Cyclization and Cycloaddition Reactions of Cyclopropyl Carbonyls and Imines

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Received: The date will be inserted once the manuscript is accepted.

Abstract: Activated cyclopropanes, such as vinyl and carbonyl cyclopropanes, are useful building blocks in organic chemistry due to their exceptional reactivity. This review focuses on the use of cyclopropyl carbonyls and imines in cyclization and cycloaddition reactions for the synthesis of cyclic compounds. Cycloisomerization and other cyclization reactions are treated first, followed by formal cycloaddition reactions and applications in total synthesis. For each class of reactions, key pioneering works are shortly presented and emphasis is then set on recent results. Indeed, the utility of activated cyclopropanes in organic synthesis has been significantly increased in the last years by combining modern catalytic methods with the well-established reactivity of these building blocks. Together with progress in the synthesis of the cyclopropanes, these new methods allowed a better control over the diastereoselectivity and enantioselectivity of the reactions as well as their use for the synthesis of complex natural products.

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Keywords: activated cyclopropanes, cyclizations, cycloadditions, isomerizations, stereoselective synthesis.

1 Introduction and Scope of the Review

Small rings, especially cyclopropanes, occupy a privileged position in organic chemistry. The rigidity of the cyclopropyl group makes it an excellent scaffold for medicinal chemistry. The ring strain energy confers an exceptional reactivity to the three-membered ring, which has been best described using the Walsh orbitals. Indeed, a partial π character is observed, which can be used to explain several unique properties of cyclopropanes, such as carbocation stabilization, addition reactions and rearrangements.

Despite its ring strain, cyclopropanes are usually chemically relatively inert, unless further activating groups are introduced on the ring. Especially, vinyl and carbonyl substituents have been traditionally used to enhance the reactivity of cyclopropanes. Recently, more reactive derivatives like alkylidene cyclopropanes and cyclopropanes have also been extensively examined. The importance of vinyl cyclopropanes has been largely demonstrated in rearrangement reactions, such as the vinylcyclopropyl to cyclopentene and the divinylcyclopropyl rearrangements. Furthermore, their use in metal-catalyzed cycloaddition reactions, for example [5+2] cycloadditions has been intensively investigated. In all these processes, the ring-opening reactions of the three-membered ring is used to generate larger ring-systems, especially 5 and 7-membered rings, which are not so easily accessed via other methods. The use of carbonyl cyclopropanes is even older and their potential to generate dissonant functional groups relationship via “homoconjugate” additions has been discovered already in 1895 by Perkin. Since then, opening cyclopropyl carbonyls has become a routine reaction and has been extensively used in organic synthesis. In contrast, the generation of new ring systems via the ring-opening step has been less extensively studied than in the case of vinyl cyclopropanes. Despite promising pioneering works mostly in the seventies by the group of Stork, Danishefsky and Corey among others on intramolecular cyclization reactions of activated cyclopropanes, progress in the field has been slow. A notable exception was the introduction of more reactive donor-acceptor cyclopropanes, especially by the groups of Wenkert and Reissig. Nevertheless, it is only very recently that the full potential of carbonyl cyclopropanes has been fully realized, especially as exceptional building blocks for the construction of ring systems in catalytic reactions. This progress has also become possible due to important advances in the synthesis of cyclopropanes, including asymmetric methods.

The goal of this review is to highlight the high potential of carbonyl cyclopropanes in cyclization and cycloaddition reactions. Although this particular topic has never been reviewed specifically, several important applications of activated cyclopropanes have appeared in other works covering the special reactivity of donor-acceptor cyclopropanes, the reactivity of cyclopropanes in the presence of transition metals, the activation of cyclopropanes using silyl groups and intramolecular addition reactions. These previously covered topics will be treated only shortly when necessary to gain a complete picture of the reactivity of carbonyl cyclopropanes, but the main focus will be on new recent progress, which has not yet been described extensively in the secondary liter-
nature. The review will be focused on reactions where the carbonyl plays the main role in activation and processes where other functional groups are controlling the reactivity (for examples rearrangements involving vinyl cyclopropanes) will not be examined here.

In order to better classify cyclization and cycloaddition reactions involving cyclopropyl carbonyls, we have ordered them according to the number of exogenous atoms introduced during the process (Scheme 1). Cyclization reactions without introduction of exogenous atoms will be treated first (Ch. 2), followed by reactions where one external atom (usually a heteroatom nucleophile) are introduced (Ch. 3). Cycloaddition reactions with two atoms (Ch. 4) and larger fragments (Ch. 5) will be examined next. Many of these reactions are only formal cycloadditions, as they often proceed via stepwise mechanisms with no continuous overlap of orbitals in the transition state. For the sake of simplicity, however, we will just call them according to the total amount of atoms obtained in the product and consider the cyclopropane ring as a three atoms fragment. Finally, the review will cover recent applications of cyclopropyl carbonyls in the total synthesis of natural products (Ch. 6).

