

Metal Homoenoates from Siloxycyclopropanes

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Table of Contents

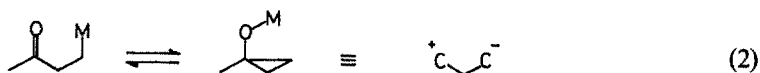
| | |
|--|----|
| 1 Introduction | 3 |
| 2 Preparation of Siloxycyclopropanes | 5 |
| 3 Preparation and Reactions of Isolable Metal Homoenoates | 7 |
| 3.1 Preparation | 7 |
| 3.1.1 Group 4 Metal Homoenoates | 7 |
| 3.1.2 Group 12 Metal Homoenoates | 8 |
| 3.1.3 Group 13 Metal Homoenoates | 9 |
| 3.1.4 Group 14 Metal Homoenoates | 9 |
| 3.1.5 Group 15 Metal Homoenoates | 10 |
| 3.1.6 Group 16 Metal Homoenoates | 11 |
| 3.1.7 Metal Homoenoates of Other Groups | 11 |
| 3.2 Carbon-Carbon Bond Forming Reactions of Metal Homoenoates | 12 |
| 3.2.1 Cyclopropane Formation | 12 |
| 3.2.2 Elimination | 13 |
| 3.2.3 Carbonylation | 14 |
| 3.2.4 Carbonyl Addition | 15 |
| 3.2.5 Conjugate Addition | 18 |
| 3.2.6 Substitution Reaction | 20 |
| 3.2.7 Acylation | 23 |
| 4 Other Routes to Reactive Metal Homoenoates | 23 |
| 4.1 Anionically Protected Lithium Homoenoate | 23 |
| 4.2 From 3-Stannyl to 3-Titanio Propionate | 24 |
| 4.3 From 3-Stannyl to 3-Palladio Oxime | 24 |
| 4.4 From 3-Iodo Esters to Zinc Propionate | 25 |

| | |
|--|----|
| 5 Reactions of Transient Homoenoates Generated from Siloxycyclopropanes | 25 |
| 5.1 Iron (III) Homoenoate | 25 |
| 5.2 Copper (II) Homoenoate | 26 |
| 5.3 Silver Homoenoate | 28 |
| 5.4 Palladium Homoenoate | 28 |
| 5.5 Zinc Homoenoate | 30 |
| 5.6 Lead (IV) Homoenoate | 31 |
| 6 Mechanism of Cyclopropane Ring Cleavage | 31 |
| 7 Homoenoates in Natural Product Synthesis | 34 |
| 7.1 Steroidal Side Chains: Depresosterol and 24-epi-Depresosterol . . . | 35 |
| 7.2 (\pm)-Cortisone | 36 |
| 7.3 (\pm)-Muscone | 37 |
| 7.4 (\pm)-Sabinene | 37 |
| 8 References | 38 |

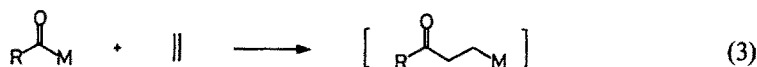
The potential of metal homoenoates as multifunctional reagents in organic synthesis has become recognized in the last decade. Ring opening of siloxycyclopropanes by Lewis acidic metals currently provides the best route to the metal homoenoates, which are either isolable as a stable complex or exist only as a transient organometallic species. This review summarizes, for the first time, the research activities of metal homoenoate chemistry. Other synthetically useful routes to metal homoenoates are also described.

1 Introduction

Although the chemistry of metal enolate/ α -metallo ketone tautomeric pairs Eq. (1) has attracted the interest of chemists for a long period, it still represents an important subject of organic chemistry. Recent vigorous activities in achieving stereocontrol in the aldol reaction, for instance, resulted in further refinement of enolate chemistry. Unlike enolates, the homo-enolate tautomeric pair Eq. (2) [1] in which the carbonyl group and the β -anionic center are homoconjugated, has eluded detailed investigation, in particular, that of synthetic applications [2].



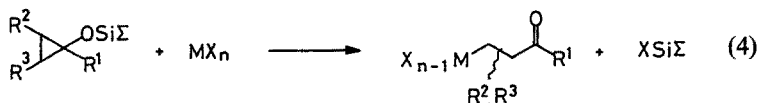
Like that of an enolate, the value of a homo-enolate stems from its amphoteric nature (Cf. Eqs. 1, 2). In addition, the homo-enolate serves as an archetypal synthon in the concept of Umpolung [3], acting as a nucleophilic, inverse-polarity Michael acceptor. Despite such conceptual importance, practical problems set great restrictions on the actual application of homo-enolate chemistry in organic synthesis. First, unlike the enolate anion, the homo-enolate anion cannot be stoichiometrically generated by deprotonation of a carbonyl compound, since the pK_a value of the β -hydrogen is only very slightly lowered [2]. An additional problem is created by an intrinsic property of reactive homo-enolates; namely sodium or lithium homo-enolates spontaneously cyclize to the cyclopropanolate tautomer [2]. This alkoxide tautomer has never reacted as a carbon-nucleophile toward standard electrophiles (except a proton). Therefore, in the subsequent paragraphs, the word homo-enolate refers specifically to the carbanionic form of the homo-enolate tautomeric pair Eq. (2). Transition metal homo-enolates have been postulated in the reactions of acyl transition metal complexes with olefins, which is a common process in reactions in a carbon monoxide atmosphere Eq. (3) [4]. However, without suitable precautions to stabilize the complex [5], these transition metal homo-enolates undergo further reactions.



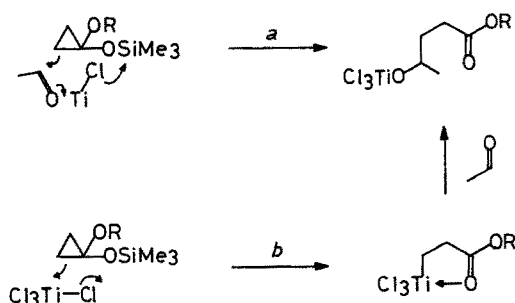
Nonetheless, "homo-enolates" have been much talked about as a species useful for carbon-carbon chain extension, and a number of "homo-enolate equivalents" have been prepared and used for organic synthesis. Reviews on these species have been published [6].

The last few years have seen the development of an entirely new methodology in which the metal homo-enolate is prepared by ring opening of siloxycyclopropanes with metal halides Eq. (4). In these reactions, a very subtle balance of

kinetic and thermodynamic factors allows certain metal halides to form reactive metal homoenolates which do not close back to the three-membered ring. Although the reaction in Eq. (4) tolerates a broad spectrum of structural variation with respect to the substituents, the nature of the substituent on the ring, particularly that at C-1, has a great influence on the chemistry following the ring cleavage. 1-Alkoxy substituents (R^1) exert particularly great effects, allowing the preparation of a variety of ester homoenolates. Cyclopropanes with $R^1 =$ alkyl or aryl thus far remain less viable as precursors to the corresponding homoenolates.



The chemistry of cyclopropanol [7] has long been studied in the context of electrophilic reactions, and these investigations have resulted in the preparation of some 3-mercurio ketones. As such mercury compounds are quite unreactive, they have failed to attract great interest in homoenolate chemistry. Only recent studies to exploit siloxycyclopropanes as precursors to homoenolates have led to the use of 3-mercurio ketones for the transition metal-catalyzed formation of new carbon-carbon bonds [8] (vide infra).



In 1977, an article from the authors' laboratories [9] reported an TiCl_4 -mediated coupling reaction of 1-alkoxy-1-siloxy-cyclopropane with aldehydes (Scheme 1), in which the intermediate formation of a titanium homoenolate (path b) was postulated instead of a then-more-likely Friedel-Crafts-like mechanism (path a). This finding some years later led to the isolation of the first stable metal homoenolate [10] that exhibits considerable nucleophilic reactivity toward (external) electrophiles. Although the metal-carbon bond in this titanium complex is essentially covalent, such titanium species underwent ready nucleophilic addition onto carbonyl compounds to give 4-hydroxy esters in good yield. Since then a number of characterizable metal homoenolates have been prepared from siloxycyclopropanes [11]. The repertoire of metal homoenolate reactions now covers most of the standard reaction types ranging from simple

elimination to substitution reactions. Homoenoates are now a reality in organic synthesis rather than a presumed intermediate of exotic reactivity. The purpose of this review is to summarize the current stage of development of the siloxycyclopropane route to metal homoenoates and convey information to chemists engaged in organic synthesis as well as organometallic chemistry. A few other recent routes to metal homoenoates are also reviewed briefly.

2 Preparation of Siloxycyclopropanes

In 1972 and 1973, four laboratories [12–15] reported the Simmons-Smith cyclopropanation of enol silyl ethers as a very flexible route to siloxycyclopropanes, Eq. (5). Reagents prepared either from a zinc/copper couple [13–15] or a zinc/silver couple [12] have been successfully used for the cyclopropanation of enol silyl ethers from ketones (Table 1). Regioselectivity is noted with polyolefinic substrates, the electron-rich enol silyl ether moiety being attacked preferentially. The reaction is stereospecific with retention of the double bond configuration in the starting material. Prolonged heating of the reaction mixture results in a Zn(II)-catalyzed rearrangement of siloxycyclopropanes to allylic ethers. Termination of the cyclopropanation by addition of pyridine, aqueous NH_4Cl [15], or gaseous ammonia [16] prevents side reactions which may otherwise occur during workup owing to the Zn(II) residues. Table I shows some representative types of compounds prepared by this carbenoid route.

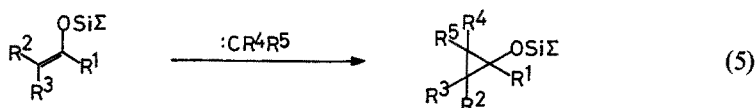
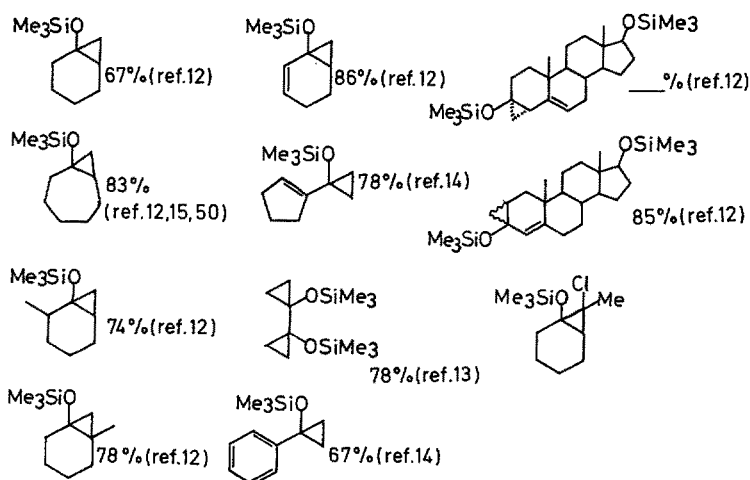
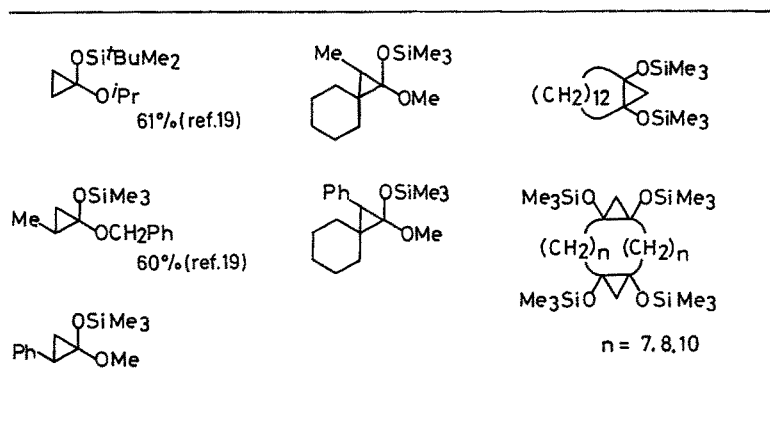


Table 1. Siloxycyclopropanes prepared by the Simmons-Smith reaction

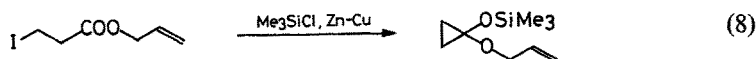
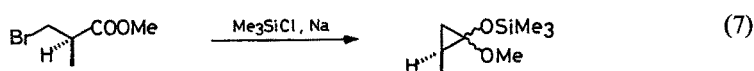
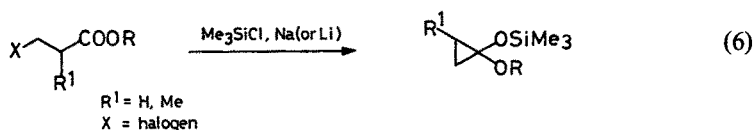


The carbenoid from $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$ [17], particularly when generated in the presence of oxygen [18], is more reactive than the conventional Simmons-Smith reagents. The milder conditions required are suitable for the preparation of 1-[16, 19] or 2-alkoxy-1-siloxycyclopropanes [20], which are generally more sensitive than the parent alkyl substituted siloxycyclopropanes (Table 2). Cyclopropanation of silyl ketene acetals is not completely stereospecific, since isomerization of the double bond in the starting material competes with the cyclopropanation [19].

