π-1,1-Dimethyleneallylmetal and Homologous Complexes: Their Application in Organic Synthesis

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Received March 16, 2004

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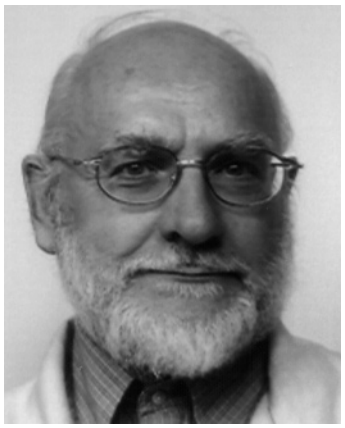

Jacques Salaün was graduated Engineer from the Ecole Supérieure de Chimie de Caen in 1962. He obtained the Doctor-Engineer and Doctorat-ès-Sciences Physiques degrees from the University of Caen in 1965 and 1967, respectively, for research undertaken with Professor J. M. Conia, on the synthesis and conformational studies of cyclobutanones by spectroscocopies. As postdoctoral fellow, he did work on the [10]annulene system with Professor S. Masamune at the University of Edmonton, Canada (1968–1969) and in the field of vinyl cations with Professor M. Hanack at the Universities of Saarbrücken (1974) and Tübingen (1976), Germany. Recently retired, he was Directeur de Recherche in the Centre National de la Recherche Scientifique (C.N.R.S.) at the Institut de Chimie Moléculaire et des Matriaux d'Orsay (I.C.M.M.O.) in the Université de Paris-Sud. His main recent research interests deal with the chemistry, organometallic, and biochemistry of strained small rings.

1. Introduction

Acyclic and cyclic allylic substrates, even bearing poor leaving groups (e.g., acetate, carbonate, phosphonate), underwent nucleophilic substitution under mild conditions, when the reaction was performed in the presence of some transition metals (palladium, molybdenum, nickel, tungsten, rhodium).[1a−g,2a−c] This carbon−carbon bond formation was generally achieved with high degrees of chemo-,[1a−e] regio-,[2a−c] diastereo-,[3] and enantioselectivity.[4] Furthermore, taking into account recent requirements, this attractive method allowed carrying out "atom economy"[5a,b] and environmentally friendly syntheses especially efficient to overcome the structural complexity of natural products.

The cyclopropane ring, which provided building blocks of high synthetic potential,[6a−d] rarely underwent substitution by nucleophiles with retention of the three-membered ring, as a result of peculiar and inherent ring strain.[7a−c] Consequently, nucleophilic substitutions of 1-(1-alkenyl)cyclopropyl esters have been investigated under transition metal catalysis, to offer an access to the challenging subunits that occurred in the cyclopropane-containing natural compounds recently isolated from plants, fungi, and microorganisms.[8a−c] It is a matter of fact that many

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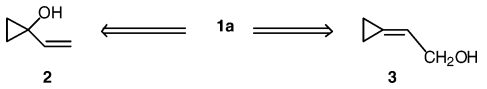
10.1021/cr040201b CCC: $53.50
Published on Web 01/12/2005

of these bioactive cyclopropanes, which serve as high-energy intermediates in metabolism as storage elements to release energy-rich compounds or as trigger components to provide a driving force and ensure irreversible inhibition, may be used as potential drug leads and provide suitable tools for the study of enzyme mechanisms.[9] The present review will focus on the preparation and synthetic applications of π-1,1-dimethyleneallylmetal complexes **1a** (n = 1), comparatively to homologous π-1,1-polymethyleneallylmetal complexes **1b**−**d** (n = 2−4).

1a-d (n=1–4; M=Pd, Mo, Ni, Zn)

Following known procedures,[1a−g,2a−c] esters (acetate, carbonates, sulfonates) of 1-ethenylcyclopropanol **2** or of 2-cyclopropylideneethanol **3** derivatives were required to attempt the formation of complexes **1a** (Scheme 1).[10a−c]

Scheme 1[10a−c]

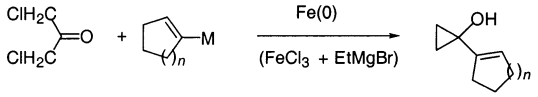


2. Preparation of 1-Ethenylcyclopropanols

2.1. From 1,3-Dichloroacetone

The addition of a vinylic Grignard reagent, for instance, (1-cyclopentenyl)magnesium bromide **5a** (n = 1, M = MgBr) or (1-cyclohexenyl)lithium **5b** (n = 2, M = Li) to commercially available 1,3-dichloroacetone **4**, in the presence of a catalytic amount of iron(0), prepared in situ by the simultaneous addition of a solution of ferric chloride (0.07 equiv) in diethyl ether and of an excess of ethylmagnesium bromide (6 equiv) in diethyl ether, provided readily the 1-(1-cyclopentenyl)- and the 1-(1-cyclohexenyl)cyclopropanols **6a** and **6b** in 55 and 60% yields, respectively. Addition of vinylmagnesium chloride under the same conditions gave the parent 1-vinylcyclopropanol **2** (R = H) in 55% yield (Scheme 2).[11]

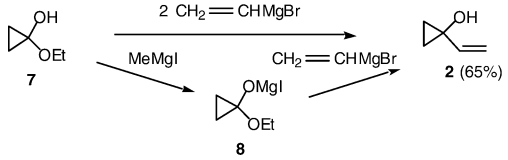
Scheme 2[11]



2.2. From Cyclopropanone Hemiacetals

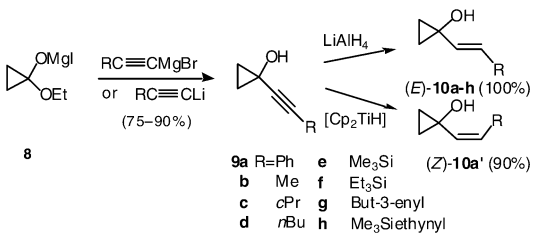
The simple addition of vinylmagnesium bromide (2 equiv) to the cyclopropanone ethyl hemiacetal **7** (available from the addition of ethanol to cyclopropanone,[12a,b] from the addition of an etheral solution of diazomethane containing ethanol to ketene,[13a] or from sodium-mediated cyclization of ethyl 3-chloropropanoate in the presence of trimethylchlorosilane, followed by methanol induced desilylation[14a,b]) gave the 1-ethenylcyclopropanol **2** in 65% yield.[13a,b] An alternative approach consists of addition of methylmagnesium iodide (1 equiv) to the hemiacetal **7**, to give the intermediate cyclopropanone hemiacetal magnesium salt **8**,[15] which underwent vinylation by 1 equiv of vinylmagnesium bromide to generate also the 1-ethenylcyclopropanol **2** in 61% yield[13c,d] (Scheme 3).

Scheme 3[13a−d]



Addition of arylethynylmagnesium bromides (1 equiv) or arylethynyllithiums (1 equiv) to the cyclopropanone hemiacetal magnesium salt **8** furnished the 1-(arylethynyl)cyclopropanols **9a** (R = Ar) in 75−90% yields.[16−18] Subsequent lithium aluminum hydride reduction of the 1-ethynylcyclopropanol derivatives **9a** led stereoselectively and quantitatively to the (*E*)-1-styrylcyclopropanols **10a**, while reduction by dicyclopentadienyltitanium hydride (formed in situ by the reaction of Cp_2TiCl_2 (4%) with isobutylmagnesium bromide[19a,b]) yielded exclusively the (*Z*)-1-styrylcyclopropanol **10a′** (Scheme 4).[16−18]

Scheme 4[16−18]

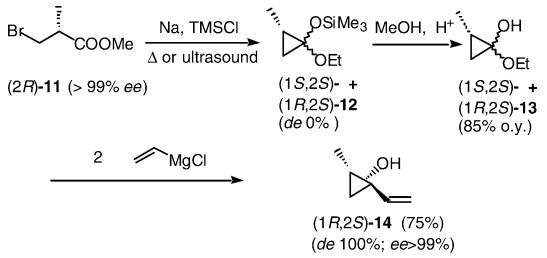


Use of other acetylenic nucleophiles, e.g., propynyl-, cyclopropylethynyl-, 1-hexynyl-, trimethylsilyl- and triethylsilylethynyl-, hex-5-en-1-ynylmagnesium bromides as well as trimethylsilylbutadiynyllithium offered the corresponding 1-ethenylcyclopropanols **9b**−**h** also in high yields.[17]

Methyl (2*R*)-3-bromo-2-methylpropionate **11** [prepared from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (>99% *ee*) upon treatment with carbon tetrabromide and triphenylphosphine in dichloromethane[20]] underwent cyclization by treatment with highly dispersed sodium in the presence of chlorotrimethylsilane in diethyl ether at reflux to give in 85% yield a 1:1 diastereomeric mixture of (1*S*,2*S*)- and (1*R*,2*S*)-**12**.[20] This procedure was simplified and improved under sonochemical activation.[21a,b] Acid-catalyzed methanolysis (MeOH, $ClSiMe_3$) of **12** led to a 1:1 diastereomeric mixture of hemiacetals **13** in 85% overall yield from ester (2*R*)-**11**, which, upon addition of vinylmagnesium chloride (2 equiv), gave the pure (1*R*,2*S*)-1-ethenyl-2-methylcyclopropanol **14** (*de* 100%; *ee* > 99%) as revealed by its ^1H and ^{13}C NMR spectra (Scheme 5).[20] Its enantiomer (1*S*,2*R*)- could be obtained similarly from commercially available methyl (2*R*)-3-hydroxy-2-methylpropionate.

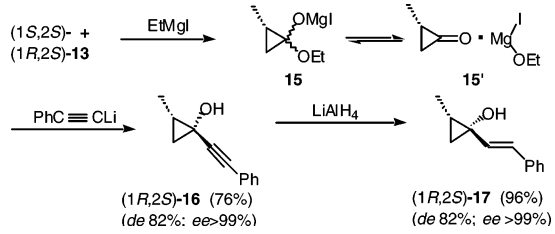
Addition of ethylmagnesium iodide (1 equiv) to the 1:1 diastereomeric mixture of hemiacetals (1*S*,2*S*)- and (1*R*,2*S*)-**13** gave the magnesium salt **15**, which

Scheme 5[20]



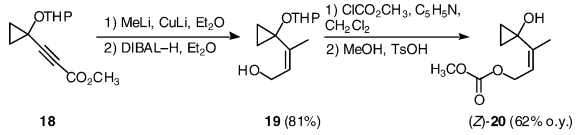
behaved as expected from the (2*S*)-2-methylcyclopropanone **15′**, most probably stabilized by ligation with EtOMgI,[17] to furnish upon treatment with phenylethynyllithium a 91:9 diastereomeric mixture of cyclopropanols (1*R*,2*S*)- and (1*S*,2*S*)-**16** in 76% yield. Then lithium aluminum hydride reduction led in 96% yield to the (1*R*,2*S*)-2-methyl-1-(*E*)-styrylcyclopropanol **17** (*de*: 82%; *ee* > 99%) as the major product (Scheme 6).[20]

Scheme 6[20]



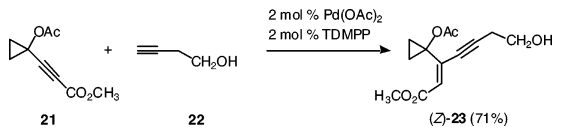
Cuprate addition to the *O*-protected 1-ethynylcyclopropanol derivative **18** (available from the cyclopropanone hemiacetal **7**[14a,b]), followed by reduction gave only the (*Z*)-allylic alcohol **19** in 81% yield. Then formation of the corresponding carbonate and *O*-deprotection provided the 1-ethenylcyclopropanol derivative **20** in 62% overall yield (Scheme 7).[22]

Scheme 7[22]



Likewise, palladium-catalyzed addition of but-3-yn-1-ol **22** to the 1-alkynylcyclopropyl acetate **21** produced directly the (*Z*)-1-ethenylcyclopropyl acetate **23** in 71% yield (Scheme 8).[22]

Scheme 8[22]



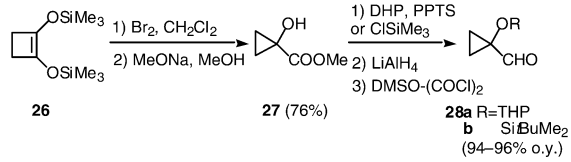
Reaction of propargylmagnesium bromides with the iodomagnesium salt of the cyclopropanone hemiacetal **8**[15] gave mixtures of acetylenic and propadienyl cyclopropanols. However, treatment of the propargyl bromides **24a**–**d** (R = Ph, *n*Hex, Me_3Si, *t*$BuMe_2Si$) with powdered aluminum and a catalytic amount of mercuric chloride led to propargylaluminum reagents, which reacted with the iodomagnesium salt **8** to furnish the corresponding substituted 1-(1,2-propadienyl)cyclopropanols **25a**–**d** in moderate-to-good yields (Scheme 9).[23]

Scheme 9[23]

2.3. From 1-Hydroxycyclopropanecarbaldehydes

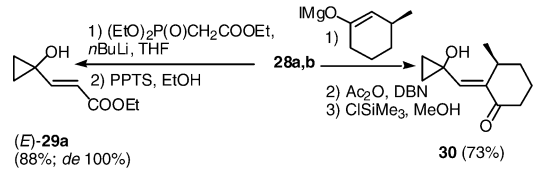
Bromination of 1,2-bis(trimethylsiloxy)cyclobutene **26**, the product of acyloin condensation of diethyl succinate by highly dispersed sodium in the presence of chlorotrimethylsilane[24,25a–c] (the procedure was also simplified and improved under sonochemical activation[21a,b]), followed by the addition of sodium methoxide in methanol to the resulting 1,2-cyclobutanedione, gave the hydroxyester **27** in 76% yield.[26a,b] After *O*-protection either by 3,4-dihydro-2*H*-pyran or by *t*-butylchlorodimethylsilane (imidazole, DMF), lithium aluminum hydride reduction, Swern oxidation of the resulting cyclopropylcarbinols led to the cyclopropanecarbaldehydes **28a**,**b** (R = THP, *t*$BuMe_2$-Si) in 94–96% overall yields from the hydroxy ester **27** (Scheme 10).[26a,b–28]

Scheme 10[26a,b–28]



The Wittig reaction of the cyclopropanecarbaldehydes **28a**,**b** with various phosphorus ylides provided 1-(1-alkenyl)cyclopropanols in high yields.[26a,b] Otherwise, addition of triethyl phosphonoacetate carbanion [$(EtO)_2P(O)CH_2$-CO_2Et, *n*-BuLi] to **28a** followed by *O*-deprotection produced diastereoselectively the ethyl (*E*)-3-(1-hydroxycyclopropyl)prop-2-enoate **29a** in 88% yield,[27] while addition to **28b** of the enolate anion resulting from cuprous iodide-catalyzed addition of methylmagnesium iodide to cyclohex-2-en-1-one, followed by dehydration and desilylation gave in 73% overall yield the enone **30** suitable precursor of spirovetivanes (Scheme 11).[28]

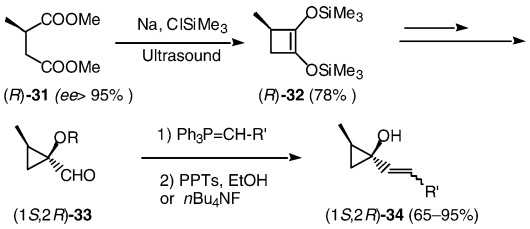
Scheme 11[27,28]



Porcine pancreatic lipase (PPL)-catalyzed hydrolysis of dimethyl 2-methylsuccinate leads, on a preparative scale, to the diester (*R*)-**31** (or its (*S*)-enantiomer) with an enantioselectivity higher than 95%.[29a,b] This compound can also be prepared by the stereoselective alkylation of chiral oxazolidinones (prepared from L-valinol or (+)-norephedrine).[30] Sodium-mediated acyloin type cyclization of (*R*)-**31** in

the presence of chlorotrimethylsilane[21a,b,24,25a−c] provided in 78% yield the (*R*)-1,2-disiloxy-3-methylyclobutene **32**, which, following the same procedure used to get **28a**,**b** from **26** (Scheme 10),[26a,b−28] led to the aldehyde derivatives (1*S*,2*R*)-**33** (R = THP, *t*BuMe$_2$Si). The Wittig reaction with various alkylidenetriphenylphosphoranes,[26a,b,31a−d] provided after cleavage of the hydroxy protective group a (*Z*,*E*) mixture of cyclopropanols (1*S*,2*R*)-**34** in 65−95% yields (Scheme 12).[26a,b,31a−d,32]

Scheme 12[26a,b,31a−d,32]

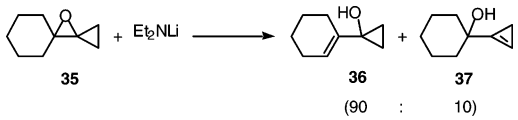


Use of these chiral synthons for the preparation of natural compounds have proven that the optical purity of the asymmetric carbons of (1*S*,2*R*)-**34** could be higher than 95% *ee*.[31a−d,33]

2.4. From Oxaspiropentanes

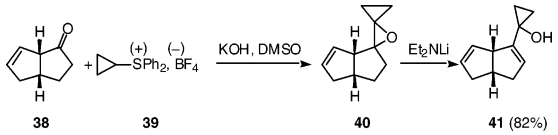
Oxaspiropentanes, which were prepared by simple epoxidation of alkylidenecyclopropanes,[6a,b] underwent ring opening by lithium dialkylamides under various conditions. For instance, reaction of 3-oxadispiro-[2.1.5.0]decane **35** with lithium diethylamide in pentane gave a 90:10 mixture of 1-(1-cyclohexenyl)-cyclopropanol **36** and of 1-(1-cyclopropenyl)cyclohexanol **37** (Scheme 13).[34]

Scheme 13[34]



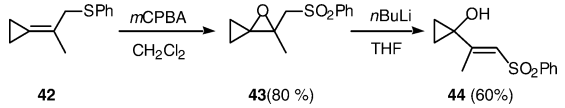
Otherwise, condensation of the bicyclo[3.3.0]oct-7-en-2-one **38** with cyclopropyldiphenylsulfonium fluoroborate **39** in DMSO containing powdered potassium hydroxide led to the oxaspiropentane **40**, which underwent ring opening on addition of Et$_2$NLi to provide the cyclopropanol **41** in 82% yield (Scheme 14).[35]

Scheme 14[35]



On the other hand, oxidation of the cyclopropylidenealkyl sulfide **42** [prepared by Wittig reaction of (3-bromopropyl)triphenylphosphonium bromide with the suitable carbonyl compound] gave in 80% yield the sulfone epoxide **43**, which underwent readily ring opening with *n*-butyllithium to furnish the cyclopropanol **44** in 60% yield yield (Scheme 15).[36]

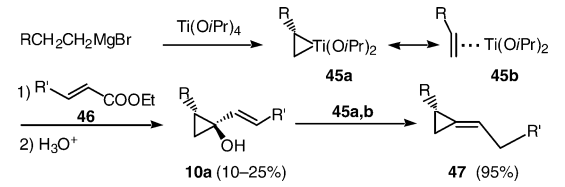
Scheme 15[36]