1 Cyclization Reactions

2.1 Nucleophile Attached to the Carbonyl

In the case of cyclization reaction of carbonyl cyclopropanes, the simplest case is the attack of the carbonyl oxygen itself on the cyclopropane. This reaction is the equivalent of the vinylcyclopropane to cyclopentene rearrangement and is indeed one of the oldest known reactions of cyclopropyl carbonyls. It is especially facile in the case of donor activated cyclopropanes, for which a mild acid is usually enough to catalyze the rearrangement. The reaction becomes faster if the cyclopropane is further activated with two ester groups and become spontaneous if one of the esters is exchange by a ketone. Indeed, the metal-catalyzed cyclopropanation of electron-rich double bonds (i.e. vinyl ethers) with diazo keteesters or diketones usually leads directly to the dihydrofuran product. The intermediacy of a cyclopropyl is still a matter of debate, and depending on the reaction conditions, the formation of dihydrofuran has been shown to be possible via a cyclopropane intermediate or via a direct pathway. In 1999, Davies and co-workers developed a more reliable alternative using silyl enol ethers 2 as the diazo reagents to obtain cyclopropanes 3 in good yields. Simple deprotection with TBAF induced smooth formation of dihydrofuran 4 (Scheme 2). Alternatively, a Corey-Chaykovsky cyclopropanation-isomerization sequence has also been reported.

Recently, the isomerization event has been incorporated in more complex processes for the synthesis of heterocycles. Hu and co-workers reported the synthesis of angular dihydrofuroquinoline 6 via a Friedel-Crafts-isomerization sequence (Scheme 3). Liu and co-workers developed a general access to linear furoquinoline derivatives 8 (Scheme 4). In this case, SnCl4-mediated dihydrofuran formation was proposed to occur first, followed by electrophilic aromatic substitution and water elimination.

![Scheme 1](image1.png)

![Scheme 2](image2.png)

The necessity of using multiply-activated cyclopropanes and/or harsh conditions is one of the major limitations for the use of carbonyl cyclopropanes in the synthesis of furan derivatives. Recent progress in this area includes the use of acyl silanes, the introduction of a silyl group to promote ring-opening via stabilization of carbocationic intermediates and the first reports on transition-metal mediated isomerization. Especially impressive is the
Pd-catalyzed isomerization of alkylidene carbonyl cyclopropanes 9 developed by Ma and co-workers.\textsuperscript{25a,b}

\begin{equation}
\text{Scheme 3} \quad \text{Friedel-Craft-cycloisomerization sequence for the synthesis of angular dihydrofuroquinoline 6.}
\end{equation}

Depending on the reaction conditions, 4H-pyrans 10, 1,2,3-trisubstituted furans 11 or tetrasubstituted furans 12 can be obtained (Scheme 5). For the synthesis of 4H-pyran 10, a chloropalladation of the alkylidene was proposed as a first step (Scheme 6, A). β-Carbon elimination generated then a Pd enolate II. Intramolecular insertion of the alkene led to a Pd-dihydropyran intermediate III. Equilibration to IV followed by elimination of PdCl\(_2\) generated finally 4H-pyran 10.\textsuperscript{26} Strikingly, furan product 11 was observed instead when the reaction was run in the presence of NaI (Scheme 6, B). In this case, the Pd catalyst was not required and a nucleophilic attack of iodide to induce ring-cleavage followed by intramolecular SN\(_2\)' attack of enolate V was proposed to rationalize the formation of the observed product 11 after isomerization of the initially formed exo-alkene VI. The use of iodide to open activated cyclopropanes has indeed be successful in several reactions of cyclopropyl carbons (\textit{vide infra}). Finally, reaction in the presence of a Pd(0) catalyst proceeds probably via oxidative addition on the cyclopropane followed by intramolecular attack of enolate VIII on the Pd-allyl moiety to give the observed tetrasubstituted furan 12 after double bond isomerization (Scheme 6, C).

\begin{equation}
\text{Scheme 4} \quad \text{Domino ring-opening/recyclization reactions for the synthesis of furoquinolines derivatives 8.}
\end{equation}

\begin{equation}
\text{Scheme 5} \quad \text{Cycloisomerization of alkylidene carbonyl cyclopropanes 9.}
\end{equation}

\begin{equation}
\text{Scheme 6} \quad \text{Proposed mechanism for the cycloisomerization reactions of alkylidene carbonyl cyclopropanes 9.}
\end{equation}

In 2006, Bowman and Johnson reported that vinyl diketone cyclopropanes could be isomerized to the corresponding dihydrofuran using a Ni(0) catalyst.\textsuperscript{25c} The possibility to form a stabilized Ni-allyl intermediate upon ring-opening allowed to use very mild conditions. Most importantly, it was shown that the stereochemical integrity of cyclopropane 13 was completely conserved during the cycloisomerization reaction (Equation 1).
The cycloisomerization of carbonyl cyclopropanes is not limited to the formation of furan derivatives. Indeed, one of the oldest reports on such reactions by Cloke described the related isomerization of cyclopropyl imines to pyrrolines. 27 This reaction was then extensively developed by Stevens and co-workers for the synthesis of alkaloid natural products. 28 Purely thermal rearrangement appeared to be excessively slow, and a stepwise mechanism involving protonation of imines 15 and ring-opening with a halide followed by cyclization to give pyrrolines 16 has been proposed (Scheme 7). 29

The use of β-amino-cyclopropyl imines 18 has starting material was described by De Meijere and co-workers for the synthesis of pyrroles 19. 30 In this case, cyclopropane stannane 17 was lithiated and added to a nitrile to give 18. Addition of acid led to formation of pyrroles 19 after amine elimination (Scheme 8).