Table 2. Alkoxy siloxy cyclopropanes prepared by $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$.



Acyloin-type reactions of esters provide the simplest route to 1-siloxy-1-alkoxycyclopropane [21, 22] Eq. (6). The reaction of commercial 3-halopropionate with sodium (or lithium) in refluxing ether in the presence of Me_3SiCl can easily be carried out on a one mole scale [21]. Cyclization of optically pure methyl 3-bromo-2-methylpropionate [23], available in both *R* and *S* form, gives a cyclopropane, which is enantiomerically pure at C-2, yet is a 1:1 diastereomeric mixture with respect to its relative configuration at C-1 Eq. (7). Reductive silylation of allyl 3-iodopropionate with zinc/copper couple provides a milder alternative to the alkali metal reduction [24] Eq. (8).



3 Preparation and Reactions of Isolable Metal Homoenoates

The recent surge of interests in metal homoenoate chemistry has been stimulated by the recognition that the siloxycyclopropane route can afford novel reactive homoenoate species that are stable enough for isolation, purification, and characterization. The stability of such homoenoates crucially depends on the subtle balance of nucleophilic and electrophilic reactivity of the two reactive sites in the molecule. Naturally, homoenoates with metal-carbon bonds that are too stable do not serve as nucleophiles in organic synthesis.

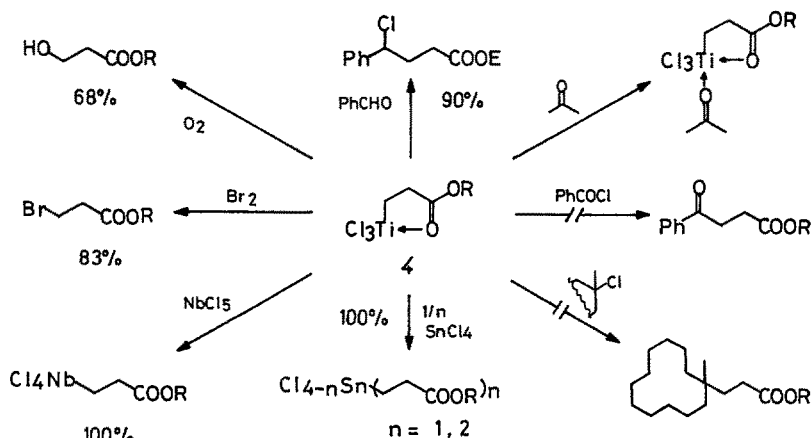
3.1 Preparation

3.1.1 Group 4 Metal Homoenoates

An exothermic reaction between cyclopropane **1** and TiCl_4 in methylene chloride produces a wine-red solution of a mixture of titanium homoenoate **2** and chlorotrimethylsilane [10, 19]. When the reaction is performed in hexane, the titanium species precipitates in the form of fine violet needles (approx 90% isolated yield, Eq. (9)).



This complex, while sensitive to oxygen and moisture, is stable for extended periods either neat or in solution. Its carbonyl stretching band (approx. 1610 cm^{-1}) in the IR spectrum in dilute solution clearly indicates a chelate structure, which endows the carbon-titanium bond of this complex with very high stability, as compared with that of simple alkyltrichlorotitaniums [25].



Scheme 2

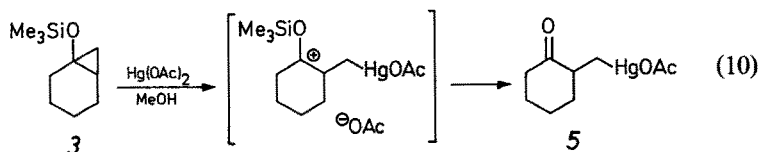
The chemical reactivities of such titanium homoenolates are similar to those of ordinary titanium alkyls (Scheme 2). Oxidation of the metal-carbon bond with bromine or oxygen occurs readily. Transmetalations with other metal halides such as SnCl_4 , SbCl_5 , TeCl_4 , and NbCl_5 proceed cleanly. Reaction with benzaldehyde gives a 4-chloroester as the result of carbon-carbon bond formation followed by chlorination [9]. Acetone forms an addition complex. No reaction takes place with acid chloride and *tert*-alkyl chlorides.

The reaction of the cyclopropane **1** with ZrCl_4 gave a complex mixture [11].

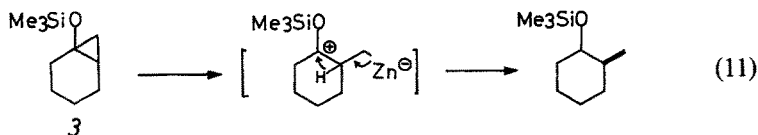
3.1.2 Group 12 Metal Homo-enolates

Cyclopropanols react with mercuric salts to give a variety of 3-mercurio ketones, and the chemistry of this ring cleavage has been thoroughly studied from the mechanistic viewpoint [7].

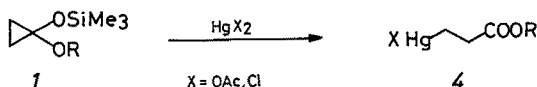
Similarly, siloxycyclopropanes (e.g., **3**) react smoothly with mercuric acetate in methanol at 20 °C to give 3-mercurio ketones (e.g., **4**) [8]. The attack of the metal occurs in such a way that the less alkyl-substituted bond is cleaved. Thus, starting from the enol silyl ether, the overall sequence represents α -mercurio-methylation of the parent ketone. The reaction is likely to proceed via an ionic intermediate Eq. (10).



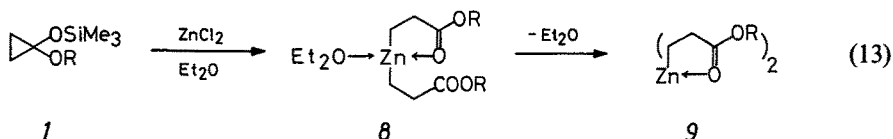
Isomerization of siloxycyclopropane **3** to the allylic silyl ether in the presence of ZnI_2 has close mechanistic similarity to the homo-enolate formation, Eq. (11) [26]. The initial zwitterionic intermediate after ring cleavage undergoes a hydride shift rather than elimination of the silyl group.



1-Alkoxy-1-siloxycyclopropanes **1** are also cleaved readily by HgCl_2 , $\text{Hg}(\text{OAc})_2$, or $\text{Hg}(\text{OCOCF}_3)_2$ to give monoalkylated mercuriaer **5** in high yield Eq. (12) [11]. Further alkylation of **5** was not observed. The methyl-substituted cyclopropane **6** produces 3-mercurio-2-methylpropionate as a single product, while the phenyl-substituted **7** gives a mixture of 2- and 3-phenylesters [27]. CdCl_2 reacts slowly in CDCl_3 under ultrasound irradiation at room temperature to give the cadmium homo-enolate [11].

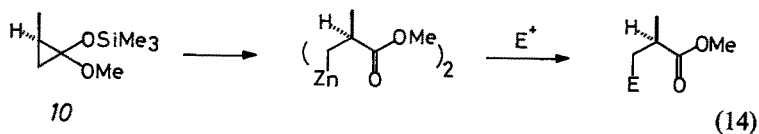


ZnCl₂ cleanly reacts with cyclopropane **1** in ether within a few hours at room temperature to give the zinc homoenoate etherate **8** in high yield Eq. (13) [11, 28]. Removal of the solvent gives the ether-free complex **9**, which can also be generated albeit, in lower yield, in a halomethane solvent. The zinc homoenoate, though sensitive to oxygen and water, is thermally very stable. The ring cleavage reaction is in fact an equilibrium, which in ether favors the homoenoate formation ($K = \text{approx } 30$) [29].



Methylcyclopropane **6** reacts selectively (>98%) with ZnCl₂ at the less hindered site to give the homoenoate of 2-methylpropionate, whereas phenyl substituted analogue **7** is cleaved selectively (>98%) at the more substituted site [27]. The latter homoenoate however suffers in situ protonation under the reaction conditions and could not be isolated.

The optically active cyclopropane **10** gave the chiral homoenoate of isobutyrate Eq. (14), an ethereal solution of which is both chemically and configurationally stable for a week at room temperature, and consequently can serve as a useful chiral building block [23].



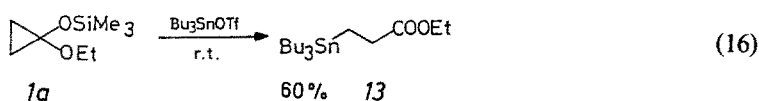
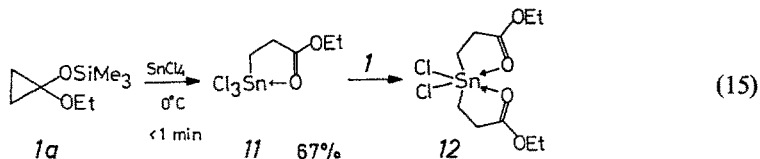
3.1.3 Group 13 Metal Homoenoates

The common Lewis acids in this group, AlCl₃ and BX₃, do not form metal homoenoates in their reaction with siloxycyclopropanes, only GaCl₃ reacts with 1-alkoxy-1-siloxycyclopropanes **1** to give propionate homoenoates [11].

3.1.4 Group 14 Metal Homoenoates

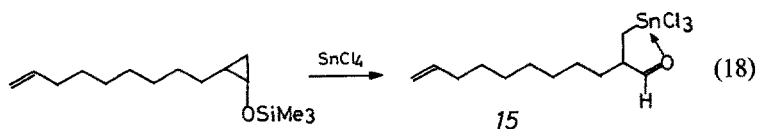
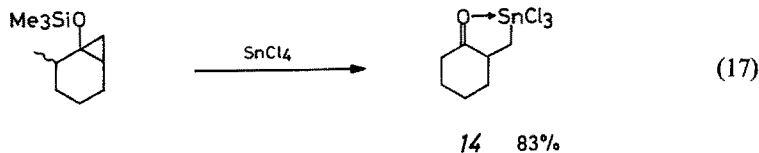
Upon addition of cyclopropane **1** to one equivalent of SnCl₄ in methylene chloride at 0 °C, an exothermic reaction occurs to give 3-stannyl propionate **11** in approx. 70% yield [9, 11]. Addition of a second equiv of the cyclopropane slowly converts **11** to the dialkylated tin compounds, **12** Eq. (15). No further alkylation was observed. Chelate structures of such homoenoates implied by their spectral properties are supported by single crystal X-ray analysis [30].

The cyclopropane is inert to tributyltin chloride, but reacts readily with more highly Lewis acidic tributyltin trifluoromethanesulfonate (triflate) [11]. The 3-stannyl ester **13** showed no sign of internal chelation Eq. (16).



The cyclopropane **1** was inert to GeCl_4 , SiCl_4 , Me_3SiCl , trimethylsilyl triflate, and PbCl_2 [11].

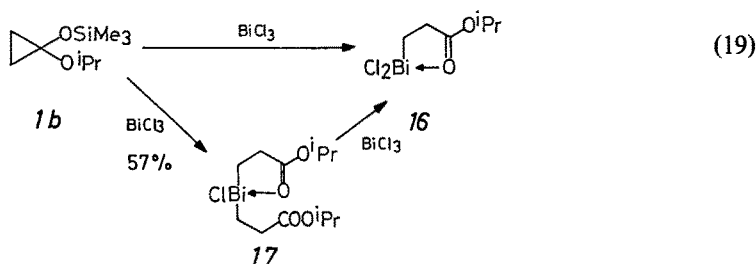
Siloxycyclopropanes corresponding to ketone homoenolates (e.g. **3**) also react smoothly with SnCl_4 at 15°C to give 3-stannyl ketones (e.g. **14**) Eq. (17) [31]. In the same manner, the 3-stannyl aldehyde **15** has been prepared in good yield. Eq. (18).



