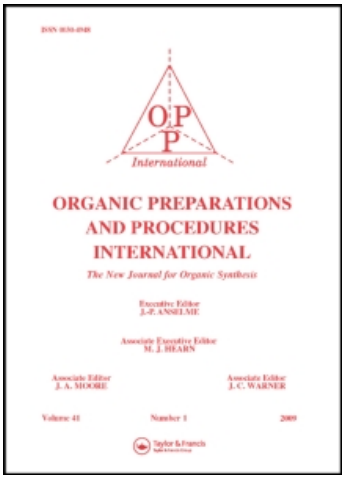

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α-, β-,γ- AND ω-CYCLOPROPYLPHOSPHONATES. PREPARATION AND BIOLOGICAL ACTIVITY

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α- , β- , γ- AND ω-CYCLOPROPYLPHOSPHONATES. PREPARATION AND BIOLOGICAL ACTIVITY

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INTRODUCTION

Many phosphonate derivatives possess pharmacological activity. For instance, they have been widely used in the treatment of several bone diseases,[1-5] and have recently been utilized successfully against many parasites.[6-9] Numerous synthetic routes to different types of phosphonates with specific potency and pharmacological activity have been described.[10-13] In the same vein, introduction of a cyclopropyl group into chemical structures may increase the potential for biological activity.[14-17] Accordingly, the juxtaposition of both cyclopropyl and phosphonate groups in the same compound may endow it with desirable pharmacological properties. For instance, cyclopropylphosphonates can act as *N*-methyl-D-aspartate (NMDA) receptor antagonists,[18] selective anti-HBV agents,[19] insecticides,[20] and cytostatic agents.[21] They also possess anti-proliferation properties,[22] are virostatics,[23] anti-diabetics,[24] anti-tumor agents,[25] and display antiviral activity.[26] The methods for the synthesis of cyclopropylphosphonates depend on the relative location of the cyclopropyl and phosphonate groups. The synthesis and chemistry of the cyclopropyl group have been well studied and discussed in several review articles.[27-36] This survey presents the major synthetic routes and pharmacological applications of cyclopropylphosphonates, which are divided into four groups α-, β-, γ- and ω-cyclopropylphosphonates, and cyclopropanes bearing other phosphorus groups.

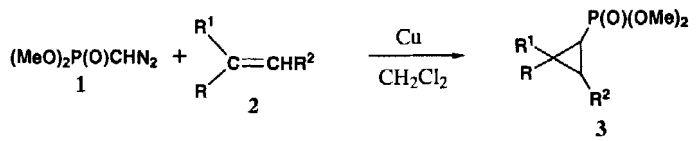
I. α-CYCLOPROPYLPHOSPHONATES

α-Cyclopropylphosphonates, in which the cyclopropyl ring is directly substituted with a phosphonate group, are obtainable by several methods. This particular class of cyclopropylphosphonates possesses diverse and noteworthy biological activity.

1. *via Diazomethylphosphonate (DAMP)*

One of the main methods for the synthesis of cyclopropylphosphonates is the addition of diazomethylphosphonate to alkenes. The nature of the catalytic system is crucial to achieve the maximum yield.

Dimethyl diazomethylphosphonate (DAMP **1**) underwent divalent carbon transfer reactions with olefins when stirred at 0°C with a large excess of the olefin in the presence of copper powder and dichloromethane as a co-solvent to produce cyclopropylphosphonates **3a-d** (*Scheme 1*). In the absence of dichloromethane, the yields were markedly reduced, possibly as a result of the low solubility of the diazoalkane in some of the olefins used in the study. Copper



a) R = C_5H_{11}, $R^1 = R^2 = H$ (55%) b) $R^1, R^2 = -(CH_2)_4$, $R^1 = H$ (39%)

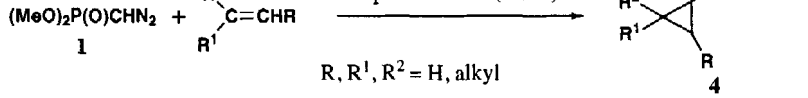
c) R = Me_3SiCH_2, $R^1 = R^2 = H$ (67%) d) R, R^1 = Me, $R^2 = H$ (14%)

Scheme 1

powder was found to be the most effective catalyst, giving higher yields and less tar than in reactions employing copper(I) chloride or copper(II) acetylacetonate. A possible mechanism involves copper-catalyzed diazoalkane decomposition to carbene-Cu(I) complexes which react with the olefin to form the cyclopropane.[36a]

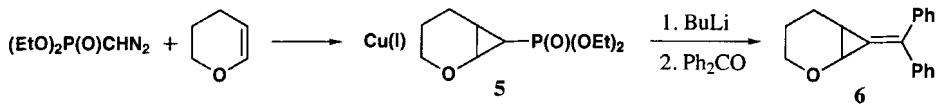
Similarly, Lewis and co-workers reported that the addition of DAMP to an alkene in the presence of cuprous triflate (2-5%) in dichloromethane led to the formation of the corresponding cyclopropylphosphonates **4**.

The scope of this reaction was explored using a variety of mono- and disubstituted alkenes. Notably, only a two- to three-fold excess of the alkene is required using this procedure. In addition, the unreacted olefin can be recovered and recycled if necessary (*Scheme 2*).[36f]



Scheme 2

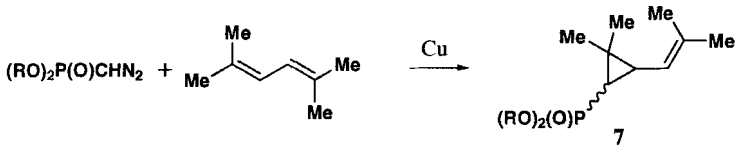
In addition, Lewis *et al.* found that cuprous trifluoromethanesulfonate is a highly efficient catalyst for cyclopropanation of olefins using DAMP. The resultant cyclopropylphosphonates underwent Wadsworth-Emmons olefination with aromatic carbonyl compounds. Thus, cyclopropanation of dihydropyran with DAMP in the presence of cuprous triflate gave cyclopropylphosphonate **5** (71%), which upon Wadsworth-Emmons olefination with Ph_2CO in the presence of BuLi, yielded of the arylidenecyclopropane **6** (63%) (*Scheme 3*).[37]



5 6

Scheme 3

In a similar manner, other cyclopropylphosphonate analogs of chrysanthemic esters **7** were synthesized in 2-27% yields by the reaction of $(RO)_2P(O)CHN_2$ with 2,5-dimethyl-2,4-hexadiene in the presence of copper powder. Compounds **7** showed satisfactory insecticidal activity *(Scheme 4)*.[20]

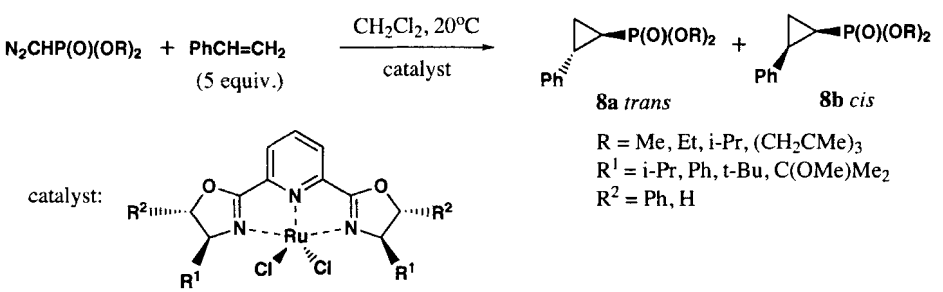


7

a) R = *m*-$PhOC_6H_4CH_2$ b) 2,4,6-$Me_3C_6H_2CH_2$
c) p-$H_2C{=}CHCH_2C_6H_4CH_2$ d) 5-benzyl-3-furylmethyl

Scheme 4

The use of *trans*-$RuCl_2$((S,S)-*i*-Pr-pybox)(ethylene)-catalyzed cyclopropanation of styrene with diisopropyl diazomethylphosphonate in CH_2Cl_2 led to the formation of the stereoisomeric phenylcyclopropylphosphonates **8a** and **8b** (80%) as shown in *Scheme 5, Table 1*.[38] This

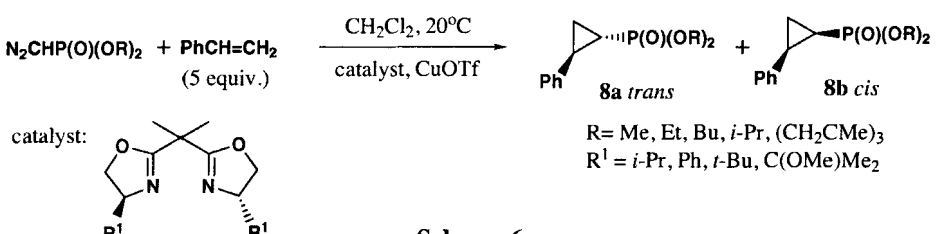


8a *trans* **8b** *cis*

R = Me, Et, i-Pr, $(CH_2CMe)_3$
R^1 = i-Pr, Ph, t-Bu, $C(OMe)Me_2$
R^2 = Ph, H

Scheme 5

reaction also proceeded efficiently using a copper catalyst to furnish compounds **8** (*Scheme 6, Table 2*). In addition, using a rhodium catalyst afforded cyclopropyl-phosphonates **9a-e**

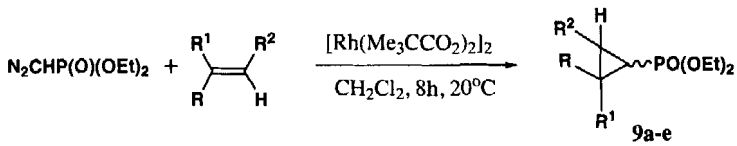


8a *trans* **8b** *cis*

R= Me, Et, Bu, *i*-Pr, $(CH_2CMe)_3$
R^1 = *i*-Pr, Ph, *t*-Bu, $C(OMe)Me_2$

Scheme 6

(50-80%), (*Scheme 7*). Evans' Cu•bis(oxazoline) and Nishiyama's Ru•pybox were found to be the best catalysts for the asymmetric variation.



9a-e

a) R = Me, R^1 = Ph, R^2 = H, 72% [*trans*:*cis* (57:43)]; b) R = H, R^1 = Ph, R^2 = H, 85% [*trans*:*cis* (55:45)]; c) R = R^1 = Ph, R^2 = H, 72%; d) R = H, R^1 = *n*-Bu, 70% [*trans*:*cis* (50:50)]; e) R = Me, R^1 = Ph, R^2 = Me, 72% [*trans*:*cis* (75:25)]

Scheme 7

Table 1. Formation of **8** *via* Ru Catalysis (*Ref. 38, Scheme 5*)

Entry	R	R^1	R^2	Yield (%)	*trans*:*cis*	ee (*trans*) (%)
1	Et	Me	Ph	68	98:2	52
2	Et	Ph	H	60	78:22	49
3	Me	*i*-Pr	H	65	90:10	76
4	Et	*i*-Pr	H	65	98:2	96
5	*i*-pr	*i*-Pr	H	70	98:2	96
6	$CH_2C(CH_3)_3$	*i*-Pr	H	70	98:2	96

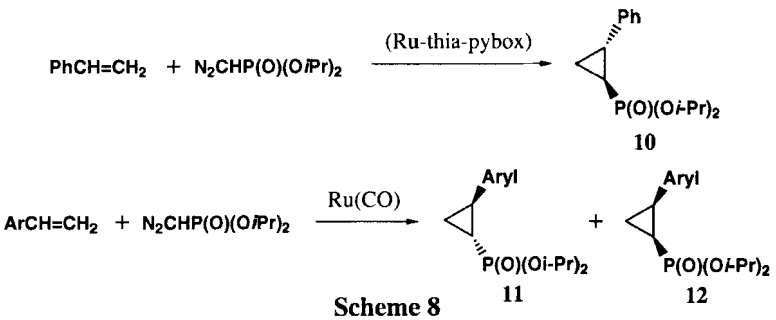
Table 2. Formation of **8** *via* Cu Catalysis (*Ref. 38, Scheme 6*)

Entry	R	Yield (%)	*trans*:*cis*	ee (*trans*:*cis*) (%)
1	Me	72	81:19	76:61
2	Me	75	80:20	79:83
3	Me	74	86:14	93:99
4	Et	72	80:20	75:67
5	Et	86	78:22	80:74
6	Et	50	83:17	92:99
7	Et	65	84:16	92:99
8	Bu	65	88:12	91[a]
9	*i*-Pr	65	90:10	92[a]
10	$[CH_2C(CH_3)_3$	67	92:8	92[a]

[a] Not determined.

