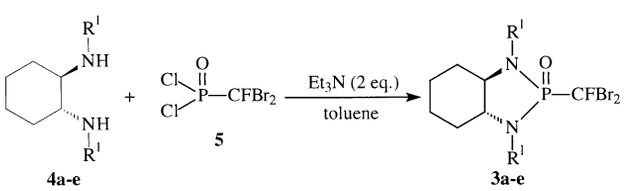
Table 2 Electrosynthesis of α-fluorinated cyclopropylphosphonamides **7**–**12** from chiral phosphonamides **3**

Entry	Chiral phosphonamide **3**	Product	R^2	Yield (%)[a]	*trans* : *cis* ratio[b]	*trans* de (%)[b]	*cis* de (%)[b]
1	**3a**	**7**	Me	62	70 : 30	36	24
2[c]	**3a**	**7**	Me	65	95 : 5	36	70
3	**3a**	**8**	*t*Bu	54	63 : 37	32	20
4	**3b**	**9**	*t*Bu	30	78 : 22	20	42
5	**3c**	**10**	*t*Bu	—[d]	90 : 10	40	95
6	**3d**	**11**	*t*Bu	—[d]	72 : 28	27	12
7	**3e**	**12**	*t*Bu	35	70 : 30	22	18

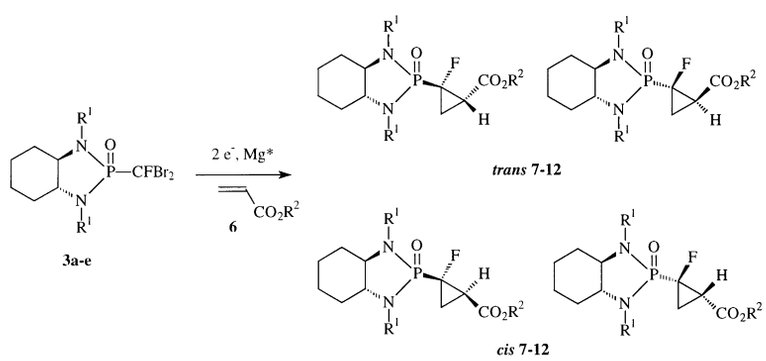
[a] Product purified by flash chromatography over silica gel (see Experimental for eluents) and characterized by ^1H and ^{13}C NMR spectroscopy. [b] Measured by ^{19}F NMR spectroscopy on the crude product. [c] The electrolysis was performed at 0 °C. [d] Unpurified product.

Electrosynthesis of α-fluorinated cyclopropylphosphonamides from chiral dibromofluoromethylphosphonamides 3 and Michael acceptors

The main part of this study was concerned with the electrolysis of dibromofluoromethylphosphonamides **3a**–**e** in the presence of Michael acceptors **6** (Scheme 4). Electroreductions of **3a**–**e**, in DMF between a carbon-felt cathode and a magnesium sacrificial anode in a one-compartment cell,[17] performed in the presence of two equivalents of Michael acceptor, afforded α-fluorinated cyclopropylphosphonamides **7**–**12**. In this study, we started our investigations with methyl acrylate **6a** as Michael acceptor (Table 2, entry 1). α-Fluorinated cyclopropylphosphonamide **7** was obtained in a good isolated yield (62%) as a mixture of four diastereoisomers. The *trans* : *cis* ratio was 70 : 30 and the diastereoisomeric excesses were low (*trans*-**7** de: 36%, *cis*-**7** de: 24%). Performing the electrolysis at 0 °C (Table 2, entry 2) enhanced not only the *trans* : *cis* ratio (95 : 5), but also the diastereoisomeric excess (de: 70%) of the *cis*-**7** products. Nevertheless, the main problem encountered with methyl acrylate was that we were unable to separate the two *trans* diastereoisomers from the two *cis*. For this reason, we then decided to use *tert*-butyl acrylate **6b**, instead of **6a**. With this Michael acceptor, the two *trans* products could be easily separated from the two *cis* ones by flash chromatography on silica gel. This feature was very important in terms of stereochemical assignments (see NMR part below). The different results obtained using *tert*-butyl acrylate **6b** and various dibromofluoromethylphosphonamides **3a**–**e** are collected in Table 2. In each case, we observed the presence of four diastereoisomers. The selectivity observed by Hanessian, based on the hypothesis that, for steric and stereoelectronic reasons, the electrophile would approach the α-carbanion derived from (*R*,*R*)-alkylphosphonamides from the 'left cleft' (diastereofacial approach), did not occur in our case. It seemed that under the conditions of electrosynthesis, the diastereofacial discrimination was low. Using *N*,*N*-dibenzylphosphonamide **3a**, the *trans* : *cis* ratio as well as the diastereoisomeric excesses were low (Table 2, entry 3). Using the *N*,*N*-dimethylphosphonamide **3b**, similar results were obtained. Increasing the steric hindrance on the two nitrogens, by using the neopentyl moiety (**3c**), enhanced the *trans* : *cis* ratio as well as the diastereoisomeric excesses of the *trans* mixture and, more importantly, of the *cis* mixture (Table 2, entry 5). This last result indicates that steric hindrance on the two nitrogens is



Scheme 3 Synthesis of dibromomethylphosphonamides **3a**–**e**.