Recently, the Cloke-like rearrangement of thioiminate has been reported by Kuduk and co-workers. 31 Another useful extension of the methodology was introduced by Yang and Shi for the cyclization of cyclopropyl amides 20 to the corresponding γ-lactams 21 via an in situ formed bromo-imidate 1 (Scheme 9). 32 Importantly, no further activating group beside the amide is needed on the cyclopropane.

The ring-opening reaction of esters and acids to give lactones is also a well-established process, especially by the work of Wenkert. 10 This reaction has proven very useful for the synthesis of fused γ-lactone/furan or pyran ring systems 23 (Equation 2). 33 Wang and Du also reported the combination of the cycloisomerization reaction with an aldol condensation reaction in the case of activated vinyl-carboxylate cyclopropanes. 34 Werz and co-workers used the iterative bidirectional cycloisomerization of donor-acceptor carboxaldehyde cyclopropanes for the synthesis of anti-oligoannelated THF structure 26 (Scheme 10). 35 In this case, oxidation of alcohol 24 with IBX led directly to isomerization without isolation of the aldehyde.

Recent efforts have focused on the development of similar procedures for the synthesis of γ-lactams starting from amides. Lautens and co-workers described the ring-extension of methylene cyclopropyl amide 27 catalyzed by MgI₂ (Scheme 11). 36 The Lewis acidity of Mg is thought to activate cyclopropyl amide 27 for ring-opening with iodide. The generated intermediate 1 can then cyclize to generate the observed unsaturated lactam 28 after proton transfer. If an electrophile, for example an aldehyde or a tosyl imine, is added, product 29 resulting from reaction of the γ position of the conjugated enolate is observed. This reactivity towards electrophiles is highly dependent on the substitution on the amide, as for tertiary amides a formal [3+2] cycloaddition is observed (vide infra). The reaction was later extended to substituted alkylidene cyclopropyl amides. 36b In this case, lactams with an exo double bond were favored.
In 2007, Lautens and co-workers reported the first cycloisomerization of methylene cyclopropyl hydrazones 30 (Scheme 12). Two different azadiene products 31 and 32 could be obtained selectively depending on the reaction conditions. In this case, an intramolecular attack of the hydrazone on the cyclopropane without involvement of an allyl halide intermediate was proposed. Further investigations are still needed to rationalize the exquisite selectivity observed depending on reaction conditions.

The cyclization reaction of cyclopropyl imides is another alternative to obtain pyrrolidone products. In 2008, Shibasaki developed a ring-opening-aldol-cyclization sequence for the diastereoselective synthesis of γ lactams 34 starting from cyclopropyl imides 33 (Equation 3). The reaction was initiated by electrophilic activation with a Sc Lewis acid, followed by homo-conjugate addition of iodide to form an enolate intermediate 31 (Scheme 13). A diastereoselective aldol reaction via a chair transition state was proposed to account for the observed diastereoselectivity. Finally, proton transfer and cyclization to form lactam 34 closed the catalytic cycle.

An alternative strategy for the synthesis of pyrrolines starting from cyclopropanes makes use of the imines derived from β-amino-cyclopropane carboxylates. Finally, another approach starting from β-azido-cyclopropane dicarboxylates for the synthesis of lactams has been reported by De Kimpe and co-workers.

A mechanistically new approach has been recently introduced for the N-heterocyclic carbene (NHC) cycloisomerization of keton-carboxaldehyde cyclopropane to 3,4-dihydropyrones. Based on pioneering work about the redox opening of formyl cyclopropanes, Du and Wang reported a single example of this reaction in 2008. You and co-workers then demonstrated the generality of the reaction for the generation of dihydropyrones 37 (Equation 4). Mechanistically, this reaction is thought to proceed via addition of the NHC on aldehyde, followed by proton-transfer and ring opening to give an enol intermediate 33 (Scheme 14). After enol-ketone tautomerization, the attack of the enolate oxygen leads to formation of pyrone 37 and release of the catalyst 36.
A different set of reactions is possible when the nucleophile is not directly part of the carbonyl functionality. This kind of reactions is mostly limited to electron-rich double bonds and aromatic groups. The first example of such reaction was introduced by Murphy and Wattanasin in 1980 for the synthesis of tetralones 39 from aryl cyclopropyl ketones 38 using excess SnCl₄ (Scheme 15). This reaction corresponds formally to a homologous variation of the well-known Nazarov cyclization. In contrast to the concerted Nazarov reaction, a stepwise process via carbocationic intermediates I and II has been proposed. In accordance with this mechanism, the cyclization was successful only if the cyclopropane was substituted with an electron-rich aromatic group. Furthermore, only electron-rich benzene rings were used on the ketone.

In 2005, Otto and co-workers showed that ketones bearing a furan or a thiophene substituent were also good substrate for the cyclization reaction. In 2008, Yadav and Kumar greatly expanded the scope of the reaction by using a bulky silyl group to stabilize the carbocationic intermediate (Equation 5). Several heterocyclic ketones 40 could be cyclized in good yield using 4 equivalents SnCl₄ at 80 °C. Importantly, the first example of oxygen substituent as donor group was also reported in this work (40c in Equation 5).

