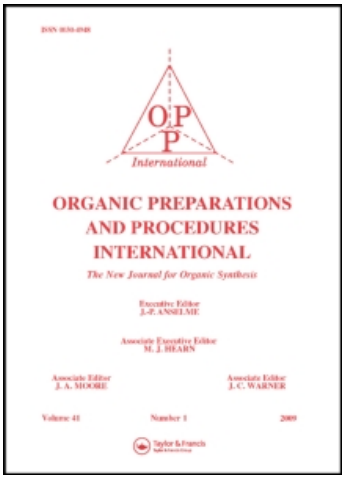

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INTRODUCTION

Cyclopropylimines have been used extensively in organic syntheses since the first rearrangement reported by Cloke.[1] The versatility of these compounds is related to the presence of two reacting sites, which allow their use in various different reactions. Because the bond angles are significantly less than the ideal 109°, the cyclopropane moiety suffers from considerable angular strain, as well as torsional strain from the eclipsed bonds. Thus, the cyclopropane ring is subject to chemical transformations that are only possible because of its unique bonding and high energy content. This energy content is the driving force of the diradical opening of the cyclopropane, especially when at least one of the resulting radicals becomes part of a delocalized allylic system, as in the case of the cyclopropylimines. The diradical ring-opening of cyclopropylimines, when followed by 1,5-closure of the system, leads to the formation of nitrogenated five-membered heterocycles (pyrrolines). This kind of rearrangement is one of the most characteristic reactions of cyclopropylimines, and belongs to a more general category of reactions, best represented by the vinylcyclopropane–cyclopentene rearrangement.[2] Due to the formal relationship with this well-studied transformation, cyclopropylimine rearrangements have been used to unveil mechanistic aspects of the reaction, as well as being used as intermediates in the synthesis of five-membered rings. This strategy has been used a number of times in the synthesis of pyrrolines, pyrroles, alkaloids and related compounds. Besides, these versatile compounds can be used in the synthesis of larger heterocycles through different mechanisms. Cyclopropylimines have been also used in the synthesis of cyclopropane α-amino acids (ACCs). These compounds have drawn considerable attention on account of their biological activities and pharmaceutical interest. Several naturally occurring ACCs have been isolated and many more have been synthesized because of their potential as conformationally restrained peptide mimetics.

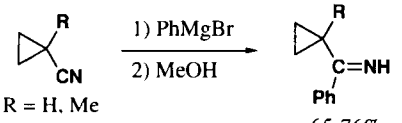
Two different classes of cyclopropylimines, *N*- and *C*-cyclopropylimines, are possible depending on the atom bonded to the cyclopropane moiety. Although these two types of compounds share several features, their synthesis, reactivity and applications are sufficiently different to require separate treatment.

I. SYNTHESIS

1. *C*-Cyclopropylimines

The presence of two different reactive functionalities in the cyclopropylimine skeleton brings about the use of quite diverse but convergent synthetic routes. No general method has been described to synthesize these molecules, but two main types of reactions have been developed depending on the order in which the cyclopropane and imine moieties are incorporated.

When the cyclopropane ring is already present in the starting material, one of the easiest approaches is to generate the imine moiety using the classical reaction of nitriles and Grignard reagents. This was indeed the reaction used by Cloke in 1929 to generate *C*-cyclopropylimines.[1] The same approach has been used more recently to synthesize several compounds (*Scheme 1*).[3] The substituent placed in the iminic carbon is easily modified since it comes from the Grignard



Scheme 1

reagent. Thus the main drawback of this method is the availability of the starting cyclopropane. Included in this category is the condensation of cyclopropylcarbonyl compounds and amines to afford *C*-cyclopropylimines. This approach allows a wider range of substituents in the molecule, and it can be used to carefully design the desired cyclopropylimine by combination of the two fragments. This group of reactions is reviewed in *Synthesis Section 1. a).*

The reactions included in the other category, where the last step in the synthesis corresponds to cyclopropanation, usually have more drawbacks, since the substrates for the cyclopropanation reaction already include most of the molecular complexity. Structural diversity is often difficult to introduce using this strategy. Furthermore, cyclopropanation in the presence of an imine moiety raises some chemo- and stereoselectivity issues that are not always easy to solve. However, the syntheses of a number of compounds have been reported through these methods (see *Synthesis section 2. b*). The choice of one strategy over the other should be based on the consideration of all substituents present in the target molecule.

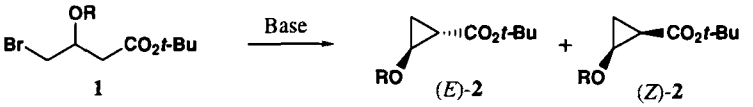
a) From Cyclopropylcarbonyl Compounds

When a carbonyl group is bonded to the cyclopropane, *C*-cyclopropylimines can be achieved by simple condensation with amines. In these cases, the synthetic problem is reduced to

the generation of the carbonyl compound, since the imine formation is usually simple. A general method is heating the reactants in refluxing toluene with water removal (Dean-Stark technique, molecular sieves). The resulting imine is generally formed in good yield. This section will review different methods to synthesize the carbonyl components. Standard transformations such as ester reduction to form ketones or aldehydes will be omitted.

General strategies for the synthesis of cyclopropanes, such as stereoselective cyclopropanations,[4] synthesis of *gem*-dihalocyclopropanes[5] or synthesis of donor-acceptor disubstituted cyclopropanes[6] have been recently reviewed. Here we will focus on synthetic routes suitable for the preparation of cyclopropylcarbonyl compounds and, eventually, the derived *C*-cyclopropylimines.

Intramolecular cyclization of γ-haloesters is one of the classical entries for cyclopropyl esters, which can be transformed into cyclopropylcarbonyl derivatives by standard techniques. For example, ring closure of 4-bromo-butanoate **1** in the presence of a base affords *tert*-butyl carboxylates **2** in high yields and very good *E/Z*-diatereoselectivity (*Scheme 2*).[7] Three different bases were tested for this reaction. Potassium *tert*-butoxide produced excellent yields (up to 98%) but low diastereoselectivity (just 50% d.e. in better cases). Much better diastereoselectivity (up to 85%) was observed with LDA but the yields were lower. The best results were achieved with LiHMDS, which gave very good yields (80–90%) and excellent diastereoselectivities (>99%), favorable to the *E* isomers.

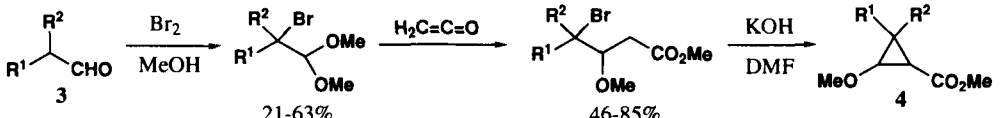


1 (*E*)-2 (*Z*)-2

R = alkyl

Scheme 2

Starting from substituted acetaldehydes **3** and using in sequence bromine in methanol and ketene to form the γ-bromoester, Rasmussen *et al.*[8] were able to generate substituted cyclopropanecarboxylic esters **4** in good yields (*Scheme 3*). Cyclization is achieved by using solid potassium hydroxide in DMF. As regards the stereochemistry of **4**, the thermodynamically more stable *trans* compounds are formed exclusively.

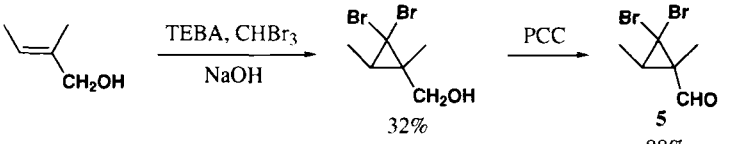


3 21-63% 46-85% 4 76-96%

R^1 = H, alkyl, aryl
R^2 = H, alkyl

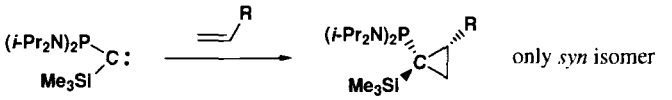
Scheme 3

Another classical approach to substituted cyclopropanes is the addition of a carbene to an alkene. Brinker *et al.*[9] used dibromocarbene to generate cyclopropanecarbaldehyde **5**, which, in turn, was used to synthesize *C*-cyclopropylimines (*Scheme 4*).