Scheme 4 Electrolysis of α-fluorinated cyclopropylphosphonamides.

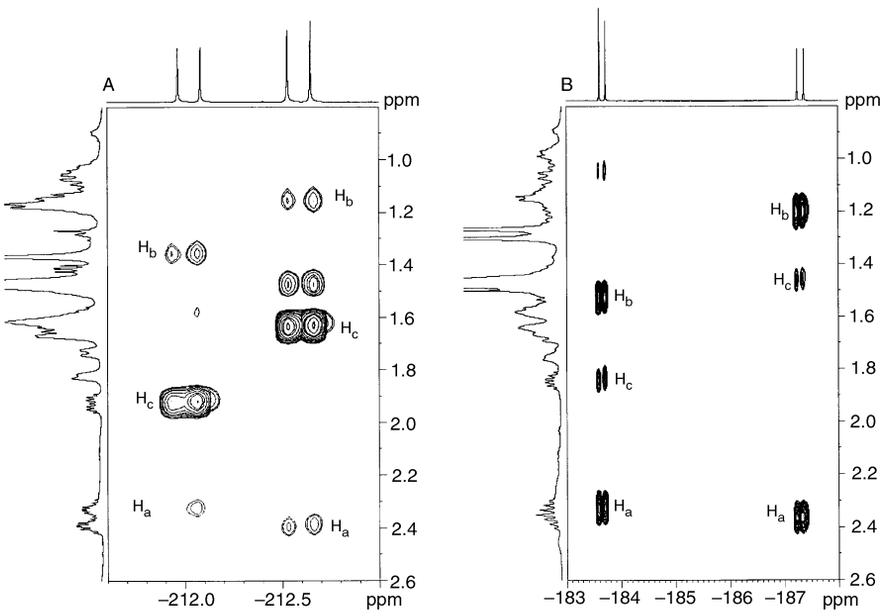


Fig. 1 Part of ^1H–^{19}F NMR HOESY spectra obtained in $CDCl_3$ at 298 K, with the 1D ^1H and ^{19}F spectra along the side and the top. The experiment was recorded with a mixing time of 300 ms. (A) cyclopropylphosphonamides *trans*-**8** (B) cyclopropylphosphonamides *cis*-**8**.

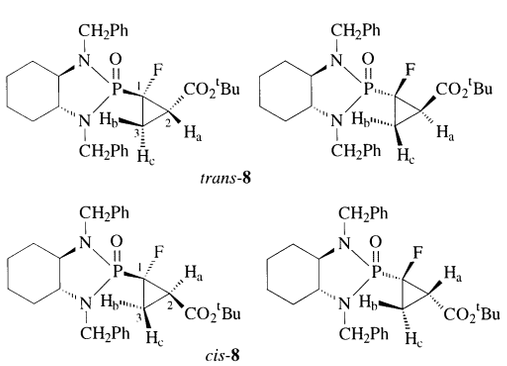
important for the level of diastereoselectivity. The homologation of the neopentyl group (phosphonamide **3d**) induced a spectacular drop of the diastereoisomeric excesses (Table 2, entry 6).

Finally, we tested phosphonamide **3e**, which contains a methoxy group (we assumed that it could induce chelation between the oxygen atom and the Mg^{2+} cations to stabilize the carbanion and also to fix its conformation), but phosphonamide **3e** led to very low diastereoisomeric excesses.

In summary, the diastereoisomeric excesses obtained for the asymmetric electrosynthesis of α-fluorinated cyclopropylphosphonamides **7**–**12** were generally low. The best result was obtained using phosphonamide **3c**, for which a 90 : 10 *trans*-**10** : *cis*-**10** ratio and 40 and 95% de of *trans*-**10** and *cis*-**10**, respectively were observed. The diastereoisomeric excesses were measured by ^{31}P NMR after the complete identification of the four diastereoisomers by HMQC, ^1H–^{19}F HETEROCOSY and ^1H–^{19}F HOESY NMR experiments.