The cyclization of the related vinyl cyclopropyl ketones has been much less examined. In 1986, Tsuge and co-workers described the cyclization of several vinyl-cyclopropyl ketones in the presence of large excess of polyphosphoric acid, but a mixture of different products were usually obtained under these conditions. In 2009, Waser and co-workers introduced cross-polarized substrates 42 for the first time in the homo-Nazarov reaction. Similar cross-polarized substrates were used successfully in the related Nazarov cyclization. This work resulted in the development of the first catalytic method for the formal homo-Nazarov cyclization (Equation 6). The mild reaction conditions (20 mol% TsOH, CH₃CN, RT) were essential to prevent extensive polymerization of the sensitive substrates. The polarizing heteroatom α to the ketone could also be replaced by a silyl group as in 44, in which case complete diastereoselectivity was observed in the formation of the new chiral center and the double bond was formed only at the position of the silyl group to give 45 (Equation 7). Current limitation of this methodology is the necessity of having an electron-rich aromatic substituent on the cyclopropanes to promote the cyclization.
In another type of cyclization process, Junjappa and co-workers introduced ketenedithioacetal as a nucleophile to react with the carbocationic intermediate. In this case, formation of the five-membered ring was observed. In the first works, the stabilized cations obtained after cyclization were just quenched with water, and either thioesters or decarboxylated cyclopentanones could be obtained depending on the reaction conditions (Equation 8). More recently, Junjappa and co-workers developed further cationic domino cyclization processes, involving electron-rich benzene rings or heterocycles (Scheme 16).

Despite these early successes, similar intramolecular cyclization reactions have been less intensively used in the following years. Smith and co-workers developed one pot cyclopropanation-cyclization sequences. Reissig and co-workers described the intramolecular ring-opening of donor-acceptor cyclopropanes with alcohol nucleophiles. The use of a phenolate nucleophile was reported by Wood and co-workers in the context of model studies towards the synthesis of the original proposed structure of the diazonamides. Bohm and Reiser developed a two steps procedure for the synthesis of butyrolactone starting from carboxaldehyde donor-acceptor cyclop propane (Scheme 18). A highly diastereoselective addition of nucleophiles to aldehyde was followed by transesterification using Otera’s catalyst, cyclopropane ring opening, lactonization and acetal formation. Importantly, the enantiopure donor-acceptor cyclopropanes needed for this methodology could be accessed easily in two steps (asymmetric cyclopropanation and ozonolysis) from furan derivatives.

In 2008, Wang and co-workers reported the Yb-catalyzed intramolecular addition of aromatic nucleophiles on alkylidinene cyclopropane dicarboxylates (Equation 9). Activation with the Yb Lewis acid resulted in formation of a zwitterionic intermediate followed by intramolecular attack to form the less strained ring systems.

### Scheme 17
Some typical examples of intramolecular cyclization of activated cyclopropanes developed in the groups of Stork and Danishefsky.

### Scheme 16
Cationic domino reactions using ketenedithioacetals and 51 with double bond or indoles as final nucleophiles and using keteneaminothioacetals and aromatic group as final nucleophile.

2.2 Nucleophile Attached to the Cyclopropane

The intramolecular attack of nucleophiles attached on the cyclopropane ring of carbonyl cyclopropanes has been extensively examined in the groups of Stork and Danishefsky among others in the 60’s and 70’s. These methods have proven highly useful in the synthesis of natural products. As this work has been already reviewed, only a few relevant examples are given in Scheme 17.
Scheme 18 Conversion of carboxaldehyde donor-acceptor cyclopropane 61 to butyrolactone 63.

Scheme 19 The water addition-aldol condensation-cyclization-esterification sequence.

Examples of addition-cyclization of amine nucleophiles have also been reported. Wurz and Charette reported the addition of primary amines to activated cyclopropanes 71 followed by oxidation for the synthesis of pyrrole heterocycles 72 (Equation 11). Addition of primary amine to alkylidene cyclopropyl ketones 73 by Ma and co-workers allowed a redox neutral one step synthesis of pyrrole heterocycles 74 (Equation 12).

A different type of cyclization is observed for cyclopropyl dicarbonyls 75 in the presence of hydrazine or hydroxylamine salts (Scheme 20). In this case, condensation precedes ring opening by an external nucleophile and the carbon atoms of the cyclopropane are consequently not included in the formed pyrazole and isoxazole heterocycles 76. Based on the same principle, Lang and co-workers developed the reaction of 1,1-diacylcyclopropanes with 1,3-bis-silyl enol ethers for the synthesis of highly substituted benzene rings.

In 2006, Zhang and Schmalz reported an interesting use of carbonyl cyclopropanes 77 for the synthesis of furans 78 via gold catalysis (Equation 13). Detailed calculations by Phillips and co-workers allowed a deeper insight in the reaction mechanism (Scheme 21). Activation of acetylene 77 with the gold catalyst leads to intramolecular attack of the ketone oxygen to form an oxonium ion II. The increased electrophilicity of the cyclopropane allows then an easy attack of an external nucleophile.

Equation 9

**3. Cyclization Reactions Involving incorporation of Exogenous Atom(s)**

An alternative to the intramolecular attack of a nucleophile onto an activated cyclopropane is an external attack of a heteroatom nucleophile, followed by cyclization (involving the introduced heteroatom or not, see Scheme 1). The simplest nucleophile, water, was used by Singh and Danishefsky for the efficient synthesis of trans-fused 6-lactone 67 (Equation 10) starting from cyclopropane 66 derived from Meldrum’s acid.

