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Synthesis and Synthetic Applications of 1-Donor Substituted Cyclopropanes with Ethynyl, Vinyl and Carbonyl Groups

H.-U. Reißig
Donor-Acceptor-Substituted Cyclopropanes: Versatile Building Blocks in Organic Synthesis

M. S. Baird
Functionalised Cyclopropenes as Synthetic Intermediates

Small Ring Compounds in Organic Synthesis III

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Editor: A. de Meijere

With Contributations by
M. S. Baird, H.-U. Reißig, J. R. Y. Salaün

With 1 Figure and 11 Tables

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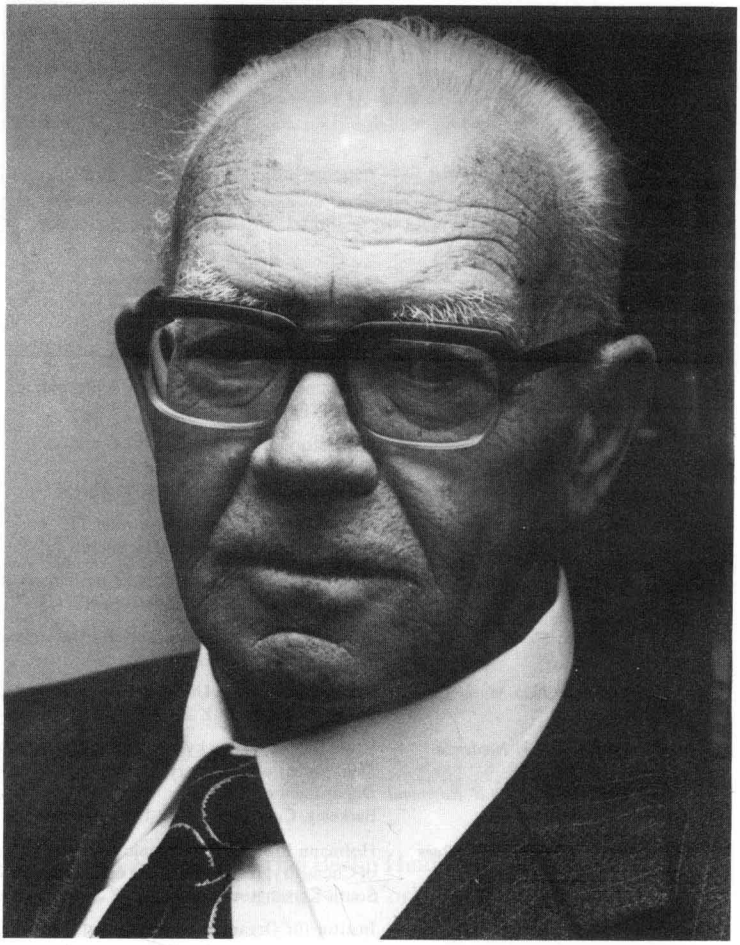

Prof. emer. Dr. Dr. h.c. mult. Georg Wittig
1897–1987

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Georg Wittig 16. 6. 1897–26. 8. 1987

Georg Wittig, Professor Emeritus died August 26th, 1987 in Heidelberg a few weeks after his ninetieth birthday. With him the members of the international community of organic chemists have lost one of their greatest representatives of this century.

Georg Wittig was born in Berlin. He studied chemistry in Marburg/Lahn where he obtained his Ph.D. and became Privatdozent in 1926. A few years later he moved to the Technische Hochschule Braunschweig. In 1937 he was appointed Professor Extraordinarius at Freiburg/Breisgau and in 1944 Professor Ordinarius and Director of the Chemical Institute at the University of Tübingen. In 1956 he succeeded Karl Freudenberg at the University of Heidelberg where he formally retired in 1967.

Wittig is best known for his work on phosphorus ylides, which condense with carbonyl compounds to form alkenes. The WITTIG REACTION has obtained great value far beyond its usefulness in academic research. By means of this reaction vitamins, hormones, pharmaceuticals and many other desirable classes of organic compounds are nowadays synthesized on a large industrial scale. The most familiar examples are Vitamin A and β-carotene. Here we find an impressive example of fundamental research finally leading to important and wide ranging applications.

