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Contribution

1,1-Dimethyleneallyl Palladium Complexes: Preparation and Synthetic Potential.

Jacques SALAÜN,
Laboratoire des Carbocycles (Associé au CNRS),
Institut de Chimie Moléculaire d'Orsay Bât. 420,
Université de Paris-Sud, 91405 ORSAY (France)

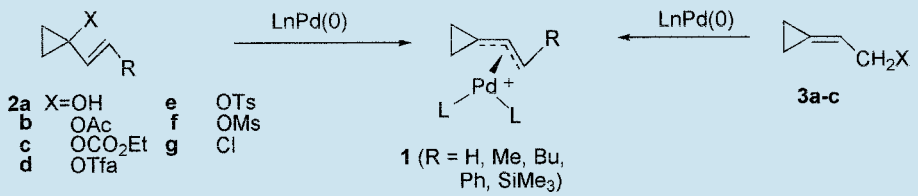
Introduction

The cyclopropane ring is unique among carbocycles in both its properties and reactions because of its unusual bonding and inherent ring strain (27.5 kcal.mol^{-1}). Its chemical reactivity closely resembles that of an olefinic double bond; effectively, both groups interact with neighbouring π-electron systems and *p*-electron centers, add acids, halogens and ozone, undergo catalytic hydrogenation and cycloadditions, form metal complexes, etc...[1] Cyclopropane derivatives not only provide building blocks of unprecedented synthetic potential,[1] but they are also endowed with a large spectrum of biological properties ranging from antibiotic, antiviral, antifungal, insecticidal, hormonal, neurochemical, antitumoral activities to enzyme inhibitions.[2] Key intermediates in many biosynthetic processes, they are widely used as mechanistic probes and for the design of new drugs.[2,3] Therefore cyclopropane containing compounds are of great general interest to synthetic organic chemists as well as to bioorganic chemists.

Specific reactivity of the cyclopropane moiety can be strongly influenced by the substituents on the ring. Thus, vicinally donor–acceptor substituted cyclopropanes undergo ring opening reactions leading to polyfunctional compounds or to carbocyclic and heterocyclic systems,[4] while substituted on the same carbon by an electron donating group and adjacent multiple bond the three-membered ring can undergo stereoselective C_3 ¤ $C_{4\text{-}20}$ ring expansions which have been incorporated into many effective synthetic schemes.[5,6] A new and promising area of the cyclopropane chemistry has been recently investigated from the palladium(0) catalyzed nucleophilic substitution of 1-(l-alkenyl)cyclopropyl esters, which involves the intermediate formation of π-1,1-dimethyleneallyl palladium complexes **1**.[7]

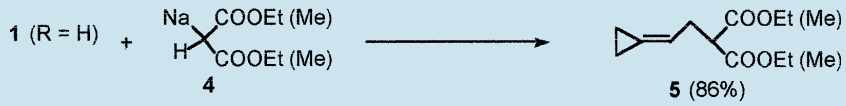
Preparation

1-(1-Alkenyl)cyclopropanols **2a** are conveniently available either from 1,3-dichloroacetone,[8] cyclopropanone hemiacetal,[9] 1-hydroxycyclopropanecarboxylic acid[10] or from the titanium(IV) catalyzed reaction of organomagnesium compounds with 2-alkenecarboxylates.[11,12] Then esterification of **2a** by acetyl chloride, ethyl chloroformate, trifluoroacetic anhydride, tosyl or mesyl chlorides led readily to the allylic esters **2b**-**f**.[7,12,13] Otherwise,1-chloro-1-ethenylcyclopropanes **2g** can be prepared either by addition of 1-chloro ethenylcarbene onto alkenes,[14] or from 1-chloro-1-trichloroethenylcyclopropanes.[15] The isomeric acetate **3b** and carbonate **3c** result from the esterification of 2-cyclopropylideneethanol **3a**,[7] also readily available from the cyclopropanone hemiacetal.[9,16,17]



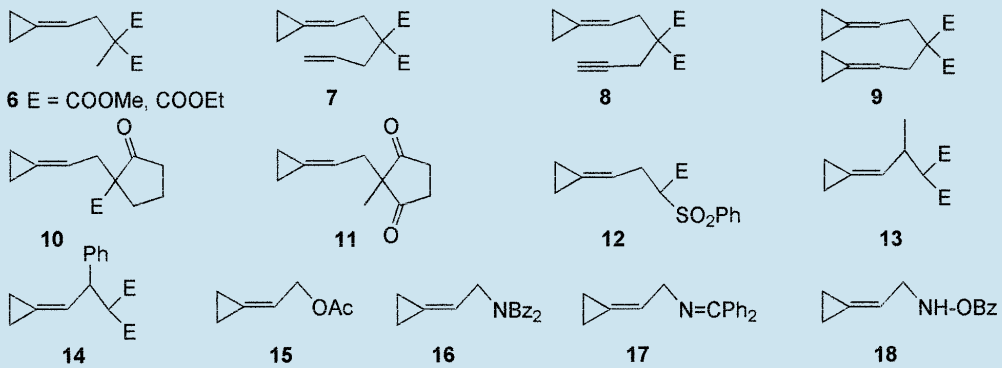
Allyl acetates and carbonates form with palladium(0) π-allyl palladium complexes, which are able to react *in situ* with nucleophiles. These transition metal catalyzed carbon–carbon or carbon–heteroatom bond formations allowed to achieve a wide number of allylic substitutions under particularly mild conditions.[18] However under the typical conditions generally used for the substitution of allyl acetates by soft nucleophiles (*stabilized anions*) *i.e.*, in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], the acetate **2b** (R = H) did not undergo any reaction with diethyl 2-sodium malonate **4** upon heating in THF at reflux for

5 days. But the isomeric allyl acetate **3b** reacted with **4** in the presence of $Pd(PPh_3)_4$ in THF at reflux for 36 h to provide in 80% yield the diethyl (2-cyclopropylideneethyl)malonate **5**.[7]