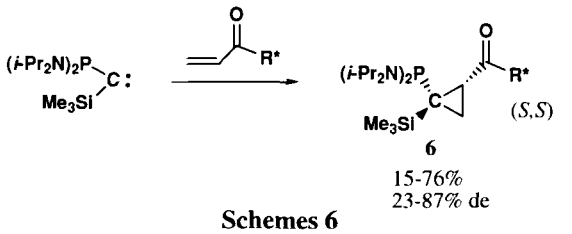
Scheme 4

Complete diastereoselectivity in carbene additions can be achieved by cyclopropanation of monosubstituted olefins with stable singlet nucleophilic (phosphino)(silyl)carbenes (*Scheme 5*).[10] A further modification of this methodology allowed the synthesis of cyclopropanes with complete diastereoselectivity and a high level of enantioselectivity. Chiral acrylates yielded



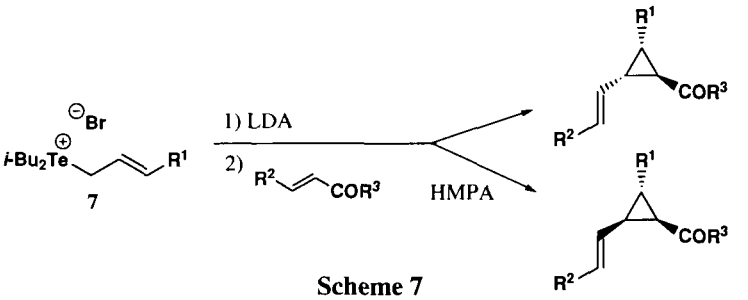
Scheme 5

the corresponding cyclopropanes in moderate yields. Cleavage of the chiral auxiliary and the trimethylsilyl group was also achieved. Saponification of a methanol solution of each of the diastereomers **6** cleanly gave the corresponding enantiomers (*Scheme 6*).[11] X-ray diffraction analyses of diastereomers **6** confirmed the *syn* diastereoselectivity of the cyclopropanation reaction, and the *S*- and *R*-absolute configurations at the two newly formed chiral centers of the major and minor isomers **6**, respectively.



Schemes 6

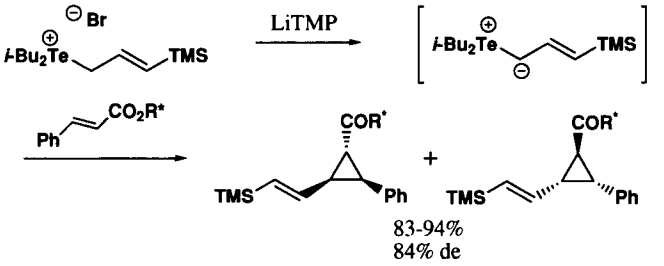
Vinylcyclopropyl esters can be obtained in high yields with high stereoselectivity from α,β-unsaturared esters or ketones and telluronium allylides **7** (*Scheme 7*). Interestingly, the



Scheme 7

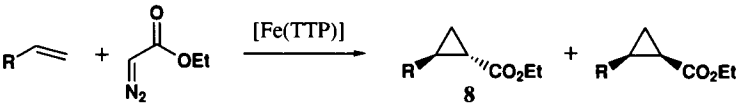
stereoselectivity of the reaction of telluronium allylides with α,β-unsaturated esters or amides could be controlled by the choice of the base used for the formation of ylide or by the use of HMPA as solvent. Thus, either of the two geometrical isomers of a polyfunctionalized 3-vinylcyclopropane could be obtained at will with high stereoselectivity.[12]

This methodology can be further improved to get chiral auxiliary-controlled access to the optically active trimethylsilylvinylcyclopropane derivatives via ylide routes. Several chiral auxiliaries and bases were explored, and the best results, both in terms of chemical yield and diastereoselectivities, were obtained with LiTMP and (–)-8-phenylmenthol (*Scheme 8*). Different α,β-unsaturated compounds can be used with this methodology, and the chiral auxiliaries can be easily recovered. Also, the presence of the trimethylsilyl group allows further functionalization of the molecules.



Scheme 8

Iron porphyrin complexes are active catalysts for the cyclopropanation of alkenes by ethyl diazoacetate. Fe(TTP) (TTP = *meso*-tetra-*p*-tolylporphyrin), an isolated iron(II) porphyrin complex, can be used as the catalyst, or the iron(II) complexes of several porphyrins can be generated *in situ*. The reactions produce synthetically useful excesses of the trans cyclopropyl ester product **8** (*Scheme 9*).[13]



R = alkyl, aryl, alkoxy

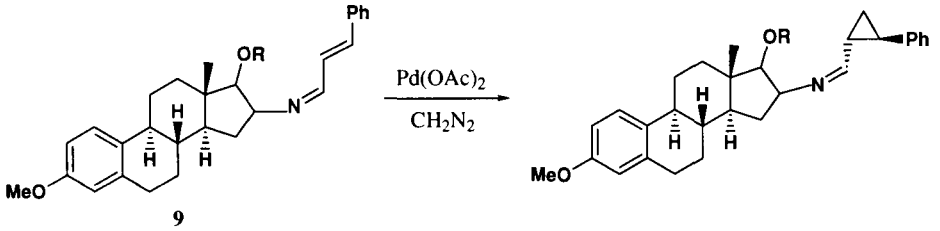
Scheme 9

The catalysts are active for more than 4000 cycles and the ratio of *trans/cis* products was 11:1 in the best case. Different iron catalysts were used and the *trans* isomer was always the major product. The iron porphyrins catalyzed the cyclopropanation of 1-alkenes and 1,1-disubstituted olefins very efficiently, but alkenes with other substitution patterns were poor substrates. The catalysts also exhibited pronounced preferences based on the electronic nature of the alkene. In general, olefins with aromatic or π-donating heteroatoms were better substrates.

b) Cyclopropanations to C-Cyclopropylimines

The second group of synthetic routes leading to *C*-cyclopropylimines consists of the cyclopropanation of species where the imine moiety is already present. These routes start from

α,β-unsaturated imines (1-azadienes) and differ in the cyclopropanating agent. One sequence to synthesize substituted cyclopropanes is the Pd-catalyzed reaction of substituted olefins with diazomethane. Using diastereomeric steroidal *cis*-17-silyloxy-16-cinnamic aldimines **9**, high diasteroselectivities in the cyclopropanation reaction were observed (*Scheme 10*).[14]

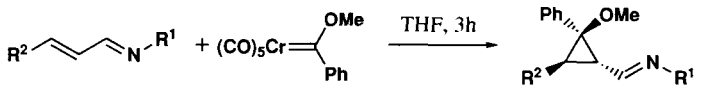


9

R = $SiPh_2t$-Bu

Scheme 10

Cyclopropanation of 1-azadienes can also be carried out by Fischer carbene-complexes. These organometallic species are well-known cyclopropanating agents for electron-deficient olefins. Refluxing 1-azadiene and pentacarbonyl(methoxy)phenylchromium in THF for 3 h yields the corresponding *C*-cyclopropylimine (*Scheme 11*).[15] Longer reaction times or higher temperatures lead to pyrrole or furan formation. In a similar way, imine-substituted Fischer carbene complexes were reported to cyclopropanate alkenes (see Synthesis section 2. *b*).



R^1 = *t*-Bu, Ph, (*R*)-CH(Me)Ph

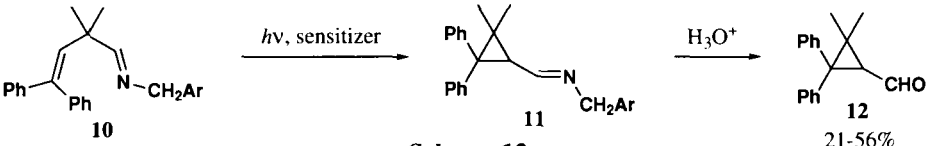
R^2 = Ph, Me, CH=CHMe

60-80%

trans-cis 5:1

Scheme 11

Although not synthetically useful, the photochemically driven aza-di-π-methane rearrangement of azahexadienes also results in *C*-cyclopropylimine formation. The acetophenone-sensitized irradiation of 2-azahexa-2,5-dienes **10** yielded the cyclopropylimines **11**. However, these compounds were not isolated but hydrolyzed to the corresponding aldehydes **12** (*Scheme 12*).[16,17]



10 **11** **12**

21-56%

Scheme 12

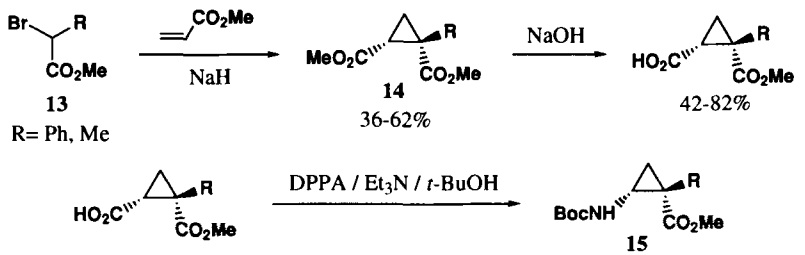
2. *N*-Cyclopropylimines

As in the case of *C*-cyclopropylimines, two main synthetic pathways can be used for the preparation of *N*-cyclopropylimines, depending on the moiety synthesized last. Cyclopropanation of substrates in which the imine moiety is already present seems more straightforward, but it is

not always easy to achieve. The alternative route, starting from a cyclopropylamine, is usually longer but more versatile. As noted in the previous section, the global structure of the target molecule will dictate the choice of one strategy over the other. Interest in most of the work in this subject has been spurred by the importance of 1-aminocyclopropane-1-carboxylic acid (ACC) and derivatives. This sub-structure appears frequently in the syntheses reviewed. ACC and analogues are important plant growth regulators and control the flowering and ripening of fruits. Besides, derivatives of ACC have also been studied in the light of the construction of peptides containing sterically constrained α-amino acids in order to gain defined conformational changes, the ultimate goal being the design of modified enzymes.