Equation 10

Shi and co-workers developed a water-mediated cyclopropane ring-opening-aldol condensations cascade for the synthesis of diverse heterocycles. For example, a ring-opening-aldol condensation-cyclization sequence allowed a new access towards spiroacetals 70 (Scheme 19). In situ reaction with allene esters led directly to the formation of aromatic products. In 2006, Zhang and Schmalz reported an interesting use of carbonyl cyclopropanes 77 for the synthesis of furans 78 via gold catalysis (Equation 13). Detailed calculations by Phillips and co-workers allowed a deeper insight in the reaction mechanism (Scheme 21). Activation of acetylene 77 with the gold catalyst leads to intramolecular attack of the ketone oxygen to form an oxonium ion II. The increased electrophilicity of the cyclopropane allows then an easy attack of an external nucleophile.
Finally, proton transfer liberates the gold catalyst. In 2008, Huang and co-workers reported that a similar cyclization process was also possible using stoichiometric electrophiles, such as I$_2$ or PhSeBr, to activate the alkyne.$^{63}$

$^{63}$

Equation 13

Scheme 20 Formation of heterocycles 76 from cyclopropane dicarbonyls 75 using hydrazine or hydroxylamine.

Scheme 21 Proposed mechanism for the gold catalyzed furan synthesis with methanol as nucleophile.

Finally, a mechanistic intriguing conversion of alkylidene cyclopropane carboxaldehydes 79 to the corresponding chlorocyclobutanes 81 has been reported by Huang and Miao (Scheme 22).$^{64}$ This ring expansion reaction was proposed to proceed via acylation of the aldehyde, intramolecular attack of the cation by the double bond to form a bicyclobutanium ion II and ring opening with chloride.

Scheme 22 Proposed mechanism for ring expansion of alkylidene cyclopropane carboxaldehydes 79.


The heterolytic cleavage of one of the bonds of activated cyclopropanes results in the formation of a 1,3-dipole ideally suited for cycloaddition reactions. Especially formal [3+2] cycloaddition reactions with olefins, carbonyls and imines have been highly successful for the synthesis of cyclopentane, furan and pyrroline derivatives respectively.

4.1 [3+2] Cycloaddition Reactions with Olefins

The 1,3-dipolar cycloaddition of activated cyclopropanes has been known for a long time (Scheme 23).$^{9,65}$ A few selected early examples include the reactions of diverse activated cyclopropanes with electron-rich double bonds, such as enamines 82,$^{65a,b}$ enol ethers 85,$^{65c}$ and ketene acetals 88,$^{65d}$ (Scheme 23, A-C), electron-poor double bonds 91,$^{65c}$ (Scheme 23, D) and non-activated olefins 94$^6$ and 96$^6$ (Scheme 23, E-F).
In view of the synthesis of natural products, the recent introduction of indoles as nucleophilic partners in [3+2] cycloaddition with activated cyclopropanes is particularly interesting. Kerr and co-workers reported that the result of the reaction of indole derivatives with aryl substituted activated cyclopropanes is highly dependent from the substitution pattern on indole (Scheme 24). No cyclization was observed with an hydrogen at the 3 position of the indole, but the [3+2] addition product was obtained in good yield in the other cases. If the 2 position of the indole was unsubstituted, cycloadduct could be rearranged to the open form upon heating. In 2006, Junjappa and co-workers observed that consistent formation of the [3+2] product was observed with all substitution pattern using BF$_3$•OEt$_2$ in nitromethane. In 2007, Pagenkopf and co-workers reported the use of oxygen-substituted activated cyclopropanes with TMSOTf as activator (Equation 14). This reaction was especially well-suited for the synthesis of tetracyclic indole derivatives. The observed diastereoselectivity was highly dependent on the cyclopropane used. In 2009, the use of donor-acceptor cyclopropanes was extended to [3+2] cycloaddition reactions with furan heterocycles by Budynina and co-workers.

More recently, the scope of electron-rich olefins has been expanded to allyl and allenyl silanes. Efficient catalytic systems for the reaction of donor-acceptor cyclopropanes with enol silyl ethers have been developed using triflimide or scandium triflate as catalysts. Acetylene have also been used as two carbons partners. In 2004, Yadav and Sriramurthy reported the first general use of terminal acetylenes using a silyl group to activate the cyclopropane (Equation 15). In 2008, Qi and Ready used silyl yno ethers in the cycloaddition reaction with donor-acceptor cyclopropanes (Equation 16). Direct treatment of the reaction mixture with HF•pyridine led to silyl group removal followed by β-elimination to form cyclopentanones. Interestingly, Qi and Ready showed that only air-aged Me$_2$AlCl was able to promote the reaction in good yield. They proposed that oxidation of one of the Al-carbon bond led to a Lewis acid more able to promote the reaction.
Finally, Liu and Montgomery have introduced a mechanistically new approach for the Ni-catalyzed formal [3+2] cycloaddition of cyclopropyl ketones 113 with Michael acceptors 114 (Equation 17). This work constituted an important breakthrough in the field, as for the first time simple cyclopropyl ketones could be used in cycloaddition reactions with olefins. Furthermore, good diastereoselectivities were achieved, which has always been a major challenge in this type of cycloaddition reactions. In the first step of the proposed reaction mechanism, oxidative addition of Ni(0) onto the less hindered cyclopropane C-C bond led to metallacycle I (Scheme 25). As such, this cleavage selectivity is reversed to the one observed with Lewis acid, which is under electronic control. Insertion of olefins 114 was followed by reductive elimination to form product 116 and regenerate the catalyst. The Ti additive was not absolutely necessary for the reaction but led to better yield and shorter reaction time. Cyclopropyl carboxaldehyde could not be used in this reaction, but cycloaddition was successful with the corresponding aldimines.