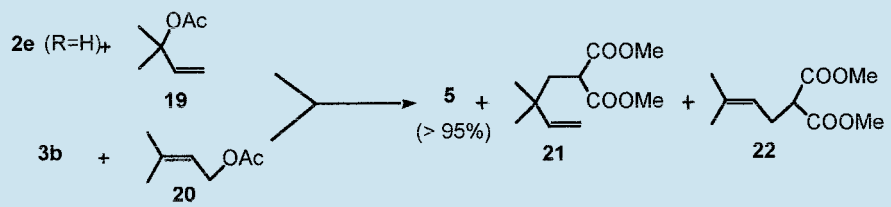


Formation of **1** (R = H) entailed at least partially, a positive charge on the three-membered ring, as the cyclopropyl cation is more strained (SE = 42 kcal.mol^{-1}) than the cyclopropane ring (SE = 27.5 kcal.mol^{-1}), therefore the cleavage of the acetate bond in **2b** (R = H) is not chemically favoured. On the other hand, formation of **1** (R = H) from the acetate **3b** (SE = 40.9 kcal.mol^{-1}) increased only slightly the ring strain. Use of Pd(0) complex generated *in situ* from bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] and 1,2-bis(diphenyl-phosphino)ethane (dppe) for the reaction of **2b** (R = H) with nucleophile **4** in THF at reflux for 24 h, provided **5** in 31% yield, besides a ring opening by-product (6%); longer reaction times (48 h, 65°C) led to less selective reactions.[7] Under neutral conditions,[19] the carbonate **2c** (R = H) did not react with diethylmalonate even in the presence of $Pd(dba)_2$/dppe, contrary to the isomeric carbonate **3c** which led to **5** in 76% yield (rt, 4 h). Better leaving groups increased the reactivity; thus, the trifluoroacetate **2d** (R = H) underwent the nucleophilic substitution in 23 [$Pd(PPh_3)_4$, 65°C, 48 h] and 55% yields [$Pd(dba)_2$/dppe, rt, 48 h]; while felicitously, the sulfonates **2e**,**f** (R = H) were substituted much more rapidly by **4**, whatever the nature of the palladium(0) ligands, to provide in 84–86% yields within 5 min at ambient temperature the dimethyl malonate **5**, *exclusively*.[7] The chloride **2g** (R = H) underwent also the Pd(0) catalyzed substitution at room temperature within 24 h, to give **5** in 51 and 66% yields depending on the bidendate bisphosphine ligands, dppe or 1,4-bis(diphenylphosphino)-butane (dppb), respectively.[20]

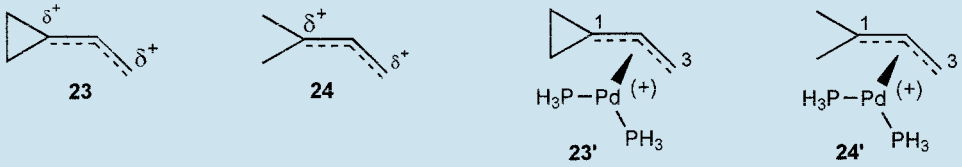
The (2-cyclopropylideneethyl)malonates and related compounds **6**–**12** have been obtained in high yields (72–93%) from the substitution of **1** (R = H) by the suitable nucleophiles; while malonates **13** (89%) and **14** (94%) have been obtained from **1** (R = Me) and **1** (R = Ph), respectively.[7] Use of potassium acetate in the presence of [18]-crown-6 ether, of dibenzylamine, of benzophenone imine and of benzyl-oxylamine for the nucleophilic substitution of **1** (R = H) provided readily the (2-cyclopropylideneethyl)-acetate **15** (80%), and allylamine derivatives **16**-**18** (84–95%).[7,21]



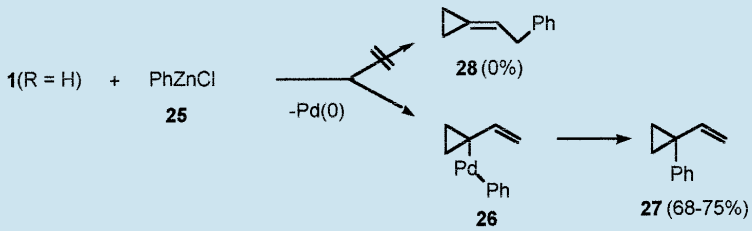
Alkylidenecyclopropanes form a peculiar class of strained olefinic compounds, with remarkable synthetic potential. Thus they undergo transition metal catalyzed ring opening, [3+2] cycloaddition with olefinic and acetylenic substrates, [1,3] dipolar cycloaddition with nitrones, Pauson Khand cyclization with acetylene dicobalt hexacarbonyl complexes.[22] Among the various alkylidenecyclopropane syntheses recently extensively reviewed,[23] this new method appeared so far the best to comply with all the requirements of chemo-, regio-, stereoselectivity and atom economy.[24] Competition experiments between 1-ethenylcyclo-propyl tosylate **2e** (R = H) and 1,1-dimethylallyl acetate **19**, or between cyclopropylideneethyl acetate **3b** and 3,3-dimethylallyl acetate **20**, in their Pd(0) catalyzed reactions with **4** provided 19 : 1 and 99 : 1 mixtures of **5** (>95%) and isomeric malonates **21** and **22** (ratio 7/3).



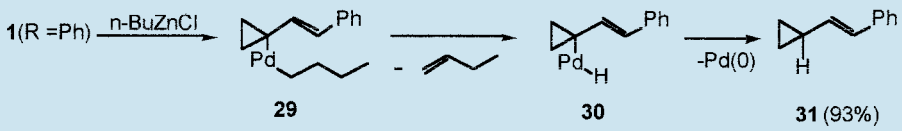
Different structures have been considered for the complex **1** (R = H) and the corresponding π-1,1-dimethylallyl palladium complex arising from **19** and **20** to explain such an unexpected behaviour. High level calculations (STO-3G, 6-31G and 6-31G*) have indicated a higher positive charge on the primary carbon of the 1-ethenylcyclopropyl cation **23**, whereas MINDO/3, AM1 and *ab initio* calculations have predicted a higher positive charge on the tertiary center of 1,1-dimethylallyl cation **24**.[7] Calculations performed over both π-allyl palladium complexes **23'** and **24'** having two molecules of PH_3 as ligands, using the semi empirical method PM3 (tm) and refining the results with *ab initio* calculations with 3-21G* basis, suggested that in **23'** palladium is closer to the cyclopropyl carbon C_1, contrary to **24'** where the transition metal was closer to the primary carbon C_3.[25] These data can explain both the higher reactivity and regioselectivity observed for the substitution of **1** (R = H) by stabilized (*soft*) nucleophiles.



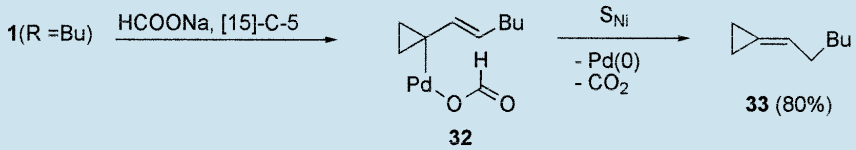
Inversely reaction of **1** (R = H) [prepared either from **2e** (R = H) or from **3b** and $Pd(dba)_2$/dppe] with phenylzinc chloride **25** provided in 68 and 75% yields respectively, the 1-ethenyl-1-phenylcyclopropane **27**, *exclusively*. The lack of (2-phenylethylidene)cyclopropane **28**, arising from substitution at the primary carbon center, suggested that the reaction follows a quite different mechanism with non stabilized (*hard*) nucleophiles. Effectively organometallics reacted by transmetalation, *i.e.*, by transfer of the organic moiety from zinc to palladium to form the σ-complex **26** (with Pd on the cyclopropane ring), which then underwent Pd(0) reductive elimination to provide **27**.[7]



