133 Topics in Current Chemistry

Small Ring Compounds in Organic Synthesis I

Guest Editor: A. de Meijere

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With Contributions by
K.-L. Lau, K.-F. Tam, B. M. Trost, H. N. C. Wong

With 1 Figure and 27 Tables

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Introduction

Small ring compounds have come of age. The year 1985 marked the 100th anniversary of Adolf von Baeyer's "theory of ring strain" (published in 1885) as well as his 150th birthday. Now, a handsome one hundred years after the first cyclopropane and cyclobutane derivatives were synthesized and their propensity for ring opening discovered by William Henry Perkin, synthetic organic chemists have begun to realize on a wide scope that there is more to these compounds than fun and intellectual exercise for the structurally oriented chemist.

The past 30 years have seen the development of a broad spectrum of widely applicable preparative methods for three- and four-membered carbocycles and the accumulation of detailed knowledge about their structure-reactivity relationships. Nowadays, more and more synthetic methodology is being developed, which utilizes the potential of small ring compounds as reactive entities. Cyclopropyl and cyclobutyl moieties in a molecule can be regarded as unique functional groups; they allow transformations which are far more difficult or impossible with any of the more conventional functional groups.

To the extent that the bonding in a three-membered ring resembles that in a C=C double bond, most of the chemistry of cyclopropane derivatives can be rationalized by analogy to similarly substituted olefins. By their electronic nature, therefore, cyclopropanes are nucleophilic, that is to say their high reactivity especially towards electrophilic agents is not solely governed by ring strain. Furthermore, the philicity of a cyclopropane can be modified in any desired way by substituents. Like a double bond, it can be made susceptible to nucleophilic attack (e.g. the Michael addition) with strongly electron withdrawing substituents; practically then, cyclopropyl ketones are "homoenones". Electron donating groups increase the nucleophilicity drastically; consequently cyclopropyl ethers behave as "homoenolethers", cyclopropanolates as "homoenolates". In all cases the cyclopropyl homologues of the corresponding olefins always lead to a substitution pattern after ring opening which could otherwise only be achieved by way of an "Umpolung". In essence, the use of a cyclic array of three carbons is one way of performing an "Umpolung" at the γ-carbon of a three carbon chain and has therefore been termed the "cyclopropane trick" [1].

The combination of a donor and an acceptor on one cyclopropane ring creates yet another potentially useful reaction path. Finally, cyclopropanes may also be substituted in such a way that they are most easily opened by radical attack.

Vinylcyclopropanes are now widely used as precursors to five-membered rings. Various methods have been designed to construct vinylcyclopropanes and bring about their rearrangement — most frequently thermolytically — to cyclopentenes.

Some rather general ways of cyclopentene-anellations are based on this scheme. Substituents effects once again have been used successfully to facilitate the rearrangement, which — in the extreme case — occurs at room temperature. More recently, alkinylcyclopropanes have found interesting applicability as building blocks for organic synthesis, as have methylenecyclopropanes and cyclopropenes. Transition metal chemistry is starting to play a major role in this field, since many of the reactions of small rings can also be achieved with the help of catalysts. More work needs to be done in this area and some is already in progress.

The cyclobutyl moiety has also come to be quite frequently used as an all carbon functional group in efforts directed toward the synthesis of complex organic molecules. Four-membered ring chemistry can likewise be tuned by the appropriate choice of substituents. In addition to various chemoselective ring openings there are ring enlargements to five- and ring contractions to three-membered carbocycles, all of which have their specific range of applications.

This volume of "Topics in Current Chemistry" and another one, projected to appear within the next year are intended to cover most of the above-mentioned aspects of small ring chemistry, with emphasis being placed on the application in organic synthesis. "State of the art" reviews will be presented by individual authors who are themselves engaged in research on one or more of the subtopics. This exciting field has become so active that no single author would feel competent to write a comprehensive, up-to-date monograph.

Armin de Meijere

Reference

1. Cf. D. Seebach, *Angew. Chem.* 91, 259–278 (1979); *Angew. Chem. Int. Ed. Engl.* 18, 239 (1979).

Strain and Reactivity: Partners for Selective Synthesis

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The unusual bonding of cyclopropanes and the strain release associated with cleavage of cyclopropanes and cyclobutanes offer the possibility of recognizing that structural unit when it is a part of a larger molecule. These structural fragments may be considered as "pseudofunctional groups" which may be chemoselectively manipulated. The structural and reactivity concepts have evolved into the development of reagents that incorporate a cyclopropyl ring into substrates to permit the development of chain extensions and annulations.