Stereochemical assignments using HMQC, ^1H–^{19}F HETEROCOSY and ^1H–^{19}F HOESY NMR experiments

An NMR investigation of the stereochemical structure of cyclopropylphosphonamides **8** was carried out after separation



of the two *trans* diastereoisomers from the two *cis*. The 600 MHz ^1H and ^{19}F NMR spectra of *trans*-**8** and *cis*-**8** show that all the proton and fluorine resonances split in two signals corresponding to the two diastereoisomers (Fig. 1). In order to identify the stereochemical structure of cyclopropylphosphonamides **8**, assignment of protons H_a, H_b and H_c was performed by using 2D NMR experiments.

Table 3 ^{19}F and ^1H chemical shifts (in ppm) of the cyclopropane fragment of cyclopropylphosphonamides **8**[a]

Product	^{19}F	H_a	H_b	H_c
trans-**8**[b]	−212.61	2.39	1.16	1.64
trans-**8**[c]	−212.01	2.33	1.59	1.92
cis-**8**[b]	−183.65	2.33	1.53	1.84
cis-**8**[c]	−187.31	2.37	1.20	1.46

[a] Values of ^1H and ^{19}F chemical shifts are, respectively, referred to external TMS and $CFCl_3$. [b] Major diastereoisomer. [c] Minor diastereoisomer.

In the first step, identification of the H_a, H_b and H_c proton resonances in the ^1H NMR spectrum of each sample was achieved by using a combination of two-dimensional NMR experiments: ^1H–^1H COSY[18] and ^1H–^{13}C HMQC.[19] In a second step, cross peak connectivities observed in the ^1H–^{19}F hetero-COSY[20] spectrum allowed us to associate these protons, previously identified, with the corresponding diastereoisomers. The chemical shift values of protons of the cyclopropane and fluorine resonances at 298 K are summarized in Table 3.

Identification of the *trans* or *cis* stereoisomers was deduced from the analysis of 2D ^1H–^{19}F HOESY[21] spectra. The ^1H–^{19}F HOESY spectra of cyclopropylphosphonamides **8** (Fig. 1) exhibited an interesting set of cross peaks between the fluorine and the protons H_a, H_b, and H_c. For the *trans*-**8** stereoisomer (Fig. 1A), a strong correlation was observed between the fluorine and proton H_c, indicating that this proton is spatially close to the fluorine, while for the *cis*-**8** stereoisomer (Fig. 1b) the correlation between the fluorine and protons H_a and H_b were much stronger than with H_c. The first type of connectivity is encountered in *trans* stereoisomers, while the other two characterize *cis* stereoisomers.

In conclusion, we have described our first attempts at the asymmetric electrosynthesis of α-fluorinated cyclopropylphosphonamides using chiral dibromofluoromethylphosphonamides. The influence of different parameters (solvent, temperature, nature of the chiral inductor) on the diastereoselectivity during the electrochemical process is under study within our laboratory and will be reported in due course.

Experimental

General

Solvents were purified by conventional methods prior to use. *N*,*N*-Dimethylformamide was purified by distillation under reduced pressure on BaO. The cathodes, purchased from Le Carbone Lorraine, were carbon-felt plates (45 × 35 mm, depth: 5 mm, specific area: 0.3 $m^2\ g^{-1}$). The magnesium anodes, purchased from Prolabo, were rods (diameter: 15 mm). TLC was performed on Merck 60F-250 silica gel plates and column chromatography over silica gel SI 60 (230–240 mesh). Mps were taken on a Kofler apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba EA 1100 analyser. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and are reported in units of 10^{-1} deg $cm^2\ g^{-1}$. NMR spectra were recorded on a Bruker DXP 300 spectrometer operating at 300 MHz for proton, 75.4 MHz for carbon, 121.5 MHz for phosphorus and 282 MHz for fluorine. All 2D NMR spectra were collected on a Bruker Advance DMX 600 spectrometer. NMR spectra were obtained using a 5 mm Bruker triple resonance $^{19}F/^{13}C/^{1}H$ probe with channels pretuned to the ^{19}F (564.68 MHz), ^{13}C (150.90 MHz) and ^{1}H (600.123 MHz) frequencies. This probe is equipped with pulsed-field (*z*) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for ^{1}H and ^{13}C nuclei, to H_3PO_4 for ^{31}P nuclei and to $CFCl_3$ for ^{19}F nuclei; coupling constants (*J*) are given in hertz; coupling multiplicities are reported using conventional abbreviations. All the C_2-symmetric diamines **3a**–**e** were prepared by literature procedures (refs. 9*a*–*c*).