Substitution of **1** (R = Ph) [from 1-styrylcyclopropyl tosylate and $Pd(dba)_2$, 2 PPh_3] by *n*-butylzinc chloride led in 93% yield to the 1-styrylcyclopropane **31**, *exclusively*. Most likely, the hydrogenolysis occurred through the *n*-butyl substituted σ-Pd complexe **29** (*transmetalation*), which underwent β-elimination to form the σ-palladium hydride species **30**, which after Pd(0) reductive elimination provided **31**. Usually, Pd(0)-catalyzed reaction of allyl acetates with alkylzinc derivatives containing β-hydrogens have been reported to provide reduction products, resulting of the attack of hydride at the less-substituted site;[26] the reverse regioselectivity was still observed with the 1,1-dimethyleneallyl palladium complexes.[7,27,28]



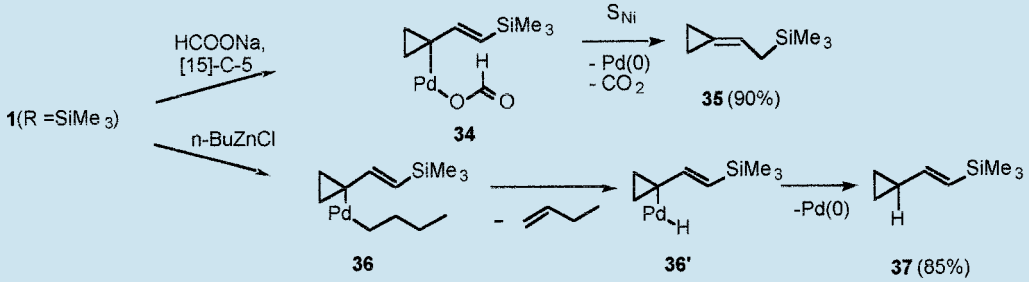
Substitution of **1** (R = Bu) [from 1-(1-hexenyl)cyclopropyl tosylate and $Pd(dba)_2$, 2 PPh_3] by sodium formate in the presence of [15]-crown-5 ether gave in 80% yield, the hexylidenecyclopropane **33**, *exclusively*.[27,28] Likely, this hydrogenolysis occurred through the formate σ-Pd complex **32** which underwent S_Ni transfer of hydride. Otherwise reaction of **1** (R = Bu) with *n*-butylzinc chloride led in 85% yield to 1-(1-hexenyl)cyclopropane, *exclusively*. In the same way hydrogenolysis of **1** (R = Ph) by sodium formate gave **28** in 81% yield.[27,28]



These Pd(0)-catalyzed reductions have been extended to homologous 1-(1-alkenyl)cycloalkyl esters; the regioselectivity can be monitored not only by the ring strain, but also by the steric effect of the phosphorus

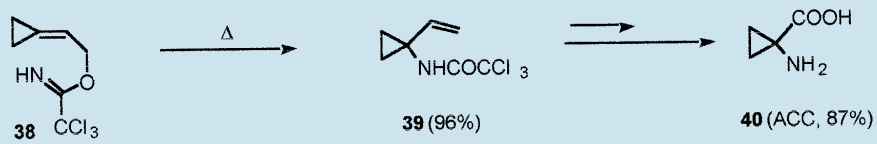
ligands. They can provide a convenient alternative to the Wittig olefination, particularly when the substrates are sensitive to the basic ylides.[27,28]

Substitution of **1** (R = $SiMe_3$) [from 1-(2-trimethylsilylethenyl)cyclopropyl tosylate and $Pd(dba)_2$, 2 PPh_3] by sodium formate and [15]-crown-5 ether provided in 90% yield, the (2-trimethylsilylethylidene)cyclopropane **35**, *exclusively*, likely through the σ-complex **34** and S_Ni hydride transfer. Inversely, reaction of **1** (R = $SiMe_3$) with *n*-butylzinc chloride led in 85% yield, to the (2-trimethylsilylethenyl)cyclopropane **37** *exclusively*, likely through the σ-complexes **36** and **36'**.[28,29]

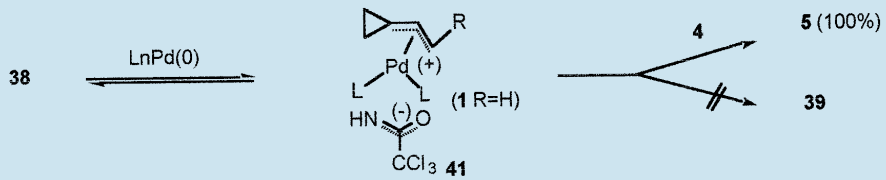


Allylsilanes and vinylsilanes constitute very useful and versatile synthetic intermediates;[30] these Pd(0) catalyzed reductions which have been extended to homologous trialkylsilylallyl esters offered a new, convenient, regio- and stereoselective access to these useful electrophilic reagents.[28,29]

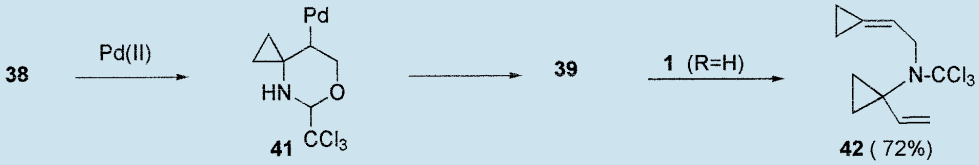
While the nucleophilic substitution of **1** (R = H) by amine, imine, hydroxylamine, carbamate derivatives provided (2-cyclopropylideneethyl)amines such as **16**–**18**, resulting from *exclusive* amination of the less substituted allylic end (*vide supra*),[21] amination of the cyclopropane ring was investigated from the (2-cyclopropylideneethyl) acetimidate **38**, which was readily available from **3a** and trichloroacetonitrile.[31] Thus **38** underwent thermally induced aza-Claisen rearrangement into l-ethenylcyclopropylacetamide **39** (96% yield) upon simple heating in toluene at 100°C. Then oxidation of **39** ($NaIO_4$, $RuCl_3$) and acidic cleavage of the amide bond (3 N HCl) provided in 87% overall yield the l-aminocyclopropanecarboxylic acid (ACC) **40**, which currently attracts special attention due to its phytochemical, enzymatic, antibiotic and neurochemical activities.[2]



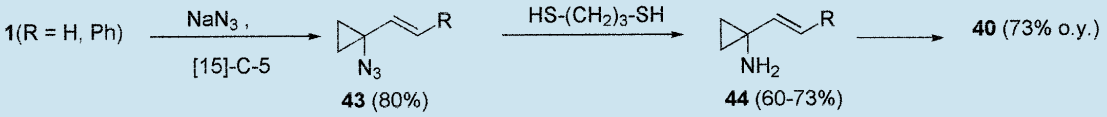
Such thermal [3,3] sigmatropic rearrangements could be also generally achieved under transition metal catalysis. However treatment of **38** with Pd(0) [from $Pd(dba)_2$ and 2 PPh_3 or dppe] did not lead to **39** as expected; apparently imidate **38** was inert to Pd(0) catalysis and was recovered unaltered. In fact, **1** (R = H) and the trichloroacetamide anion **41** were likely formed under these conditions but, as oxygen was more nucleophilic than nitrogen, the reaction was reversible and gave back **38**. Whereas treatment of **38** by Pd(0) in the presence of 2-sodiummalonate **4** provided **5** quantitatively as previously (*vide supra*), proving beyond question the occurrence of **1** (R = H).[31]



