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Small rings in focus: recent routes to cyclopropyl-group containing carbo- and heterocycles†

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The development of modern synthetic methodologies and advanced analytical tools during almost 130 years after the first preparation of a three-membered carbocycle made it possible that several unusual and initially exotic hydrocarbons with cyclopropane rings have become common laboratory reagents. These hydrocarbons not only exhibit unusual physical and thermochemical properties: as the cyclopropane ring is a functional group itself, all of these molecules and their derivatives constitute oligofunctional building blocks, and they can be involved in transformations of the initially formed intermediates or products in sequential reactions or multistep cascade reactions. In many cases, this results in the formation of carbo- and heterocycles with cyclopropyl substituents on a framework or cyclopropyl groups incorporated in a structure. Some of these products exhibit significant biological activities, the cyclopropyl groups exerting favorable or beneficial effects in a number of senses.

Small rings have come a long way. In the 1870s, trendsetting chemists like Viktor Meyer were convinced that three-membered rings could not exist.[1] In 1882, August Freund demonstrated that the reaction of 1,3-dibromopropane with sodium yields a structural isomer of propene, which does not react with bromine, and this was the first synthesis of cyclopropane.[2] Two years later, William Henry Perkin reported the first synthesis of a cyclopropane derivative, diethyl cyclopropane-1,1-dicarboxylate, and its ring-opening reaction with hydrogen bromide.[3] In 1906, Otto Wallach finalized the structural elucidation of thujene, a monoterpene with a three-membered ring.[4(*a*)] The structurally related thujone, a monoterpene ketone, had been isolated as early as 1892 by Semmler[4(*b*)] and confirmed by Wallach a year later.[4(*c*)] The correct structure of thujone was suggested in 1900 by Semmler[4(*d*)] and confirmed by Tschugaev.[4(*e*)] Thujone and thujene were the first cyclopropane derivatives being isolated from natural materials. Many more followed, and when Ruzicka and Staudinger[5,6] in 1924 elucidated the structure of the natural insecticide pyrethrine also containing a three-membered ring, the chemical world started to be convinced that cyclopropane derivatives play an important role in nature.[7] With the development of new general methods for the synthesis of cyclopropanes,[8] starting with the discovery of carbene additions to alkenes by Doering *et al.* in 1954,[9] almost any connectivity of cyclopropane units with themselves or with other substructures can be realized nowadays.

Armin de Meijere, born 1939, studied chemistry in Freiburg and Göttingen, receiving a doctoral degree (Dr. rer. nat.) in 1966 in Göttingen, completing postdoctoral training at Yale University in 1967–1969, and receiving Habilitation in 1971 in Göttingen. He was appointed full professor of organic chemistry in Hamburg, 1977–1989 and ever since has been in Göttingen. He was visiting professor at the University of Wisconsin, the IBM Research Laboratories, the Technion in Haifa, Israel, Princeton University, the Universities of Aix-Marseille III, Paris-Sud, Orsay, Rennes, Toulouse, Bordeaux, Firenze, the Ecole Normale Supérieure, Paris, the Universities of Florida at Gainesville and Colorado at Boulder, Indian Institute of Science in Bangalore, University of Santiago de Compostela, Spain. His awards and honors include German Merit Foundation (Studienstiftung des Deutschen Volkes), 'Dozentenstipendium' of the Fonds der Chemischen Industrie, member of the Norwegian Academy of Sciences, Alexander von Humboldt/Gay Lussac prize, member of the Braunschweigische Wissenschaftliche Gesellschaft, Honorary Professor of St. Petersburg State University in Russia, Fellow of the Japan Society for the Promotion of Science, Paul Tarrant Distinguished Lecturer at the University of Florida, Lady Davis Distinguished Visiting Professor at the Technion in Haifa, the Merck-Eurolab Distinguished Lecturer of the French Chemical Society, Novartis Lecturer, Parke-Davies Lecturer, Adolf von Baeyer Medal of the German Chemical Society, Dr. honoris causa of the Russian Academy of Sciences and Editor or member of the editorial board of a number of scientific journals, periodicals and books including Houben-Weyl, Chemical Reviews, Topics in Current Chemistry, Science of Synthesis, Synlett, and Chemistry – A European Journal. His scientific achievements have been published in over 700 original publications, review articles, and book chapters, as well as 25 patents. His current research interests include the development of new small ring building blocks and their application in the syntheses of natural and non-natural compounds, new highly strained polycyclic compounds, novel organometallic complexes with interesting properties and transition-metal-mediated and -catalyzed transformations for efficient organic synthesis.

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† Part 158 in the series 'Cyclopropyl Building Blocks for Organic Synthesis'. For Part 157, see: S. I. Kozhushkov, K. Wagner-Gillen, A. F. Khlebnikov and A. de Meijere, *Synthesis*, 2010, in press. For Part 156, see: A. de Meijere, V. Chaplinski, H. Winsel, M. Kordes, B. Stecker, V. Gazizova, A. I. Savchenko and F. Brackmann, *Chem. Eur. J.*, 2010, **16**, published online, DOI: 10.1002/chem.201001550.

The number of newly discovered biologically active natural products containing one, two or even more cyclopropyl groups keeps growing, and so does the number of pharmaceutical and crop protection products, in which a cyclopropyl group or two is an essential feature. Nowadays, no discovery chemist in these industries will leave out to consider replacing ordinary alkyl or cycloalkyl substituents in a lead structure by the peculiar cyclopropyl group.[10] Thus, it has become increasingly important to develop appropriate preparative methods, by which cyclopropyl groups as a whole can be attached to existing skeletons or such skeletons with cyclopropyl groups can be assembled employing viable building blocks already containing cyclopropyl entities.[11]

Over the past 30 years, we have engaged ourselves in the preparation and synthetic application of reactive cyclopropane derivatives such as **1**–**14** (Figure 1) and their substituted analogues. By far the overwhelming amount of chemistry has been done with bicyclopropylidene **9**[11(*a*),(*c*),(*d*)] and methyl 2-chloro-2-cyclopropylideneacetate **13**-Me.[11(*b*)]

Functionally substituted derivatives of vinylcyclopropane **1** have been used to access cyclopentenes,[12] and a large variety of functionalized methylenecyclopropanes, such as **16**, **17**, **19**, **20**–**22**, as well as vinylcyclopropanes **15**, **18**-N$_3$ and **18**-N(TMS)$_2$, have been prepared by palladium-catalyzed regioselective substitution on 1-ethenylcyclopropyl tosylate **18**-OTs and 1-ethenylcyclopropyl chloride **18**-Cl (Scheme 1).[13]

Several compounds have been further employed as precursors for, *e.g.*, cyclopropyl-group containing amino acids[14] and as building blocks for more complex organic skeletons.[15] Relatively complex molecules have also been obtained by an interesting cascade reaction of 2,3-dicyclopropylallene **3** with aryl halides and dienophiles.[16]

The allene **3** was prepared in three steps from easily accessible dicyclopropylacetylene **5**[17] *via cis*-1,2-dicyclopropylethene **23** and *cis*-2,3-dicyclopropyl-1,1-dibromocyclopropane **24**.[16] Under palladium catalysis, compound **3** reacts with an aryl halide **25** by carbopalladation, cyclopropyl-ring opening and β-hydride elimination to furnish the 1,3,5-hexatriene **27**, which is trapped by a dienophile **26** present in the same flask to yield the highly substituted diastereomeric cyclohexene derivatives *trans*- and *cis*-**28** (Scheme 2).

