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A New and Efficient Electrosynthesis of Polysubstituted Cyclopropylphosphonates, Using Electrochemically Activated Magnesium

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Abstract : The diastereoselective electrosynthesis of polysubstituted α-chloro cyclopropylphosphonates is efficiently achieved by electroreduction of diisopropropyl trichloromethylphosphonate in the presence of Michael acceptors, in a one-compartment cell equipped with a magnesium sacrificial anode.

INTRODUCTION

Many phosphonate derivatives have found applications in the areas of medicinal[1] and agricultural chemistry,[2] owing to their biological activity.[3] On the other hand, the cyclopropane ring is often encountered in natural occuring compounds having interesting biological properties.[4,5] 1-Amino-1-cyclopropanecarboxylic acid (ACC), which is the biosynthetic precursor of ethylene in plants,[6] and esters of *trans*-chrysanthemic acid, an important class of natural insecticides,[7] are two representative and popular examples of these bioactive cyclopropane-containing compounds. Therefore, it is not surprising that cyclopropylphosphonate derivatives have focused interest of chemists, who have proposed several methods for their synthesis. Three main synthetic ways have been investigated, for this purpose :

- the phosphonylation of halocyclopropanes, either by Arbuzov or Michaelis-Becker reactions, but these methods give low yields of phosphonate derivatives.[8,9]

- the chemical,[10,11] thermal,[12] or photochemical[13,14] decomposition of α-diazophosphonates in the presence of alkenes, and conversely, the reaction of alkenylphosphonates with diazo compounds.[15,16] These methods generally afforded high yields, but the instability and toxicity of diazo derivatives make them unsatisfactory.

- the use of α-phosphonylated carbanions or sulfur ylides. In the first case, the carbanion may be cycloalkylated with 1,2-*bis*-electrophilic ethane,[17-19] or added to Michael acceptors leading to cyclopropane ring formation after intramolecular expulsion of a suitable leaving group.[20-23] In the second approach, the cyclopropanation of an electron deficient alkenylphosphonate was achieved by using either the dimethylsulfonium methylide,[24] or a nitroalkane in the presence of alumina-supported potassium fluoride.[25]

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We have recently tested, within this laboratory, the reliability of these methods in preparing numerous α-functional cyclopropylphosphonates by the cycloalkylation route,[26] as well as some α-silylated, α-chlorinated cyclopropylphosphonates, by the tandem Michael addition-cycloalkylation sequence.[27]

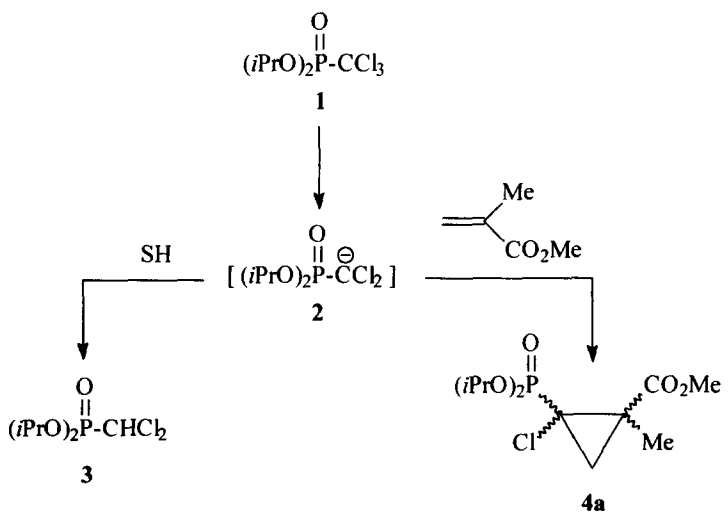
Electrochemical techniques are widely used for promoting all kinds of cyclization processes,[28-30] however, to the best of our knowledge, no example of electrochemical synthesis of substituted cyclopropyl phosphonates have yet been published, although other functional cyclopropanes were prepared by electroreduction of dihalomalonates[31] or of *gem*-polyhalo compounds[32] in the presence of Michael acceptors. In recent papers,[33-35] we described a phenomenon called "electrochemical activation of magnesium", illustrated by improved electrosyntheses of *gem*-difluoroalkenes, of diisopropyl 1,1-dichloromethyl phosphonates and of diisopropyl cycloalkylphosphonates.

We decided to extend the scope of this phenomenon and we now report an efficient synthesis of diisopropyl α-substituted cyclopropylphosphonates from the readily available diisopropyl trichloromethylphosphonate **1**.[36]

RESULTS AND DISCUSSION

1. *Preliminary study: optimization of the electrosynthesis of diisopropyl 1-chloro-2-methoxycarbonyl-2-methylcyclopropylphosphonate* **4a** :

Electrochemical reduction of **1** in DMF, between a carbon felt cathode and a sacrificial anode (Zn, Al or Mg) in a one-compartment cell, in the presence of 1.2 equivalent of methyl methacrylate (Scheme 1), afforded phosphonate **4a**, the formation of which being monitored by ^{31}P NMR spectroscopy (Table 1).