2.5. Titanium(IV)-Mediated Cyclopropanation of Esters

Addition of carboxylic acid esters to a mixture of titanium(IV) isopropoxide (1 equiv) and an alkylmagnesium bromide (3 equiv) at low temperature (−78 to 0 °C) affords 1-alkylcyclopropanols.[37] This simple and efficient procedure could also be achieved in a catalytic version when the order of reagents was inverted, i.e., by addition of the Grignard reagent to the mixture of ester and titanium(IV) isopropoxide.[38a−e] The intermediate diisopropyloxytitana(IV)cyclopropanes **45a** and/or their (η^2-olefin) diisopropyloxytitanium(II) resonance forms **45b** have been considered to act as 1,2-dicarbanionic equivalents performing a 2-fold alkylation of alkoxy-carbonyl groups to provide diastereoselectively (*E*)-cyclopropanols in good or excellent yields.[38a−c] However, treatment of α,*β*-unsaturated esters **46** with Grignard reagents (e.g., EtMgBr or *n*-BuMgBr) in the presence of titanium-(IV) isopropoxide [Ti(O*i*Pr)$_4$] (0.2−1.1 equiv) under various experimental conditions, gave the expected 1-ethenylcyclopropanols **47** in unusably low yields (<10−25%).[39] When the (*E*)-1-styrylcyclopropanol **10a** (R = H, R′ = Ph), unequivocally prepared from the cyclopropanone hemiacetal magnesium salt **8** (Scheme 4),[7b] was treated with EtMgBr/Ti(O*i*Pr)$_4$, i.e., with the reagent **45a**,**b** under the conditions of the cyclopropanation reaction,[38a−e] then reductive elimination of the hydroxy group occurred to provide the (2-phenylethylidene)cyclopropane **47** in 95% yield (Scheme 16).[40]

Scheme 16[39,40]

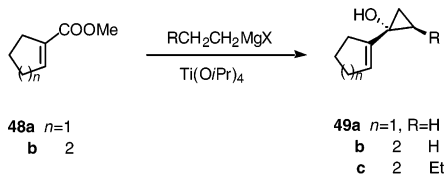


Therefore, this subsequent reaction could be responsible for the low yields observed in the titanium-(IV)-mediated cyclopropanation of conjugated esters.[39,40]

Nevertheless, cyclopropanation of the commercially available methyl (1-cycloalkenyl)carboxylates **48a**,**b** (n = 1, 2) by ethylmagnesium bromide (R = H, X = Br) in the presence of Ti(O*i*Pr)$_4$, provided the cyclopropanols **49a** (n = 1; R = H) and **49b** (n = 2; R = H) in 86 and 95% yields, respectively, while cyclopropanation of **48b** by *n*-butylmagnesium chloride (R = Et, X = Cl) under the same conditions, led to the trans cyclopropanol **49c** in 54% yield (Scheme 17).[41a,b]

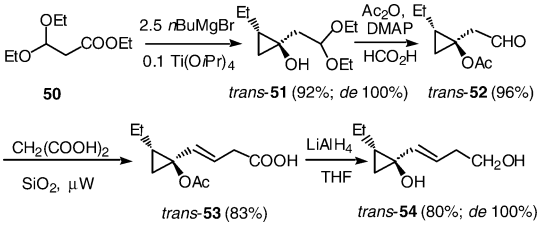
On the other hand, titanacyclopropane-mediated cyclopropanation of the commercially available ethyl 3,3-diethoxypropionate **50** upon treatment with *n*-BuMgBr (2.5 equiv) and Ti(O*i*Pr)$_4$ (0.1 equiv) gave diastereoselectively the trans cyclopropanol **51** in 92% yield. *O*-Protection to avoid ring opening[6a−d] and

Scheme 17[41a,b]



deacetalization provided the trans aldehyde **52** in 96% overall yield. Microwave irradiation (300W, 150 °C for 15 min) of an equimolar mixture of *trans*-**33** and malonic acid adsorbed on silica gel led to the *trans*-but-3-enoic acid **53**, which finally underwent reduction to provide the *trans*-cyclopropanol **54** in 80% yield (Scheme 18).[42]

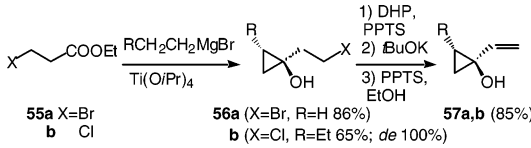
Scheme 18[42]



In the same way, the titanium-mediated cyclopropanation of various α- and β-oxyesters offered diastereoselectively the corresponding trans cyclopropanols in good yields, from which the allylic double bond could be created subsequently.[40] Nevertheless, attempted asymmetric syntheses of 1-ethenylcyclopropanols by using chiral titanium ligands [(TADDOL)$_2$, BINOL, BINOL/TADDOL, (*S*)-1,3-butanediol][41] gave either low enantiomeric excesses (6−52% *ee*) or low yields (6−44%). Otherwise, cyclopropanation of chiral esters, e.g., ethyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate (available from diethyl (*S*)-malate) afforded in 80% yield a 4:4:2 diastereomeric mixture of optically active (*SSS*)-, (*SRR*)-, and (*SRS*)-2-substituted cyclopropanols, but difficulty in their separation precluded their further application.[39,43]

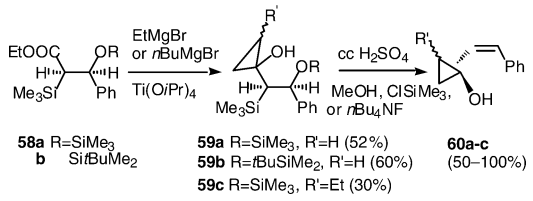
Titanium(IV)-mediated reaction [0.5 equiv of Ti(O*i*Pr)$_4$] of ethyl 3-bromopropionate **55a** (X = Br) with ethylmagnesium bromide (2 equiv) gave the 1-(2-bromoethyl)cyclopropanol **56a** (R = H, X = Br) in 86% yield, while reaction of chloroester **55b** (X = Cl) with *n*-butylmagnesium bromide (2.5 equiv) and Ti(O*i*Pr)$_4$ (0.2 equiv) in THF led diastereoselectively to the *trans*-cyclopropanol **56b** (R = Et, X = Cl) in 65% yield (*de* 100%). After *O*-protection,[6] the resulting tetrahydropyranyl ethers underwent base-induced dehydrohalogenation, followed by cleavage of the THP group to provide the 1-ethenylcyclopropanol **57a** and *trans*-**57b** (*de* 100%) in high yields (Scheme 19).[44]

Scheme 19[44]



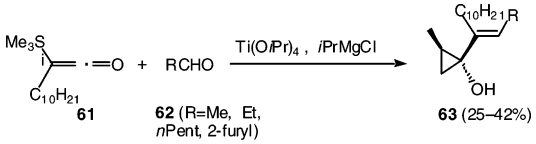
Mercuric iodide-catalyzed condensation of bis-(trialkylsilyl)ketene acetals with benzaldehyde gave 1:1 mixtures of *erythro*- and *threo*-adducts. However, only the *threo* propionates **58a**,**b** (R = SiMe$_3$, Si*t*BuMe$_2$) underwent titanium(IV)-mediated cyclopropanation by Grignard reagents (EtMgBr or *n*-BuMgBr) to lead to the cyclopropanols **59a**−**c** (R′ = H, Et) in 52, 60, and 30% yields, respectively. This difference of reactivity has been interpreted by computational studies of the transition structures (semiempirical ZINDO method). Acid-induced Peterson olefination by concentrated H_2SO_4 in THF at −78 °C, by acidic MeOH (ClSiMe$_3$) or by tetra-*n*-butylammonium fluoride in THF at room temperature, provided the 1-[(*Z*)-styryl]cyclopropanols **60a** (R′ = H) in 50−100% yields and the *trans*- and *cis*-2-ethyl-1-[(*Z*)-styryl]cyclopropanols **60c** (R′ = Et) in 75% yield (Scheme 20).[45]

Scheme 20[45]



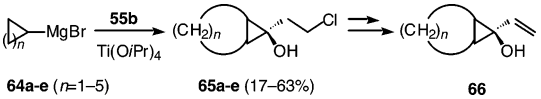
The reaction of the (trimethylsilyl)ketenes **61** with aldehydes **62** (R = Me, Et, *n*Pent, 2-furyl) in the presence of the reagent **45a**,**b**, arising from the reaction of Ti(O*i*Pr)$_4$ (2 equiv) with an excess of *i*PrMgBr, in diethyl ether at −30 °C, gave in moderate yields (25−42%) the *trans*-2-methyl-1-[(*Z*)-1-alkenyl]cyclopropanols **63** (Scheme 21).[46]

Scheme 21[46]



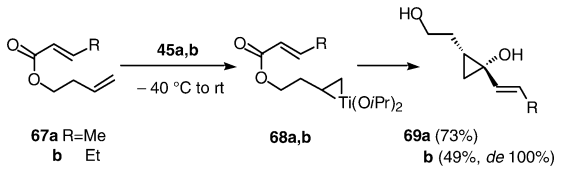
Preparation of *fused* cyclopropanols, i.e., of (2-chloroethyl)bicyclo[n.1.0]alkanols **65a**−**e** has been recently attempted from the titanium(IV)-mediated reaction of ethyl 3-chloropropionate **55b** with the cycloalkylmagnesium bromides **64a**−**e** (*n* = 1−5). While cyclopropylmagnesium bromide **64a** (*n* = 1) underwent, even in the presence of Ti(O*i*Pr)$_4$, classical addition to ester **55b** to furnish the corresponding tertiary alcohol, the Grignard reagents **65b**−**e** (*n* = 2−5) led to the expected adducts **66b**−**e** in good yields, except cyclohexylmagnesium bromide **64d** (*n* = 4), which provided besides expected **65d** (17% yield), 1-cyclohexylcyclopropanol as major products (46% yield). The diastereoselectivity appeared strongly depending on the ring size. After *O*-protection and dehydrochlorination (*t*BuOK) following the same procedure, the *fused* 1-ethenylcyclopropanols **66** could be obtained (Scheme 22).[47]

Scheme 22[47]



Homoallyl α,β-unsaturated esters **67a**,**b** (R = Me, Et) underwent cyclopropanation by the reagent **45a**,**b**[48] to give the pure *cis*-cyclopropanols **69a** and **69b** in 73 and 69% yields, respectively (Scheme 23).[37,40] Most probably the reaction occurred through

Scheme 23[40]

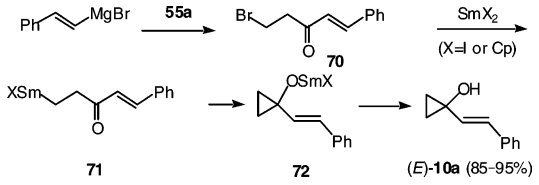


the formation of the intermediate titanacyclopropanes complexes **68a**,**b**, arising from replacement of coordinated propene in complex **45a**,**b** by the vinyl moieties of **67a**,**b**.[49a,b] Enantioenriched **69b** was obtained with 22% enantiomeric excess upon treatment of homoallyl ester **67b** with *i*PrMgBr (4 equiv) and Ti(TADDOL)$_2$ (2 equiv).[40]

2.6. Samarium(II) Iodide Induced Cyclization of β-Haloketones

Intramolecular reductive cyclization of β-halo substituted carbonyl compounds was also performed under the action of samarium(II) diiodide.[50] Thus, treatment of ethyl 3-bromopropionate **55a** with (*E*)-styrylmagnesium bromide (1 equiv) in the presence of SmI_2 (HMPA/THF) (2 equiv) or of bis-cyclopentadienylsamarium(II) (samarocene) (2.5 equiv) at −78 °C to avoid double alkylation of the ester gave the (*E*)-styrylcyclopropanol **10a** in 95 and 85% yields, respectively (Scheme 24).[51]

Scheme 24[51]

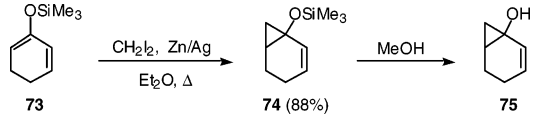


The reaction was reported to involve the single addition of the Grignard reagent to the ester moiety of **55a** to form the β-bromoketone **70**, which underwent intramolecular Barbier-type reaction mediated by SmX_2 (X = I or Cp). Then the resulting 3-samario ketone **71** would cyclize to form the samarium cyclopropyloxide **72**, and finally hydrolysis offered (*E*)-**10a**.[51]

2.7. Carbene or Carbenoid Cyclopropanation of Trialkylsilyl Enol Ethers

Trimethylsilyl enol ethers of saturated,[52a,b] as well as of unsaturated aldehydes and ketones[53a,b] underwent regioselective cyclopropanation by the modified Simmons-Smith reagent.[54a,b] For example, reaction of the 2-trimethylsiloxycyclohexa-1,3-diene **73** resulting from *O*-silylation of cyclohex-2-enone (LDA, Me_3SiCl), with diiodomethane (1.1 equiv) in the presence of Zn/Ag couple[54a,b] in boiling diethyl ether provided the trimethylsiloxycyclopropane **74** in 88% yield,

Scheme 25[53a,b]



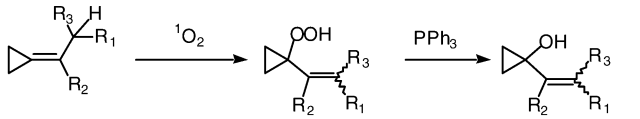
which on simple methanolysis led to the bicyclo[4.1.0]-hept-2-en-1-ol **75** (Scheme 25).[53a,b]

Likewise, modified Simmons-Smith cyclopropanation (CH_2I_2, Zn/Cu) of 2-(2-methoxyethoxy)butadiene occurred on the more electron-rich double bond to produce 1-(2-methoxyethoxy)-1-ethenylcyclopropane in 53% yield.[53c]

2.8. Photooxygenation of Alkylidenecyclopropanes

The dye-sensitized photooxygenation of alkylidenecyclopropanes **76a**−**d** at −50 °C gave the hydroperoxides **77a**−**d**, which were reduced in situ by triphenylphosphine to provide the 1-alkenylcyclopropanols **78a**−**d** in 65−70% yields (Scheme 26).[55] At higher

Scheme 26[55]

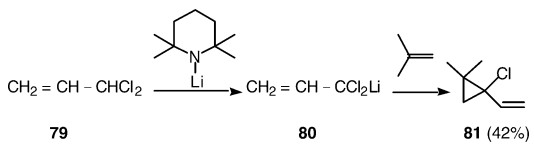


temperature, **77a**−**d** underwent ring opening into 3-oxopenta-1,4-diene derivatives, or into 1-hydroxy-3-oxo-4-pentene derivatives when pyridine was added.[55]

2.9. From Chloro- and Perchlorovinylcarbenes

1-Ethenylcyclopropyl chlorides could also be considered as suitable precursors for the formation of the π-1,1-dimethyleneallylmetal complexes **1a** (*n* = 1). However, taking into account that cyclopropanes did not undergo simply nucleophilic substitution with retention of the three-membered ring,[7a−c] the rather difficult direct access to 1-chloro-1-ethenylcyclopropanes has significantly limited their use. Nevertheless, addition of lithium 2,2,6,6-tetramethylpiperidide to a solution 3,3-dichloropropene **79**, obtained from acrolein and phosphorus(V) chloride, in isobutene for instance, gave through the carbenoid **80**, the cyclopropane **81** in 42% yield (Scheme 27).[56a] Analogously,

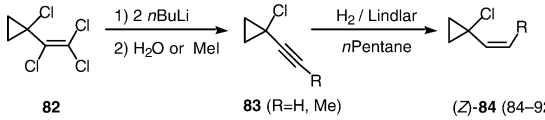
Scheme 27[56a]



reaction of 1,1,3-trichloro-2-alkenes with *t*BuOK generated (2-chlorovinyl)chlorocarbenes, which were sufficiently stable to be added to olefins to furnish 1-(2-chloroethenyl)cyclopropyl chlorides in 60−67% yields.[56b]

Otherwise, reaction of the commercially available 1-chloro-1-(trichloroethenyl)cyclopropane **82** (arising from thermal ring opening of tetrachlorocyclopropene and trapping of the resulting perchlorovinylcarbene[57a−c] by ethylene[58]) with *n*-butyllithium (2 equiv) and subsequently with the corresponding electrophiles (e.g., H_2O, MeI) provided the 1-chloro-1-(1-alkynyl)cyclopropanes **83** (R = H, Me).[59a,b] Then catalytic hydrogenation using deactivated Lindlar-catalyst (5% Pd on $CaCO_3$, lead poisoned with 2% quinoline added) led to the chlorocyclopropanes **84** in 84 and 92% yields, respectively (Scheme 28).[60] A

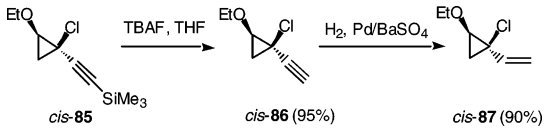
Scheme 28[60]



wide range of derivatives **84** with various substituents on the three-membered ring as well as on the ethenyl moiety were accessible by this procedure.[59a,b,60]

Analogously to the procedure disclosed in Scheme 4,[17] desilylation of the *cis*-1-chloro-2-ethoxy-1-(trimethylsilylethynyl)cyclopropane **85**[59b] with tetra-*n*-butylammonium fluoride (TBAF) led to the *cis*-chlorocyclopropane **86** in 95% yield, which then underwent hydrogenation over Lindlar catalyst to give the *cis*-chlorocyclopropane **87** in 90% yield. (Scheme 29).[61]

Scheme 29[61]

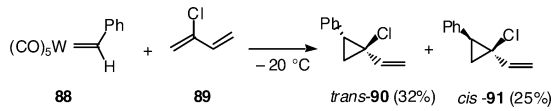


Likewise, addition of dichloro- and dibromocarbenes, generated from chloro- or bromoform under phase transfer conditions, to 2-chlorobutadiene provided 2-ethenyl-1,1,2-trichlorocyclopropane and 2-chloro-1,1-dibromo-2-ethenylcyclopropane in 28% yields, along with 5% of adducts derived from attack at the non-chlorinated alkene.[62]

2.10. Transfer of Benzylidenepentacarbonyl from Tungsten Complexes

Benzylidene transfer from the benzylidenepentacarbonyl complex **88** to 2-chloro-1,3-butadiene **89** at −20 °C was reported to occur regiospecifically to the more electron-rich double bond to give a 3:2 mixture of *trans*- and *cis*-cyclopropanes **90** and **91** in 32 and 25% yields, respectively (Scheme 30).[63]

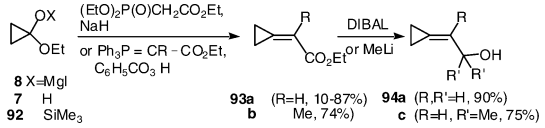
Scheme 30[63]



2.11. Wittig and Wittig–Horner Reactions of Cyclopropanone Hemiacetals

The Wittig reaction of arylidenetriphenylphosphoranes with the cyclopropanone hemiacetal magnesium salt **8** (X = MgI) produced arylidenecyclopropanes in moderate yields,[15,17] but the Wittig−Horner reaction of the carbanion of triethyl phosphonoacetate (NaH) with the salt **8** gave the expected ethyl cyclopropylideneacetate **93a** (R = H) in only 10% yield.[15] However, the Wittig reaction of cyclopropanone hemiacetal **7** (X = H) with (carbethoxymethylene)triphenylphosphoranes provided the acetates **93a**,**b** (R = H, Me) in 87 and 74% yield, respectively, when the reaction was catalyzed by 10% of benzoic acid.[64a−c] Otherwise, 1-ethoxy-1-trimethylsiloxycyclopropane **92** (X = $SiMe_3$)[13c] underwent after cleavage of the trimethylsiloxy group by tetra-*n*-butylammonium fluoride (1 equiv) benzoic acid-mediated Wittig olefination in a convenient one-pot procedure.[65] Then, diisobutylaluminum hydride reduction (DIBAH, CH_2Cl_2, −78 °C) of the conjugated ester **93a** finally furnished the 2-cyclopropylideneethanol **94a** (R, R′ = H) in 90% yield; otherwise, addition of methyllithium (2 equiv) to **93a** led to the 1-cyclopropylidene-2-methylpropan-2-ol **94c** (R = H, R′ = Me) in 75% yield (Scheme 31).[10c]