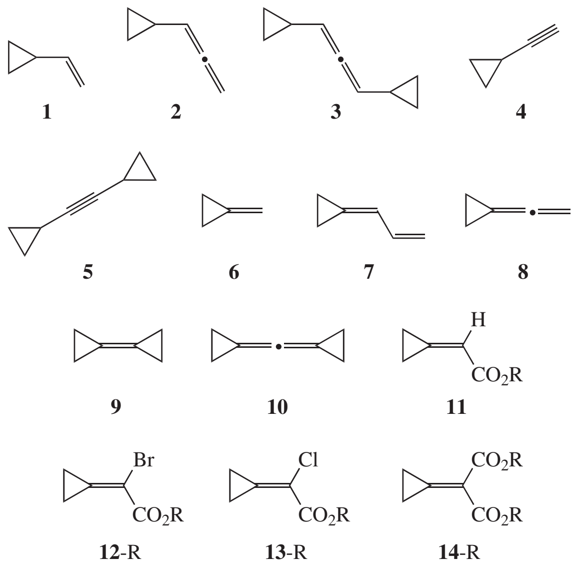
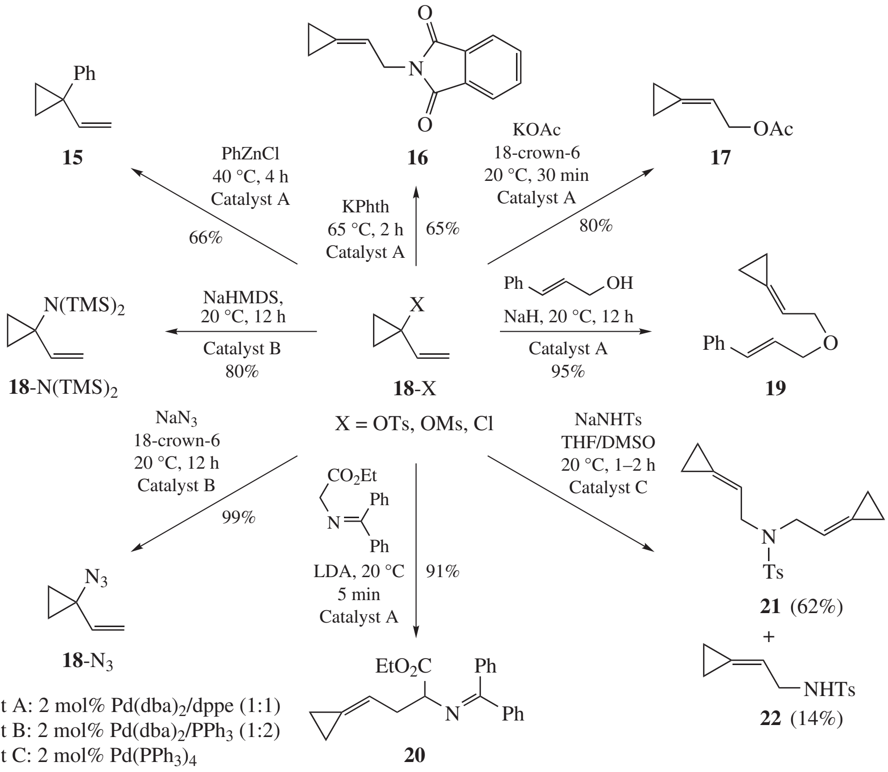


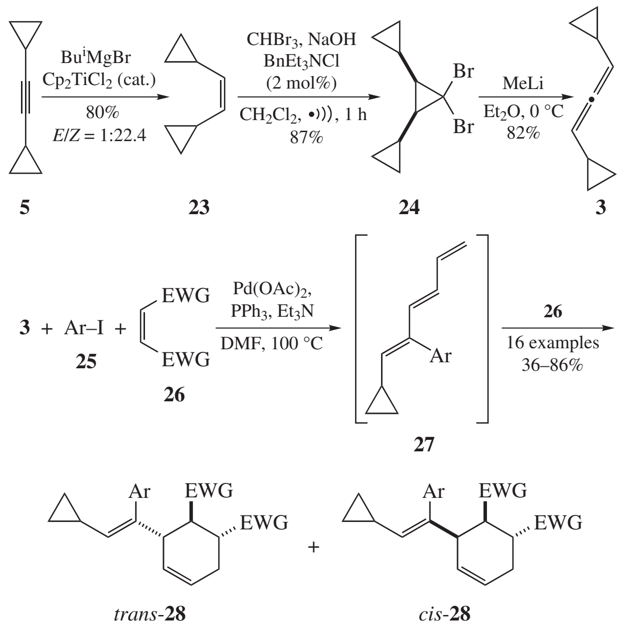
Figure 1

The unique tetrasubstituted ethylene derivative, bicyclopropylidene **9**, was just an exotic hydrocarbon,[18] until it was made accessible in large quantities by an easily scalable three-step synthesis in 1993.[19] Commercially available methyl cyclopropanecarboxylate **29** is converted by the Kulinkovich reaction[20] into 1-cyclopropylcyclopropanol **30**, in virtually quantitative yield, and the latter reacts with triphenylphosphine–bromine to give 1-cyclopropylcyclopropyl bromide **31**, which is dehydrobrominated to **9** with potassium *tert*-butoxide in DMSO. The overall yield is about 62%, and with ordinary laboratory equipment one can routinely prepare 50–100 g. The procedure has also been employed on a 5 kg scale.



Catalyst A: 2 mol% Pd(dba)$_2$/dppe (1:1)
Catalyst B: 2 mol% Pd(dba)$_2$/PPh$_3$ (1:2)
Catalyst C: 2 mol% Pd(PPh$_3$)$_4$

Scheme 1



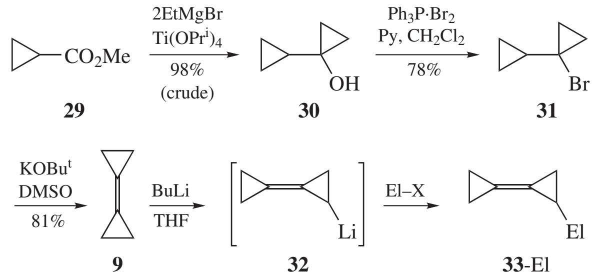
e.g., EWG = CO_2Me, Ar–I = PhI, yield 86%, ratio 4:1

Scheme 2

One of the eight equivalent allylic positions in **9** is readily deprotonated upon treatment with *n*-butyllithium in tetrahydrofuran, and lithiobicyclopropylidene **32** can be trapped by various electrophiles to give corresponding monosubstituted bicyclopropylidene derivatives **33**-El in good to very good yields (Scheme 3).[21]

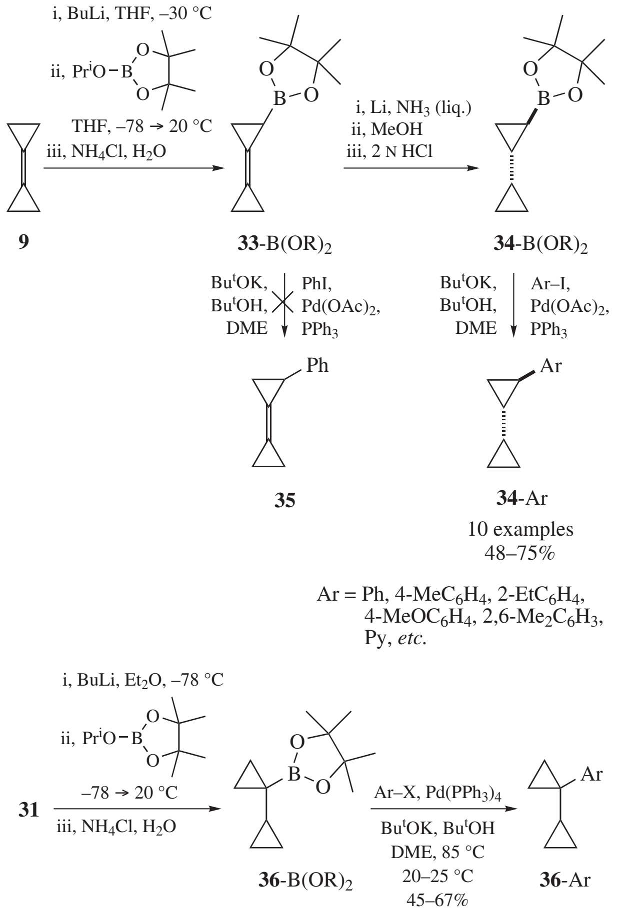
These derivatives have been used for further elaboration,[22,23] *e.g.*, the boronate **33**-$B(OR)_2$ has been reduced under Birch conditions to bicyclopropyl-2-boronate **34**-$B(OR)_2$, which was employed in Suzuki cross-coupling reactions to yield 2-aryl-1,1-bicyclopropyl derivatives **34**-Ar (Scheme 4).[23]

