Abstract

In this section, the synthesis of saturated N- and O- heterocycles via formal cycloaddition is presented. The main focus is on metal-catalyzed reactions involving C-C or C-X σ bond cleavage in three- or four- membered rings. After a fast presentation of pioneering works, the important breakthroughs of the last two decades are presented. The section starts with reactions involving three-membered rings. Formal [3+2] cycloadditions of donor-acceptor-substituted cyclopropanes and methylenecyclopropanes with carbonyls and imines are important methods to access tetrahydrofuran and pyrrolidine heterocycles. Formal [3+3] cycloadditions have emerged more recently. On the other hand, reactions of epoxides and aziridines with carbon monoxide or cumulenes are now well-established method to access heterocycles. These processes have been completed more recently with cycloaddition with olefins, carbonyls and imines. The section ends with the emerging field of four-membered ring activation for cycloaddition with π systems.

7. Synthesis of Saturated Heterocycles via Metal-Catalyzed Formal Cycloaddition Reactions that Generate a C–N or C–O Bond

7.1 Introduction: Definitions and Scope of the Section

The discovery of classical cycloaddition reactions, such as the (hetero) Diels-Alder and 1,3-dipolar cycloadditions, has contributed tremendously to a more efficient access towards both carbocycles and heterocycles. The introduction of the term cycloaddition was necessary to distinguish these new types of reactions from previously discovered processes leading to cyclic structures, such as the famous Robinson annulation. In principle, each cycloaddition can be considered as a special case of the more general annulation process, but from which point on an annulation can be called a cycloaddition has been the topic of intensive discussions for decades, and is still not settled today. In 1968, Huisgen proposed a set of rules for the definition of cycloaddition, and the two first are still largely recognized as prerequisite:[1]

- Huisgen Rule 1: "*Cycloadditions are ring closures in which the number of σ bonds increases.*"
- Huisgen Rule 2: "*Cycloadditions are not associated with the elimination of small molecules or ions. The cycloadduct corresponds to the sum of the components.*"

The current official definition of cycloaddition by IUPAC is very close to these first two rules of Huisgen:

" *A reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond mu1tiplicity.*"

Although the rule that all the atoms of the starting materials have to be included in the product is not explicitly included in the definition, this requirement is usually recognized by most organic chemists. Even if electrocyclic cyclization processes were included in the original definition of Huisgen, the term cycloaddition is mostly used today for those reactions proceeding via the formation of at least two new bonds. Nevertheless, several researchers think that the term cycloaddition should be more strictly limited to reactions involving a continuous overlap of π electrons, and consequently allowing a concerted process. In fact, in his seminal publication, Huisgen already introduced further rules, in particular rule number 3, which explicitly stated that cycloadditions should not involve the cleavage of sigma bonds:

- Huisgen Rule 3: "*Cycloadditions do not involve the cleavage of σ bonds.*"

Unfortunately, in the same publication, Huisgen also described several reactions proceeding via σ-bond cleavage as cycloaddition.

To solve this definition dilemma, several researchers have used the term of "formal cycloaddition". Although this term has not yet been strongly defined, we propose to use it here for those reactions following the rules 1 and 2 of Huisgen and the IUPAC definition, but not the more strict criteria of rule 3 and the non-interrupted π system of electrons (Scheme 7.1). In contrast to annulation reactions, the formation of small molecules or changes in the connectivity of atoms not involved in the formation of the new bonds in the ring are not allowed in this case. For example, even if the alcohol intermediate formed first in the Robinson annulation formally contains all the atoms of the starting materials, the position of the indicated hydrogen has changed. Although also highly useful, such processes will not be included in this section. Furthermore, we will limit ourselves to reactions for which the definition is valid for the used starting materials, and not on transiently generated reactive intermediates:

Definition of "formal cycloaddition" in this section: *A reaction in which two or more molecules (or parts of the same molecule) combine with the formation of a cyclic adduct, involving the formation of at least two new σ bonds and the cleavage of at least one σ bond, but not associated with the elimination of small molecules or changes in the connectivity of atoms except for ring formation."*
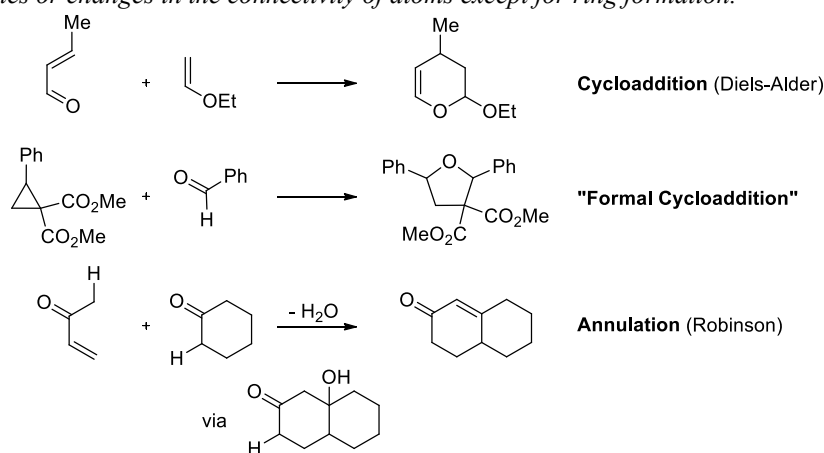

Scheme 7.1: Examples of cycloaddition, formal cycloaddition and annulation as defined in this section.

This type of reaction is highly useful for the synthesis of heterocycles, as it gives a direct access to more saturated derivatives, in contrast to classical cycloadditions involving only π systems, but still conserves the perfect atom-economy of the process. On the other hand, the cleavage of σ bonds is much more difficult than the rearrangement of π electrons. To increase the reactivity of the substrates, the use of ring strain, often together with the further polarization of σ bonds with functional groups has been the most successful, and this section will be limited to this approach. In order especially to highlight the synthetic complemen-

tarity with cycloadditions of conjugated systems, we will limit the discussion to reactions giving access to heterocycles with no more than one unsaturated center and leading to O- or N- containing heterocycles.

In order to give a better systematic overview of this fast growing field, the section has been organized according to the following criteria (Scheme 7.2):

A) Ring size of the formal cycloaddition substrate (three, four or larger)
B) Structure of the ring: all carbons, with one oxygen or one nitrogen and with more than one heteroatom.
C) Number of added atoms during the cycloaddition process: one, two (divided in isolated π systems and cumulenes) and larger.
D) Structure of the reacting partner: all carbon, with one oxygen or one nitrogen and with more than one heteroatom.

Classification Criteria

A: ring size
B: ring structure
C: partner size
D: partner structure
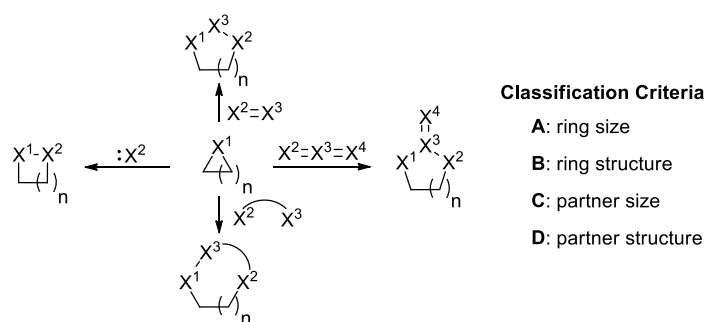
Scheme 7.2: Classification criteria for formal cycloaddition reactions.

7.2 Reactions Involving Three-Membered Rings

Three-membered rings have been by far most often used in formal cycloaddition reactions. This is probably due first to the activation of the σ-bond originating from ring strain, which is essential to allow cycloaddition under mild conditions. Secondly, there are numerous synthetic methods to access three-membered rings, especially cyclopropanes, epoxides and aziridines. This has led to a widespread use of these substrates in cycloaddition and annulation reactions.

### 7.2.1 Reactions with Cyclopropanes

Cyclopropanes are very important in organic chemistry, both as structural elements of synthetic and bioactive compounds and as platforms for further functionalization. They are also interesting from the theoretical point of view, and are best described by the use of Walsh orbitals, which explain their partial π character. For these reasons, they can be considered as one-carbon homologues of olefins. Despite their high strain energy (26 Kcal/mol), cyclopropanes are still stable compounds, and most useful formal cycloadditions of cyclopropanes have relied on further activation of the C-C bond via polarization, especially through the intro-

duction of vicinal donor and acceptor groups (donor-acceptor substituted cyclopropanes).[2-8] A second possibility for further activation is the introduction of unsaturation, which further increases ring strain and stabilizes potential reactive intermediate, as exemplified by the rich chemistry of alkylidenecyclopropanes.[9]

7.2.1.1 Formal [3+2] Cycloadditions with Isolated π Systems

7.2.1.1.1 C-O Bond Formation

The formal cycloaddition of cyclopropanes with carbonyl compounds gives a fast and atom-economical access to important tetrahydrofuran derivatives. Pioneering works of Reissig and co-workers in the eighties have already shown the potential of oxygen substituted cyclopropanes to access either tetrahydrofurans or lactones (Scheme 7.3, **A** and **B**).[10-15] Oshima and co-workers later showed that that unsubstituted cyclopropanes could also be used for the cycloaddition (Scheme 7.3, **C**),[16] and Yadav introduced in 2006 silyl activated cyclopropanes as another alternative (Scheme 7.3, **D**).[17] In 2011, Dobbs and co-workers demonstrated that cycloaddition of silylmethyl substituted cyclopropanes was also possible in the absence of the diester activating group.[18]
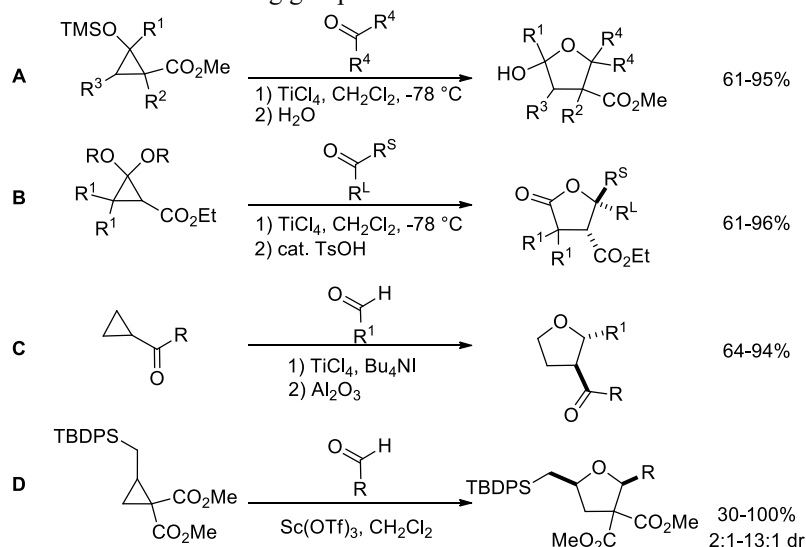
Scheme 7.3: Pioneering examples of formal [3+2] cycloaddition of cyclopropanes with carbonyl compounds.