Synthesis of dibromofluoromethylphosphonic dichloride 5

An excess of thionyl chloride (52.3 cm^3, 0.716 mol, 10.3 eq.) was added dropwise to a round-bottom flask containing diisopropyl dibromofluoromethylphosphonate (24.8 g, 0.696 mol, 1 eq.) and pyridine (0.85 cm^3). The reaction mixture was protected from moisture and refluxed for 3 days. Thionyl chloride was removed by fractional distillation and the crude product **5** was directly used in the next step. Orange oil (quantitative yield, evaluated by ^{31}P NMR spectrospcopy); δ_P 26.7 (d, *J* 107.8); δ_F −75.3 (d, *J* 107.8); δ_C 89.7 (dd, *J* 334.2, 164.6).

Typical procedure for the synthesis of dibromofluoromethylphosphonamides 3

To a solution of diamine **4a**–**e** (1 eq.) in toluene (50 cm^3) was added triethylamine (2 eq.) and the mixture was stirred at 25 °C. A solution of dibromofluoromethylphosphonic dichloride **5** (1 eq.) in toluene (50 cm^3) was added dropwise over a period of 30 min, and the reaction mixture was stirred for two hours (monitored by ^{31}P NMR spectroscopy). The resulting precipitate was filtered over a Celite pad and washed with ethyl acetate. The solvent was evaporated and the residue was purified by silica gel chromatography to give the desired dibromofluorophosphonamide **3a**–**e**.

Dibromofluoromethylphosphonamide 3a. Pale yellow solid, mp 133 °C, purified by chromatography over silica gel and elution with dichloromethane (R_f = 0.2); $[\alpha]_D^{20}$ = −62 (*c* = 0.67, $CHCl_3$) (Found: C, 47.57; H, 4.56; N, 5.28. $C_{21}H_{24}Br_2FN_2OP$ requires C, 47.27; H, 4.57; N, 5.16); δ_P 23.1 (d, *J* 67.2); δ_F −68.5 (d, *J* 67.2); δ_H 0.84 (m, 1H, CH_2CH_2CHN), 1.04 (m, 2H, CH_2CH_2CHN + 1H, CH_2CH_2CHN), 1.56 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN), 2.75 (m, 1H, CH_2CH_2CHN), 3.30 (m, 1H, CH_2CH_2CHN), 4.1 (dd, *J* 16.2 and *J* 7.7, 1H, CH_2Ph), 4.3 (dd, *J* 16.2 and *J* 4.6, 1H, CH_2Ph), 4.6 (dd, *J* 14.9 and *J* 14.9, 1H, CH_2Ph), 4.8 (dd, *J* 16.2 and *J* 9.2, 1H, CH_2Ph), 7.25–7.45 (m, 10H, *H*arom.); δ_C 23.0 (s, CH_2CH_2CHN), 23.2 (s, CH_2CH_2CHN), 28.4 (d, *J* 2.2, CH_2CH_2CHN), 28.5 (d, *J* 4.7, CH_2CH_2CHN), 45.7 (d, *J* 4.6, CH_2Ph), 48.4 (d, *J* 2.4, CH_2Ph), 65.7 (dd, *J* 9.2 and *J* 1.1, CH_2CH_2CHN), 63.7 (d, *J* 7.7, CH_2CH_2CHN), 92.8 (dd, *J* 147.3 and *J* 339, O=P-*C*-F), 126.18, 126.2, 126.3, 126.8, 127.3, 127.4 (6s, *C*arom.), 136.5 (d, *J* 5.7, C_{ipso}), 138.3 (d, *J* 4,3, C_{ipso}).

Dibromofluoromethylphosphonamide 3b. Pale yellow solid, mp 84 °C, purified by chromatography over silica gel and elution with dichloromethane–methanol (98 : 2) (R_f = 0.5); $[\alpha]_D^{20}$ = −46 (*c* = 0.56, $CHCl_3$) (Found: C, 28.77; H, 4.35; N, 7.56. $C_9H_{16}Br_2FN_2OP$ requires C, 28.60; H, 4.27; N, 7.41); δ_P 24.2 (d, *J* 67.9); δ_F −69.4 (d, *J* 67.9); δ_H 1.2–1.3 (m, 2H, CH_2CH_2-CHN + 2H, CH_2CH_2CHN), 1.8–2.0 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN), 2.72–2.75 (2d, *J* 7.8, 6H, CH_3 + m, 1H, CH_2CH_2CHN), 3.0 (m, 1H, CH_2CH_2CHN); δ_C 24.6 (d, *J* 1.0, CH_2CH_2CHN), 24.7 (d, *J* 1.1, CH_2CH_2CHN), 28.2 (d, *J* 7.4, CH_2CH_2CHN), 28.7 (d, *J* 9.5, CH_2CH_2CHN), 29.1 (d, *J* 4.0, N-CH_3), 31.7 (d, *J* 1.2, N-CH_3), 63.6 (dd, *J* 8.9 and *J* 1.8, CH_2CH_2CHN), 66.0 (d, *J* 7.0, CH_2CH_2CHN), 93.6 (dd, *J* 144.3 and *J* 339, O=P-*C*-F).