Interestingly, the unsaturated bicyclopropylideneboronate **33**-$B(OR)_2$ did not undergo the Suzuki coupling under the same conditions, possibly because the enhanced reactivity of the double bond in **33**-$B(OR)_2$ competes with that of the B–C bond (see below). Since compounds **34**-Ar and the isomeric 1-aryl-1,1-bicyclopropyl derivatives **36**-Ar are gaining increasing attention in pharmaceutical and plant protection research,[24] it was of interest to test the possibility of doing Suzuki cross-couplings with bicyclopropyl-1-boronate **36**-$B(OR)_2$. The latter is accessible directly from the corresponding bromide **31**; indeed, it undergoes cross coupling under palladium catalysis to furnish aryl derivatives **36**-Ar in moderate yields (Scheme 4).[25]



El–X	El	Yield (%)
Me_3SiCl	$SiMe_3$	85
$(PhS)_2$	SPh	77
C_2Cl_6	Cl	73
$(CH_2Br)_2$	Br	65
n-$C_7H_{15}I$	*n*-C_7H_{15}	74
CO_2, then H^+	CO_2H	95
Me_2CO	Me_2COH	82

Scheme 3



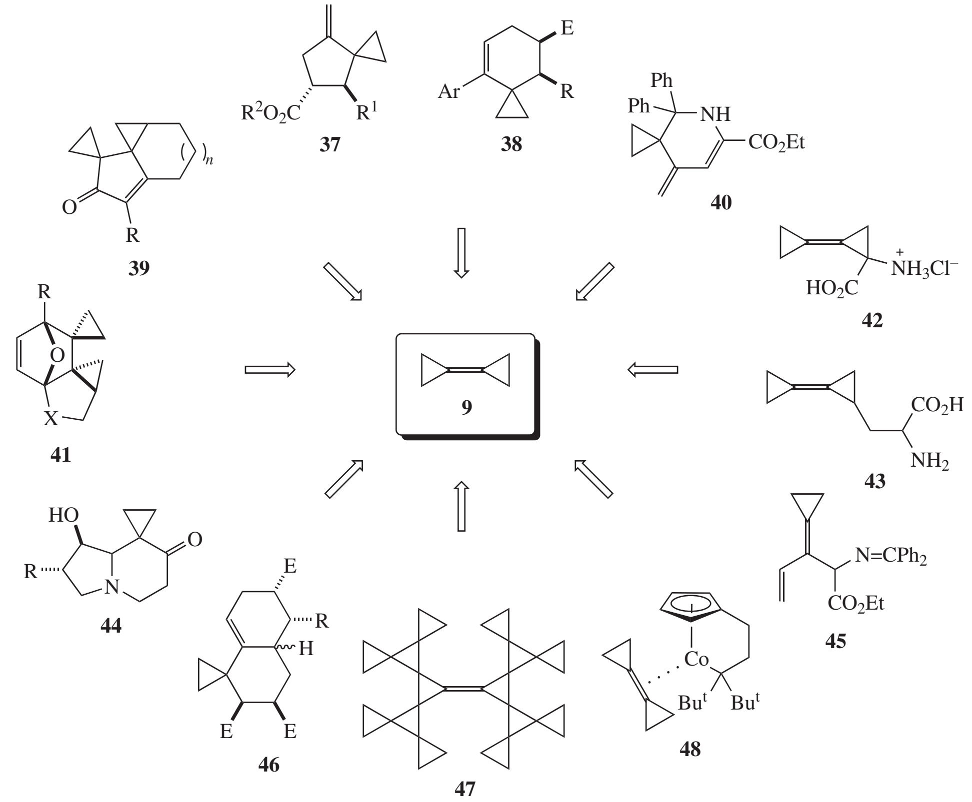
Ar = Ph, 4-MeC_6H_4, 2-EtC_6H_4,
4-$MeOC_6H_4$, 2,6-$Me_2C_6H_3$,
Py, *etc.*

Ar = Ph, 4-$F_3CC_6H_4$,
4-$MeOC_6H_4$, Py, *etc.*

Scheme 4

Due to its unique reactivity and oligofunctionality, bicyclopropylidene **9** has evolved as a very versatile building block for organic molecules of increased complexity.[11(*a*),(*c*),(*d*)] Compounds **37**–**48** (Scheme 5) and many more have been prepared, several in single-pot operations, from the hydrocarbon **9**, which is highly reactive towards radicals, 1,3-dipoles and various electrophiles.

Bicyclopropylidene **9**, although it is a tetrasubstituted alkene, easily participates in Heck reactions with aryl and alkenyl halides. These reaction cascades start with an oxidative addition of the halide to an active palladium(0) species, and ensuing carbopalladation of the double bond in **9**. The thus formed intermediate **49** undergoes a rapid cyclopropylmethyl- to homoallylpalladium rearrangement, and subsequent β-dehydropalladation in **50** leads to 1-arylallylidenecyclopropanes **7**-Ar, *i.e.*, substituted derivatives of **7**, which undergo rapid Diels–Alder cycloaddition with dienophiles that are present in the reaction media to give 4-arylspiro[2.5]octene derivatives **52**.[26] The intermediate 1,3-dienes **7**-Ar can be isolated, but the yields in this overall transformation are higher, in some cases virtually quantitative, if it is carried out as a one-pot three component reaction (Scheme 6). This reaction can favorably be performed in multi-parallel runs with a synthesizing robot. In such a way, a library of more than 200 such biaryl mimics **52** has been composed, because appropriately substituted biaryl compounds often possess interesting biological activities, and several are actually used as drugs. A high degree of diversity can be achieved by the variation of aryl halides **25**-X, the dienophile **53** or even by substitution of the bicyclopropylidene.[22]

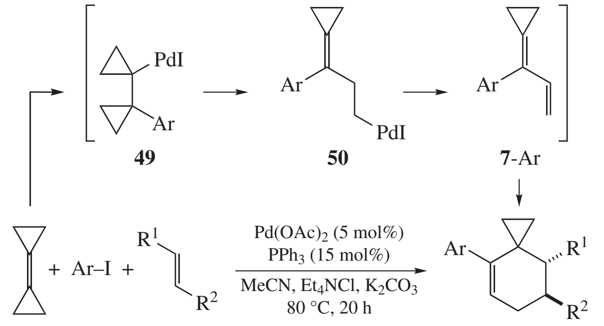


Scheme 5

Heteroatoms can easily be brought in with the aryl halide, *e.g.*, **54f**, or the dienophile, *e.g.*, **54c** and **54d** (Scheme 7). Carbonyl and azo dienophiles provide better yields, when the intermediate (1′-arylallylidene)cyclopropanes **7**-Ar are isolated and then treated with a dienophile.[27]