Nevertheless, despite these promising studies, the interest in [3+2] cycloadditions remained limited for several decades, probably because the factors control-

ling the stereoselectivity of the reaction were poorly understood. The situation changed dramatically when Johnson and co-workers demonstrated in 2005 that the Lewis acid catalyzed [3+2] cycloaddition of aryl-diester substituted cyclopropanes with carbonyl compounds was not only diastereoselective, but also highly enantiospecific (Scheme 7.4).[19-20] The reaction was successfully extended to alkenyl and alkyl substituted cyclopropanes. To rationalize the observed enantiospeficity, Johnson and co-workers proposed that the reaction proceeded via a tight ion pair **II**.[21-22] The existence of such "intimate ion pairs" has also been proposed by other authors.[23-25] A stereoselective anti attack of the aldehyde followed by a fast bond rotation of 120 °C would lead to the favored envelope conformation **IV**, in which all groups are in favorable pseudo-equatorial positions. Finally, C-C bond formation would give the observed tetrahydrofuran. The proposed mechanism was further confirmed by the stereospecificity observed when a deuterium label was introduced on one of the two ester groups of the cyclopropane.
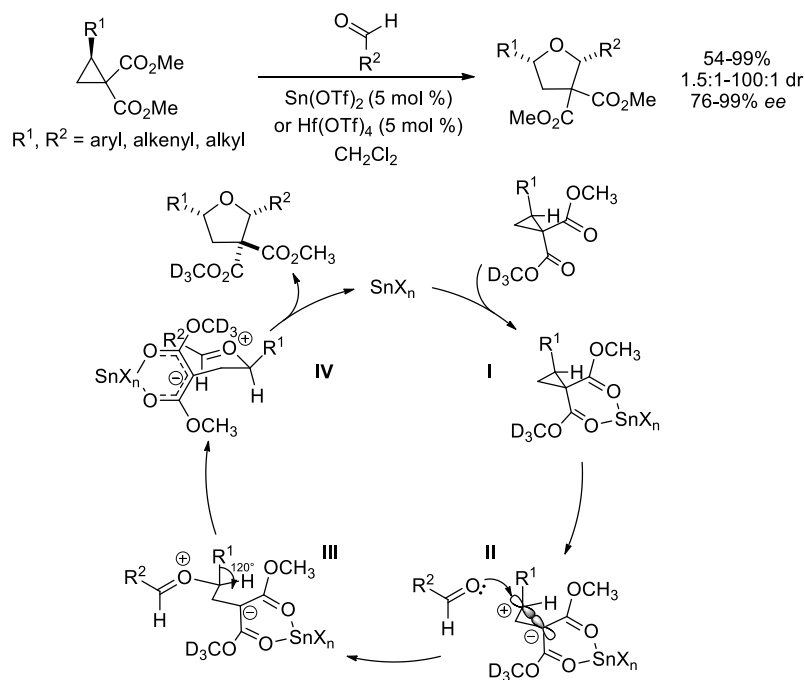

Scheme 7.4: Enantiospecific formal [3+2] cycloaddition reported by Johnson and co-workers.

With electron-rich aryl substituents, racemization of the starting material was observed. This result opened the way for the development of the first dynamic kinetic asymmetric formal [3+2] cycloaddition of aldehydes and cyclopropanes, using a magnesium PYBOX catalyst (Equation 7.1).[26]
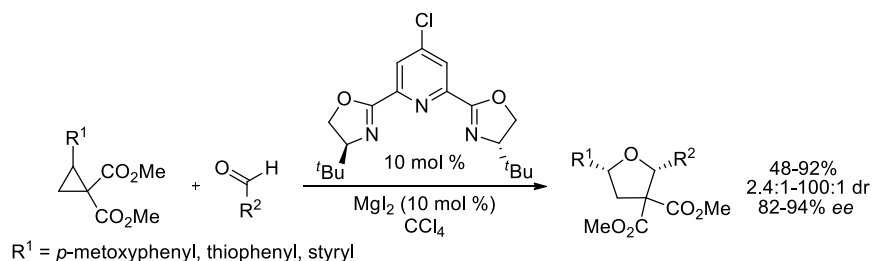
Equation 7.1: Dynamic kinetic asymmetric [3+2].formal cycloaddition.

Further recent extensions of this reaction include highly diastereoselective formal cycloadditions catalyzed by $AlCl_3$[27] and the use of cyclopropanes bearing a quaternary donor site.[28] In the case of vinyl-substituted cyclopropanes, activation with a palladium catalyst became possible, due to the formation of a stable π-allyl intermediate.[29] The broad applicability of the method was further demonstrated in the total synthesis of natural products, including (+)-virgatusin,[30] (+)-polyanthellin A[31-32] and (+)-isatisine A[33-34] (Figure 7.1). Finally, Wang and co-workers developed intramolecular variations of this reaction to give both fused and bridged polycyclic systems and applied the method to a formal synthesis of platensimycin.[35]


(+)-Virgatusin
Johnson 2009

(+)-Polyanthellin A
Johnson 2009

(+)-Isatisine A
Kerr 2010
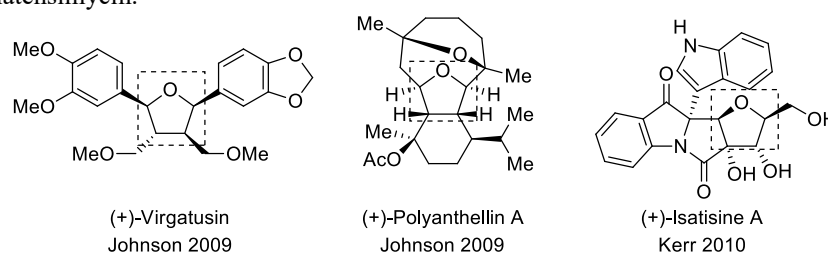
Figure 7.1: Natural products synthesized via the intermolecular formal [3+2] cycloaddition of diester cyclopropanes and carbonyl compounds.

The seminal work of Johnson and co-workers had enhanced tremendously the range of applications of formal [3+2] cycloadditions to access tetrahydrofurans. Nevertheless, it remains limited to the use of donor-acceptor cyclopropanes bearing an alkyl (aryl/alkenyl) group and diester substituents. Recently, Wang and co-workers reported two intramolecular approaches with other types of cyclopropanes: the first one involves oxycyclopropanes used in intramolecular cycloadditions to access bridged cyclopropanes (Scheme 7.5, **A**),[36] whereas the other made use of ketone substituted alkynyl cyclopropanes (Scheme 7.5, **B**).[37] In the latter case, more saturated furan derivatives could also be accessed via an alternative [4+2] annulation process if a gold catalyst was used.
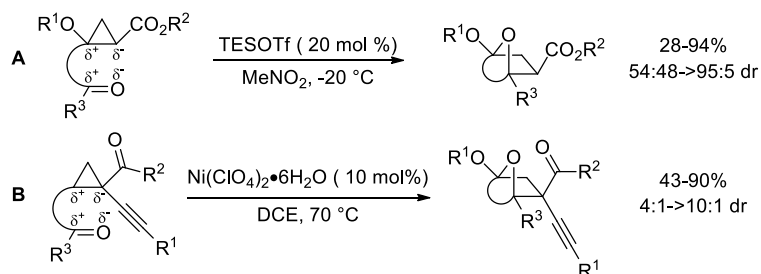
Scheme 7.5: Extending the scope of formal [3+2] cycloaddition reaction to oxy- and alkynyl-substituted cyclopropanes.

In 2012, Waser and co-workers reported the first use of amino-substituted cyclopropanes in the formal [3+2] cycloaddition with both aldehydes and ketones (Scheme 7.6). The reaction with aldehydes proceeded at room temperature with an iron catalyst and gave racemic products when starting from enantiopure cyclopropanes (**A**).[38] In contrast, the tin-catalyzed annulation with ketones was enantiospecific (**B**).[39] The obtained amino-substituted tetrahydrofurans are important heterocycles, as they constitute the core of natural DNA and RNA, as well as numerous synthetic drugs.
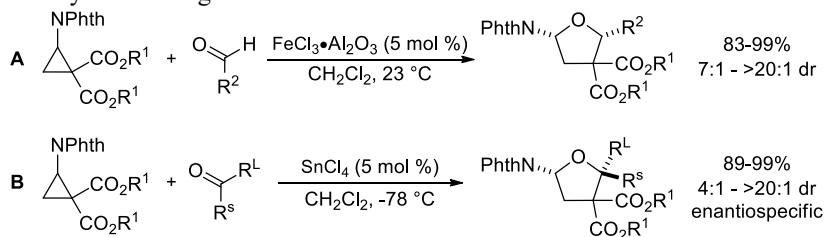
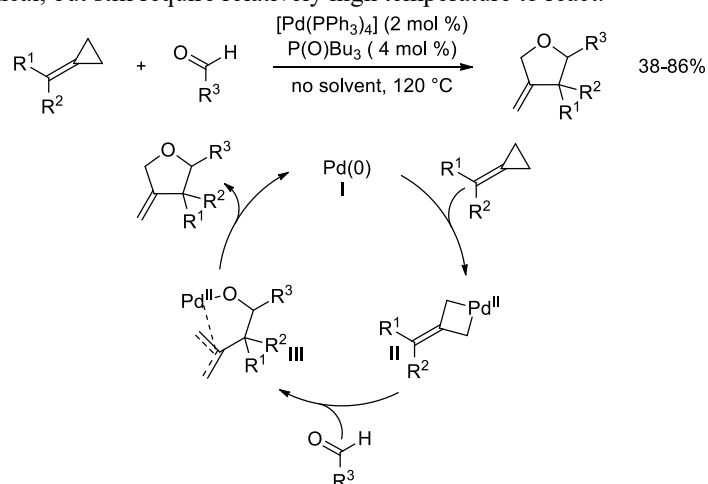**Scheme 7.6**: Formal [3+2] cycloaddition of aminocyclopropanes.

Apart from the introduction of polarizing group, the introduction of an exo double bond is another important approach to increase the reactivity of cyclopropanes.[40] In fact Nakamura and Yamago already demonstrated in 1990 that the formal cycloaddition of methylene cyclopropane acetal with aldehydes and ketones occurred spontaneously upon heating to 80 °C (Equation 7.2).[41] A trimethylenemethane intermediate can be proposed for this reaction, leading to a true cycloaddition after ring-opening has occurred.
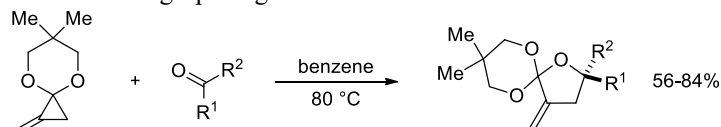
Equation 7.2: Thermal Formal [3+2] cycloaddition of methylenecyclopropane.

The use of a palladium catalyst allowed Yamamoto and co-workers to extend the scope of cycloaddition reactions between alkylidene cyclopropanes and aldehydes (Scheme 7.7).[42] The reaction has been proposed to proceed via oxidative addition of Pd(0) onto the C-C bond of the cyclopropane to form a palladium-stabilized trimethylenemethane intermediate **II**. Nucleophilic addition onto the aldehyde to give a π-allyl intermediate **III** followed by reductive elimination then regenerates the catalyst. When compared to other precursors of trimethylenemethane in catalysis,[43] alkylidene cyclopropanes are perfectly atom economical, but still require relatively high temperature to react.

Scheme 7.7: Palladium-catalyzed formal [3+2] cycloaddition of alkylidenecyclopropanes.

Finally, the use of Lewis acid to promote the cycloaddition between alkylidenecyclopropanes and carbonyl compounds has also been reported, but most reactions remain limited in scope or lead to mixture of products.[44-47]

7.2.1.1.2 C-N Bond Formation

In a similar way as tetrahydrofurans are obtained via the [3+2] cycloaddition of cyclopropanes and carbonyls, pyrrolidines are generated from cyclopropanes and imines. It is consequently not surprising that many methods established in the case of carbonyls were later extended to imines.