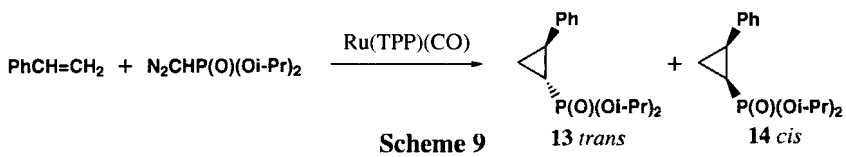
Asymmetric Ru-catalyzed cyclopropanations with phosphonate diazoesters were also reported by Simonneaux and co-workers. Using chiral 2,6-*bis*(thiazolinyl)pyridine ligands, enantioselectivity (>90%) was achieved to afford the *trans*-cyclopropylphosphonate **10**.[39] Ru–thia–Pybox complexes were also effective in catalyzing styrene cyclopropanation with diiso-

propyl diazomethylphosphonate. In addition, asymmetric addition of diisopropyl diazomethylphosphonate to styrene derivatives was carried out successfully using chiral ruthenium porphyrins. The reaction proceeded under mild conditions and gave *trans*-cyclopropylphosphonates in good yields and high *ee* (up to 92%). A progressive increase in enantiomeric excess was observed as a function of the number of chiral groups linked to the ruthenium porphyrins to produce compounds **11** and **12** (*Scheme 8*).[40]



Scheme 8

Cyclopropanation of 4-substituted styrenes with DAMP catalyzed by several carbonyl ruthenium porphyrin complexes was also studied (*Scheme 9*, *Table 3*). The products **13** and **14** were obtained from a variety of ring-substituted styrenes. The regio- and stereoselectivity of the



Scheme 9

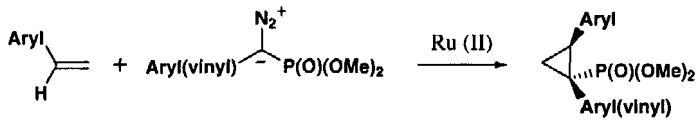
products were compared to those observed in the presence of other metalloporphyrins.[41] Competition studies between cyclopropanation with diisopropyl diazomethylphosphonate and diazo insertion into heteroatom-hydrogen bonds were reported; similar studies of the competition between cyclopropanation and the sigmatropic reaction were also described.

Table 3. Cyclopropanation of Styrenes Catalyzed by Ru(TPP)(CO) (*Ref. 41, Scheme 9*)

Styrene	*cis* (%)	*trans* (%)	Yield (%)	DAMP dimer (%)
4-Methoxystyrene	2	94	96	4
Styrene	6	84	90	10
4-Chlorostyrene	7	91	98	2
4-Trifluoromethylstyrene	20	73	93	7

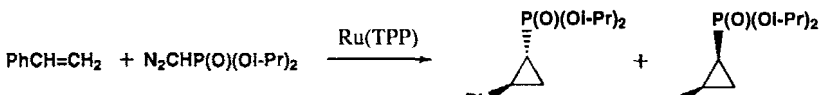
Simonneaux *et al.* found that Ru_2(*S*-biTISP)$_2$ catalyzed reactions of dimethyl aryldiazomethylphosphonates generated donor/acceptor-substituted rhodium carbenoid intermediates

capable of cyclopropanation of styrenes to produce in high yields (85-96%), high diastereoselectivity (98% de), and reasonable enantioselectivity (76-92% ee).[42] In addition, a general method for the enantioselective synthesis of cyclopropylphosphonates containing a quaternary stereocenter using *D*2-symmetric dirhodium complexes as catalysts was discussed (*Scheme 10*).



Scheme 10 **15**

When the catalytic systems were derived from Ru(CO)porphyrins, a monocarbene complex Ru(TPP)(CH[P(O)(O*i*-Pr)$_2$]) was isolated as the possible catalytically active species. Cyclopropylphosphonates **16** and **17** were obtained in high yields (90%) with a preference of 12:1 towards the *anti* isomer (*Scheme 11*).



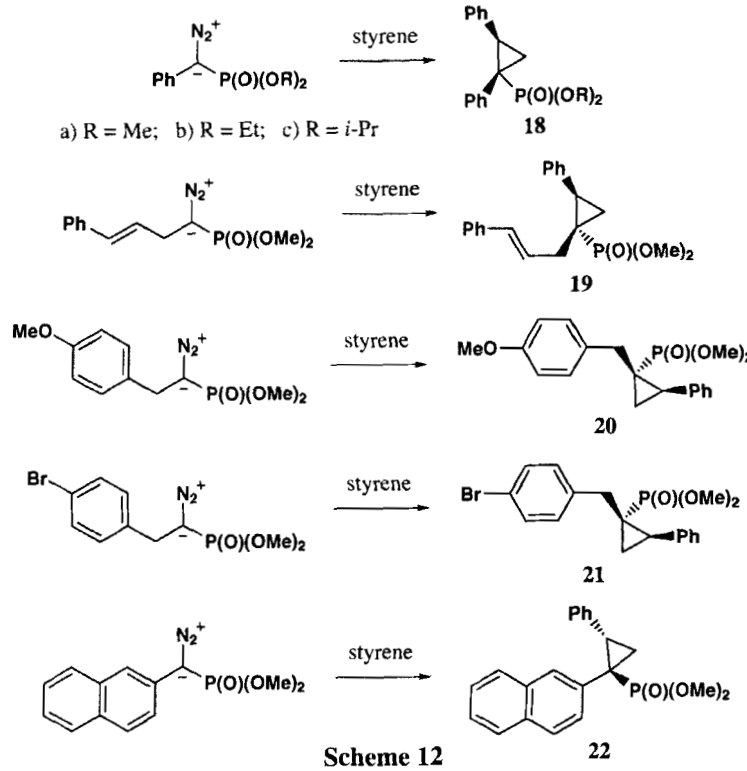
Scheme 11

In addition, Davies *et al.* found that Rh_2(S-biTISP)$_2$ catalyzed reactions of diaryldiazomethylphosphonates generated donor/acceptor-substituted rhodium carbenoid intermediates capable of cyclopropanation of styrene in high yields (85-96%), diastereoselectivity (≥98% de), and moderate enantioselectivity (76-92% ee) **18-22** (*Scheme 12*). In a typical reaction, styrene and the rhodium catalyst were heated under reflux in 2,2-dimethylbutane, followed by addition of phenyldiazomethylphosphonate, to produce (1*S*,2*S*)-diphenylcyclopropylphosphonic acid dimethyl ester **18a** in 89% yield with 98% de and 88% ee.[43] Cyclopropylphosphonates **19-22** were also prepared under similar conditions.

Treatment of RCOCH$_2$P(O)(OMe)$_2$ with tosyl azide and NaH in THF-C_6H_6 resulted in the formation of the diazomethylphosphonate RCOC(=N$_2$)P(O)(OMe)$_2$ **23** (80-96%).

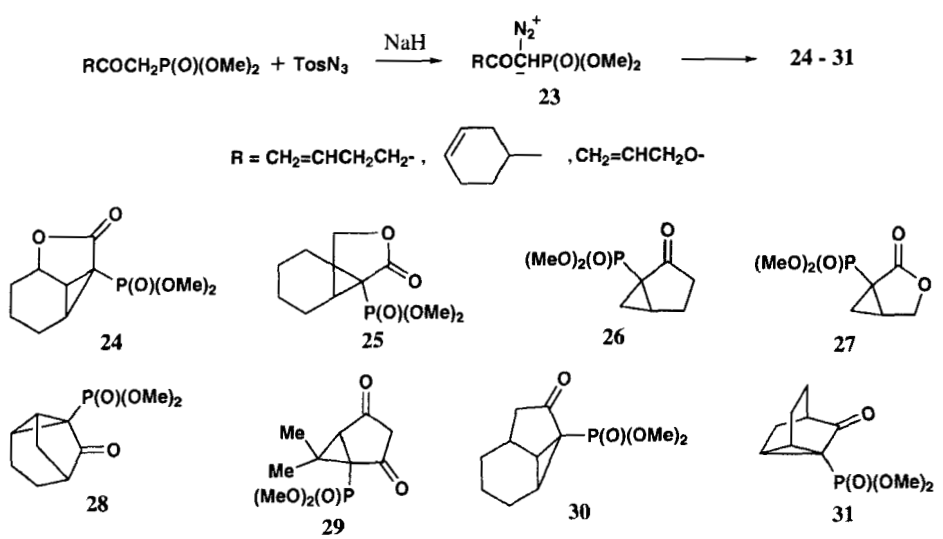
Intramolecular cyclopropanation of diazophosphonates **23** whose R groups contain a double bond, in the presence of catalysts (the best was Cu powder) resulted in the generation of cyclopropylphosphonates **24-31** (> 90%). In a typical example, refluxing **23** (R = 3-cyclohexenyl) with Cu in cyclohexane, provided **31** (*Scheme 13*).[44]

Moore *et al.* developed an effective approach to the synthesis of bicyclic *P*-chiral phosphonates **32-35** based on a diastereotopic differentiation strategy using a phosphonoacetate template. This approach utilized $Rh_2(OAc)_4$ to catalyze intramolecular cyclopropanation employing the (*R*)-pantalactone auxiliary in the ester functionality of the phosphonoacetate as shown in *Scheme 14*.[45] The olefinic diastereofacial selectivity was governed by inherent electronic and steric interactions in the reacting carbene intermediate, while the group selectivity was dictated by the chiral auxiliary.

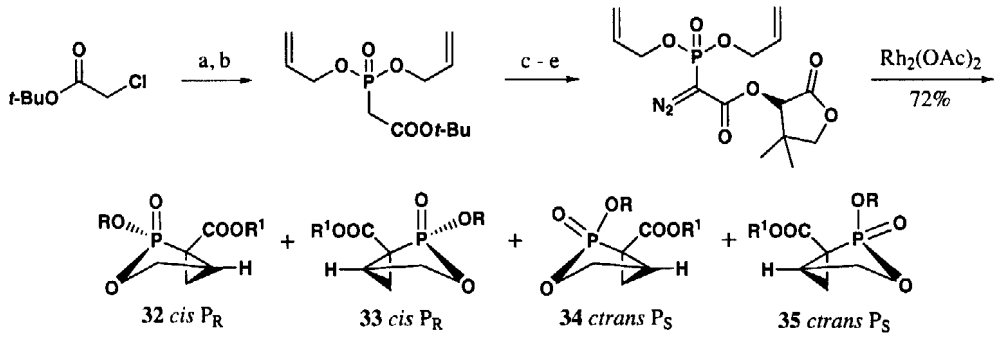


Scheme 12

The versatile *tert*-butyl phosphonoacetate moieties $t\text{-BuO}_2\text{CCN}_2\text{P(O)(OR)}_2$ [R = allyl, **36**] were used to derive a series of mono- and bicyclic α-Boc-aminocyclopropyl-phosphonates by intramolecular cyclopropanation mediated by $Rh_2(OAc)_4$.[46] By utilizing the *tert*-Bu esters in



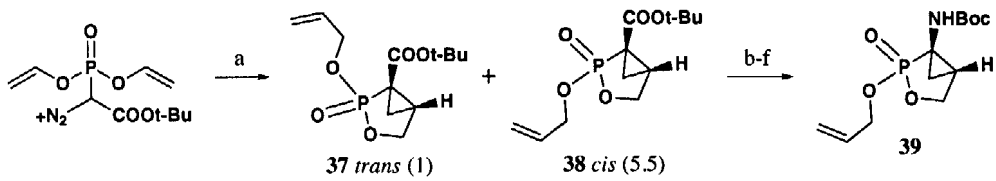
Scheme 13



a) KI, CH_3CN, > 99%; b) $P(OAllyl)_3$, neat, 88%; c) HCO_2H, neat, > 99%; d) HBTU, TEA, (R)-pantolactone, CH_3CN, 83%; e) NaH, TsN_3, THF, 90%

Scheme 14

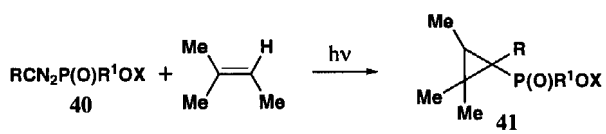
36 as the precursors of the amino group, a Curtius rearrangement provided an efficient route toward the targeted α-Boc-aminocyclopropylphosphonate **39** *via* the major product, cyclopropylphosphonate **38** (*Scheme 15*).



a) $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 91%; ds 5.5:1; b) formic acid, neat; c) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0°C to rt; d) NaN_3, CH_3CN, H_2O quantitative yield; e) toluene, reflux; f) *t*-BuOH, reflux, 50% (five steps)

Scheme 15

Photolysis of dimethyl phenyldiazomethylphosphonate, $PhC(N_2)P(O)(OMe)(OX)$ (**40**; X = Me) with Me_2C=CHMe in MeOH gave PhCH(OMe)P(O)(OMe)(OX) (18%), and a mixture (81%) of the *syn-/anti*-cyclopropylphosphonate **41a**. On the other hand, photolysis of **40** (X = Na) gave PhCH(OMe)P(O)(OMe)(OX) (73%) and **41a** (16%) (*Scheme 16*).[47] The results were rationalized in terms of a strong interaction of the vacant p-orbital of the neighboring with the phosphonate oxygen, thus making it unavailable for bonding.