a) From Cyclopropylamines

The condensation of primary cyclopropylamines with a carbonyl compound yields *N*-cyclopropylimines directly. In these cases, the synthesis can be longer but the route permits control over the substituents present in both the imine and cyclopropyl parts. An important group of syntheses of primary cyclopropylamines involve Curtius-type rearrangements, thus the amine moiety is derived from cyclopropanecarboxylic acids and derivatives, which result from diverse cyclopropanation reactions. One of these syntheses is depicted in *Scheme 13*.[18] The reaction

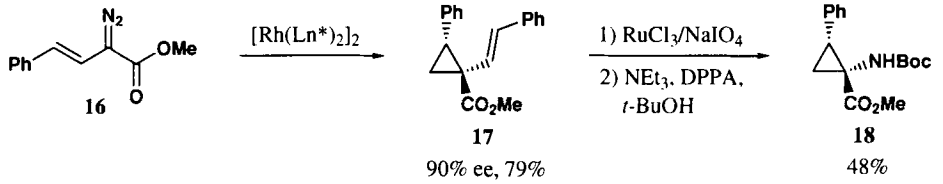


Scheme 13

between acrylates and enolates derived from α-bromo esters **13** provides ready access to *cis*-cyclopropanedicarboxylates **14**. From the corresponding 1-aryl- and 1-alkylcyclopropane-1,2-dicarboxylates **14**, regioselective mono-saponification of the least sterically hindered ester function and subsequent Curtius reaction leads to *cis*-1-alkyl and 1-aryl-2-aminocyclopropanecarboxylic esters **15**. However, it should be noted that non-protected cyclopropylamines with vicinal electron-withdrawing groups (1,2-push-pull-substituted cyclopropanes) are unstable and spontaneously rearrange to acyclic products.[18]

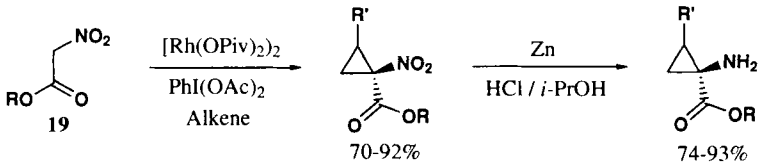
A completely different route, reported by Davies and co-workers, has been used for isomeric 1-aminocyclopropanecarboxylic acid (ACC) derivatives. Cyclopropanation of a variety of alkenes with vinyldiazo ester **16** in the presence of a chiral rhodium (II) carboxylate catalyst proceeded in high yields and good enantioselectivities (*Scheme 14*).[19] The amine was then incorporated in a sequence involving oxidative cleavage of the vinylcyclopropane (for example, styrene derivative **17**), followed by a Curtius rearrangement with the resulting carboxylic acid, leading to the protected aminocyclopropane ester **18** in modest yields for the two-step sequence.

In this case, compound **18** does not exhibit the instability of **15** upon deprotection, and the primary amine can be isolated after removal of the Boc protecting group.



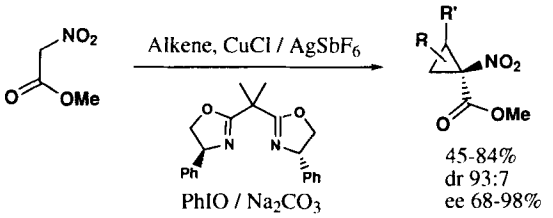
Scheme 14

In an attempt to reduce the number of steps required for the synthesis of cyclopropane α-amino acids and allow for the synthesis of substituted ACCs with sensitive functionalities, Charette *et al.*[20] used iodobenzene diacetate to effect the direct cyclopropanation reaction between α-nitrocarbonyls **19** and olefins in the presence of a catalyst. This cyclopropanation presumably proceeds *via* an iodonium ylide intermediate formed *in situ*. Both electron-rich and electron-deficient olefins can be employed and afford good yields (70–90%) and diastereoselectivities. Subsequent reduction of the nitro group by zinc dust affords the cyclopropylamines (*Scheme 15*). This reaction gave the corresponding compounds in good yields and diastereocontrol but with poor enantiocontrol. However, Cu(I)-*bis*(oxazoline) complex is highly efficient in



Scheme 15

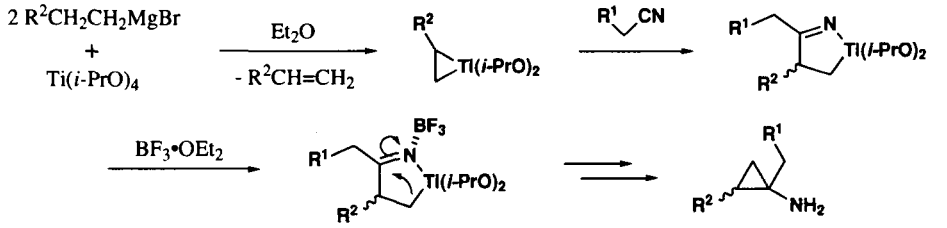
the catalytic asymmetric cyclopropanation with phenyliodonium ylides. Using sodium carbonate as an additive, hexafluoroantimoniate as the Cu(I) counterion and non-polar solvents enantioselectivities of up to 98% ee were obtained (*Scheme 16*).[21]



Scheme 16

Different organometallic species have also been successfully applied in the direct synthesis of cyclopropylamines, employing Grignard reagents and titanum species. After the

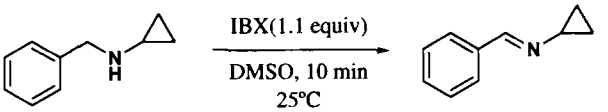
group of de Meijere adapted the Kulinkovich procedure for the preparation of substituted cyclopropanols[22] to the synthesis of tertiary cyclopropylamines from dialkylcarboxamides,[23] similar protocols have been developed for the preparation of primary cyclopropylamines from nitriles.[24] The mechanism of the transformation is depicted in *Scheme 17*. Similar methodologies have been reported in the synthesis of bicyclic cyclopropylamines,[25] primary 1-arylcyclopropylamines[26] and 1-alkenylcyclo-propylamines.[27]



R^1= Ar, OR, NR_2, SR...
R^2= H, Et, Ph, cycloalkyl

Scheme 17

Finally, as an alternative to the condensation reaction between carbonyl compounds and cyclopropylimines, dehydrogenation of cyclopropylamines also allows the synthesis of cyclopropylimines. Using *O*-iodoxybenzoic acid (IBX) as an oxidant, this reaction can be carried out under very mild conditions (*Scheme 18*).[28] However, this procedure seems to be limited to benzylic amines. In such cases, the condensation between benzaldehyde and a primary cyclopropylamine is normally the method of choice.



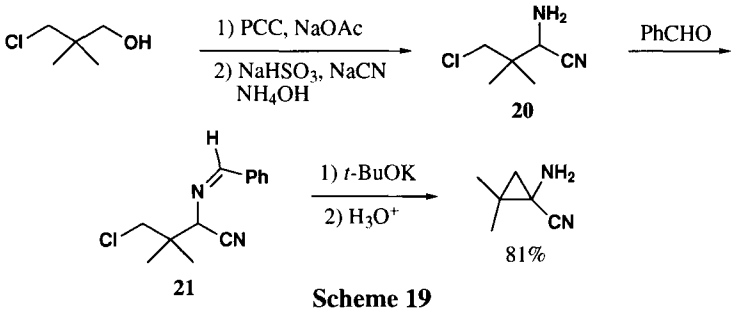
Scheme 18

b) Cyclopropanations to N-Cyclopropylimines

It should be noted that the methods included in this section could also have been described in the previous section. Since the imine moiety of *N*-cyclopropylimines can be easily hydrolized, the following methods are also suitable routes to cyclopropylamines. Thus, the sequence *N*-cyclopropylimine–cyclopropylamine–(*N*-cyclopropylimine)' can be used to carry out a carbonyl interchange, which can be useful for the synthesis of otherwise inaccesible compounds.