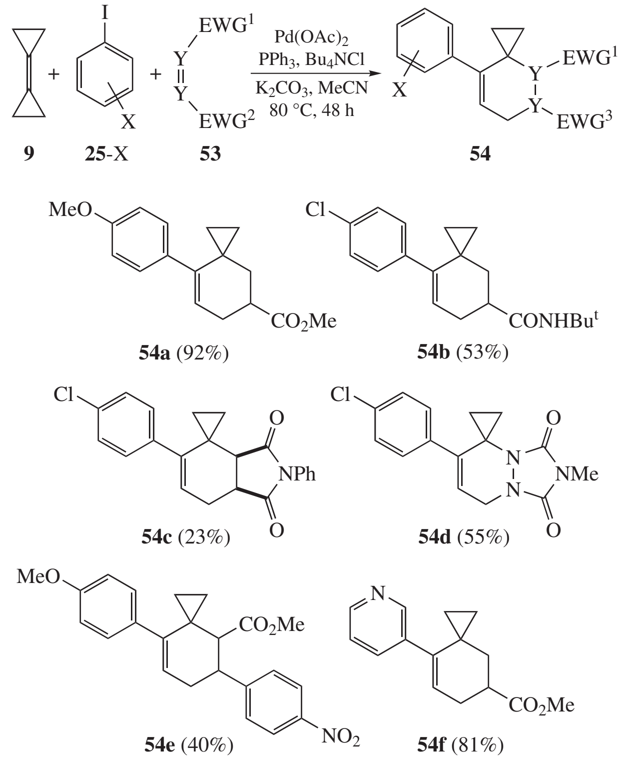
When the Heck coupling of bicyclopropylidene **9** is performed with an ethenyl instead of an aryl iodide, a cross-conjugated triene (so-called dendralene[‡]) is formed and trapped by a dienophile in a cascade of two consecutive [4 + 2] cycloadditions (so-called transmissive cycloadditions[29]) to provide skeletons of higher complexity than that of **54**.[26(c)] Even more complex skeletons can be attained with the same building block **9**. 1,4-Di-, 1,3,5-tri- and even 1,2,4,5-tetraiodobenzene have successfully been employed in the three-component cascade reaction with **9** and methyl acrylate **56**. With a 12-fold excess, each of **9** and **56**, triiodide **55** gave the heptacyclic system **57** in 72% yield (Scheme 8).[26(c)]

Various combinations of the bicyclopropylidene cascade (Scheme 6) with an initiating intramolecular carbopalladation



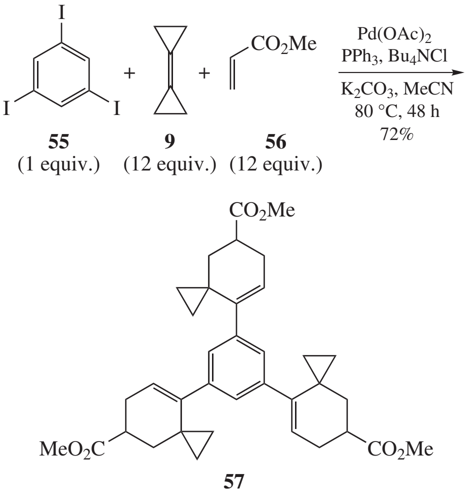
Ar	R¹	R²	Yield (%)
Ph	H	CO_2Me	100
Ph	H	CO_2Bu^t	87
Ph	CO_2Me	CO_2Me	97
4-Tol	CO_2Me	CO_2Me	99
4-Pyr	H	CO_2Bu^t	81
4-Pyr	CO_2Me	CO_2Me	60

Scheme 6



Scheme 7

[‡] Dendralenes are acyclic, branched, cross-conjugated oligo-alkenes. The name ‘dendralene’ is pulled together from the words ‘dendrimer’, ‘linear’ and ‘alkene’. The simplest dendralene is butadiene or [2]dendralene.[28]

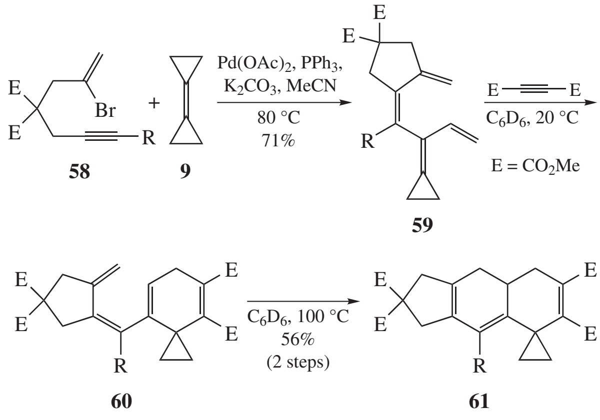


Scheme 8

of a 2-bromohepta-1,6-enyne **58** have also been realized. Under the typical conditions of a Heck reaction, bromoenynes **58** and **9** gave cross-conjugated tetraenes **59**, which could be trapped with dimethyl acetylenedicarboxylate. The resulting 1,3,5-hexatrienes **60** then underwent clean 6π-electrocyclization to furnish tetracycles **61** (Scheme 9).[30]

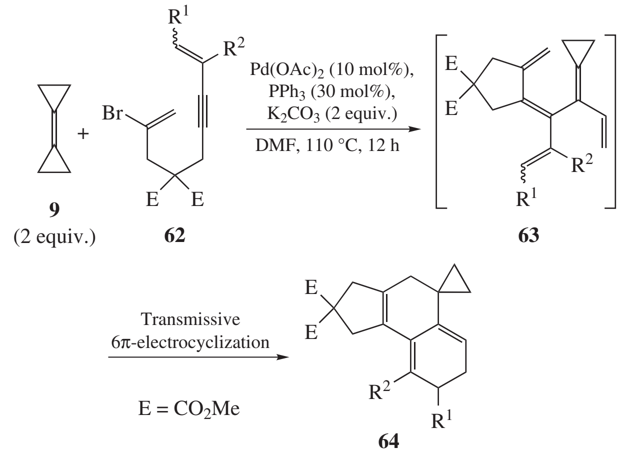
With an additional alkenyl group attached to the acetylene terminus of the bromo-1,6-enyne as in **62**, the palladium-catalyzed cascade reaction provides cross-conjugated pentaenes **63**, which undergo a cascade of two consecutive 6π-electrocyclizations to give tetracyclic systems **64** in low yields (Scheme 10).[30] Four new C–C bonds are formed in the latter cascade reaction.

An interesting queuing cascade reaction involving bicyclopropylidene **9** and carbon monoxide, in which five new bonds are formed, occurs with *ortho*-iodophenol **65**-OH and *ortho*-iodotoluenesulfonylaniline **65**-NTs under palladium catalysis. The initially formed (by oxidative addition) arylpalladium iodide apparently first inserts carbon monoxide into the palladium–carbon bond to give an acylpalladium iodide, which carbopalladates the reactive double bond in **9**. After the usual cyclopropylmethyl- to homoallylpalladium rearrangement, the intermediate inserts another molecule of CO to form **68**, which undergoes intramolecular carbopalladation of the methylenecyclopropane moiety with 5-*endo* ring closure, and thus formed homoacylpalladium intermediate **69** undergoes a second five-membered ring closure to yield the tetracyclic spiro compounds **66**-O and **66**-NTs, respectively (Scheme 11).[31]



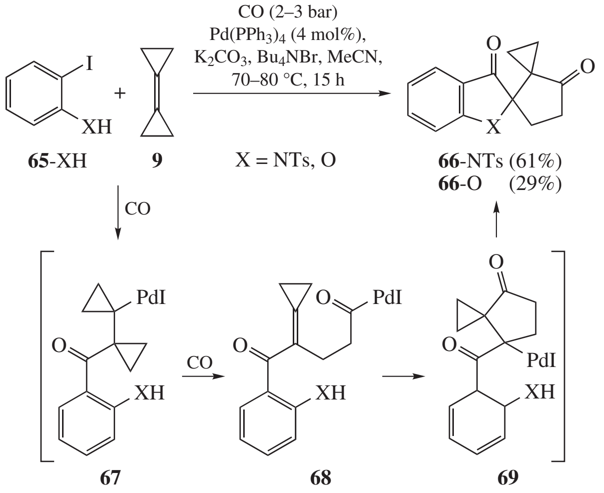
R	Yield (%) (1st step)	Yield (%) (2nd step)
Bu^t	58	–
$SiMe_2Bu^t$	64	70