Scheme 31[10c,15,64c,65]

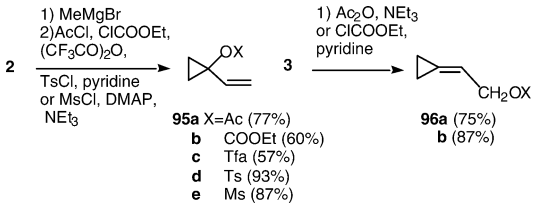


As shown further in this review, the acetate of **94a** was formed in 80% yield from the palladium(0)-catalyzed nucleophilic substitution of 1-ethenyl-1-tosyloxycyclopropane by potassium acetate in the presence of [18]-crown-6 ether (vide infra).[10a−c]

3. Formation of π-1,1-Dimethyleneallylpalladium Complexes

Consequently, various substituted 1-ethenylcyclopropanol frameworks, even enantiomerically pure [see for instance 1*R*,2*S*-**14** (Scheme 5)[20]], became readily available for this aim. 1-Ethenylcyclopropanol **2**, upon successive treatment with methylmagnesium bromide (1 equiv) and acetyl chloride, ethyl chloroformate, or trifluoroacetic anhydride at 0 °C, was converted into its acetate **95a** (X = Ac, 77%), ethyl carbonate **95b** (X = CO_2Et, 60%), and trifluoroacetate **95c** (X = Tfa, 57%), respectively. While reaction of **2** with *p*-toluenesulfonyl- or methanesulfonyl chloride provided the tosylate **95d** (X = Ts, 93%) and the mesylate **95e** (X = Ms, 87%). Otherwise, the isomeric acetate **96a** and ethyl carbonate **96b** were obtained from the 2-cyclopropylideneethanol **3** upon treatment with acetic anhydride and ethyl chloroformate in 75 and 86% yields, respectively (Scheme 32).[10a−c]

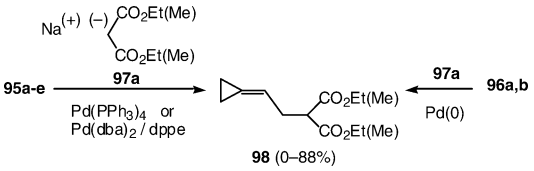
Scheme 32[10a−c]



3.1. Substitution by Soft Nucleophiles

In the presence of tetrakis(triphenylphosphine)-palladium(0) [$Pd(PPh_3)_4$] as catalyst, allylic acetates generally underwent substitution by stabilized anions (*soft* nucleophiles).[2a−c] Under these conditions, the acetate **95a** and the carbonate **95b** did not undergo any reaction with the diethyl sodiomalonate **97a**, even in refluxing THF for 120 h, contrary to the isomeric allylic acetate **96a** and carbonate **96b**, which provided regioselectively the diethyl (2-cyclopropylideneethyl)malonate **98** in 80 and 88% yields, respectively (Scheme 33). The intrinsic ring strain energy (SE) of the three-membered ring should be responsible for this amazingly different behavior; as a matter of fact cleavage of the cyclopropyl acetate (or carbonate) bond in **95a**,**b** entailed at least partially a positive charge on the cyclopropane ring and consequently increased the ring strain energy (SE = 27.5 and 48 kcal mol^{-1} for the cyclopropane ring[66a] and the 1-methylcyclopropyl cation,[66b] respectively). On the other hand, cleavage of the allylic acetate (or carbonate) bond of **96a**,**b** did not significantly increase the ring strain (SE = 40.9 kcal mol^{-1} for methylenecyclopropane).[66a] However, use of better leaving groups increased the reactivity of 1-ethenylcyclopropyl esters; thus, the trifluoroacetate **95c** and tosylate **95d** underwent in refluxing THF palladium-(0)-catalyzed substitution by the nucleophile **97a** to give the expected malonate **98**, in 23 and 85% yield, respectively. Bidentate ligand catalyst generated in situ from bis(dibenzylideneacetone)palladium [Pd-$(dba)_2$] and 1,2-bis(diphenylphosphine)ethane (dppe),[67] allowed performing the nucleophilic substitution of esters **95c**,**d** and **96a**,**b** in THF at room temperature, to furnish the adduct **98** in 55, 86, 85, and 88% yield, respectively (Scheme 33).[10a−c]

Scheme 33[10a−c]



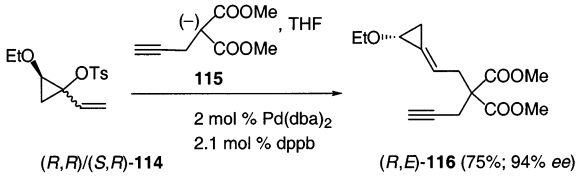
Use of the anions of substituted 2-methyl-, 2-(propen-2-yl)-, and 2-(propyn-2-yl)malonates **97b**−**d** and of malonate **98** as nucleophiles for the palladium(0)-mediated substitution of tosylate **95d** provided the (2-cyclopropylidenethyl)malonates **99**−**102** in high yields. From the tosylates of 1-styrylcyclopropanol (*E*)-**10a** (R = Ph) and of 1-(1-propenyl)cyclopropanol (*E*)-**10b** (R = Me), the malonates **103** and **104** were also obtained in high yields. Otherwise, use of 2-methoxycarbonylcyclopentanone **97e**, 2-methyl-1,3-cyclopentanedione **97f**, and 2-phenylsulfonyl acetate **97g** sodium enolates led to the adducts **105**−**107** also in high yields. A series of oxygen and nitrogen nucleophiles, e.g., the anions of potassium acetate **97h** in the presence of [18]-crown-6 ether, of sodium phenylallyl oxide **97j**, and of potassium phthalimide **97k**, as well as dibenzylamine **97l**, benzophenone imine **97m**, *O*-benzylhydroxylamine **97n** displayed the behavior of *soft* nucleophiles toward the tosylate of 1-ethenylcyclopropanol **95d** or toward the acetate and carbonate of 2-cyclopropylideneethanol **96a**,**b**, to offer the acetate **108**, the 3-phenyl-2-propenyl ether **109** or the allylamine derivatives **110**−**113**, regioselectively (Table 1).[10a−c,68]

Table 1. Palladium(0)-Catalyzed Nucleophilic Substitution of 1-Ethenylcyclopropyl Tosylate 95d[10a−c,68]

Entry	Tosylate	Nucleophile	Adducts	% Yields
1	**95d**	**97b**	**99**	82
2	**95d**	**97c**	**100**	91
3	**95d**	**97d**	**101a**	91
4	**95d**	**98**	**102**	91
5	(*E*)-**10a**	**97a**	**103**	94
6	(*E*)-**10b**	**97a**	**104**	94
7	**95d**	**97e**	**105**	93
8	**95d**	**97f**	**106**	72
9	**95d**	**97g**	**107**	92
10	**95d**	**97h**	**108**	80
11	**95d**	**97j**	**109**	95
12	**95d**	**97k**	**110**	65
13	**95d**	**97l**	**111**	85
14	**95d**	**97m**	**112**	95
15	**95d**	**97n**	**113**	84

In the same way, the (*R*,*R*)- and (*S*,*R*)-1-ethenyl-2-ethoxy-1-tosyloxycyclopropanes **114**, prepared from enantiomerically pure 2-alkoxy-1-ethenylcyclopropanes,[61] reacted smoothly at room temperature in THF with dimethyl sodiumpropargylmalonate **115** in the presence of catalytic Pd(dppb) [generated in situ from $Pd(dba)_2$ and 1,4-bis(diphenylphosphano)butane]. Both diastereomers gave the same single product, the dimethyl malonate (*R*)-**116** in 75% yield and 94% of enantiomeric excess; however, the trans isomer reacted more slowly (Scheme 34).[61]

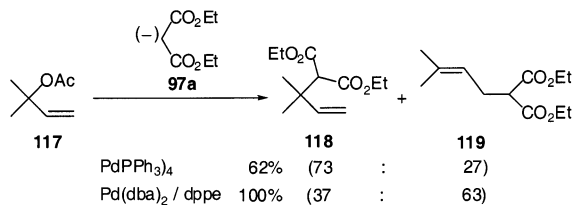
Scheme 34[61]



Alkylidenecyclopropanes form a peculiar class of strained olefinic compounds (SE = 40.9 kcal mol^{-1})[66a] with remarkable synthetic potential. Thus, they can undergo transition metal catalyzed ring opening, [3+2] cycloaddition with olefinic and acetylenic substrates, [1,3] dipolar cycloaddition with nitrones or Pauson Khand cyclization with acetylene dicobalt hexacarbonyl complexes (vide infra).[69a,b] Among the varied syntheses extensively reviewed recently,[70] this new method appears so far the best in terms of regioselectivity, stereoselectivity, and atom economy,[5a,b] to allow the preparation of alkylidenecyclopropanes.

The regioselectivity observed for the palladium(0)-catalyzed substitution of the tosylate **95d**, which occurred exclusively at the terminal vinylic end either with C-nucleophiles (e.g., dimethyl sodiomalonate) as well as with oxygen and nitrogen nucleophiles (see Table 1) was surprising. On the other hand, it has been reported that the 1,1-dimethylallyl acetate **117**, in fact, the ring-opened analogue of **95a**, underwent palladium(0) [$Pd(PPh_3)_4$] catalyzed substitution by diethyl sodiomalonate **97a** in THF at reflux, to give a 73:27 mixture of regiomeric 2-substituted diethyl malonates **118** and **119**, in 62% yield, while use of $Pd(dba)_2$/dppe led quantitatively to a 37:63 mixture of **118** and **119**. Actually, the regioselectivity was dependent on the catalyst (Scheme 35).[71]

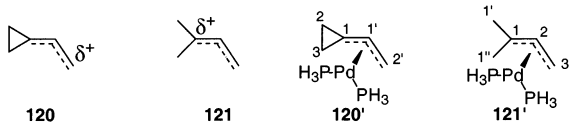
Scheme 35[71]



Competition experiments between 1-ethenylcyclopropyl tosylate **95d** and 1,1-dimethylallyl acetate **117**, or between 2-cyclopropylideneethyl acetate **96a** and its ring-opened derivative, i.e., 3,3-dimethylallyl acetate, in their palladium(0)-catalyzed substitution by **97a** gave 19:1 and 99:1 mixtures of **98** and isomeric malonates **118** and **119**, disclosing a surprising higher reactivity for **95d**.[10a–c]

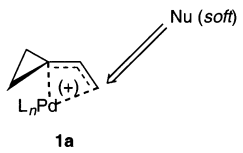
Different structures have been considered for the complex **1a** (M = Pd) and the π-1,1-dimethylallylpalladium complex arising from the acetate **117** or from the 3,3-dimethyallyl acetate. First of all, high level calculations (STO-3G, 6-31G, and 6-31G*) have indicated a higher positive charge on the primary carbon of the 1-ethenylcyclopropyl cation **120**, whereas MINDO/3, AM1, and 6-31G* have predicted a higher positive charge on the tertiary center of the 1,1-dimethylallyl cation **121**.[10c] However, calculations performed over both corresponding π-allylpalladium complexes **120′** and **121′** having two molecules of PH_3 as ligands, using the semi-emperical method PM3 (tm) and refining the results with ab initio calculations with 3-21G* basis, have suggested that in the complex **120′** palladium is closer to the cyclopropyl carbon C_1 than to the other allylic terminus $C_{2'}$ (2.14 and 2.29 Å, respectively), while in the complex **121′** the trend is reversed with the transition metal being closer to the primary carbon C_3 than to the tertiary carbon C_1 (2.20 and 2.31 Å, respectively) (Scheme 36).[10c,72,73]

Scheme 36[10c,72,73]



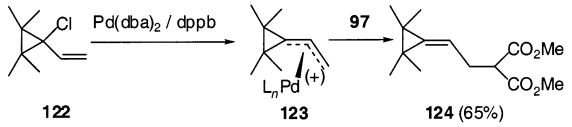
These computer data provided evidence for the occurrence of the intermediate unsymmetric complex **1a**, and in the lack of any relevant electronic or steric effects, for the higher reactivity and regioselectivity toward the attack of *soft* nucleophiles (Scheme 37).[10c,72,73]

Scheme 37[10c,72,73]



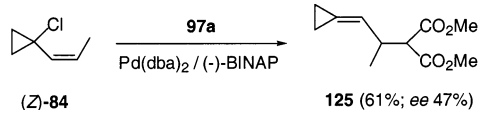
1-Chloro-1-ethenylcyclopropane **84** (R = H) (Scheme 28) reacted also with dimethyl sodiomalonate **97a**, like tosylate **95d** or mesylate **95e** in the presence of 0.2 mol % of $Pd(dba)_2$/dppe or 1,4-bis(diphenylphosphino)butane (dppb) to give **98**, exclusively, in 51 or 66% yield, depending on the ligand; however, when a mixture of tosylate **95d** (1 equiv) and chloride **84** (1 equiv) were reacted with dimethyl sodiomalonate **97a** (1 equiv) in the presence of $Pd(dba)_2$/dppb (5%), in a competition experiment, it was observed that the tosylate reacted with a preference superior to 98:2.[60] Although highly sterically hindered, the chlorocyclopropane **122** underwent substitution by the sodiomalonate **97a** in the presence of $Pd(dba)_2$/dppb at room temperature to give, likely via the complex **123**, exclusively the product **124** in 65% yield (Scheme 38).[60]

Scheme 38[60]



In the presence of (*S*)-(−)-BINAP as chiral palladium(0) ligand,[74] the (*Z*)-1-(1-propenyl)cyclopropylchoride **84** (R = Me) underwent alkylation by **97a** to provide in 61% yield, the malonate **125** with 47% of enantiomeric excess (Scheme 39).[60]

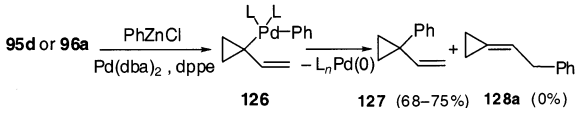
Scheme 39[60]



3.2. Substitutions by Hard Nucleophiles

Substitution of 1-ethenylcyclopropyl tosylate **95d** or of 2-cyclopropylideneethyl acetate **96a**, by phenylzinc chloride (4 equiv) in the presence of 5% of palladium(0) [Pd(dba)$_2$/dppe] in THF at 40 °C, produced exclusively the cyclopropane **127** in 68 and 75% yields, respectively. The fact that no trace of **128a** was formed, resulting from substitution at the primary carbon center as observed with *soft* nucleophiles, suggested then a different mechanism.[75a] Effectively, organometallics were known to react by transmetalation,[76] i.e., in this case by transfer of the organic moiety from zinc to palladium to form a σ-palladium complex **126**, which then underwent reductive elimination of Pd(0) from cross coupling reaction with carbon−carbon bond formation to finally produce **127** (Scheme 40).[10c]

Scheme 40[10c]

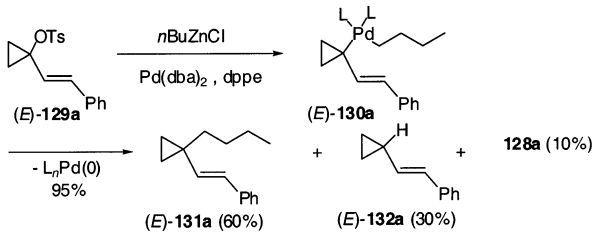


Otherwise, treatment of **95d** with phenylmagnesium bromide in the presence of nickel(II) chloride and triphenylphosphine as catalyst in diethyl ether at room temperature, gave in 90% yield, an 84:16 mixture of phenyl-substituted products **127** and **128a**, which manifestly emphasized the regioselectivity induced by the palladium catalyst.[10c]

The reaction of tosylate (*E*)-**129a** [obtained in 90% yield upon treatment of 1-styrylcyclopropanol (*E*)-**10a** (Scheme 4) with tosyl chloride in pyridine] with *n*-butylzinc chloride in the presence of 5% of palladium(0) [Pd(dba)$_2$, dppe] led in 95% yield, via the σ-complex (*E*)-**130a** to a 6:3:1 mixture of 1-*n*-butyl-1-styrylcyclopropane (*E*)-**131a**, besides 1-styrylcyclopropane (*E*)-**132a** (30%) and **128a** (10%) as reduction products resulting from β-elimination (vide infra), (Scheme 41).[10a−c]

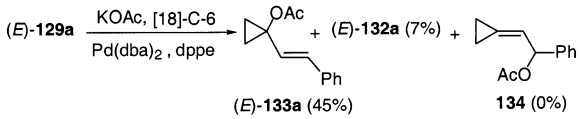
However, unexpected was the reaction of tosylate (*E*)-**129a** with potassium acetate (3 equiv) in the presence of [18]-crown-6 ether (10%) and 5% of Pd(dba)$_2$, dppe in THF at reflux, which yielded the acetoxycyclopropane (*E*)-**133a** (45%) besides a small

Scheme 41[10a−c]



amount of (*E*)-**132a** (7%) as reduction product. The lack of 2-cyclopropylidene-1-phenylethyl acetate **134** resulting from substitution at the secondary allylic end, as observed with tosylate **95d** (see Scheme 34) and resulting likely from an electronic effect was noteworthy (Scheme 42).[10c]

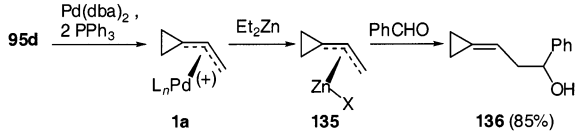
Scheme 42[10c]



3.3. Substitution by Electrophiles: Diethylzinc-Mediated Umpolung

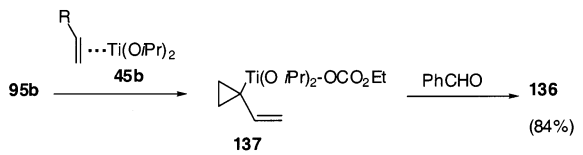
In the presence of diethylzinc (2 equiv), the π-1,1-dimethyleneallylpalladium complex **1a** (Scheme 37) underwent transmetalation involving an alkyl−allyl reaction exchange and entailing formation of the π-1,1-dimethyleneallylzinc complex **135**, which was then able to react with benzaldehyde (*umpolung*) to form in 85% yield, the 3-cyclopropylidene-1-phenyl-1-propanol **136**, exclusively (Scheme 43).[77]

Scheme 43[77]



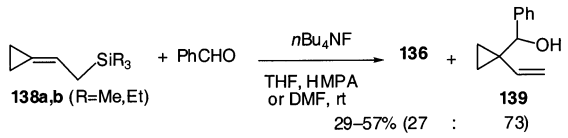
In a similar vein, the allyltitanium complex **137**, formed from the 1-ethenylcyclopropyl carbonate **95b** (Scheme 32) and the (η^2-propene)Ti(O*i*Pr)$_2$ **45b** (R = Me), generated from isopropylmagnesium bromide and Ti(O*i*Pr)$_4$ (Scheme 16), was reported to undergo reaction with benzaldehyde to provide **136** in 84% yield, with the same regioselectivity (Scheme 44).[78]

Scheme 44[78]



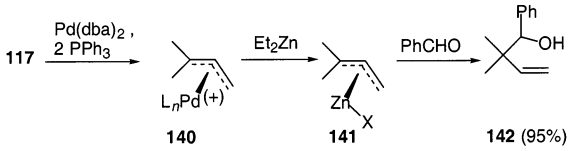
On the other hand, cleavage by tetra-*n*-butylammonium fluoride of the allylsilyl bond of the 1,1-dimethyleneallylsilane **138a**,**b** (R = Me, Et) [arising from palladium(0)-catalyzed reduction of the tosylate of the cyclopropanes (*E*)-**10f**,**h** (R = SiMe$_3$ or SiEt$_3$, Scheme 4) by sodium formate (vide infra)], followed by reaction with benzaldehyde gave a 27:73 mixture of **136** and of regiomeric cyclopropane **139**, in 29 and 57% yields, respectively (Scheme 45).[79]

Scheme 45[79]



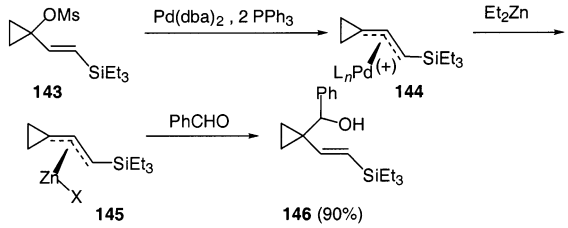
Again in contrast to **1a**, the π-1,1-dimethylallylpalladium complex **140**, formed upon treatment of 1,1-dimethylallyl acetate **117** with palladium(0) (Scheme 35), led upon treatment with diethylzinc to the complex **141**, which reacted with benzaldehyde to furnish exclusively the butenol **142** in 95% yield (Scheme 46).[79]

Scheme 46[79]



However, the regioselectivity observed in the electrophilic substitution of π-1,1-dimethyleneallylzinc complexes can be reversed by a trialkylsilyl effect. Thus, the mesylate **143** [prepared from the cyclopropanol (*E*)-**10h** (Schemes 4 and 32)] gave upon treatment with a catalytic amount of palladium(0) [from $Pd(dba)_2$, 2 PPh_3] the palladium complex **144**, which after transmetalation with Et_2Zn to form the zinc complex **145**, underwent electrophilic substitution by benzaldehyde to produce the cyclopropylcarbinol **146** in 90% yield (Scheme 47).[77] Therefore, the trialkyl-

Scheme 47[77]

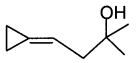
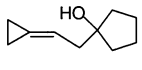
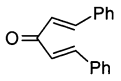
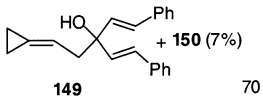
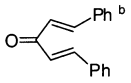
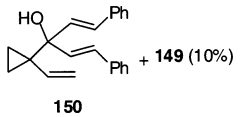


silyl group, appeared able to overcome the ring strain effect (substitution at the primary allylic end, Scheme 37) and entailed electrophilic substitution on the three-membered ring.