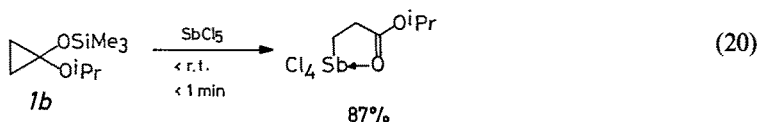
3.1.5 Group 15 Metal Homo-enolates

Treatment of cyclopropane **1** with one equivalent of dry BiCl_3 in methylene chloride results in an exothermic reaction producing monoalkylbismuth derivative **16** in 80% yield Eq. (19) [11]. Addition of another equivalent of the cyclopropane then affords the dialkylated bismuth species **17**, which in turn reacts with BiCl_3 to give the monoalkyl species. IR absorptions due to the carbonyl groups indicate the chelate structures shown. The two propionate moieties in the dialkylated compound **17** give rise to two distinctive carbonyl bands in the IR spectrum,

but are indistinguishable by ^1H NMR, indicating rapid internal ligand exchange at 35°C .

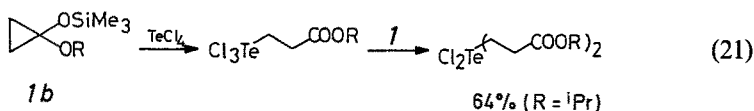


Strongly Lewis acidic SbCl_5 rapidly reacts with one equivalent of the cyclopropane **16** in chloroform to give monoalkylated antimony derivate **18** in 87% yield Eq. (20) [11]. The internal chelation is especially strong, as indicated by the carbonyl band in the IR spectrum at 1600 cm^{-1} . In contrast to the common monoalkyltetrachloroantimony, the chelated homoenoate **18** is stable at room temperature for many hours.



3.1.6 Group 16 Metal Homoenoates

Among the group 16 elements, mostly non-metallic ones like TeCl_4 were examined [11]. The reaction with TeCl_4 proceeds in a stepwise manner giving the monoalkyltellurium and the dialkyl compound in accordance with the stoichiometry of the reagents Eq. (21). As in the case of tin and bismuth, the second alkylation is much slower than the first and the dialkyl species could not be alkylated any further.

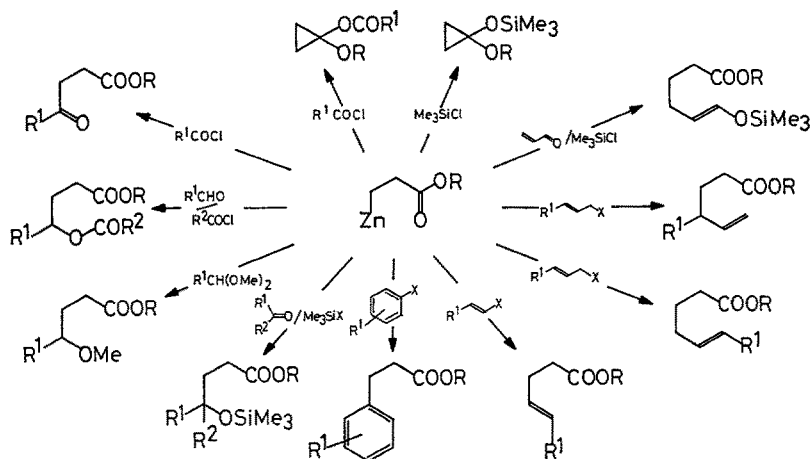


3.1.7 Metal Homoenoates of Other Groups [11]

The cyclopropane **1** reacts with none of the group 1 and 2 metal chlorides. Among early transition metal chlorides, NbCl_4 reacted with **1** in moderate yield to give the same homoenoate obtained by the reaction of equimolar amounts of titanium homoenoate **2** and NbCl_4 (Scheme 2). TaCl_5 , CrCl_3 , MoCl_5 , and WCl_5 did not give any characterizable products.

3.2 Carbon-carbon Bond Forming Reactions of Metal Homoenoates

Various types of carbon-carbon bond forming reactions of metal homoenoates have been reported, some of which are highly synthetically useful. Scheme 3 illustrates reaction types of zinc homoenoates (**8** or **9**). In this section the reactions of stable homoenoates are presented according to the reaction types. Examples, in which siloxycyclopropanes generate transient, unstable homoenoates, are described in Sect. 5.

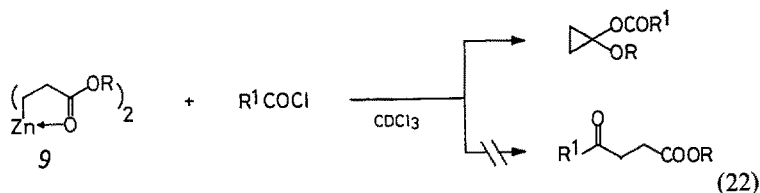


Scheme 3

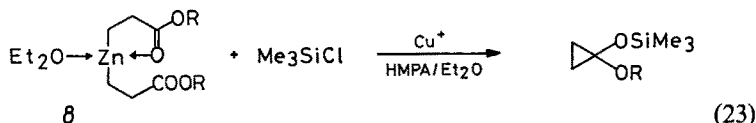
3.2.1 Cyclopropane Formation

Internal nucleophilic cyclization leading to alkoxy cyclopropanes is the most typical reaction of reactive metal homoenoates [1, 2]. The nature of stable homoenoates, however, is such that the anionic carbon C-3 forms a covalent bond with the metal atom and does not show high nucleophilic reactivity.

Among isolable metal homoenoates only zinc homoenoates cyclize to cyclopropanes under suitable conditions. Whereas acylation of zinc alkyls makes a straightforward ketone synthesis [32], that of a zinc homoenoate is more complex. Treatment of a purified zinc homoenoate in CDCl_3 with acid chloride at room temperature gives O-acylation product, instead of the expected 4-keto ester, as the single product (Eq. (22) [33]). The reaction probably proceeds by initial electrophilic attack of acyl cation on the carbonyl oxygen. A C-acylation leading to a 4-keto ester can, however, be accomplished in a polar solvent Eq. (44).

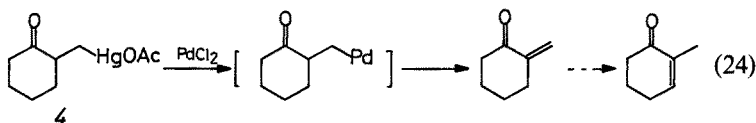


Treatment of zinc homoenoates with Me_3SiCl in a polar solvent also results in cyclopropane formation Eq. (23). This provides a very mild route to the siloxycyclopropanes [24].



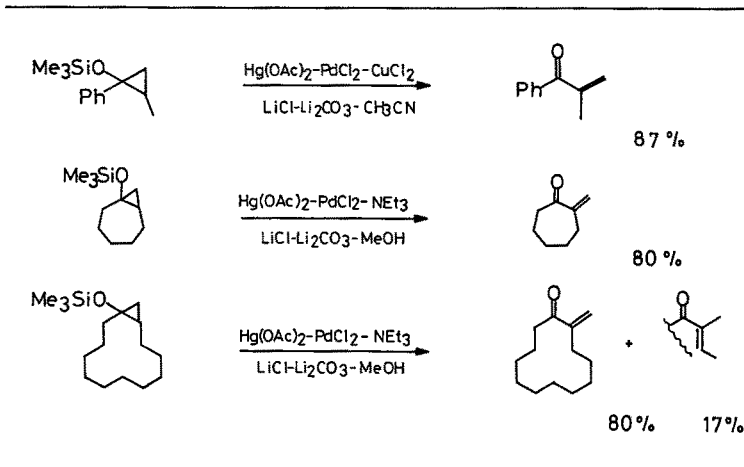
3.2.2 Elimination

Next to the cyclopropane formation, elimination represents the simplest type of a carbon-carbon bond formation in the homoenoates. Transition metal homoenoates readily eliminate a metal hydride unit to give α,β -unsaturated carbonyl compounds. Treatment of a mercurio ketone with palladium (II) chloride results in the formation of the enone presumably via a 3-palladio ketone (Eq. (24), Table 3) [8]. The reaction can be carried out with catalytic amounts of palladium (II) by using CuCl_2 as an oxidant. Isomerization of the initial exo-methylene derivative to the more stable *endo*-olefin can efficiently be retarded by addition of triethylamine to the reaction mixture.



Heating of the 3-trichlorostannyl ketone in DMSO also results in formation of 2-methylcyclohexanone (Eq. (25), Table 4) [31], which is formally the reverse reaction of a hydrostannylation of the enone with HSnCl_3 . This alternative route

Table 3. Synthesis α -methylene ketones via mercurio ketones (Ref. [8])



to α -methylene ketones has an obvious advantage over the above mentioned mercurial-palladium approach, but the overall reaction conditions of the latter are essentially neutral. The utility of the stannyl ketone route is illustrated by the preparation of an unstable α -methylene aldehyde, Eq. (26).

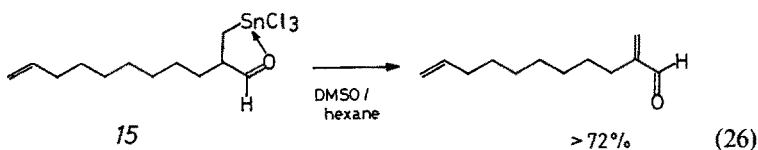
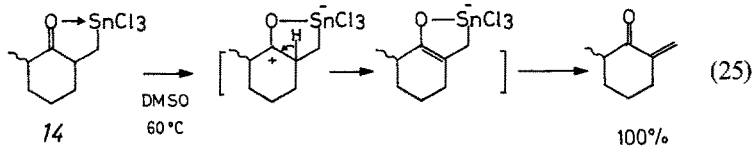
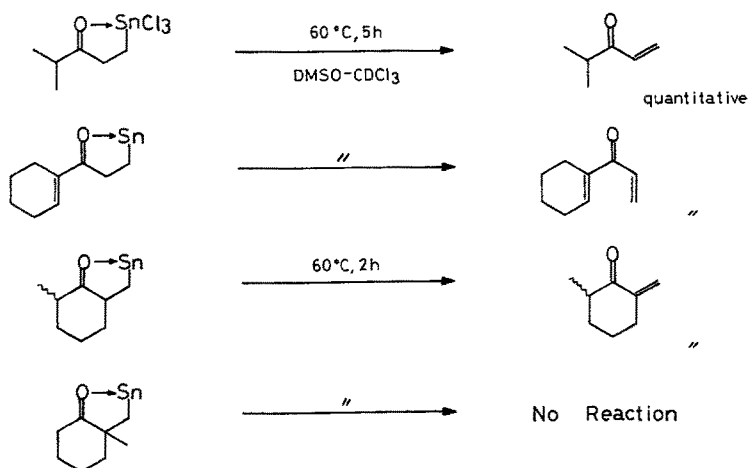
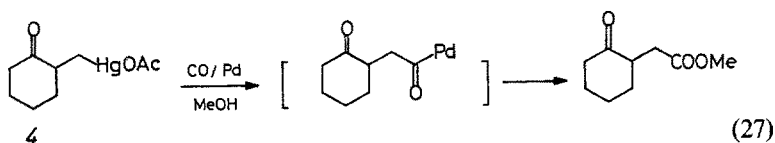


Table 4. Synthesis of α -methylene ketones from stannyl ketones (Rev. [3])

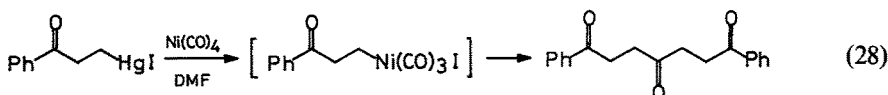


3.2.3 Carbonylation

The treatment of the mercurio ketone with palladium (II) in the presence of carbon monoxide and methanol, Eq. (27) results in the formation of a γ -keto ester with incorporation of one molecule of carbon monoxide [8]. The overall conversion of a siloxycyclopropane to the keto ester may be performed without isolation of the mercurio ketone.



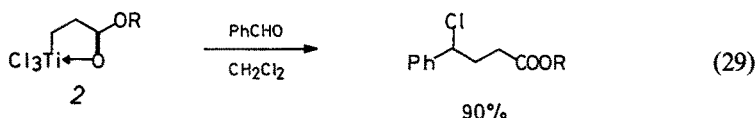
Treatment of the mercurio ketone with $\text{Ni}(\text{CO})_4$ results in a symmetrical coupling with incorporation of one molecule of carbon monoxide to give a triketone presumably via a 3-nickel substituted ketone Eq. (28) [34]. This symmetrical coupling reaction is general for alkyl mercury compounds.