Nevertheless, one of the first examples of the synthesis of pyrrolidines derived from oxindoles was developed by Carreira and co-workers based on a unique stepwise mechanism (Scheme 7.8).[48] In this reaction catalyzed by MgI$_2$, nucleophilic attack by iodide was proposed as the first step. The generated enolate **I** would then add onto the imine, followed by cyclization via an SN^2 process. The broad potential of the method was further demonstrated in the total synthesis of spiroxindole alkaloids, including horsfiline,[49] strychnofoline,[50-51] and spyrotry-

prostatin B,[52-53] as well as in the production of small molecule libraries with a pyrrolidine core.[54-61]
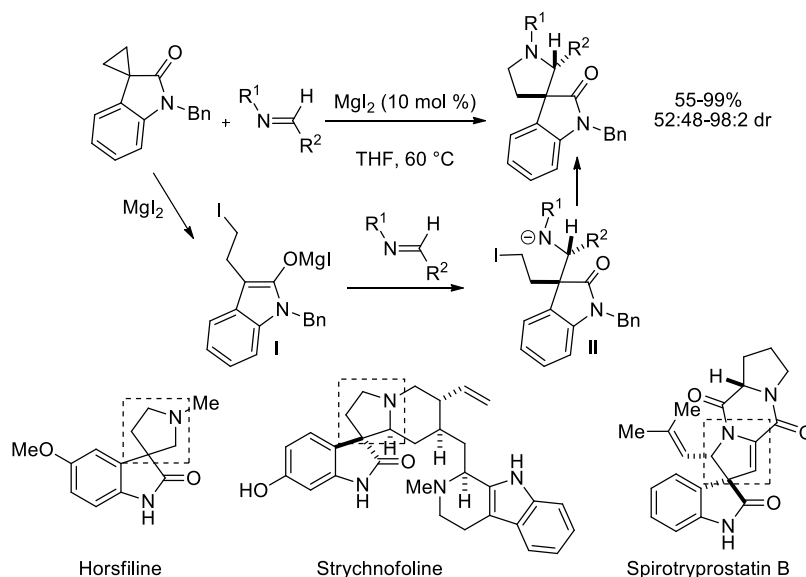
Scheme 7.8: MgI₂-catalyzed [3+2] annulation of cyclopropanes with imines and application in the total synthesis of spiroxindole alkaloids.

Kerr and co-workers were the first to apply the principle of diester activation for the intramolecular annulation between imines and cyclopropanes (Scheme 7.9).[62] The reaction proceeded in one-pot from the hydroxylamine derivatives and was catalyzed by Yb(OTf)₃. Interestingly, the formation of the *cis* or *trans* diastereoisomer depended on the order of addition of catalyst or aldehyde. Kerr and co-workers proposed that in the absence of aldehyde, nucleophilic attack of the nitrogen on the cyclopropane was the first step, followed by condensation with the aldehyde and ring-closing. When the aldehyde was added first, the formation of the oxime would occur initially, followed by attack on the cyclopropane, resulting in an inversion of the diastereoselectivity.

More recently, the methodology was also extended to the synthesis of bridged systems[63] and of bicyclopyrazolidines starting from hydrazines.[64] As the N-O or N-N bond is easily cleaved in the obtained products, they are easily further functionalized, as has been demonstrated by Kerr and co-workers in the total synthesis of (+)-allosecurinine[65] and FR901483.[66] In 2010, Tomilov and co-workers have also reported a first example of intermolecular reaction between aryl-diester substituted cyclopropanes and pyrazolines.[67]
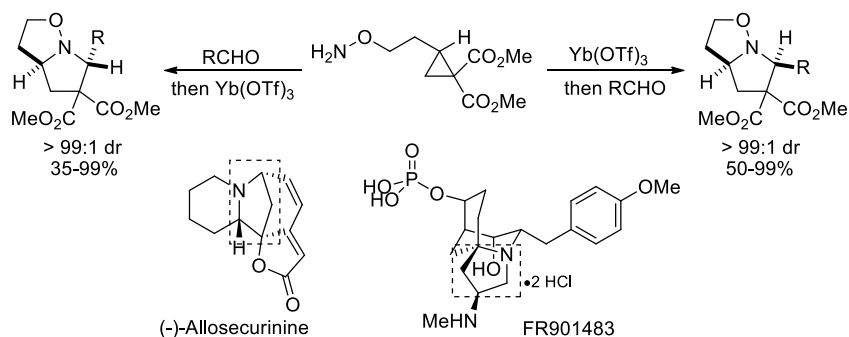
Scheme 7.9: Intramolecular [3+2] annulation of cyclopropanes with oximes and applications in the total synthesis of alkaloids.

In 2010, Johnson and co-workers reported that the dynamic kinetic asymmetric formal cycloaddition they have developed for aldehydes could also be used in the case of imines (Equation 7.3).[68] In this case, the choice of protecting group was key to obtain good asymmetric induction, diastereoselectivity and yield in the reaction.


R^1 = *p*-metoxyphenyl, thiophenyl, styryl
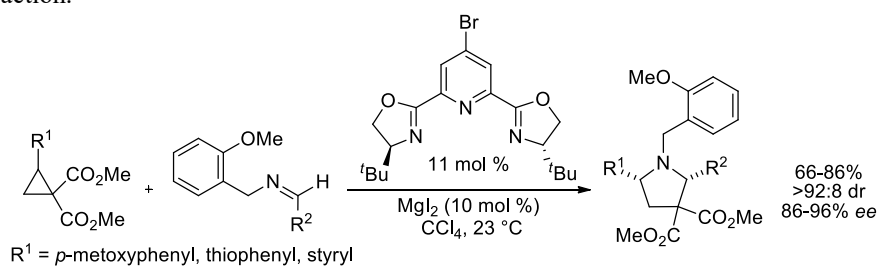
Equation 7.3: Dynamic kinetic asymmetric [3+2] formal cycloaddition.

Like in the case of cycloadditions with carbonyls, alkylidenecyclopropanes have also been used for the reaction with imines. Nakamura and co-workers were again able to use alkylidenecyclopropane acetals for a thermal cycloaddition with oximes (Scheme 7.10).[69] The reaction was proposed to proceed via a concerted cycloaddition of a trimethylenemethane singlet intermediate after cyclopropane opening. Interestingly, cycloaddition occurred on the two less substituted carbon atoms of the trimethylenemethane in contrast to the result with carbonyl compounds. The obtained keteneacetal can be easily hydrolyzed to the corresponding ester to give trisubstituted pyrrolidines. Later, the method could also be extended to sulfonyl and acyl imines as substrates.[70] As in the case of furans, the use of a palladium catalyst allowed Yamamoto and co-workers to significantly expand the scope of alkylidenecyclopropanes used in cycloaddition reactions with imines.[71-72] More recently, Shi and co-workers have reported that non-activated alkylidene-cyclopropanes could react thermally with imines in an intramolecular reaction.[73]
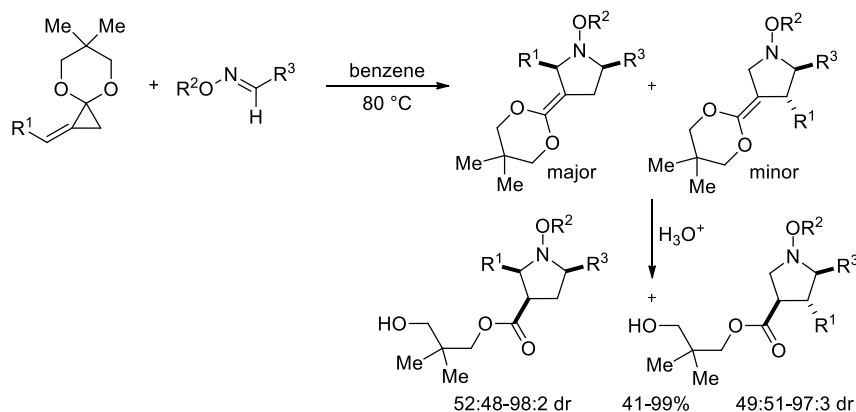
Scheme 7.10: Cycloaddition of alkylidenecyclopropanes and oximes under thermal conditions.

An important progress in the use of alkylidenecyclopropanes activated by an electron-withdrawing group was realized by Lautens and co-workers using cooperative iodide-Lewis acid catalysis (Scheme 7.11).[74] The use of MgI_2 led to the formation of the formal [3+2] cycloaddition products. The reaction probably proceeds via ring-opening of the Lewis acid activated cyclopropane by the iodide, followed by addition of the formed enolate **I** to the imine to give **II** and finally intramolecular SN^2 reaction leading to the pyrrolidine. Interestingly, the use of the bulky MAD Lewis acid led to the attack of the γ position instead and the formation of a different product via **III**.[75]
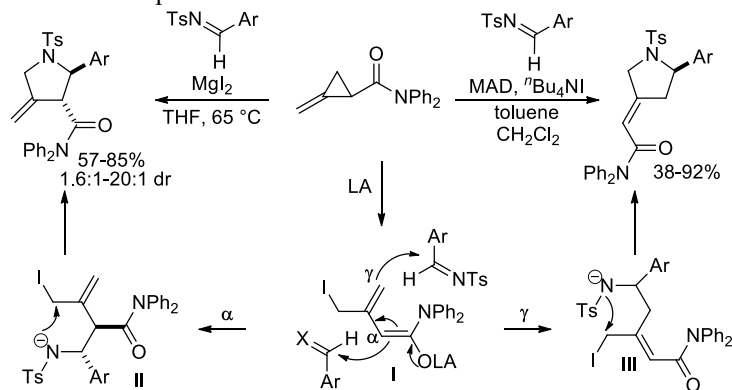
Scheme 7.11: MgI2-catalyzed formal cycloaddition and other annulation reaction of methylidenecyclopropanes.

In order to access enantiopure products, Lautens and co-workers subsequently introduced a chiral sulfoxide auxiliary on the imine and obtained excellent diastereoselectivity (Scheme 7.12, **A**).[76-77] In 2007, they finally reported the first ex-

ample of catalytic asymmetric formal cycloaddition using a chiral BOX ligand on the magnesium catalyst (Scheme 7.12, **B**).[78]
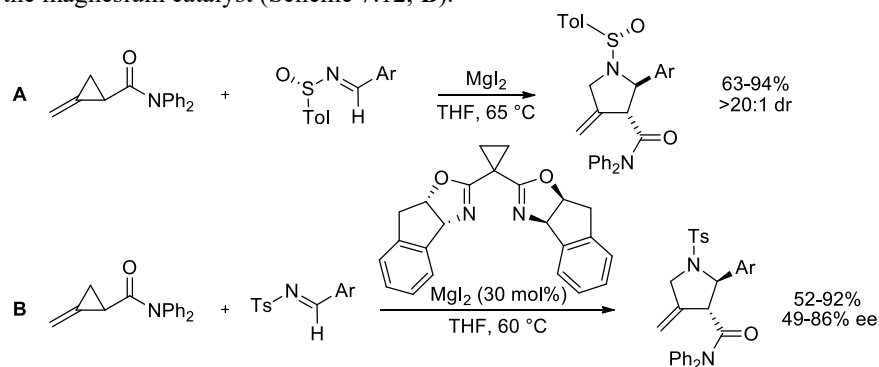
Scheme 7.12: Asymmetric approaches for the formal cycloaddition between methylidenecyclo-propanes and imines.