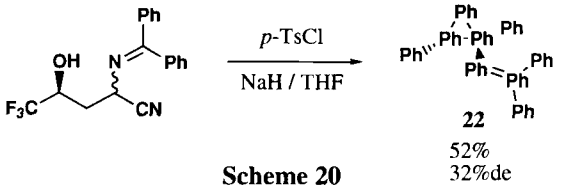
A simple and efficient example of this route uses 2-amino-4-chloro-3,3-dimethylbutanenitrile (**20**), easily accessible from the corresponding δ-chloroalcohol *via* oxidation with pyridinium chlorochromate and subsequent reaction with ammonium hydroxide in the presence

of sodium cyanide and sodium bisulfite. Compound **20** was found to react with benzaldehyde to give the functionalized aldimine **21**, which was conveniently 1,3-dehydrochlorinated by potassium *tert*-butoxide and subsequently hydrolyzed in acid medium to afford 1-amino-2,2-dimethylcyclopropane-1-carbonitrile. (*Scheme 19*).[29]



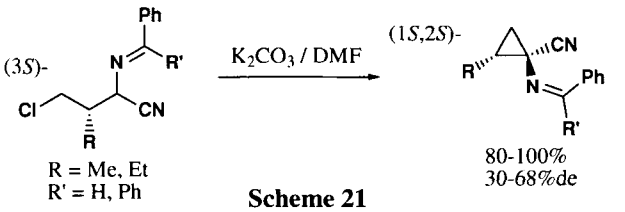
Scheme 19

A related strategy with a different leaving group has been developed. The molecule was designed to incorporate all the components needed: imine, electron-withdrawing group and leaving group. Intramolecular S_N2 reaction yields the cyclopropane with the imine group as a substituent. This method allows for some degree of stereocontrol in the synthesis of cyclopropylimines. The synthesis of **22** (*Scheme 20*) is representative.[30] Better results where obtained by



Scheme 20

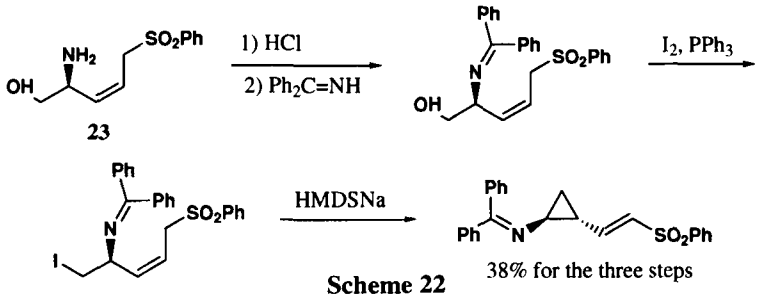
Salaün,[31] both in terms of yield and diastereomeric excess using a similar strategy (*Scheme 21*).



Scheme 21

An enantiomerically pure cyclopropylimine was recently synthesized in a one pot-three step procedure by Diez from allylsulfone **23** (*Scheme 22*).[32] The versatility of the vinylsulfone group of the final product makes this procedure a good entry to the synthesis of C2-substituted *N*-cyclopropylimines through group transformations.

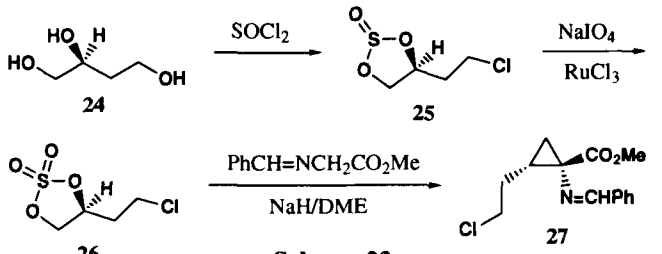
A different approach to the stereocontrolled synthesis of cyclopropylimines was developed by Hercouet (*Scheme 23*).[33] Butanetriol **24** was converted to the chlorosulfite **25** which was



23

Scheme 22

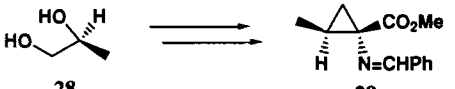
in turn oxidized to sulfate **26**. Condensation of this sulfate with methyl benzylideneglycinate at room temperature in DME in the presence of two equivalents of sodium hydride gave the alkylated imine **27** in good yield. This reaction is diastereospecific, only the *Z* isomer is obtained.



24 25 26 27

Scheme 23

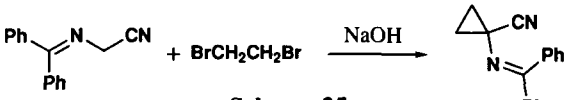
Using the same protocol but starting from a different compound (**28**), the same authors[33] were able to synthesize a new cyclopropylimine (**29**) in 95% yield and also diastereospecifically (*Scheme 24*).



28 29

Scheme 24

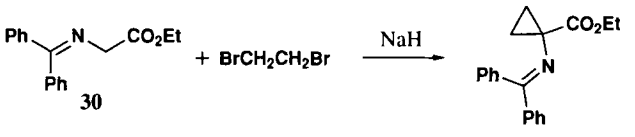
Related reactions also based on nucleophyllic substitution, but in the intermolecular fashion, have been described. Several *N*-(diphenylmethylene)amino derivatives with electron-withdrawing groups have been used together with 1,2-dibromoethane under phase-transfer conditions to yield *N*-cyclopropylimines. This strategy was first used by O'Donnell[34] in the synthesis of amino acid derivatives using a cyano group (*Scheme 25*).



Scheme 25

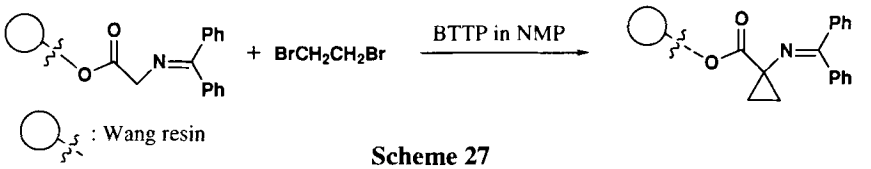
This synthetic pathway requires a very stable imine substrate and only simple dihaloethanes can be employed for the double alkylation. Thus, imine moiety is required to bear

aryl substituents to successfully yield the cyclopropylimine. The cyano group only acts here as an electron-withdrawing substituent to make the hydrogen atoms more acidic and can be easily replaced by other electron-withdrawing group. The use of ethyl benzylideneglycinate **30** with 1,2-dibromoethane affords the cyclopropylimine **31** (*Scheme 26*).[35] The same procedure has been



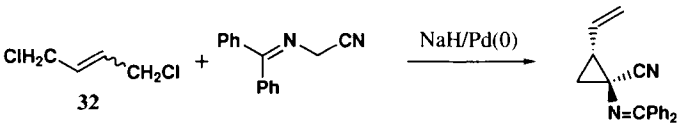
Scheme 26

also used in its solid-phase version.[36] The alkylation of the Schiff base of a resin-bound glycinate with dihaloethane yields the polymer-supported cyclopropylimine under mild conditions using Schwesinger's base *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP) in *N*-methyl-2-pyrrolidone (NMP) (*Scheme 27*).



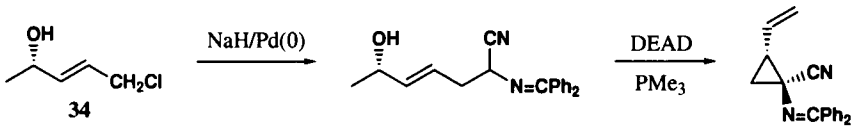
Scheme 27

In a series of papers, Salaün described a new method to generate *N*-cyclopropylimines through a one-pot tandem alkylation and S_N' cyclization using Pd(0) as catalyst and starting from *E* or *Z*-dichlorobut-2-ene **32**. This methodology afforded cyclopropylimine **33** in good yield and diastereochemically pure (*Scheme 28*).[37]



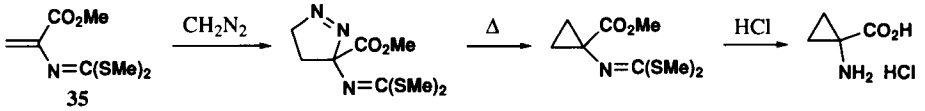
Scheme 28

Further efforts to make this methodology enantioselective failed due to the reversibility of the palladium-induced vinylcyclopropane ring opening. Thus, when the reaction was performed on asymmetric substrates or in the presence of chiral catalyst ligands, low enantioselectivity (≤ 32% ee) resulted.[38] However, this epimerization problem was overcome by conducting the cyclization step under Mitsunobu reaction conditions in the absence of Pd(0). The use of this strategy with (*4S*)-1-chloropent-2-en-4-ol **34** as a chiral analogue of **32** afforded the asymmetric synthesis of **33** in good yield (*Scheme 29*).[39]



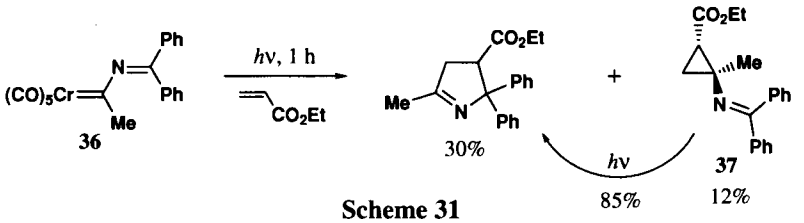
Scheme 29

Carbene cyclopropanations have been used for the synthesis of ACC derivatives as well. Starting from *N*-[bis(methylthio)methylen]-2-aminoacrylate (**35**), Cativiela[40] developed a simple and efficient route to analytically pure ACC in nearly quantitative yields (*Scheme 30*).