Scheme 1

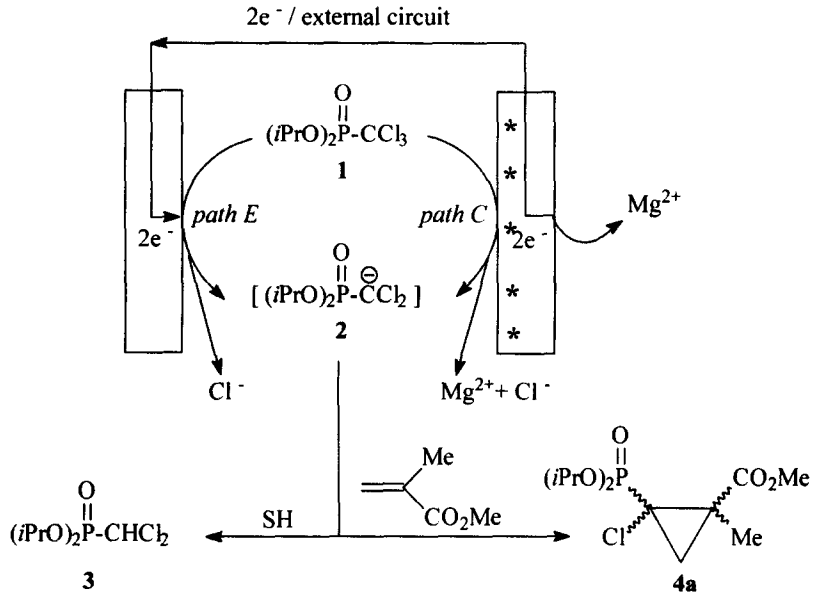
Table 1. Electrosynthesis of **1**, in the presence of methyl methacrylate (1.2 equiv.) in DMF (40 mL) containing Bu_4NBF_4 (0.02 mol. L^{-1}) ; I = 150 mA.

Entry	Anode	Evaluated yield (%)[c] in **4a**	Isolated yield (%) in **4a**[d]	Diastereomeric excess (%)[f]	Q ($F.mol^{-1}$)[g]	% of **3** in the crude mixture[c]
1	Al	75	45	34	2	10[h]
2	Zn	44	-[e]	62	1.7	22[h]
3	Mg[a]	82	70	66	1	10[h]
4	Mg[b]	97	81	82	0.8	3

[a] In a one-compartment cell thermostated at 14°C.
[b] In a non-thermostated one-compartment cell ; the temperature was autoregulated near to 35°C during the overall electrolysis.
[c] Determined on the crude mixture by ^{31}P NMR integration measurements, as the percentage contribution of any particular peak to the summation of all peak heights of the spectrum.
[d] Product characterized by ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopies.
[e] Non isolated.
[f] Determined on the crude product by ^{31}P NMR integration measurements.
[g] Electricity quantity measured at the end point of the reaction (characterized by the disappearance of the signal of **1**, in ^{31}P NMR spectroscopy).
[h] Besides **4a** and **3**, some other unidentified phosphorus derivatives were detected in these mixtures.

As shown in Table 1, the nature of the anode has a significant effect, not only on the yield in cyclopropylphosphonate **4a**, but also on the diastereoselectivity of the reaction, and on the length of the electrolysis. When carried out with an aluminium anode (Table 1, entry 1), the electrolysis of phosphonate **1** afforded cyclopropylphosphonate **4a** as expected, in moderate yield and with low diastereoselectivity. Moreover, the length of the electrolysis was in agreement with a classical bi-electronic reduction process, consuming two Faraday per mole of phosphonate **1**. Using a zinc anode (entry 2), a lower electrolysis yield was observed and **4a** was not isolated in pure form from the crude mixture. Here too, electrochemical reduction consumed nearly 2 F per mole of **1**, but we noted an increase of the diastereoselectivity of the reaction. With a magnesium anode, the previously described activation phenomenon[33-35] occurred again, with the following beneficial consequenses. First, a decrease of the quantity of electricity consumed because of a lowering in the length of electrolysis (Table 1, entries 3 and 4), leading to a very high faradaic yield (200 and 300 %, respectively). Secondly, a remarkable enhancement of the yield of cyclopropylphosphonate **4a**, which was obtained in a good diastereomeric ratio by using the non-thermostated cell (entry 4). In brief, this preliminary study unambiguously proved the pre-eminence of sacrificial magnesium anode, in connection with the electrochemical magnesium activation phenomenon. This activation process allows two complementary ways of reduction to take place simultaneously (Scheme 2).

Following path *E* (*Electrochemical*), phosphonate **1** is reduced at the cathode by a classical bi-electronic electrochemical reduction process,[37] but following path *C* (*Chemical*), phosphonate **1** undergoes direct reduction at the anode, by the magnesium rod activated on its surface through the anodic process (activated sites are noted * in Scheme 2).