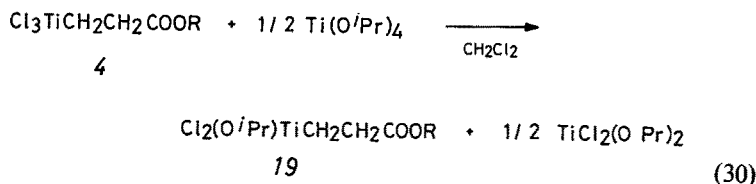
3.2.4 Carbonyl Addition

Addition of a homoenoate onto a carbonyl compound, which may be viewed as a "homo-aldol reaction", poses a significant conceptual problem. The nature of the homoenoate is such that the reaction with the internal carbonyl group is entropically greatly favored over that with the external target carbonyl group. Such a reaction can only compete with the internal electrophile, when it has a great enthalpic advantage. Up till now two types of homoenoates are known to undergo intermolecular addition onto carbonyl compounds, namely titanium [9, 10, 19] and zinc homoenoates of esters [33].

Trichlorotitanium homoenoate **2** smoothly adds to aldehydes at 0 °C [9, 10]. Due to the strongly acidic reaction conditions, however, addition products of aromatic aldehydes tend to undergo further transformations Eq. (29). The trichlorotitanium homoenoate does not react with ketones (Scheme 2).

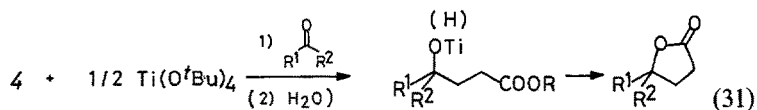


Ligand exchange provided a simple and effective solution to these problems. Addition of 0.5 eq. of $\text{Ti}(\text{O}^i\text{Pr})_4$ to the trichlorotitanium homoenoate produces an alkoxytitanium species **19** which is more reactive than the original homoenoate, Eq. (30). This allows the addition to proceed under nearly neutral conditions. Preparation of 4-hydroxy esters by this method is summarized in Table 5. The structure of **19** has been studied by ^1H NMR spectroscopy [19].



An even more reactive complex which is particularly useful for reactions with ketones is available by ligand exchange with $\text{Ti}(\text{O}^t\text{Bu})_4$, Eq. (31). The

initial adduct tends to cyclize in situ to a γ -lactone, unless the reaction is carried out at low temperatures. The results are summarized in Table 6.



These alkoxytitanium homoenolates show high propensity for equatorial attack in their ir reactions with substituted cyclohexanones (Table 6). The basic trend of their chemical behavior is similar to that of simple titanium alkyls [35]. Chemo-selectivity of the reagent **19** is also noteworthy. The alkoxytitanium homoenolate reacts preferentially with an aldehyde even in the presence of a ketone Eq. (32). A notable difference of rate between the reaction with cyclohexanone and that with 2-methylcyclohexanone was also observed, the latter being far less reactive toward the homoenolate.

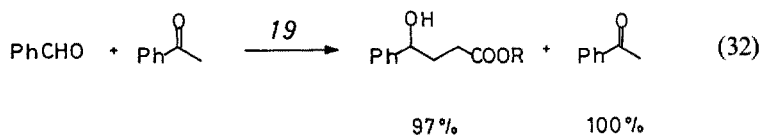
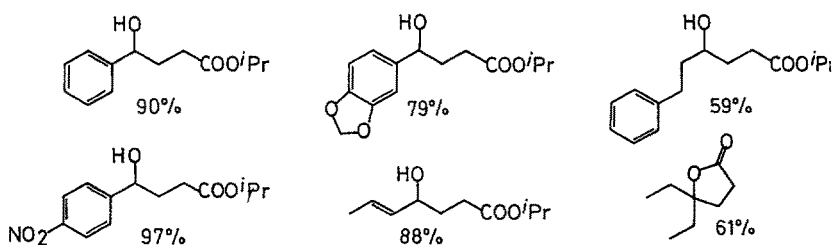
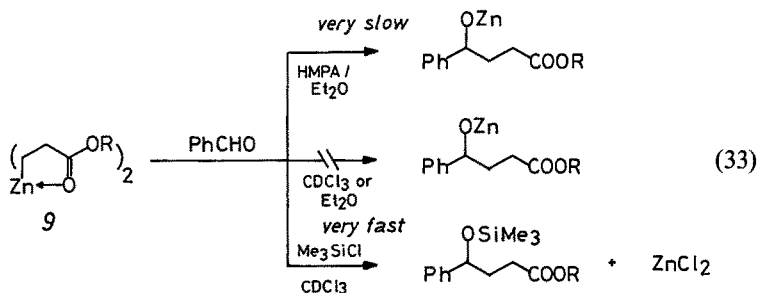
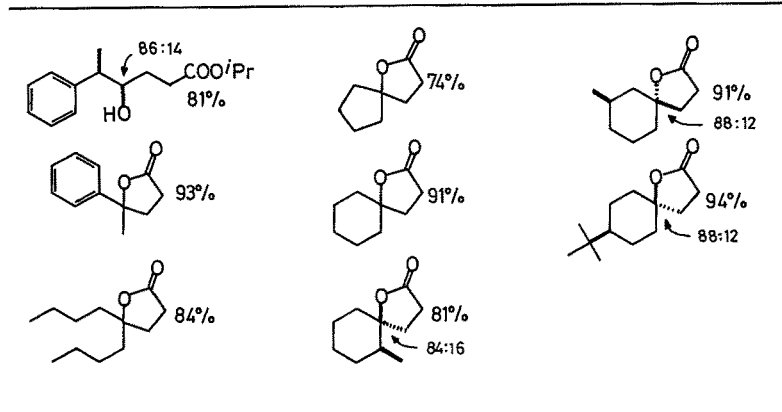


Table 5. 4-Hydroxyesters by Homo-Reformatsky addition of isopropoxytitanium homoenolate (Ref. [19])



In line with the chemistry of dialkylzinc [36], the zinc homoenolate is inert to carbonyl compounds in a variety of solvents, Eq. (33). Slow addition occurs only in an HMPA/THF mixture. When the reaction is conducted in halomethane in the presence of Me_3SiCl , however, a very rapid addition reaction occurs [33]. Control experiments indicate that the acceleration is due to the activation of the carbonyl group by Me_3SiCl . The activating effect of the chlorosilane disappears in ethereal solvents.

Table 6. Lactones by Homo-Reformatsky addition of *tert*-butoxytitanium homoenolate (Ref. [19])

ZnCl_2 is generated in the Me_3SiCl mediated reaction, Eq. (33). Taking advantage of this fact as well as the accelerating effect of the chlorosilane, the cyclopropanes (**1**, **6**, and **7**), and aldehydes have been coupled directly in the presence of ZnCl_2 . ZnI_2 , which in situ produces Me_3SiI , is an even more effective catalyst, only 1/1000 eq. of which suffices to obtain 4-siloxy esters in high yield Eq. (34) [33]. ZnI_2 , but not ZnCl_2 , promotes the addition reaction of 1-*tert*-butyldimethylsiloxy-1-isopropoxycyclopropane **20**. ZnI_2 also catalyzes the reaction of acetophenone or benzaldehyde dimethyl acetal, which fail to react under ZnCl_2 catalysis. Results of such of ZnX_2 catalyzed “homo-Reformatsky” reactions are summarized in Table 7.

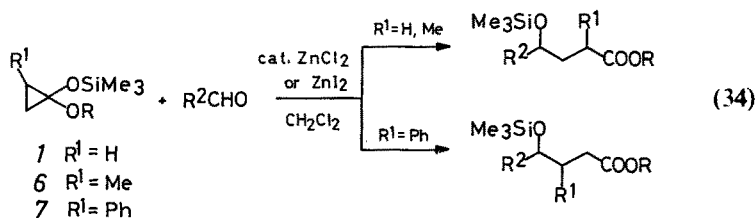
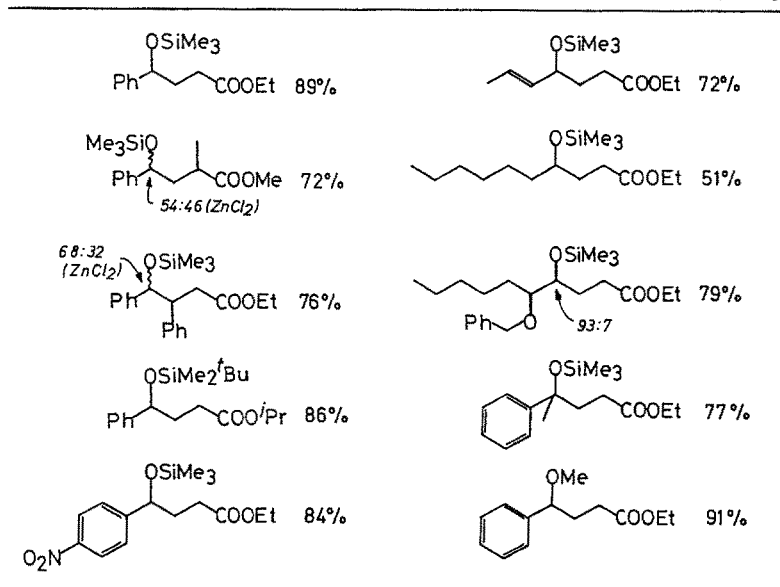
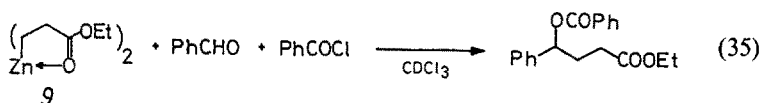


Table 7. 4-Siloxy esters by ZnX_2 -catalyzed Homo-Reformatsky reaction (Ref. [29, 33])

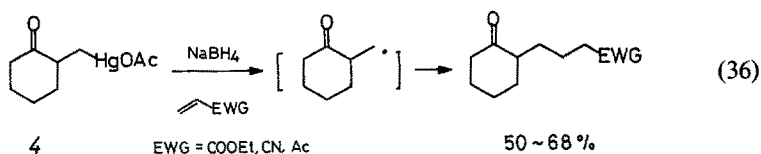
Interestingly, the carbonyl addition of the zinc homoenolate, in the presence of acid chloride, affords 4-acyloxyesters Eq. (35) [27].



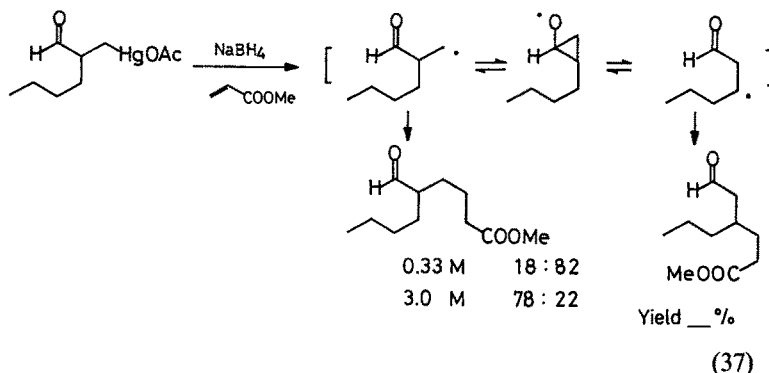
The fact that the above reactions allow isolation of 4-hydroxyesters, which are often unstable and lactonize quickly, is a merit of the homoenolate chemistry. Mesylation of the hydroxy group followed by appropriate operations provides stereocontrolled routes to γ -lactones and cyclopropane carboxylates [19]. Through application of such methodology steroid total synthesis has been achieved (Section 7).

3.2.5 Conjugate Additions

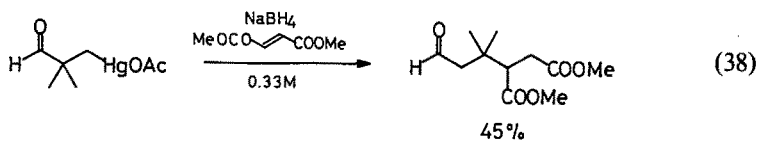
The mercurio ketone **4** upon reduction with NaBH_4 yields a radical which is trapped in situ by reactive acceptors such as vinyl ketones [37]. Treatment of a 1:3 mixture of mercurio ketone **4** and electron deficient terminal alkenes (or fumarate) in CH_2Cl_2 with a concentrated solution of NaBH_4 in water gives conjugate adducts, Eq. (36).