\[
\text{Equation 15}
\]

\[
\text{Equation 16}
\]

\[
\text{Scheme 25 Proposed mechanism for the Ni-catalyzed formal [3+2] cycloaddition reaction.}
\]

4.2 [3+2] Cycloaddition Reactions with Aldehydes and Ketones

The [3+2] formal cycloaddition of activated cyclopropanes and carbonyls give useful tetrahydrofuran derivatives. Most early works focused on the use of donor-acceptor cyclopropanes (117, 119 and 121, Scheme 26, A-C). Achieving high diastereoselectivities is generally difficult, except in the case of fused ring systems 122 (Scheme 26, C). A single example using unsubstituted cyclopropyl ketones 123 was also reported by Oshima and co-workers in 2001 (Scheme 26, D).

\[
\text{Equation 17}
\]

\[
\text{Scheme 26 Selected examples for early reports of cycloaddition reactions of activated cyclopropanes with carbonyl compounds.}
\]

In 2006, the scope of donor-acceptor cyclopropanes used in these reactions was expanded to silyl-methyl substituted cyclopropanes by Gupta and Yadav.
Since 2005, Johnson and co-workers have studied extensively the Sn or Hf-catalyzed cycloaddition of donor-acceptor cyclopropanes 125 with aldehydes (Equation 18). This work can be considered as a breakthrough in the application of activated cyclopropanes for [3+2] cycloaddition reactions with carbonyl compounds, as not only aromatic substituents could be used on the cyclopropanes and the aldehydes, but also alkenes and even simple alkanes. Furthermore, the reaction was nearly completely diastereoselective and stereospecific, allowing a new access to enantiopure furan derivatives 126 starting from enantiopure cyclopropanes 125. Especially the high stereospecificity is intriguing for this reaction, as racemization would be expected if a defined cationic intermediate was formed. Indeed, the observed regioselectivity for C-C bond cleavage is in accordance with an ionic model. To explain these results, Johnson and co-workers proposed a tight ion pair II as intermediate (Scheme 27). Attack of the aldehyde is followed by a very fast 120 °C C-C bond rotation towards a sterically favored envelope conformation IV, where all the substituents are in a pseudo-equatorial conformation. From this intermediate, a very fast C-C bond formation is possible, before any racemization can occur. The complete stereospecifieity observed using deuterated ester 127 further supported the proposed mechanism. Several other groups have also proposed similar tight ion-pairs as intermediates.

During their work, Johnson and co-workers observed that in the presence of more electron-rich substituents, racemization was indeed observed if the reaction time was too long. This observation lead to the development of the first catalytic asymmetric [3+2] cycloaddition of aldehydes to racemic cyclopropanes 129 via dynamic resolution (Equation 19). In this case, high enantioselectivity could be achieved by the use of a Mg catalyst together with a chiral PYBOX ligand 130.

In 2008, Johnson and co-workers also reported a mechanistically different approach using Pd(0) catalysis (Scheme 28). As this method is based on the formation of stabilized Pd-allyl intermediate I and II, it is limited to activated vinyl-cyclopropanes like 132 as substrates.

4.3 [3+2] Cycloaddition Reactions with Imines and Nitriles

The [3+2] formal cycloaddition of activated cyclopropanes with imines leads to useful pyrrolidine heterocycles, which are omnipresent in natural products and pharmaceutical substances. A first useful process was developed for the synthesis of spiropyrrrolidin-3,3′-oxindoles 135 by Carreira and co-workers using MgI2 as catalyst (Scheme 29). In fact, the idea to use double activation using a Lewis acid like magnesium and a nucleophile like iodide has been highly successful in the chemistry of activated cyclopropanes. Ring-opening with iodide led to a nuclophilic magnesium enolate interme-
diate $\mathbf{I}$, which then reacted with the imine. Intramolecular nucleophilic substitution in $\mathbf{II}$ then afforded the pyrrolidines $\mathbf{135}$ in good yield and diastereoselectivity.

In 2002, Olsson and co-workers demonstrated that this approach could be applied for a one-pot synthesis of pyrrolidine heterocycles $\mathbf{137}$ starting directly from cyclopropyl ketones $\mathbf{136}$, aldehydes and amines with good anti selectivity (Equation 20).

Kerr and co-workers further studied the intramolecular variation of the cycloaddition reaction. In this case, a striking dependence of the diastereoselectivity from the order of addition of the reagents was observed (Scheme 30). When the aldehyde was added first, selective condensation to the more stable trans oxime $\mathbf{141}$ occurred (Scheme 31). Cyclopropane ring opening and cyclization then led selectively to the trans product $\mathbf{139}$. If the Lewis acid was added first, attack onto cyclopropane $\mathbf{138}$ preceded condensation. To avoid an $\Lambda^{1,3}$ interaction with the diester substituent, formation of cis oxime intermediate $\mathbf{II}$ was favored to give selectively the cis product $\mathbf{140}$ after cyclization.