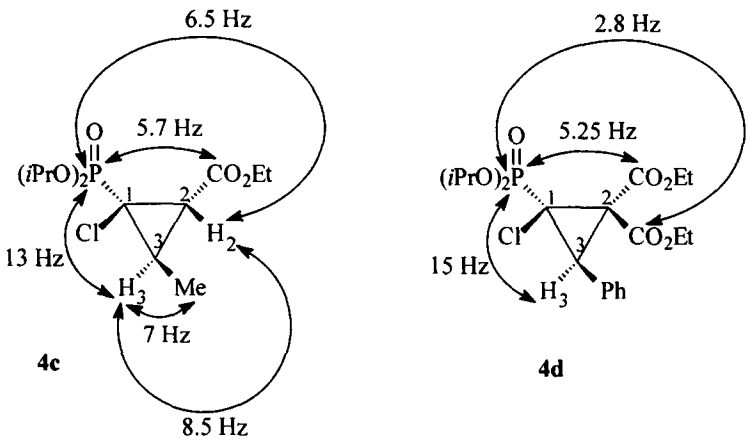
Scheme 2

2. Application to the synthesis of variously substituted α-chloro cyclopropylphosphonates

The experimental conditions selected above have been used for the electrosynthesis of substituted diisopropyl α-chlorocyclopropylphosphonates **4** from phosphonate **1** and various Michael acceptors (Table 2). In most cases (entries 1 to 5), the electrochemical cyclopropanation reaction was nearly quantitative, within about 3 h, affording phosphonates **4** in very good yield. When ethyl cinnamate was used as electrophile (entry 6), the result was more deceptive : the cyclopropanation reaction was incomplete, and at the end of the reaction, we obtained a mixture of diisopropyl α-chlorocyclopropylphosphonate **4f** (~ 44%), and diisopropyl α,α-dichloromethylphosphonate **3** (~ 66%) [^{31}P NMR ($CDCl_3$), δ = 7.2] resulting from the protonation of carbanion **2**.

Moreover, except in one case (entry 5), the electrochemical cyclopropanation reaction occurred with very good diastereoselectivity. The relative configuration of substituted cyclopropylphosphonates **4** was elucidated by measuring the 3-bond proton-phosphorus and carbon-phosphorus coupling constants. As example, phosphonates **4c** and **4d**, which were obtained each as only one diastereomer, served as model compounds for illustrating these assignements (Scheme 3).

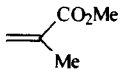
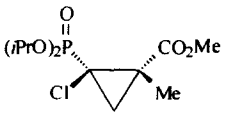
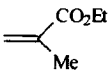
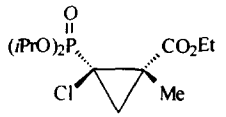
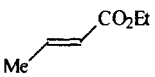
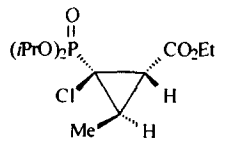
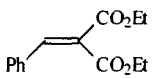
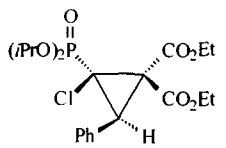
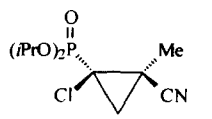
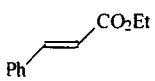
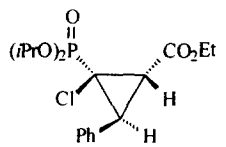
From the ^{1}H NMR spectrum of **4d** (see experimental part), the *cis*-relationship between the phosphorus atom and proton H_3 was supported by a measured $^3J_{PH3}$ coupling constant of 15 Hz (lit.[13, 38], $^3J_{PHcis}$: 14.5 to 20 Hz), and therefore established the relative configuration of this diastereomer. Moreover, in the $^{13}C\{^1H\}$ NMR spectrum of **4d**, one ethyl ester carbonyl carbon exhibited a $^3J_{CP}$ coupling constant of 5.25 Hz, characteristic of a *cis*-relationship between this carbon and the phosphorus atom ; the second ester carbon was coupled with phosphorus by 2.8 Hz, suggesting a *trans*-orientation between these nuclei. These values are significantly lower than those deduced from the Karplus-type relationship for the vicinal $^3J_{PC}$ coupling in phosphonates (namely ~13.5 Hz for a 0° dihedral angle and ~5 Hz for a 120° angle),[39] but the presence of an electronegative atom in the α position of the phosphorus (here, the chlorine atom) is expected to decrease the magnitude of $^3J_{PC}$.[39] In the case of **4c**, ^{1}H NMR resonance of the proton H_3 appeared as a doublet doublet quartet, revealing coupling constants of 13 Hz ($^3J_{H3P}$), 8.5 Hz ($^3J_{H3H2}$)[40] and 7 Hz ($^3J_{H3Me}$), while H_2 signal was a doublet doublet ($^3J_{H2H3}$ = 8.5 Hz and $^3J_{H2P}$ = 6.5 Hz). The above vicinal coupling constants are in agreement with a *cis*-orientation between P and H_3 and with a *trans*-orientation between P and H_2, and determine the relative configuration of the diastereomer. Finally, the measurement, in the $^{13}C\{^1H\}$ NMR spectrum of **4c**, of a $^3J_{CP}$ coupling constant of 5.7 Hz for the ethyl ester carbonyl carbon, confirmed the *cis*-relationship of this carbon with phosphorus.