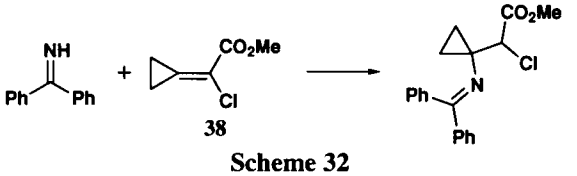
Scheme 30

Metal carbene complexes have been also employed. As previously stated in *Section 1. b)*, Fischer carbene complexes can be used as cyclopropanating agents. Similarly, imine-substituted Fischer carbene complexes **36** were reported to cyclopropanate alkenes.[41] In this case, the imine moiety is part of the carbene complex, and thus simple alkenes can be used to yield *N*-cyclopropylimines (*Scheme 31*). The reaction requires photochemical activation of the imino-carbene. Normally, subsequent photorearrangement of the *N*-cyclopropylimine takes place, but under controlled reaction conditions, intermediate *N*-cyclopropylimine **37** could be isolated.



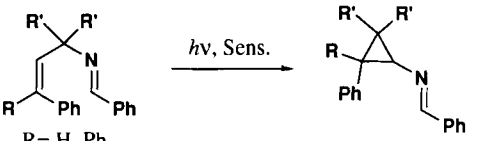
Scheme 31

A completely different strategy was developed by de Meijere,[42] based on the Michael addition of benzophenone imine to 2-chloro-2-cyclopropylideneacetate **38** (*Scheme 32*). The scope of this reaction was subsequently widened to include different substituents on both the imine and cyclopropylidene moieties.[3]



Scheme 32

Finally, triplet-sensitized irradiation of 2-aza-1,4-dienes affords *N*-cyclopropylimines via 2-aza-di-π-methane rearrangement pathways. However, this method is not general since several aryl groups are needed to stabilize the species involved, and the yields are very low, even in the most favorable cases (*Scheme 33*).[43]



R= H, Ph
R'= Me, Ph

4 -11%

Scheme 33

II. REACTIVITY

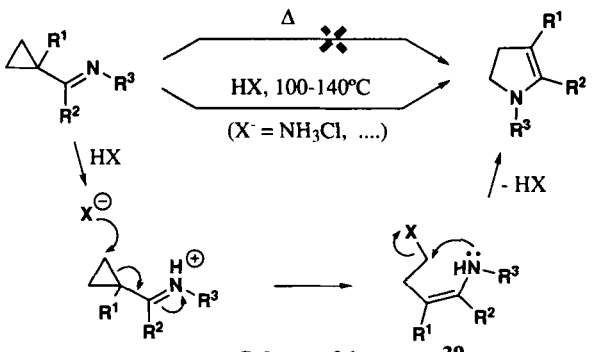
1. Rearrangements of *C*-Cyclopropylimines

This section will review the reactivity of *C*-cyclopropylimines and will focus on the rearrangements leading to pyrrolines, although different heterocyclic products are possible as well. A variety of conditions can be applied, which allow the use of diverse methods depending on the target molecule and the substituents present. Other possible reaction paths, apart from rearrangements, include cycloadditions to yield larger heterocycles.

a) Rearrangement of C-Cyclopropylimines to 2-Pyrrolines

i. Cloke-Stevens-Boeckman Rearrangements

The thermal rearrangement of *C*-cyclopropylimines, first reported by Cloke in 1929,[1] was later exploited by Stevens, who applied the transformation as a general method toward the synthesis of five-membered-ring nitrogenated alkaloids. Stevens devised several synthetic routes to alkaloids starting from suitable substituted 2-pyrrolines. He chose the rearrangement of appropriately substituted cyclopropyl imines under acidic catalysis at temperatures ranging from 110 to 150°C as a reliable and convenient method for the preparation of 2-pyrrolines. This reaction turned out to be the key step in many syntheses of natural products. This remarkable synthetic work, reviewed in 1977,[44] emphasized that the rearrangement is not a purely thermal process and that an acid catalyst with a nucleophilic counterion is required. The generally accepted mechanism for this process is outlined in *Scheme 34*. It involves the protonation of the N atom, nucleophilic attack of the counterion producing the ring opening and final re-closure of the intermediate. However, the method suffers from several limitations, related to the acidic reaction conditions and the relatively high temperatures. Thus, there are inherent factors that reduce significantly the scope of the process, especially for applications involving complex and sensitive multifunctional molecules. In some cases, under mild non-acidic conditions, the intermediate species **39** has been detected by early hydrolysis of the corresponding acyclic halo-imine prior to the final cyclization step, proving the existence of the intermediate.[45]



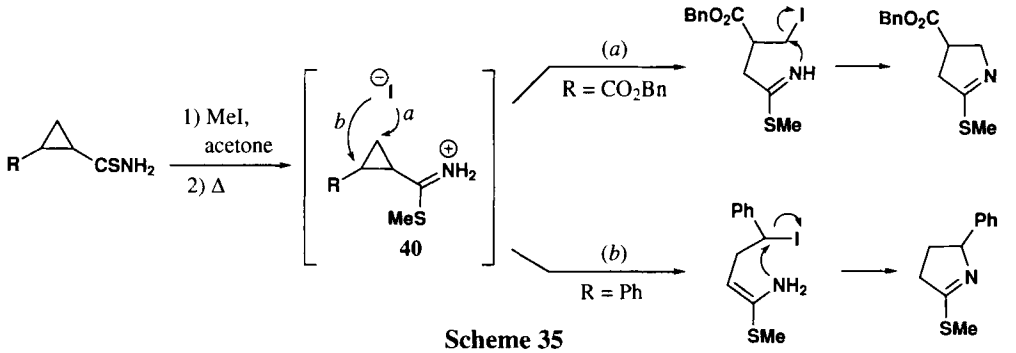
Scheme 34

The rearrangement can also be carried out with iminium ions, where the N atom carries a positive charge, which avoids the use of acids to protonate the iminic N. Hence, the transformation of these compounds is achieved under milder conditions, by heating in the presence of catalytic amounts of salts like LiCl or LiBr. This cyclopropyliminium ion rearrangement has been applied to the synthesis of a number of pyrroline-derived compounds. The scope, mechanism and applications toward alkaloid synthesis have been reviewed.[46] In the last decade of the past century, the procedure has been applied in several syntheses of alkaloid-type compounds, showing that this method is still a valid tool for the synthetic chemist. It has been used for the synthesis of indolizidine alkaloids, like slaframine,[47,48] azanicotine,[49] *Strychnos* alkaloids like dehydrotubifoline[50] or intermediates for the synthesis of lycorine.[51] In these approaches, the cyclopropylimine rearrangement is normally the key step that provides the basic skeleton of the alkaloid. Although the strategy behind these syntheses is basically the same used by Stevens, some modifications were introduced to improve the method in specific cases, such as carrying out the desired rearrangement at a much lower temperature using catalytic amounts of Me_3SiCl and NaI in DMF.[50]

In some cases, the cyclopropyliminium ion rearrangement can be coupled with a second reaction (*e.g.* elimination, cyclization).[51] Such "tandem reactions" or "molecular cascades" provide remarkable chemical transformations.

In the last years, an analogous process has been described for the thiomethylimidate cyclopropane rearrangement.[52,53] The factors affecting the regioselectivity of this rearrangement have been examined.[53] Interestingly, opposite regioisomers are observed for phenyl- and benzyl ester groups (*Scheme 35*). Probably, the stabilization of an incipient positive charge produced by the phenyl substituent in intermediate **40** drives the attack of the iodide and the regiochemistry in this case, while the steric factors are of greater importance in the case of the benzyl ester moiety.