The use of activated methylene cyclopropanes $\mathbf{143}$ opens several different pathways for reactivity, as a conjugate enolate $\mathbf{I}$ is formed upon ring-opening (Scheme 32). In 2002, Lautens and co-workers first reported that $\alpha$ alkylation followed by intramolecular alkylation was observed with diphenylamide substrates and MgI$_2$ as Lewis acid to give pyrrolidine $\mathbf{144}$ (pathway a), whereas $\mathbf{147}$ was obtained via $\gamma$ alkylation followed by intramolecular acylation with oxazolidinone imides and MgI$_2$ as Lewis acid (pathway d). In 2007, they further reported that $\gamma$ alkylation followed by intramolecular alkylation was possible for diphenyl amides in the presence of MAD and $^4$BuNI to give pyrrolidine $\mathbf{146}$ (pathway c). The last possibility, $\alpha$ alkylation followed by intramolecular acylation leading to $\mathbf{145}$, has not been reported so far (pathway d). The Lautens groups further developed an asymmetric synthesis of pyrrolidines $\mathbf{144}$ from methylenecyclopropanes $\mathbf{143}$ using either an imine $\mathbf{148}$ bearing a sulfoxide chiral auxiliary (Equation 21) or a chiral catalyst (Mg-Box system, Equation 22).
The reaction of activated cyclopropanes with nitrogen-containing electrophiles is not limited to imine derivatives. Pagenkopf and co-workers reported the cycloaddition of nitriles with oxygen-substituted donor-acceptor cyclopropanes. Depending on the substrate, the obtained dihydro[1,3]pyrroles 151 were stable (Equation 23) or subsequent elimination of the oxygen substituent was observed to form the corresponding pyrrole heterocycles (Equation 24).

The first useful [3+3] cycloaddition reaction involving nitrones and activated cyclopropanes was then introduced by Kerr and co-workers in 2003. Activation of cyclopropane dicarboxylate with mild Lewis acids like Yb(OTf)$_3$ or MgI$_2$ led to the corresponding tetrahydro-oxazine heterocycles in good yield and cis-selectivity (Equation 27). DFT studies showed that both [3+3] cycloaddition reactions involving nitrones and activated cyclopropanes have been developed only more recently. In 2002, Junjappa and co-workers reported the dimerization of indole substituted cyclopropyl ketones, which constituted a formal [3+3] cycloaddition reaction. The formed 6-membered rings was further oxidized to the corresponding benzene derivatives. The first useful [3+3] cycloaddition reaction involving nitrones and activated cyclopropanes was then introduced by Kerr and co-workers in 2003. Activation of cyclopropane dicarboxylate with mild Lewis acids like Yb(OTf)$_3$ or MgI$_2$ led to the corresponding tetrahydro-oxazine heterocycles in good yield and cis-selectivity (Equation 27). DFT studies showed that both [3+3] cycloaddition reactions involving nitrones and activated cyclopropanes have been developed only more recently. In 2002, Junjappa and co-workers reported the dimerization of indole substituted cyclopropyl ketones, which constituted a formal [3+3] cycloaddition reaction. The formed 6-membered rings was further oxidized to the corresponding benzene derivatives. The first useful [3+3] cycloaddition reaction involving nitrones and activated cyclopropanes was then introduced by Kerr and co-workers in 2003. Activation of cyclopropane dicarboxylate with mild Lewis acids like Yb(OTf)$_3$ or MgI$_2$ led to the corresponding tetrahydro-oxazine heterocycles in good yield and cis-selectivity (Equation 27). DFT studies showed that both
a concerted asynchronous pathway and a stepwise pathway with nucleophilic attack of the oxygen atom of the nitrone on the cyclopropane preceding cyclization were possible. In all cases, further activation of the cyclopropane by the Lewis acid was essential. Studies using more substituted cyclopropanes 163 and 165 allowed a better understanding of the observed diastereoselectivity (Scheme 33). Using cis substituted cyclopropane 163, the usual 1,4-cis selectivity was observed. The reaction was proposed to occur stepwise. Attack of the oxygen atom of nitrone 160 led to a zwitterionic intermediate I. Cyclization then proceeded via a favored chair transition state. In the case of trans substituted cyclopropane 165, the reaction was much slower and the 1,4-trans tetrahydro-oxazine 166 was the major product. In this case, the chair conformer II was destabilized by a severe 1,3 diaxial interaction between the Me and the Ph groups. Instead, a boat conformer III leading to the 1,4-trans product 166 was favored.

In 2005, Sibi and co-workers developed the first catalytic asymmetric [3+3] cycloaddition of nitrones 160 with activated cyclopropanes 167 using a Ni catalyst with Ph-DBFOX as ligand (Equation 28). Tang and co-workers reported the kinetic resolution of chiral activated cyclopropanes 169 via the [3+3] cycloaddition reaction using a Ni catalyst with a trisoxazoline ligand 170 (Equation 29). Finally, Wang and co-workers used methylene cyclopropanes in the cycloaddition reaction and Wu and co-workers developed a domino reaction involving cyclization of an alkyne onto an oxime followed by [3+3] cycloaddition.