Scheme 3

The above criteria have been used for determining the relative configuration of all α-chloro-cyclopropyl-phosphophonates **4** prepared, which presented a remarkable structural homogeneity (Table 2).

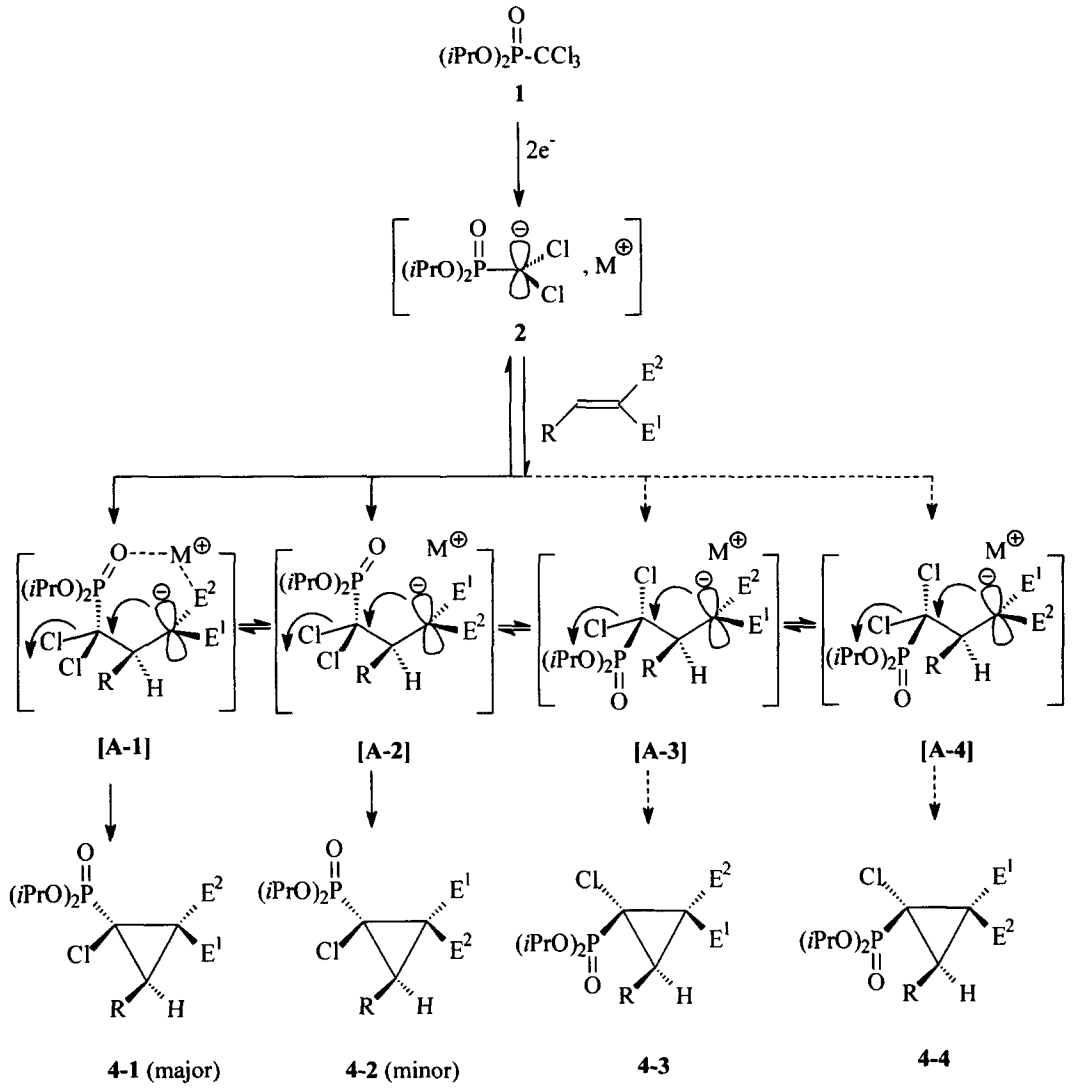
Table 2. Electrosynthesis of diisopropyl α-chlorocyclopropylphosphonates **4**

Entry	Alkene	Product	Yield (%)[a] [Evaluated yield (%)][b]	d.e. (%)[c]	Major Diastereomer[d]
1		**4a**	81 [97]	82	
2		**4b**	78 [97]	80	
3		**4c**	64 [93]	100	
4		**4d**	60 [96]	100	
5		**4e**	72 [93]	26	
6		**4f**	32 [44]	100	

[a] Yield of isolated, purified product.
[b] Determined by ^{31}P NMR spectroscopy on the crude product, at the end of the reaction.
[c] Diastereomeric excess, determined by ^{31}P NMR spectroscopy, on the crude product.
[d] Only one enantiomer of each diastereomer is represented.