Scheme 9



R^1	R^2	Yield (%)
H	Me	14
$-(CH_2)_4-$		21
OMe	H	9

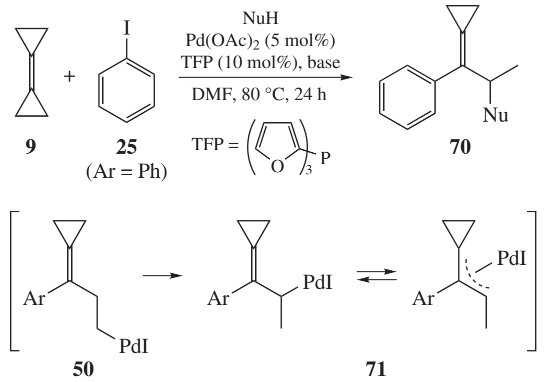
Scheme 10



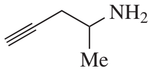
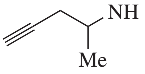
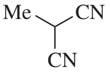
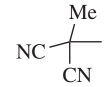
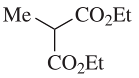
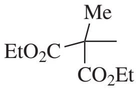
Scheme 11

Another versatile three-component cascade reaction of **9**, which requires slightly different conditions from those for the transformation to compounds **7**-Ar (Scheme 6), involves an aryl iodide and a nucleophile. In the presence of tris(2-furyl)phosphine (TFP) and palladium acetate in acetonitrile or dimethylformamide, the homoallylpalladium intermediate **50** undergoes a formal rearrangement to the σ-allyl-/π-allylpalladium iodide **71**, most probably, by β-dehydropalladation to **7**-Ar (Scheme 6) and recarbopalladation with the opposite regioselectivity – and the allylpalladium iodide **71** is then trapped by the added nucleophile to give methylenecyclopropane derivatives **70**. The nucleophiles can be oxygen-, nitrogen- and carbon-centred, and the yields are usually good to very good, particularly with primary amines (Scheme 12).[32]

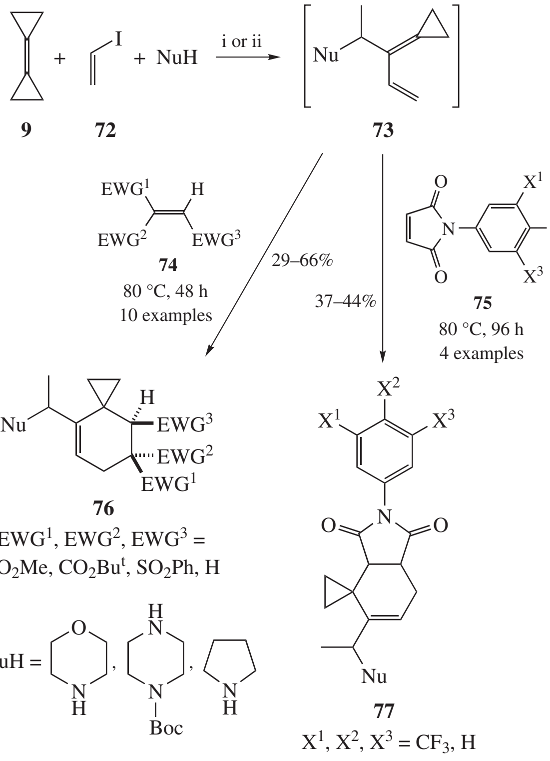
When iodoethene **72** instead of iodobenzene **25** (Ar = Ph) is employed in this three-component reaction, the resulting products are allylidenecyclopropanes **73** with allyl-positioned heteroatom substituents. These undergo, as has been shown for allylidenecyclopropanes **7** formed in a different way (Scheme 6), rapid [4 + 2] cycloadditions with added dienophiles **74** to provide highly substituted spiro[2.5]octene derivatives **76**. The complexity and diversity can be increased by using *N*-arylmaleinimides to furnish spirocyclopropanated heterobicycles **77** of potential interest in active compounds research (Scheme 13).[33]



9 **25** **70** **50** **71**

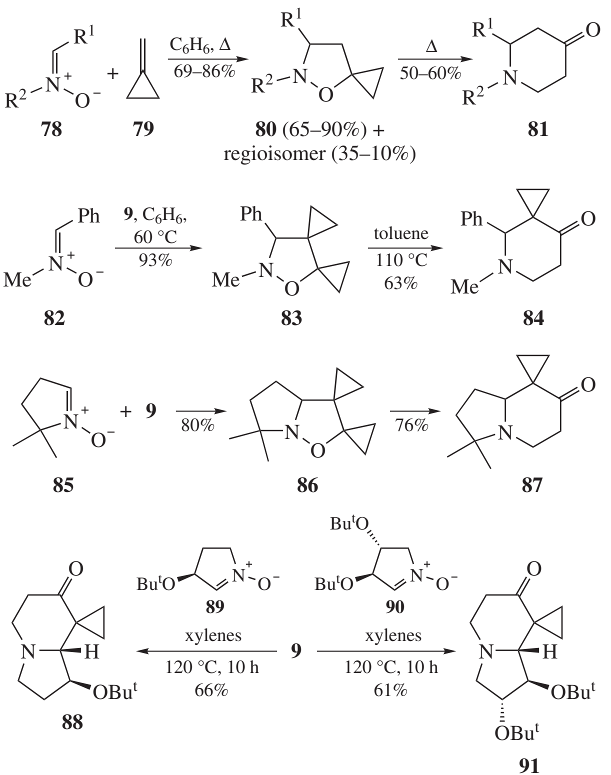
NuH	Base	Nu	Yield (%)
$\mathrm{BnNH_2}$	–	BnNH	60
$\mathrm{Bu^iNH_2}$	–	$\mathrm{Bu^iNH}$	85
$\mathrm{Bu^tNH_2}$	–	$\mathrm{Bu^tNH}$	95
	$\mathrm{Et_3N}$		38
	$\mathrm{Et_3N}$		77
	$\mathrm{Et_3N}$		57

Scheme 12



9 **72** **73** **74** **75** **76** **77**

Scheme 13 *Reagents and conditions*: i, $\mathrm{Pd(OAc)_2}$, TFP, $\mathrm{NEt_3}$, 2 h, 80 °C, DMF; ii, $\mathrm{Pd(OAc)_2}$, TFP, $\mathrm{K_2CO_3}$, $\mathrm{Et_4NCl}$, 2 h, 80 °C, MeCN.



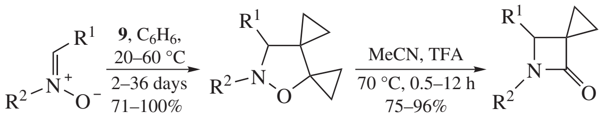
78 **79** **80** **81** **82** **83** **84** **85** **86** **87** **88** **89** **90** **91**

Scheme 14

The double bond in bicyclopropylidene **9** is particularly reactive not only towards electrophiles but also towards radicals[34] and towards dienes to undergo Diels–Alder reactions,[35] and it readily reacts with nitrones and nitrile oxides in 1,3-dipolar cycloadditions.[36] Since **9** is a symmetrical methylenecyclopropane, its cycloadducts cannot be regioisomeric as those of methylenecyclopropane **79**. Thus, the methylenecyclopropane chemistry developed by Brandi *et al.*,[37] can favorably be applied to compound **9**. The resulting bis-spirocyclopropanated isoxazolidines **83**, at temperatures above 100 °C, undergo clean thermal rearrangement to 5-azaspiro[2.5]octan-8-ones **84**, *i.e.*, spirocyclopropanated analogues of piperidin-4-ones **81** derived from nitrone cycloadducts **80** of methylenecyclopropane (Scheme 14). The sequence of 1,3-dipolar cycloaddition to **9** and thermal rearrangement of the isoxazolidine can favorably be carried out as a one-pot operation by running the reaction at an elevated temperature (120 °C), and with cyclic nitrones such as **89** and **90**, interesting heterocyclic analogues of Illudin and Ptaquilosin sesquiterpenes are obtained.[38] In spite of their only vague similarity, some of these analogues do have moderate DNA cleaving ability.