Dibromofluoromethylphosphonamide 3c. White solid, mp 112 °C, purified by chromatography over silica gel and elution with cyclohexane–diethyl ether (90 : 10) (R_f = 0.2); $[\alpha]_D^{20}$ = −51 (*c* = 0.35, $CHCl_3$) (Found: C, 41.92; H, 6.75; N, 5.82. $C_{17}H_{32}Br_2FN_2OP$ requires C, 41.65; H, 6.58; N, 5.71); δ_P 21.2 (d, *J* 61.6); δ_F −62.8 (d, *J* 61.6); δ_H 0.9, 1.0 (2s, 18H, $C(CH_3)_3$), 1.26 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN), 1.8 (m, 2H, CH_2CH_2CHN), 1.93 (m, 1H, CH_2CH_2CHN), 2.16 (m, 1H, CH_2CH_2CHN), 2.48 (m, 1H, $NCH_2C(CH_3)_3$), 2.87 (m, 1H, $NCH_2C(CH_3)_3$), 3.2 (m, 1H, $NCH_2C(CH_3)_3$ + 2H CH_2CH_2-CHN), 3.45 (m, 1H, $NCH_2C(CH_3)_3$); δ_C 24.7 (d, *J* 1.4, CH_2CH_2-CHN), 25.2 (s, CH_2CH_2CHN), 28.6 (d, *J* 6.8, CH_2CH_2CHN), 28.7 (s, $C(CH_3)_3$), 29.7 (s, $C(CH_3)_3$), 31.0 (d, *J* 8.3, CH_2CH_2-CHN), 32.2 (d, *J* 0.96, $C(CH_3)_3$), 33.9 (s, $C(CH_3)_3$), 54.0 (d, *J* 3.3, $NCH_2C(CH_3)_3$), 54.5 (dd, *J* 2.8 and *J* 0.9, NCH_2-$C(CH_3)_3$), 62.4 (d, *J* 9.9, CH_2CH_2CHN), 65.9 (dd, *J* 10.4 and *J* 3.2, CH_2CH_2CHN), 96.2 (dd, *J* 126.0 and *J* 342.7, O=P-*C*-F).

Dibromofluoromethylphosphonamide 3d. White solid, mp 122 °C, purified by chromatography over silica gel and elution with cyclohexane–ethyl acetate (70 : 30) (R_f = 0.6); $[\alpha]_D^{20}$ = −43 (*c* = 0.59, $CHCl_3$) (Found: C, 43.72; H, 6.89; N, 5.54. $C_{19}H_{36}Br_2FN_2OP$ requires C, 44.03; H, 7.00; N, 5.40); δ_P 22.7 (d, *J* 68.4); δ_F −69.2 (d, *J* 68.4); δ_H 0.9 (s, 18H, $C(CH_3)_3$), 1.33 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN), 1.9 (m, 4H, NCH_2-$CH_2C(CH_3)_3$), 1.84 (m, 2H, CH_2CH_2CHN), 2.05 (m, 2H, CH_2CH_2CHN), 3.0 (m, 2H, CH_2CH_2CHN), 3.1–3.4 (m, 4H, $NCH_2CH_2C(CH_3)_3$); δ_C 24.6 (s, CH_2CH_2CHN), 24.8 (s, CH_2CH_2CHN), 28.8 (d, *J* 6.8, CH_2CH_2CHN), 29.6 (d, *J* 6.6, CH_2CH_2CHN), 29.66 (s, $C(CH_3)_3$), 29.67 (s, $C(CH_3)_3$), 38.7 (d, *J* 4.5, CH_2-$C(CH_3)_3$), 41.4 (d, *J* 2.0, CH_2-$C(CH_3)_3$), 42.8 (s, N-$CH_2CH_2C(CH_3)_3$), 43.1 (d, *J* 3.4, N-$CH_2CH_2C(CH_3)_3$), 62.3 (d, *J* 9.65, CH_2CH_2CHN), 64.4 (d, *J* 8.2, CH_2CH_2CHN), 95.5 (dd, *J* 145.9 and *J* 339.5, O=P-*C*-F).