The WITTIG REACTION was discovered in connection with the successful synthesis of pentacovalent derivatives of the elements of the fifth main group.

Other outstanding contributions of Wittig are the observation of the halogen-metal-exchange reaction and the discovery of dehydrobenzene as early as in 1939 and 1942, respectively. This work stimulated fundamental work in the field of carbanion chemistry and led for example to the concept of the *ate* complexes, which is now generally accepted. In extension of the dehydrobenzene studies the class of small cycloalkynes was found: many of these intermediates with a strained carbon-carbon triple bond can be easily generated and are now versatile building blocks in organic syntheses. In a rather late stage of his academic career Wittig developed the directed aldol condensation, an extremely elegant method for the carbon-carbon-bond formation between carbonyl compounds in a manner which was not possible previous-

ly. It is interesting to note that some of his last publications were devoted to the formation of diradials, a topic in which he was already engaged at the very beginning of his research.

Georg Wittig is also well known for his engagement regarding scientific literature. For a long period he was a member of the editorial boards of many national and international journals. From 1963 for instance he was one of the editors of Topics in Current Chemistry.

His own impressive activities are documented in more than 300 scientific papers published between 1924 and 1980.

In 1979 Georg Wittig together with Herbert C. Brown was awarded the Nobel prize for Chemistry. The Royal Swedish Academy honored Brown and Wittig "for their development of boron and phosphorus compounds, respectively, into important reagents in organic synthesis". Apart from the Nobel prize Georg Wittig received a great number of awards, honorary doctorates and other appointments. The honorary doctorate he received from Sorbonne, Paris in 1957 as the first German after World War II was an acknowledgement of his merits in reestablishing the reputation of German science after the war.

During his long career as scientist and academic teacher, more than 300 graduate students and post-doctoral co-workers were associated with Wittig. Many of them now hold important positions in industry and at universities throughout the world. Those of us who were privileged to accompany Georg Wittig for a few years on his long way through the fascinating field of organic chemistry were deeply impressed by his sincere and honest personality. He set a high standard of expectation on his students' abilities, qualifications, enthusiasm and decency as well as being always open for personal problems and most helpful in solving them.

On November 17th 1987 the Chemische Gesellschaft zu Heidelberg held a colloquium in memoriam of Georg Wittig attended by respresentatives of the University and the City of Heidelberg, members of the faculty of chemistry, colleagues and former students in reverence to his esteemed personality and his great contributions to science.

Werner Tochtermann

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Synthesis and Synthetic Applications of 1-Donor Substituted Cyclopropanes with Ethynyl, Vinyl and Carbonyl Groups

Jacques R. Y. Salaün

Laboratoire des Carbocycles, UA 478 du CNRS, Université de Paris-Sud, 91405 Orsay Cedex, France

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Substituted on the same carbon by an electron donating group and an adjacent multiple bond, cyclopropanes provide building blocks of unprecedented synthetic potential. They are readily available along different routes involving: cyclopropanone hemiacetals, oxaspiropentanes, alkylidenecyclopropanes, 1-heterosubstituted lithiocyclopropanes, α-enone silyl enol ethers, 1,3-dichloroacetone and 1-hydroxycyclopropylcarbonyl derivatives as main sources.

First of all, they undergo acid-induced $C_3 \rightarrow C_4$ ring expansion to four-membered rings, in particular to the 2-vinylcyclobutanone system, which is an efficient precursor of C_5, C_6 and C_8 homologous rings by subsequent acid- and base-induced, thermal, or photolytic ring enlargements. On the other hand, they undergo thermal $C_3 \rightarrow C_5$ ring expansion providing cyclopentanone enol ethers or derivatives with high chemo-, regio- and stereoselectivity.