X = Me, Na

a) R = Ph, R^1 = OMe; b) R = R^1 = Ph; c) R = *p*-chlorobenzyl, R^1 = OMe

Scheme 16

The phosphonate carbenes are experimentally classified as typical nucleophiles, and their nucleophilicity was dramatically reduced when the neighboring group was changed from

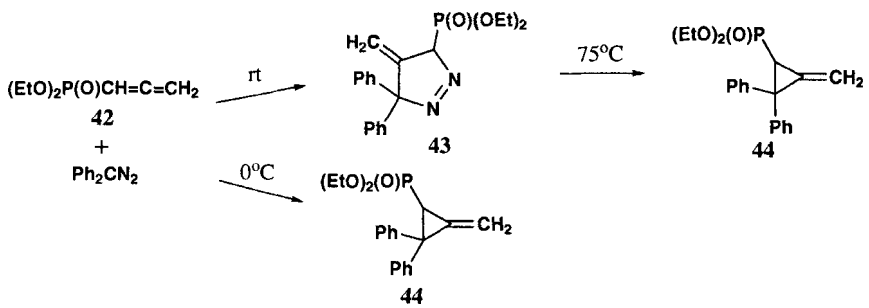
the phosphonate ester to the acid anion. This reaction was also used to prepare cyclopropylphosphonates **41b-c**.

The discussion above indicates that the choice of the catalytic system is of major importance. For instance, Ru and Rh catalysts were the most efficient for most of these reactions unlike Cu which gave good results in only few cases.

2. *via Carbon-transfer from Diazoalkanes to Vinylphosphonates*

A reverse addition method for cyclopropylphosphonates preparation is the addition of a diazoalkane to an alkenylphosphonates. However, vigorous conditions were required in these reactions, and the yields were lower compared to the diazophosphonate addition to alkenes.

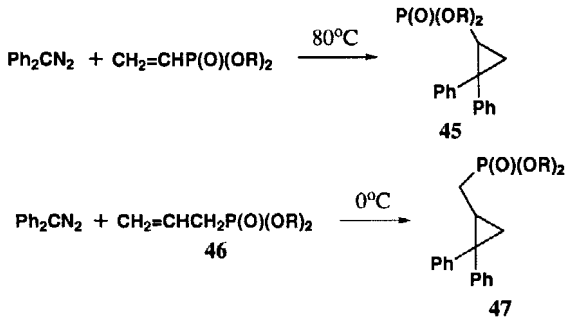
Treatment of the allenephosphonate $(EtO)_2P(O)CH=C=CH_2$ **42** with Ph_2CN_2 at room temperature produced the heterocycle **43** (37%). Upon being heated to 75°C, **43** was converted to 3-(diethoxyphosphinyl)-2,2,3-triphenyl-1-methylenecyclopropane (**44**) while the same product was also formed upon standing (36%) after 20 days at 0°C (*Scheme 17*).[48]



Scheme 17

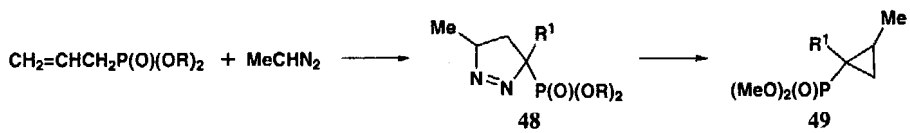
The addition of diphenyldiazomethane to diethyl vinylphosphonate $[CH_2=CHP(O)(OEt)_2]$ at 80°C for 3-4 hrs furnished diethyl 2,2-diphenylcyclopropyl-phosphonate (**45b**, 75%). The analogous dimethyl (**45a**), dipropyl (**45c**), and dibutyl (**45d**) analogues were similarly obtained. When the reaction was carried out in the presence of a catalytic amount of $CuSO_4$ for 30 min, the desired cyclopropylphosphonate **47** (25%) was obtained in addition to other side-products including benzophenone azine (26%), benzophenone (3.5%), and some unreacted vinylphosphonate. Heating diphenyldiazomethane and $CH_2=CHCH_2P(O)(OEt)_2$ at 140-150°C reduced the yield of diethyl (2,2-diphenylcyclopropylmethyl)phosphonate **47** to12.8% whereas a 73% yield was obtained when the reaction with **46** was carried out at 0°C in petroleum ether for 3 days. (*Scheme 18*).[49]

Moreover, it was shown that the addition of $MeCHN_2$ to the vinylphosphonate $CH_2=CR^1P(O)(OR)_2$ (R, R^1 = Me, Me; Me, Et; Me, Me_2CH; Et, Me; Me_2CH, Me) occurred non-stereospecifically to give mixtures of *cis*- and *trans*-**49**. Stereospecific formation of *cis*- and



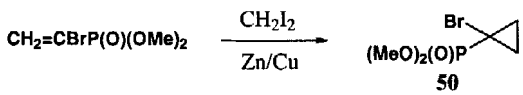
a) R = Me; b) R = Et; c) R = *n*-Pr; d) R = *n*-Bu

Scheme 18



Scheme 19

trans-**49** (R = R_1 = Me) was achieved by rapid closure of the biradical intermediate produced upon photolysis of **49** (*Scheme 20*).[51]



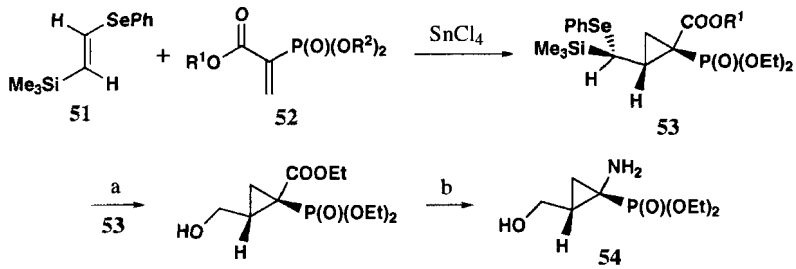
Scheme 20

3. *via Other Carbon-transfer Methods*

Satisfactory to good yields of cyclopropylphosphonates were obtained by other carbon transfer reactions reported in the literature.

Dimethyl (1-bromocyclopropyl)phosphonate (**50**) was synthesized by bromination of dimethylvinylphosphonate, dehydrobromination of the dibromide, and cyclopropanation of the α-bromovinylphosphonate CH_2=CBrP(O)$(OMe)_2$ with the Simmons-Smith reagent CH_2I_2/Zn/Cu (*Scheme 20*).[51]

The highly functionalized cyclopropylphosphonates **53** are versatile starting materials for biologically important compounds. Their stereoselective synthesis was achieved by $SnCl_4$ promoted [2+1] cycloaddition reaction of 1-seleno-2-silylethene [Me_3SiC=CSePh] with 2-phosphonoacrylates, $R(O)_2CC(=CH_2)P(O)(OR')_2$ (R = Me, Et, *t*-Bu, and (l)-menthyl, R' = Me, Et, *i*-Pr) in high yields (*Scheme 21*, *Table 4*).[52] By utilization of the cycloadduct **53** (R' = R" = Me), a stereoselective synthesis of a novel functionalized α-aminophosphonic acid **54** was accomplished. This product is considered an analog of (Z)-2,3-methanohomoserine.[53]



$R^1 = R^2 = Me$

a) $NaIO_4$, THF-H_2O, (97%), $NaBH_4$, *i*-PrOH, (94%); b) 1N NaOH (91%), NH_3, MeOH, Ac_2O, cat. DMAP, Net_3, CH_2Cl_2, (87%), $Pb(OAc)_4$, *t*-BuOH, (96%), H_2CO_3, MeOH, HCl-ether, $NaHCO_3$, TMSI, propylene oxide, (64%)

Scheme 21

Table 4. [2+1] Cycloaddition of **51** to **52** to give **53** (*Ref. 52, Scheme 21*)[a]

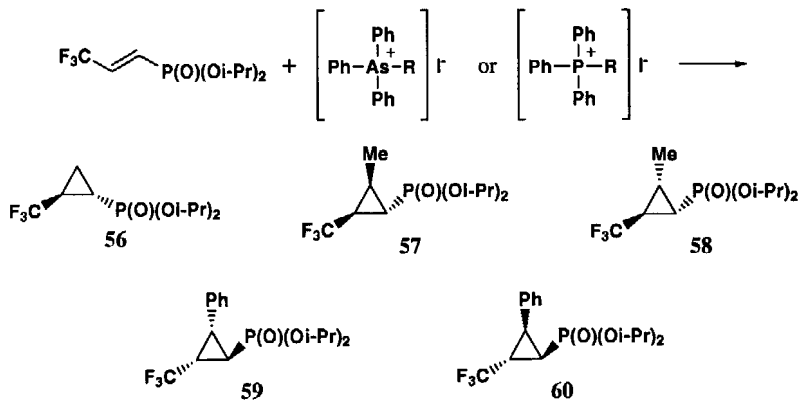
Entry	^{1}R	^{2}R	Time/hr	Product 53	Yield (%)
1	Me	Me	3	a	96
2	Et	Et	6	b	92
3	Bu-t	Me	4	c	52
4	CH_2CH_2TMS	Et	4	d	66
5	Et	*i*-Pr	4	e	85
6	1-menthyl	Me	4	f	70

a) Reactions were carried out at -78 ≡C, 0.4 M for **51** in CH_2Cl_2.

Trifluoromethylated cyclopropylphosphonates **56-60** were conveniently synthesized by the reaction of phosphoranes or the more reactive arsoranes with diisopropyl (*E*)-(3,3,3-trifluoro-prop-1-en-1-yl)phosphonate (**55**). The reaction conditions were milder (20°C, 2 hr), and the yields were higher (60%) with the arsoranes. When $Ph_3AsCH_2Ph^+ I^-$ was treated with BuLi in THF, the intermediate Ph_3As=CHPh generated, in turn reacted with (*E*)-CF_3CH=CHP(O)(O*i*-Pr)$_2$ to produce a mixture of **59** and **60** (78:22 respectively) in a yield of 52% (*Scheme 22*).[54]

Condensation of $(EtO)_2P(O)CH_2R$ (**61**; R = COOEt) with cinnamaldehyde in the presence of piperidine gave a 1:1 mixture of (*Z,E*)- and (*E,E*)-$(EtO)_2P(O)CR$=CHCH=CHPh [(*Z,E*)- and (*E,E*)-**62**] in an 82% yield; a similar reaction using **61** (R = CN or S(O)OMe) gave (*E,E*)-**62** exclusively in 78% and 93% yields respectively. The reaction of **62** (R = COOEt, CN, S(O)OMe) with $H_2CS(O)Me_2$ provided mixtures of (*E*)- and (*Z*)-styrylcyclopropylphosphonates **63** ($R^1 = R^2 = H$) in good yields. Treatment of **62** (R = COOEt) with phosphonium ylides $Ph_3P^+C^-R^1R^2$ ($R^1 = R^2 = Me$; $R^1 = H$, R^2 = pentyl, *p*-$CH_3OC_6H_4$) provided **63** in moderate yields (*Scheme 23*).[55]

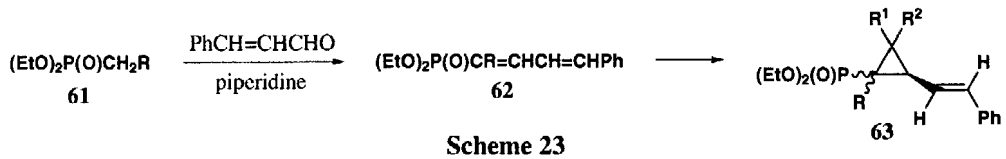
Reaction of benzyl 2,3-anhydro-4-O-trifluoromethylsulfonyl-α-D-ribopyranoside (**64**) or benzyl 2,3-anhydro-4-O-trifluoromethylsulfonyl-β-L-ribopyranoside (**65**) with diethyl cyanomethylphosphonate resulted in the formation of the 3,4-cyclopropanated monosaccharide



R = CH_2Ph, CH_2Me_3, CMe_3

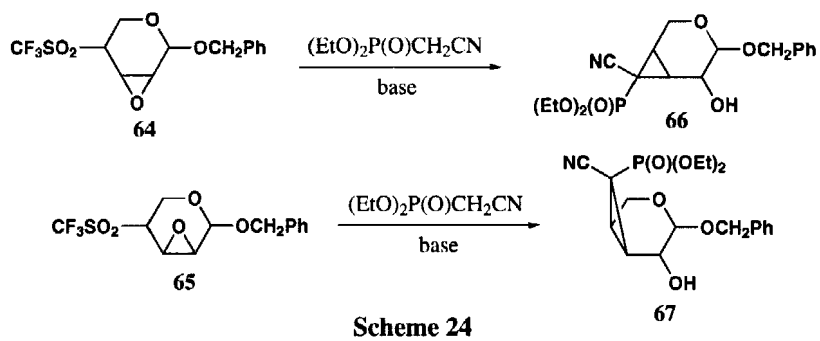
Scheme 22

derivatives benzyl 3,4-(diethyl cyanomethylenephosphonate)-3,4-dideoxy-β-L-arabinopyranoside (**66**), and benzyl 3,4-(diethyl cyanomethylenephosphonate)-3,4-dideoxy-β-L-arabinopyranoside (**67**), respectively (*Scheme 24*).[56] The cyclopropanated sugar derivatives are of interest because of their structural relation to the antibiotic phosphonomycin.