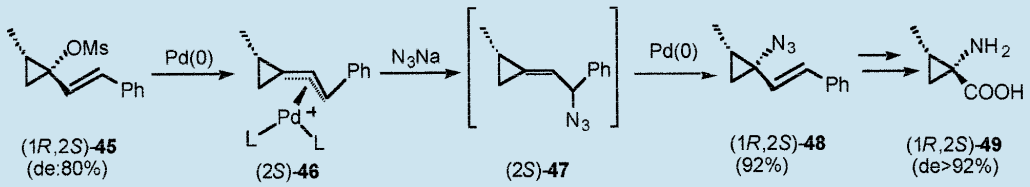
Treatment of **38** with Pd(II) catalyst [from $PdCl_2(CH_3CN)_2$ or $PdCl_2(PhCN)_2$] induced the aza-Claisen into the expected cyclopropylamide **39**, *via* the palladium bound six-membered cyclic carbonium ion intermediate **41**.[32] But the complex **1** (R = H), likely arising also from **41** or directly from **38**, was also formed *in situ* and then reacted with **39** to give in 72% yield the unexpected *N*-(2-cyclopropylideneethyl)-*N*-(1-ethenylcyclopropyl)trichloroacetamide **42**. Nevertheless **39** could be obtained in 74% yield under Pd(II) catalysis, when **38** was previously *N*-protected (*e.g.*, as *N*-C_6H_4OMe), in order to avoid the subsequent reaction **39** ¤ **42**.[31]



Reaction of **1** (R = H, Ph) with sodium azide in the presence of [15]-crown-5 ether (10%) offered in 79–80% yield the 1-azido-1-ethenylcyclopropanes **43** (R = H, Ph), *exclusively*,[21] while allyl acetate **20** and 1-ethenylcyclohexyl acetate have been reported to undergo Pd(0) catalyzed azidation with the reverse regioselectivity.[33] Reduction of **43** (R = H, Ph) by 1,3-propanedithiol [$HS(CH_2)_3SH$] in methanol or by triphenylphosphine in aqueous sodium hydroxide gave in 60–79% yield the 1-ethenylcyclopropylamines **44** (R = H, Ph). Oxidative cleavage ($NaIO_4$, $RuCl_3$) of the styryl moiety of **44** (R = Ph) led also to the amino acid (ACC) **40** in 73% overall yield.[21]

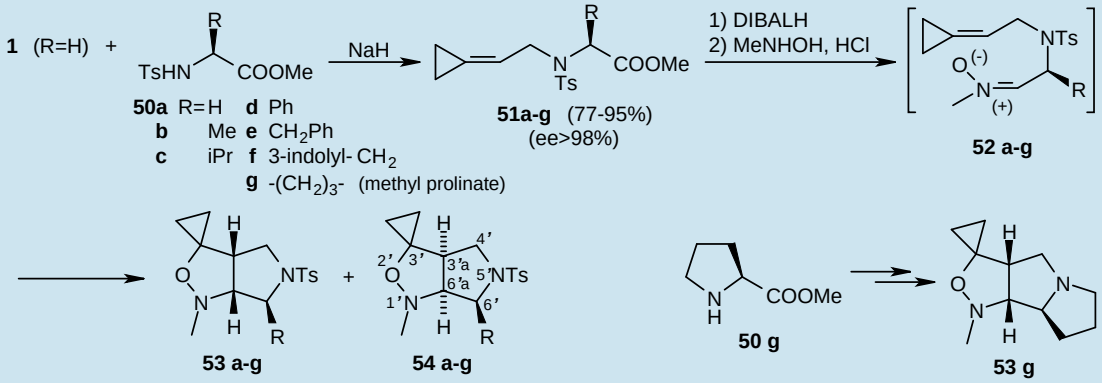


The mesylate (1*R*,2*S*)-**45** (de : 80%) was prepared from the commercially available optically pure (2*S*)-3-hydroxy-2-methylpropionate. It underwent Pd(0) catalyzed stereoselective azidation (NaN_3, [15]-C-5), likely *via* the complex (2*S*)-**46**, to provide in 85% yield the azide (1*R*,2*S*)-**48** (de >92%) exclusively.[34]

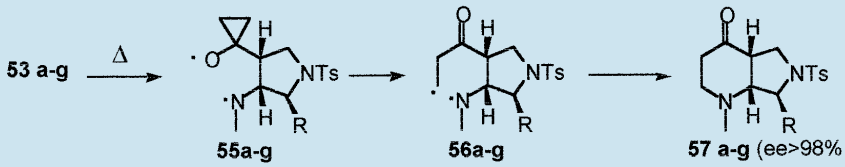


Pd(0) catalyzed azidation of allyl esters occurs generally with *overall retention* of configuration,[33] however substitution of (2*S*)-**46** with the required *inversion* of configuration should lead as previously shown to the (cyclopropylideneethyl)azide (2*S*)-**47** (*soft* nucleophile behaviour, *vide supra*), while substitution of (2*S*)-**46** with *retention* of configuration should rather lead to the corresponding (1*S*,2*S*)-azide (*hard* nucleophile behaviour). The *exclusive* formation of (1*R*,2*S*)-**48** must therefore be the result of a subsequent Pd(0)-induced isomerization of (1*R*,2*S*)-**47**, stereocontrolled by the palladium moiety coordinated to the double bond.[34] Whatever it may be, subsequent reduction of (1*R*,2*S*)-**48** [$HS(CH_2)_3SH$] and oxidative cleavage ($NaIO_4$, $RuCl_3$) led conveniently to the bioactive *norcoronamic acid* (1*R*,2*S*)-**49**, with >99% enantiomeric excess.[34]