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The usefulness of these ring enlargements has been illustrated by the total synthesis of some natural products with four- (grandisol), five- (α-cuparenone, prostanoid, jasmanoid, methylenomycin B, spirovetivane, aphidicolin, dicranenone), six- (β-selinene, compactin) and eight-membered rings (poitediol). Regioselective α or α′ monomethylation of α-enones is based on the base-induced ring opening of trimethylsiloxycyclopropanes whereas, stereoselective alkylation can be obtained by the base-induced ring opening of cyclobutanones (grandisol, deoxypodocarpate). Finally, these attractive building blocks provide a convenient key to enter the field of the homoenolate chemistry.

1 Introduction

Although cyclopropane derivatives have been known for more than 100 years [1], is was not until about 1960 that the exploration of the cyclopropane chemistry really began. In fact the utility of such building blocks for organic synthesis has been recognized only in the recent years.

The chemical reactivity of a cyclopropane ring, closely resembles that of an olefinic double bond: both groups interact with neighbouring π-electron systems and p-electron centers, add acids, halogens and ozone, undergo catalytic hydrogenation and cycloaddition, form metal complexes, etc. [2]. More specifically, the three-membered ring can undergo ring openings induced by solvolysis, bases, electrophiles, nucleophiles, metals as well as thermally and photolytically [3]. With an adjacent electron deficient center, the cyclopropane ring readily ring enlarges to four-membered ring derivatives [3]. Substituted by a vinylic moiety it undergoes $C_3 \rightarrow C_5$ ring enlargement to five-membered ring derivatives, a process which provides an efficient three-carbon annelation method [3,4]. The cyclopropane ring undergoes interconversions with related cyclobutane and open-chain derivatives [5], but it is also produced in high yields in a ring contraction of four-membered cyclic systems bearing both electron donating and leaving groups, in a vicinal arrangement [3].

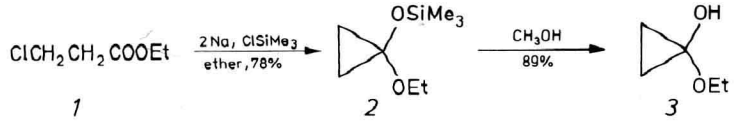
Like that of most other functional groups, the reactivity of the cyclopropane moiety can be strongly influenced by the substituents on the ring. Thus, for instance, specific reactivity originates from combinations of a three-membered ring with an adjacent multiple bond. Furthermore, cyclopropanes with multiply bonded groups and an electron donating substituent on the same carbon exhibit unexpected and unprecedented synthetic utility. This review summarizes the preparation of such building blocks and exemplifies their use in organic synthesis.

2 Preparation of 1-Donor Substituted Ethynylcyclopropanes

2.1 From Cyclopropane Hemiacetal

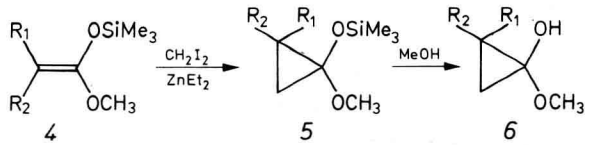
Cyclopropanone chemistry has received considerable attention in recent years [6]; nevertheless, the chemistry of this unusually reactive class of ketones has previously found limited use in synthesis mainly because of the difficulties encountered in the preparation and handling of such strained systems. However, the discovery of derivatives capable of delivering the parent three-membered ring ketone or equivalent species *in situ*, has brought the development of cyclopropanone chemistry a decisive step forward. Among them, the cyclopropanone hemiacetal *3*, which is now readily available [7], became a substrate of choice in a number of useful chemical transformations including the formation of cyclopropanols, methylenecyclopropanes, cyclobutanones, β-lactames, γ-butyrolactones, cyclopentanones, pyrroline derivatives, etc. [8]. Previously prepared by the tedious and quite hazardous addition of diazomethane to ketene in the presence of one equivalent of methanol [9] or ethanol [10], the cyclopropanone hemiacetal can now be obtained readily in high yield by simple methanolysis of 1-ethoxy-1-(trimethylsiloxy)cyclopropane *2*, the product of the

acyloin-type cyclization of commercial ethyl 3-chloropropanoate *1* by sodium in refluxing ether in the presence of chlorotrimethylsilane, Eq. (1) [7].