Scheme 23

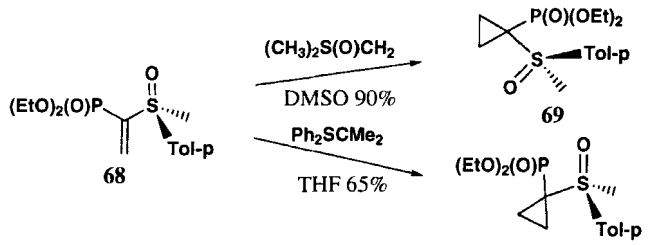
Sulfur chiral sulfoxide (*S*)-(+)-**68** underwent stereoselective cyclopropanation with a sulfoxonium ylides $(CH_3)_2S(O)CH_2$ in DMSO to produce the corresponding cyclopropane **69** in



Scheme 24

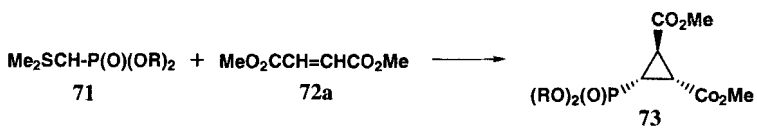
high yield. The reaction of (S)-(+)-**68** with diphenylsulfonium isopropylide resulted in the formation of diethyl 2,2-dimethyl-L-[(S)-*p*-tolylsulfinyl]cyclopropanephosphonate (+) **70** as a single diastereomer (*Scheme 25*).[44]

The phosphinyl methylides $Me_2SCHP(O)(OR)_2$ reacted efficiently with α,β-unsaturated esters **72** to form the cyclopropylphosphonate, 3-(diethoxyphosphinyl) dimethyl ester (1α, 2β, 3α)-1,2-cyclopropanedicarboxylic acid **73** (*Scheme 26*).[57]



Scheme 25

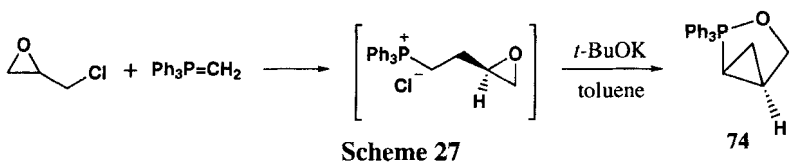
The stereochemistry of **74**, obtained by the reaction of (R)- and (S)-epichlorohydrin with methylenetriphenylphosphorane, followed by treatment with l-(+)-tartaric acid and subsequent



R = Me, Et

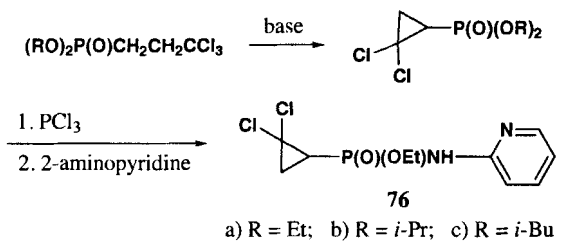
Scheme 26

Wittig reaction with formaldehyde, was revised. The product (-)-oxaphospholane **74** has the *S,S* configuration (*Scheme 27*).[58]

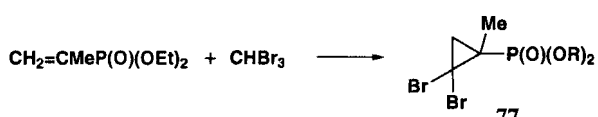


Scheme 27

Under olefination conditions, trichloropropylphosphonates $(RO)_2P(O)CH_2CH_2CCl_3$, produced dichlorocyclopropylphosphonates [**75a-c**, a) R = Et, b) R = *i*-Pr, c) R = *i*-Bu]. Reaction of cyclopropylphosphonate **75a** with PCl_3 followed by amidation with 2-aminopyridine, led to the formation of the dichlorocyclopropylphosphonate **76** (*Scheme 28*).[59] On the other hand,



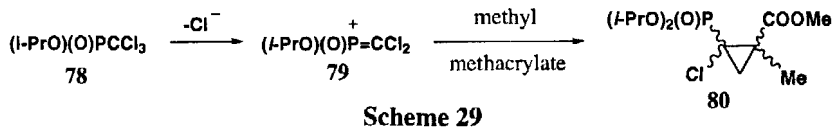
a) R = Et; b) R = *i*-Pr; c) R = *i*-Bu



Scheme 28

cyclopropanation of α-methylvinylphosphonate with $CHBr_3$, under similar reaction conditions, gave dibromocyclopropylphosphonate **77** (10%).

Diastereoselective electrosynthesis of polysubstituted α-chlorocyclopropylphosphonates was efficiently achieved by electroreduction of diisopropropyl trichloro-methylphosphonate in the presence of Michael acceptors in a one-compartment cell equipped with a magnesium sacrificial anode.[60] As shown in *Table 5*, the nature of the anode and the electrolysis time have a significant effect, not only on the yield of cyclopropylphosphonate **80**, but also on the diastereoselectivity of the reaction (*Scheme 29*).



Scheme 29

When the reaction was carried out with an aluminum anode, phosphonate **78** afforded cyclopropylphosphonate **80** as expected (*Table 5, Entry 1*) albeit in only moderate yield and ilow diastereoselectivity. This reaction was successfully carried out with various other alkenes. The length of the electrolysis was in agreement with a classical bi-electronic reduction process consuming two Faradays per mole of phosphonate **78**. With a zinc anode (*Entry 2*), a lower yield of **80** was obtained and efforts to isolate the product from the crude reaction mixture were unsuccessful. Moreover, in the latter case, electrochemical reduction consumed approximately two Faradays per mole of **78** although an increase in the diastereoselectivity was observed. The best results were obtained with a magnesium anode.

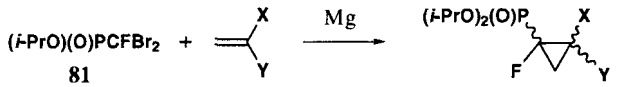
Table 5. Electrosynthesis of Diisopropyl α-chlorocyclopropylphosphonates (**80**)

Entry	Anode	Conversion of % 80[c]	Isolated yield % of 80[d]	Diastereomeric excess %[f]	Q(F/mol)[a]
1	Al	75	45	34	2
2	Zn	44	[e]	62	1.7
3	Mg[a]	82	70	66	1
4	Mg[b]	97	81	82	0.8

(Ref. 60, Scheme 29)

a) In a one-compartment cell thermostated at 14°C. b) In a non-thermostated one-compartment cell; the temperature was autoregulated 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 spectroscopy. E) Not 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 96 in ^{31}P NMR spectroscopy). h) Some other unidentified phosphorus derivatives were detected in these mixtures.

Goumain *et al.* reported an efficient method for the synthesis of α-fluorinated cyclopropylphosphonates **82a-d** by electroreduction of diisopropyl dibromofluoromethylphosphonates **81a-d** in the presence of Michael acceptors in a one-compartment cell equipped with a magnesium sacrificial anode (*Scheme 30*, *Table 6*).[62]

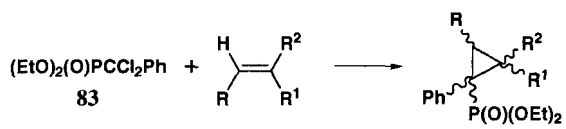


Scheme 30

Table 6. Electrosynthesis of α-Fluorinated Cyclopropylphosphonates **82a-d** (*Ref. 62, Scheme 30*)

Entry	X	Y	Yield of **82**	Isolated yield	De (%)
a	H	CO_2Me	60	43	70
b	H	CO_2Bu	60	49	80
c	CH_3	CO_2Me	50	11	34
d	CH_3	CN	90	58	10

The synthesis of α-aryl substituted cyclopropylphosphonates was also achieved by electroreduction of diethyl R,R-dichlorobenzylphosphonate **83** in the presence of Michael acceptors in a one-compartment cell equipped with a magnesium sacrificial anode. Electroreductions of **83** in a DMF medium, between a carbon-felt cathode and a sacrificial anode in a one-compartment cell at ambient temperature, performed in the presence of 5 equiv of Michael acceptors, afforded diethyl α-substituted cyclopropylphosphonates **84** in moderate to good yields (*Scheme 31*, *Table 7*). The diastereoselectivity observed during the reaction was largely dependent on the Michael



a) R, R_1 = H, R^2 = COOMe; b) R, R^1 = H, R^2 = COO*t*-Bu; c) R, R^1 = H, R^2 = CN; d) R = R = H, R^1 = Me, R^2 = COOMe; e) R = H, R^1 = Me, R^2 = CN; f) R = Me, R^1 = H, R^2 = COOEt

Scheme 31

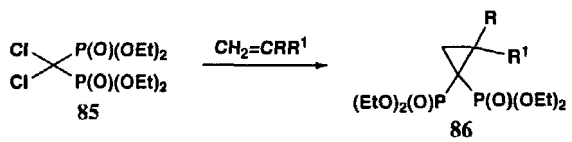
acceptor (*Table 7*). For instance, electrolysis with *tert*-butyl acrylate (*Entry 2*) instead of methyl acrylate (*Entry 1*), enhanced the diastereoselectivity, while methyl methacrylate (*Entry 4*) provided a single diastereoisomer. On the other hand, when acrylonitrile was used as Michael acceptor (*Entry 3*), pure cyclopropylphosphonate **84c** could not be obtained. This phenomenon is probably due to the competing reduction of acrylonitrile.

With a 1,2-disubstituted olefinic acceptor (*Entry 6*), cyclopropanation occurred but several by-products were detected, and purification of **84f** could not be achieved.[63]

Table 7. Diethyl α-Arylated β-Substituted Cyclopropylphosphonates **84** (*Ref. 63, Scheme 31*)

Entry	Product 84	Estimated Yield (%)	Isolated Yield (%)	De (%)
1	a	80	55	40
2	b	100	60	70
3	c	45	-	4
4	d	100	64	>98
5	e	100	73	40
6	f	67	----	4

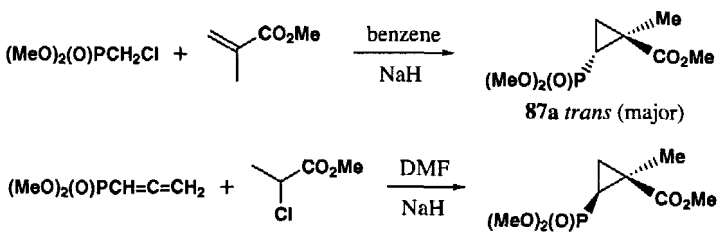
Several substituted cyclopropyl*bis*phosphonates **86a-e** were easily and rapidly prepared (40-75%) under mild conditions in MeCN by electrolysis of tetraethyl dichloromethyl*bis*phosphonate ($Cl_2C[PO(OEt)]_2$, **85**) in the presence of Michael acceptors CH_2=CRR^1 (R = H, R^1 = COOMe, CN, COMe, R = Me, R^1 = COOMe, CN) in a two-compartment cell (*Scheme 32*).[64]



a) R = H, R^1 = Ac; b) R = H, R^1 = COOMe; c) R = Me, R^1 = COOMe
d) R = H, R^1 = CN; e) R = Me, R^1 = CN

Scheme 32

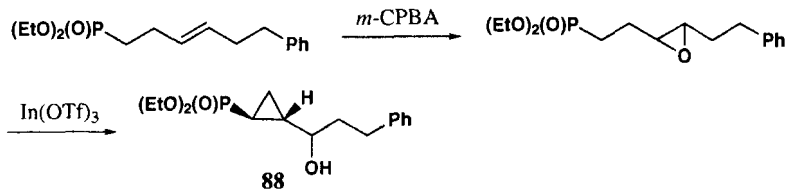
Hellmuth and co-workers[61] reported the synthesis of dimethyl (2-methyl-2-carbomethoxycyclopropyl)phosphonate (**87a** and **87b**) by the reaction of CH_2=CMeCOOMe with $ClCH_2P(O)(OMe)_2$ and NaH in various solvent systems ranging from pure benzene to benzene-DMF and to pure DMF (*Scheme 33*). Two isomers were formed in all solvents. The assigned



Scheme 33

stereochemistry was based on NMR analysis. The ratio of *trans* to *cis* isomer was determined by GC and confirmed by NMR analysis in variable yields (6-38%). The reaction was found to be solvent dependent; the *cis* isomer predominated in DMF, and the *trans* isomer was the major product in benzene. The authors also reported an alternate route to the *cis* isomer (**87b**) from the reaction of dimethyl propa-1,2-dienylphosphonate with methyl chloropropanoate.