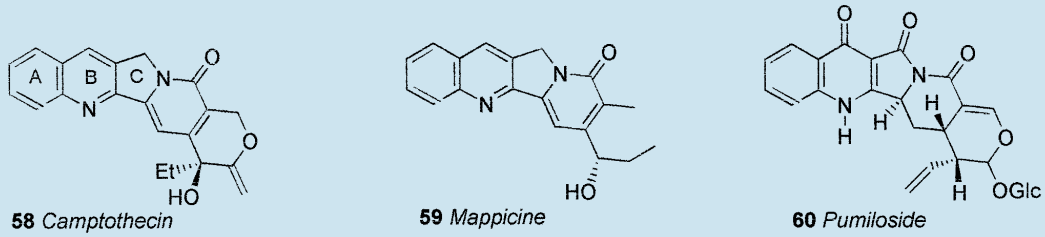
Substitution of **1** (R = H) by methyl *N*-tosylamino acid esters **50a-g** in the presence of NaH (1 equiv) produced the methyl *N*-(2-cyclopropylideneethyl)-*N*-tosy1amino acid esters **51a-g** in 77-95% yields; no epimerization of the chiral center was observed for **51b-g** (ee >98%) obtained from asymmetric **50b-g**. Partial reduction of esters **51a-g** [DIBALH (0.9 equiv) or DIBALH (2.5 equiv) and DMSO/$(COCl)_2$] provided the corresponding aldehydes which reacted at room temperature with *N*-methylhydroxylamine to give the *N*-methyl nitrones **52a-g**. Spontaneously, these nitrons **52a-g** evolved into the *cis*-fused tricyclic isoxazolidines **53a-g** and **54a-g** in 46–95% yields. The strain of the cyclopropylidene ring (ΔS = 40.9 kcal/mol) strongly increased the cycloaddition rate of this regioselective intramolecular 1,3-dipolar cycloaddition,[36] with a diastereoselectivity depending on the steric effect of the R substituents on the amino acids moieties. Thus R = Me was too small to induce a diastereoselectivity in **53b** and **54b** (de : 10%); bulkier substituents R = *i*-Pr, $PhCH_2$ favored the formation of **54c,e** (de : 22–24%), whereas R = 3-indolyl-CH_2 favored the formation of **53f** (de : 22%). On the other hand R = Ph and -$(CH_2)_3$- (methyl prolinate) afforded diastereoselectivity pure cycloadducts **53d,g** (de >99%).[34] Calculation of transition state energies by molecular mechanic calculation (MAD), demonstrated effectively that the *exo*-R and *endo*-R transition states leading either to cycloadducts **53a-g** or **54a-g**, respectively, were only slightly differentiated in energy when R = Me (ΔE =1.5 kcal.mol), but markedly better when R = Ph and proline (ΔE = 4.39 and 10 kcal.mol), therefore justifying beyond doubt this diastereoselection.[25,35]



The pure cycloadducts **53a-g** underwent thermally induced ring expansion into the pyrrolo[3,4-*b*]pyridin-7-ones **57a-g** in satisfactory yields (41–73%), on simple heating in xylenes at 130–140˚C. This rearrangement proceeded through thermal cleavage of the weak N–O bond to give the cyclopropyloxy diradical intermediates **55a-g**, which then readily underwent cyclopropane ring opening with strain release into the diradicals **56a-g**. Then intramolecular radical coupling between the nitrogen and the terminal carbon atoms of **56a-g** led with complete chemo-, regio-, diastereo- and enantioselectivity to the optically pure bicyclic products **57a-g** (ee >98%). The same thermal behaviour was observed from pure cycloadducts **54b,c,e**.[25,35] This whole process occurred with the maximum "*atom economy*" as no added reagent or catalyst was required after the nitrone formation.[24]

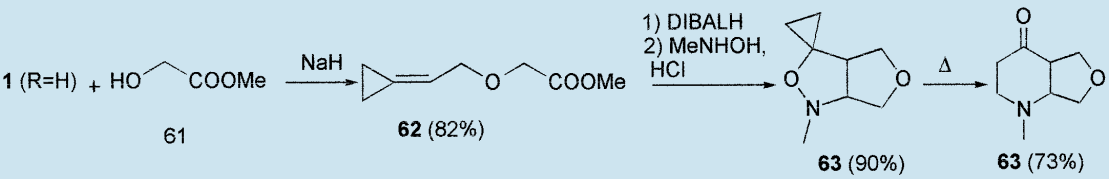


Very recently the derivatives of this diazabicyclo[3.4]nonanone system showed interesting biological activity as substance P antagonists,[37] or as potent DNA gyrase inhibitors;[38] they appeared as promising therapeutic agents for the treatment of important diseases (asthme, inflammation, pain, migraine, vascular headaches).[39] Moreover this pyrrolo[3,4-*b*]pyridine (or 4-azaisoindole) ring system is present in the B and C rings of the potent antitumoral agent *camptothecin* **58**,[40] of the potent antiviral agent *mappicine* **59**.[41] and of related natural like *pumiloside* **60** or in non natural products.[42]

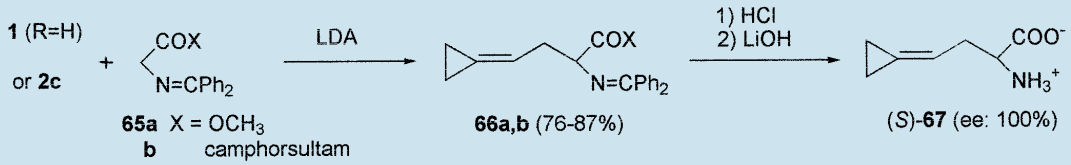


58 *Camptothecin* **59** *Mappicine* **60** *Pumiloside*

Reaction of **1** (R = H) with methyl glycolate **61** in the presence of NaH (1 equiv), gave the *O*-(2-cyclopropylideneethyl) glycolate **62** in 82% yield. Likewise partial reduction of **62** (DIBALH), and addition of *N*-methylhydroxylamine gave the corresponding nitrone which, spontaneously evolved into the furo[3,4-*c*]isoxazole **63**, in 90% yield. This tricyclic isoxazolidine **63** underwent also the thermally induced ring expansion to produce the furo[3,4-*b*]pyridine derivatives **64**, in 73% yield.[25] This convenient new process has been also achieved successfully from the corresponding cyclopropylidenealkylnitrile oxides.[25]



Alternatively use of *N*-(diphenylmethylene)glycine esters **65a** (X = OMe) as nucleophile in the presence of base (LDA), following exactly the same process, was shown to provide within 5 min at room temperature the 2-(2-cyclopropylideneethyl)glycine derivative **66a** in 87% yield. From the carbonate **2c** (R = H), this Pd(0) catalyzed C-alkylation occurred with the Schiff base **65a** without any added base, to provide **66a** in 76% yield.[7,43] Use of the camphorsultam modified glycine equivalent **65b**[44] (X = camphorsultam) led to **66b** with a good diastereoselectivity (de >90%). Deprotection of **66b** (0.5 HCl, 0.25 N LiOH) gave the enantiomerically pure (*S*)-2-amino-4-cyclopropylidenebutyric acid **67**, the chiral auxiliary being recovered in >90% yield.[43]

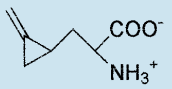


65a X = OCH_3
b camphorsultam

66a,b (76-87%)

(*S*)-**67** (ee: 100%)

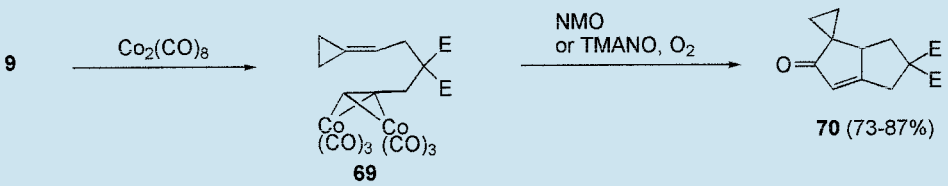
The non natural compound (*S*)-**67** is an isomer of Hypoglycine A [3-(2-methylene-cyclopropyl)alanine] **68** isolated from the unripe fruit of the ackee tree (*Blighia sapida* Kon) and which is the causative agent in Jamaican vomiting sickness, giving rise to lethal hypoglycemia and organicacidaemia.[45] (*S*)-**67** considered as *allo*-hypoglycine inhibited also the metabolism of pyruvate into glycose,[45] but was not active in inducing the mitochondrial oxidation of fatty acids.[2]