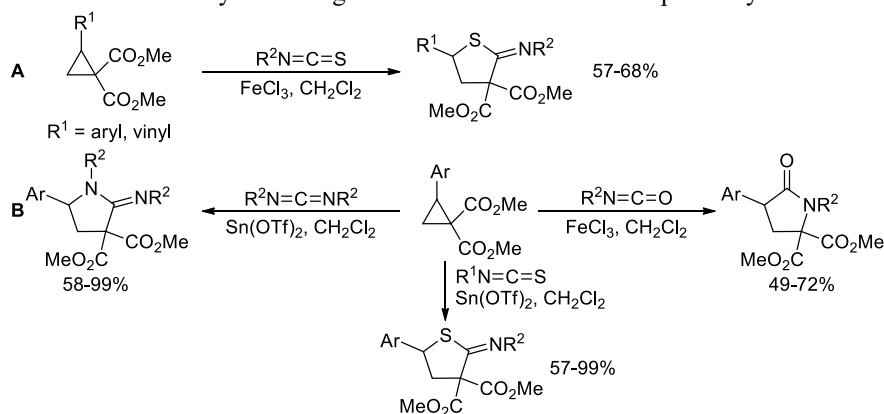## 7.2.2.2 Formal [3+2] Cycloadditions with Cumulenes

Formal cycloadditions with cumulenes, especially CO_2, are very important reactions with small heterocyclic substrates like epoxides or aziridines (*vide infra*). In contrast, these reactions have been only rarely studied with cyclopropanes, although the palladium-catalyzed reaction of alkylidenecyclopropanes with CO_2 was reported initially in 1979 by Inoue and co-workers (Equation 7.4).[79] In 2011, Shi and co-workers studied this transformation in greater detail and were able to significantly increase its scope.[80] Nevertheless, controlling the regiochemistry of the addition still remains a major challenge for this transformation.
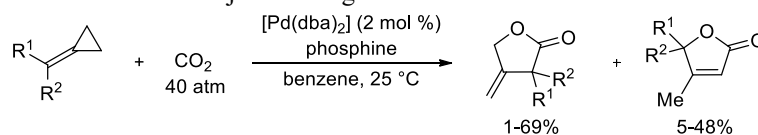
Equation 7.4: Formal [3+2] cycloaddition of alkylidenecyclopropanes with CO_2.

Until 2012, examples of cycloadditions of cyclopropanes with other heterocumulenes were rare, with single examples reported with carbon disulfide,[81] phenylisocyanate,[82] phenylisothiocyanate,[83] diazenes,[84-85] and a special [3+1+1] process involving isonitriles.[86] In 2012, Li and co-workers reported first the iron-mediated formal cycloaddition of aryl- and vinyl- cyclopropane diesters with isothiocyanates (Scheme 7.13, **A**).[87] In this work, the products were suggested to be thiolactams. However, Stoltz and co-workers reported shortly afterwards that the obtained product were more probably thioimidates, which were in their case obtained via the same transformation, but using a tin(II) catalyst (Scheme 7.13,

B).[88] Stoltz and co-workers also reported the first cycloaddition reactions of carbodiimides and isocyanates to give amidines and imidates respectively.

Scheme 7.13: Formal [3+2] cycloadditions with isothiocyanates, carbodiimides and isocyanates.
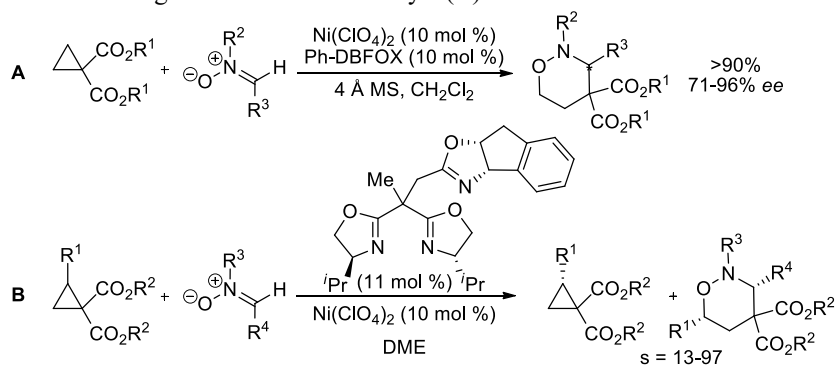
7.2.2.1 Formal [3+n] Cycloadditions

Formal cycloaddition of cyclopropanes with larger partners have been much less investigated. Most research has focused on the [3+3] cycloaddition of donor-acceptor substituted cyclopropanes with nitrones. The seminal studies on this reaction were reported by Kerr and co-workers in 2003, and the reaction was first called a homo [3+2] cycloaddition reaction (Scheme 7.14).[89-95] The reaction proceeded with good yield and stereoselectivity to give 1,2-tetrahydrooxazines. The obtained heterocycles are interesting, as they are found at the core of natural products, such as phyllantidine, which was synthesized by Kerr using this methodology in 2006.[96] Furthermore, the N-O bond can be easily reduced with samarium iodide. After activation of the alcohol and intramolecular nucleophilic substitution, ring-contracted pyrrolidines are obtained, which led to an alternative strategy to the direct [3+2] formal cycloaddition between cyclopropanes and imines discussed previously. This approach was successfully applied in an impressive synthesis of the alkaloid nakadomarin A[97-98] and the core of the natural product yuremamine.[99] Interesting further extensions of the methodology include the use of cobalt complexes of alkynyl cyclopropanes diesters as a new approach for donor-acceptor activation of the three-membered ring,[100] the use of nitrones derived from isatin to obtain important spiroxindole products,[101] and the use of cyclic nitrones as substrates.[102]
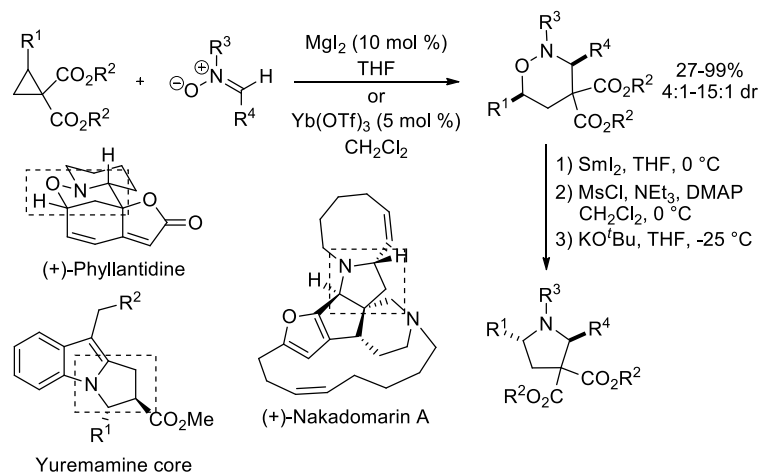
Scheme 7.14: Formal [3+3] cycloadditions of cyclopropanes with nitrones and applications in the total synthesis of natural alkaloids.

An important breakthrough for the further development of formal [3+3] cycloaddition of cyclopropanes and nitrones was the discovery of a catalytic asymmetric variation of the reaction (Scheme 7.15). Using a Nickel-DBFOX catalyst, Sibi and co-workers were able to develop in 2005 an enantioselective cycloaddition using unsubstituted cyclopropanes (**A**).[103] In 2007, Tang and co-workers reported a kinetic resolution of substituted cyclopropanes using a C1-symmetric modified BOX ligand on the nickel catalyst (**B**).[104]

Scheme 7.15: Asymmetric Formal [3+3] cycloadditions of cyclopropanes with nitrones.

In 2008, Charette and co-workers further demonstrated that the [3+3] cycloaddition between azomethine imines and donor-acceptor cyclopropanes was also possible (Equation 7.5).[105] In 2013, Tang and co-workers developed a highly enantioselective variation of this reaction using a C1-symmetric modified BOX ligand on the nickel.[106] Wu and co-workers developed domino-reactions in which

the nitrone[107] or the azomethine imine[108] are generated in situ by addition of a nucleophile on a triple bond (Scheme 7.16, **A** and **B**). In the case of the azomethine imine, a three component reaction starting directly from an alkynyl aldehyde, a hydrazine and the cyclopropane was possible.
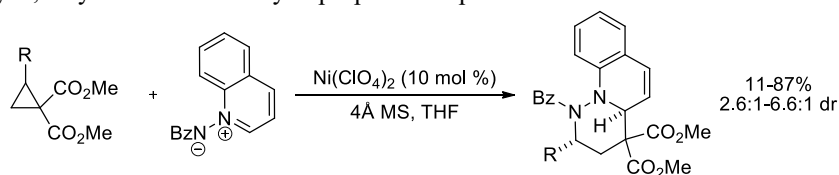
Equation 7.5: Formal [3+3] cycloadditions of cyclopropanes and azomethine imines.
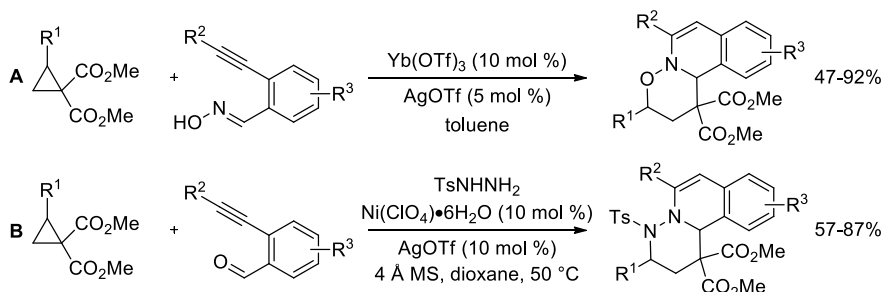
Scheme 7.16: Domino-cyclization cycloaddition from alkynes.

Finally, two recent examples make use of cyclopropanes bearing a further exo double bond (Scheme 7.17): Wang and co-workers reported the first use of alkylidenecyclopropane diesters in the formal cycloaddition with esters in 2009 (**A**).[109] In 2010, Wu and Shi reported that the reaction with vinylidenecyclopropane diesters proceeded with different regiochemistry (**B**).[110] The obtained allenes were unstable and rearranged to form the ketones.
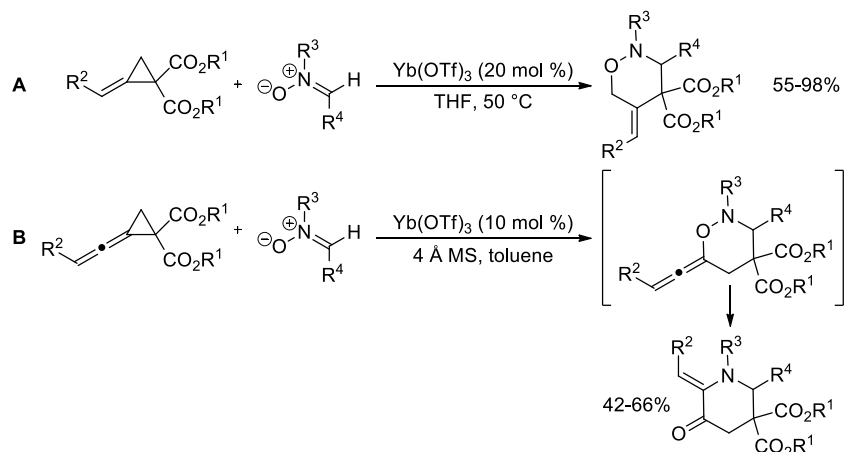
Scheme 7.17: [3+3] Cycloaddition with alkylidene- and vinylidene-cyclopropanes.