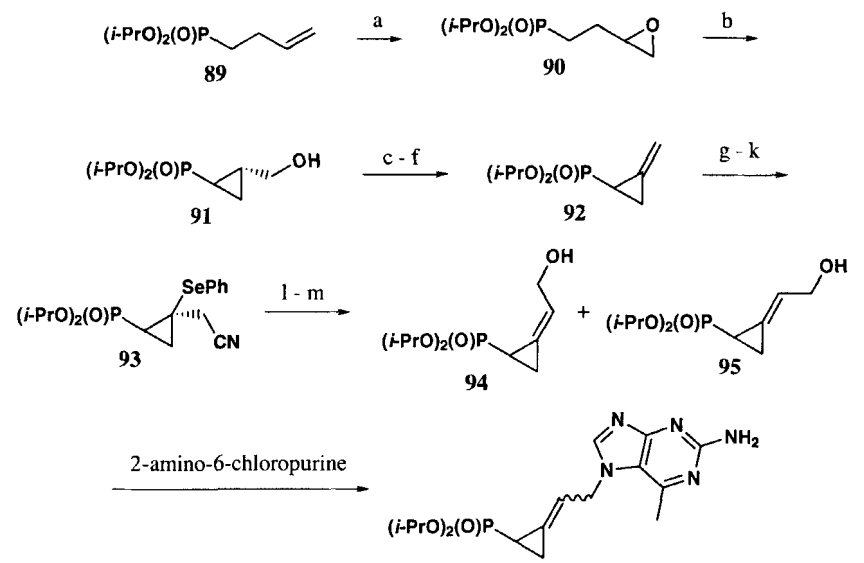
Stereoselective synthesis of hydroxy-containing cyclopropylphosphonates from ethyl phosphonates was described.[68] Metallation of diethyl methylphosphonate by BuLi/CuI followed by coupling with 1-bromo-5-phenyl-2-pentene (afforded 6-phenyl-3-hex-enylphosphonate, which was epoxidized with *m*-chloroperbenzoic acid (MCPBA). The resulting epoxide was rearranged to diethyl *trans*-2-[(1-hydroxy-3-phenylpropyl)cyclopropyl]phosphonate (**88**, *Scheme 34*).[68]



Scheme 34

4. *via Intramolecular Cyclization*

Several intramolecular cyclopropanation reactions were reported with satisfactory yields. Cyclopropylphosphonate **91** was prepared by intramolecular opening of the oxirane ring in **90** (*Scheme 35*). Then cyclopropylphosphonate **91** was transformed in four steps to methylenecyclopropane phosphonate **92** which was converted in seven steps to the key *Z*- and *E*-methylenecyclopropane alcohols (**94** and **95**) by selenoxide elimination. Once **94** and **95** isomers were



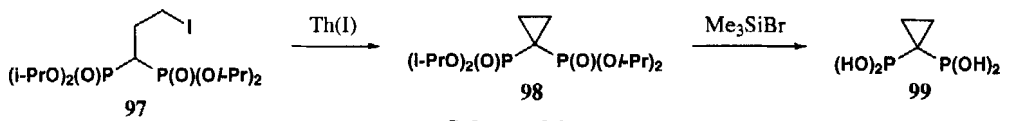
96 Z- and E-isomers

a) MCPBA, CH_2Cl_2; b) BuLi, THF, -78°C; c) Ph_3P, Br_2, CH_2Cl_2; d) $(PhSe)_2$, EtOH, NaOH, NaBH; e) H_2O_2, THF; f) $(i\text{-}Pr)_2NEt$, toluene; g) $(PhSe)_2$, NBS, CH_2Cl_2; h) Me_3SiCN, BuNF, MeCN; i) HCl, MeOH; j) $LiBH_4$, THF; k) Ac_2O, pyridine; l) H_2O_2, THF; m) K_2CO_3, MeOH/H_2O

Scheme 35

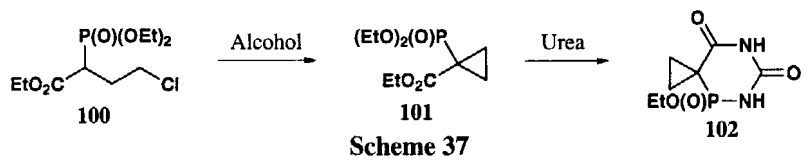
isolated by chromatography, they were converted to the bromides. Alkylation of 2-amino-6-chloropurine with these bromides produced isomeric cyclopropylphosphonates **96**. This method made possible the synthesis of the adenine and guanine methylenecyclopropane nucleoside analogs, which were tested *in vitro* against various viruses including HSV-1, HSV-2, HCMV, EBV, VZV, HIV-1 and HBV. Guanine analogs **96** were found to be potent inhibitors of the replication of *Epstein-Barr* virus (EBV) in *Daudi* cells with EC_{50}/CC_{50} (μM) 1.1 and 0.03/300, respectively.[69]

Tetraisopropyl 1,1-cyclopropyl*bis*(phosphonate) (**98**) was synthesized by an intramolecular cyclization of the thallium(I) salt of tetraisopropyl (3-iodo-1,1-propyl)-*bis*(phosphonate) (**97**). Cleavage of the tetraisopropyl ester **98** led to the formation of 1,1-cyclopropyl*bis*(phosphonic acid) **99** in 60% yield (*Scheme 36*).[66]



Scheme 36

Alcohol-induced cyclocondensation of α-phosphono-γ-chlorobutanoate **100** produced α-phosphoryl cyclopropanecarboxylate **101**, which was then transformed to 1,3,4-diaza-phosphorinane **102** in the presence of urea (*Scheme 37*).[67] The result of the cyclization reaction was dependent on the amounts of the alcohol and the temperature.

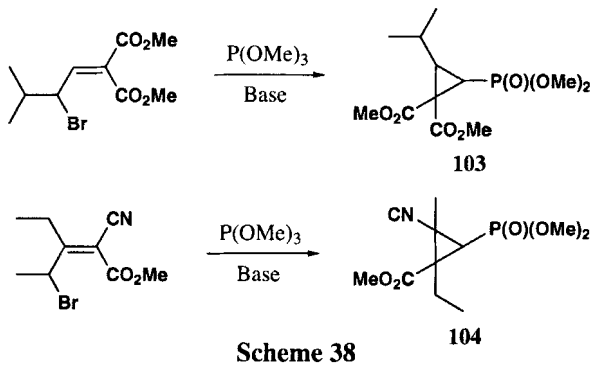


Scheme 37

A variety of cyclopropylphosphonates were prepared in moderate to good yields by Michael Induced Ring Closure (MIRC) of trialkyl phosphites with the corresponding β-bromoalkylidene cyanoacetates and malonates. Thus, Knoevenagel condensation of Me_2CHCHO with $CH_2(COOMe)_2$ in the presence of piperidine/AcOH gave Michael acceptor $Me_2CHCH{=}C(COOMe)_2$ which, upon bromination with NBS/benzoyl peroxide in CCl_4, afforded $Me_2CBrCH{=}C(COOMe)_2$. A Michael Induced Ring Closure (MIRC) reaction of $Me_2CBrCH{=}C(COOMe)_2$ and related β-bromoalkylidene cyanoacetate with $P(OMe)_3$ yielded cyclopropylphosphonates **103** and **104** (72%), respectively (*Scheme 38*).[61]

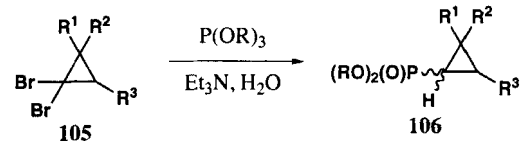
5. *via Arbuzov Reactions*

An alternate route for the preparation of cyclopropylphosphonates involves the introduction of the phosphonate group to the cyclopropane and was achieved in good yield by Arbuzov reactions. Phosphonation of *gem*-dibromocyclopropane **105** [R^1 = *n*-C_6H_{13}, H, Ph, $SiMe_3$, CN; R^2 = H, Me; R^3 = H; R^2, R^3 = $(CH_2)_4$, $(CH_2)_6$] with $P(OR)_3$ (R^4 = Et, Me_2CH)] in the



Scheme 38

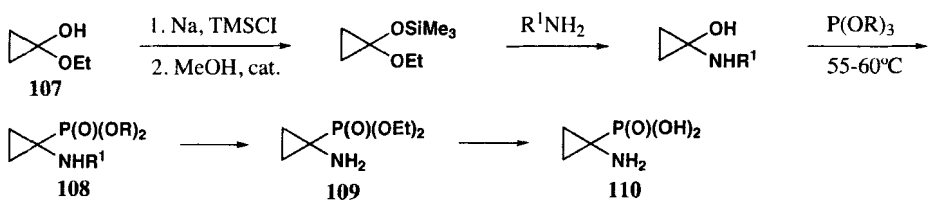
presence of Et_3N and water surprisingly gave *cis*- and *trans*-cyclopropylphosphonates **106,** together with the corresponding monobromocyclopropanes (*Scheme 39*).[70]



[R^1 = n-C_6H_{13}, H, Ph, $SiMe_3$, CN; R^2 = H, Me; R^3 = H; R^2R^3 = $(CH_2)_4$, $(CH_2)_6$ with $P(OR)_3$ (R = Et, Me_2CH)]

Scheme 39

Addition of chlorotrimethylsilane to a solution of cyclopropanol **107** in ethanol followed by the successive addition of H_2NR' (R^1 = CH_2Ph, (R)-CH(Me)Ph, racemic CH(Me)Ph), acetic acid, and $P(OR)_3$ (R = Me or Et), produced aminocyclopropanephosphonates **108** (same R and R', 68-95% yields). The resultant product **108** (R = Et, R^1 = (R)-CH(Me)Ph) was then added to Pearlman's catalyst in ethanol and stirred at room temperature for 3 hrs under hydrogen to afford aminophosphonate **109** (95% yield). When a solution of **109** in HCl was heated at reflux for 20 h followed by the addition of propylene oxide, it was transformed to 1-aminocyclopropanephosphonic acid **110** (87% yield) (*Scheme 40*).[59] The method

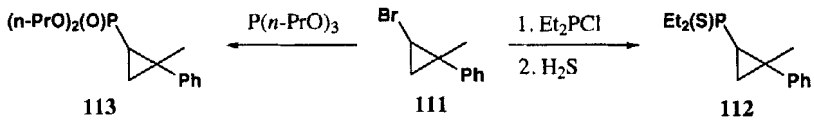


Scheme 40

described is considered a facile and efficient three-step synthesis of 1-aminocyclopropanephosphonic acid from cyclopropanol **107** (77% overall yield).

Reaction of **111** with $(n\text{-PrO})_3P$ proceeded *via* an Arbuzov rearrangement to provide

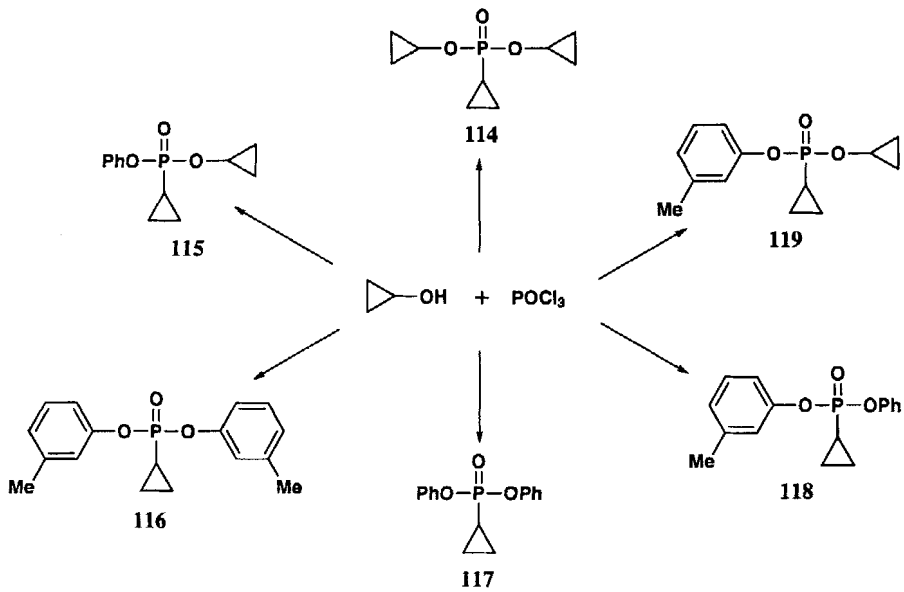
113. In addition, diethyl (2-methyl-2-phenylcyclopropyl)phosphine sulfide **112** was prepared by the reaction of cyclopropane **111** with Et_2PCl, followed by treatment with H_2S (*Scheme 41*).[71]



113 111 112

Scheme 41

Cyclopropylphosphonate **114** was reported to be formed by the dropwise addition of 3.5 moles of cyclopropanol to one mole $POCl_3$ at 25-35°C. Five other cyclopropylphosphonates (**115-119**) were similarly obtained (*Scheme 42*).[72] In addition, a two-step conventional method

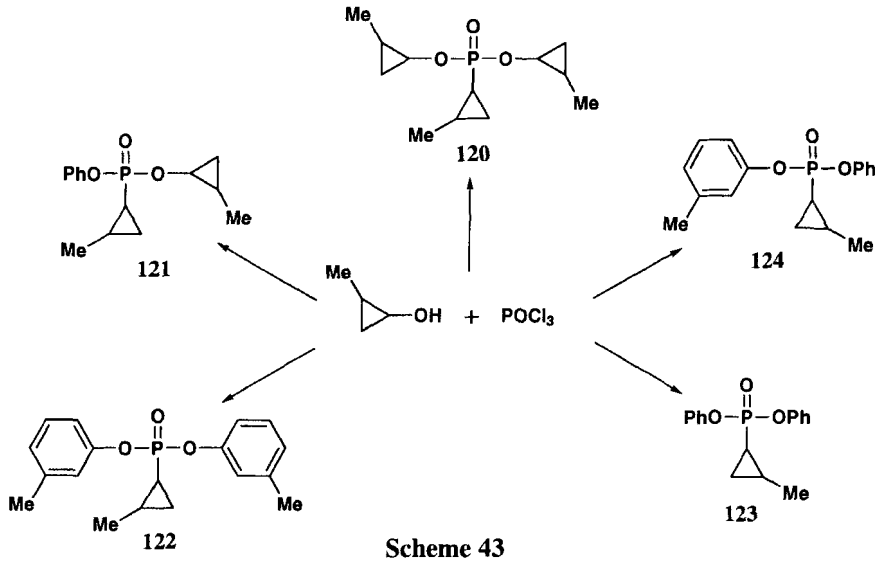


Scheme 42

for the synthesis of analogous cyclopropylphosphonates **120-124**, containing the methylcyclopropyl group, and phenyl or tolyl groups, *e. g.* $POCl_3$ and 2-methylcyclopropyl alcohol, was reported. These products are thermally stable compounds and are used as fire resistant hydraulic fluids, especially for aircrafts. Moreover, they have good lubricity, boundary lubricity, anti-wear properties, viscosity, viscosity-temperature behavior, and miscibility with additives (*Scheme 43*);[73] no rationalization was provided for the missing oxygen in these products.