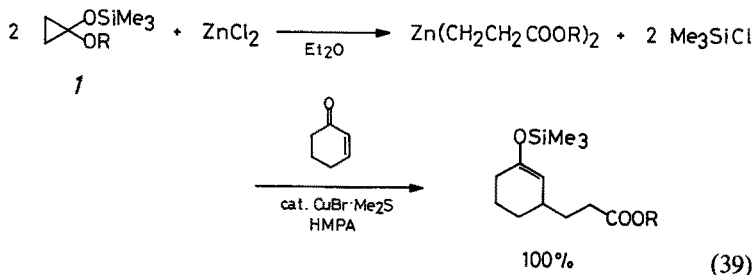
A highly intriguing isomerization of the "homoenolate radical" which probably proceeds via formation of a cyclopropyloxy radical, was noted in the reaction of a mercurio aldehyde [37]. The product ratio should reflect the ratio of internal/external trapping, and in fact the ratio of unrearranged and rearranged product depends on the concentration of the trapping reagent, Eq. (37).



When the stabilities of the two corresponding radicals are grossly different as in the case of gem-dimethyl homoenolate, one may obtain the product originating from the more stable homoenolate radical as the sole product, Eq. (38). A related isomerization reaction, albeit proceeding in the opposite direction, has often been recorded for anionic homoenoates.



A general method for the conjugate addition of ester homoenolate to an α,β -unsaturated ketone has been realized in a Cu(I)-catalyzed reaction of the zinc homoenolate [28]. Thus, successive addition of an enone, copper catalyst, and HMPA to the crude ethereal solution of the zinc homoenolate containing Me_3SiCl results in quantitative formation of the enol silyl ether (Eq. 39, Table 8). Me_3SiCl strongly accelerates the conjugate addition of intermediary organocopper species [38]. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ also enhances the rate, but may give different stereochemical results [39].



The reaction with an acetylenic ketone produced an allenic enol ether (Table 8), which upon hydrolysis gave the corresponding enones as an *E/Z* mixture. Dimethyl acetylenedicarboxylate gave the (*Z*)-olefinic adduct as a major product in accordance with the general behavior of organocopper conjugate addition. A high degree of chemoselectivity has been observed in this conjugate addition.

Table 8. Products of conjugate addition of zinc homoenolate in the presence of Cu(I) and Me₃SiCl (Ref. [28, 29])

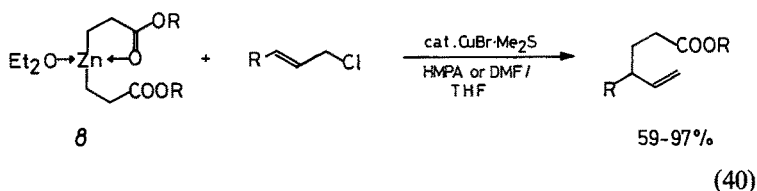
| | | | |
|--|-----|--|-----|
| | 92% | | 95% |
| | 78% | | 1:1 |
| | 91% | | 75% |
| | 75% | | 73% |
| | 75% | | 63% |

3.2.6 Substitution Reactions

Among the characterized metal homoenolates, only zinc homoenolate of alkyl propionate undergoes substitution reactions with electrophiles under suitable conditions. Two types of metal catalysts, copper(I) and metals of the nickel triad (e.g. Pd), have successfully been used to effect allylation, arylation, and vinylation reactions.

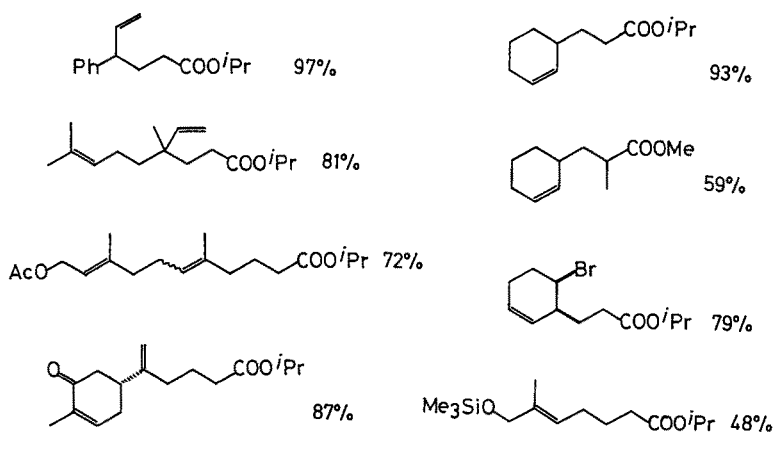
Zinc homoenolate reacts with allylic halides and diene monoepoxides under copper catalysis [29]. Treatment of the zinc homoenolate with a catalytic amount of Cu(II) in a polar solvent (e.g. hexamethylphosphoramide, HMPA, *N,N*-dimethylacetamide, DMA) generates a copper species which undergoes clean S_N2' allylation reactions Eq. (40). Polar solvents not only accelerate the reaction but greatly improve the S_N2' selectivity. A variety of allylating reagents can be employed in this reaction (Table 9). The S_N2'/S_N2 ratio is particularly high (close to 100%) when the allylated carbon bears no substituents. The reaction of

trans-1,4-dibromo-2-cyclohexene gives a single stereoisomer which is presumably the *cis*-isomer arising from an *anti*-attack in the S_N2' reaction.

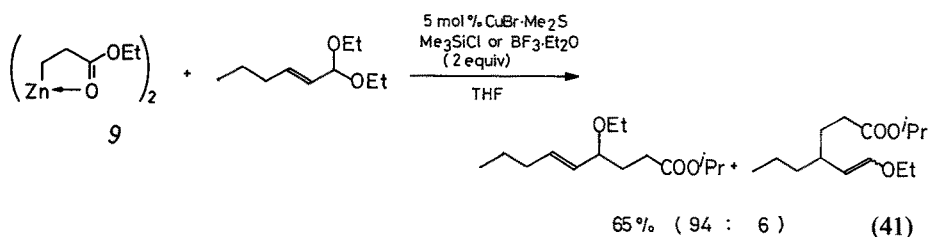


The allylation and the conjugate addition (vide supra) of zinc homoenoate proceed under essentially the same conditions except that the latter requires the presence of Me_3SiCl as well. Due to this subtle difference, selective allyl substitution is possible even with an enone function is present in the same molecule (Table 9).

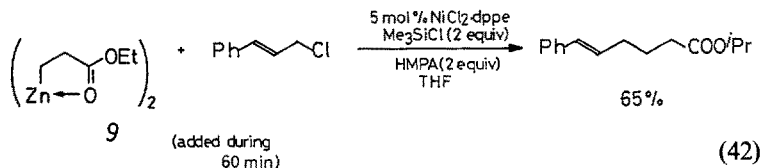
Table 9. Unsaturated esters by S_N2' -allylation of zinc homoenoate of esters (Ref. [29])



Copper catalyzed reaction of the homoenoate **9** with an acetal of an unsaturated aldehyde proceeds in an S_N2 manner, Eq. (41), the net reaction representing a 1,2-addition of the homoenoate. The presence of Me_3SiCl or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is mandatory in this reaction [29].



The nickel catalyzed reaction of **9** with an allyl chloride also proceeds in an S_N2 manner Eq. (42). Nickel dichloride complexed with a bidentate ligand (e.g. 1,2-bis(diphenylphosphino)ethane) effects a highly selective ($>99\%$) S_N2 reaction with cinnamyl chloride [29].



Substitution reactions involving aryl and vinyl halides have been achieved with the aid of palladium catalysts, among which $\text{PdCl}_2(o\text{-Tol}_3\text{P})_2$ with $o\text{-Tol}_3\text{P}$ ligands is the most efficient [40]. A variety of aryl bromides and iodides can serve as the electrophile in this reaction (Table 10). The coupling with vinyl halides occurs stereoselectively. Vinyl trifluoromethanesulfonates (vinyltriflates), readily available from ketones [41], react rapidly with the homoenolate. Mild reaction conditions keep ketone functions intact during the arylation reaction.

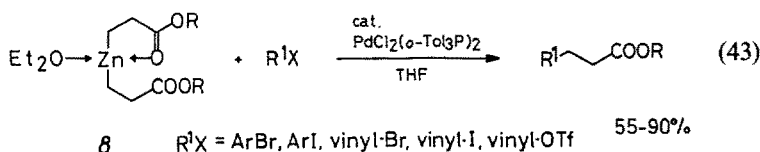
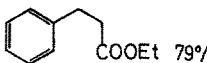
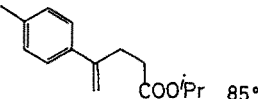
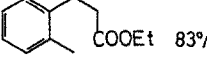
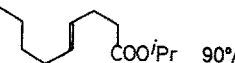
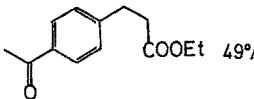
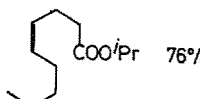
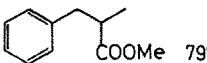
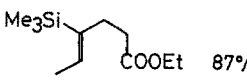
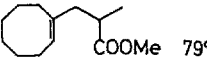
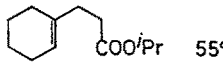
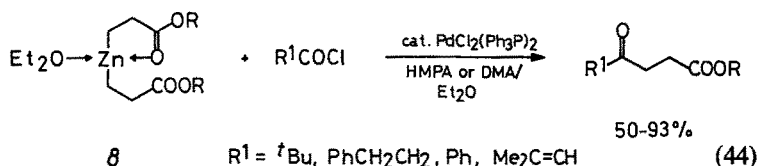


Table 10. Arylated and vinylylated propionates by palladium-catalyzed reaction of zinc homoenolate (Ref. [29, 40])

| | | | |
|---|-----|---|-----|
|  | 79% |  | 85% |
|  | 83% |  | 90% |
|  | 49% |  | 76% |
|  | 79% |  | 87% |
|  | 79% |  | 55% |

3.2.7 Acylation

The reaction of zinc homoenoate **9** with acid chlorides in ethereal solvents containing 2 equiv of HMPA rapidly produces 4-ketoesters in high yield Eq. (44) [33]. A palladium catalyst [40] (or less effectively a copper catalyst) [28] accelerates the reaction. This is in contrast to the cyclopropane formation in a nonpolar solvent see (Eq. 22 above).

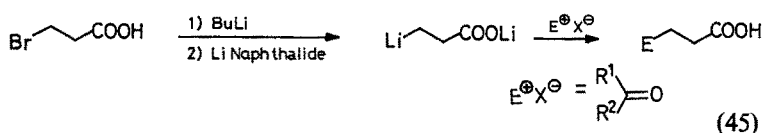


4 Other Routes to Reactive Metal Homoenoates

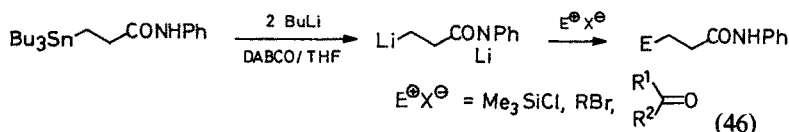
This section presents a summary of some recent reports on the chemistry of reactive metal homoenoates, which are generated by methods other than the siloxycyclopropane ring cleavage.

4.1 Anionically Protected Lithium Homoenoate

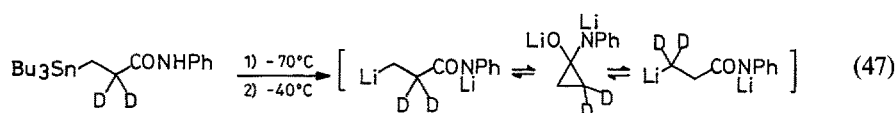
An early effort to generate a 3-lithiated propionic acid derivative and react it with (external) electrophiles was reported in 1978 [42]. Since simple 3-lithioesters failed to undergo the required reaction, the alkyl carboxylate portion was protected by preceding conversion to the carboxylate anion. Treatment of lithium 3-bromopropionate with lithium naphthalide generated the desired dilithiated propionic acid, which gave moderate yields of γ -hydroxy acid addition products with carbonyl compounds, Eq. (45).



Treatment of 3-stannylpropionamide with two equivalents of butyllithium at low temperature (-78°C) generates a similar dianionic homoenoate, which reacts with standard electrophiles Eq. (46) [43]. It is interesting to note that the propionate moiety rather than the butyl groups is selectively cleaved off the tin in the tin-lithium exchange.