Actually, for cyclopropylphosphonates prepared from unsaturated carboxylic esters, the predominant or exclusive diastereomer obtained is that in which the phosphonate and the carboxylate groups are *cis* to each other. Moreover, for those derived from β-substituted carboxylic esters (entries 3, 4, 6), the phosphonate group and the substituent (Me or Ph) have a *trans* relative orientation.

This preferred relative configuration might be tentatively explained by considering the mechanistic scheme usually accepted for such cyclopropanation process,[41] which involves a Michael addition followed by ring closure (Scheme 4).



Scheme 4

If we expect a possible equilibration of the initial adduct by free rotation about sigma bonds, four different conformational anions ([**A-1**] to [**A-4**]) might result from the addition of the electro-generated anion **2** to a β-substituted (R ≠ H) Michael acceptor having two different functional groups ($E^2 \neq E^1$). Subsequent intramolecular S_N2 cyclization of these anions leads to four possible diastereomeric cyclopropanes **4-1** to **4-4**.

The large predominance of diastereomer of type **4-1**, when E^2 is a carboxylate group, may be rationalized by the assumption that the preferred conformation of the initial adduct is one in which steric interactions between the bulky phosphonate and R groups are minimized (excluding **[A-3]** and **[A-4]**), and which also allows the phosphonyl and the carboxylate groups to act as a bidentate ligand for the metal cation. Anion **[A-1]** best fulfils these requirements and can provide a rationale for the stereochemical outcome observed in these syntheses.

Moreover, in the absence of a carboxylate group in the Michael acceptor, the intermediate carbanions **[A-1]** and **[A-2]**, which fullfil the steric requirements, are of comparable stability and gave a mixture of **4-1** and **4-2** in a low diastereomeric excess (entry 5, Table 2). On the other hand, diastereomers **4-3** and **4-4** were never observed in our experiments. Briefly, even in a polar solvent such as DMF, the *cis*-stabilization of the initial adduct by metal-chelation seems to be a reasonable hypothesis in order to explain the stereoselective formation of most cyclopropylphosphonates of type **4**, and therefore, it was not surprising that the diastereoselectivity of the reaction was markedly influenced by the nature of the metal of the anode, as noted in Table 1.[42]

CONCLUSION

In this work, we describe an efficient and stereoselective electrosynthesis of α-chloro polysubstituted cyclopropylphosphonates, from diisopropyl trichloromethylphosphonate and various Michael acceptors. The use of a magnesium sacrificial anode causes a substantial lowering of the length of electrolysis and leads to a high degree of diastereoselectivity, when unsaturated carboxylic esters were used as acceptors. Moreover, in comparison with the usual carbanionic way, the electrochemical method avoids the use of lithiated bases and low temperature conditions, what is a real advantage for large-scale syntheses.

EXPERIMENTAL SECTION

General : Gas chromatography (GC) was perfomed on a Varian 3300 chromatograph with a 2m SE 30 column. The NMR spectra were recorded in $CDCl_3$, on a Brucker AC-200 spectrometer; the chemical shift (δ) are expressed in ppm relative to tetramethylsilane for ^1H and ^{13}C and to H_3PO_4 for ^{31}P nucleus; the coupling constants (J) are given in Hz; conventional abbreviations are used. High resolution mass spectra (HRMS) were recorded on a Jeol AX 500 spectrometer, under chemical ionization at 200 eV. N,N-dimethylformamide (DMF) was dried on 4 A° molecular sieves.

Electrosynthesis of cyclopropylphosphonates 4. Typical procedure for the synthesis of 4a : In a one-compartment cell, equiped with a carbon felt cathode (S = 25 cm^2) and a magnesium rod as anode (immersion height 5 cm), a solution of diisopropyl trichloromethylphosphonate **1** (6.24 g, 22 mmol) and of methyl methacrylate (2.5 g, 25 mmol) in DMF (40 mL) containing Et_4NBr (0.02 $mol.L^{-1}$) was introduced.

A 150 mA constant current was applied. The complete formation of phosphonate **4a** was reached after 3h (monitored by ^{31}P NMR spectroscopy). The reaction mixture was poured in THF (80 mL), then made acidic by addition of 1N HCl (100 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with 1N HCl (2 x 50 mL) and dried. The solvents were evaporated in vacuo to give **4a**. Further purification by bulb-to-bulb distillation led to the pure diisopropyl cyclopropylphosphonate **4a**, obtained as a mixture of diastereomers **4a-1** and **4a-2** (in a 91:9 ratio). Oily product, $bp_{0.6}$ = 120 °C. HRMS required for $C_{12}H_{23}ClO_5P$ (MH^+) : 313.0972 (^{35}Cl) ; found : 313.0970 (^{35}Cl).