Other [3+3] cycloaddition involving activated cyclopropanes have been much less investigated. Charette and co-workers reported the [3+3] cycloaddition of azomethine imines 172 with activated cyclopropanes 173 (Equation 30). Finally, Kerr and Sapeta studied the formal [3+3] cycloaddition reaction of activated cyclopropanes with trimethylene methane equivalents (2-chloromethyl allyl silanes). However, a two step procedure was necessary in this case.
tions are also possible. A rare example of [4+3] cycloaddition reaction has been reported by Ivanova and co-workers in 2008. The Yb catalyzed cycloaddition of activated cyclopropanes 175 with 1,3-diphenylisobenzofuran 176 led to the bicyclic cycloaddition products 177 in good yield with low exo selectivity (Equation 31). Anthracene derivatives could also be used in this cycloaddition reaction.

Equation 31

6. Application in Total Synthesis

In the 70’s, cyclization and cyclosomerization reactions of activated cyclopropanes were extensively studied for the total synthesis of natural products. Seminal pioneering works have been achieved in the group of Danishefsky, Wenkert and Stevens. Since then, these methods have been less extensively used in total synthesis. Based on the work of Danishefsky, Snyder and co-worker reported in 2001 the use of an activated cyclopropane 179 derived from Meldrum acid for the introduction of a pyrrolidine ring in the total synthesis of Martinellic acid (181) (Scheme 34). In contrast to cyclization reactions, the use of cycloaddition reactions involving activated cyclopropanes in total synthesis has been developed only more recently. The total synthesis of cedrene by Corey and Balanson using a formal intramolecular [3+2] cycloaddition reaction (Scheme 23, E) constituted a notable exception. The broad potential of this class of reaction became evident when Carreira and co-workers successively disclosed the synthesis of horsfiline (190), strychnofoline (194) and spirotryprostatin B (198) using the [3+2] cycloaddition of imines with oxindole cyclopropanes to form spiro[pyrrolidin-3,3'-oxindoles] (Scheme 36).

In the case of horsfiline (190), methyl imine was generated in situ from the corresponding trimer 188. For strychnofoline (194), cyclic imine 192 was used and only the desired diastereoisomer 193 was obtained. In the case of spirotryprostatin B (198), a substituted cyclopropane 195 was needed. The desired diastereoisomer 197 was obtained with 6:1 selectivity for the two centers conserved in the natural product.
Scheme 36 Synthesis of horsfiline (190, A), strychnofoline (194, B) and spirotroprostatin B (198, C) using the [3+2] cycloaddition of imines and oxindole cyclopropanes.

Leduc and Kerr recently reported the use of their intramolecular [3+2] cycloaddition between oxime and activated cyclopropane for the total synthesis of (-)-allosecurinine (202) (Scheme 37). Cleavage of the N-O bond in bicyclic product 200 led to 201 with the pyrrolidine ring constituting the core of the natural product. Carson and Kerr also made used of an intramolecular cycloaddition between an imine and an activated cyclopropane in 203 to build up the core 204 of the natural product FR901483 (205) (Scheme 38).

Scheme 37 Total synthesis of (-)-allosecurinine (202).

Scheme 38 Total synthesis of FR901483.

Pagenkopf and co-workers used the cyclization of donor-acceptor cyclopropane 207 with nitrile 206 for the synthesis of indole alkaloids (Scheme 39). Tetrahydroindole 208 obtained in the cycloaddition reaction was oxidized in the presence of Pd on carbon to give the corresponding indole 209. Indole 209 could then be converted either to goniomitine (210) or quebrachamine (211).
in the total synthesis of (+)-phyllantidine (216) by Carson and Kerr in 2006 (Scheme 40).103a

The use of the [3+3] cycloaddition was not limited to the synthesis of tetrahydrooxazine ring-containing natural products. Indeed, the N-O bond was easily cleaved to give the amino alcohol. Activation of the alcohol and cyclization gave access to pyrrolidine rings, which are much more frequently encountered in natural products. This strategy led to the successful total synthesis of (+)-nakadomarin A (222) by Kerr and co-workers (Scheme 41).103b,c The ring-cleavage cyclization strategy also allowed access to the core of yuremamine (228), although the total synthesis of this natural product has not been reported yet using this strategy (Scheme 42).103d
7. Conclusion

Since the “golden age” of the 70’s, cyclization and cycloaddition reactions of activated cyclopropanes have been used regularly in organic synthesis. However, it is only more recently that their broad potential in conjunction with modern catalytic methods has been fully recognized. As more and more efficient cyclopropanation methods are introduced, the synthesis of activated cyclopropanes becomes easier and their transformations more important. The introduction of highly diastereoselective methods as well as the first catalytic asymmetric methods for [3+2] and [3+3] cycloaddition reaction have opened the way for the use of these processes in more complex settings, as demonstrated by the recent surge of publication on the total synthesis of natural products using these methods. Nevertheless, the field is still in its infancy, and further efforts are needed to control and use the exceptional reactivity of carbonyl and imine cyclopropanes and to fully exploit their potential in organic synthesis.

Acknowledgment

The EPFL is acknowledged for financial support. We thank Prof. K. Gademann of the Chemical Synthesis Laboratory at EPFL for proofreading this manuscript.

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(47) For a more detailed discussion of the reaction mechanism, see ref. 258.


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Cyclization and Cycloaddition Reactions of Cyclopropyl Carbonyls and Imines

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