1 *2* *3* (1)

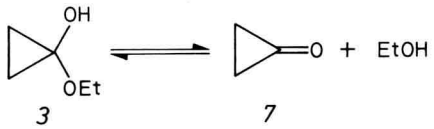
Another access to 1-alkoxy-1-siloxycyclopropanes *5*, precursors of substituted cyclopropanone hemiacetals *6*, was developed with the addition of carbenes, generated from alkylidene iodides and diethylzinc, to the trimethylsilyl enol ethers of carboxylic esters *4*, Eq. (2) [11].



4 *5* *6* (2)

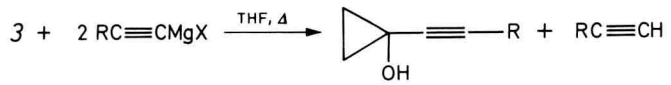
Similarly, the addition of the Simmons-Smith reagent (CH_2I_2 + Cu-Zn couple) to 1-ethoxyvinylacetate (or benzoate) provided 1-ethoxycyclopropylacetate, which upon reaction with methanol or ethanol yielded *3* or the corresponding methyl hemiacetal [12].

The chemical properties of cyclopropanone hemiacetals have been reviewed [8]. Besides oxidative cleavage with low oxidation potential metals (Cu^{II}, Fe^{III}, Ce^{II}, ...) or with molecular oxygen and peroxides, these hemiacetals underwent acid and base induced ring openings. Furthermore, they were subject to nucleophilic attack by various reagents providing an efficient pathway to 1-substituted cyclopropanols. Therefore, the ethyl hemiacetal of cyclopropanone *3* now constitutes a convenient and storable source of the parent ketone *7*, on the basis of the equilibrium shown in Eq. (3) [10, 12].



3 *7* (3)

However, owing to this formal equilibrium, two equivalents of the acetylenic Grignard reagents *8*, were required to obtain the propargylic cyclopropanols *9*, Eq. (4) [10, 13].



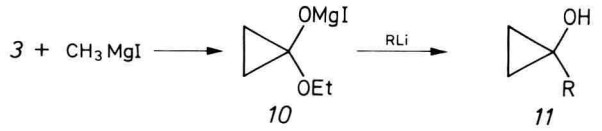
8 21-86% *9*

R = H[10], OEt[14]
CH_3, C_6H_5, $pCH_3C_6H_4$, $pCH_3OC_6H_4$,
CH_2=CH[15]

(4)

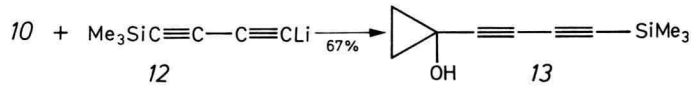
On the other hand, the cyclopropanone hemiacetal *3* did not react with nucleophilic lithium reagents such as lithium cyanide [16], ethynyllithium [16] or aryllithium [17].

This difficulty was overcome by first treating *3* with an equimolar amount of methylmagnesium iodide, to convert it into a species, most likely the magnesium derivative *10*, which did react with various organolithium reagents to give the expected 1-substituted cyclopropanols *11*, Eq. (5) [16,17].



10 11 (5)

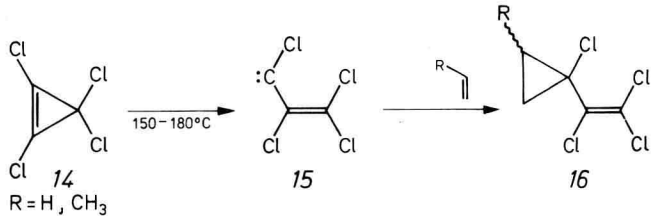
For instance, the trimethylsilylbutadiynyl lithium derivative *12*, resulting from the selective monodesilylation of bis-silylbutadiyne [18], when treated with the magnesium salt *10* provided good yields of the 1-(trimethylsilylbutadiynyl) cyclopropanol *13*, which was successfully used as a prostaglandin precursor, (*vide infra*, Sect. 5.5.2.1) Eq. (6) [15].