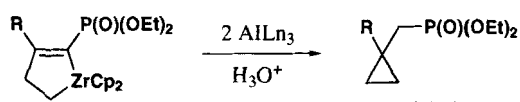
II. β-CYCLOPROPYLPHOSPHONATES

Over the last few years, Quntar and Srebnik have been investigating the conversion of 1-alkynylphosphonates to highly substituted vinylphosphonates with group IV reagents.[74] It has



Scheme 43

been shown that the intermediate metallocycles are very sensitive to reaction conditions. Various substituted vinylphosphonates can be obtained from the same electrophile by changing both the quantities of reagents required to generate the reactive group IV species and the metal additives.[75] Furthermore, interesting vinylphosphonates were obtained utilizing the five-membered rings **125** which were formed from the reaction of 1-alkynylphosphonates with Cp_2ZrCl_2/2EtMgBr (>97%).[76,77,78] Intermediates **125** are thermally stable at room temperature and are smoothly inserted into various electrophiles. Surprisingly, it has been found that addition of 2 equiv. of $AlMe_3$ or $AlEt_3$ led to the exclusive formation of cyclopropylmethylphosphonates **126b** (65%). Optimization of the reaction conditions by using $AlCl_3$, rather than AlR_3, improved the yield of **126b** to 95% (*Scheme 44*, *Table 8*).[79]



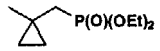
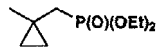
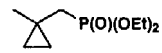
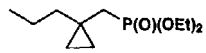
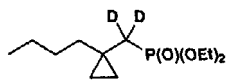
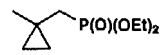
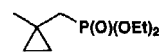
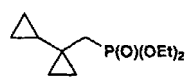
125 **126a-i**

Scheme 44 Ln = Me, Et, Cl

The phosphonate ester moiety influenced the rate of the reaction, *i. e.* the diphenylphosphonate required overnight stirring to give an 85% yield of the zirconacyclopentene diphenylphosphonate **126f** (*Table 8*). Apparently, the phosphonate oxygens coordinate with the $AlEt_3$ and Cp_2ZrCl_2. Indeed, when hex-1-ynylphosphonate was stirred with one equivalent of $AlEt_3$ in $CDCl_3$, the upfield shift in the ^{31}P NMR was observed from δ -4 to -8 is indicative of Lewis acid complexation with the phosphonate oxygens. It is thus necessary to generate the much more reactive zirconacyclopentene first which is subsequently can be transmetallated with $AlCl_3$ to afford the aluminacyclopentenes. Even with pre-formed zirconacyclopentenes **125**, two equivalents of $AlCl_3$ are required. One equivalent reacts with **125** to form the aluminacyclopen-

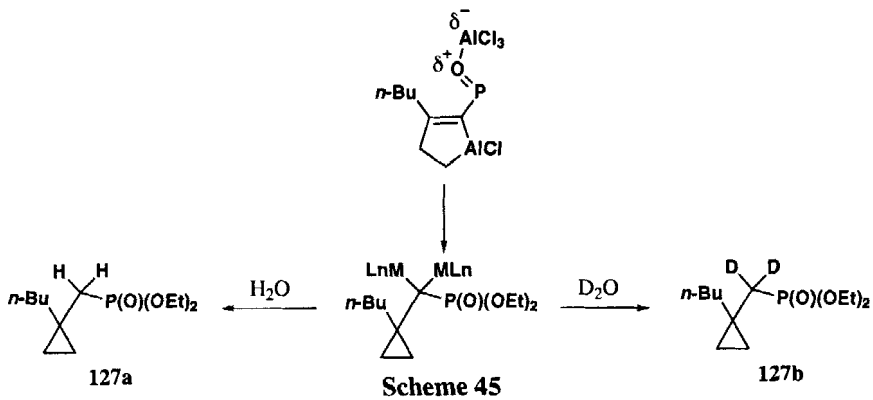
tenylphosphonate, while it is surmised that the other equivalent remains coordinated to the phosphonate oxygens.

Table 8. Formation of Cyclopropymethyl Phosphonates **126** (*Ref. 79, Scheme 44*)

Conversion[a]/Yield[b]	126	Entry
95/75		**a**
95/81		**b**
95/72		**c**
95/72		**d**
95/73		**e**
95/68		**f**
80/57		**g**
95/71		**h**
95/68		**i**

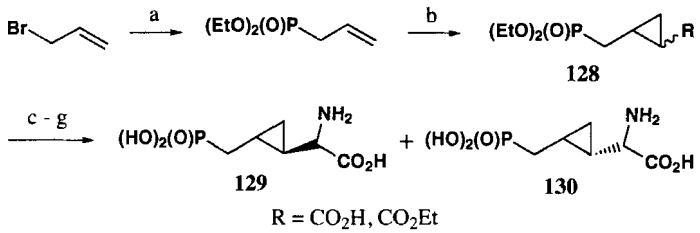
[a]Determined by ^{31}P NMR. [b] After chromatography

The alumina cyclopentenylphosphonate spontaneously ring-contracts to a cyclopropylmethyl-bimetallic intermediate (**126**), which upon deuterolysis, gave deuterated product **127b**, which is consistent with formation of a cyclopropylmethylbimetallic compound prior to workup (*Scheme 45*). This must be due to the presence of the electron-withdrawing phosphonate group which stabilizes the negative charges on the α-carbon.



127a **Scheme 45** **127b**

Diethyl cyclopropylmethylphosphonates **128** was obtained (30% yield) by the Arbuzov reaction between allyl bromide and triethyl phosphate, followed by copper- catalyzed decomposition of ethyl diazoacetate (*Scheme 46*). 2-Amino-5-phosphonopentanoic acid (**AP5**) analogs to

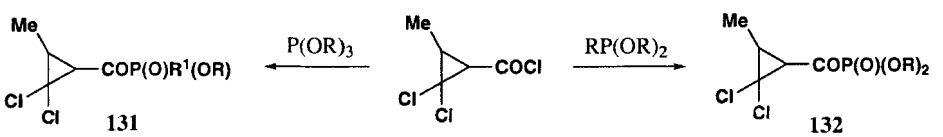


a) $P(OEt)_2$, 100°C; b) N_2CHCO_2Et, $CuSO_2$, $CuSO_4$, reflux; c) KOH, THF/H_2O; d) BH_3-THF, THF; e) PCC, CH_2Cl_2; f) KCN, NH_4Cl, A1203, CH_3CN, ultrasound; g) 6N HCl, reflux

Scheme 46

129 and **130** were synthesized by hydrolysis of the ester to the acid, followed by the reduction to the alcohol, oxidation to the aldehyde conversion to aminonitriles *via* alumina-catalyzed ultrasound followed by hydrolysis of the nitrile and phosphonate groups. The biological activity of these analogs was assessed as competitive antagonists for the *N*-methyl-D-aspartate (**NMDA**) receptor.[18] *In vitro* receptor binding using [^{3}H]-L-glutamate as the radioligand provided affinity data, while modulation of [^{3}H]MK-801 binding was used as a functional assay. These analogs were also evaluated in [^{3}H]kainate binding to assess selectivity over non-NMDA glutamate receptors. The analogs showed potent selective NMDA antagonism.

Arbuzov rearrangement of 1-methyl-2,2-dichlorocyclopropylcarbonyl chloride with phosphonites [$R^1P(OR)_2$], or with trialkyl phosphates [$P(OR)_3$] gave alkyl (1-methyl-2,2-dichlorocyclopropylcarbonyl)arylphosphonates **131** and dialkyl 1-methyl-2,2-dichlorocyclopropylcarbonylphosphinates **132**, respectively (*Scheme 47*).[80]

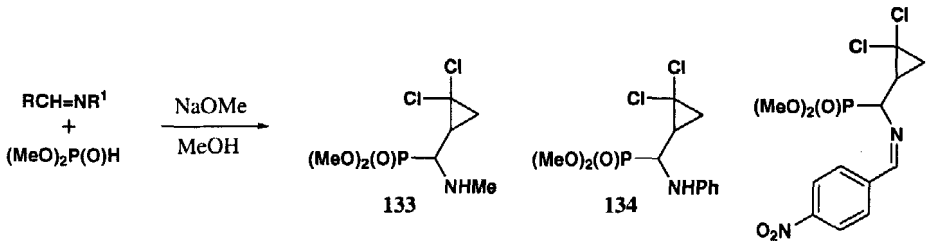


a) R = Me, R^1 = 4-$Me_2NC_6H_4$
b) R = Et, R^1 = 4-$Me_2NC_6H_4$

a) R = CH_2CH_2Cl; b) R = *n*-Bu; c) R = *i*-Pr

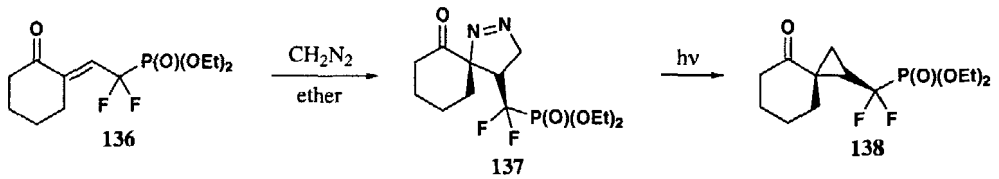
Scheme 47

Cyclopropylaminomethylphosphonates **133-135**, among others, were obtained (50-100%) by the reaction of imines RCH=NR^1 [R = 2,2-dichlorocyclopropyl, R^1 = Me, Ph, 4-$AcNHC_6H_4$, 2-pyridyl; R = Ph, 4-$Me_2NC_6N_4$, 2-HOC_6H_4, 4-$O_2NC_6H_4$, R^1 = (2,2-dichlorocyclopropyl)methyl] with dimethyl phosphonate $(MeO)_2P(O)H$ in MeOH containing NaOMe. In addition to their insecticidal activity, compounds **133-135** possessed antiviral and antifungal activities (*Scheme 48*).[81]



Scheme 48

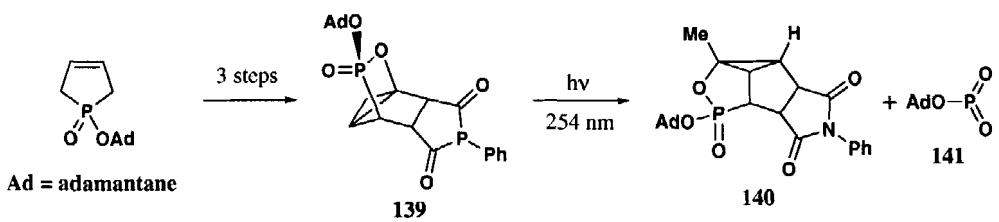
1,3-Dipolar cycloaddition of diazomethane to (1,1-difluoroallyl)phosphonates gave pyrazolines functionalized by a (diethoxyphosphoryl)difluoromethyl moiety. These pyrazolines were easily converted to cyclopropane derivatives possessing a (diethoxyphosphoryl)difluoromethyl functionality by photolysis. Thus, (*E*)-2-iodomethylenecyclohexanone was converted to the phosphonate **136** (63%) by cross-coupling reaction with $BrZnCF_2PO_3Et_2$ in the presence of CuBr in DMF. Treatment of (*E*)-**136** with a large excess of diazomethane in ether gave the adduct **137** (65%). Photolysis of **137** in acetone by irradiation with a high-pressure Hg-lamp (500 W) gave **138** (91%) (*Scheme 49*).[82]



Scheme 49

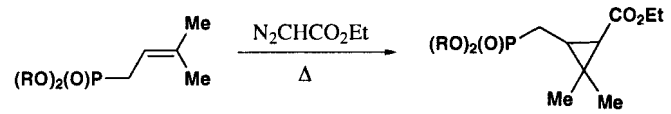
III. γ-CYCLOPROPYLPHOSPHONATES

Although the synthesis of γ-cyclopropylphosphonates and their chemistry are not widely described in the literature, a few synthetic methods have been reported. The unstable adamantylphosphole oxide underwent a rapid intermolecular Diels-Alder dimerization to produce the 2,3-oxaphosphabicyclo[2.2.2]octene ring system. Rearrangement of the later by irradiation at -75°C afforded the novel multicyclic compound **139** with a cyclopropane unit (*Scheme 50*).[83] Further irradiation of **139** at -75°C resulted in a novel rearrangement to give predominantly **140** together with some extracted adamantyl metaphosphate **141**.