Otherwise, ketones such as acetone and cyclopentanone or even conjugated ketones, for instance, (*E*,*E*)-1,3-dibenzylideneacetone [dba, ligand of Pd(0)], were efficient electrophiles for the substitution of the zinc complex **135** (Scheme 43) and provided the adducts **147**−**149** in 82, 74, and 75% yields, respectively (Table 2).[77]

In fact, reaction of the zinc complex **135** [prepared from tosylate **95d** (1 equiv), Pd(0) (0.05 equiv), and Et_2Zn (2 equiv)] with dba (1 equiv) gave in 75% yield a 93:7 mixture of regiomeric adducts **149** and **150**, while reactions of 1 equiv of palladium complex **1a** [prepared from **95d** (1 equiv), $Pd(dba)_2$ (1 equiv), and PPh_3 (2 equiv)] with Et_2Zn (2 equiv) provided on the other hand in 70% yield a 10:90 mixture of **149** and **150**.[77]

Table 2. Electrophilic Substitution of π-1,1-Dimethyleneallylzinc Complexes by Ketones[77]

Entry	Zinc Complex	Ketone	Adducts	% Yields
1	 **135**[a]	CH_3–CO–CH_3	 **147**	82
2	**135**[a]		 **148**	74
3	**135**[a]		 **149** + **150** (7%)	70
4	**135**[b]		 **150** + **149** (10%)	63

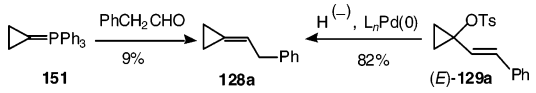
[a] From **95d** (1 equiv), $Pd(dba)_2$ (0.05 equiv), 2 PPh_3 (0.10 equiv), and Et_2Zn (2 equiv). [b] From **95d** (1 equiv), $Pd(dba)_2$ (1 equiv), 2 PPh_3 (2 equiv), and Et_2Zn (2 equiv).

4. Applications

4.1. Regioselective Hydride Reduction

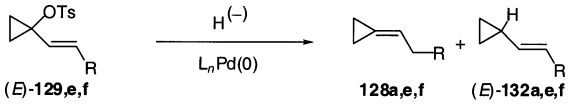
In general Wittig olefination of aldehydes and ketones by the cyclopropylidenetriphenylphosphorane **151** led to a wide range of alkylidenecyclopropanes with satisfactory yields.[80a,b] But the reaction did not occur or it occurred in rather low yield when the carbonyl compound was readily enolizable; thus, for instance, the reaction of phenylacetaldehyde with the phosphorane **151** provided the expected (2-cyclopropylidenethyl)benzene **128a** in only 9% yield. On the other hand, palladium(0)-catalyzed hydride reduction of the tosylate (*E*)-**129a** (Scheme 41) allowed overcoming this limitation and gave **128a** in 82% yield (Scheme 48).[81]

Scheme 48[81]



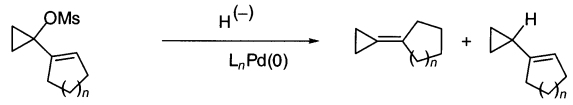
However, the regioselectivity of the reduction appeared highly dependent on both on the hydride source and on the ligands L_n of palladium(0) (Table 3). Thus, reaction of the cyclopropyl tosylate (*E*)-**129a** with *n*-butylzinc chloride in the presence of 5% of palladium(0) [$Pd(dba)_2$, 2 PPh_3], a system known to usually perform hydrogenolysis by attack of hydride resulting from β-elimination at the less substituted site of π-allylpalladium complexes,[82] gave on the other hand in 93% yield the styrylcyclopropane (*E*)-**132a** exclusively (Table 3, entry 1). Use of trimesitylphosphine as palladium ligand induced likely by a steric effect the formation in 75% yield of a 16:84 mixture of regiomeric cyclopropylidene **128a** and (*E*)-**132a** (entry 2). Hydrogenolysis of (*E*)-**129a** by sodium formate in the presence of [15]-crown-5 ether (10%) catalyzed by $Pd(dba)_2$ and dppe as bidentate ligand

Table 3. Palladium(0)-Catalyzed Hydrogenolysis of 1-(1-Alkenyl)Cyclopropyl Sulfonates[95]



(*E*)-**129,e,f** **128a,e,f** (*E*)-**132a,e,f**

Entry	R	H(–)	L_n	Θ°	y%	
1	Ph	*n*BuZnCl	PPh_3		93	(0 : 100)
2	Ph	*n*BuZnCl	$P(mesityl)_3$		75	(16 : 84)
3	Ph	HCOONa[a]	dppe	125	90	(37 : 63)
4	Ph	HCOONa[a]	PPh_3	145	95	(62 : 38)
5	Ph	HCOONa[a]	$P(p\text{-anisyl})_3$	145	90	(78 : 22)
6	Ph	HCOONa[a]	$P(\alpha\text{-naphthyl})_3$	160	45	(0 : 100)
7	Ph	HCOONa[a]	$P(o\text{-tolyl})_3$	194	94	(85 : 15)
8	Ph	HCOONa[a]	$P(o\text{-anisyl})_3$	194	90	(90 : 10)
9	Ph	HCOONa[a]	$P(mesityl)_3$	212	19	(0 : 100)
10	Ph	HCOONa[a]	dppf		80	(20 : 80)
11	*n*Bu	*n*BuZnCl	PPh_3		85	(0 : 100)
12	*n*Bu	HCOONa[a]	dppe		81	(50 : 50)
13	*n*Bu	HCOONa[a]	PPh_3		80	(100 : 0)
14	$SiMe_3$	*n*BuZnCl	PPh_3		85	(0 : 100)
15	$SiMe_3$	HCOONa[a]	PPh_3		90	(100 : 0)



151a,b (*n*=1 or 2) **152a,b** **153a,b**

16	1	*n*BuZnCl	PPh_3		83	(0 : 100)
17	1	HCOONa[a]	PPh_3		80	(98 : 2)
18	2	HCOONa[a]	PPh_3		85	(98 : 2)

[a] In the presence of 10 mol % of [15]-crown-5-ether.

of the palladium catalyst produced in 90% yield a 37:63 mixture of reduction products **128a** and (*E*)-**132a** (entry 3), while use of PPh_3 as ligand led in 95% yield to a 62:38 mixture of these reduction products, favoring then the formation of nonconjugated **128a** (entry 4).

The steric effect of trivalent phosphorus ligand plays a dominant role in the chemical behavior of transition metal complexes.[75b,83a,b] For instance, the effects of phosphine sterics has been observed in the control of isomeric distribution in the cyclooligomerization of butadiene on nickel-phophorus ligand catalyst,[84] and in the regioselectivity of the α-arylation of acylic enol ethers (the Heck reaction).[85] The steric parameter for symmetric ligands is the apex angle θ of a cylindrical cone centered 2.28 Å from the center of the phosphorus atom, which touches the van der Waals radii of the outermost atoms of the ligand (Figure 1).[83a,86]

These angles have been correlated with a wide variety of phenomena including stabilities,[87] fluxional behavior,[88] rate constants,[89a,b] catalytic activities,[90]

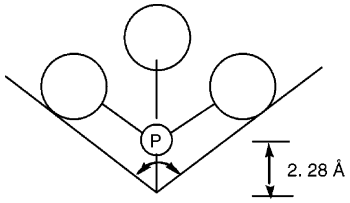


Figure 1. Cone angle.[83a,86]

and specificities in product formation.[90] Correlation has been established between proton NMR shifts and the cone angles providing convenient means for determining the size of phosphorus ligands;[91] combinations of steric and electronic factors have been pointed out to explain the ligand effect on the formation of products resulting from rhodium-catalyzed hydroformylation of conjugated dienes.[92]

As shown in Table 3, the regioselectivity of the palladium(0)-catalyzed hydrogenolysis of (*E*)-**129a** by sodium formate and [15]-crown-5 ether appeared also greatly affected by the nature of the metal ligands. An increase of the size of the substitutents on phosphorus will increase the cone angle θ and the bond lengths of metal to phosphines, so decreasing their coordinating ability (reduction of the *s* character in the phosphorus lone pair) and favoring coordination of other competitive ligands, for instance, the π-allyl moiety.[86] Thus, varying θ from 145 [PPh_3, entry 4; or P(*p*-anisyl)$_3$, entry 5] to 194° [P(*o*-tolyl)$_3$, entry 7; or P(*o*-anisyl)$_3$, entry 8] appeared to favor the formation of the alkylidenecyclopropane **128a**, from 62 to 90%, although more strained than the styrylcyclopropane (*E*)-**132a** [SE(methylenecyclopropane) − SE(cyclopropane) = 13.4 kcal/mol][93] and not conjugated. On the other hand, bidendate diphosphines such as dppe (θ = 125°) which are more metal chelating,[73] favored (*E*)-**132a** (entry 3). Too large of an increase of the size of the phosphine ligands can hamper the reaction and shift the site of the nucleophilic attack;[94] likely steric hindrance entailed formation of an unsymmetric complex with the palladium now not positioned closer to the cyclopropane ring. Thus, P(mesityl)$_3$ (θ = 212°), one of the highest cone angle reported values,[86] gave in 19% yield exclusively (*E*)-**132a**, besides the starting sulfonate (*E*)-**129a** (entry 9). Surprising, however, were the hydrogenolyses in the presence of Pd(dba)$_2$-tri(α-naphthyl)-phoshine (θ = 160°) and with bis (diphenylphosphino)-ferrocene (dppf; θ not determined) providing (*E*)-**132a** either exclusively in 45% yield (entry 6) or as a major product (80%) in 80% yield (entry 10). Competing steric and electronic factors could then control this regioselectivity; thus, an electronic effect was clearly observed by using P(*p*-anisyl)$_3$ (θ = 145°), which induced the major formation of **128a** (78%; entry 5) comparatively to PPh_3 (θ = 145°), which gave **128a** (62%, entry 4). It could also explain the increased ratio of **128a** when using P(*o*-tolyl)$_3$ (85%) and P(*o*-anisyl)$_3$ (90%), respectively, although both phosphine ligands have the same cone angle (θ = 194°; entries 7 and 8).[95]

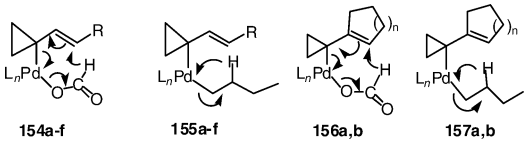
Hydrogenolysis of the cyclopropyl tosylate (*E*)-**129e** (R = nC_4H_9) (Schemes 4, 32) by *n*-butylzinc chloride in the presence of 5% of Pd(dba)$_2$, 2 PPh_3, gave exclusively the (*E*)-1-(1-hexenyl)cyclopropane **132e** in

85% yield (entry 11), while hydrogenolysis by sodium formate and [15]-crown-5 ether (10%) in the presence of 5% of $Pd(dba)_2$, dppe led in 81% yield to a 50:50 mixture of hexylidenecyclopropane **128e** and of (*E*)-**132e** (entry 12). But hydrogenolysis of (*E*)-**132e** by HCOONa and [15]-crown-5 ether in the presence of $Pd(dba)_2$, 2 PPh_3 entailed in 80% yield the exclusive formation of **128e** (entry 13). Hydrogenolysis of the cyclopropyl tosylate (*E*)-**132f** (R = $SiMe_3$) (Schemes 4 and 32) by *n*-butylzinc chloride in the presence of $Pd(dba)_2$, 2 PPh_3 provided exclusively in 85% yield the (*E*)-(2-trimethylsilylethenyl)cyclopropane (*E*)-**132f** (entry 14), while reaction of (*E*)-**129f** with sodium formate and [15]-crown-5 ether in the presence of $Pd(dba)_2$, 2 PPh_3 gave in 90% yield exclusively the regiomeric cyclopropane **128f** (entry 15).

Hydride reduction of the cyclopropyl mesylate **151a** ($n = 1$) (Schemes 2 and 32) by *n*-butylzinc chloride in the presence of $Pd(dba)_2$, 2 PPh_3 formed exclusively in 83% yield the (1-cyclopentenyl)cyclopropane **153a** (entry 16), while hydrogenolysis by sodium formate and [15]-crown-5 ether gave in 80% yield a 98:2 mixture of cyclopentylidenecyclopropane **152a** and regiomeric **153a** (entry 17). Likewise, the cyclopropyl mesylate **151b** ($n = 2$) (Schemes 2 and 32) underwent hydrogenolysis by sodium formate and [15]-crown-5 ether in the presence of $Pd(dba)_2$, 2 PPh_3 to provide in 85% yield a 98:2 mixture of cyclopropanes **152b** and **153b** (entry 18).[81,95]

From unsymmetric π-1,1-dimethyleneallylpalladium complexes such as **1a** (Scheme 37), two σ-cyclopropylpalladium complexes **154a**−**f** and **155a**−**f** have been considered as intermediaries to take into account the regioselectivity observed in the palladium(0)-catalyzed reduction of 1-(1-alkenyl)cyclopropylsulfonates **129a**−**f** by sodium formate and by *n*-butylzinc chloride, respectively. Likewise, two σ-cyclopropyl complexes **156a**,**b** and **157a**,**b** have been considered as intermediaries in the hydrogenolyses of the mesylates **151a**,**b** (Scheme 49).[81,95] Then, the σ-complexes **154a**−**f** and **156a**,**b** underwent S_Ni hydride transfer from the formate ligand, decarboxylation, and palladium reductive elimination, while the σ-complexes **155a**−**f** and **157a**,**b** underwent β-elimination of 1-butene, formation of σ-palladium hyride complexes, and palladium reductive elimination.[96a−e]

Scheme 49

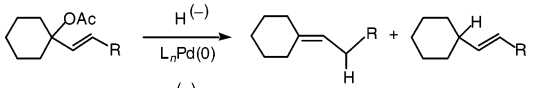


154a-f 155a-f 156a,b 157a,b

These hydrogenolyses, which offer an efficient solution to the limitation of the classical Wittig olefination due to competitive enolization of the carbonyl moieties and the difficulties met in the Wittig reaction of the cyclopropanone hemiacetal **7** (Scheme 32), provided not only mono- and disusbstituted olefins [i.e., (*E*)-**132a**,**e**,**f**], but also readily tri- or even tetrasubstituted olefins, i.e., **128a**,**e**,**f** and **132a**,**b** in high yields.[81,95] As tosylates of chiral 1-ethenylcyclopropanols, e.g., (1*R*,2*S*)-**14**, (1*R*,2*S*)-**17**, (1*S*,2*R*)-**34**, were readily available with high enantiomeric excesses (Schemes 5, 6, and 12),[31a−d,33] these regioselective palladium(0)-catalyzed hydrogenolyses offered a wide range of useful synthetic applications.

In the absence of ring strain, palladium(0) [Pd(dba)$_2$, 2 PPh_3] catalyzed hydrogenolysis of 1-(1-alkenyl)cyclohexyl acetates **158a**−**d** by *n*-butylzinc chloride offered 99:1 (R = H), 61:39 (R = *n*-Bu), 88:12 (R = $SiMe_3$), and 63:37 (R = $SiEt_3$) mixtures of alkylidenecyclohexanes **159a**−**d** and (1-alkenyl)cyclohexanes **160a**−**d** in high yields, while sodium formate and [15]-crown-5 ether as hydride source furnished 13:31 (R = H), 42:58 (R = *n*-Bu), 89:11 (R = $SiMe_3$), and 96:4 (R = $SiEt_3$) mixtures of **159a**−**d** and **160a**−**d** also in yields (Scheme 50).[95]

Scheme 50[95]

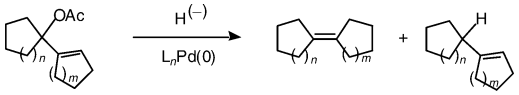


		$H^{(-)}$	y%	159a-d		160a-d
158a	R=H	*n*BuZnCl	83	(99	:	1)
b	*n*Bu	*n*BuZnCl	79	(61	:	39)
c	$SiMe_3$	*n*BuZnCl	87	(88	:	12)
d	$SiEt_3$	*n*BuZnCl	81	(63	:	37)
158a		HCOONa[a]	87	(13	:	31)
b		HCOONa[a]	85	(42	:	58)
c		HCOONa[a]	87	(89	:	11)
d		HCOONa[a]	86	(96	:	4)

[a] In the presence of 10 mol% of [15]-crown-5 ether.