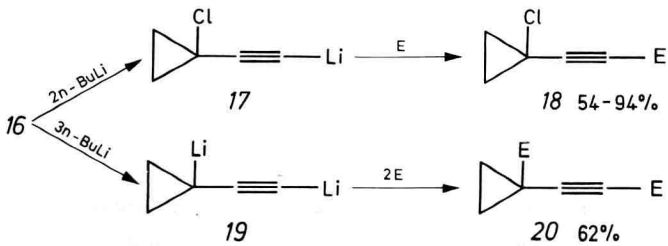
12 13 (6)

2.2 From Tetrachlorocyclopropene

Addition of dichlorocarbene to trichloroethylene gave pentachlorocyclopropane which was smoothly dehydrochlorinated by aqueous potassium hydroxide into tetrachlorocyclopropene *14* [19]. On heating at 150–180 °C, *14* provided an efficient source for tetrachlorovinylcarbene *15*, which could be trapped intermolecularly by olefins to give the 1-chloro-1-(trichlorovinyl)cyclopropanes *16*, Eq. (7) [20].



14 R = H, CH_3 15 16 (7)

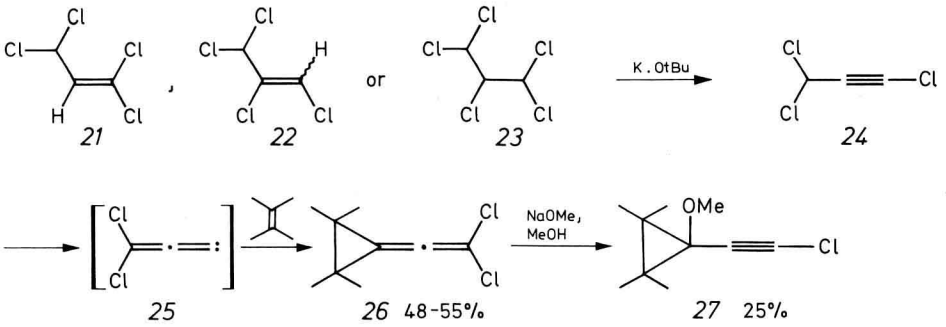


17 18 54–94% 19 20 62% (8)

Upon reaction with two moles of *n*-butyllithium the adducts *16* gave the 1-chlorocyclopropylethynyllithium reagents *17* which could be trapped by a wide variety of electrophiles (CO_2, $ClCO_2Me$, Me_3SiCl, H_2CO, R_1COR_2, NCS, CH_3SSCH_3 ...) to give the corresponding cyclopropylacetylene derivatives *18*. Further metalation with three equivalents of *n*-BuLi gave the dianion *19* which, on electrophilic substitution, led to difunctional cyclopropylacetylenes *20* with any desirable combination of donor or acceptor functional groups, Eq. (8) [21].