The attachment of a cyclopropyl ring to a carbonyl group requires the development of cyclopropyl anions. Of special interest are those bearing a heteroatom substitutent either at the anionic carbon or an adjacent one. The ability of sulfur to stabilize an anionic center has proved to be particularly beneficial for generating reagents of the first type. Two reagents 1-lithiocyclopropylphenyl sulfide and diphenylsulfonium cyclopropylide generate a great flexibility for structural variation. Mimics of these reagents bearing oxygen and selenium substituents in place of the sulfur substituent have also evolved.

An alternative strategy invokes a need for an electrophilic cyclopropyl reagent to introduce the small ring at a carbon alpha to a carbonyl group via the corresponding enol or enolate. Two reagents belonging to this class, 1-phenylthiocyclopropane-1-carboxyaldehyde and 1-tetrahydropyranoxycyclopropane-1-carboxyaldehyde, utilize an aldol reaction to incorporate the small ring conjunctive reagent into the organic molecule.

Two major types of reactions of the small ring systems provide the greatest versatility. Ring enlargement to cyclobutyl systems creates another class of strained ring compounds that permit selective structural variation. Ring cleavage exemplified by the secosulfenylation of the cyclobutanones illustrate the development of a diastereoselective geminal alkylation of a carbonyl group. Further ring enlargement of the cyclobutyl ring to a five membered ring provides syntheses of both carbocycles, i.e. cyclopentanones, and heterocycles, i.e. γ-butyrolactones. An alternative provides vinylcyclopropanes and vinylcyclobutanes which can be induced to rearrange to cyclopentenes and cyclohexenes respectively. Cyclopentanone and cyclohexanone annulation result from these reactions.

The versatility of cyclopropyl conjunctive reagents permits the development of synthetic strategy to many types of complex molecules. The concepts of seco-alkylation-geminal alkylation produce total syntheses of methyl deoxypodocarpate, hinesol, grandisol, trihydroxydecipiadiene, acorenone B and a verrucarol intermediate. Lactone annulation and substitutive spiroannulation create the basis for synthesis of plumericin, allamcin, allamandin, a verrucarol intermediate, and dodecahedrane. Cyclopentyl syntheses not involving γ-butyrolactones as intermediates lead to synthese of α-cuparenone, aphidicolin, spirovetivane, α-vetispirene, 11-deoxyprostaglandin E, and isoretronecarrol. A synthesis of β-selinene exemplifies the vinylcyclobutane rearrangement. A synthesis of methyl trisporate B illustrates the use of these small ring conjunctive reagents for formation of *acyclic chains*.

1 Introduction

The ability to perform selective transformations at one point in a multifaceted molecule requires a distinctive structural feature that can be recognized either due to

its intrinsic reactivity or by the nature of the reagent or the catalyst. The latter area represents a major endeavor — especially with respect to the concept of enzyme modelling. For example, selective oxidation of a C—H bond at various "unactivated" positions in a steroid may mimic oxidases but also have practical synthetic uses. However, the former area, in one sense, is the more classical. The concept of functional groups which mean π (carbonyl, olefin, arene, etc.) or heteroatomic (oxygen, sulfur, nitrogen, etc.) systems formalizes this thinking. For example, deeply imbedded into the thinking of organic chemistry is the widespread utility of a carbonyl group for further structural elaboration. Regardless of how many other types of bonds that may be present in a molecule, we can manipulate around the carbonyl group quite selectively. While we have a well recognized list of such functional groups, the question arises as to whether the synthetic chemist can add to this list.

As an outgrowth of the extensive physical and theoretical studies of strained rings, the extension of the functional group concept to three and four membered rings becomes attractive. The unique bonding of cyclopropanes combined with the release of the strain of both the cyclopropane (117 kJ/mole, 28 Kcal/mole [1]) and the cyclobutane (109 kJ/mole, 26 Kcal/mole) [1] rings provide a recognition mechanism for unique molecular reorganization of that portion of the molecule. To realize the benefits of such a "pseudo-functional group" we must develop ways for their creation or incorporation.