Attempted hydrogenolysis of the cyclopentyl acetate **161a** ($n = 1$, $m = 2$), either with sodium formate and [15]-crown-5 ether or with *n*-butylzinc chloride, as hydride sources, in the presence of $Pd(dba)_2$, 2 PPh_3 provided exclusively 1-(1-cyclopentenyl)cyclohexene resulting from elimination of acetic acid (1 equiv). But the cyclohexyl acetate **161b** ($n = 2$, $m = 1$) underwent hydrogenolysis by *n*-butylzinc chloride in the presence of $P(dba)_2$, 2 PPh_3 to give in 79% yield a 52:48 mixture of cyclohexanes **162b** and **163b**; use of sodium formate and [15]-crown-5 ether as hydride source led in 88% yield to a 26:74 mixture of products **162b** and **163b** in 88% yield (Scheme 51). These

Scheme 51[95]



	$H^{(-)}$	y%	162a,b		163a,b
161a *n*=1, *m*=2	*n*BuZnCl	0	–		–
–	HCOONa[a]	0	–		–
b *n*=2, *m*=1	*n*BuZnCl	79	(52	:	48)
	HCOONa[a]	88	(26	:	74)

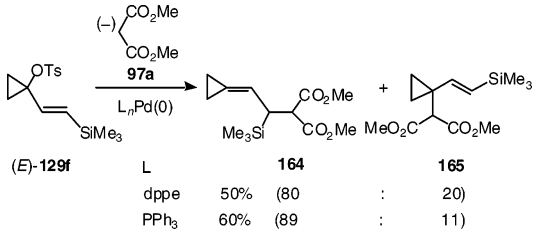
[a] In the presence of 10% mol of [15]-crown-5 ether.

results have obviously underlined the ring strain effect on the regioselectivity of these hydrogenolyses.[95]

Frontier orbital control opposed to charge control has been reported to direct attacking nucleophiles on η^3-allyl moieties[97a] and trialkylsilyl groups were considered to polarize the frontier orbitals on the γ-carbon of such complexes. Thus, *soft* (stabilized) nucleophiles, which react with the carbon having the largest coefficient in the LUMO, have been reported to provide vinylsilanes, *exclusively*.[97b,c] On the other

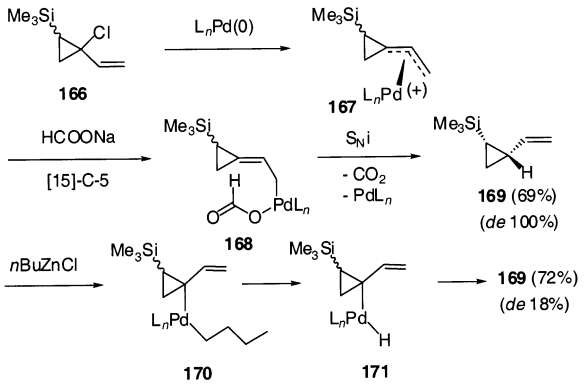
hand, palladium(0)-catalyzed reduction of (*E*)-**129f** by sodium formate and [15]-crown-5 ether was observed exclusively on the carbon bearing the trimethylsilyl group to give in 90% yield, the allylsilane **128f** (Table 3, entry 15). Although in general, *soft* and *hard* nucleophiles substituted π-allylpalladium complexes with opposite regioselectivity, substitution of (*E*)-**129f** by the enolate of dimethyl malonate **97a** as *soft* nucleophile, occurred still preferentially on the carbon substituted by the trimethylsilyl group to provide 80:20 and 89:11 mixtures of 3,3-dimethyleneallylsilane **164** and of 2-cyclopropylvinylsilane **165**, in 50 and 60% yields depending on the palladium ligands dppe or PPh_3, respectively (Scheme 52).[79]

Scheme 52[79]



However, when located on the cyclopropane ring, the trimethylsilyl group appeared able to thwart the driving effect of the ring strain and to direct the substitution on the three-membered ring. Thus, when a 70:30 mixture of *cis*- and *trans*-1-chloro-1-ethenyl-2-(trimethylsilyl)cyclopropane **166**[60] was submitted to palladium(0) [$Pd(dba)_2$, 2 PPh_3] catalyzed hydrogenolysis by sodium formate in the presence of [15]-crown-5 ether (10%), the diastereochemically pure *cis*-1-ethenyl-2-(trimethylsilyl)cyclopropane **169** (*de* 100%) was obtained in 69% yield, exclusively. Most likely, **169** was formed through the π-palladium complex **167** and after substitution by the formate anion, through the σ-palladium complex **168** which underwent S_Ni hydride transfer (Scheme 49). Otherwise, palladium(0)-catalyzed reduction of the diastereomeric mixture of **166** by *n*-butylzinc chloride as hydride source, gave in 72% yield, likely through the π−complex **167** and the σ-complexes **170** and **171** (Scheme 49), a 58:42 diastereomeric mixture of **169** (Scheme 53).[79]

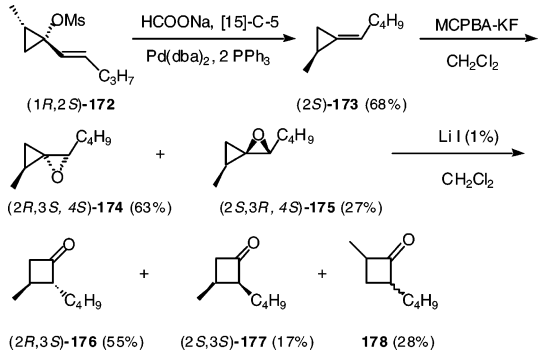
Scheme 53[79]



Nevertheless, this effect could be reversed by the simultaneous presence of trimethylsilyl groups, both on the cyclopropane ring and on the 1-ethenyl moiety, which provided in high yields, either (*E*)-(2-trimethylsilylethylidene)-2-trimethylsilylcyclopropane (*de* 100%) or 1-(2-trimethylsilylethenyl)-2-(trimethylsilyl) cyclopropane depending again on the hydride source.[79]

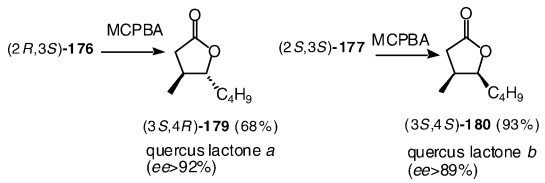
Alkylidenecyclopropanes[70a,b] offer considerable potential in organic syntheses,[69a,b,98] and for example as the most suitable precursors for the cyclobutanones synthesis.[6a−c,99a−c] Palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] hydrogenolysis by sodium formate in the presence of [15]-crown-5 ether of the mesylate (1*R*,2*S*)-**172** prepared from (1*R*,2*S*)-2-methyl-1-(1-pentenyl)cyclopropanol (Scheme 12) gave in 68% yield the diastereochemically pure cyclopropane (*E*)-(2*S*)-**173**, besides 16% of readily separable isomeric 2-methyl-1-(pent-1-yl)cyclopropane.[32] Epoxidation of pure (2S)-**173** by a preformed *m*-chloroperbenzoic acid−potassium fluoride complex (MCPBA-KF) in dichloromethane provided in 90% yield a 70:30 mixture of oxaspiropentanes (2*R*,3*S*,4*S*)-**174** and of its diastereomer (2*S*,3*R*,4*S*)-**175**. Upon treatment with a catalytic amount of lithium iodide (1%) oxaspiropentanes **174** and **175** underwent quantitative $C_3 \rightarrow C_4$ ring expansion,[6a−d] to provide a 55:17:28 mixture of cyclobutanone (2*R*,3*S*)-**176**, of its diastereomer (2*S*,3*S*)-**177**, and of the regioisomeric cyclobutanone **178** (Scheme 54).[33]

Scheme 54[33]



Baeyer−Villiger oxidation of the unseparable mixture of cyclobutanones (2*R*,3*S*)-**176** and **178** with MCPBA led to a 68% yield after purification by flash chromatography of the pure butanolide (3*S*,4*R*)-**179**, known as quercus lactone *a* with >92% enantiomeric excess, while Baeyer−Villiger oxidation of the pure cyclobutanone (2*S*,3*S*)-**177** provided in 93% yield the butanolide (3*S*,4*S*)-**180**, known as quercus lactone *b*, with >89% enantiomeric excess (Scheme 55).[33]

Scheme 55[33]

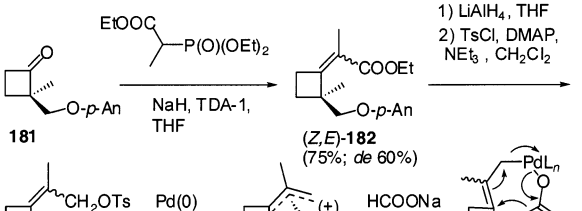


Alternatively, the butanolide (3*S*,4*S*)-**180** and its optically active precursor the cyclobutanone (2*S*,3*S*)-**177** have been obtained from the diastereoselective trifluoroboron-etherate (BF_3-Et_2O) catalyzed ring expansion of the (1*R*,2*S*)-1-[1-(*t*butyldimethylsiloxy)-2-methylcyclopropyl]pent-1-en-3-ol, readily

available from the cyclopropanecarbaldehyde (1*R*,2*S*)-**33** (Scheme 12).[31a−d] The 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.[100]

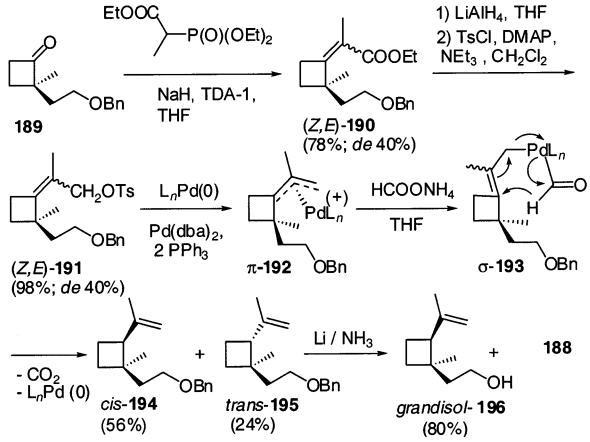
Analogously, the regioselective and stereospecific palladium(0)-induced reduction of 2-cyclobutylidene propyl esters, involving homologous π-1,1-trimethyleneallylpalladium complexes, offered a new and convenient entry to diastereomeric four-membered ring monoterpernoids.[101] Thus, the Wittig−Horner reaction of the cyclobutanone **181**, readily available from ring expansion of the suitable oxaspiropentane,[102] with sodium triethyl 2-phosphonopropionate provided in 75% yield an unseparable 80:20 mixture of ethyl (*Z*) and (*E*) propionates **182**. Reduction followed by tosylation led in 80% overall yield to the (*Z*)- and (*E*)-allylic tosylates **183**. Palladium(0) [Pd(dba)$_2$, 2 PPh$_3$] catalyzed reduction of (*Z,E*)-**183** by sodium formate in the presence of [15]-crown-5 ether occurred likely through the π-1,1-trimethyleneallylpalladium complex **184**, which upon nucleophilic addition of formate anion formed the σ-1,1-trimethyleneallylpalladium formate complexes **185**. Then, S_Ni transfer of the hyride to the cyclobutanic allylic end and decarboxylation of the formate ligand provided in 77% yield an 80:20 mixture of *trans*- and *cis*-1,1,2-trisubstituted cyclobutanes **186**. Finally, cleavage of the *O*-protective group by ammonium cerium(IV) nitrate (CAN) gave in 74% yield after chromatography, the diastereochemically pure *trans*-cyclobutylcarbinol **187**, a reported convenient precursor after homologation of the primary alcohol,[103] of racemic *fragranol* **188**, a monoterpenoid isolated from the roots of *Artemisia fragans Willd*[104] (Scheme 56).[101]

Scheme 56[101]



Wittig−Horner reaction of the cyclobutanone **189** readily available in 98% yield from ring expansion of 4-benzyloxy-2-[1-(phenylthio)cyclopropyl]butan-2-ol (prepared from addition of 1-(phenylthio)cyclopropyllithium to 4-benzyloxybutan-2-one)[101] provided in 78% yield an unseparable 70:30 mixture of ethyl (*Z*) and (*E*) propionate **190**. Reduction and tosylation of the corresponding allylic alcohols gave in 98% overall yield the crude tosylates (*Z*,*E*)-**191**. Palladium(0)-catalyzed reduction of the mixture of (*Z*,*E*)-**191** by ammonium formate, which most probably occurred through the π-palladium complex **192** and σ-1,1-trimethyleneallylpalladium formate complexes **193**, analogously to the σ-complexes **185** (Scheme 56), led in 80% yield to a 70:30 mixture of cyclobutanes *cis*-**194** and *trans*-**195**. After *O*-deprotection *cis*-**194** released in 80% yield the racemic *grandisol* **196**, a monoterpenoid main constituent of the aggregation male-produced pheromone of the cotton boll weevil *Anthonomous Grandis* Boheman[105] and of the sex pheromones of other pests responsible for conifer infestations in North America and Central Europe, like *Bark weevils*[106] and *Bark beetles*.[107] On the other hand, *O*-deprotection of *trans*-**195** released in 80% yield the *fragranol* **188** (Scheme 57).[101]

Scheme 57[101]



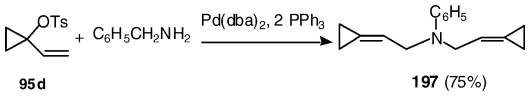
In fact, the palladium(0)-catalyzed reduction of 2-cyclobutylidenepropyl sulfonic esters by the formate anion (from HCOONa or HCOONH$_4$) involving π-1,1-trimethyleneallylpalladium complexes, appeared completely regioselective since the hydride substitution occurred exclusively on the cyclobutyl end of the complexes σ-**185** and σ-**193**, contrary to the σ-1,1-dimethyleneallylpalladium complexes **154a**−**f** and **156a,b**, (Scheme 49). The hydrogenolysis appeared also stereospecific since the reduction of the 80:20 diastereomeric mixture of the allylic sulfonic esters (*Z*)- and (*E*)-**183** provided an 80:20 mixture of *trans*- and *cis*-cyclobutanes **186**, while hydrogenolysis of the 70:30 diastereomeric mixture of the allylic sulfonic esters (*Z*)- and (*E*)-**191** furnished a 70:30 mixture of diastereomeric cyclobutanes *cis*-**194** and *trans*-**195**. It was noteworthy that the 2-(2-benzyloxyethyl) substituent was sufficiently bulky to hamper completely one side of the palladium complexes π-**192** and/or σ-**193** and to entail the favored formation of the *cis*-2-isopropylidenecyclobutane **194**, precursor of *grandisol* **196**.[101]

In summary, the regioselective and stereospecific nucleophilic substitution of π-1,1-trimethyleneallylpalladium complexes allowed the stereocontrolled construction of cyclobutane derivatives of biological importance that bear quaternary stereocenters on the four-membered ring. (For an enantioselective construction of quaternary carbons based on enzymatic hydrolysis, see ref 108a,b).

4.2. Regioselective Amination and Azidation

The palladium(0)-catalyzed amination of the 1-ethenylcyclopropyl sulfonic esters **95d**,**e** by *N*-nucleophiles stabilized by an electron withdrawing group on the nitrogen like potassium phthalimide or dibenzylamine, benzophenone imine, or *O*-benzylhydroxylamine occurred exclusively on the less substituted allylic end to provide in high yields the 2-cyclopropylidenethylamine derivatives **110**−**113** (Table 1).[10b,c,68] However, reaction of the tosylate **95d** with an excess of benzylamine in the presence of $Pd(dba)_2$, 2 PPh_3 gave the benzylamine **197** in 75% yield because the intermediate monoallylamine was more nucleophilic than benzylamine itself (Scheme 58).[68]

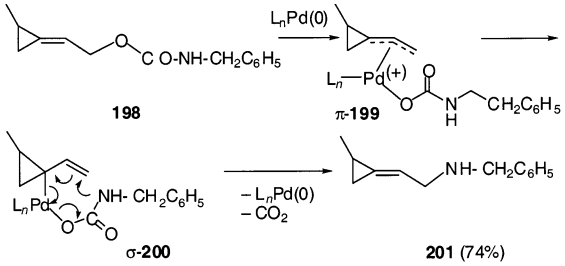
Scheme 58[68]



Although allylic amination was reported to occur in general on the more substituted end of π-allyl groups when using ferrocenylphosphine−palladium complexes,[109] on the other hand use of PPh_3 or of bis-(diphenylphosphino)ferrocene as ligand in the palladium(0)-catalyzed amination of allylic esters **95d**,**e** with dibenzylamine led exclusively to the product of amination at the primary vinylic end of the π-1,1-dimethyleneallylpalladium complex **1a** (Scheme 37).[68]

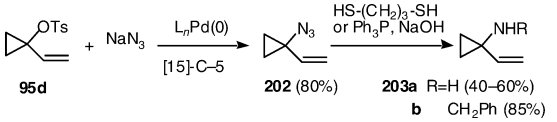
The *N*-benzylcarbamate **198** resulting from the simple addition of benzylisocyanate to 2-(2-methylcyclopropylidene)ethanol underwent palladium(0)-catalyzed transfer of benzylamine exclusively on the less substituted end regardless of whether the ligand was PPh_3 or PBu_3.[110] Most probably, the reaction occurred through the palladium complexes π-**199** and σ-**200**, which analogously to the complexes σ-**154a**−**f** and σ-**156a**,**b** (Scheme 49), underwent S_Ni benzylamine transfer, decarboxylation, and palladium reductive elimination to produce in 74% yield the ethylamine **201** (Scheme 59).[68]

Scheme 59[68]



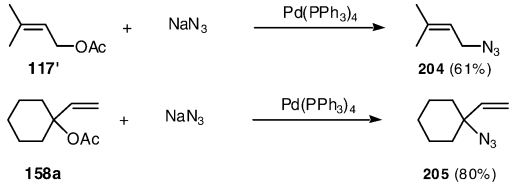
On the other hand, palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] azidation of the allylic ester **95d** with sodium azide (NaN_3) in the presence of [15]-crown-5 ether (10%) gave in 80% yield the azidocyclopropane **202** exclusively. Treatment of **202** with 1,3-propanedithiol in methanol or with triphenylphosphine in aqueous sodium hydroxide gave the highly volatile 1-ethenylcyclopropylamine **203a** (R = H) in 40 or 60% yields, respectively, but successive treatment of **202** with PPh_3 and benzaldehyde and reduction of the resulting imine provided the aminocyclopropane **203b** (R = CH_2Ph) in 85% yield (Scheme 60).[68]

Scheme 60[68]



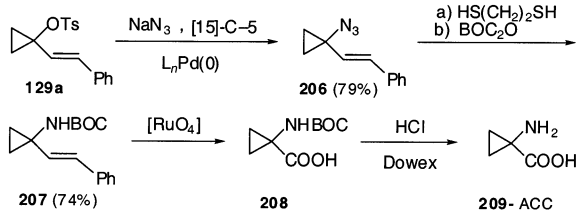
Comparatively, reactions of 3,3-dimethylallyl acetate **117′** and of 1-ethenylcyclohexyl acetate **158a** with NaN_3 in the presence of $Pd(PPh_3)_4$ were reported to give the 1-azido-3-methylbut-3-ene **204** and the azidocyclohexane **205**, in 61 and 80% yield, respectively (Scheme 61).[111]

Scheme 61[111]



Therefore, the regioselectivity observed in the palladium(0)-catalyzed azidation of the tosylate **95d**, i.e., the apparent *hard* nucleophile behavior of sodium azide (vide supra, paragraph 3.2) was unexpected. Likewise, palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] azidation of the cyclopropyl tosylate **129a** (Scheme 41) by NaN_3 in THF containing [15]-crown-5 ether gave in 79% yield the nonvolatile azidocyclopropane **206**. Reduction of the azide **206** with 1,3-propanedithiol for instance, followed by the one-pot addition of di-*t*butyl dicarbonate led in 74% overall yield to the *N*-BOC protected 1-styrylcyclopropylamine **207**. Ruthenium tetroxide ($RuCl_3$, $NaIO_4$) oxidative cleavage of the styryl double bond and treatment with 6 N HCl of the resulting *N*-BOC protected amino acid **208** produced in 73% overall yield after ion-exchange chromatography (Dowex 50WX 8.100) the parent *2,3-methanoamino acid* (ACC) **209** (Scheme 62).[68]

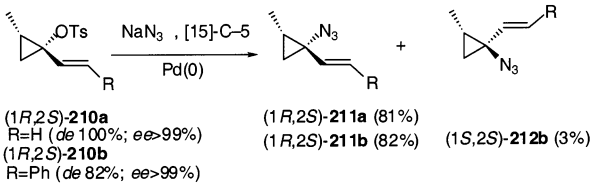
Scheme 62[68]