68 *Hypoglycine A*

A general and convenient method for the preparation of enantiomerically pure α-allyl-α-amino acids was based on this palladium-catalyzed allylation of the chirally modified glycine equivalent.[43]

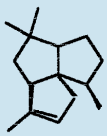
Among the recent methods for the construction of five-membered carbocyclic ring systems, the cobalt mediated cycloaddition of an alkyne to an alkene with carbonyl insertion, known as Pauson-Khand reaction (PKR), which provides a cyclopentenone has attracted particular interest.[46] The alkynecobalt complex **69** was prepared under standard conditions from octacarbonyldicobalt [$Co_2(CO)_8$] and the dimethyl (2-cyclopropylideneethyl)propargyl-malonate **8**, which was readily available from **1** (R = H) (*vide supra*). Treatment of **69** either with *N*-methylmorpholine *N*-oxide (NMO) or with triethylamine *N*-oxide (TMANO) under oxygen, gave the bicyclo[3.3.0]octenone **70** in 73 and 87% yield, respectively. In contrast, the analogous dimethyl 2-(2-isopropylideneethyl)-2-propargylmalonate derived from **22** did not cyclize under identical conditions, illustrating once more, the huge ring strain effect on reactivity.[47] This sequence was applied to a variety of differently substituted 6-cyclopropylidene-1-hexynes to provide spirocyclopropane bicyclo[3.3.0]oct-1-en-3-ones in good to very good yields.[47]



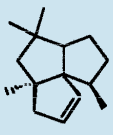
69

70 (73-87%)

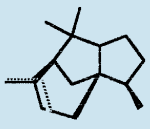
It is noteworthy that **70** possesses the basic framework of triquinane sesquiterpenes such as *senoxydene* **71**, *silphinene* **72**, *α,β-cedrenes* **73** and *modhephene* **74**. Effectively **70** has been transformed by simple Michael addition of a 2-dioxanylethylcuprate, followed by an aldol reaction into a suitable precursor of triquinanes **71** and **72**.[48]



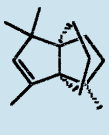
71- *Senoxydene*



72- *Silphinene*

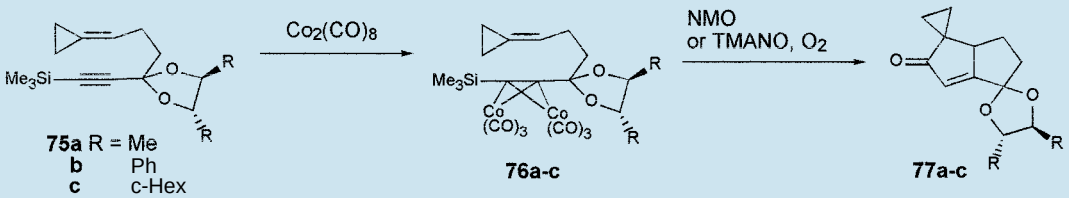


73- α,β–*Cedrenes*

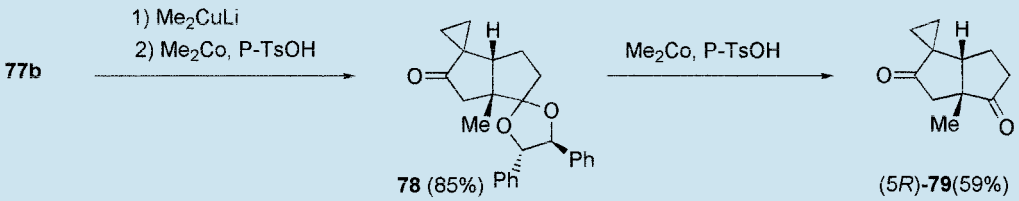


74- *Modhephene*

The asymmetric 1,6-enynes **75** were prepared from **1** (R = H) using chiral ethanediol derivatives. Although heavily substituted (PKR is highly sensitive to steric hindrance),[46] **75a-c** underwent trialkylamine oxides (NMO or TMANO) promoted cyclization to provide through the cobalt complexes **76a-c**, the spirocyclopropanebicyclo[3.3.0]oct-1-en-3-ones **77a-c** in 63, 69 and 76% yield, respectively. The diastereoselection in the cyclization was low for **77a** (de : 33%) when R = Me, but increased for **77b** (de : 67%) with R = Ph and for **77c** (de : 73%) with R = cyclohexyl.[47]

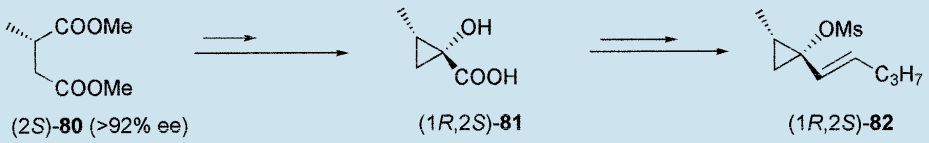


Further transformation of (*S*)-**77b** separated by column chromatography was achieved with lithium dimethylcuprate, which gave after desilylation (Me_2CO, *p*-TsOH) in 85% overall yield the bicyclo-[3.3.0]octanone **78** and after prolonged heating (acetone, *p*-TsOH), in 59% yield the enantiomerically pure (5*R*)-dione **79**.[47,48]

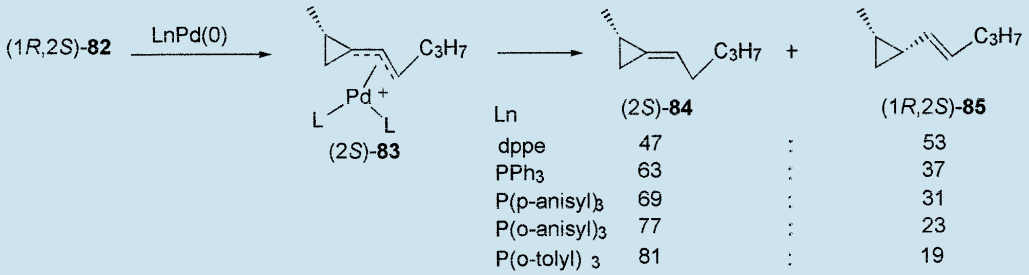


It has been pointed up that the most convenient current method to get readily alkylidene-cyclopropanes possessing a remarkable synthetic potential,[22,23] was based either on the substitution of complexes **1** by soft nucleophiles or on their reduction by HCOONa as hydride source (*vide supra*). Obviously, asymmetric π-1,1-dimethyleneallyl palladium complexes such as (2*S*)-**46** for instance, can lead to optically active alkylidenecyclopropanes.