Dibromofluoromethylphosphonamide 3e. Brown oil, purified by chromatography over silica gel and elution with dichloromethane–methanol (98 : 2) (R_f = 0.2); $[\alpha]_D^{20}$ = −37 (*c* = 0.68, $CHCl_3$) (Found: C, 33.55; H, 5.22; N, 6.23. $C_{13}H_{24}Br_2FN_2O_3P$ requires C, 33.50; H, 5.19; N, 6.02); δ_P 22.7 (d, *J* 69.3); δ_F −69.1 (d, *J* 69.3); δ_H 1.25 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2-CHN), 1.8 (m, 2H, CH_2CH_2CHN), 2.1 (m, 2H, CH_2CH_2CHN), 2.9 (m, 1H, CH_2CH_2CHN), 3.1–3.6 (m, 15 H: 1H, CH_2CH_2-CHN + 6H, OCH_3 (3.3, s) + 4H, CH_2OCH_3 + 4H, NCH_2-CH_2OCH_3); δ_C 24.6 (s, CH_2CH_2CHN), 24.7 (s, CH_2CH_2CHN), 28.8 (d, *J* 6.6, CH_2CH_2CHN), 29.3 (d, *J* 9.4, CH_2CH_2CHN), 41.4 (d, *J* 4.7, $NCH_2CH_2OCH_3$), 43.9 (s, $NCH_2CH_2OCH_3$), 59.2 (s, $NCH_2CH_2OCH_3$), 59.3 (s, $NCH_2CH_2OCH_3$), 63.5 (d, *J* 9.2, CH_2CH_2CHN), 64.9 (d, *J* 8.1, CH_2CH_2CHN), 72.3 (s, $NCH_2CH_2OCH_3$), 72.6 (d, *J* 3.8, $NCH_2CH_2OCH_3$), 95.0 (dd, *J* 146.6 and *J* 338.6, O=P-*C*-F).

General procedure for the electrosynthesis of α-fluorinated cyclopropylphosphonamides 7–12

In a purged one-compartment cell, equipped with a carbon-felt cathode ($S = 16$ cm^2), a magnesium rod as anode and a magnetic stirrer, a solution of **3** (4 mmol, 1 eq.) and Michael acceptor (8 mmol, 2 eq.) in DMF (35 cm^3) containing Et_4NBr (0.02 mol dm^{-3}) was introduced. A 100 mA constant current was applied. The electrolysis was continued until total consumption of **3** was achieved (monitored by ^{31}P NMR spectroscopy). The reaction mixture was poured into THF (100 cm^3), then basified with a solution of saturated aqueous sodium hydrogen carbonate (500 cm^3), and extracted with ether (3 × 100 cm^3). The organic layers were washed with $NaHCO_3$ (2 × 200 cm^3) and dried. The solvents were evaporated *in vacuo* to give **7**–**12**.

α-Fluorinated cyclopropylphosphonamides 7. Obtained as an inseparable mixture of four diastereoisomers. Pale yellow oil. Purified by chromatography over silica gel and elution with cyclohexane–ethyl acetate (70 : 30) ($R_f = 0.3$). *trans*-**7**: δ_P 32 (d, *J* 64.9, major), 31.9 (d, *J* 64.9, minor); δ_F −211.5 (d, *J* 64.9, major), −211.1 (d, *J* 64.9, minor). *cis*-**7**: δ_P 32.5 (d, *J* 64.9, major), 30.5 (d, *J* 64.9, minor); δ_F −188.5 (d, *J* 64.9, major), −185.9 (d, *J* 64.9, minor).