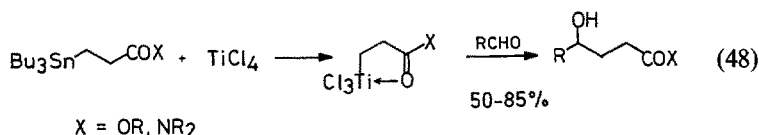


Dianions of the above types may not fall into the category of homoenolate in a strictly formal sense. Nevertheless the amide dianion does show a behavior typical of the homoenolate. Thus, the reaction of the isotopically labeled stannylpropionate results in scrambling of the label probably via a cyclopropane intermediate Eq. (47) [44]. As the result of such an equilibration, isomerization of α -methyl and α -phenyl substituted propionate homoenolates may occur to give the thermodynamically more favorable isomers, respectively.

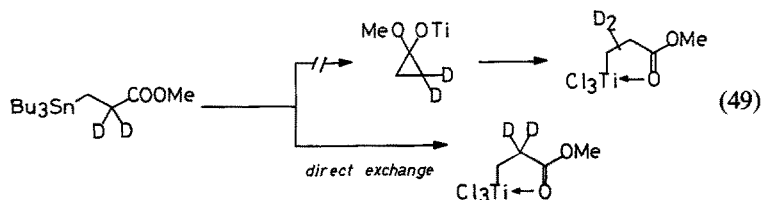


4.2 From 3-Stannyl- to 3-Titaniopropionate

Two groups independently reported the formation of titanium homoenolates by the transmetalation reaction of 3-stannyl-propionate esters with TiCl_4 , Eq. (48) [45, 46]. Amide homoenolates become available along this route [47]. The trichlorotitanium species thus obtained have been shown (^1H NMR) to be similar to that generated along the siloxycyclopropane route and indeed exhibit very similar reactivities. This method does provide a convenient alternative to the siloxycyclopropane route.



Isotopic labelling, Eq. (49), indicated that the transmetalation occurs via direct tin-carbon bond cleavage rather than via intermediate formation of an alkoxy-cyclopropane [45].



4.3 From 3-Stannyl- to 3-Palladioketoxime

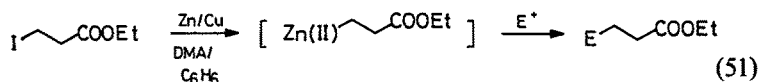
Selective transfer of the homoenolate moiety characterizes the transmetalation from tin to titanium described in the previous section. A very facile transmetalation of the same kind occurs for 3-stannylketoxime, Eq. (50) [48]. Reaction of the (*E*)-3-(tributyltin)ketoxime with dichlorobis(benzonitrile)palladium in CH_2Cl_2 at 0°C for 30 min yields 78% of the transmetalation product. The

facility with which this reaction produced the stable palladium complex, and the high selectivity with which the oxime group carrying alkyl group is cleaved off, are remarkable. The reaction certainly proceeds with prior coordination of the metal to the oxime group, but the precise mechanism of the transmetalation remains unclear.



4.4 From 3-Iodoesters to Alkyl β -Zincpropionate

A very practical route to zinc homo-enolate involves reduction of 3-iodoesters with zinc/copper couple in the presence of a polar solvent, e.g. DMF, DMA [49] Eq. (51). The nature of the species obtained in this approach is not well-defined, but appears to be essentially the same as the one obtained along the siloxycyclopropane route. Acylation, arylation, and vinylation reactions have been reported.



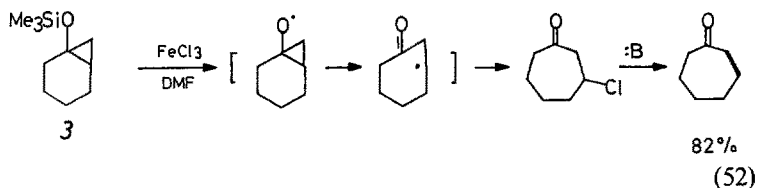
5 Reactions of Transient Homo-enolates Generated from Siloxycyclopropanes

There have been several reports on reactions of siloxycyclopropanes involving transient metal homo-enolates which eluded characterization owing to their instability.

5.1 Iron(III) Homo-enolates

Most ring cleavages of siloxycyclopropanes occur at the less substituted bond next to the siloxy group to give the more stable anionic species (Cf. Eq. 34). Chlorination with FeCl_3 in DMF provides a unique way to cleave the ring in the opposite direction, Eq. (52) [50]. Treatment of 1-siloxybicyclo[n.1.0]alkanes with FeCl_3 in DMF produces 3-chloro-ketones with cleavage of the internal bridging bond. Such regiochemistry has not been observed for ionic cleavages of siloxycyclopropanes, and must be due to the radical character of the intermediate formed in the reaction. It is not even clear whether a metal homo-enolate is involved in this reaction at all, and the reaction is believed to proceed with initial cyclopropoxy radical formation. The regiochemistry is consistent with the results obtained for reactions of discrete "homo-enolate radicals" (vide supra) for

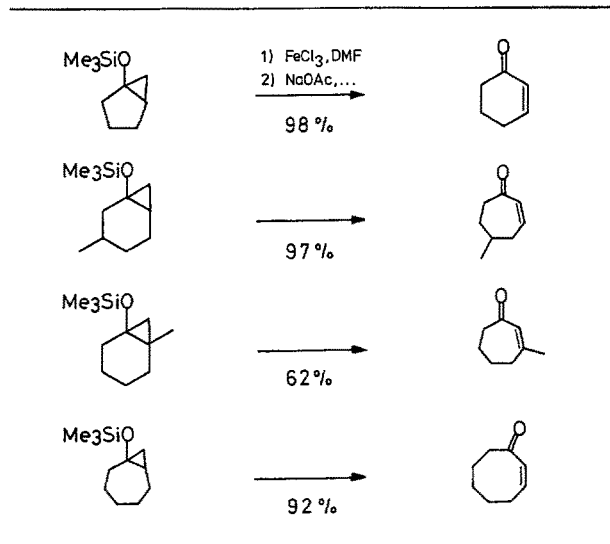
which thermodynamically more stable secondary radicals result by very rapid equilibration via cyclopropano radicals.



The overall sequence of cyclopropanation of a cyclic silyl enol ether, chlorination with FeCl_3 , and dehydrochlorination represents a very reliable one-carbon ring expansion method for cycloalkanone (Table 11).

Application of this ring enlargement and oxidation procedure to 2-alkoxy-1-siloxycyclopropanes incorporated in a large ring provides macrocyclic diketones which act as potent chelating agents for metal cations [50].

Table 11. Synthesis of 2-cycloalkanones by FeCl_3 -oxidation (Ref. [50])



5.2 Copper(II) Homo-enolates

Reaction between a siloxycyclopropane and $\text{Cu}(\text{BF}_3)_2$ in ether gives a product due to symmetrical coupling of two homo-enolate moieties (Eq. 53, Table 12) [51]. This is particularly noteworthy as a simple route to 1,6-ketones superior to classical approaches such as the Kolbe electrolysis [52]. Several lines of evidence suggest the intermediacy of $\text{Cu}(\text{II})$ homo-enolates. AgBF_3 and CuF_2 effect the same reaction albeit with lower yields. The reactions with cupric halides give

complex mixtures containing these homocoupled product and halogenated compounds [53].

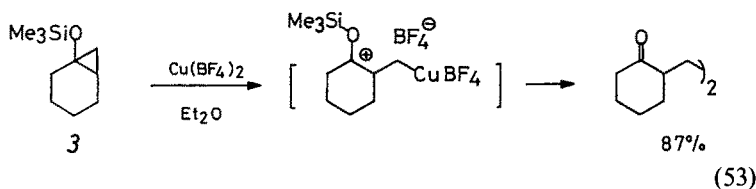
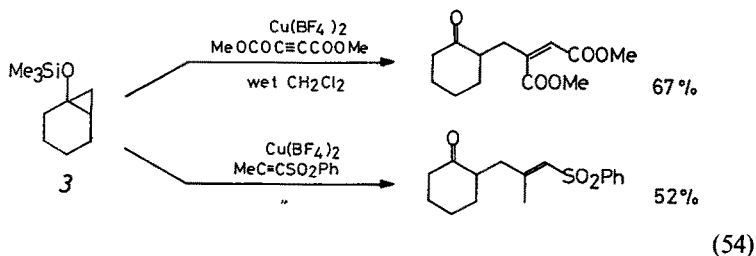


Table 12. 1,6-Diketones by homocoupling of siloxycyclopropanes in the presence of AgBF_4 or $\text{Cu}(\text{BF}_4)_2$ (Ref. [5])

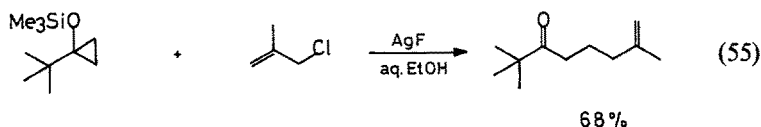
| | | | |
|--|-----|--|-----|
| | 78% | | 74% |
| | 81% | | 69% |
| | 68% | | 70% |
| | 87% | | 63% |

When the siloxycyclopropane and $\text{Cu}(\text{II})$ are allowed to react in the presence of dimethyl acetylenedicarboxylate or propynyl phenyl sulfone in wet CH_2Cl_2 , conjugate adducts are obtained in good yields Eq. (54) [54]. The same reaction conducted in CH_2Cl_2 containing D_2O gives the stereoselectively α -deuterated products, indicating the intermediacy of vinylcopper intermediates. Under strictly dry conditions homocoupling products are produced from these vinyl copper species.



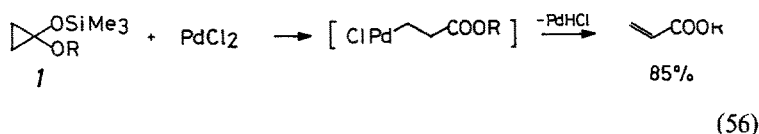
5.3 Silver Homo-enolates

A silocyclopropane reacts with an allylic chloride in the presence of AgF in aqueous ethanol to give an allylated product Eq. (55) [55]. In this case, the structure of the product does not reflect the regiochemistry of the nucleophilic attack on the starting allyl halide.

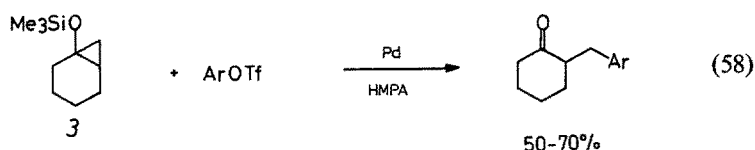
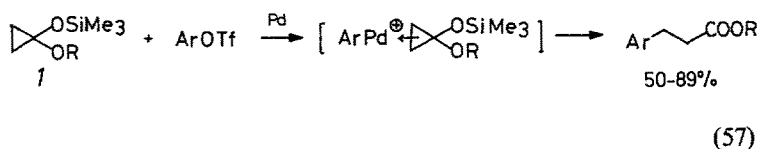


5.4 Palladium Homo-enolates

Palladium(II) chloride or its phosphine complex smoothly reacts with siloxycyclopropane **1** to produce acrylic ester and a palladium mirror. This reaction probably involves the formation of a chloropalladium homo-enolate followed by elimination of palladium hydride (Eq. (56) [56].

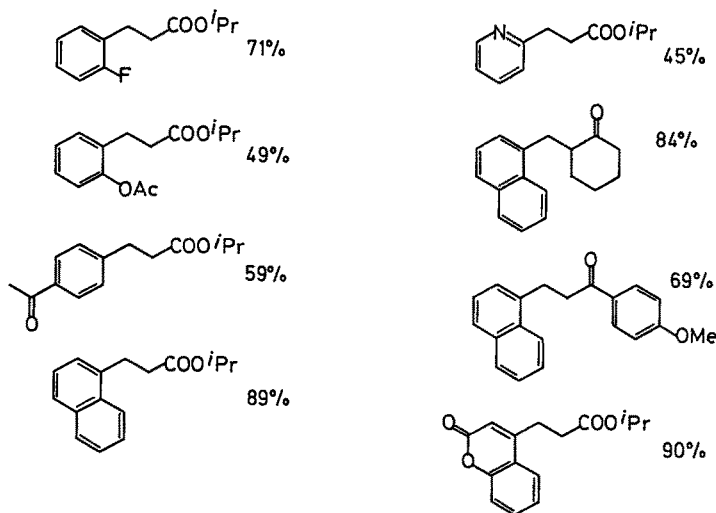


Nevertheless, the palladium homo-enolate can serve as a useful reaction intermediate. If certain requirements are met, such an organopalladium homo-enolate can be generated directly from the siloxycyclopropane, and then allowed to reductively eliminate to give an organylated homo-enolate. Heating a mixture of siloxycyclopropane **1** and an aryl triflate in benzene in the presence of a palladium catalyst effects such a transformation to give 3-arylpropionate Eq. (57) [57]. A siloxycyclopropane corresponding to a ketone homo-enolate (e.g. **3**) also undergoes reactions with aryl triflates, now in HMPA, to give arylated products Eq. (58) [57]. These results are summarized in Table 13.