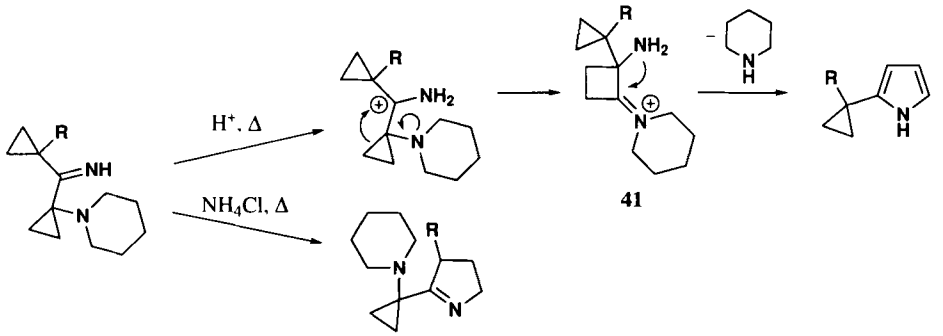
These pyrrolothiomethylimidate derivatives are versatile intermediates and can be reacted with primary and secondary amines, yielding 2,3-diaminodihydropyrroles (starting from *N*-protected 1-amino-cyclopropanethioamides)[52] or can be transformed into diaryl pyrrolines through the addition of Grignard reagents in the presence of a Pd catalyst.[53]



Scheme 35

ii. Thermal Rearrangements without Acid/Nucleophilic Catalyst

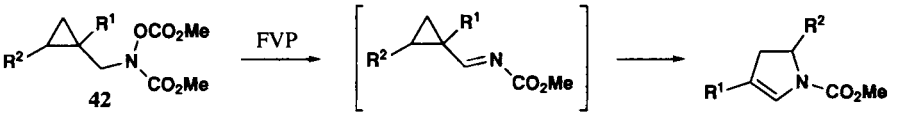
In some cases, *C*-cyclopropylimines can rearrange under acid catalysis without the need for a nucleophilic counterion, through a different mechanism. Wasserman and Dion[54] showed that, even without the attack of a nucleophile, *C*-cyclopropylimines undergo acid-catalyzed rearrangement if there is sufficient stabilization of the positive charge formed during the ring-opening process, through donor-stabilized cyclobutyl cations like **41**, as depicted in *Scheme 36*. When this procedure is applicable (*i. e.*, when electron-donor groups are placed on C1 in the cyclopropane ring), it permits the preparation of pyrroles using non-nucleophillic acids (like tetrafluoroboric acid) in refluxing xylene (about 140°C). The pyrroles are formed by rearrangement of the corresponding cyclopropylimines, followed by elimination of the functional group attached to C1 (a piperidine in this case). When two different cyclopropyl substituents are attached to the imine, the rearrangement proceeds through activation of the cyclopropane ring possessing a donor group (*Scheme 36*). The yields of pyrrole (32–42%) are of limited synthetic interest, but this process shows how the regiochemistry of the rearrangement can be directed, through the activation of one or the other cyclopropane rings, depending on the reaction conditions.



Scheme 36

In other cases, there is even no need for an acid catalyst and pure thermal rearrangements can be observed, although normally higher temperatures are required. To this group belongs the thermal rearrangement of *N*-acylcyclopropylimines **42** (*Scheme 37*), which are

generated *in situ* through Flash Vacuum Pyrolysis (FVP) conditions, and subsequently pyrolized at 400-500°C.[55] Derivatives with phenyl or acyl substitution in the ring were rearranged in moderate yields to the corresponding 2-pyrrolines. In these systems, there is a thermodynamic shift due to the resonance stabilization of the amide linkage (carbamate) in the 2-pyrroline (about 20 kcal/mol), compared to the weak interaction of the acyl group and the iminic N in the substrate, that makes up for the >10 kcal/mol of difference between the π-C=C bond and the more stable π-C=N bond, allowing the cyclopropane strain energy to drive the reaction. This rearrangement was monitored over a temperature range from 350 to 550°C and the 2-pyrroline yield was at a maximum at 500°C. However, when other groups were present in the cyclopropane (H or methyl) only ring-opened mixtures, decomposed fragments, and polymerization tars were observed, diminishing the generality of this transformation. The effect of substitution in the reaction outcome is consistent with a diradical intermediate.

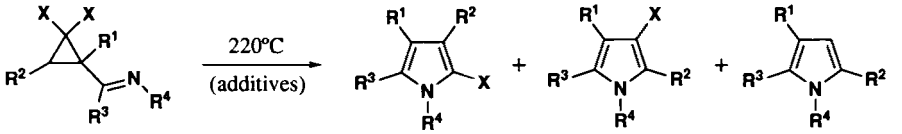


42

R^1 = H, Ph, CO_2Me
R^2 = H, Ph, COPh

Scheme 37

Finally, the formation of pyrrole products in the thermolysis of (2,2-dihalocyclopropyl)-methyleneamines, in which the rearrangement is initiated by cleavage of a C–halogen bond, has been reported.[56] This provides a synthetic path for 2- or 3-halo-4-phenylpyrroles (*Scheme 38*). The reaction conditions are in general somewhat harsh and require the use of different additives (*e.g.* inorganic salts, bases, metal oxides). The yields vary significantly depending on the additive used and the structure of the substrate, but in general they are low. Nevertheless, the method can be a useful process for the preparation of certain substituted halo-pyrroles.



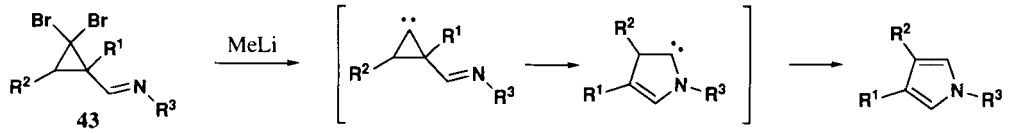
X = Cl, Br, F
R^1= H, Me, Ph
R^2= Me, Ph
R^3= H, Me
R^4= Ph, $PhCMe_2$, *t*-Bu, Cy, 1-adamantyl

0-87% 0-90% 0-18%

Scheme 38

iii. Carbene-carbene Rearrangements

Analogous to the Skattebøl rearrangement in VCP systems,[57,58] this type of rearrangement has been also described for *C*-cyclopropylimines (*Scheme 39*). Substrates **43** are normally prepared by cyclopropanation with dihalocarbenes, providing the geminal dihalo-substituted

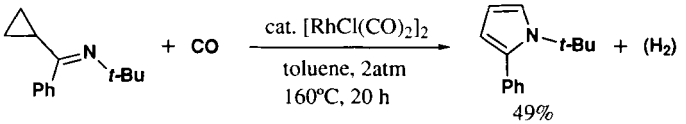


Scheme 39

substrates, which, in turn, is the starting point for the generation of a new carbene, thus inducing the rearrangement. The transformation takes place at moderate temperatures (0-25°C). The yields are in general low, and a major drawback is that not many functional groups are compatible with the exposure to MeLi without reaction, thus the use of protecting groups is required.[9,59] The mechanism of the transformation has not been thoroughly explored, but the behavior of these systems should be analogous to that of the all-carbon system.[58] Accordingly, cyclic products predominate at lower temperature, while higher temperature favors the formation of acyclic allenic products.

iv. Metal-catalyzed Rearrangements

In general, there are few examples of metal-catalyzed rearrangements of *C*-cyclopropylimines affording five-membered rings (pyrroles or pyrrolines). In most cases, larger rings are formed, incorporating fragments from the ligands of the metal complex. These reactions will be examined below. Nevertheless, some particular examples of five-membered heterocycle formation have been described (*Scheme 40*).[60] This reaction is more an exception than a rule, since the usual path of these processes leads to six-membered heterocycles.