1-Aminocyclopropanecarboxylic acids or 2,3-*methanoamino acids* (ACC) not only provide enzyme inhibitors and biological probes for mechanistic studies allowing the design of new drugs, but their incorporation into peptide chains affords conformationally constrained peptidomimetics with enhanced biological activities and stabilities (reduced proteolytic degradation).[8a−d] Therefore, different methodologies have been investigated for the total synthesis of these challenging α-amino acids.[8a−d,112a−c]

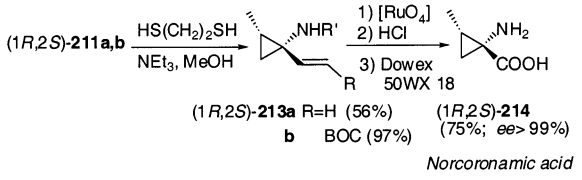
The tosylate (1*R*,2*S*)-**210a** (R = H) resulting from the esterification (TsCl) of the optically pure cyclopropanol (1*R*,2*S*)-**14** [prepared from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate, (Scheme 5)][20] underwent palladium(0) [$Pd(dba)_2$, 2 PPh_3] catalyzed azidation (NaN_3, [15]-crown-5 ether) to give in 81% yield the single azide (1*R*,2*S*)-**211a** exclusively. Otherwise, a 91:9 diastereomeric mixture of mesylates (1*R*,2*S*)- and (1*S*,2*S*)-**210b** (R = Ph) of the cyclopropanols (1*R*,2*S*)-**17** (*de* 82%, Scheme 6)[20] underwent palladium(0)-catalyzed azidation under the same conditions to furnish a 96:4 diastereomeric mixture of azides (1*R*,2*S*)-**211b** and (1*S*,2*S*)-**212b** in 85% yields (Scheme 63).[20]

Scheme 63[20]



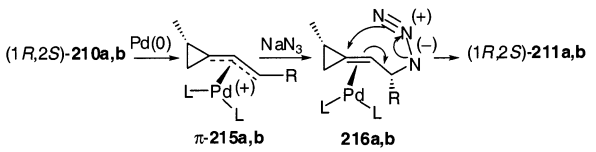
Reduction of the pure azide (1*R*,2*S*)-**211a** with 1,3-propanedithiol gave in 56% yield the corresponding volatile primary cyclopropylamine (1*R*,2*S*)-**213a** (R′ = H); while reduction of the azide (1*R*,2*S*)-**211b**, purified by flash chromatography, followed by *N*-BOC protection provided in 97% yield (1*R*,2*S*)-**213b** (R′ = BOC). Finally oxidative degradation of the styryl group by ruthenium tetroxide, followed by *N*-deprotection and ion-exchange chromatography led in 75% overall yield to the nonnatural (1*R*,2*S*)-*norcoronamic acid* **214**,[113] whose enantiomeric purity (>99%) was determined by ^2H NMR of its deuterated methyl ester in a cholesteric lyotropic liquid crystal (Scheme 64).[114]

Scheme 64[20]



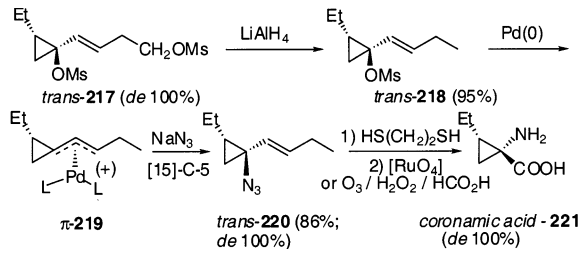
Most probably the azidation of (1*R*,2*S*)-**210a**,**b** occurred through the π-palladium complexes **215a**,**b** formed with inversion of configuration. Taking into account as reported that the palladium(0)-catalyzed azidation of allyl esters occurs with overall retention of configuration,[100] nucleophilic substitution of π-**215a**,**b** with inversion of configuration should form the azides **216a**,**b**, which then should undergo subsequent palladium(0)-induced known isomerization,[111] stereocontrolled by the palladium moiety coordinated to the double bond, to produce diastereoselectively the azides (1*R*,2*S*)-**211a**,**b** (*de* 92−100%) (Scheme 65).[20]

Scheme 65[20]



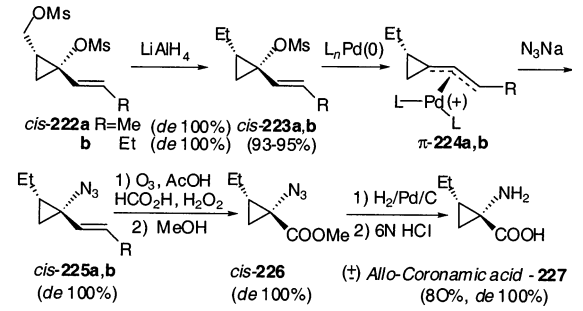
Regioselective lithium aluminum hydride reduction of the dimesylate *trans*-**217**, prepared by double esterification (3 MsCl, NEt_3, Et_2O, 88%) of the cyclopropanol *trans*-**54** (Scheme 18)[42] gave in 99% yield the monomesylate *trans*-**218**, which underwent palladium(0) catalyzed [$Pd(dba)_2$, 2 PPh_3] azidation to provide through the palladium complex π-**219**, again with complete retention of configuration, the single *trans* cyclopropyl azide **220** in 86% yield. Finally, azide reduction and oxidative cleavage of the double bond afforded in 77% yield overall yield the diastereomerically pure racemic *coronamic acid* **221** (Scheme 66).[40,42]

Scheme 66[40,42]



Regioselective reduction of the dimesylate *cis*-**222a**,**b** (R = Me, Et), resulting from the double esterification (100% yield) of the cyclopropanols **69a** (Scheme 23)[39,40] gave the *cis*-cyclopropyl mesylates **223a**,**b** in 93−95% yield. Palladium(0)-catalyzed azidation (NaN_3, [15]-crown-5 ether) of allyl mesylates, took place by way of the π-allylpalladium complexes **224a**,**b** to afford the cis cyclopropyl azides **225a**,**b**. Selective ozonolysis and esterification gave the azido esters *cis*-**226**, which underwent reduction to lead, after acidic hydrolysis (6 N HCl) and ion-exchange chromatography (Dowex 50WX 18), in 80% yield to the diastereomerically pure *cis-allo-coronamic acid* **227** (Scheme 67).[39,40] Converted into 1-butene by

Scheme 67[39,40]

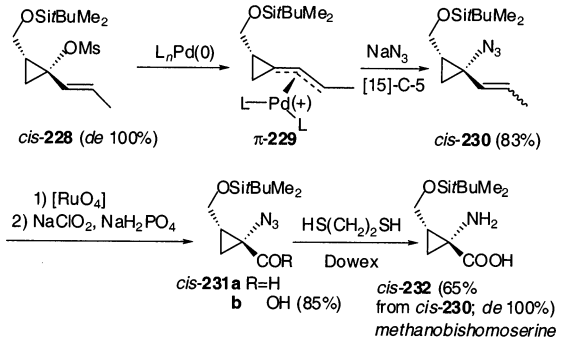


plant tissues, the nonnatural 2,3-methanoamino acid *cis*-**227** was used for plant growth and fruit ripening control.[8b,c]

Prepared from the diastereomerically pure *cis*-diol **69a** (Scheme 23), the diastereoselectively pure cyclopropyl mesylate *cis*-**228** underwent palladium(0)-catalyzed azidation, through the π-palladium complex **229** to produce in 83% yield the cyclopropyl azides *cis*-**230** bearing either (*E*)- or (*Z*)-1-(1-propenyl) substituents (75:25 mixture). RuO_4-mediated double bond cleavage produced the *cis*-cyclopropanecarboxaldehyde **231a** (R = H), which upon further oxidation led to the *cis*-azido acid **231b** in 85% yield. Finally,

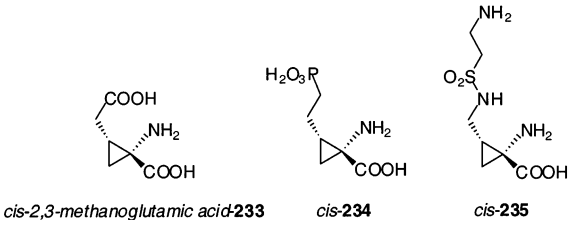
reduction and ion-exchange chromatography provided in 65% overall yield from *cis*-**230**, the diastereoselectively pure *cis-methanobishomoserine* **232** (Scheme 68).[40]

Scheme 68[40]



Various known *2,3-methanoamino acids* of biological interest,[8b,c] such as for instance the *cis*-2,3-*methanoglutamic acid* **233**, a potential agonist of metabotropic glutamate receptors (mGLuRs),[115] the cyclopropyl analogue of 2-amino-5-phosphonopentanone acid *cis*-**234** assessed as competitive antagonist for the *N*-methyl-D-aspartate (NMDA) receptor,[116] and *cis*-**235** used to prepare thermally stable peptide table salt substitutes,[117] are now available following this totally diastereoselective procedure (Scheme 69).[40]

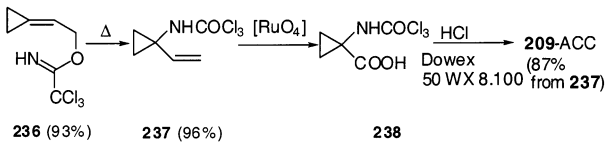
Scheme 69[40]



As a matter of fact, the diastereoselectivity observed in the palladium(0)-catalyzed azidation of the π-1,1-dimethyleneallylpalladium complexes **215a**,**b**, **219**, **224a**,**b**, and **229**, which occurred with complete retention of the configurations of the cyclopropyl sulfonic esters (1*R*,2*S*)-**210a**,**b**, *trans*-**217**, *cis*-**223a**,**b**, and *cis*-**228**, appeared fully noteworthy.[39,40]

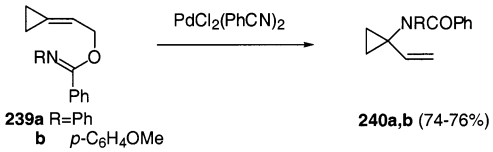
An alternative entry to the parent *2,3-methanoamino acid* ACC-**209** was provided by the thermally induced and transition metal catalyzed aza-Claisen rearrangement of 2-cyclopropylideneethyl imidates.[118] Thus, addition of trichloroacetonitrile (1.5 equiv 10% NaH) to the 2-cyclopropylideneethanol **94a** (Scheme 31) gave in 93% yield the trichloroacetimidate **236**, which on heating (100 °C for 48 h or 110 °C for 36 h) underwent [3,3] sigmatropic aza-Claisen rearrangement[108] to provide in 96% yield the trichloroacetamide **237**. Oxidation furnished the cyclopropanecarboxylic acid **238**, treatment with HCl and ion-exchange chromatography gave also the parent 1-aminocyclopropanecarboxylic acid ACC-**209** in 87% overall yield from the amide **237** (Scheme 70).[118]

Scheme 70[118]



However, attempted aza-Claisen rearrangement of **236** failed under catalytic conditions. Thus, treatment of **236** with mercuric trifluoroacetate[119a,b] provided an anti-Claisen product, i.e., the *N*-(2-cyclopropylideneethyl)trichloroacetimidate, and treatment with nickel(II) catalyst [$NiCl(dppe)_2$] or with palladium-(0) [from $Pd(dba)_2$, 2 PPh_3 or dppe] were not effective.[118] Otherwise, the benzimidates **239a,b** (R = Ph, *p*-Anisyl) obtained by reaction of the sodium salt of **94a** (NaH) with *N*-phenyl- and *N*-*p*-anisylbenzimidoyl chlorides, respectively, underwent the aza-Claisen rearrangement on heating in benzene at 50 °C in the presence of palladium(II) catalyst [$PdCl_2(CH_3CN)_2$ or $PdCl_2(PhCN)_2$] to give the cyclopropylamines **240a**,**b** in 76 and 74% yields, respectively (Scheme 71).[118]

Scheme 71[118]

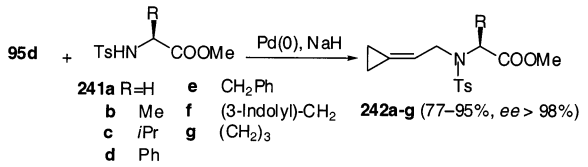


A related synthesis of cyclopropylamine derivatives as efficient precursors of 2,3-methanoamino acids, involving π-allylpalladium complexes, was based on the one-pot palladium(0)-catalyzed alkylation and S_Ni cyclization of 1,4-dichlorobut-2-ene by *N*-(diphenylmethylene)aminoacetonitrile.[120]

4.3. Intramolecular Cycloaddition of Alkylidenecyclopropane Nitrones

The palladium(0)-catalyzed [$Pd(dba_2$, dppe] nucleophilic substitution of the sulfonic ester **95d** (Scheme 32) by the monoprotected methyl *N*-tosylamino esters **241a**−**g** [to avoid double alkylation of the nitrogen (see Scheme 58)] derived from glycine (R = H), L-alanine (R = Me), L-valine (R = *i*Pr), L-phenylglycine (R = Ph), L-phenylalanine (R = CH_2Ph), L-triptophane (R = 3-indolyl-CH_2), and L-proline (R = -$(CH_2)_3$-) in the presence of NaH (1 equiv) gave in excellent yields (77−95%) the amino esters **242a**−**g** (Scheme 72).[121a,b] The regioselectivity of the substitu-

Scheme 72[121a,b]

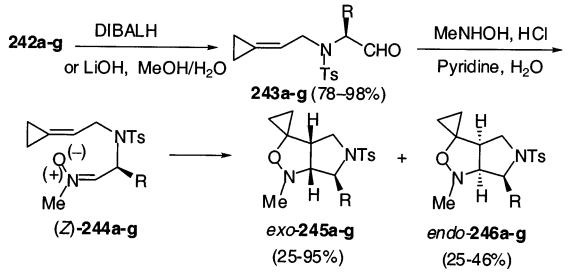


tion was complete (*soft* nucleophile behavior, paragraph 3.1) and C-alkylation as observed with *N*-(diphenylmethylene)glycine ester (Scheme 83)[122] did not occur. Moreover, optically active amino esters

241b−**g** led to the products **242b**−**g** with >98% enantiomeric excess.[121a,b]

Partial reduction of the esters **242a**−**g** gave in 78−98% yields the aldehydes **243a**−**g** with total retention of the stereochemistry at the α-carbon. Addition of *N*-methylhydroxylamine to **243a**−**g** formed the (*Z*)-methylnitrones **244a**−**g**, which spontaneously underwent intramolecular 1,3-dipolar cycloaddition to provide in 46−95% yields the tricyclic spirocyclopropane isoxazolidines *exo*-**245a**−**g** and *endo*-**246a**−**g**. While the phenylglycine **245d** and the proline derivative **245g** afforded a single *exo*-diastereomer, the other substituted substrates afforded mixtures of diastereomeric *exo*- and *endo*-adducts with >98% enantiomeric excesses [except **245a** (R = H) and **245d** (R = Ph), which underwent racemization]. Only *fused* cycloadducts were obtained because the strain caused by the chain joining the two reactive sites of the cycloaddition prevented the formation of regiomeric *bridged* cycloadducts[123] (Scheme 73).[121a,b] In fact, the

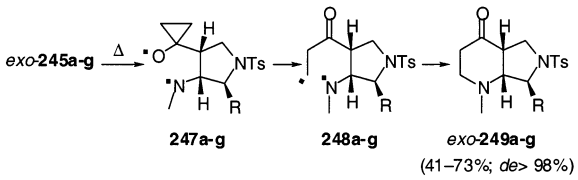
Scheme 73[121a,b]



methyl group of **244b** (R = Me) was too small to induce any diastereoselectivity in the formation of the cycloadducts *exo*-**245b** and *endo*-**246b** (*de* 10%), whereas bulkier substitutents favored the formation of *endo*-**246c** (R = *i*Pr) and *endo*-**246e** (R = CH_2Ph) (*de* 22 and 24%, respectively). On the other hand, diastereoselectively pure cycloadducts *exo*-**245d** and *exo*-**245g** (*de* > 99%) were obtained with substrates substituted by phenyl and proline groups. Calculations of transition-state energies by molecular mechanics calculation allowed interpreting this total diastereoselectivity.[121a,b]

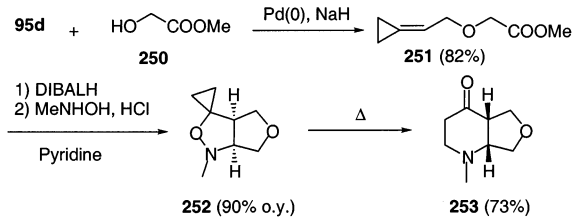
Separated by simple flash chromatography, these diastereomeric cycloadducts underwent on heating in xylenes (126 to 140 °C) ring expansion, through homolysis of the weak N−O bond in *exo*-**245a**−**g**, followed by opening of the three-membered ring in the cyclopropyloxy diradicals **247a**−**g** and intramolecular radical coupling between the nitrogen and the terminal carbon atom of **248a**−**g**, to provide the *exo*-pyrrolo[3,4-*b*]pyridin-4-ones **249a**−**g** as single products in satisfactory yields (41−73%). The rearrangement was completely chemo- and regioselective, and the stereochemistry at the stereogenic centers of *exo*-**245a**−**g** was retained at the corresponding positions in *exo*-**249a**−**g** (Scheme 74).[121a,b] *Endo*-isoxazolines **246b**,**c**,**e**,**f** underwent analogous thermal selective ring expansion.[121a,b] Similarly, palladium(0)-catalyzed nucleophilic substitution of the tosylate **95d** by methyl glycolate **250** gave the glycolate **251** in 82% yield. Successive partial reduction and addition of *N*-methylhydroxylamine provided the racemic furano-

Scheme 74[121a,b]



[3,4-*c*]isoxazole **252** in 90% overall yield, which underwent thermal ring expansion to provide in 73% yield the octahydrofuranopyridine **253** (Scheme 75).[121a,b] Recent interests in the application of the 6*H*-

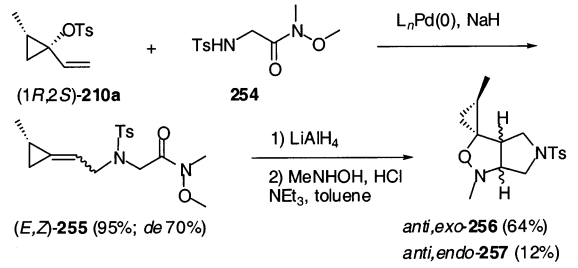
Scheme 75[121a,b]



pyrrolo- or furano[3,4-*b*]pyridine ring systems for the synthesis of bioactive compounds[124] have stimulated their investigation and the study of possible modification of their structures.[125a−c,126a−d]

Palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] nucleophilic substitution of the optically pure tosylate (1*R*,-2S)-**210a** (Schemes 5 and 63) by the *N*′-methoxy-*N*′-methyl-*N*-tosylglycinamide **254**[127] gave in 95% yield an 85:15 mixture of *N*-tosylglycinate (*E*)- and (*Z*)-**255**. Attempts to increase the diastereoselectivity by monitoring the phosphorus ligand steric effect failed.[86,95] Reduction of (*E*,Z)-**255** and addition of MeNHOH, HCl provided an 85:15 mixture of the fused isoxazolidines *anti,exo*-**256** and *anti,endo*-**257** in 75% yield (Scheme 76).[128] The regio- and diaste-