Asymmetric α-alkylsuccinates were readily available on preparative scale either from enzymatic (lipase, esterase) hydrolysis of their dimethyl racemates,[49,50] or from the stereoselective alkylation of chiral imide enolates.[51] For instance, (2*S*)-**80** (ee >92%) underwent acyloin type cyclization (Na, $ClSiMe_3$) and C_4 ¤ C_3 ring contraction (Br_2, H_2O) to provide the (1*R*,2*S*)-1-hydroxy-2-methylcyclopropanecarboxylic acid **81**,[52] used as suitable precursor of the mesylate (1*R*,2*S*)-**82**.[12]

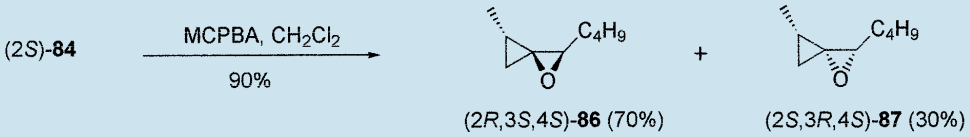


Pd(0) catalyzed hydrogenolysis of (1*R*,2*S*)-**82** by sodium formate and [15]-crown-5 ether (*vide supra*) gave in high yields (79–85%) separable mixtures of diastereomerically pure (*E*)-(2*S*)-pentylidene(2-methylcyclopropane) **84** and of (1*R*,2*S*)-2-methyl-1-(1-pentenyl)cyclopropane **85**, with a regioselectivity greatly affected by the nature of the ligands. As a matter of fact the steric effect of trivalent phosphorus ligands was known to dominate the chemical behaviour of transition metal complexes.[53] As previously observed for complexes **1** (R = Ph, Bu),[27,28] an increase of the size of the substituents on phosphorus favoured the formation of the alkylidenecyclopropane (2*S*)-**84** when HCOONa was used as hydride source, and inversely favoured the formation of the vinylcyclopropane derivative (1*R*,2*S*)-**85** when *n*-butylzinc chloride was the hydride source. Thus successive use of PPh_3, P(*p*-anisyl)$_3$, P(*o*-anisyl)$_3$ and P(*o*-tolyl)$_3$ increased the (2*S*)-**84**/(1*R*,2*S*)-**85** ratio from 63/37 to 81/19.[12]

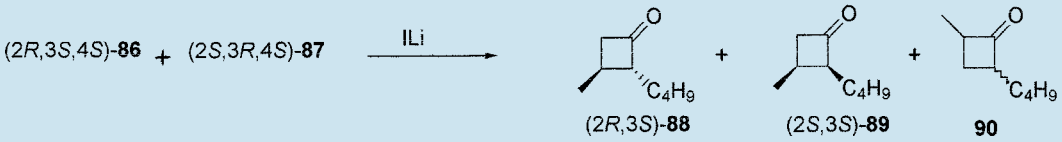


Ln	(2S)-84		(1R,2S)-85
dppe	47	:	53
PPh_3	63	:	37
P(p-anisyl)$_3$	69	:	31
P(o-anisyl)$_3$	77	:	23
P(o-tolyl)$_3$	81	:	19

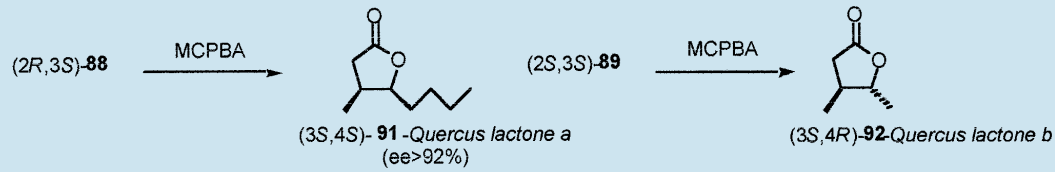
Then, epoxidation of (2*S*)-**84** (de : 100%) by *m*-chloroperbenzoic acid (MCPBA) gave in 90% yield a 7 : 3 mixture of (2*R*,3*S*,4*S*)-**86** and (2*S*,3*R*,4*S*)-**87**, which constituted the first total synthesis of asymmetric oxaspiropentanes.[54]



Upon treatment with a catalytic amount of lithium iodide (1%) this mixture of epoxides underwent quantitative C_3 ¤ C_4 ring expansion[5] to provide a 55 : 17 : 28 mixture of diastereomeric (2*R*,3*S*)-**88** and (2*S*,3*S*)-2-butyl-3-methylcyclobutanone **89**, besides the regioisomeric 2-butyl-4-methylcyclobutanone **90**.

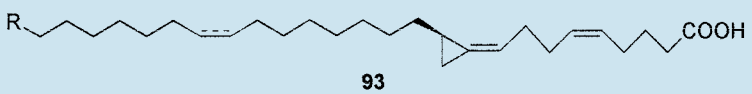


Further treatment of separated cyclobutanone (2*R*,3*S*)-**88** with MCPBA gave the (3*S*,4*R*)-4-butyl-3-methylbutanolide **91** (ee >92%); while (2*S*,3*S*)-**89** led under the same conditions to the diastereomeric lactone (3*S*,4*S*)-**92** (ee >89%).[54] These two butanolides, known as *Quercus lactones a* and *b*, have been isolated from white oak wood and are found in wines and spirits kept in oak barrels for maturing.[55] It is noteworthy that the configuration of the stereogenic center of the succinate precursor (2*S*)-**80** (ee >92%) was totally retained during the whole synthetic sequence involving the palladium complex (2*S*)-**83**.[54]



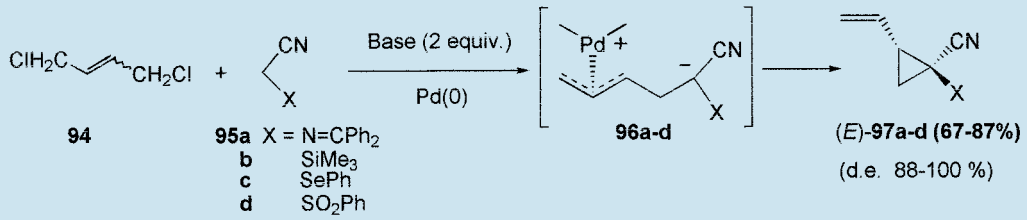
The first asymmetric synthesis of these butanolides involved the acid induced ring expansion of 1-vinylcyclopropanol derivatives, arising also from the α-hydroxy acid (1*R*,2*S*)-**81** and succinate (2*S*)-**80**.[52] Asymmetric cyclobutanones such as (2*R*,3*S*)-**88** and (2*S*,3*S*)-**90**, now readily available provide not only suitable precursors to γ-butyrolactones (MCPBA) but, also to cyclopentanones (CH_2N_2) and γ-butyrolactams ($ArSO_2ONH_2$).[56]

Amphimic acids **93** (R = H, Me) have been recently isolated from australian marine sponge of the genus *Amphimedon*. These strained fatty acids (C_{27}–C_{28}), which possess a cyclopropylidene moiety (SE : 40.9 kcal.mol^{-1}), were 100-fold more active than linear C_{18} fatty acids as inhibitors of DNA topoisomerase I and showed also cytotoxicity against P388 leukemia cells (IC_{50} : 1.8 μM).[57] Their total asymmetric synthesis, involving π-1,1-dimethyleneallyl palladium complexes such as **1** is under current investigation.[58]