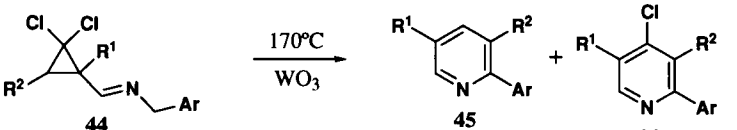
Scheme 40

v. Photochemistry of C-Cyclopropylimines

To our knowledge, there are no reports about photo-rearrangement of *C*-cyclopropylimines to afford five-membered rings. Moreover, a number of *C*-cyclopropylimines have been synthesized by photochemical means, as photo-stable products, by the 1-aza-di-π-methane rearrangement,[16,17] as shown in Part I (*Synthesis*). These observations point out the inefficiency of the rearrangement for *C*-cyclopropylimines after the absorption of a photon, which is in sharp contrast to the case of isomeric *N*-cyclopropylimine substrates (see *Reactivity Section 2 a) ii.*). As noted before (*Reactivity Section 1. a) ii.*), the reason for this contrasting reactivity for the two isomeric systems stems from the different thermodynamic balance of each type of rearrangement, provided that no catalyst is involved.

b) Rearrangements to Larger Heterocycles

The formation of six-membered heterocycles has been described in the rearrangement of 3,3-dichloro-*N*-cyclopropylimines **44** (*Scheme 41*).[61] Pyridines **45** and halopyridines **46** were synthesized through thermolysis of the 3,3-dichlorocyclopropane precursors. In this rearrangement, an extra carbon atom is added to the C_4N system (cyclopropane + imine) from a *N*-benzyl moiety. The reaction occurs in apolar solvents and it is promoted by WO_3, allowing the process to occur at lower temperatures (220°C is required without catalyst). In general yields are moderate, and the reaction temperature for the catalyzed reaction (170°C, reached in boiling phenetole or using sealed tubes) is still too high to be compatible with a wide variety of



44
R^1= H, Ph
R^2= Me, Ph, *p*-Tol
Ar = Ph, *p*-Tol, *o*-ClPh

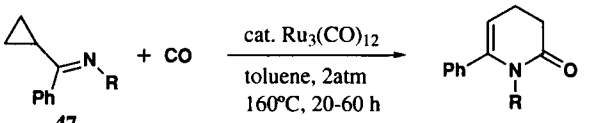
45
18-65%

46
0-15%

Scheme 41

substituents. Several pathways discussed for this rearrangement led to the conclusion that the most plausible mechanism begins with dechlorination followed by bond breaking (between C–R1 and C–R2) and hydrogen abstraction from the benzylic position, yielding an azatriene that finally suffers an electrocyclization to the pyridine(s). However, the details of every step in this mechanism remain unclear. Interestingly, it is noted that 3,3-dichlorocyclopropane imines such as **44**, as distinct from cyclopropane imines, do not rearrange under the typical conditions of the Cloke rearrangement. The reason for the lack of reactivity could have a steric basis. Further examples of this pattern will be discussed below, when the photochemistry of 3,3-dimethyl-*N*-cyclopropylimines is discussed.

Scheme 42 presents a completely different type of metal-catalyzed reaction.[60] In this case, the extra C atom is derived from the inclusion of a CO molecule from the ligands of the metal complex into the final product. The reaction conditions are analogous to the process



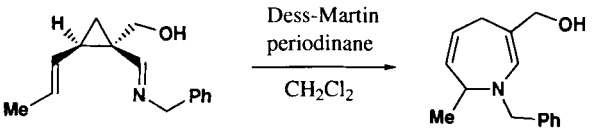
47
R = Bu, *t*-Bu, Cy

10-76%

Scheme 42

described in *Scheme 40*, but using a different ruthenium catalyst, which results in substrates **47** being rearranged to different products. Other catalysts were also explored, including Ru, Ir, and Co complexes, albeit without success.

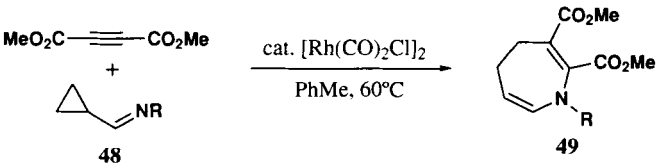
Finally, seven-membered rings (dihydroazepines) can be formed through the Cope-type rearrangement of 2-vinylcyclopropylimines (*Scheme 43*). Only one example is described here, initiated in this case by Dess-Martin oxidation.[62] The reaction conditions include 2.5–3 equivalents of oxidant and several equivalents of pyridine, at room temperature.



Scheme 43 95%

c) Cycloaddition Reactions

Cycloaddition reactions, commonly catalyzed by transition metal complexes, constitute a different group of reactions. Seven-membered ring formation, arising from a cycloaddition reaction between *C*-cyclopropylimines and alkynes or allenes has been described.[63] This reactivity is analogous to that of vinylcyclopropanes[64] and represents the first example of transition metal-catalyzed hetero-[5+2] cycloaddition, leading in this case to the dihydroazepine skeleton. This reaction is illustrated in *Scheme 44*, showing the reaction of *C*-cyclopropylimines **48** with



48

R = Cy, Bn, alkyl...

49

Scheme 44

dimethyl acetylenedicarboxylate in the presence of a rhodium catalyst, affording dihydroazepines **49** in good to excellent yields. This route to dihydroazepines could be further simplified through *in situ* imine formation. The sequence imine formation–aza-[5+2] cycloaddition enables dihydroazepine synthesis from three commercially available starting materials in one operation, effectively a three-component cycloaddition. This reaction works with aldimines, ketimines, and substituted cyclopropanes. Single regioisomers are obtained. These reactions are also readily scaled up, generating multigram quantities of the substituted dihydroazepines, compounds of use as synthetic building blocks and as scaffolds for combinatorial synthesis.

Although these examples are limited to *C*-cyclopropylimines, there are no *a priori* reasons to prevent *N*-cyclopropylimines from being tested for cycloaddition reactions. The reactivity of these isomeric molecules is reviewed in the next section.

2. Rearrangements of *N*-Cyclopropylimines

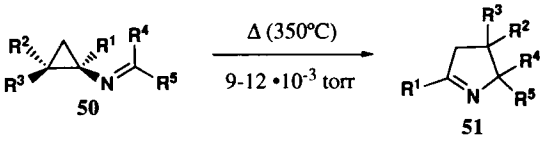
In this section, the rearrangements of *N*-Cyclopropylimines are reviewed. As in the case of the *C*-analogs, the main reaction is the rearrangement to yield pyrrolines. However, it should be noted that the diversity of attempted reaction conditions in this case is clearly smaller. Since

the transformations carried out in both types of substrates proceed in a similar fashion it is possible that certain useful reactions still remain to be uncovered.

a) Rearrangements of N-Cyclopropylimines to 1-Pyrrolines

i. Thermal Rearrangements

The first references on the thermal rearrangement of *N*-cyclopropylimines originate from two papers of Huisgen,[65,66] and derive from the study of 1,3-dipolar cycloadditions. Some *N*-cyclopropylaldimines (**50**, $R^2 = R^3 = Ph$, $R^4 = H$, *Scheme 45*), that possess geminal diphenyl groups activating the cyclopropane ring, were rearranged in solution to yield the corresponding 1-pyrrolines **51** at moderate temperatures, around 150°C. A mechanistic exploration of this



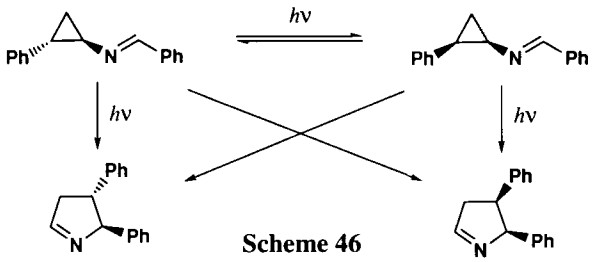
Scheme 45

process emphasized the absence of a noticeable solvent effect. This fact and the absence of catalyst suggest a mechanism similar to the vinylcyclopropane–cyclopentane rearrangement. In this context, diradical intermediates were postulated. This is in contrast to the thermal rearrangement of isomeric *C*-cyclopropylimines, which involve ionic intermediates, as stated earlier. More recently, the scope of these thermal rearrangements has been extended through the use of FVP conditions at temperatures around 350°C.[67] The process is very similar to that described in *Scheme 37* for *C*-cyclopropylimines **42**, although the scope is wider in the case of the *N*-cyclopropylimine–1-pyrroline rearrangement. Compared to the analogous C-cyclopropylimine rearrangement (see *Reactivity Section 1. a) ii.*), there is less thermodynamic driving force since the unsaturated moiety (a C=N bond) is present in both the substrate and the product. The driving force derives from release of the strain energy of the cyclopropane. The reaction is regiospecific and supports different substituents in virtually any position of the C_4N structure, including heterocycles. The yield of pyrroline formation depends on the reaction temperature, with better results being obtained between 350 and 450°C, according to the substitution pattern. The upper limit of yields is due to the pyrroline ring opening reaction once it is formed, producing acyclic butanenitriles.

ii. Photochemical Rearrangements

In general, *N*-cyclopropylimines **50** can also be rearranged at room temperature to 1-pyrrolines **51** through a photochemical process.[68] In all cases, the regiochemistry of the process is the same as for the thermal rearrangement, and only one of the two possible regioisomers is detected. With regard to the stereochemistry, analysis of the photo-rearrangement of 2-phenyl

substituted substrates indicated good stereoselectivity in the products, but depended on the conditions and the irradiation time (more than 10:1 for low conversions; about 5:1 for 80% conversion). The *trans*-pyrroline is the favored product starting from the *trans*-cyclopropane substrate, whereas the *cis*-substrate produces mainly the *cis*-pyrroline, the ratio being virtually identical in both cases.[69] The rate of ring isomerization is very close to the rate of the favored rearrangement, so the stereoselectivity remains high only at relatively low conversions. If the conversion of the substrate is carried forward, the increasing concentration of the ring isomer competes for the absorption of photons, leading to a decrease on the final *cis/trans* ratio of the products. This is in contrast with the thermal rearrangement, where the stereoselectivity is very low (<1.5:1), approaching the 1:1 ratio when the temperature is increased above 350°C. The higher stereoselectivity of the photochemical rearrangement, together with the opportunity of selecting the proper wavelength to selectively excite the chromophore, without disturbing other moieties, makes this transformation a useful path to the synthesis of pyrrolines (*Scheme 46*).