In addition to [3+3] formal cycloadditions, there are few examples of reactions with larger partners, but they usually lead to more saturated heterocycles.[111]

7.2.2 Reactions with Epoxides

In contrast to cyclopropanes, for which the most frequent reactions have been with isolated π systems such as carbonyls and imines, the chemistry of epoxides and aziridines is dominated by formal cycloadditions with CO and CO_2. These reactions are very important for the synthesis of heterocycles, and they would require a dedicated chapter to be described in details. As this chemistry has already been described in several reviews,[112-116] we will present only a few seminal studies and concentrate more on other transformations, which have been less in the focus of attention.

7.2.2.1 Formal [3+1] Cycloadditions

The formal cycloaddition of epoxides with carbon monoxide is an important reaction for the synthesis of β-lactones. One of the major challenges associated with this process is to prevent subsequent polymerization of the formed lactones. Except for scattered publications and patents describing this transformation in low yield, the first truly efficient protocol was reported by Alper and co-workers in 2001 (Scheme 7.18, **A**).[117] Key for success was the use of a zwitterionic cobalt catalyst and a Lewis acid as a co-catalyst. Coates and co-workers later developed a more efficient catalyst, in which the cation of the zwitterionic cobalt catalyst is itself a Lewis acid (Scheme 7.18, **B**).[118-119] Best results were initially obtained with

an aluminium salen complex, but later other Lewis acids were found to be even more efficient.[120-122]
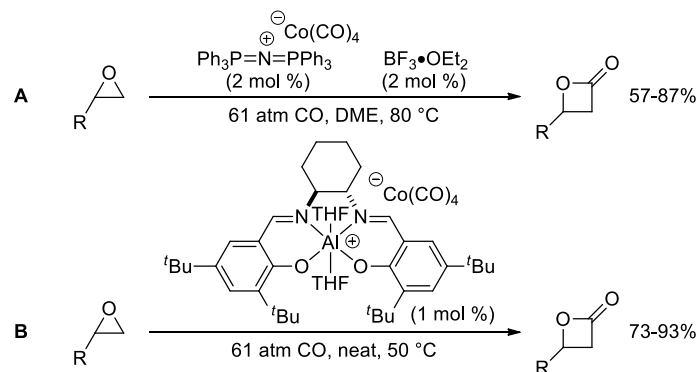
Scheme 7.18: Formal [3+1] cycloaddition of epoxides and carbon monoxide.

Following the discovery of the carbonylation reaction, intensive mechanistic studies have given a deeper insight in the catalytic cycle (Scheme 7.19).[123-124] The reaction is initiated by dissociation of a weakly bound ligand from aluminium to generate Lewis acidic complex **I**. Activation of the epoxide (**II**) is followed by nucleophilic attack of cobalt to give five-coordinated aluminium alkoxide complex **III**. Insertion of CO into the C-Co bond then gives intermediate **IV**, which reacts with CO to give complex **V**. The subsequent four-membered ring formation from **V** to give **VI** has been proposed to be rate-limiting, and the intermediacy of **V** was supported by IR spectroscopy and kinetic studies. Finally, release of the product regenerates the active catalyst **I**. In accordance with the proposed mechanism, the reaction proceeded with high stereocontrol, and *cis* lactones were obtained starting from *trans* epoxides.
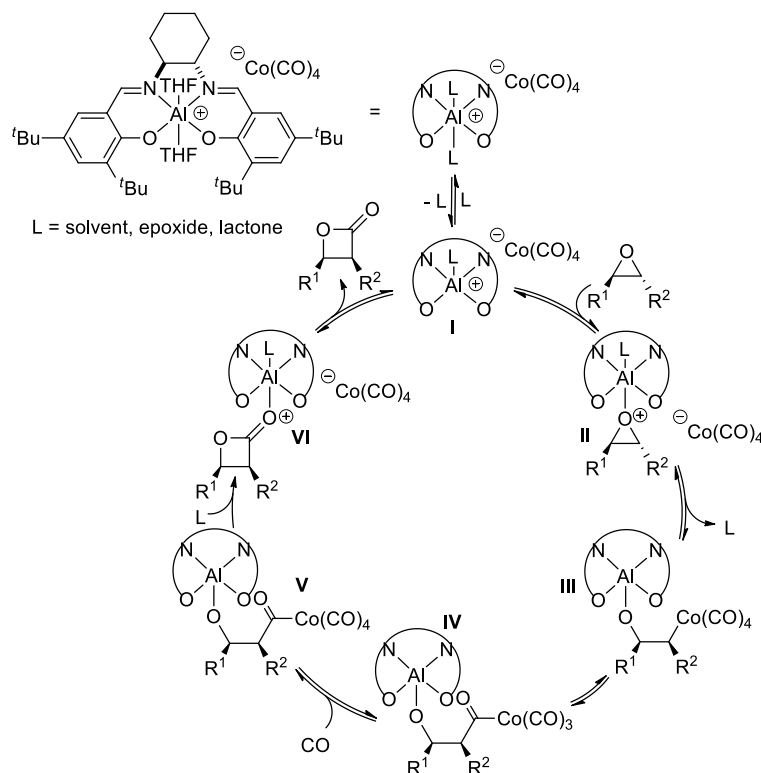
Scheme 7.19: Proposed catalytic cycle for the carbonylation of epoxides.

Interesting recent extensions of the reaction are the use of alkylidenecyclopropanes as substrates,[125] the synthesis of anhydrides via a double carbonyl insertion process,[126] and the first example of carbonylative desymmetrization of meso-epoxides using a chiral chromium Lewis acid.[127]

7.2.2.2 Formal [3+2] Cycloadditions with Isolated π Systems

In principle, the reaction of epoxides with two-carbon π systems can occur either via C-C bond cleavage or via C-O bond cleavage. In contrast to cyclopropanes, a lone pair is available on the oxygen of the epoxide and allows a concerted ring opening to give a carbonyl ylide intermediate, which can then undergo a concerted [3+2] cycloaddition with olefins or carbonyl compounds. In fact, the thermal or photochemical ring-opening of epoxides was one of the first methods used to generate carbonyl ylides for cycloaddition reactions.[128] Nevertheless, ring-opening occurs under relatively mild conditions only with specific substituents, especially cyano and aryl groups. Probably for this reason, other methods to generate car-

bonyl ylides are nowadays favored. As these reactions can be considered as "true cycloadditions", they will not be discussed here.

Surprisingly, Lewis acid activation of epoxides for (formal) cycloaddition reactions has not been investigated in detail until the work of Zhang and co-workers in 2011 (Scheme 7.20).[129] Inspired by the successful design in the field of donor-acceptor cyclopropanes, they discovered that Lewis acid activation of diester substituted epoxides was possible to give dioxolanes with excellent diastereoselectivity after cycloaddition with aldehydes. In contrast to what has been observed with cyclopropanes, racemization of the starting material was observed, indicating a probable carbonyl ylide intermediate **II**. As the reaction was accelerated with electron-rich aldehydes, Zhang and co-workers then proposed a stepwise process via intermediates **III** and **IV** to finally give the dioxolane. Using the same activation principles, Zhang and co-workers also developed a [3+2] formal cycloaddition with alkynes[130] and a [4+3] annulation between nitrones and alkynyl substituted epoxides,[131] but these reactions gave access to more saturated heterocycles. Finally, they reported in 2012 the formal [3+2] cycloaddition of cyclopropanes with indoles (Equation 7.6).[132]
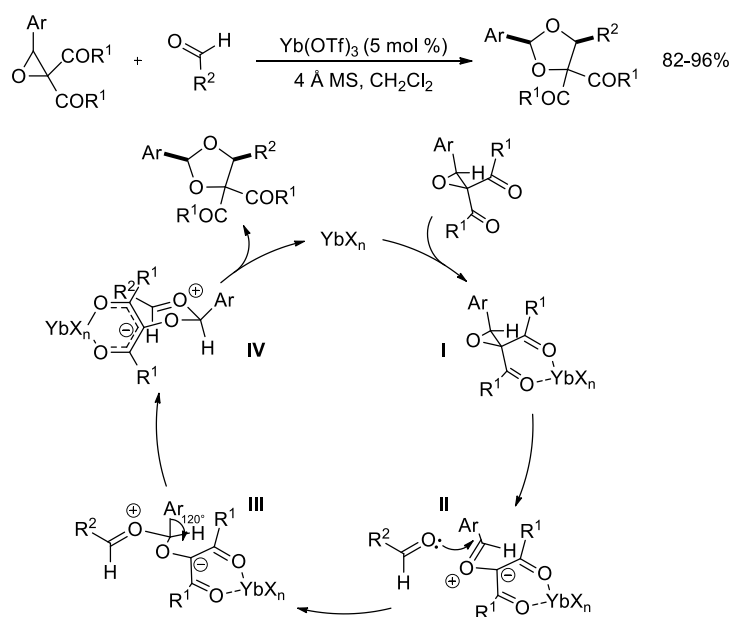
Scheme 7.20: Formal [3+2] cycloaddition of epoxides and aldehydes and proposed reaction mechanism.
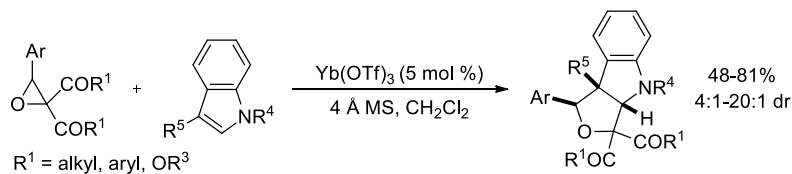
Equation 7.6: Formal [3+2] cycloaddition of epoxides and indoles.

In principle, reactions proceeding via C-C cleavage and carbonyl ylides can be concerted cycloadditions. On the other hand, reactions involving C-O cleavage does not allow a continuous overlap of orbitals and are thus clearly formal cycloadditions. A first approach was developed in the special case of vinyl epoxides: based on the well-established access to palladium-π-allyl complex from vinyl epoxides (*vide infra*), Shim and Yamamoto reported in 1998 the formal [3+2] cycloaddition of this class of substrates with electron-poor olefins (Scheme 7.21).[133] The reaction proceeded in good yield, but with low diastereoselectivity. The first step in the catalytic cycle was proposed to be formation of the palladium π-allyl intermediate **II**. Michael addition of the alkoxide to give **III**, followed by reductive elimination will then give the observed product and regenerate the Pd(0) catalyst **I**. In 1999, they then extended the methodology to the synthesis of oxazolidine by formal cycloaddition of vinyl epoxides and tosyl imines (Equation 7.7).[134-135]
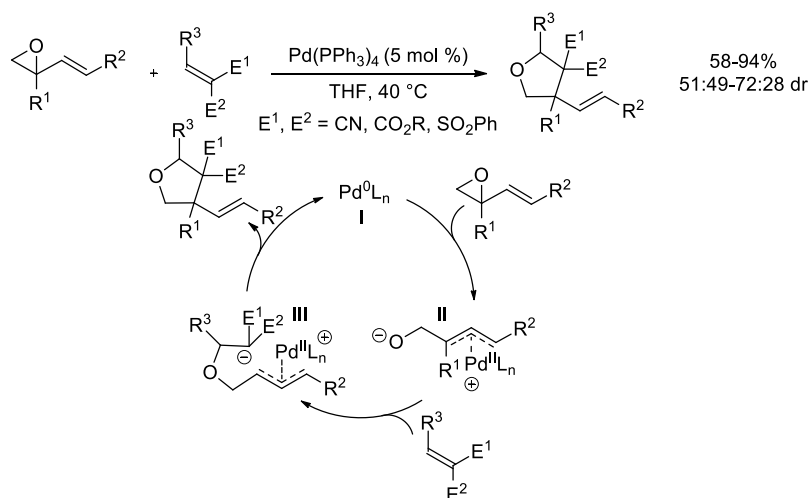
Scheme 7.21: Palladium-catalyzed formal [3+2] cycloaddition of vinyl epoxides and electron poor olefins and proposed reaction mechanism.
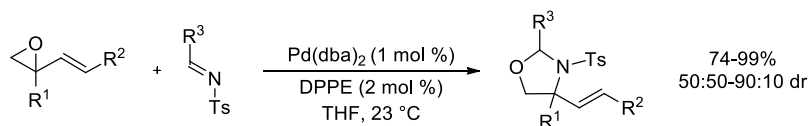
Equation 7.7: Palladium-catalyzed formal [3+2] cycloaddition of vinyl epoxides and imines.