The discovery of carbene and carbenoid additions to olefins was the major breakthrough that initiated the tapping of this structural resource for synthetic purposes. Even so, designed applications of cyclopropane chemistry in total syntheses remain limited. Most revolve around electrophilic type reactions such as acid induced ring opening or solvolysis of cyclopropyl carbinyl alcohol derivatives. One notable application apart from these electrophilic reactions is the excellent synthesis of allenes from dibromocyclopropanes [2].

An alternative mode for harvesting this resource is to design conjunctive reagents that will directly introduce this structural feature into organic molecules. The widespread presence of a carbonyl group in organic molecules make it a target for attachment of the strained ring. Two types of reactivity derives from a carbonyl group — nucleophilic addition to the carbonyl carbon atom and electrophilic substitution at the α-carbon through the intermediacy of enols and enolates. For the first type of reactivity, cyclopropyl anions are required; for the latter, a cyclopropyl ring bearing a carbonyl group or another electrophilic functional group are desired. Of course, these types of reagents will not be limited to combining with carbonyl groups as some of the examples will demonstrate. For most cases, the cyclopropyl product is not the final goal, but an intermediate to acyclic or ring systems commonly needed in theoretical and natural products chemistry. For such applications, the parent ring system is less useful than those bearing additional substituents, especially heteroatomic groupings.

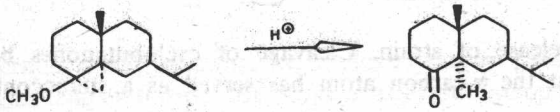
In designing conjunctive cyclopropyl reagents, we should consider some of the types of structural modifications that appear most useful for further synthetic goals. Such considerations define the nature of the substituents on the cyclopropyl ring and the type of reaction to be utilized.

2 Ring Opening

The cleavage of the cyclopropyl ring with its relase of the total strain is a powerful driving force. Electrophilic attack on the electron rich ring does provide one approach as shown in Eq. 1 [3]. The lack of selectivity in the cleavage of one of the

(1)

three cyclopropyl bonds usually makes it useful to incorporate directing substituents such as oxygen (Eq. 2) [4].

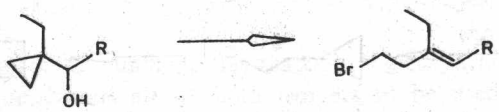


(2)

A cyclopropylcarbinyl cation can be trapped to form either a cyclopropane product (Path a, Eq. 3) or a homoallyl product (Path b, Eq. 3). The latter has proven useful to create acyclic units containing olefins of defined geometry as in the synthesis

(3)

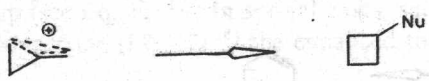
of juvenile hormones (Eq. 4) [5].



(4)

3 Ring Expansions

The unusual nature of the cyclopropyl carbinyl cation allows yet another mode of attack to form cyclobutane products. Because this mode of attack releases little strain, normally some special structural features are required to direct the reaction along this pathway.



(5)

The utility of this pathway mainly derives from the further reactions of the cyclobutanes. Since they possess nearly as much strain as the cyclopropanes,

powerful driving forces for further structural modification still exist. For example, ring expansion to cyclopentyl rings or γ-butyrolactones (Eq. 6 [6,7] and 7 [8])

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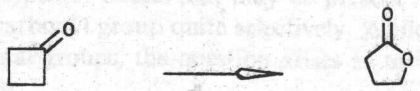
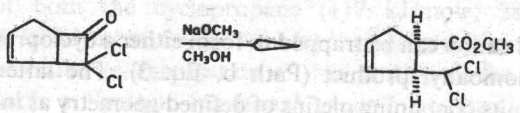


(7)

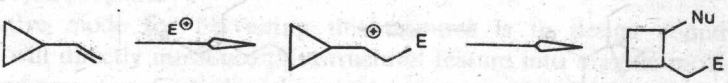
provide dramatic release of strain. Cleavage of cyclobutanones bearing anion stabilizing groups at the α-carbon atom has served as a stereocontrolled olefin



(8)

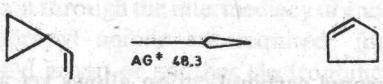
vicinal alkylation since the starting dichlorocyclobutanone or related systems can derive from ketene cycloaddition [9,10]. Since any cyclobutanone can be elaborated in such fashion, ring expansions to cyclobutanones become particularly valuable.