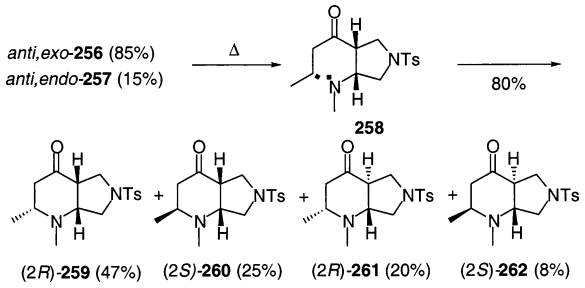
Scheme 76[128]



reoselectivity of this cycloaddition induced by the presence of the (2*S*)-methyl group on the three-membered ring was confirmed by molecular mechanics calculation. Inseparable by chromatography, the 85:15 mixture of isoxazolidines *anti,exo*-**256** and *anti,endo*-**257** underwent on heating in xylenes (reflux) thermal rearrangement to provide in 80% yield a 47:25:20:8 diastereo- and enantiomeric mixture of pyrrolopyridinones **259**−**262** (*ee*: 70%). The N−O isoxazolidine bond homolysis was regioselective since only 2-methyl derivatives **259**−**262** resulting from the cleavage of the more substituted cyclopropane bond were obtained, but the ring closure of the intermediate diradicals **258** was not diastereoselective as a 67:23 mixture of (2*R*)-**259** and (2*R*)-**261**, and

of (2*S*)-**261** and (2*S*)-**262** were formed. Moreover, partial enolization of the carbonyl group at C_4 occurred likely resulting in increased strain induced by the methyl substitutent to give (2*R*)-**260** (20%) and (2*S*)-**262** (8%). Nevertheless, the formation from a 85:15 mixture of isoxazolidines **256** and **257** of the pyrrolopyridinones **259**−**262** with 70% enantiomeric excesses evidenced that the rearrangement was enantiospecific (Scheme 77).[128] Double asymmetric

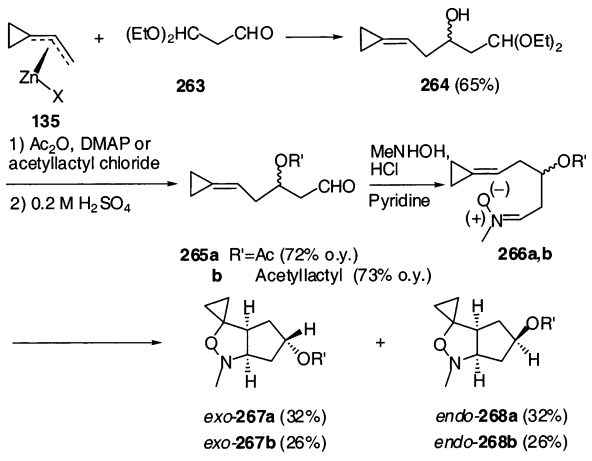
Scheme 77[128]



induction obtained by using (2*S*)-*N*′-methoxy-*N*′-methyl-*N*-tosyl-L-alaninamide as nucleophile in the palladium(0)-catalyzed substitution of (1*R*,2*S*)-**210a**, allowed, following this procedure, the preparation of enantiomerically pure pyrrolo[3,4-*b*]pyridin-4-ones (> 98% *ee*).[128]

Electrophilic substitution of the π-1,1-dimethyleneallylzinc complex **135** (Scheme 43) by the 3,3-diethoxypropanal **263** provided in 65% yield 3-hydroxypentane **264**. *O*-Protection and acidic deacetalisation led to the pentanal **265a** (R′ = Ac) in 72% overall yield. Addition of *N*-methylhydroxylamine hydrochloride gave the corresponding *N*-methylnitrone **266a**, which spontaneously envolved to a 50:50 mixture of *fused exo*-isoxazolidine **267a** (32%) and of its diastereomer *endo*-**268a** (32%) (Scheme 78).[129]

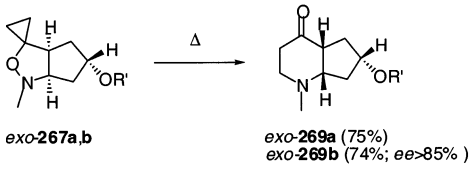
Scheme 78[129]



Calculations of the transition-state energies by semiempirical methods have effectively pointed out that the transition states leading to *exo*-**267a** and *endo*-**268a**, respectively, were only slightly different in energy [Δ(TSE) = 0.4 kcal mol^{-1}].

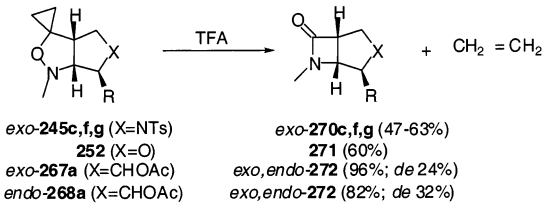
Separated by flash chromatography, the pure cycloadduct *exo*-**267a** underwent on heating in xylenes (126−140 °C), ring expansion with formation in 75% yield of the pyridinone *exo*-**269a** (Scheme 79).[129] Otherwise, *O*-protection of **264** by (2*S*)-acetyllactyl chloride (*n*-BuLi, 1 equiv) followed by deacetalisation (HCOOH) gave in 73% yield the cyclopropylidenepentanal **265b** [R = (2*S*)-acetyllactyl]. Following the same procedure, addition of MeNHOH and spontaneous rearrangement of the resulting nitrone **266b** gave again a 50:50 diastereomeric mixture of *fused* isoxazolidines *exo*-**267b** (26%) and *endo*-**268b** (26%) (Scheme 78).[129] Separated by chromatography pure *exo*-**267b** underwent likewise ring expansion on heating in xylenes at reflux, to provide in 74% yield the enantiomerically enriched octahydropyridin-4-one *exo*-**269b** (Scheme 79).[129] Cleavage of the acetoxy protective group of *exo*-**269a** and of the chiral auxiliary group of *exo*-**269b** were achieved with quantitative yields under basic conditions (K_2CO_3, MeOH).[129]

Scheme 79[129]



On the other hand, the thermal behavior of the 5-spirocyclopropane isoxazolidines was completely different after protonation. Thus, in the presence of trifluoroacetic acid (TFA), the enantiopure isoxazolidines *exo*-**245c**,**f**,**g** [R = *i*Pr, (3-indolyl)methyl, -$(CH_2)_3$-; X = NTs] and the racemic **252** (R = H; X = O) underwent a clean different rearrangement at 70−110 °C with loss of *ethylene*, to afford the heptan-7-ones **270c**,**f**,**g** in 47−63% yields, and **271** in 60% yield, with conservation of the relative and absolute configuration. Under the same conditions, both *exo*-**267a** (R = H; X = CHOAc) and *endo*-**268a** were converted into 62:38 and 66:34 diastereomeric mixtures of *exo*- and *endo*-**272** in 96 and 82% yields, respectively (Scheme 80).[130a,b]

Scheme 80[130a,b]

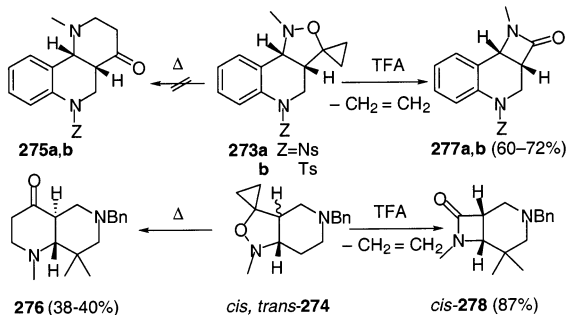


The homologous *spirofused* isoxazolidines **273a**,**b** (Z = Ns, Ts), and *cis*- and *trans*-**274** were obtained following the same strategy from the palladium(0)-catalyzed substitution of **95d** using anthranilic acid or 3-amino-2,2-dimethylpropanol derivatives as nucleophiles. On heating the sample to 120 °C, the cycloadducts **273a**,**b** failed to furnish the pyridones **275a**,**b**. But the *cis*- and *trans*-fused isoxazolidines **274** underwent ring expansion by heating in refluxing xylenes to offer both the *trans-fused* bicyclic ketone **276** in 40 and 38% yield, respectively. Under acidic conditions, i.e., in the presence of a small excess of TFA, the tetracyclic isoxazolidines **273a**,**b**

underwent ring contraction and loss of ethylene to produce the cis-*fused β-lactams* **277a**,**b** in 60 and 72% yield, respectively. The same reaction occurred by heating **273a**,**b** in toluene in the presence of *p*-toluenesulfonic acid (*p*-TsOH) or in refluxing ethanol containing HCl, as well as on treating directly the aldehyde corresponding to **243a**−**g** (Scheme 73) with MeNHOH, HCl in refluxing ethanol in absence of pyridine or NEt_3.

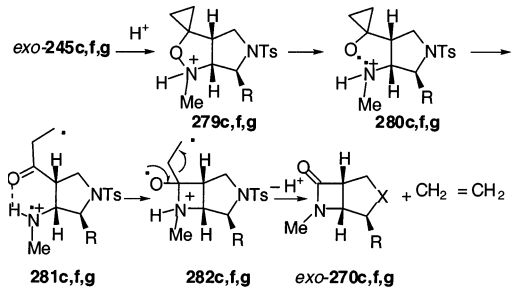
The *cis-fused* isoxazolidine **274** was converted under thermal acidic conditions (TFA, 110 °C) into the *cis-β-lactam* **278** with ethylene extrusion in 87% yield, while its *trans*-fused isomer **274** failed to produce strained *trans*-fused bicyclic azetidin-2-one and underwent a different rearrangement with a methyl shift into a 1,6-naphthyridinone derivative (Scheme 81).[130a,b] To rationalize the mechanism of

Scheme 81[130a,b]



β-lactam formation from 5-spirocyclopropane isoxazolidinines such as *exo*-**245c**,**f**,**g**, involvement of either homo- or heterolytic cleavage of the protonated N−O bond of *exo*-**279c**,**f**,**g** have been considered. However, collected evidence strongly supports the occurrence of transient cation diradical intermediairies *exo*-**280c**,**f**,**g**, which evolved to the relatively more stable ionic diradical *exo*-**281c**,**f**,**g**, with formation of a strong intramolecular bond preventing the radical ring closure to the piperidones *exo*-**249c**,**f**,**g** (see Scheme 74). On the other hand, the hydrogen bond might keep the nitrogen and the C=O group close enough and with the required orbital overlap for the closing of a four-membered ring with formation of a N−CO bond. Finally, the *β*-lactam *exo*-**270c**,**f**,**g** could be formed from *exo*-**282c**,**f**,**g** by radical fragmentation and deprotonation (Scheme 82).[130b]

Scheme 82[130b]

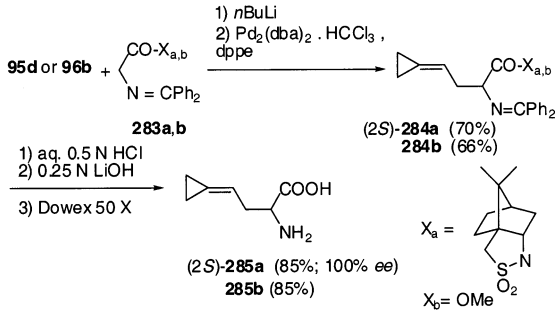


In conclusion, the palladium(0)-catalyzed substitution of 1-ethenyl-1-tosylcyclopropane **95d** with asymmetric *N*-tosylamino esters could provide optically pure *N*-(2-cyclopropylideneethyl)amino esters **242a**−**g**. Their nitrone derivatives underwent spontaneous intamolecular 1,3-dipolar cycloaddition to form spirocyclopropane isoxazolidines, which then underwent either thermal ring expansion into tetrahydropyridones or protic acid induced ring contraction into *β-lactam* derivatives (*ee* > 98%). This last process proceeded with *ethylene* extrusion mimicking the biosynthesis of this phytohormone from the 1-aminocyclopropanecarboxylic acid ACC-**209** (Scheme 62).[8b,c]

4.4. Asymmetric C-Allylation

Palladium(0)-catalyzed [$Pd_2(dba)_3$·$HCCl_3$, dppe] nucleophilic substitution of the sulfonic ester **95d** or of the ethyl carbonate **96b** (Scheme 32) by the anion of the modified glycine equivalent **283a** (X_a = camphorsultam[132a−f]) gave exclusively the product of C-allylation **284a**. This is in contrast to the *N*-tosylamino esters **241a**−**g** (Scheme 72). The nucleophile was generated from **283a** by *n*-butyllithium or LDA, but addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) enhanced the rate of formation of **284a**, which underwent deprotections to provide the enantiomerically pure cyclopropylidenebutyric acid **285a**, in 85% yield after purification by ion exchange chromatography (Scheme 83).[122] The chiral auxiliary X_a was recovered in 90% yield; racemic **285b** was analogously prepared from the achiral glycine ester Schiff base **283b** (X_b = OMe).[122]

Scheme 83[122]



When applied to various allylic acetates and carbonates, this protocol allowed the preparation of α-allyl α-amino acids in high yields. When the asymmetric glycine derivative **283a** was used, the α-allyl α-amino acids were obtained with diastereoselectivities better than 90%. It was considered that the π-1,1-dimethyleneallylpalladium complex **1a** (Scheme 37) attacked the nucleophile **283a** on the same *β*-face as did allylbromide.[122,131a−c]

The nonnatural α-amino acid (2*S*)-**285a** (*isohypoglycine*) is an isomer of the (2*S*,4*S*)-3-(2-methylcyclopropyl)alanines called *hypoglycine A* **286a** (R = H) and *B* **286b** (R = *γ*-glutamyl), which are the toxic principle of the *isin* (Nigeria) and *ackee* (Jamaica) fruit *Blighia sapida*. In fact, unripe *ackee* fruits or seeds cause severe hypoglycaemia entailing lethal gluconeogenesis inhibition and organicacidaemia.[8b,c,133] Biological assays have shown that at relatively high concentration the isomeric methylenecyclopropane substituted alanine (2*S*)-**285a** inhibited the metabolism of pyruvate into glucose (Scheme 84).[122]

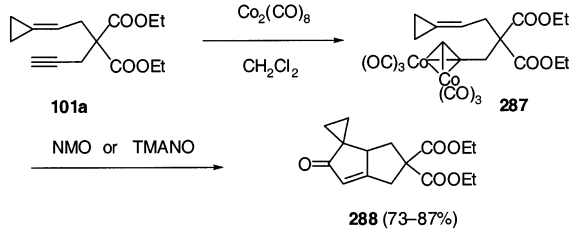
Scheme 84[122]

(2*S*)-**285a** *Isohypoglycine* (2*S*,4*S*)-**286a** *Hypoglycine A* (R=H)
(2*S*,4*S*)-**286b** *Hypoglycine B* (R=γ-glutamyl)

4.5. Intramolecular Pauson-Khand Reaction

The cobalt-mediated cycloaddition of an alkyne to an alkene with carbonyl insertion yielding a cyclopentanone (the Pauson-Khand reaction, PKR) is one of the most efficient methods for the construction of five-membered carbocyclic rings.[134a−n] Methylenecyclopropanes have been successfully used in intermolecular[135a,b] as well as in intramolecular reactions.[61,65,136a−c] Thus, addition of octacarbonyldicobalt [$Co_2(Co)_8$] to the diethyl (2-cyclopropylidenemethyl)-2-(2-propynyl)malonate **101a** (Table 1)[10] and then treatment of the resulting cobalt complex **287** either with *N*-methylmorpholine *N*-oxide (NMO) or with trimethylamine *N*-oxide (TMANO) provided the bicyclo[3.3.0]octenone **288** in 73 and 87% yields, respectively (Scheme 85).[136a]

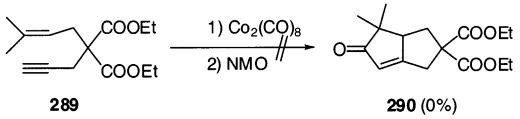
Scheme 85[136a]



101a **287** **288** (73–87%)

Comparatively, the isopropylidene analogue **289** did not cyclize under identical conditions to give the corresponding bicyclo[3.3.0]octenone **290** (Scheme 86).[136a]

Scheme 86[136a]

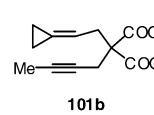
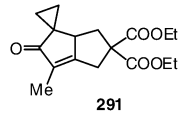
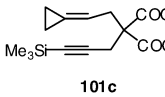
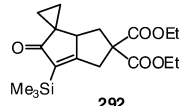
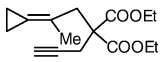
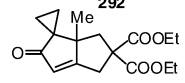
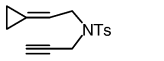
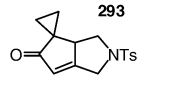
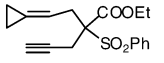
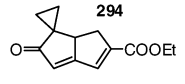
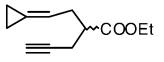
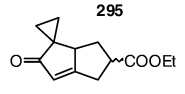


289 **290** (0%)

When applied to variously substituted 6-cyclopropylidene-1-hexynes **101b**−**g**, prepared from the palladium(0) catalyzed substitution of the sulfonates **95d**,**e** with the suitable nucleophiles, this sequence furnished the corresponding spirobicyclooctenones **291**−**296** in good yields, except for **295** (prepared from enyne **101f** arising from sodiopropargylsulfonyl), which underwent sulfonyl elimination. It was noteworthy that, contrary to trisubstituted alkenes which were cyclized under the intramolecular Pauson-Khand reaction with poor yields,[137] even the tetrasubstituted enyne **101d** could lead to **295** in 64% yield (Table 4).[136a]

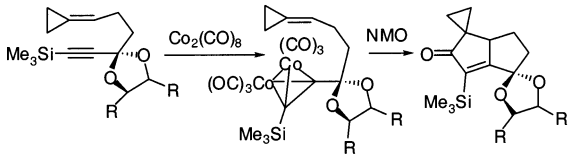
The heavily substituted cyclopropylidenealkynes **297a**−**c** (R = Me, Ph, *c*Hex), prepared by transacetalization with the appropriate ethanediols [(*R*,*R*)-butanediol, (*S*,*S*)-diphenylethanediol, (*S*,*S*)- and (*R*,*R*)-dicyclohexylethanediol] and trimethyl orthoformate, underwent the Pauson-Khand reaction [$Co_2(Co)_8$],

Table 4. Intramolecular Paulson-Khand Cyclization of 6-Cyclopropylidene-1-hexynes[136a]

Entry	Enynes	Cycloadducts	% Yields
1	 **101b**	 **291**	75
2	 **101c**	 **292**	35
3	 **101d**	 **293**	64
4	 **101e**	 **294**	80
5	 **101f**	 **295**	15
6	 **101g**	 **296**	73

through the dicobalt complex **298** which then underwent trialkylamine oxide (NMO or TMANO) induced cyclization to provide the bicyclo[3.3.0]oct-1-en-3-ones **299a**−**c** in good yields (63−76%), with 33, 67, and 79% of diastereoselectivity, respectively (Scheme 87).[138]

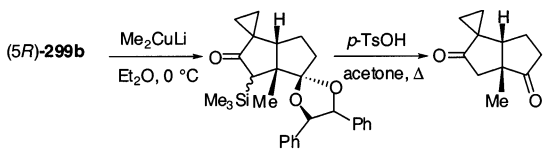
Scheme 87[138]



297a R=Me **298** **299a** (63%, *de* 33%)
b Ph **b** (69%, *de* 67%)
c *c*Hex **c** (76%, *de* 79%)

After separation of the sample by chromatography, the major diastereomer (5*R*)-**299b** underwent addition of lithium dimethylcuprate to produce in 86% yield an 88:12 mixture of 2-*exo*- and 2-*endo*-**300b**. Acetal cleavage and protodesilylation gave in 57% yield the enantiomerically pure bicyclooctanedione (5*R*)-**301** (Scheme 88).[138]