In 2009, Jarvo and co-workers developed the first asymmetric version of the reaction between vinyl epoxides and imines (Scheme 7.22).[136] When using a rhodium catalyst, the reaction was enantiospecific. The retention of the stereochemistry indicated a mechanism involving double inversion. In contrast, when using a palladium catalyst, a dynamic kinetic asymmetric transformation (DYKAT) was possible, and enantioenriched products could be obtained from a racemic mixture. Both methods gave the oxazolidine in good enantiopurity, but only moderate diastereose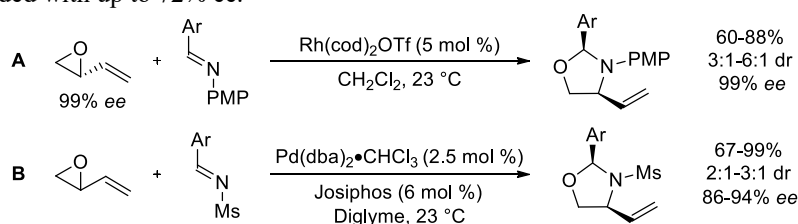lectivity. In 2011, Matsubara and co-workers reported that a nickel catalyst could also be used for the formal cycloaddition of vinyl epoxides and unsaturated ketones.[137] Finally, Hou and co-workers reported the first examples of palladium-catalyzed cycloaddition of nitro olefins and vinyl epoxides, which proceeded with up to 72% ee.[138]

Scheme 7.22: Enantiospecific and enantioselective formal [3+2] cycloaddition of vinyl epoxides and imines.

The main limitation of the palladium-based methods is the requirement for a π-allyl intermediate. In principle, a simple Lewis acid activation would have less limitation. Nevertheless, there are only two reports of Lewis-acid catalyzed formal [3+2] cycloaddition of epoxides with two-carbon π systems: Su and co-workers first reported the ytterbium-catalyzed cycloaddition of imines and epoxides to give oxazolidines in 2007 (Scheme 7.23, **A**).[139] In 2012, Zhang and co-workers studies the ring-opening of diester-substituted epoxides more in details, and found out that the reaction could proceed either via C-C or C-O cleavage depending on the catalyst (Scheme 7.23, **B**).[140] With a nickel catalyst, C-C cleavage was observed, and the products were obtained in good yield and *cis* stereoselectivity. In contrast, C-O cleavage was favored in presence of a tin(II) catalyst and the reaction proceeded with lower diastereoselectivity. The origin of the regioselectivity was rationalized based on calculation: the nickel catalyst favored chelation of the two ester carbonyl group, leading to C-C bond activation. In contrast, the tin catalyst is bound

preferentially to the oxygens of one carbonyl group and the epoxide, leading to C-O bond cleavage. Finally, a last approach was reported by Liu and co-workers in 2004 based on the oxidation of chalcone epoxides with aminium cations.[141] The obtained radical cation intermediate is very reactive and can be used in cycloaddition reactions with non-activated or electron-rich olefins.
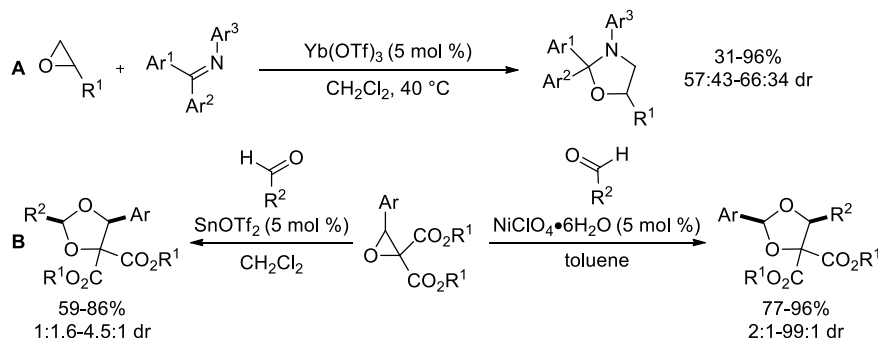
Scheme 7.23: Lewis acid-catalyzed formal [3+2] cycloaddition of vinyl epoxides with imines and aldehydes.

7.2.2.3 Formal [3+2] Cycloadditions with Cumulenes

The most important cycloaddition of epoxide with cumulenes is by far the reaction with carbon dioxide. The obtained carbonates can be easily polymerized to give polycarbonates, which are an important class of polymer. With the right catalyst, the polymer can also be obtained directly. More than one hundred publications have been focused on this reaction, and a full description of this work goes far beyond the scope of this section. Fortunately, several recent reviews have been dedicated to this transformation.[142-145] One of the most successful classes of catalysts are cobalt, chromium and aluminium salen complexes, which have also allowed the development of asymmetric variations of the reaction.[146]
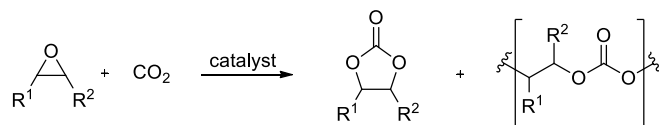
Equation 7.8: Formal [3+2] cycloaddition of epoxides and carbon dioxide.

The reaction with cumulenes is not limited to CO_2. In particular, isocyanates, isothiocyanates and carbodiimides react with epoxides to give the corresponding five-membered heterocycles. One of the main challenges in this transformation is to control the regioselectivity of the formal cycloaddition. Earlier work in this field focused on the use of halide salts, such as tetrabutylammonium iodide,[147]

lithium bromide,[148] tetraphenylstibonium iodide[149-151] or tributyltin iodide-Lewis base complexes.[152-153] The halide has been proposed to play a key role for nucleophilic ring opening of the epoxide (Scheme 7.24). The formed alkoxide can then add on the cumulene and a SN[2] ring closure finally gives the heterocycles. More recently, the methodology has been used in the synthesis of libraries of bioactive compounds[154-155] and the first example involving isoselenocyanates has been reported.[156]
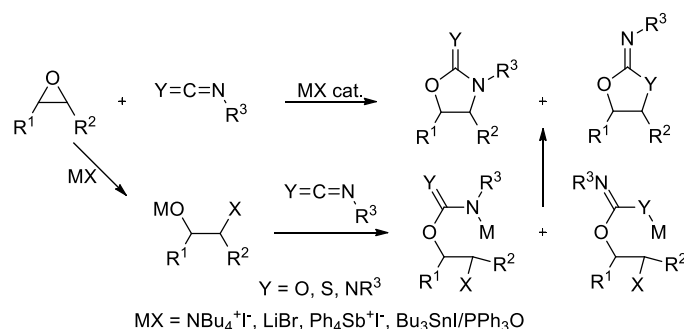
Scheme 7.24: Halide salt-catalyzed formal cycloaddition of epoxides and cumulenes.

The only attempt of asymmetric induction using a ytterbium-Pybox catalyst was reported by Barros and Phillips in 2010 (Equation 7.9).[157] However, only moderate enantioselectivity was obtained and the yield was low, due to the formation of regioisomers and chlorohydrin side products.
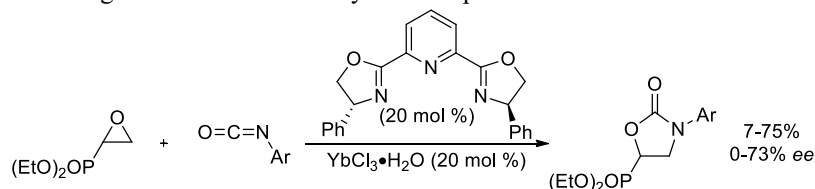
Equation 7.9: Enantioselective [3+2] cycloaddition of epoxides and isocyanates.

Like in the case of formal cycloaddition with two-carbon π systems, a successful solution to the challenge of regio- and stereo-selectivity was found in the use of palladium catalysts with vinyl epoxides. In fact, the first reaction of this type was reported by Trost and Sudhakar with isocyanates in 1987 (Scheme 7.25, **A**).[158] Interestingly, the reaction was stereospecific when tosyl isocyanate was used, but became stereoconvergent with the use of isocyanates bearing a bulky aryl group.[159-160] In this case, high *cis* stereoselectivity was observed regardless of the configuration of the epoxide. Isomerization of the π-allyl intermediate was proposed to rationalize this result. In 1997, Larksarp and Alper reported the first enantioselective variation of the method using TolBINAP as a ligand (Scheme 7.25, **B**).[161-162] This reaction gave high enantioselectivity for both isocyanates and carbodiimides as substrates.
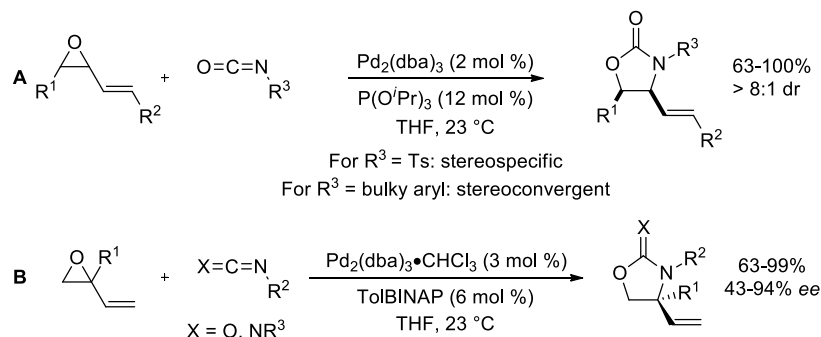
Scheme 7.25: Pd-catalyzed formal [3+2] cycloaddition of vinyl epoxides and cumulenes.

In addition to formal cycloadditions involving cumulenes with two heteroatoms, Baba and co-workers have reported a single example of cycloaddition of ketenes with epoxides (Equation 7.10).[163] Independent of substrate structure and solvent, the tetraphenylstibonium iodide-catalyzed reaction proceeded in high yield for the formation of either the γ-lactone or the ketene acetal product.
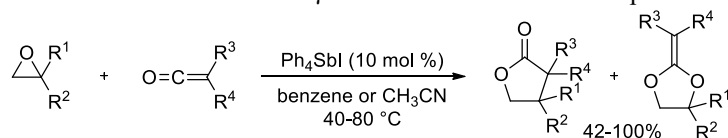
Equation 7.10: Formal [3+2] cycloaddition of epoxides and ketenes.