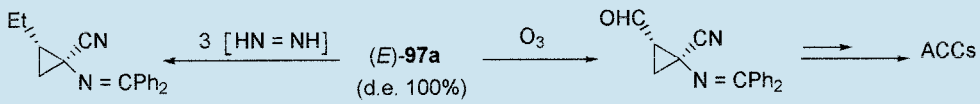
93

An alternate pathway to highly functionalized cyclopropanes (*E*)-**97a-d** was recently offered by the one pot palladium(0) catalyzed tandem alkylation and $S_{N'}$, cyclization of commercially available 1,4-dichlorobut-2-ene **94** by the anion of different α-substituted acetonitriles **95a-d**. The reaction which provided in 67–87% yields the 2-ethenyl-1-substituted cyclopropanecarbonitriles (*E*)-**97a-d**, occurred likely through the zwitterionic intermediate π-allyl palladium complexes **96a-d**. The $S_{N'}$ cyclization of **96a-d** was highly diastereoselective (de : 88–100%); it took place by attack of the π-allyl palladium moiety by the carbanion with inversion of configuration involving sterically favored *syn* relationship of the ethenyl and nitrile groups.[59]



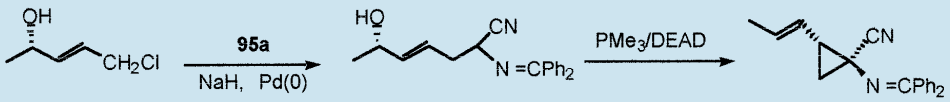
94 **95a** X = N=CPh$_2$; **b** SiMe$_3$; **c** SePh; **d** SO$_2$Ph **96a-d** (*E*)-**97a-d (67-87%)** (d.e. 88-100 %)

For instance simple diimide reduction of (*E*)-**97a** (de : 100%) gave (*E*)-**98**, which was used as suitable precursor of *coronamic acid*.[59,60] Otherwise ozonolysis can provide the cyclopropane-carboxaldehyde (*E*)-**99**, also convenient precursor of 2,3-methanoamino acids (ACCs),[61] of biological importance.[2]



(*E*)-**98** (*E*)-**99**

Several attempts to achieve asymmetric synthesis by means of this new procedure, using either chiral palladium ligands [*e.g.*, (*S*)- or (*R*)-BINAP], chiral aminoacetonitrile [from 1-hydroxypinanone] or chiral allyl chlorides [from (2*S*)-ethyl lactate] have led to (1*S*,2*R*)-**97a** and derivatives with a complete diastereoselectivity (de = 100%), but low enantioselectivity (ee ≤ 32%).[61] In fact, these results have pointed up the reversibility of the cyclization step **96a** ¤**97a**, consequence of the facile Pd(0) induced ring opening of vinyl cyclopropanes.[62] To overcome this problem the 2-amino-6-hydroxyhept-4-enenitrile (6*S*)-**101** was prepared in 97% yield from Pd(0) catalyzed alkylation of the allyl chloride (4*S*)-**100** [available from (2*S*)-ethyl lactate, ee >94%] by the anion of the Schiff base **95a**. In the absence of Pd(0), but under the Mitsunobu reaction conditions (DEAD/PMe$_3$) (6*S*)-**101** underwent the expected diastereoselective cyclization to provide in 77% yield, the 1-aminocyclopropane-carbonitrile derivative (1*S*,2*R*)-**102** (ee >83%), which also constituted an efficient precursor of ACCs.[61]



(4*S*)-**100** (ee> 94%) (6*S*)-**101** (97%) (1*S*,2*R*)-**102** (ee> 83%)

It can be concluded that the presence of allylic leaving groups on 1-(1-alkenyl)cyclo-propyl esters **2b-g** or **3b,c**, (1*R*,2*S*)-**45** and (1*R*,2*S*)-**82** was essential to preclude the three–membered ring opening and to entail irreversibly the formation of π-1,1-dimethyleneallyl palladium complexes such as **1**, (2*S*)-**46** and (1*S*)-**83**.

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This work was also financially supported by the Centre National de la Recherche Scientifique and the University de Paris-Sud (XI) at Orsay.

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About the Author

Jacques Salaün

Director of Research of the CNRS, at the Institut de Chimie Moléculaire d'Orsay
Université de Paris-Sud, Orsay (France)

Jacques Salaün was graduated Engineer from the "*Ecole Supérieure de Chimie de Caen*" in 1962. He obtained the Doctor-Engineer and Doctorat és-Sciences Physiques degrees from the University of Caen in 1965 and 1967, respectively, for research undertaken with *Professor J.M. Conia* on the synthesis and conformational studies of cyclobutanones by UV, IR and NMR spectroscopies.
As post-doctoral fellow he did works on the [10]annulenes system with *Professor S. Masamune* at the University of Alberta, Edmonton, Canada (1968-69), and in the field of vinyl cations with *Professor M. Hanack* at the Universities of Saarbrücken (1974) and Tübingen (1976), Germany. He is presently Directeur de Recherche (first class) in the Centre National de la Recherche Scientifique (C.N.R.S.) at the "*Institut de Chimie Moléculaire d'Orsay*" (I.C.M.O.) from the Université de Paris-Sud.

His main research interests deal with:
- the chemistry and biochemistry of the cyclopropyl group (cyclopropanone hemiacetals, 1-vinylcyclopropanols, 1-hydroxycyclopropanecarboxaldehyde derivatives,...).
- new strategies towards highly functionalized cyclopropanes.
- the thermal and transition metal induced by C_3–C_n ring enlargements (n=4–8).
- the specific rearrangements induced by metal salts (*e.g.*, $FeCl_3$) absorbed on silica gel.
- the enzymatic resolution of organic (*e.g.*, succinates, malonates) and organometallic (e.g., arene-tricarbonylchrome complexes) precursors for the total asymmetric synthesis of natural and non natural compounds (sesquiterpenes, terpenes, lactones, amino acids,...).
- the transition metals and small ring compounds chemistry:
  a) Pd(0) catalyzed nucleophilic substitution of 1-alkenylcyclopropyl esters.
  b) Pd(0) catalyzed reduction of allyl esters as alternative to the Wittig reaction.
  c) Pd(0) catalyzed reduction of trialkylsilylallyl esters as new regioselective preparation of allylsilane and vinylsilanes.
  d) Pd(0) catalyzed total asymmetric synthesis of amino acids (α-allyl-α-aminoacids, methanoamino acids).
  e) Pd(0) catalyzed tandem alkylation and $S_{N'}$ cylization of 1,4-dichlorobut-2-ene derivatives.
  f) Cobalt octacarbonyl complex induced intramolecular cyclisation of methylene cyclopropylalkynes and of cyclopropylalkynylalkenes as a direct asymmetric access to polyquinanes (Pauson-Khand reaction).
  h) Intramolecular 1,3-dipolar cycloaddition of cyclopropylidenealkylnitrones arising from Pd(0) catalyzed *N*-allylation of amino acids, followed by thermal ring expansion, as a new and efficient strategy to the asymmetric diazaheterobicyclic framework of bioactive alkaloids.
  i) Titanium(IV) catalyzed formation of titanacyclopropanes as new and convenient access to three-membered rings.