Vinylcyclopropanes represent particularly useful functionality. They do permit a ring expansion to cyclobutanes via the cyclopropylcarbinyl cation manifold (Eq. 9). Equally important, such systems suffer smooth thermal rearrangement to cyclopen-



(9)

tenes (Eq. 10) [11]. Rate studies reveal that substitution at the one (Eq. 11) or two



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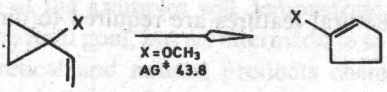

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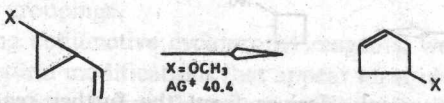
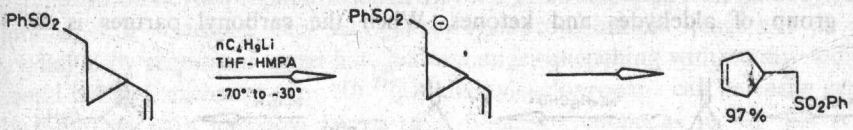


(12)

(Eq. 12) position of the cyclopropyl ring dramatically lowers the activation energy of this process [12]. In addition charge accelerated vinylcyclopropane rearrangements

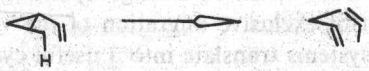
have been noted (Eq. 13) [13]. The structural flexibility offered by substituents



(13)

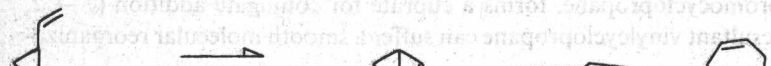
allows us to take maximum advantage of these rate accelerations.

Vinylcyclopropanes bearing a cis alkyl substituent undergo a competitive prototropic shift accompanying ring opening (Eq. 14) [14]. In such cases, temperature



(14)

adjustment permits either pathway, i.e. cyclopentene or 1,4-diene formation, to dominate. Higher temperatures (> 650 °C) generally favor cyclopentene formation [15]. The presence of a β-vinyl substituent permits yet another pathway to intervene — the divinylcyclopropane rearrangement to cycloheptadienes (Eq. 15) [16]. While



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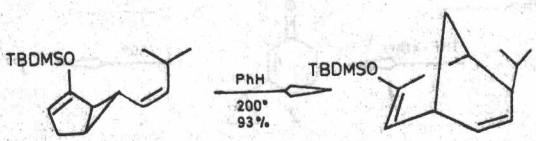
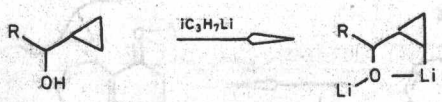


(15b)

only the cis isomer can undergo this reaction, the easy trans-cis isomerization under the reaction conditions allows both isomers to be used. Thus, manipulation of cyclopropyl substituents can provide diverse opportunities for a wide array of structural variations.

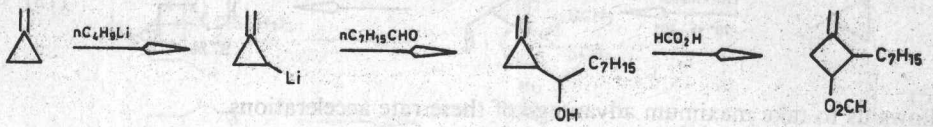
4 Cyclopropyl Anions

While thermodynamically, the direct metalation of cyclopropane can be envisioned from a synthetic point of view, this approach has been rarely used. A major obstacle appears to be kinetics which can be overcome by incorporation of a hydroxyl group (see Eq. 16) [17]. In special cases, such as bicyclo [1.1.0] butane and methylenecyclopropane (Eq. 17) [18] the enhanced thermodynamic acidity is accom-



(16)

panied by an enhanced kinetic acidity as well. In the latter case, the anion adds to the carbonyl group of aldehydes and ketones. When the carbonyl partner is an



(17)