α-Fluorinated cyclopropylphosphonamides 8. Obtained as a mixture of four diastereoisomers. Yellow oil. Purified by chromatography over silica gel and elution with cyclohexane–diethylether (40 : 60). *trans*-**8**: $R_f = 0.3$; δ_P 31.6 (d, *J* 64.9, minor), 32.9 (d, *J* 67.8, major); δ_F −212.6 (d, *J* 67.8, major), −212.0 (d, *J* 64.9, minor); δ_H 1.1 (m, 1H, CH_2CH_2CHN), 1.2 (m, 2H, CH_2CH_2CHN + 1H, CH_2CH_2CHN + 1H, H_b, major), 1.35 (s, 9H, $C(CH_3)_3$, minor), 1.5 (2s, 9H, $C(CH_3)_3$, major), 1.65 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN + 1H, H_b, minor + 1H, H_c, major), 1.90 (m, 1H, H_c, minor), 2.3 (m, 1H, H_a, minor), 2.4 (m, 1H, H_a, major), 3.1 (m, 2H, CH_2CH_2CHN), 4.0, 4.1, 4.45, 4.6, 4.75 (5m, 4H, CH_2Ph), 7.35 (m, 10H, *H*arom.); δ_C 14.2 (d, *J* 10.3, C^3, major), 15.3 (d, *J* 10.4, C^3, minor), 24.4 (m, CH_2CH_2CHN), 24.6 (d, *J* 9.6, C^2, minor), 25.6 (d, *J* 10.3, C^2, major), 27.1, 28.1, 28.3 (3s, $O=COC(CH_3)_3$), 29.8 (m, CH_2CH_2CHN), 46.6, 46.9 (2d, *J* 5.3, CH_2Ph), 47.3, 47.6 (2s, CH_2Ph), 64.1, 64.7, 65.4 (3d, *J* 7.2, CH_2CH_2CHN), 75.5 (dd, *J* 241.3 and 185.2, C^1, major), 75.7 (dd, *J* 241.3 and 185.2, C^1, minor), 81.7 (s, $O=COC(CH_3)_3$, minor), 81.8 (s, $O=COC(CH_3)_3$, major), 127.2, 127.3, 127.4, 127.5, 127.6, 127.9, 128.5, 128.6 (8s, *C*arom.), 139.1, 139.3, 139.7, 140.0 (4d, *J* 5.7 and *J* 5.0, C_{ipso}), 166.5 (d, *J* 2.6, $O=COC(CH_3)_3$). *cis*-**8**: $R_f = 0.25$; δ_P 30.6 (d, *J* 64.9, minor), 33.3 (d, *J* 67.8, major); δ_F −187.4 (d, *J* 67.8, major), −183.7 (d, *J* 64.9, minor); δ_H 0.90–1.23 (m, 2H, CH_2CH_2CHN + 1H, CH_2CH_2CHN + 1H, H_b, major), 1.25–1.35 (2s, 9H, $C(CH_3)_3$), 1.47 (1H, 1.65, H_c, major), 1.52–1.75 (m, 2H, CH_2CH_2CHN + 2H, CH_2CH_2CHN + 1H, H_b, minor), 1.84 (m, 1H, H_c, minor), 2.33 (m, 1H, H_a, minor), 2.38 (m, 1H, H_a, major), 3.1 (m, 2H, CH_2CH_2CHN), 3.97, 4.05, 4.27, 4.6, 5.04 (5m, 4H, CH_2Ph), 7.35 (m, 10H, *H*arom.); δ_C 14.25 (d, *J* 9.5, C^3, major), 15.6 (d, *J* 9.1, C^3, minor), 24.6 (s, CH_2CH_2CHN), 27.8 (d, *J* 11.3, C^2, minor), 28.1 (m, $O=COC(CH_3)_3$ + C^2, major), 28.4 (s, $O=COC(CH_3)_3$), 30.1 (m, CH_2CH_2CHN), 47.1 (m, CH_2Ph), 63.8 (d, *J* 7.2, CH_2CH_2CHN), 64.6 (d, *J* 7.2, CH_2CH_2CHN), 65.2 (d, *J* 7.8, CH_2CH_2CHN), 65.9 (d, *J* 6.6, CH_2CH_2CHN), 74.6 (dd, *J* 241.3 and 185.2, C^1), 74.8 (dd, *J* 241.3 and 185.2, C^1), 82.0 (s, $O=COC(CH_3)_3$, minor), 82.2 (s, $O=COC(CH_3)_3$, major), 127.3, 127.4, 127.6, 127.8, 127.9, 128.1, 128.3 (7s, *C*arom.), 139.6 (d, *J* 5.1, C_{ipso}), 139.8 (d, *J* 4.6, C_{ipso}), 140.1 (d, *J* 5.1, C_{ipso}), 140.6 (d, *J* 5.9, C_{ipso}), 166.2, 166.5 (2s, $O=COC(CH_3)_3$).

α-Fluorinated cyclopropylphosphonamides 9. Obtained as a mixture of four diastereoisomers. Yellow oil. Purified by chromatography over silica gel and elution with cyclohexane–ethyl acetate (40 : 60). *trans*-**9**: $R_f = 0.16$; δ_P 34.4 (d, *J* 67.8, major), 33.5 (d, *J* 64.9, minor); δ_F −213.8 (d, *J* 67.8, major), −213.5 (d, *J* 64.9, minor). *cis*-**9**: $R_f = 0.22$; δ_P 35.0 (d, *J* 67.8, major), 33.1 (d, *J* 64.9, minor); δ_F −188.6 (d, *J* 67.8, major), −186.3 (d, *J* 64.9, minor).