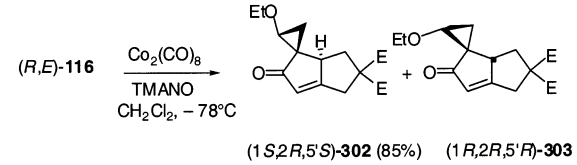
Scheme 88[138]



(5*R*)-**300b** (86%, *de* 66%) (5*R*)-**301** (57%) (*ee* 100%)

Intramolecular Pauson-Khand reaction of the optically active compound (*R*,*E*)-**116** (Scheme 34) by treatment with a stoichiometric amount of $Co_2(Co)_8$ in dichloromethane at room temperature followed by

Scheme 89[61]



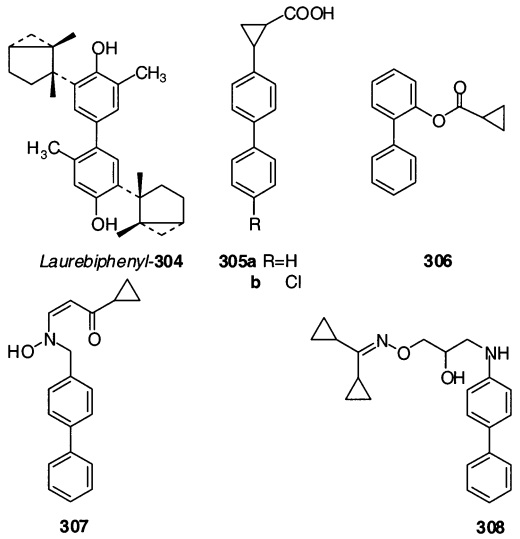
addition of TMANO gave a single enantiomer of bicyclo[3.3.0]octene (1*S*,2*R*,5′*S*)-**302** in 85% yield. However, when the cycloaddition was carried out by adding TMANO at room temperature the formation of a 3:1 mixture the two diastereomers (1*S*,2*R*,5′*S*)-**304** and (1*R*,2*R*,5′*R*)-**303** was observed (Scheme 89).[61a]

Spiro(cyclopropanebicyclo[*n*.3.0]alkenones) ($n = 3$, 4) have recently been obtained in good yields by the cobalt-mediated intramolecular cycloaddition between the double bond of methylenecyclopropane or bicyclopropylidene moieties and alkynyl substituents directly linked to the three-membered rings.[61b]

4.6. Allylation of Biphenyls

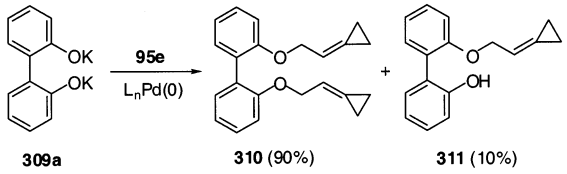
Few examples of natural cyclopropane containing biphenyls have been reported; for instance, *laurebiphenyl*-**304**, is a dimeric sesquiterpene of the cyclolaurane type, isolated from the red alga *Laurencia nidifica*.[139] However, the bioactivity of several biphenylcyclopropane derivatives has been noticed; thus, the 2-biphenylcyclopropanecarboxylic acids **305a**,**b** (R = H, Cl) were recognized for their activity in alleviating inflammation, pain, hypoglycaemia, and ketosis,[140] while ovicidal activity against spider mites was found for the 2-biphenyl cyclopropanecarboxylate **306**;[141] enzyme inhibition in the arachidonic acid cascade and inhibition of 5-lipoxygenase (rat basophilic leukemia cell line) was exhibited by the vinylogous hydroxamic acid **307**[142] high efficiency in the inhibition of isoprenaline-induced tachycardia was shown by the oxime ether **308**[143] (Scheme 90).

Scheme 90[139–143]



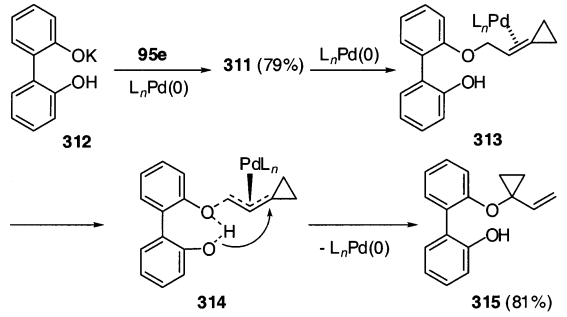
An efficient and selective method to prepare biphenyls linked to three-membered rings has been recently investigated from the 1,1-dimethyleneallylmetal complexes **1a** and **135** (Scheme 43). Thus, the dipotassium salt **309**, formed upon treatment of commercially available 2,2′-dihydroxybiphenyl with potassium carbonate (3 equiv, DMF at 60 °C), underwent palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] regioselective allylation by the allylic mesylate **95e** (2.2 equiv) (Scheme 32) at room temperature for 15 h, to provide the biphenyl **310** in 90% yield, besides 10% of the monoadduct **311** (Scheme 91).[144]

Scheme 91[144]



On the other hand, under the same conditions the monopotassium salt **312**, formed upon treatment of 2,2′-dihydroxybiphenyl with only 1 equiv of K_2CO_3, underwent palladium(0)-catalyzed allylation by **95e** to give the biphenyl **311** in 79% yield, besides the diadduct **310** (10%). Further reaction of **311** with palladium(0) [from 5% $Pd(dba)_2$ and 12% PPh_3] gave the isomeric 2-(1-ethenylcyclopropyloxy)-2′-hydroxybiphenyl **315** in 81% yield. Most probably coordination with $L_nPd(0)$ of the double bond of **311** led to the formation of the complex **313**, and after that to the π-1,1-dimethyleneallylpalladium complex **314** favored by the occurrence of a H^- bond between the oxygen and the hydroxyl group. Then, in **314** the 2′-hydroxy-2-oxybiphenyl moiety must be regarded as a leaving group and as a nucleophile, simultaneously, which reacted with the π-complex **1a** to form the adduct **315**, favored by strain release (Scheme 92).[144]

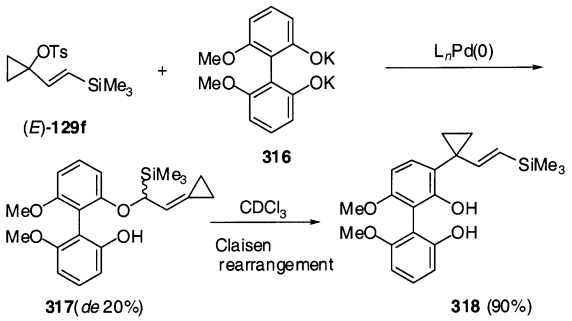
Scheme 92[144]



It must be underlined that the diadduct **310** did not undergo any rearrangement upon further treatment with $L_nPd(0)$, and that the potassium salt of **311** (K_2CO_3, 1 equiv) did not undergo palladium(0)-catalyzed rearrangement to form **315**, but led to the diadduct **310** in poor yield (9%) when treated with the mesylate **95e** and $L_nPd(0)$,[144]

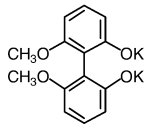
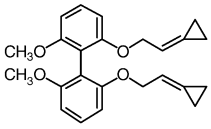
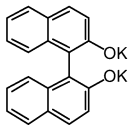
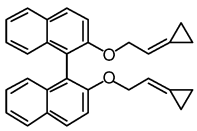
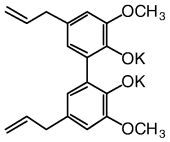
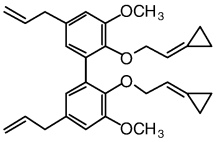
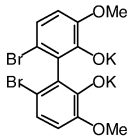
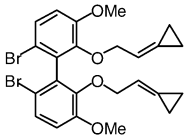
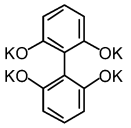
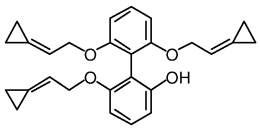
Palladium(0)-catalyzed substitution of the tosylate (*E*)-**129f** (Table 3) with the dipotassium salt **316**, formed upon treatment of 2,2′-dihydroxy-6,6′-dimethoxybiphenyl,[145] with K_2CO_3 (3 equiv, DMF, 60 °C) led to a 60:40 diastereomeric mixture of biphenyl **317**, as a result of restricted rotation along the main biphenyl axis. It was noteworthy to observe that on standing in deuteriochloroform the minor diastereomer of **317** underwent Claisen rearrangement to provide the cyclopropylbiphenyl **318** in 90% yield (Scheme 93).[144]

Scheme 93[144]



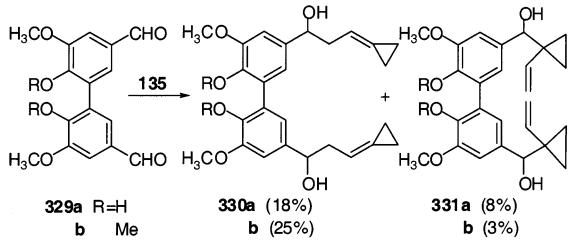
Other substituted 2,2′-bis(cyclopropylidenethoxy)-biphenyls **324**−**327** were obtained in good yields from the palladium(0)-catalyzed allylation of the potassium salts of the 2,2′-dihydroxybiphenyls or 1,1′-bi-2-naphthol **319**−**322** by the cyclopropyl sulfonates **95d**,**e**. Thus, allylation of 5,5′-bis-(2-propenyl)-2,2′-dihydroxy-3,3′-dimethoxybiphenyl **321d**, known as *dehydrodieugenol*[146] isolated from various plants and recognized as efficient hydroxyl radical scavenger[147] able to inhibit UV-induced mutagenesis and lipid peroxidation,[148] gave the diadduct **326** in 50% yield. On the other hand, allylation of the tetra-potassium salts of the 2,2′,6,6′-tetrahydroxybiphenyl **323f** provided the triadduct **328** in 60% yield, besides 15% of the expected tetraadduct, likely as a result of steric hindance (Table 5).[144]

Table 5. Palladium(0) Catalyzed Allylation of 2,2′-Dihydroxybiphenyls and 1,1′-Bi-2-naphthols Di- or Tetrapotassium Salts[44]

Entry	2,2'-Dihydroxybiphenyls and 1,1'-bi-2-naphthols	Adducts	% Yields
1	 **319**	 **324**	60
2	 **320**	 **325**	84
3	 **321**	 **326**	50
4	 **322**	 **327**	75
5	 **323**	 **328**	60

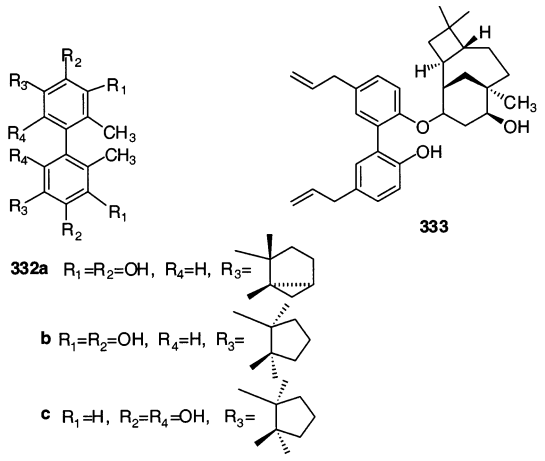
The biphenyldicarbaldehyde **329a** (R = H), a dimer of commercially available vanilin, underwent substitution by the 1,1-dimethyleneallylzinc complex **135** (Scheme 43) to provide in 26% yield a 70:30 mixture of regiomeric diadducts **330a** and **331a**, besides 40% of starting material. In comparison to benzaldehyde (Scheme 43), the biphenyldicarbaldehyde **329a** appeared less reactive, i.e., less electron demanding, likely as a result of the presence of both para-hydroxy and meta-methoxy substitutents. However, when *O*-protected the biphenyldialdehyde **329b** (R = Me) underwent substitution by the nucleophile **135** with improved regioselectivity to give in 28% yield a 90:10 mixture of regiomeric diadducts **330b** and **331b** (Scheme 94).[149]

Scheme 94[149]



Although these yields have to be increased under appropriate conditions, it must be underlined that readily available diadducts such as **330a**,**b**, opened a new entry to biphenols bearing small carbocycles, i.e., three- to five-membered rings. Effectively, naturally occurring biphenols such as **332a**−**c** and **333** have exhibited important biological activity,[139,150a−e] and these structures have been recently recognized as potent new therapeutic agents (Scheme 95).[151a−c]

Scheme 95[151a−c]

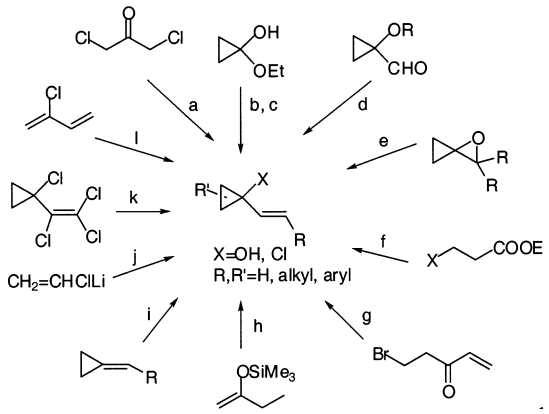


5. Summary

The required 1-ethenylcyclopropanol and 1-ethenylcyclopropyl chloride derivatives were available from various sources following different procedures (Scheme 96).

The 1-ethenylcyclopropyl sulfonic esters, as well as the analogous 1-ethenylcyclopropyl chlorides and isomeric 2-cyclopropylideneethyl acetates or carbonates, formed readily with palladium(0) unsymmetric π-1,1-dimethyleneallylpalladium complexes, which

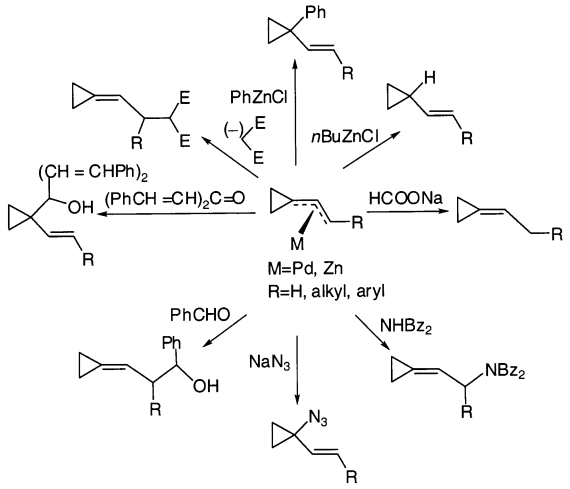
Scheme 96[a]



[a] (a) Fe(0), vinylic Grignard reagents; (b) acetylenic reagents and $LiAlH_4$ (or Cp_2TiH) or vinylic Grignard reagents; (c) Ph_3P = CR−CO_2Et, $PhCO_3H$ or $(EtO)_2P(O)CH_2CO_2Et$, *n*-BuLi; (d) Ph_3P = CHR; (e) $LiNR_2$; (f) $Ti(OiPr)_4$, R′CH_2CH_2MgX and then *t*BuOK; (g) SmX_2; (h) CH_2I_2, Zn/Ag; (i) $^1O_2$ then PPh_3; (j) olefins; (k) *n*-BuLi, H_2/Lindlar; (l) $(CO)_5W$ = CHPh.

then underwent substitutions with a regioselectivity depending highly on the *soft* or *hard* nature of the nucleophiles. Electrophilic substitutions by carbonyl derivatives of π-1,1-dimethyleneallylzinc complexes was then possible and regioselective, by the simple addition of diethylzinc (*umpolung*) (Scheme 97).

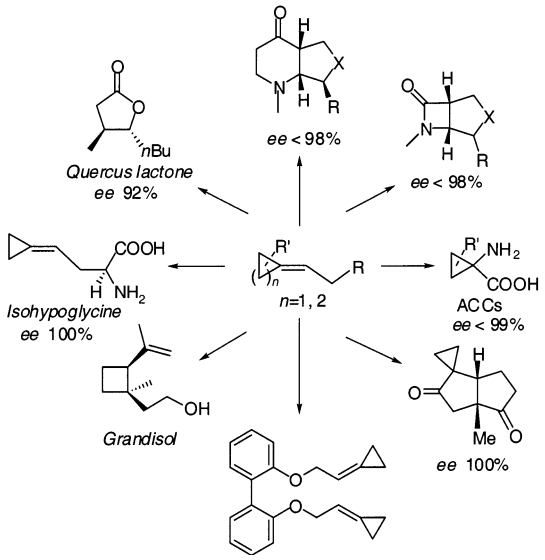
Scheme 97



First of all, these complexes have overcome the detrimental and inherent problem of cyclopropyl esters and halides as reactants, which seldom underwent nucleophilic substitutions with retention of the three-membered ring. They also offered a useful alternative to overcome the limitation of the Wittig olefination resulting in competitive enolization of the carbonyl and of steric hindrance and moreover allowed the formation of tri- and even tetrasubstituted olefins in high yields.

The alkylidenecyclopropane derivatives formed by this simple procedure constitute a peculiar class of strained olefinic compounds with remarkable synthetic potential (Scheme 98). Noteworthy was the behavior of homologous 2-cyclobutylidenepropyl sulfonic esters, which underwent palladium(0)-catalyzed stereospecific hydrogenolysis involving π-1,1-trimethyleneallylpalladium complexes by formate anion,

Scheme 98



with total but opposite regioselectivity. Comparatively, the palladium(0)-catalyzed hydrogenolysis of 1-ethenylcyclohexyl acetates, appeared in the lack of ring strain, not regioselective, while 1-ethenylcyclopentyl acetates suffered elimination of AcOH providing conjugated dienes.

Without any doubt, the formation and use of π-1,1-dimethyleneallylmetal complexes extend the scope of applications of the cyclopropane ring in synthetic organic chemistry. Many of these complexes have already exhibited their potential in the regio- and stereoselective synthesis of naturally occurring bioactive products.

6. Acknowledgment

The different results displayed in this review emerge from efficient, enriching, and kind collaborations with Professors Alberto Brandi and Andrea Goti (University of Firenze, Italy), Giovanna Delogu (CNR, Sassari, Italy), Armin de Meijere (University of Göttingen, Germany), Oleg Kulinkovich (University of Minsk, Belarus), Pier Paolo Piras (University of Cagliari, Italy) and from the contributions of our talented and enthusiastic co-workers cited in the 63 references dealing with this topic. We gratefully appreciated financial support by grants from the ANRT-DAAD within the PROCOPE programmes; CNRS−CNR French-Italian Cooperation Programmes; ERASMUS−SOCRATES European Programmes; INCO−COPERNICUS programme of cooperation of the European Community; International Association for the Promotion of Cooperation with Scientists from the Independent States of the Former Soviet Union (INTAS); Georg August Universität (Göttingen); Università di Cagliari (Monserrato); Università degli Studi di Firenze (Sesto Fiorentino); Université de Paris-Sud (XI) (Orsay); Istituto di Chimica Biomolecolare (CNR, Sassari); Centre National de la Recherche Scientifique (CNRS); Consiglio Nazionale della Ricienche (CNR); Deutsche Forschungsgermeinschaft; Regione Autonoma della Sardegna; Ministère de l'Education Nationale de la Recherche et de la Technologie (MENRT); Ministero dell' Università e

della Ricerca Scientifica e Technologica of Italy (URST); Alexander von Humbolt-Gay Lussac Fundation (MINISPEP); Volkswagen-Stiftung; Fonds der Chemischen Industrie; and Acros Organics, Degussa AG, Hoechst AG, Rhone Poulenc Industries.

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