7.2.3 Reactions with Other Three Membered Rings

Apart from epoxides and cyclopropanes, most investigations have focused on the use of aziridines, oxaziridines and diaziridines substrates. As the use of the last two for the functionalization of olefins has been already discussed in chapter 2 of this volume, the discussion will be here limited to aziridines. Not surprisingly, many parallels can be drawn with the reactions involving epoxides, and depending on the transformation, reports involving aziridines either inspired or take inspiration from similar work with epoxides.

7.2.3.1 Formal [3+1] Cycloadditions

The carbonylation of aziridines is an important method for the synthesis of β-lactams. The main research in this field was conducted by Alper and co-workers (Scheme 7.26). They first reported the rhodium-catalyzed carbonylation of aziridines (**A**).[164-166] The reaction was limited to aryl substituted aziridines. High regioselectivity was observed for insertion in the benzylic C-N bond. Furthermore, the reaction proceeded with retention of the stereochemistry at the benzylic center. In

1996, they reported a cobalt-catalyzed carbonylation (**B**).[167] The reaction was more general, and proceeded this time with inversion of the stereochemistry and insertion in the less substituted double bond. This striking result can be explained by the different mechanism of the two reactions. Like for the carbonylation of epoxides (*vide supra*, Scheme 7.19), the reaction with cobalt most probably proceeds via nucleophilic attack of a cobaltate intermediate.[168] In the case of rhodium, oxidative insertion of **I** into the C-N bond occurs first to give **II** (Scheme 7.27). Hyperconjugation with an aromatic ring is essential for this step.[169] Carbonyl insertion, followed by addition of carbon monoxide and reductive elimination then gives the lactam. Subsequently, the scope of the cobalt-catalyzed reaction was studied more in detail.[170-171] Coates and co-workers also demonstrated that the Lewis acid cobaltate complex developed for epoxide carbonylation is also more efficient for aziridine carbonylation.[119]
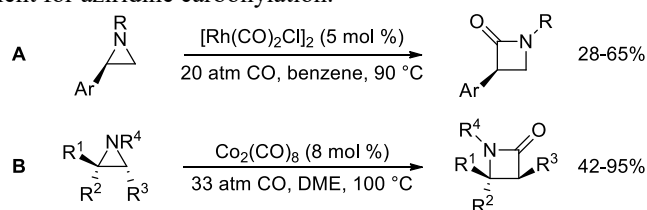
Scheme 7.26: Formal [3+1] cycloaddition of aziridines and carbon monoxide.
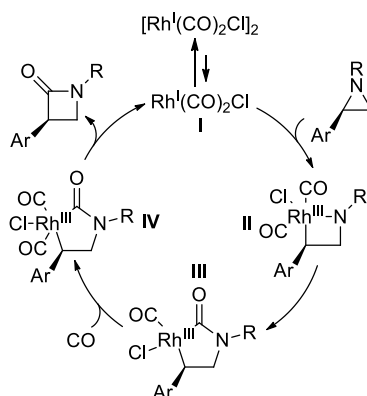
Scheme 7.27: Mechanism of the rhodium-catalyzed carbonylation of aziridines.

In addition to the most successful rhodium and cobalt catalysts, examples of carbonylation with stoichiometric nickel complexes were also reported.[172-173] Finally, the use of palladium catalysis remains limited to methylene-[174] and vinyl-[176-177] substituted aziridines.

7.2.3.2 Formal [3+2] Cycloadditions with Isolated π Systems

As for epoxides, the lone pair on nitrogen allows the thermal or photolytic opening of aziridines to generate an azomethine ylide. Again, this process is often limited to specific substituents on the aziridines and requires harsh reaction conditions. It can also be considered as a "true" cycloaddition, and will therefore not be discussed in this section.

As in the case of cyclopropanes, the use of aziridines in formal [3+2] cycloadditions has increased tremendously during the last 15 years.[178-179] The first break-throughs were reported in 1999. Bergmeier and co-workers demonstrated that the intramolecular cycloaddition of tosyl aziridines and allyl silanes could be catalyzed by boron-trifluoride etherate (Scheme 7.28, **A**).[180] Also in 1999, Mann and co-workers used the same catalyst for the intermolecular cycloaddition of aryl-substituted aziridines with enol ethers,[181] and later demonstrated that this system could also be applied to non-activated alkenes (Scheme 7.28, **B**).[182] In these early works, high diastereoselectivity could be achieved only in the case of the formation of bicyclic five-five ring systems. In 2000, Nakagawa and Kawahara then reported the scandium-catalyzed cycloaddition of unsubstituted Cbz protected aziridines with skatole and used the method in a formal synthesis of physostigmine (Scheme 7.28, **C**).[183] In 2001, Yadav and co-workers finally reported that scandium triflate was also an efficient catalyst for the reaction of aryl-substituted tosyl aziridines with enol ethers and allyl silanes.[184]
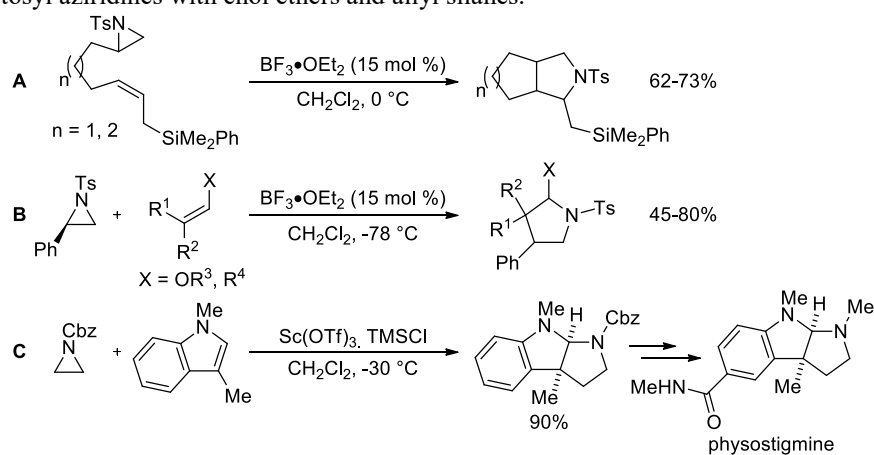
Scheme 7.28: Formal [3+2] cycloaddition of aziridines with olefins.

In 2004, Johnson and co-workers then reported that diester substituted N-aryl aziridines could be activated by Lewis acid for reaction with enol ethers (Scheme 7.29, **A**).[185] Due to the diester activation, the reaction now proceeds via C-C instead of C-N cleavage. For cyclic enol ethers, a [4+2] annulation process was observed, proceeding probably via a Friedel-Crafts reaction on the aryl ring. The re-

action could also be extended to norbornene as substrate. In the case of acyclic enol ethers, the formal [3+2] cycloaddition product was obtained with low diastereoselectivity. Although the reaction was usually performed with stoichiometric amount of zinc chloride as Lewis acid, two examples of reactions catalytic in zinc were also reported. In 2011, Zhang and co-workers demonstrated that the [3+2] cycloaddition product could be obtained for both cyclic and acyclic enol ethers when using tosyl aziridines and yttrium triflate as catalyst.[186]

As has been seen for epoxide and cyclopropanes, the use of vinyl aziridines opened the way for π-allyl palladium chemistry. The first example of [3+2] cycloaddition with an isolated two-carbon π system was reported by Aggarwal and co-workers in 2011 (Scheme 7.29, **B**).[187] Depending on the reaction conditions and substrate structure, pyrrolidine products could be obtained with high diastereoselectivity. The synthetic utility of the method was further demonstrated in a formal total synthesis of the natural product (-)-α-kainic acid. Furthermore, Shipman and co-workers reported in 2012 the first example of intramolecular formal cycloaddition of methylene aziridines with alkenes.[188]
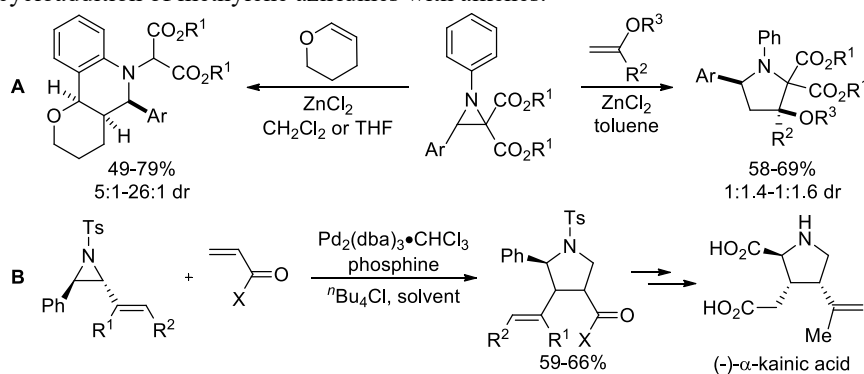
Scheme 7.29: The use of diester- and vinyl-substituted aziridines in formal cycloaddition reactions.

The formal [3+2] cycloaddition of aziridines is not limited to olefins as partners. The reaction of aziridines with aldehydes and ketones was reported by Yadav and co-workers in 2004 using a silyl group to stabilize the carbocation obtained after C-N bond cleavage (Scheme 7.30, **A**).[189] Oxazolidine products were obtained in excellent yield, but moderate diastereoselectivity. In 2007, Singh and co-workers then studied the reaction of aryl-substituted tosyl aziridines with both carbonyls and imines (Scheme 7.30, **B**).[190] This reaction was possible using zinc triflate as catalyst and also proceeded via C-N bond cleavage. In 2011, Hanamoto and co-workers finally reported the formal [3+2] cycloaddition of trifluromethyl substituted tosyl aziridines with aldehydes (Scheme 7.30, **C**).[191] This reaction proceeded also with C-N cleavage, but with opposite regioselectivity and high diastereoselectivity. As the trifluoromethyl group is not able to stabilize a carbocation

intermediate, the reaction starts most probably by a nucleophilic SN^2-like attack of the carbonyl on the less substituted carbon of the aziridine.

The use of diester-substituted aziridines allowed again cycloadditions involving C-C instead of C-N cleavage. Using different Lewis acids as catalysts, the groups of Zhang[192-193] and Wang[194] reported the cycloadditions with both carbonyls and imines (Scheme 7.30, **D**). Interestingly, good diastereoselectivity was observed for the formation of *cis*-oxazolidines and *trans*-imidazolidines.

cat. = Zn(OTf)$_2$, AgOTf, NiClO$_4$•6H$_2$O, Y(OTf)$_3$
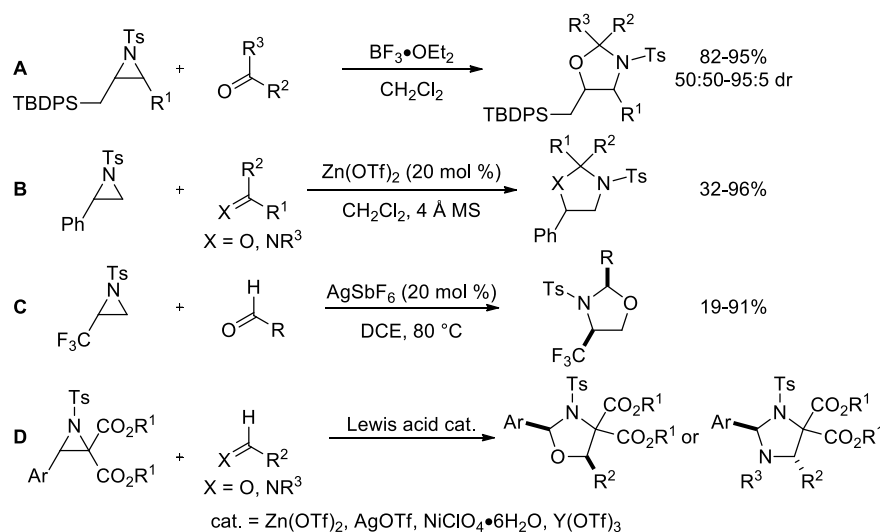
Scheme 7.30: Formal [3+2] cycloaddition of aziridines with carbonyls and imines.