Diisopropyl 1-chloro-*c*-2-methoxycarbonyl-*t*-2-methylcyclopropyl-*r*-1-phosphonate 4a-1 (major diastereomer) : $^{31}P\{^1H\}$ NMR: 13.9; ^1H NMR: 1.0 [dd, 1H, $^2J_{HH}$ = $^3J_{HP}$(trans) = 6.9; *H*-cycle]; 1.2 (m, 12H, [*(CH3)2*CH-O]$_2$P); 1.4 (s, 3H, C*H3*-cycle); 2.0 [dd, 1H, $^2J_{HH}$ = 6.9, $^3J_{HP}$(cis) = 14; *H*-cycle]; 3.55 (s, 3H, CO_2CH_3); 4.6 (m, 2H, [$(CH_3)_2$C*H*-O]$_2$P); $^{13}C\{^1H\}$ NMR: 18.5 (s, *C*H$_3$-cycle); 23.6 (4d, $^3J_{CP}$ = 3.0; [*(CH3)2*CH-O]$_2$-P); 24.3 (d, $^2J_{CP}$ = 1.5, *C3*); 32.0 (s, *C2*); 41.8 (d, $^1J_{CP}$ = 205, *C1*); 52.0 (s, CO_2CH_3); 71.0 (2d, $^2J_{CP}$ = 6.5; [$(CH_3)_2$CH-O]$_2$P); 170.3 [d, $^3J_{CP}$(cis) = 5.5; *C*O_2CH_3].

Diisopropyl 1-chloro-*t*-2-methoxycarbonyl-*c*-2-methylcyclopropyl-*r*-1-phosphonate 4a-2 (minor diastereomer) : $^{31}P\{^1H\}$ NMR: 13.3; ^1H NMR: 1.2 (m, 13H, [*(CH3)2*CH-O]$_2$P + *H*-cycle); 1.5 (s, 3H, C*H3*-cycle); 2.2 [dd, 1H, $^2J_{HH}$ = 6.9; $^3J_{HP}$(cis) = 14; *H*-cycle]; 3.6 (s, 3H, CO_2CH_3); 4.8 (m, 2H, [$(CH_3)_2$C*H*-O]$_2$P); $^{13}C\{^1H\}$ NMR: 14.8 (s, *C*H$_3$-cycle); 15.8 (d, $^2J_{CP}$ = 3.3, *C3*); 23.6 (4d, $^3J_{CP}$ = 3.0; [*(CH3)2*CH-O]$_2$P); 33.5 (s, *C2*); 38.9 (d, $^1J_{CP}$ = 204, *C1*); 51.8 (s, CO_2CH_3); 71.0 (2d, $^2J_{CP}$ = 6.5; [$(CH_3)_2$*C*H-O]$_2$P); 169.5 [d, $^3J_{CP}$(trans) = 2.8; *C*O_2CH_3].

4b Was obtained as a mixture of diastereomers **4b-1** and **4b-2** (in a 90:10 ratio). Oily product, $bp_{0.4}$ = 115 °C; HRMS required for $C_{13}H_{25}ClO_5P$ (MH^+) : 327.1128 (^{35}Cl), found : 327.1148 (^{35}Cl).

Diisopropyl 1-chloro-*c*-2-ethoxycarbonyl-*t*-2-methylcyclopropyl-*r*-1-phosphonate 4b-1 (major diastereomer): $^{31}P\{^1H\}$ NMR: 13.6; ^1H NMR: 1.1 [dd, 1H, $^2J_{HH}$ = $^3J_{HP}$(trans) = 6.2; *H*-cycle]; 1.3 (t, 3H, $^3J_{HH}$ = 7; $CO_2CH_2CH_3$); 1.35 (m, 12H, [*(CH3)2*CH-O]$_2$P); 1.6 (s, 3H, C*H3*-cycle); 2.2 [dd, 1H, $^2J_{HH}$ = 6.2; $^3J_{HP}$(cis) = 14; *H*-cycle]; 4.2 (q, 2H, $CO_2CH_2CH_3$); 4.6 (m, 2H, [$(CH_3)_2$C*H*-O]$_2$P); $^{13}C\{^1H\}$ NMR: 13.5 (s, $CO_2CH_2CH_3$); 18.7 (s, *C*H$_3$-cycle); 23.6 (4d, $^3J_{CP}$ = 3.0; [*(CH3)2*CH-O]$_2$P); 24.3 (d, $^2J_{CP}$ = 1.1, *C3*); 32.3 (s, *C2*); 41.0 (d, $^1J_{CP}$ = 205, *C1*); 61.0 (s, $CO_2CH_2CH_3$); 71.5 (2d, $^2J_{CP}$ = 6.5; [$(CH_3)_2$*C*H-O]$_2$P); 169.8 [d, $^3J_{CP}$(cis) = 5.5; *C*$O_2CH_2CH_3$].