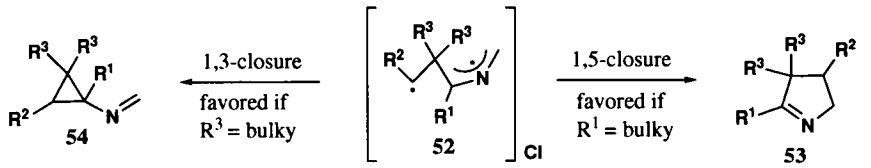


Scheme 46

The mechanism of the process has been studied by means of experimental and computational tools.[69] A conical intersection (CI) has been calculated for a model system, and the selectivity of the reaction, as well as the relative rates of the possible photo-processes, are interpreted. This study points out the absence of an intermediate for the rearrangement (several reaction paths are depicted without any energy minimum on them), leading to *ultrarapid* processes that should occur in the picosecond range. Nevertheless, there is a clear diradical-like character in the CI "funnel" that connects the electronic excited state with the ground state, comparable to a diradical transition state.

For the thermal rearrangement, a similar situation is expected, but in that case, the transition state is not reached from the *upper* energy surface of the excited state, through the CI funnel, but from thermal "excitation" along the energy surface of the fundamental state (as described by the Transition State theory). Due to the high temperature, dynamic effects become very important for the study of such processes, as in the case of the vinylcyclopropane–cyclopentane rearrangement.[2] The effects on reactivity of different substituents all over the cyclopropane and imine moieties of the *N*-cyclopropylimine structure have been examined as well,[70] and have been interpreted in the context of the computational results. First, it has been shown that 1-substituted substrates exhibit an enhanced reactivity toward rearrangement. The reasons for this effect stem from steric interactions in the CI structure **52** (*Scheme 47*). When bulky groups are placed

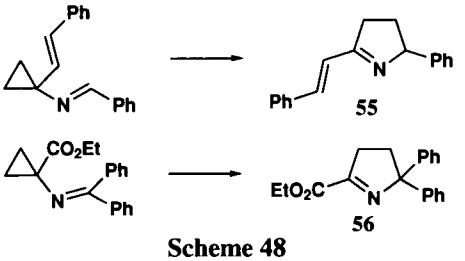
in R^1, the 1,5-closure of the diradical-like intermediate structure is favored over the 1,3-closure. The first process leads to the 1-pyrroline structure **53**, while the mentioned 1,3-closure represents a deactivation path of the excited state, leading to the initial *N*-cyclopropylimine structure **54**.



Scheme 47

Second, a lack of reactivity has been observed for encumbered cyclopropanes, which possess a 3,3-disubstitution pattern in the cyclopropane ring (*e. g.* chrysanthemic acid-like structures, R^3 = Me in *Scheme 47*). In this case as well, steric reasons are claimed to favor the 1,3-reclosure of the CI structure over the 1,5-closure, which is more difficult due to torsional effects of the bulky groups R^3. This phenomenon could be general for cyclopropane-containing systems, and has been previously documented for the Cope rearrangement of *cis*-divinyl cyclopropanes with the additional geminal dimethyl substitution.[71]

Finally, a high chemoselectivity has been observed for the *N*-cyclopropylimine–1-pyrroline rearrangement compared to the vinylcyclopropane–cyclopentene rearrangement or the cyclopropylcarbonyl–dihydrofuran rearrangement, when the imine moiety and an additional insaturated group are attached to the same carbon of the cyclopropane ring, as shown in *Scheme 48*. Only products **55** and **56** were detected, respectively, without any indication of vinylcyclopane–cyclopentene or cyclopropylcarbonyl–dihydrofuran rearrangements taking place.

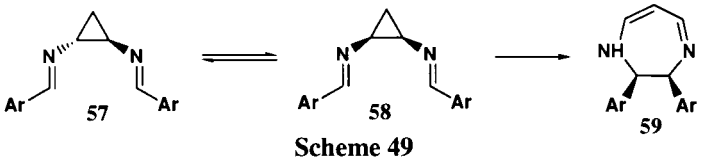


Scheme 48

b) Other Rearrangements

i. Cope Rearrangements to Dihydroazepines or Dihydrodiazepines

In the case of vicinal *bis*-imino-cyclopropanes, the diastereoselective rearrangement of *N,N'*-dibenzylidene-1,2-cyclopropanediamines **57** and **58** to *cis*-2,3-diaryl-2,3-dihydro-1*H*-1,4-diazepines **59**[72] has been described. This rearrangement can be simply thermal or catalyzed by acid, but it always involves as the first step the ring isomerization of the cyclopropane to the *cis*-isomer, which is able to undergo the di-aza-Cope rearrangement to the dihydrodiazepine ring, thus driving the diastereoselectivity to the *cis* configuration in the product (*Scheme 49*).

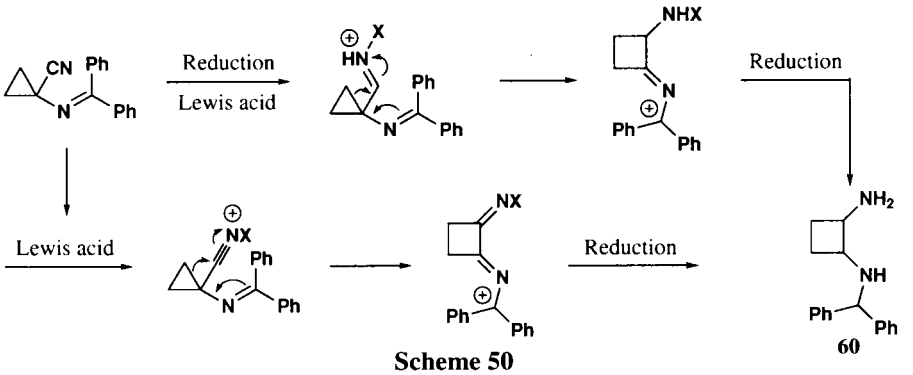


Scheme 49

For vicinal *cis*-alkenyl-imino-cyclopropanes, the corresponding aza-Cope ring expansion has also been described.[38] Even with an aromatic π-system, the rearrangement is possible, as in the synthesis of 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid through the rearrangement of an *N*-cyclopropylimine, for example.[73] Similar processes involving other nitrogen-containing unsaturated groups, such as the isocyanate moiety, are also feasible, furnishing dihydroazepinones in this case.[74]

ii. Cyclobutane Formation

Some reports indicate cyclobutane formation in the reaction of *N*-cyclopropylimines. According to the bibliography, the reduction of 1-(diphenylmethylene)amino-l-cyclopropanecarbonitrile with borane yields, in addition to the expected cyclopropyl-diamine, a small quantity of a diaminocyclobutane by-product **60** (*Scheme 50*).[75] After optimization of the process, this reaction was used for the synthesis of *trans*-1,2-diaminocyclobutane. The possible pathways of such transformation and the structure of the intermediates are shown in *Scheme 50*.



Scheme 50

Some other rearrangements yielding cyclobutene products have been described,[3] involving carbene intermediates and a more complex mechanism. Their complexity and specialized nature exclude them from the scope of this review, although they serve as examples of the versatility and synthetic potential of the cyclopropylimine system.

III. CONCLUSIONS

Through this review it has been shown that cyclopropylimines are highly versatile intermediate building blocks for the synthesis of valuable nitrogenated compounds. The main branch in the reactivity of cyclopropylimines, although not the only one, is the rearrangement to pyrro-

lines. Clearly, this synthetic path cannot be omitted when planning the synthesis of heterocycles among the pyrrole, pyrroline or pyrrolidine families. Stereoselectivity can be controlled in this rearrangement, and small changes in the structure of such a small system can fundamentally modify the course of the reaction, due to a delicate balance of stereoelectronic interactions. In conjunction with metal complexes acting as catalysts, the variety of possible heterocyclic structures is multiplied, going beyond the five-membered ring structures. Moreover, cyclopropylimines are important intermediates involved in the synthesis of the cyclopropylamine substructure. Although cyclopropylimines are well established intermediates for many syntheses, they still constitute attractive means to extend the synthetic possibilities of known processes, further enlarging the body of available products from cycloadditions and related reactions.

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