The arylation reaction is not applicable to aryl bromides and iodides. Another line of experimental evidence also indicates that an arylpalladium *halide* complex, instead of an arylpalladium *triflate* complex, is not electrophilic (Lewis acidic) enough to cleave the cyclopropane ring.

Table 13. Arylated esters and ketones by direct arylation of siloxycyclopropanes (Ref. [57])



Reaction of siloxycyclopropane **1** with acid chlorides in the presence of a palladium catalyst also proceeds cleanly to give 4-ketoesters in high yields (Eq. 59, Table 14) [57]. Chloroform is a suitable solvent. Kinetic studies have revealed that the interaction between **1** and an acylpalladium chloride complex is the rate limiting step.

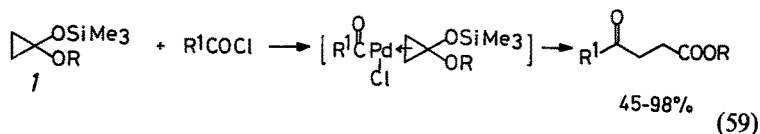
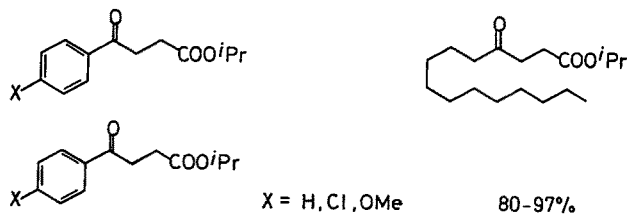
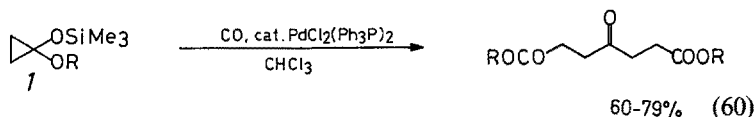


Table 14. Keto esters by direct palladium catalyzed acylation of siloxycyclopropanes (Ref. [56])



If the cyclopropane is heated in CHCl_3 in the presence of a catalytic amount of palladium-phosphine complex under CO atmosphere, a symmetrical coupling product incorporating one molecule of CO forms in high yield, Eq. (60) [57].



5.5 Zinc Homoenoates

In view of the remarkable stability of metal homoenoates of esters, the existence of homoenoate species containing a 3-halo substituent, i.e. zinc carbenoid moiety connected to an ester group, appeared to be possible. Indeed, when a silyl ketene acetal is treated with a carbenoid generated from CHBr_3 and Et_2Zn , two types of highly intriguing reactions ensue [58]. With a purely aliphatic substrate, Eq. (61), an alkyl cyclopropylcarboxylate due to intramolecular β -CH-insertion of the intermediate zinc carbenoid formed. When the substrate contained an olefinic double bond in the vicinity of the carbenoid function, Eq. (62), in particular an intermediate derived from an α,β -unsaturated ester, internal cyclopropanation occurred to give bicyclic or tricyclic product (Table 15).

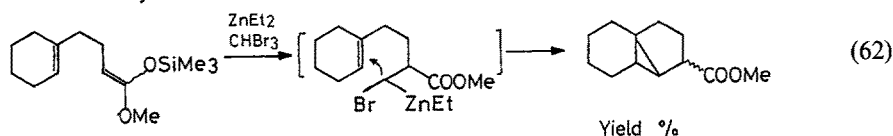
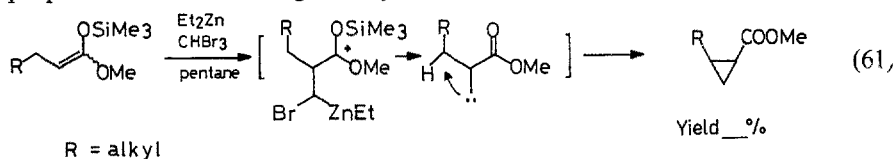
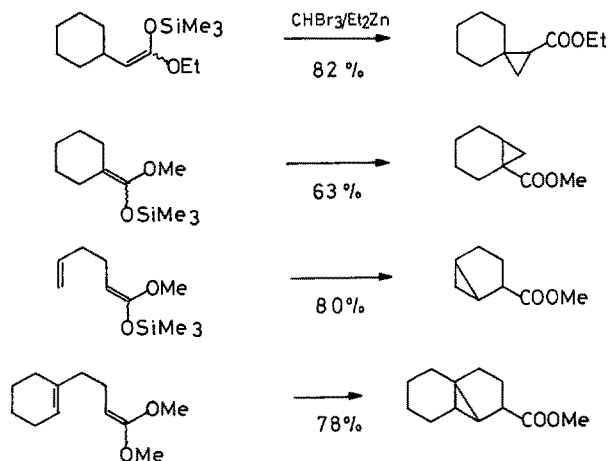
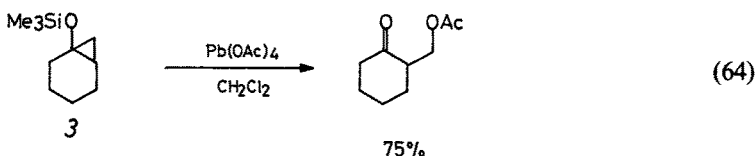


Table 15. Alkyl cyclopropanecarboxylates by carbene addition onto ketene acetals (Ref. [58])

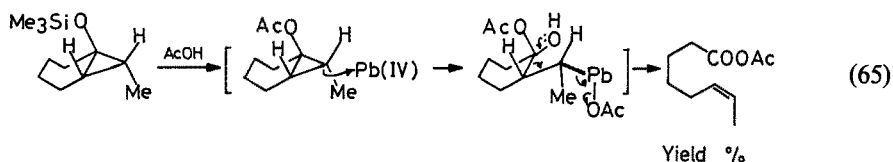


5.6 Lead(IV) Homoenoate

In contrast to the other examples in this review, the reaction of 1-siloxycyclo[n.1.0]alkenes with $\text{Pb}(\text{OAc})_4$ in acetic acid somewhat surprisingly leads to cleavage of two bonds to yield alkenoic acids, Eq. (63) [59]. The reaction involves the fission of both bonds connected to the carbon bearing the siloxy group. This reaction is considered to involve primary in situ conversion of the siloxycyclopropane to the corresponding cyclopropanol. Indeed, the siloxycyclopropane **3** reacts with $\text{Pb}(\text{OAc})_4$ in dichloromethane to give the β -acetoxyketone, Eq. (64), while the corresponding cyclopropanol undergoes the same fragmentation as with $\text{Pb}(\text{OAc})_4$ in acetic acid.



The observed stereoselectivity of this ring cleavage reaction [60] favors a mechanism, Eq. (65), in which formation of a lead(IV) homoenoate by cleavage of the external bond with inversion of configuration is followed by rapid cleavage of the second bond.

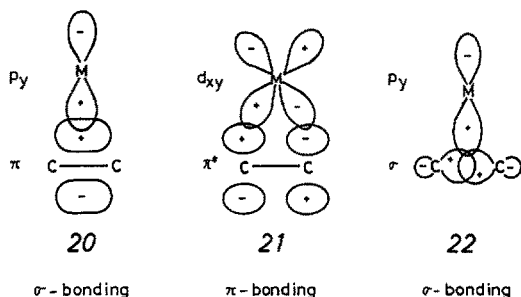


6 Mechanism of Cyclopropane Ring Cleavage

Except for some of the above reactions which proceed via radical intermediates, many of the ring cleavage reactions are likely to involve initial interaction of the metal and the cyclopropanering. The nature of this interaction between 1-siloxycyclopropane **1** with metals has been investigated by the authors in some detail, and the results are summarized below.

The Dewar-Chatt-Duncanson model of the binding of an olefin in a transition metal complex involves two types of interactions. Transfer of electron density from the relatively high-lying olefinic π -orbital to the metal (cf. 20) represents a Lewis acid Lewis base interaction (σ -bonding). A metal-olefin π -bond due to interaction

of a filled metal orbital with the π^* -orbital of the olefin (back donation) constitutes another mode of bonding (cf. 21).



Organometallic bonding to σ bonds possessing high p -character, in contrast, is due mainly to the electron donation from the carbon-carbon σ -bond into an empty metal orbital (cf. 22), because the antibonding σ^* -orbital is generally inaccessible for effective back donation from the metal [61]. It follows from such considerations that the donor character of the σ -bond of a cyclopropane derivative will be decisive. In addition, the Lewis acidity of the metal will be more important for the binding with cyclopropane. The summary chart of metals which cleave the alkoxyloxycyclopropane **1** (Table 16) [11] offers an idea for the kind of Lewis acidity needed.

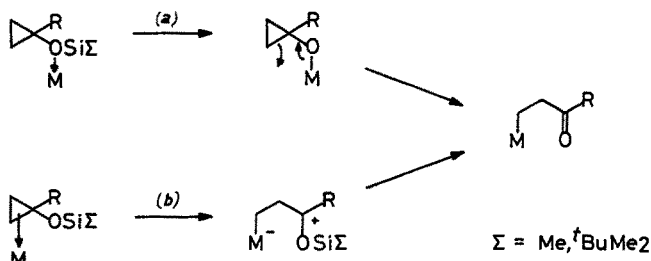
Table 16. List of metals, chlorides of **1** which react with cyclopropane **1** to form metal homoenolate (Ref. [11])^a

| 1 | 2 | 3 | 5 | 12 | 13 | 14 | 15 | 16 |
|---|-----------------|-----------------------------------|-----------------|-----------------|-----------------------------------|------------------------------------|-----------------|-----------------|
| X | X | | | | B ^{III} | | | |
| X | Cu ^I | Ti ^{IV} X ^{III} | | Zn ^I | Al ^{III} S ^{IV} | | | |
| X | X | Zr ^{IV} X ^{III} | Nb ^V | Cd ^I | Co ^{III} Se ^V | Sn ^{IV} Sr ^I | Sb ^V | Te ^V |
| X | X | | Ta ^V | Hg ^I | | Pb ^{II} Bi ^{III} | | |

^a Signs X and / indicate no reaction and formation of no detectable homoenolate, respectively

There are a few points to be addressed in order to understand the mechanism of homoenolate formation. Several lines of experimental evidence for the reaction of 1-alkoxy-1-siloxycyclopropanes have provided insights into the nature of the metal interacting with the siloxycyclopropane.

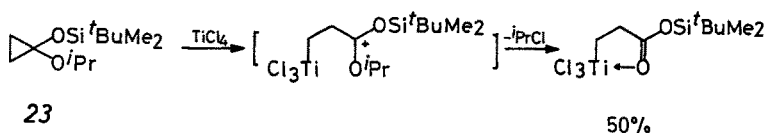
The initial interaction of the metal with the substrate (Scheme 4) may occur either on the siloxy oxygen to form a metal alkoxide (path (a)) or directly on the strained sigma bond to form an intermediate containing an oxygen-stabilized cationic center (path (b)). Molecular orbital considerations indicate that an orbital controlled interaction with a Lewis acid should occur preferentially at the ring carbons, which have the larger HOMO coefficient. Studies of the exchange of a Me₃Si group between Me₃SiOTf and silyl ethers eliminate the possibility of path (a) for a number of metal halides, including ZnCl₂ and SnCl₄ [11].



Scheme 4

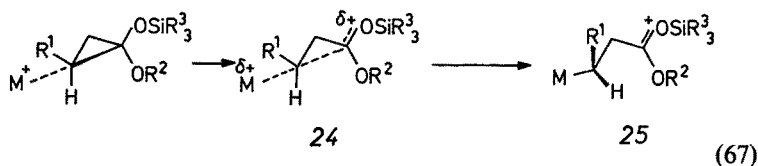
Some experimental data indicate the formation of a cationic species as postulated for path (b) and in turn show that the Si-O bond remains intact in the transition state. Evidence comes from the comparison of the reactivities of 1-trimethylsiloxy- (1) and 1-*tert*-butyldimethylsiloxycyclopropanes (23) in some reactions.