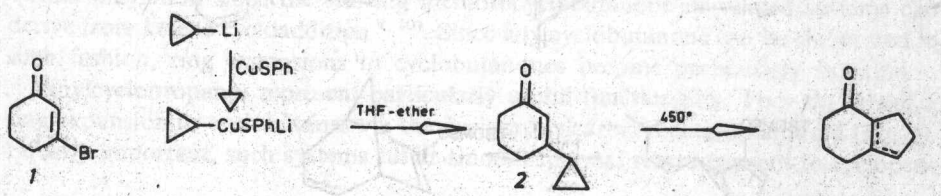
aldehyde, such as n-octanal, solvolysis leads to smooth ring expansion to give a 3-methylenecyclobutan-1-ol, the product of exclusive migration of the vinyl cyclopropyl carbon. Thus, even such simple systems translate into a useful cyclobutanol synthesis.

A more general approach utilizes metal-halogen exchanges because of the ready availability of monobromocyclopropanes by either

1) reductive monodehalogenation of dibromocyclopropanes or

2) halodecarboxylation (Hunsdiecker reaction)

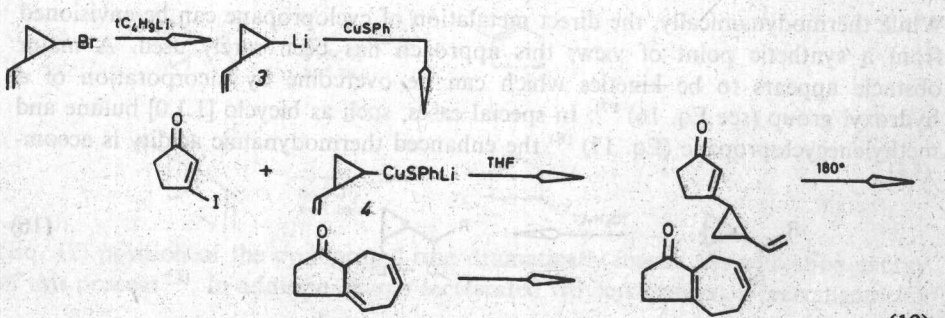
of cyclopropane-carboxylic acids. For example, the parent cyclopropyllithium, available from bromocyclopropane, forms a cuprate for conjugate addition (*1* → *2*, Eq. 18) [19]. The resultant vinylcyclopropane can suffer a smooth molecular reorganiza-



(18)

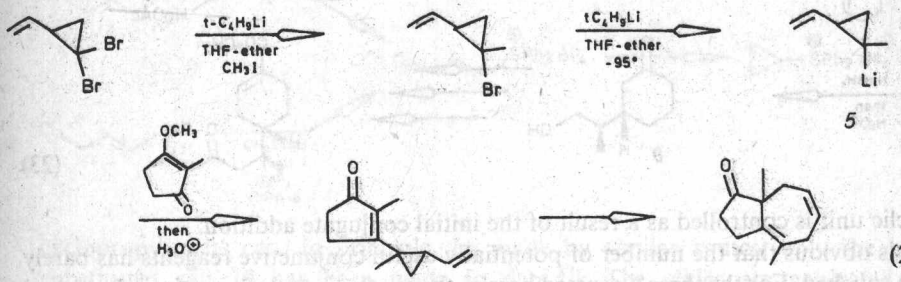
tion upon thermolysis to create a cyclopentannulation.

A slight modification of the cyclopropyl conjunctive reagent transforms a cyclopentannulation into a cycloheptannulation. Thus, the 2-vinylcyclopropyllithium reagent *3*, converted to its cuprate *4*, generates a 1,2-divinylcyclopropane. Heating to only 180 °C leads to smooth Cope type rearrangement, driven by the release of the cyclopropyl strain, to create a perhydroazulene ring system of many sesquiterpenoids (Eq. 19) [20].



(19)

The dibromocyclopropanes offer an easy entry into alkylated versions of cyclopropyl anions. For example, the methylated cyclopropyllithium reagent *5* is readily available by sequential metal-halogen exchange, quenching with methyl iodide and metal-halogen exchange (Eq. 20) [21]. A divinylcyclopropane can be easily generated by addition to a carbonyl group of a β-methoxyenone as in Eq. 20. A cycloheptannulation results upon thermolysis in a complementary process to the conjugate addition approach of Eq. 19. A synthesis of Dewar heptalene employed this approach to create the requisite carbon skeleton (Eq. 21) [22].