2.3 From 1,1,3,3- and 1,2,3,3-Tetrachlor propene and 1,1,2,3,3-Pentachloropropane

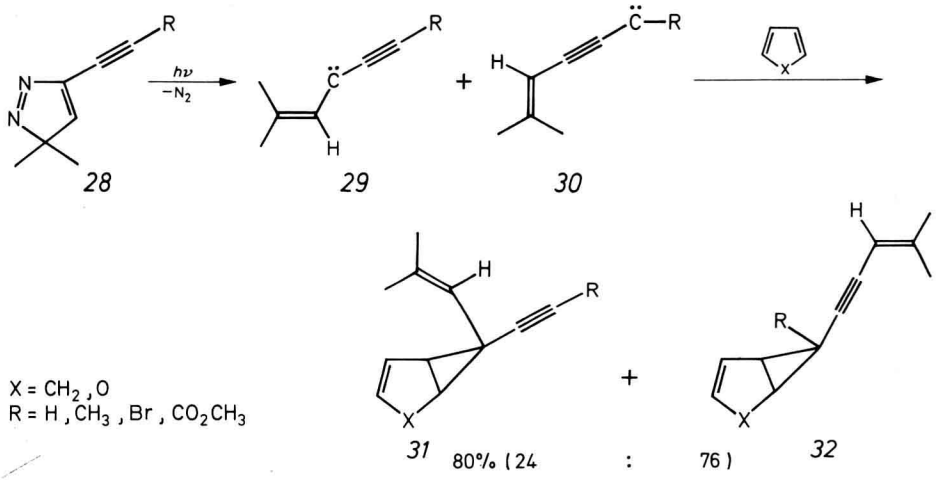
Alternatively, 1,1,3,3- and 1,2,3,3-tetrachloropropene *21* and *22* or 1,1,2,3,3 pentachloropropane *23* underwent dehydrochlorination with potassium t-butoxide to give, probably through 1,3,3-trichloropropyne *24*, the dichlorovinylidenecarbene *25* which was trapped by olefins to lead to the dichloroethenylidenecyclopropanes *26*. Then, the highly reactive allene *26* added electrophiles as well as nucleophiles such as methoxides to give, for instance, 1-methoxy(2-chloroethynyl)cyclopropane *27*, Eq. (9) [22].



(9)

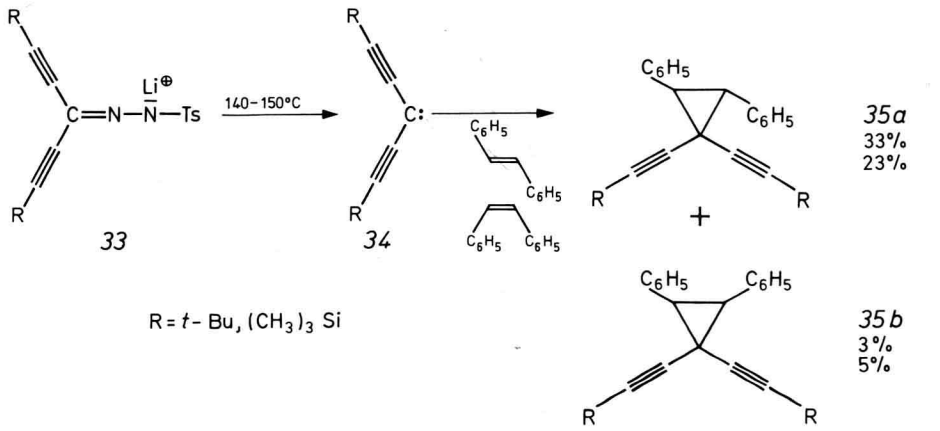
2.4 From Ethynylcarbenes

The 3,3-dimethyl-5-alkynyl-3H-pyrazoles *28*, obtained by addition of 2-diazopropane to diacetylene, were irradiated to give the alkynylvinylcarbenes *29* and *30* the relative reactivity of which depended mainly on the substituent R on the triple bond. These carbenic species were trapped by cyclopentadiene or furan to give the ethynylcyclopropane derivatives *31* and *32*, respectively, Eq. (10) [23].



(10)

The pyrolysis at 140–150 °C of the lithium salts of diethynyl ketone tosylhydrazones *33* led to the formation of the triplet diethynylcarbenes *34* which were trapped by olefins to give, in a nonstereospecific reaction, the 1,1-dialkynylcyclopropane derivatives *35a, b*, Eq. (11) [24].



(11)

2.5 From Ethynyl Vinyl Oxiranes

Upon heating to 300–350 °C the ethynyl vinyl oxiranes *36*, obtained by condensation of vinylsulfonium ylides with acetylenic carbonyl compounds, underwent a Cope-transposition into the oxacycloheptadiene *37*, followed by a Claisen-type reaction leading to a cis, trans mixture of 2-ethynylcyclopropanecarboxaldehydes *38*, Eq. (12) [25].

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