Diisopropyl 1-chloro-*t*-2-ethoxycarbonyl-*c*-2-methylcyclopropyl-*r*-1-phosphonate 4b-2 (minor diastereomer): $^{31}P\{^1H\}$ NMR: 13.0; ^1H NMR: 1.35 (m, 16H, [*(CH3)2*CH-O]$_2$P + *H*-cycle + $CO_2CH_2CH_3$); 1.55 (s, 3H, C*H3*-cycle); 2.1 [dd, 1H, $^2J_{HH}$ = 6.2; $^3J_{HP}$(cis) = 14; *H*-cycle]; 4.3 (q, 2H, $CO_2CH_2CH_3$); 4.6 (m, 2H, [$(CH_3)_2$C*H*-O]$_2$P); $^{13}C\{^1H\}$ NMR: 13.7 (s, $CO_2CH_2CH_3$); 15.9 (d, $^2J_{CP}$ = 3.2, *C3*); 17.8 (s, *C*H$_3$-cycle); 23.6 (4d, $^3J_{CP}$ = 3.0; [*(CH3)2*CH-O]$_2$P); 31 (s, *C2*); 39.0 (d, $^1J_{CP}$ = 203, *C1*); 61.3 (s, $CO_2CH_2CH_3$); 71.2 (2d, $^2J_{CP}$ = 6.5; [$(CH_3)_2$CH-O]$_2$P); 168.9 [d, $^3J_{CP}$(trans) = 2.7; *C*$O_2CH_2CH_3$].

Diisopropyl 1-chloro-*c*-2-ethoxycarbonyl-*t*-3-methylcyclopropyl-*r*-1-phosphonate 4c: obtained as a sole diastereomer, oily product, $bp_{0.4}$ = 110 °C. HRMS required for $C_{13}H_{25}ClO_5P$ (MH^+) : 327.1128 (^{35}Cl), found 327.1129 (^{35}Cl). $^{31}P\{^1H\}$ NMR: 13.1; ^1H NMR: 1.1 (t, 3H, $^3J_{HH}$ = 7; $CO_2CH_2CH_3$); 1.2 (m, 15H, [*(CH3)2*CH-O]$_2$P + CH-C*H3*); 1.8 [dd, 1H, $^3J_{HH}$ = 8.5; $^3J_{HP}$(trans) = 6.5; *H2*]; 2.1 [dqd, 1H, $^3J_{HH}$ = 7.0; $^3J_{HH}$ = 8.5; $^3J_{HP}$(cis) = 13.0; *H3*]; 4.0 (q, 2H, $^3J_{HH}$ = 7; $CO_2CH_2CH_3$); 4.6 (m, 2H, [$(CH_3)_2$C*H*-O]$_2$P); $^{13}C\{^1H\}$ NMR: 12.2 (s, *C*H$_3$-cycle); 13.6 (s, $CO_2CH_2CH_3$); 22.4 (s, *C3*); 23.5 (2d, $^3J_{CP}$ = 3.0; [*(CH3)2*CH-O]$_2$P); 37.1 (d, $^2J_{CP}$ = 1.4; *C2*);

42.0 (d, $^1J_{CP}$ = 209, *C1*); 61.3 (s, $CO_2CH_2CH_3$); 71.6 (d, $^2J_{CP}$ = 6.5; $[(CH_3)_2CH\text{-}O]_2P$); 166.6 [d, $^3J_{CP}$(cis) = 5.7; $CO_2CH_2CH_3$].

Diisopropyl 1-chloro-2,2-bis(ethoxycarbonyl)-*t*-3-phenylcyclopropyl-*r*-1-phosphonate 4d: obtained as a sole diastereomer, oily product, purified by column chromatography over SiO_2 (eluent : hexane-ether mixtures). HRMS required for $C_{21}H_{31}ClO_7P$ (MH^+) : 461.1496 (^{35}Cl) ; found 461.1502 (^{35}Cl). $^{31}P\{^1H\}$ NMR: 11.1; ^1H NMR: 1.2 (t, 3H, $^3J_{HH}$ = 7; $CO_2CH_2CH_3$); 1.4 (m, 15H, $[(CH_3)_2CH\text{-}O]_2P$ + $CO_2CH_2CH_3$); 3.7 [d, 1H, $^3J_{HP}$(cis) = 15.0; *H3*]; 4.2 (2q, 4H, $^3J_{HH}$ = 7; $CO_2CH_2CH_3$); 4.6 (m, 2H, $[(CH_3)_2CH\text{-}O]_2P$); 7.3 (s, 5H, C_6H_5); $^{13}C\{^1H\}$ NMR: 13.6 (s, $CO_2CH_2CH_3$); 23.8 (4d, $^3J_{CP}$ = 3.0; $[(CH_3)_2CH\text{-}O]_2P$); 34.6 (s, *C3*); 43.8 (d, $^2J_{CP}$ = 1.0; *C2*); 45.0 (d, $^1J_{CP}$ = 203, *C1*); 61.8 (s, $CO_2CH_2CH_3$); 71.8 (2d, $^2J_{CP}$ = 6.5; $[(CH_3)_2CH\text{-}O]_2P$); 127.4, 127.9, 129.6 (3s, $C_{o,m,p\text{-}aromatic}$); 130.8 (d, $^2J_{CP}$ = 1.7; $C_{ipso\text{-}aromatic}$); 163.0 [d, $^3J_{CP}$(trans) = 2.8; $CO_2CH_2CH_3$]; 165.3 [d, $^3J_{CP}$(cis) = 5.25; $CO_2CH_2CH_3$].