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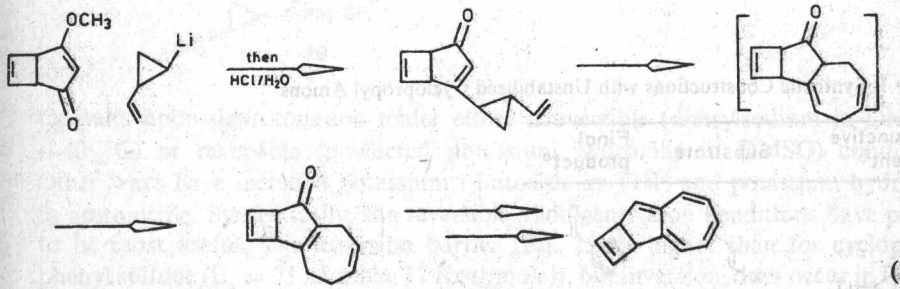
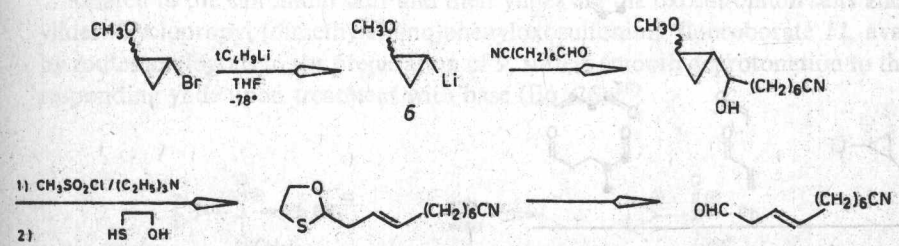


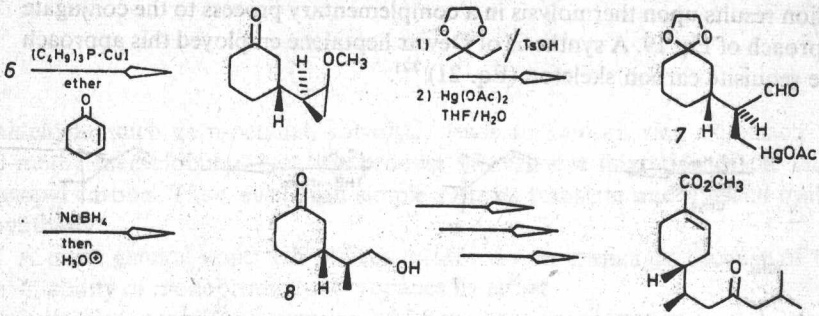
(21)

To direct a solvolytic ring opening, 2-methoxycyclopropyllithium (*6*) was developed as a chain extension conjunctive reagent. The failure of β-elimination to occur in *6* presumably derives from the high strain of cyclopropene and poor orbital overlap for elimination. The aldehyde adducts smoothly solvolyze to give β,γ-unsaturated aldehydes (Eq. 22) [23] which are best initially isolated as their hemithioacetals.



(22)

The cuprate derived from the cis isomer of this reagent undergoes conjugate addition with cyclohexenone with unusually high diastereoselectivity (5:1, Eq. 23) [24]. In this case, electrophilically initiated ring opening with mercuric acetate chemoselectively attacks the sterically least hindered cyclopropyl bond to give a branched product *7*. Reductive work-up produces *8* in which the stereochemistry of the

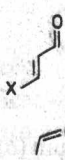
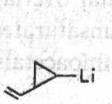
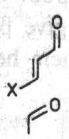
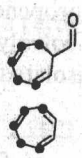
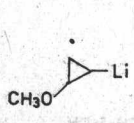
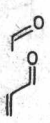
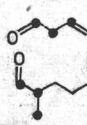


(23)

acyclic unit is controlled as a result of the initial conjugate addition.

It is obvious that the number of potentially useful conjunctive reagents has barely been touched. For the three discussed herein, the synthetic transformations developed so far are summarized in Table 1.

Table 1. Synthetic Constructions with Unstabilized Cyclopropyl Anions

Conjunctive reagent	Substrate	Final product[a]
		
		
		

[a] The carbons dotted in the product derive from the cyclopropyl conjunctive reagent.