As Brandi *et al.* have found,[39] the spirocyclopropanated isoxazolidines from methylenecyclopropanes and nitrones, upon treatment with trifluoroacetic or hydrochloric acid, undergo an interesting fragmentative rearrangement to afford β-lactams. Bis-spirocyclopropanated isoxazolidines **80** obtained from **9** can be transformed in the same way to produce spirocyclopropanated β-lactams **92** in very good yields (Scheme 15).[40]

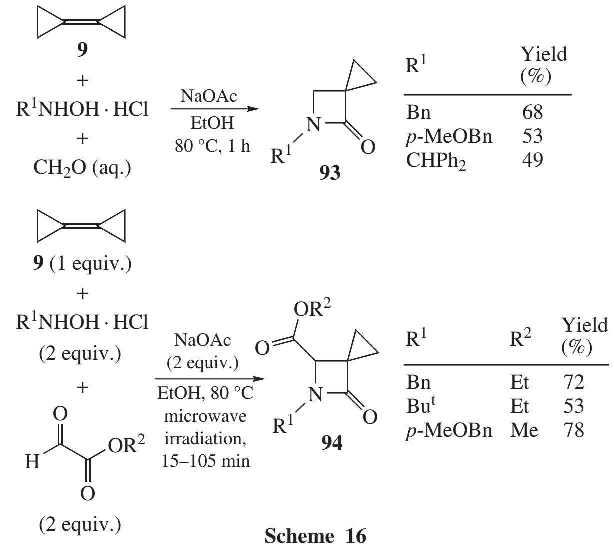
As the 1,3-dipolar cycloaddition to bicyclopropylidene **9** without thermal rearrangement of the isoxazolidines to spirocyclopropanated piperidones **81**, cannot be carried out at temperatures much higher than 60 °C, the formation of the unrearranged



78 **83** **92**

R^1	R^2	Yield of **83** (%)	Yield of **92** (%)
$\mathrm{CO_2Me}$	Bn	100	78
Ph	Bn	95	75
CN	Bn	94	75
CN	*p*-MeOBn	100	94
Ph	Me	93	96
2-Py	Me	71	96

Scheme 15



R^1	Yield (%)
Bn	68
p-MeOBn	53
$CHPh_2$	49

R^1	R^2	Yield (%)
Bn	Et	72
Bu^t	Et	53
p-MeOBn	Me	78

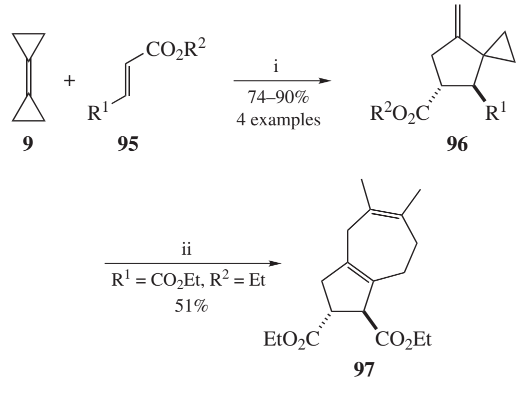
Scheme 16

isoxazolidines, in some cases, requires very long reaction times. Therefore, it is very helpful that, particularly the simple spirocyclopropanated β-lactams **93** and **94**, can be obtained in much shorter times by microwave heating of a mixture of **9**, benzylhydroxylamine hydrochloride, sodium acetate, aqueous formaldehyde or an alkyl glyoxylate, respectively, in ethanol at 80 to 100 °C (Scheme 16).[41]

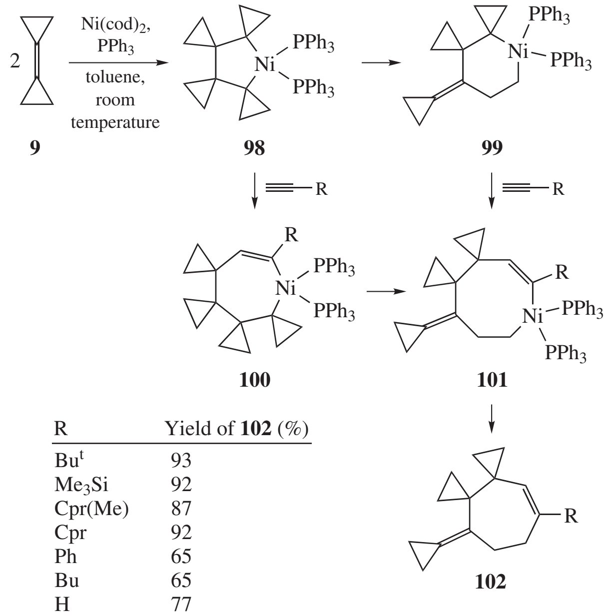
These new three-component reactions offer a very convenient access to β-lactams **93** and **94** in good yields. These can be used for the preparation of oligopeptides that have the interesting 1-(aminomethyl)cyclopropanecarboxylic acid residue[42] incorporated.[41,43] Unfortunately, other aldehydes like benzaldehyde in this one-pot reaction furnish the corresponding β-lactams only in poor yields.

Two other reaction modes of bicyclopropylidene **9** under metal catalysis, yielding spirocyclopropanated carbocycles, are worth to be mentioned in this context. One is the palladium-catalyzed formal [3 + 2] cycloaddition of **9** to acceptor-substituted alkenes **95** to give 4-methylenespiro[2.4]heptane derivatives **96** in very good yields.[44] The *s-cis*-oriented vinylcyclopropane moiety in these compounds can be thermally rearranged to an annelated cyclopentene ring,[45] or employed in a rhodium-catalyzed formal [5 + 2] cycloaddition with alkynes according to a general protocol by Wender *et al.*[46] providing the bicyclo[5.3.0]deca-1(7),3-diene **97** (Scheme 17).

Under nickel(0) catalysis, bicyclopropylidene **9** and terminal alkynes form bis-spirocyclopropanated cycloheptenes **102** in good to excellent yields, apparently with incorporation of two molecules of **9** (Scheme 18).[47]



Scheme 17 *Reagents and conditions*: $Pd(dba)_2$, $PPr^i_2Bu^t$, toluene, 110 °C, 3 h; ii, 2-butyne, $[RhCl(PPh_3)_3]$, AgOTf, toluene, 110 °C, 3 h.

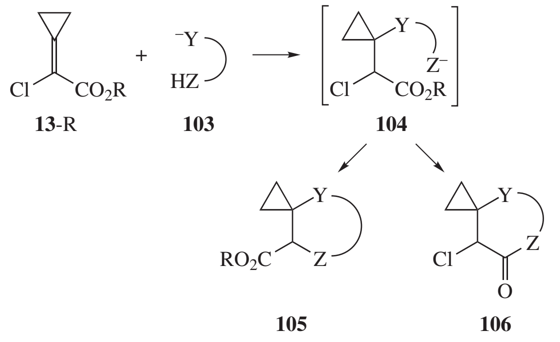


R	Yield of **102** (%)
Bu^t	93
Me_3Si	92
Cpr(Me)	87
Cpr	92
Ph	65
Bu	65
H	77
OEt	57
CO_2Me	8
CH_2OH	25
CH_2OBn	25

Scheme 18

It is assumed that an initial complexation of two molecules of compound **9** on nickel is preferred, leading to the tetraspirocyclopropanated nickelacyclopentane **98** after twofold insertion. A cyclopropylcarbinylmetal to homoallylmetal rearrangement[48] in **98** would yield the nickelacyclohexane intermediate **99**, which could insert the alkyne, and the resulting nickelacyclooctene **101** would afford the cycloheptene derivative **102** by reductive elimination. As the transition structure for the rearrangement of **98** to **99** most probably would be highly strained, it is more likely that insertion of the alkyne occurs at the stage of the nickelacyclopentane intermediate **98** to give **100**, which subsequently undergoes the cyclopropylcarbinylmetal to homoallylmetal rearrangement[48] to provide **101**, the immediate precursor to **102**.