Scheme 50

Addition of $(n\text{-BuO})_2PONa$ to 1-chloro-3-methyl-2-butene gave, after 3 hr at reflux in Et_2O the unsaturated phosphonate $MeRC{=}CHCH_2P(O)(OR_1)_2$ (R = Me, R^1 = Pr, *n*-Bu) (93%). Treatment of the later with methyl or ethyl diazoacetate and dry $CuSO_4$ for 3-4 hrs at 95-100°C resulted in gradual evolution of nitrogen and formation of the adduct which, after washing with aqueous $KMnO_4$, gave ethyl 3-(2-(dibutoxyphosphoryl)ethyl)-2,2-dimethylcyclopropanecarboxylate (**142**, *Scheme 51*).[84]



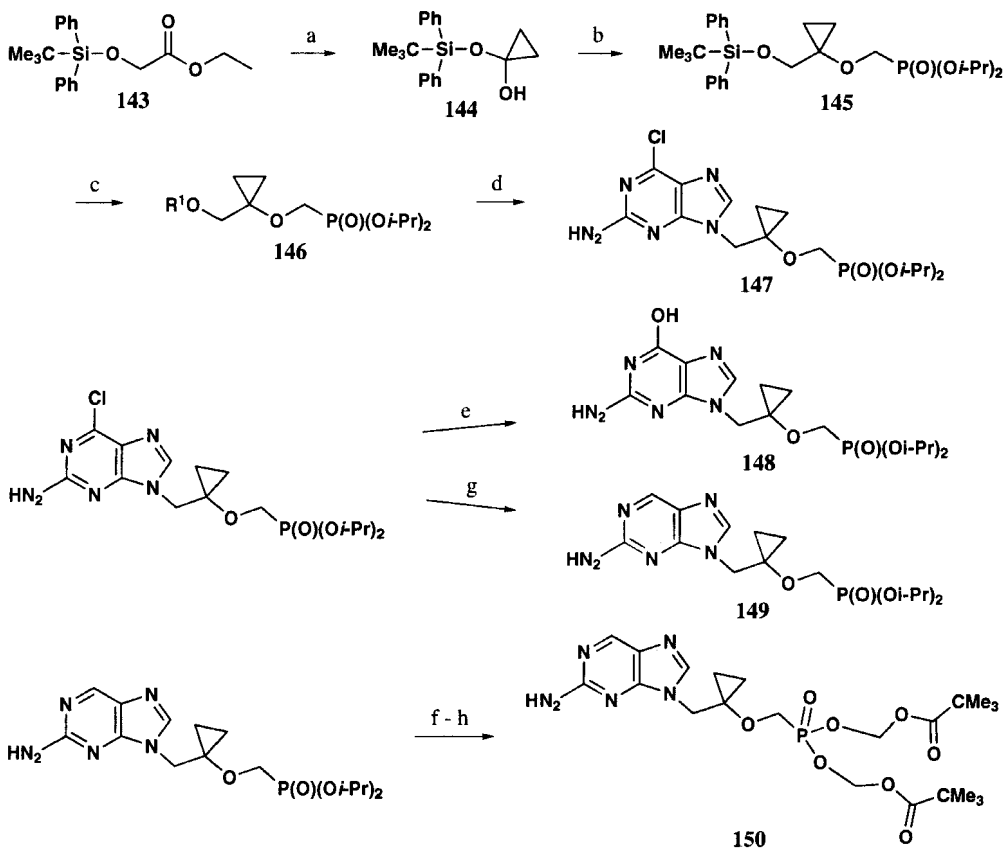
R = *n*-Bu, *i*-Pr, Et

142

90%

Scheme 51

9-[1-(Phosphonomethoxycyclopropyl)methyl]guanine (PMCG, **148**) was synthesized in seven steps from *O*-silylprotected ethyl glycolate in 17-20% overall yield as shown in *Scheme 52*. The key intermediate cyclopropanol **144** was prepared as a white solid by titanium-

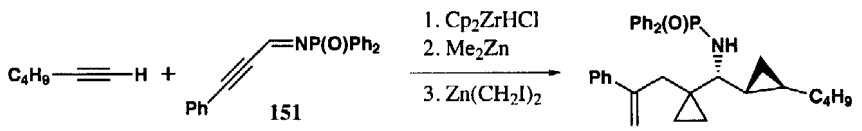


a) CH_3CH_2MgBr, $Ti(Oi\text{-}Pr)_4$ (0.25 equiv), THF, 0°C to 25°C, 10 h; b) $BrCH_2P(O)(Oi\text{-}Pr)_2$, LiO*t*-Bu, LiI (cat.), DMF, THF, 60°C, 4h; c) NH_4F, MeOH, reflux, 10 h; d) 6-chloroguanine, NaH, DMF, 80°C 4 h; e) TMSBr, MDC, reflux, 18 h; f) 2 N HCl, reflux, 6 h; g) H_2, 5% Pd on C, THF, 1 atm, 18h; h) chloromethyl pivalate, TEA, 1-methyl-2-pyrrolidinone, 25°C, 48 h

Scheme 52

mediated Kulinkovich cyclopropanation of ester **143** (> 80%). Etherification of **144** with diisopropyl bromomethylphosphonate in the presence of LiO*t*-Bu in THF and DMF at 50-60°C gave phosphonate **145** in (> 70%). The yield of this etherification was highly dependent on the base and reaction temperature.[19] Desilylation of the phosphonate **145** with ammonium fluoride, followed by mesylation and subsequent coupling reaction with 6-chloroguanine, gave the 9-substituted isomer **146** (27%). Compound **146** was hydrolyzed with trimethylsilyl bromide, followed by treatment with 2 N HCl, to afford **148** in quantitative yield. On the other hand, 9-[1-phosphono-methoxycyclopropyl) methyl]-6-deoxyguanine (PMCDG, **150**) was obtained from **146** (94%) by hydrogenation of **146** in the presence of palladium and subsequent hydrolysis with trimethylsilyl bromide which led to **149**. Then etherification of **149** with chloromethyl pivalate in the presence of triethylamine in 1-methyl-2-pyrrolidinone produced PMCDG *dipivoxil* **150** (39%).

Wipf and co-workers described the synthesis of *C,C*-dicyclopropylmethylamine **152** with the phosphine moiety by the addition of hexenylzirconocene to alkynyl imine **151** in the presence of dimethylzinc and the zinc carbenoid $Zn(CH_2I)_2$. The reaction proceeded diastereoselectively under mild conditions in a single step and resulted in the preparation of diverse structures from readily available starting materials (*Scheme 53*, *Table 9*).[85] The mechanistic pathway



Scheme 53 **152**

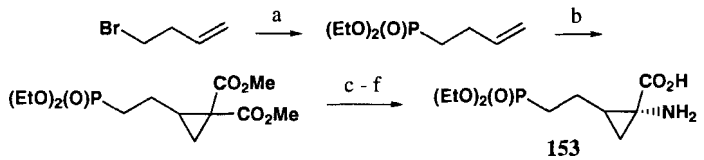
includes transmetalation of the alkenylzirconocene to dimethylzinc. Then alkyl group exchange occurred after addition of the imine to generate the zinc carbenoid which undergoes triple cyclopropanation at the allylic alkene as well as the alkyne moiety to give a bicyclo[1.1.0]butane followed by a double- bond insertion with carbenes prior cyclopropanation to afford **152** .

Table 9. Optimization of the Formation of **152** from Alkyne and Imine (*Ref. 85*, *Scheme 53*)

Entry	Equiv of Cp_2ZrHCl	Equiv of 151	Equiv of Me_2Zn	Equiv of $Zn(CH_2I)_2$	Solvent	Temp. (°C)	Yield (%)
1	3	3	3	3	CH_2Cl_2	rt	60
2	1.5	1.5	1.5	4	Toluene	rt	<50
3	1.5	1.5	1.5	4	CH_2Cl_2	rt	60
4	1.5	1.5	1.5	4	CH_2Cl_2	0	68

The use of the same strategy for the synthesis of β-cyclopropylphosphonate described by Dappen *et al.* led to γ-cyclopropylphosphonates **153** by Arbuzov reaction between triethyl phosphite and 4-bromo-1-butene followed by cyclopropanation with diazomalonate, hydrolysis to the mono acid, conversion to the acyl azide, and hydrolysis of the nitrile (*Scheme 54*).[18] Simi-

larly, ketophosphonates $(EtO)_2P(O)CHR_1CH_2C(O)R_2$ (R^1/R^2 = Ph/cyclopropyl, and other groups such as R^1/R^2 = Ph/Me, Ph/Ph, 2-furyl/Me, 2-thienyl/Me, Ph/Bn) were utilized to prepare the corresponding cyclopropylphosphonates.

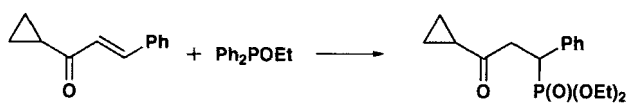


153

a) $P(OEt)_3$, 100°C; b) $N_2C(CO_2Me)_2$, $CuSO_4$, reflux; c) NaOH MeOH/H_2O; d) K_2CO_3, $EtOCO_2Cl$, 1,6-dicyclohexano-18-crown-6, THF, 0°C, NaN_3, THF/H_2O; e) *t*-BuOH, reflux; f) 6N HCl, reflux

Scheme 54

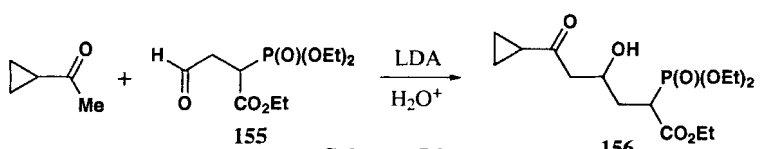
For example, 1-cyclopropyl-3-phenyl-2-propen-1-one **154** was obtained by the reaction of diphenylphosphinous acid ethyl ester with 1-cyclopropyl-3-phenylprop-2-en-1-one (*Scheme 55*). The confirmation of structure **154** was determined from ^1H NMR coupling constants.[86, 87]



Scheme 55 154

IV. ω-CYCLOPROPYLPHOSPHONATES

The reaction of methyl cyclopropylketone with ethyl 2-(diethoxyphosphoryl)-4-oxobutanoate (**155**) in the presence of lithium diisopropyamide (LDA) produced the keto ester, 1-cyclopropyl-5-(diethoxyphosphoryl)-6-ethoxy-1,6-dioxohexan-3-olate **156** (48% yield, *Scheme 56*).[88]



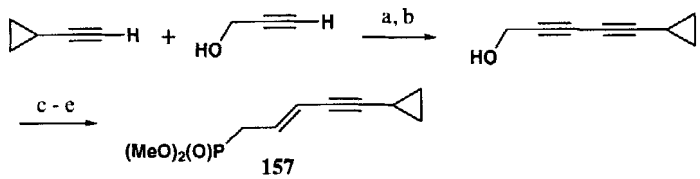
155 156

Scheme 56

A straightforward synthesis of (*E*)-dimethyl 5-cyclopropylpent-2-en-4-ynylphosphonate **157** in five steps from propargyl alcohol and 1-alkynylcyclopropane has been described.[89, 90] Compounds **157** served as building blocks for the synthesis of *callipeltoside* and *deschlorocallipeltoside* which were found to be novel antitumor agents (*Scheme 57*).