α-Fluorinated cyclopropylphosphonamides 10. Obtained as a mixture of four diastereoisomers. Yellow oil. Unpurified product. *trans*-**10**: δ_F −214.3 (d, *J* 67.8, major), −214 (d, *J* 64.9, minor). *cis*-**10**: δ_F −185.6 (d, *J* 67.8, major).

α-Fluorinated cyclopropylphosphonamides 11. Obtained as a mixture of four diastereoisomers. Yellow oil. Unpurified product. *trans*-**11**: δ_F −212.9 (d, *J* 64.9, major), −211.3 (d, *J* 64.9, minor). *cis*-**11**: δ_F −184.1 (d, *J* 64.9, major), −184.3 (d, *J* 64.9, minor).

α-Fluorinated cyclopropylphosphonamides 12. Obtained as a mixture of four diastereoisomers. Yellow oil. Purified by chromatography over silica gel and elution with cyclohexane–ethyl acetate (40 : 60). *trans*-**12**: $R_f = 0.26$; δ_P 30.1 (d, *J* 64.9, minor), 31.0 (d, *J* 67.8, major); δ_F −212.4 (d, *J* 67.8, major), −212.2 (d, *J* 64.9, minor). *cis*-**12**: $R_f = 0.20$; δ_P 29.2 (d, *J* 64.9, minor), 30.6 (d, *J* 67.8, major); δ_F −185.3 (d, *J* 67.8, major), −183.3 (d, *J* 64.9, minor).

References

1 J. Salaün and M. S. Baird, *Curr. Med. Chem.*, 1995, **2**, 511.
2 H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165.
3 *Organofluorine Compounds in Medicinal and Biomedical Applications*, eds. R. Filler, Y. Kobayashi and L. M. Yagupolski, Elsevier, Amsterdam, 1993.
4 *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, ed. V. A. Soloshonok, Wiley, New York, 1991.
5 R. Engel, *Chem. Rev.*, 1977, **77**, 349.
6 (*a*) G. M. Blackburn and D. E. Kent, *J. Chem. Soc.*, *Perkin Trans. 1*, 1986, 913; (*b*) G. M. Blackburn and M. J. Parrat, *J. Chem. Soc.*, *Perkin Trans. 1*, 1986, 1425; (*c*) G. M. Blackburn, *Chem. Ind.* (*London*), 1981, 184.
7 S. Goumain, P. Jubault, C. Feasson and J.-C. Quirion, *Tetrahedron Lett.*, 1999, **40**, 8099.
8 D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, 1977, **10**, 329.
9 (*a*) S. Hanessian, D. Andreotti and A. Gomtsyan *J. Am. Chem. Soc.*, 1995, **117**, 10393; (*b*) S. Hanessian, L.-D. Cantin, S. Roy, D. Andreotti and A. Gomtsyan, *Tetrahedron Lett.*, 1997, **38**, 1103; (*c*) for a general review, see Y. L. Bennami and S. Hanessian, *Chem. Rev.*, 1997, **97**, 3161.
10 S. Hanessian, Y. L. Bennami and Y. Hervé, *Synlett*, 1993, 35.
11 S. Hanessian, Y. L. Bennami and D. Delorme, *Tetrahedron. Lett.*, 1999, **40**, 8099.
12 M. Kinnear and E. A. Perren, *J. Chem. Soc.*, 1952, 3437.
13 C. Patois, S. Berté-Verrando and P. Savignac, *Bull. Soc. Chim. Fr.*, 1993, **130**, 485.
14 L. Maier, *Phosphorus*, *Sulfur Silicon Relat. Elem.*, 1990, **47**, 465.
15 D. E. Bergstrom and P. W. Shum, *J. Org. Chem.*, 1988, **53**, 3953.
16 J. F. Larrow and E. N. Jacobsen, *J. Org. Chem.*, 1994, **59**, 1939.
17 P. Jubault, S. Goumain, C. Feasson and N. Collignon, *Tetrahedron Lett.*, 1998, **54**, 14767.
18 K. Nagayama, A. Kumar, K. Wüthrich and R. R. Ernest, *J. Magn. Reson.*, 1980, **40**, 321.
19 A. Bax, R. G. Griffey and B. L. Hawkins, *J. Am. Chem. Soc.*, 1983, **105**, 7188.
20 J. P. Macheteau, H. Oulyadi, B. Van Hemelryck, M. Bourdoneau and D. Davoust, *J. Fluorine Chem.*, 2000, **104**, 149.
21 C. Yu and G. Levy, *J. Am. Chem. Soc.*, 1984, **106**, 6533.