The development of methyl 2-chloro-2-cyclopropylideneacetate **13**-Me, another oligofunctional and thereby extremely versatile cyclopropane building block, began as early as 1982.[49] More than 40 reports on the use of **13**-Me and analogues in the construction of more complex molecules containing cyclopropyl groups have appeared in the literature,[50] and recently published advanced syntheses of **11**-R, **12**-R and **13**-R have made this class of methylenecyclopropane derivatives more easily accessible than ever before.[51] One interesting aspect of the applicability of building block **13**-R lies in the synthesis of spirocyclopropanated heterocycles **105** and **106** by its reactions with 1,3-, 1,4- and 1,5-bisnucleophiles (Scheme 19).[52]

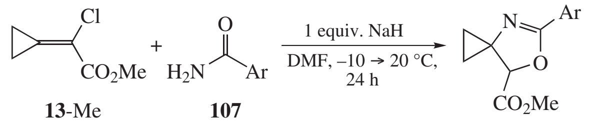


Scheme 19

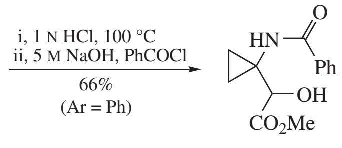
The reaction mode is determined only by the nature of the bisnucleophile.

The reactivity of **13**-Me as a Michael acceptor in comparison with other 3,3-disubstituted acrylates is so enhanced,[53] that even arenecarboxamides **107**, albeit in the presence of one equivalent of sodium hydride, undergo addition to the double bond with immediately ensuing intramolecular nucleophilic displacement of chloride in the intermediate of type **104**, to furnish spirocyclopropanated methyl 2-aryloxazoline-5-carboxylates **108**-Ar in good yields (Scheme 20).[54] The latter are protected 2-hydroxy-2-(1-aminocyclopropyl)acetates and can indeed be deprotected under mild conditions to α-hydroxy-β-amino acids. Acylation, *e.g.*, benzoylation under Schotten–Baumann conditions, occurs selectively on nitrogen, and the resulting compound **109** has been conceived as an analogue of the side-chain amino acid in Taxol. The racemic carboxylic acid obtained from methyl ester **108**-Ph has been condensed with the appropriately protected Baccatin to result in **110** and its diastereomer *epi*-**110**, and complete deprotection of the two gave two diastereomeric Taxol analogues each, **111a**,**b** and *epi*-**111a**,**b**.[55] The biological activities of these and other C3′-cyclopropanated Taxol analogues have been tested and correlated in terms of a quantitative structure–activity relationship (QSAR).[56]

Thiocarboxamides react with **13**-Me even in the presence of sodium bicarbonate in acetonitrile to give spirocyclopropanated thiazoline-4-carboxylates in good to excellent yields, *i.e.*, the sulfur is the initially attacking nucleophile in the Michael addition. The resulting thiazolinecarboxylates are protected β-thio-α-amino acids, and the latter, which are cyclopropyl-group containing cysteine derivatives, can be liberated from the heterocycles under mild conditions.[57] On the other hand, amidines do not yield spirocyclopropanated imidazolinecarboxylates, but they react with a cyclopropylmethyl to cyclobutyl cation rearrangement to afford synthetically very useful cyclobutene-annelated pyrimidinones.[58]

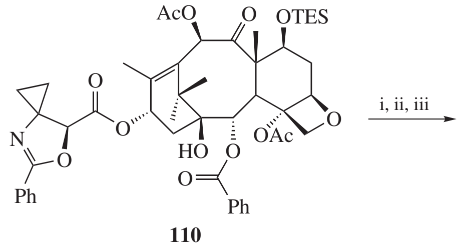


13-Me **107** **108**-Ar

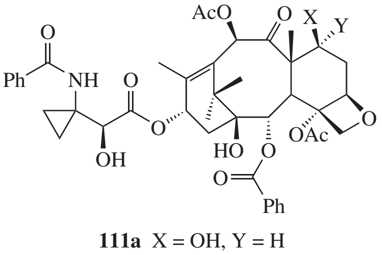


109

Ar	Yield (%)
Ph	50
2-MeOC$_6$H$_4$	69
4-BrC$_6$H$_4$	78
4-CNC$_6$H$_4$	66
2-ClC$_6$H$_4$	79
2-IC$_6$H$_4$	74
3-FC$_6$H$_4$	76
2-O$_2$NC$_6$H$_4$	38



110



111a X = OH, Y = H
111b X = H, Y = OH

Scheme 20 *Reagents and conditions*: i, HF–pyridine, THF, 0 → 20 °C, 24 h, 90%; ii, 0.1 N HCl, 1,4-dioxane (1:1), 50 °C, 1 h, 85%; iii, 0.1 N NaHCO$_3$, 1,4-dioxane (1:1), 20 °C, 6 h, 80%.

Amino acids are bifunctional building blocks per se. The naturally occurring peptidolactone Hormaomycin **112**, a signal metabolite that was isolated from a *Streptomyces griseoflavus* strain and structurally elucidated in 1989,[59] contains one molecule each of the (2*R*,1′*S*,2′*R*)- and (2*S*,1′*S*,2′*R*)-configured unusual amino acid 3-(2-nitrocyclopropyl)alanine **119** in its cyclodepsipeptide unit and the side chain, respectively. To enable a total synthesis of Hormaomycin with its interesting biological activities,[60] the absolute configuration of all of its 16 stereogenic centres had to be established,[61] and a productive synthesis of all four diastereomeric 3-(*trans*-2′-nitrocyclopropyl)alanines **119** had to be developed.[62]

Initially, enantiopure (*trans*-2-nitrocyclopropyl)methanols (1*S*,2*S*)-**115** and (1*R*,2*R*)-**115**, prepared in six steps from (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde, were used to obtain the corresponding bromides (1*S*,2*S*)-**116**-Br and (1*R*,2*R*)-**116**-Br, which were coupled with an achiral glycine equivalent like 2-[(diphenylmethylene)amino]acetate to each yield two diastereomeric 3-(*trans*-2′-nitrocyclopropyl)alanines.[63] Since this route was too tedious for multigram quantities, a productive synthesis of racemic (*trans*-2-nitrocyclopropyl)methyl iodide *rac*-**116**-I from *tert*-butyl 2,3-dibromopropionate **113** and nitromethane was developed (Scheme 21), and *rac*-**116**-I was used to alkylate the enolate of the enantiomerically pure Belokon' glycine equivalent,[64] (*S*)- or (*R*)-2-[(*N*-benzylprolyl)amino]-benzophenone (*S*)- or (*R*)-**117**. From (*S*)-**117**, an 85:15 mixture of the two diastereomeric alkylation products **118a** and **118b** precipitated after acidic hydrolysis, and the mother liquor contained **118a** and **118b** in a ratio of 25:75. Recrystallization of the fraction enriched in **118a**, deprotection and filtration through an ion-exchange resin afforded almost enantiomerically pure (2*S*,1′*R*,2′*S*)-**119**, and double recrystallization of the residue from the mother liquor, deprotection and DOWEX filtration provided diastereomeric (2*S*,1′*S*,2′*R*)-**119**. The other two diastereomeric (*trans*-2-nitrocyclopropyl)alanines (2*R*,1′*R*,2′*S*)-**119** and (2*R*,1′*S*,2′*R*)-**119** were obtained in the same way from (*R*)-**117**. With both correct stereoisomers of **119** and all the other enantiomerically pure amino acid building blocks in hand, the peptidolactone **112** with its dipeptide side chain was assembled using an appropriately adapted peptide condensation methodology.[65] This total synthesis methodology and accumulated knowledge concerning the biosynthetic pathway[66] permitted access to not only the natural product **112**, but also to about two dozen analogues with modified amino acid residues for biological testing.[67]

Dicyclopropylacetylene **5**[17] is an ideal building block for various oligocyclopropanated carbon frameworks. With dodecacarbonyltriiron at 180 °C, compound **5** reacts to give hexacyclopropylbenzene[68] and tricarbonyl(tetracyclopropylcyclopentadienone)iron[68] as major, as well as tetracyclopropyl-*p*-benzoquinone[69] and tricarbonyl(tetracyclopropylcyclobutadienyl)-iron[70] as minor products. Hydromagnesiation of **5** employing a protocol by F. Sato *et al.*[71] yields *cis*-1,2-dicyclopropylethenylmagnesium bromide **121**, which reacts with *n*-butyl formate directly to tetracyclopropylcyclopentadiene **123** (Scheme 22).[72]