Cyclopropanation, together with chain elongation, occurred in the reaction of β-keto phosphonates **158** that contained an olefinic functionality (dimethyl 2-oxohex-5-enylphosphonate) with ethyl(iodomethyl)zinc to produce dimethyl 5-cyclopropyl-3-oxopentylphosphonate

(**160**) and dimethyl 3-oxohept-6-enylphosphonate **159**. It was found that chain elongation of β-ketophosphonates that contained olefinic functionality proceeded much more rapidly than

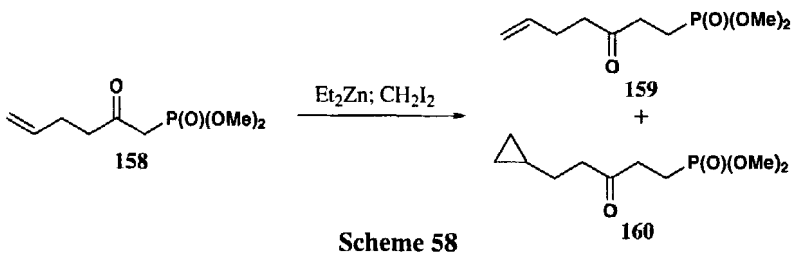


157

a) *n*-BuLi, I_2, THF, 0°C, 2 h, 80%; b) CuI, pyrrolidine, THF, 0°C to room temperature, 2 h, 38%; c) Red-Al, THF, 0°C, 1 h, 96%; d) PPh_3, CBr_4, CH_2Cl_2, -40°C, 1 h, 95%; e) $P(OMe)_3$, 100°C 6 h, 97%

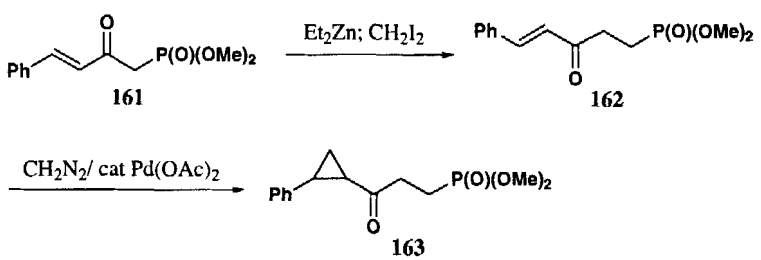
Scheme 57

cyclopropanation (*Scheme 58*). However, the primary reason for the formation of the cyclopropanation product **160** is apparently due the slow chain elongation of β-ketophosphonates.[91] The results and reaction conditions are shown in *Table 10*.



Scheme 58

It had been found that treatment of the β-ketoesters with a zinc carbenoid resulted in the generation of a cyclopropyl alcohol which fragmented to the isomeric γ-ketoesters. Although the reaction works remarkably well for simple β-ketoesters, substrates with α-substitution or cyclic substrates reacted less efficiently. Application of this methodology to β-ketophosphonates resulted in chain elongation which leads to the formation of γ-ketophosphonates. Accordingly, all initial efforts to cyclopropanate **162** with an electrophilic zinc carbenoid failed to provide **163** (*Scheme 59*).



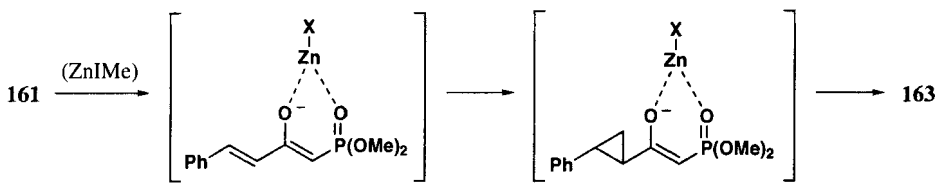
Scheme 59

Table 10. Cyclopropanation and Chain-elongation of **158** (*Ref. 90, Scheme 58*)

Entry	Method[a]	Equiv.[b]	Time[c]	Temp.°C	Yield %	Ratio (158:159:160)
1	A	6	180	25	80[d]	0:1:1[e]
2	A	6	40	25	75[d]	0:2:1[e]
3	A	3	20	25	f	4:4:1[g]
4	A	6	25	0	f	1
5	B	6	25	25	f	0:3:1[g]
6	C	6	30	25	f	0:3:1[g]
7	C	6	10	25	f	1:7.8:1.3[g]
8	C	H	30	25	f	1.4:6.6:1[g]
9	C	6	30	0	f	3.1:8:1

a) Method A: α-keto phosphonate added to preformed carbenoid. Method B: the α-keto phosphonate was mixed with 1 equiv of diethyl zinc prior to its addition to the carbenoid. Method C: excess diethyl zinc added to the α-ketophosphonate, followed by addition of methylene iodide. b) Ratio of carbenoid (1:1, Et_2Zn:CH_2I_2) to α-ketophosphonate **158**. c) Reaction time after addition of the carbenoid d) Isolated yield of the inseparable mixture of **159** and **160**. e) Determined by ^1H NMR analysis of purified material. f) No purification was attempted. g) Determined by analysis of ^1H NMR of crude reaction mixture. h) Ratio of reagents was 6:3:1 (Et_2Zn, CH_2I_2, **158**).

However, deprotonation of compound **161** made the "electron-deficient olefin" of **161** part of a cross-conjugated electron-rich π-system. The allylic heteroatom of **164** seemed to be an appropriate handle for formation of cyclopropane **165** which, when followed by chain elongation of the enolate, could account for the formation of **163** (*Scheme 60*). Although chain elongation



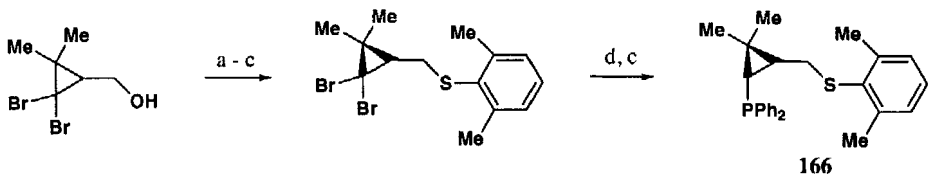
Scheme 60

prior to cyclopropane formation appears to be an explanation for the formation of **163**, cyclopropanation of the "electron-deficient olefin" might be possible if the hypothetical cyclopropyl alkoxide intermediate provided a heteroatom handle for subsequent cyclopropanation. Compound **162** was generated through chain elongation of β-ketophosphonate **161** using 3.25 equiv of ethyl(iodomethyl)zinc at 25°C for 30 minutes.

The discussion above makes it clear that most of the emphasis was on the preparation of α-cyclopropylphosphonates rather than on β-, γ- and ω-cyclopropylphosphonates, apparently due to their ease of formation, and the availability of the starting materials.

V. CYCLOPROPANE STRUCTURES WITH OTHER PHOSPHORUS GROUPS

Cyclopropanes with other phosphorus groups (other than phosphonate group) have also been discussed in several publications. Their preparation was based mostly on Arbusov-type reactions. Chiral cyclopropane-based phosphorus/sulfur ligands ((1S,2R)-2-[(2,6-dimethylphenylthio)methyl]cyclopropyldiphenylphosphine **166** was synthesized under zinc-catalyzed conditions utilizing (S)-(2,2-dibromo-3,3-dimethylcyclopropyl)-methanol followed by sulfonylation to (S)-((2,2-dibromocyclopropyl)methyl)(2,6-di-methylphenyl)sulfane by (+)-3-bromocamphor-8-sulfonic acid chloride. Optimal configuration of this reaction yielded 93% enantioselectivity.[92] However, an enantiopure ligand analog required resolution (*Scheme 61*).

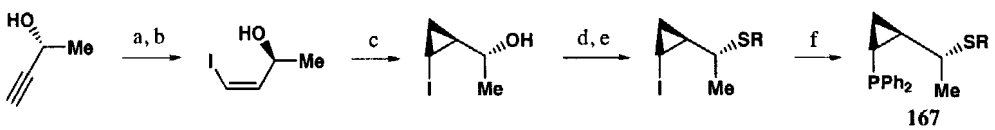


166

a) (+)-3-bromocamphor-8-sulfonic acid chloride, Et_3N; b) Resolution; c) 2,6-$(Me)_2PhSH$, K_2CO_3, DMF, 86%; d) Zn, AcOH, 6:1, 38%; e) *t*-BuLi, Ph_2PCl, 60%

Scheme 61

In addition, the synthesis of another class of ligands, [2-(1-(alkylthio)ethylcyclopropyl]diphenylphosphines (**167a-d**), was attained utilizing the commercially available (*R*)-3-butyn-2-ol (> 98% ee) that was easily iodinated and reduced with diimide. Then diethyl zinc was used to cyclopropanate the alkene, followed by sulfonylation of the alcohol and phosphorylation *via* an Arbuzov reaction (*Scheme 62*).[92]



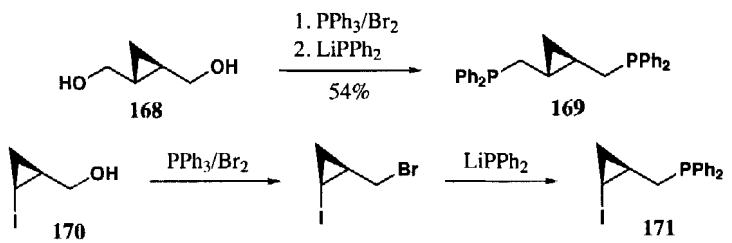
167

a) R = t-Bu; b) R = 2,6-$(Me)_2Ph$; c) R = Et; d) R = Me

a) *n*-BuLi; I_2, 98%; b) $KO_2CN_2CO_2K$, AcOH, 87%; c) Et_2Zn, CF_3CO_2H, CH_2I_2, 74%; d) PPH_3, Br_2, 5:1 dr, 91%; e) RSH, Cs_2CO_3, 35-87%; f) *t*-BuLi, Ph_2PCl, 45-84%

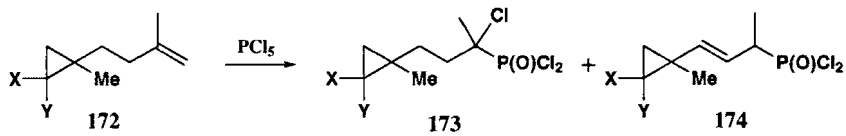
Scheme 62

Furthermore, the synthesis of 1,2-*bis*[(diphenylphosphino)methyl]cycloropanes (**169**) and [(2-iodocyclopropyl)methyl]diphenylphosphine **171** were explored using the corresponding alcohols **168** and **170** respectively (*Scheme 63*).[92]



Scheme 63

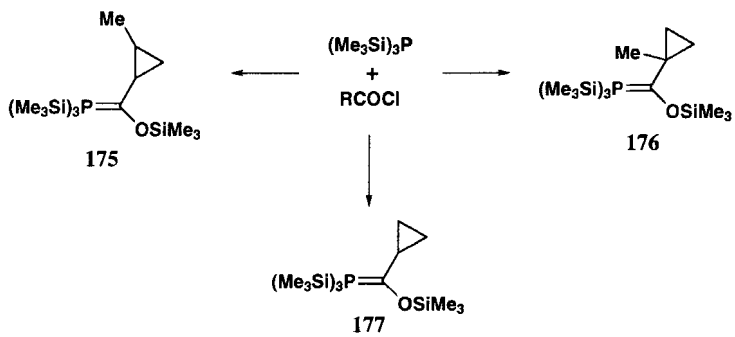
Phosphorylation of cyclopropylalkenes **172** (X,Y: Cl,Cl; H,Cl; H,H) with PCl_5 afforded phosphonic acid chlorides **173** and **174** in 76:24 ratios, respectively (*Scheme 64*).[93]



172 173 174

Scheme 64

Alkylidenephosphines containing different cyclopropane and cyclobutane substituents at the C atom of the P=C double bond were prepared from *tris*(trimethylsilyl)phosphine and acid chlorides, with acylphosphines detectable by NMR as intermediate products of the reaction. The reaction of $(Me_3Si)_3P$ with RCOCl (R = cyclopropyl, 1-methyl-cyclopropyl, 2-methylcyclopropyl, 1-methyl-2,2-dichlorocyclopropyl, cyclobutyl) was carried out in benzene at -3°C to afford the cyclopropyl products **175-177** (75-95% yields) (*Scheme 65*).[94] Similar compounds



175 176 177

Scheme 65

have also been synthesized by Kostitsyn *et al.*[95] The cyclopropanecarboxylic acid chlorides RCOCl (R = cyclopropyl, 1- and 2-methylcyclopropyl, 2,2-dichloro-1-methylcyclopropyl) reacted with *tris*(trimethylsilyl)phosphine in benzene at -2°C to furnish the corresponding cyclopropylcarbonyl-*bis*(trimethylsilyl)phosphines $RC(O)P(SiMe_3)_2$. These products underwent trimethylsilyl group shifts at 25°C to yield the phosphaalkenes $Me_3SiOCR{=}PSiMe_3$ as mixtures of *E*- and *Z*-isomers.

VI. CONCLUSIONS

In summary, it is evident from the results presented in this review that different effective methodologies have been utilized for the synthesis of chemical structures that contain both cyclopropyl and phosphorus groups. The most common methods are either the catalytic addition of diazomethylphosphonates to olefins or the addition of diazomethane to vinylphosphonates. In addition, other synthetic routes including Michael Induced Ring Closure (MIRC), intramolecular cyclization, metallocycle intermediates and Arbuzov reactions have been described. Many of these phosphorous-cyclopropyl containing compounds have been shown to possess biological activity and are useful intermediates for organic synthesis.

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