The reaction of 1-isopropoxy-1-trimethylsiloxycyclopropane (1, R = *i*-Pr) with TiCl_4 yields the titanium homoenoate of isopropyl propionate 2 (R = *i*-Pr) and Me_3SiCl (Eq. see 9). That of 23, in contrast, yields a considerable fraction of the homoenoate of silyl propionate as well, Eq. (66) [19]. Apparently, the loss of an isopropyl group from an oxygen-stabilized cationic intermediate competes with that of the silyl group with bulky substituents.

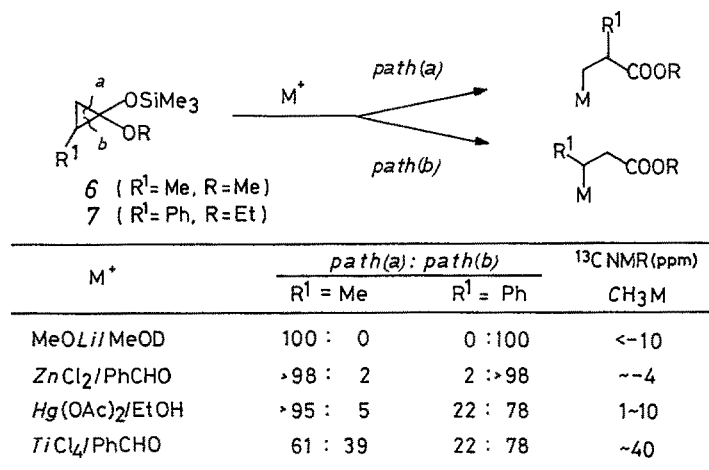


Kinetic analysis of the palladium catalyzed acylation reaction of 1 (R = *i*-Pr) and 23 indicates that the rate does not depend on the bulk of the trialkylsilyl substituent. Since the rate limiting step of this reaction is the interaction of a coordinatively unsaturated acylpalladium chloride with the cyclopropane (Cf. Eq. 59), the observed independence can reasonably be taken as an evidence that the Si-O bond remains intact in the transition state [56]. Semiquantitative data on the cleavage of 1 (R = *i*-Pr) and 23 with ZnCl_2 in ether, Eq. (13), led to the same conclusion [27].

The mechanisms of the ring cleavages which lead to Ti, Zn, and Pd homoenoates are similar to each other as described above in that the oxygen-stabilized cation is involved (path (b) in scheme 4). The fact that the regiochemistry of the ring cleavage strongly depends on the nature of the forming carbon-metal bond (Cf. Eq. 67), however, indicates that they are not identical.



Scheme 5 summarizes the regiochemistry of ring opening of methyl- (**6**) and phenyl-substituted alkoxy-siloxy-cyclopropane (**7**) by LiOMe, ZnCl₂, HgCl₂, and TiCl₄, as well as the ¹³C NMR chemical shifts of the respective metal methyls [27]. The NMR data correlate with the nature of the metal-carbon bond: The more polarized it is, the less positive the chemical shift of the methyl group.



Scheme 5

The regiochemistry with lithium methoxide and zinc chloride clearly reflects the stability of the incipient formal anionic charge on the carbon. Such a trend is less obvious for those metals which form covalent bonds to carbon. Electronic and steric factors compete with each other in the cleavage of the phenylsubstituted alkoxy-siloxy-cyclopropane **7**, in particular. In conclusion, the transition state (**24**) appears to anticipate the nature of the intermediate **25**, which on one hand reflects the property of R¹ and on the other that of the metal carbon bond (Eq. 67). More detailed information on the type of ring cleavage, namely, the choice between the side-on (i.e. **24**) or the end-on interaction (attack of the metal at the back-lobe of the opening C—C bond), is currently lacking: The mode of the mercury induced cleavage of cyclopropanols is sensitive to ring substituents [7].

7 Homo-enolates in Natural Product Synthesis

As demonstrated in the preceding chapters, metal homo-enolate chemistry centered around the ring cleavage of siloxycyclopropanes has realized a number of straightforward synthetic transformations only some of which have been possible with other existing methods.

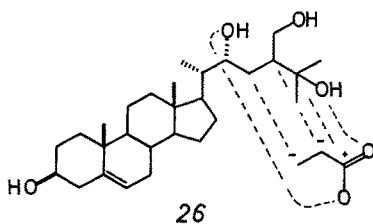
The current state of metal homo-enolate chemistry is still in its infancy, and very few examples of the actual applications have been reported. However, the diversity of reactivities of the homo-enolates shown in the preceding paragraphs will definitely lead future activities towards fruitful applications.

7.1 Steroidal Side Chains:

Depresosterol and 24-*epi*-Depresosterol [63]

Stereocontrolled functionalization of steroidal side chains in nature is closely related to the function of steroids in living organisms. The regio- and stereochemistry of functional groups exert strong influence on the biological activities of steroids. Due to their multi-functional nature, the homoenoates provide an effective tool for synthetic efforts in this field.

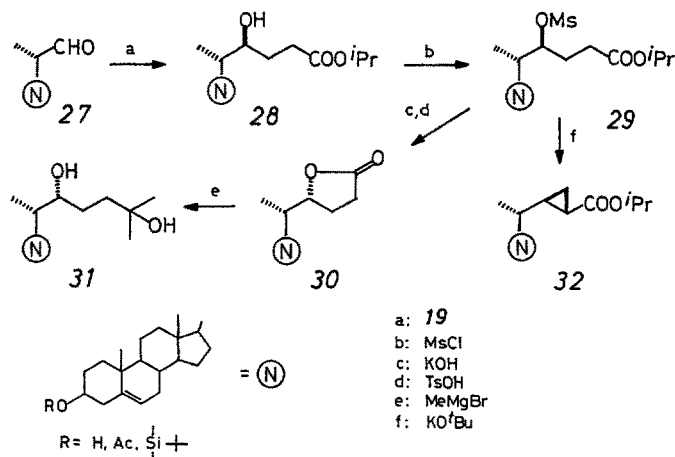
Depresosterol (**26**) is a marine natural product isolated from a soft coral in the Red Sea [64]. The structure of this sterol, in particular, the configuration at C²⁰ and C²², was assigned by comparative NMR studies, and that at C²⁴ was left unassigned. The latter configuration was of interest with respect to the biological significance of the sterol. The density of hydroxyl groups is higher than in any of the known sterols, the substitution pattern being reminiscent of the insect molting hormone, ecdysone. The synthesis of depresosterol **26** demonstrates the potential of the homoenoate as a multi-functional three carbon building block, which corresponds to the C₃ fragment C²³, C²⁴, C²⁵ in **26**. The stereochemical synthesis of both epimers at C²⁴ finalized the structure determination of this sterol [63].



The synthesis started with the “homo-Reformatsky” reaction between the alkoxytitanium homoenoate Eq. (30) and aldehyde **27**, which afforded the product **28** with Cram orientation with >6:1 selectivity. An inversion at the sterically hindered C²² position was readily achieved by mesylation, followed by KOH treatment in hot aqueous MeOH to give lactone **30** after acid-catalyzed lactonization.

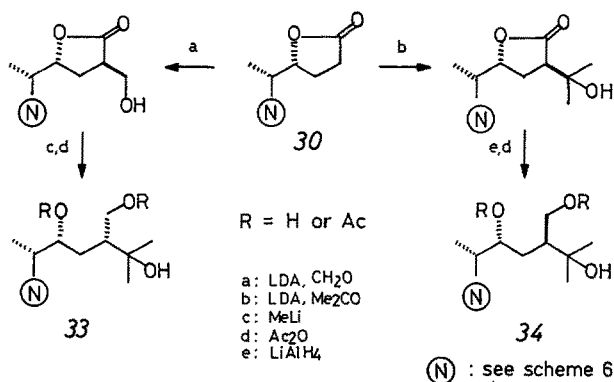
Synthesis of the 24*R* isomer was commenced by stereoselective hydroxymethylation of the enolate of lactone **30**. Introduction of methyl groups at C²⁵ and C²⁶ was achieved by addition of MeLi to give 24*R* depresosterol (**33**). Alternatively, trapping of the lactone enolate with acetone followed by LiAlH₄ reduction gave the 24*S* epimer (**34**). Spectral comparison indicated that the 24*R* sterol is identical with the natural product.

This approach not only enabled the preparation of a simpler structure such as that of ecdysone (cf. **31**), but also provides ways to introduce functional groups at C²³ and C²⁴ positions of the side chain. As an example, treatment of the mesylate **29** with non-nucleophilic *tert*-butoxide gives the cyclopropane **32** which



Scheme 6

can serve as a precursor to the structurally intriguing demethylgorgosterol [63].

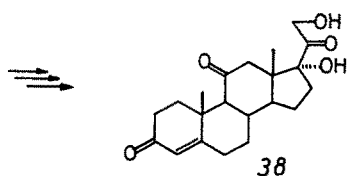
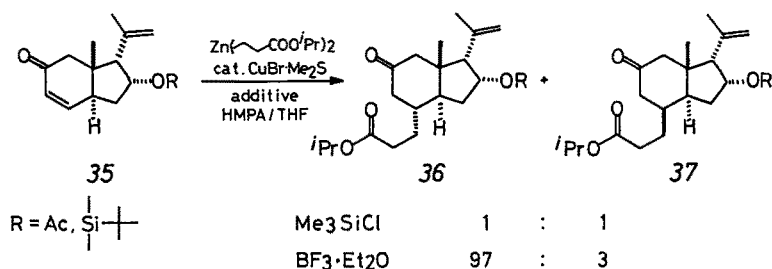


Schemes 6, 7

7.2 (\pm)-Cortisone [39]

Conjugate addition of catalytically generated zinc homoenolate (cf. Eq. 39) has been used for the stereoselective synthesis of a key intermediate to (\pm)-cortisone (**38**). Precedents of the cuprate addition onto a *trans*-fused hydrindane such as **35** was expected to give **36** but attack of the nucleophilic copper reagent from the desirable, less hindered α -side. Although treatment of the enone **35** with the zinc homoenolate under standard condition (Eq. 39, Me₃SiCl/HMPA/cat. CuBr · Me₂S) afforded the adduct in quantitative yield, the product was a 1 : 1 mixture of **36** and **37**. In contrast, use of BF₃ · Et₂O instead of Me₃SiCl gave the desired isomer **36** with better than 95% selectivity; with some additional steps

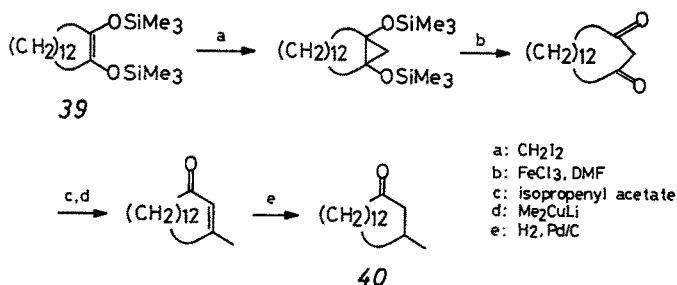
the total synthesis of **38** was completed. The precise reason for the change of the stereochemistry is currently unclear.



Scheme 8

7.3 (\pm)-Muscone [20]

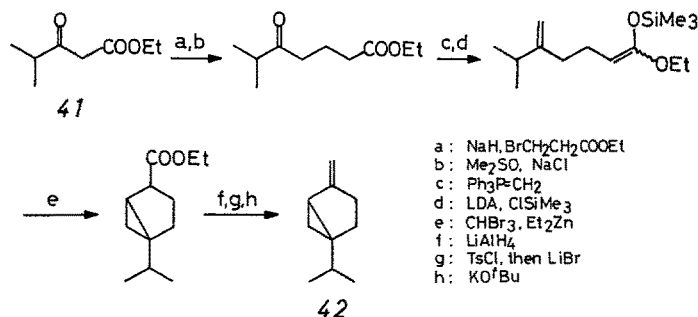
The acyloin condensation of α,ω -diesters in the presence of Me_3SiCl represents a highly efficient method for the synthesis of large rings. The application of the convenient sequence of cyclopropanation/oxidative ring cleavage for ring expansion cf. Eq. (52) to the appropriate macrocyclic enediol silyl ether **39** provided, a short, high-yield (23% overall) synthesis of muscone (**40**) [20].



Scheme 9

7.4 (\pm)-Sabinene [58]

The remarkably efficient cyclopropanation reaction with an in-situ-generated zinc carbenoid, Eq. (61) provided a straightforward synthesis of the monoterpene sabinene (**42**) starting from the β -keto ester **41** [58].



Scheme 10

8 References

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