The analogous reaction of **121**, after conversion to the organocerium analogue **122**,[§] with methyl cyclopropanecarboxylate **29** and subsequent acidic work-up furnishes pentacyclopropyl-

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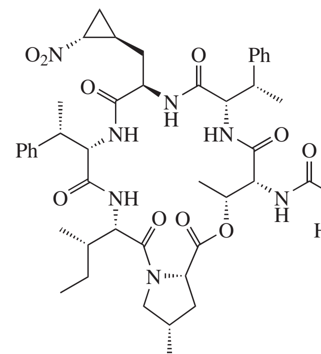
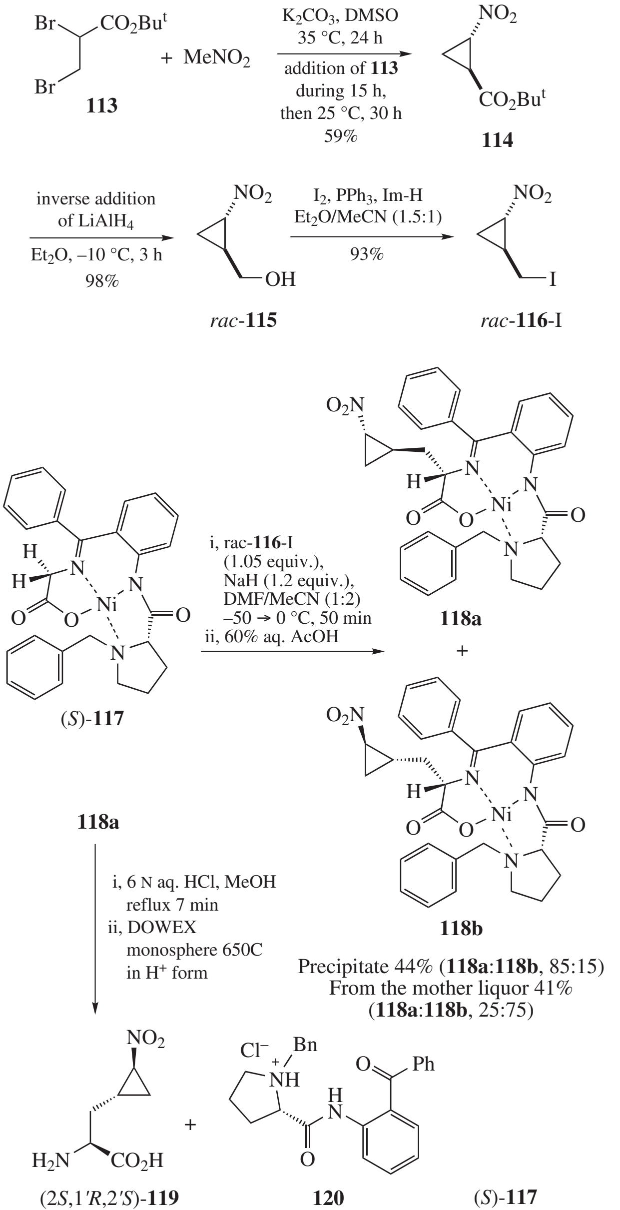
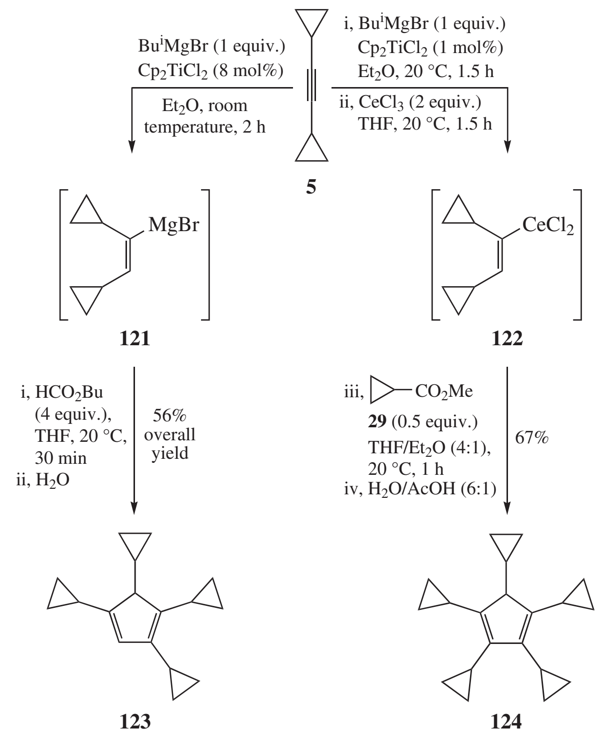
[§] Addition of cerium(III) chloride to organomagnesium halides has been found to promote 1,2-addition onto α,β-unsaturated ketones.[73]



112



Scheme 21



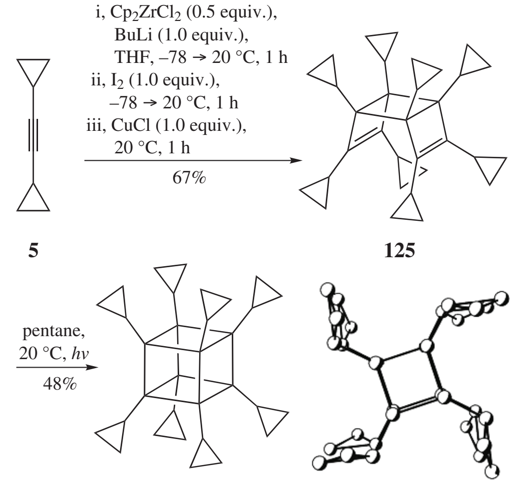
Scheme 22

cyclopentadiene **124** in 67% overall yield. With the peculiar electronic properties[10] and steric requirements of a cyclopropyl group,[74] the cyclopentadienes **123** and **124** are interesting ligands that may have useful applications in transition metal coordination chemistry.

The ultimate molecular complexity so far achieved with dicyclopropylacetylene **5** as a building block is its formal oligocyclotetramerization to octacyclopropylcubane **126**. Employing some zirconium chemistry developed by Takahashi *et al.*[75] to compound **5** led to its conversion into octacyclopropyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene **125** in 67% yield (Scheme 23).[76]

With its *syn*-configuration, **125** is well set up for a photochemical intramolecular [2 + 2] cycloaddition. Indeed, upon irradiation in pentane at ambient temperature, compound **125** is converted to octacyclopropylcubane **126** in 48% yield. This quite remarkable result is due to the steric features[74] and, possibly, the peculiar electronic properties[10] of the eight cyclopropyl groups in compounds **125** and **126**, as the octamethyl- and octaethyl-*syn*-tricyclooctadienes gave the corresponding cubanes in only 1 and 2% yield, respectively.[77]

In spite of its overall strain energy of 390 kcal mol^{-1}, **126** is remarkably stable. While cubane itself has a half-life of 24 min at 250 °C,[78] 50% of **126** survives after 3 h at 250 °C. When heated above 250 °C for elongated times, **126** completely rearranges to octacyclopropylcyclooctatetraene. In the crystal, the eight cyclopropyl substituents in **126** adopt a regular orientation, so that the overall symmetry of the molecules remains at C_{4h}



Scheme 23

(Scheme 23). Thus, the decoration of cubane with eight cyclopropyl groups leads to not only an esthetically appealing molecule, but also a compound with unusual and unexpected properties.

In conclusion, the multifacetted chemistry of relatively simple cyclopropane compounds **1**–**14** keeps evolving. All of these molecules and their derivatives constitute oligofunctional building blocks, as the cyclopropane ring itself is a functional group. Consequently, it can be involved in transformations of the initially formed intermediates or products in sequential reactions or multistep cascade reactions. On the other hand, cyclopropyl substituents on a framework or cyclopropyl groups incorporated in a structure can endow such molecules with special properties that can be favorable of beneficial in a number of senses.

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