4e Was obtained as a mixture of diastereomers **4e-1** and **4e-2** (in a 63:37 ratio): oily product, $bp_{0.6}$ = 125 °C; HRMS required for $C_{11}H_{20}ClNO_3P$ (MH^+) : 280.0869 (^{35}Cl) ; found : 280.0869 (^{35}Cl).

Diisopropyl 1-chloro-*c*-2-methyl-*t*-2-cyanocyclopropyl-*r*-1-phosphonate 4e-1 (major diastereomer): $^{31}P\{^1H\}$ NMR: 10.6; ^1H NMR: 1.4 (m, 12H, $[(CH_3)_2CH\text{-}O]_2P$); 1.7 (s, 3H, CH_3-cycle): 1.9 [dd, 1H, $^2J_{HH}$ = $^3J_{HP}$(trans) = 6.8; *H*-cycle]; 2.2 [dd, 1H, $^2J_{HH}$ = 6.8; $^3J_{HP}$(cis) = 13.5; *H*-cycle]; 4.8 (m, 2H, $[(CH_3)_2CH\text{-}O]_2P$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): 16.9 (d, $^2J_{CP}$ = 2.2, *C2*); 19.3 (s, *C3*); 23.8 (4d, $^3J_{CP}$ = 3.0; $[(CH_3)_2CH\text{-}O]_2P$); 27.7 (s, CH_3-cycle); 38.4 (d, $^1J_{CP}$ = 202.5, *C1*); 72.2 (2d, $^2J_{CP}$ = 6.5; $[(CH_3)_2CH\text{-}O]_2P$); 119.1 [d, $^3J_{CP}$(trans) = 2.0; CN].

Diisopropyl 1-chloro-*t*-2-methyl-*c*-2-cyanocyclopropyl-*r*-1-phosphonate 4e-2 (minor diastereomer): $^{31}P\{^1H\}$ NMR: 10.2; ^1H NMR: 1.4 (m, 13H, $[(CH_3)_2CH\text{-}O]_2P$ + *H*-cycle); 1.6 (s, 3H, CH_3-cycle): 1.8 [dd, 1H, $^2J_{HH}$ = 6.8, $^3J_{HP}$(cis) = 13.5; *H*-cycle]; 4.8 (m, 2H, $[(CH_3)_2CH\text{-}O]_2P$); $^{13}C\{^1H\}$ NMR: 15.6 (d, $^2J_{CP}$ = 3.1, *C2*); 20.9 (d, $^2J_{CP}$ = 1.3, *C3*); 24.0 (4d, $^3J_{CP}$ = 3.0; $[(CH_3)_2CH\text{-}O]_2P$); 27.1 (s, CH_3-cycle); 42.0 (d, $^1J_{CP}$ = 203, *C1*); 72.5 (2d, $^2J_{CP}$ = 6.5; $[(CH_3)_2CH\text{-}O]_2P$); 118.7 [d, $^3J_{CP}$(cis) = 6.1; CN].

Diisopropyl 1-chloro-*c*-2-ethoxycarbonyl)-*t*-3-phenylcyclopropyl-*r*-1-phosphonate 4f: obtained as a sole diastereomer, oily product, purified by column chromatography (eluent : hexane-ether: 80-20). HRMS required for $C_{18}H_{27}ClO_5P$ (MH^+) : 389.1284 (^{35}Cl) ; found : 389.1293 (^{35}Cl). $^{31}P\{^1H\}$ NMR: 12.1; ^1H NMR: 1.4 (m, 15H, $[(CH_3)_2CH\text{-}O]_2P$ + $CO_2CH_2CH_3$); 2.75 [dd, 1H, $^3J_{HP}$(trans) = 7.0; $^3J_{HH}$ = 7.0; *H2*]; 3.5 [dd, 1H, $^3J_{HP}$(cis) = 12.6; $^3J_{HH}$ = 7.0; *H3*]; 4.2 (q, 2H, $^3J_{HH}$ = 7.0; $CO_2CH_2CH_3$); 4.8 (m, 2H, $[(CH_3)_2CH\text{-}O]_2P$); 7.3 (s, 5H, C_6H_5); $^{13}C\{^1H\}$ NMR: 13.7 (s, $CO_2CH_2CH_3$); 23.8 (4d, $^3J_{CP}$ = 3.0; $[(CH_3)_2CH\text{-}O]_2P$); 32.6 (s, *C3*); 35.0 (d, $^2J_{CP}$ = 0.9; *C2*); 42.0 (d, $^1J_{CP}$ = 206, *C1*); 61.3 (s, $CO_2CH_2CH_3$); 72.2 (2d, $^2J_{CP}$ = 6.5; $[(CH_3)_2CH\text{-}O]_2P$); 127.5, 128.0, 128.9 (3s, $C_{o,m,p\text{-}aromatic}$); 132.5 (s, $C_{ipso\text{-}aromatic}$); 166.3 [d, $^3J_{CP}$(cis) = 5.5; $CO_2CH_2CH_3$].

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