7.2.3.3 Formal [3+2] Cycloadditions with Cumulenes

As in the case of epoxides, carbon dioxide is again the most attractive cumulene for reaction with aziridines. This reaction gives important oxazolidinones as products and constitutes an alternative to the reaction of epoxides with isocyanates. Even if early work demonstrated already in the 70's and the 80's that the cycloaddition of aziridines and CO$_2$ could be accelerated with halide salts,[195-196] progress has been much slower than in the case of epoxides, focusing mostly on technical improvements. Interesting recent results includes the use of a chromium salen catalyst by Miller and Nguyen[197] and a palladium catalyst together with vinyl aziridines by Aggarwal and co-workers[198] (Scheme 7.31, **A** and **B**). The former reaction gave excellent regioselectivity, whereas the latter reaction already proceeded at atmospheric pressure of carbon dioxide.
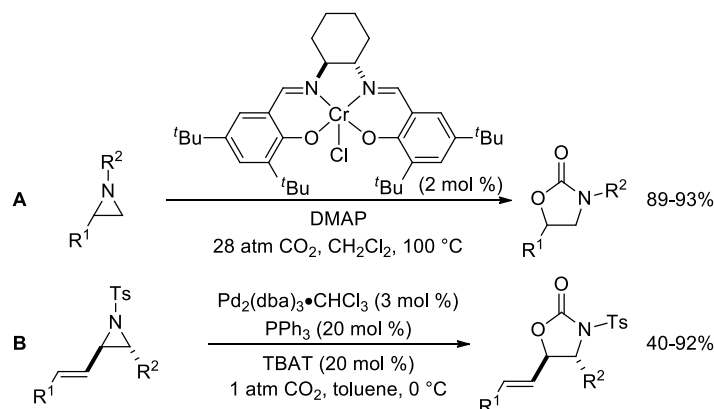
Scheme 7.31: Formal [3+2] cycloaddition of aziridines with carbon dioxide.

The reaction of aziridines with other cumulenes can be also be catalyzed by halide salts.[196] In 1992, Baeg and Alper reported the first palladium-catalyzed formal cycloaddition of aziridines with carbodiimides[199] and later extended the protocol to isocyanates and isothiocyanates (Scheme 7.32, **A**).[200] The regiochemistry of the cycloaddition was dependent of the cumulene structure. The reaction was enantiospecific. When sulfurdiimides were used, a thiourea was obtained instead of the expected product (Scheme 7.32, **B**).[201] Although the mechanism of this transformation was not yet fully elucidated, a labeling experiment showed that the extra carbon atom originated from the methylene group of the aziridine.
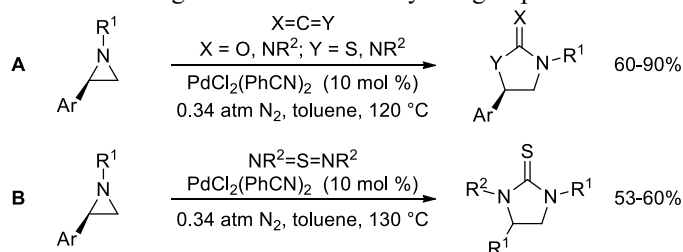
Scheme 7.32: Pd-catalyzed Formal [3+2] cycloaddition of aziridines with cumulenes.

The use of vinyl aziridines together with a palladium catalyst allowed cycloaddition with cumulenes under milder conditions. Such a process was first reported by Alper and co-workers in 2000.[202] In 2003, Trost and Fandrick reported an asymmetric variation of the cycloaddition of vinyl aziridines and isocyanates using the bis(phosphine) ligands developed in their laboratory (Equation 7.11).[203] As the reaction proceeded via a π-allyl palladium intermediate, a dynamic kinetic asymmetric cycloaddition became possible. In 2004, Dong and Alper reported a second asymmetric cycloaddition, but the enantioselectivity was moderate.[204]
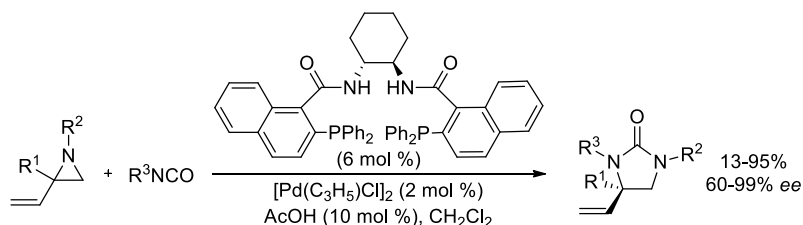
Equation 7.11: Pd-catalyzed dynamic kinetic asymmetric cycloaddition of vinyl aziridines and isocyanates.

Recently, progress using other catalysts then palladium has also emerged. In 2008, Hou and co-workers reported the use of tributylphosphine as a catalyst for the cycloaddition of aziridines with carbon disulfide and isothiocyanates.[205] Finally, Sengoden and Punniyamurthy developed in 2013 the iron-catalyzed cycloaddition of aziridines with isoselenocyanates.[206] Interestingly, this reaction could be performed "on water" under air, without the care required for more sensitive catalysts.

7.3 Reactions Involving Four-Membered Rings

In comparison with the use of three-membered ring, the field of formal cycloaddition involving four-membered ring is still in its infancy. This is probably due to the smaller strain-energy per bond, but also to the less developed synthetic methods used to access four-membered rings.

7.3.1 Reactions with Cyclobutanes

Neglected for a long time, the catalytic activation of cyclobutanes has come recently at the center of attention of the organic chemistry community.[207] Prior to 2008, only one example of cycloaddition involving a 1,2-donor-acceptor substituted aminocyclobutane had been reported by Saigo and co-workers in 1991 (Equation 7.12).[208] A mixture of half aminal and acetal was obtained, which was subsequently completely hydrolyzed to the acetal. In this pioneering work, the diastereoselectivity was low and the scope of the reaction was limited. In 1993, Saigo and co-workers then reported a multi-step [4+2] annulation procedure for the synthesis of δ-lactones starting from acetal-ester substituted cyclobutanes.[209]
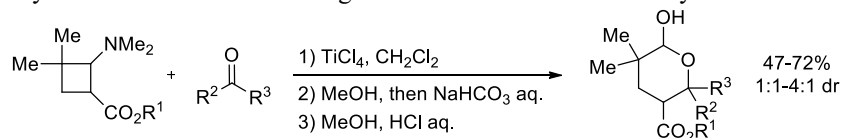
Equation 7.12: First example of formal [4+2] cycloaddition of cyclobutanes and carbonyls.

Surprisingly, it is only in 2009 that this type of transformation was studied more in detail. In this year, Parsons and Johnson reported an important break-

through by using diester-aryl/alkenyl substituted cyclobutanes in the reaction with aldehydes (Scheme 7.33, **A**).[210] The reaction was catalyzed by scandium triflate and gave tetrahydropyran products with good yield and excellent diastereoselectivity. In contrast to the similar reaction developed for cyclopropanes, racemization of the stereocenter was observed during the reaction. The required cyclobutanes were themselves synthesized by scandium-catalyzed [2+2] formal cycloaddition of olefins and methylidenemalonates, which allowed the development of a one-pot formal [2+2+2] process to access tetrahydropyrans. The same year, Pritschard, Christie and co-workers used cobalt octacarbonyl complexes of acetylenes as cation-stabilizing groups on the cyclobutane (Scheme 7.33, **B**).[211] Using again scandium triflate as catalyst, *cis*-substituted tetrahydropyrans were obtained in good yield.
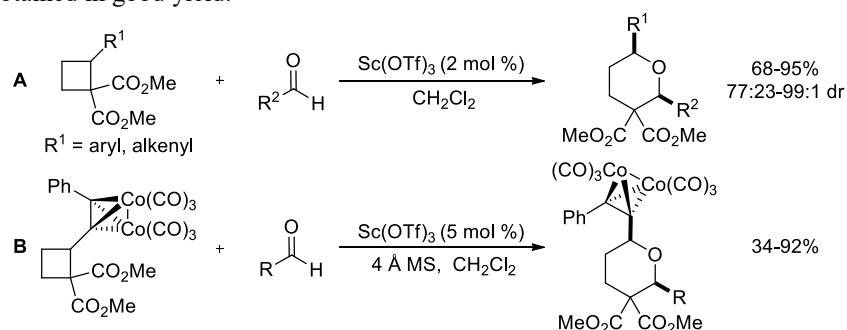
Scheme 7.33: Formal [4+2] cycloaddition of 1,2-donor-acceptor substituted cyclobutanes with aldehydes.

To further extend the scope of formal [4+2] cycloadditions, Pagenkopf and co-workers then studied oxygen-diester substituted cyclopropanes as substrates (Scheme 7.34).[212-214] The reaction was especially successful with bicyclic cyclobutanes. They first reported the cycloaddition with imines, which gave enamine products after elimination of the alcohol (**A**).[212] In this case, the reaction of aryl-diester substituted cyclobutanes gave stable piperidines as products. In a second work, they extended the reaction to aldehydes (**B**).[213] In this case, stable acetal products were obtained with high diastereoselectivity. Finally, they developed in 2011 the formal [4+3] cycloaddition with nitrones (**C**). [214] The reactions proceeded in good yield, but only with moderate diastereoselectivity. In 2012, Matsuo and co-workers further reported a one-pot reaction of 1,2-oxygen diester-substituted cyclopropanes involving cycloaddition and intramolecular lactonization.[215]
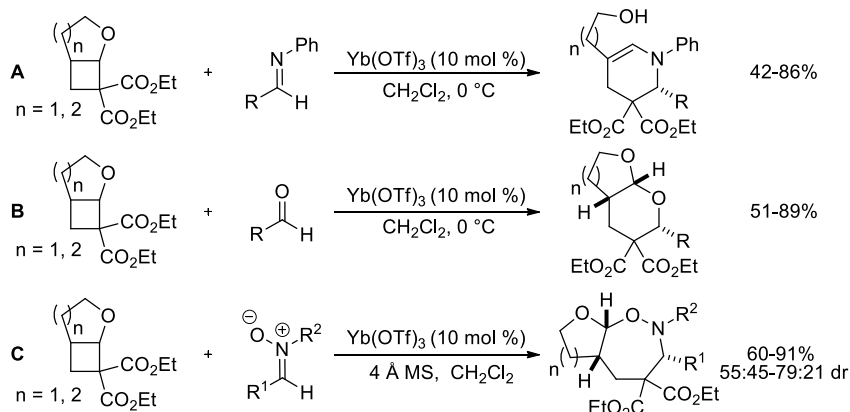
Scheme 7.34: Formal [4+2] cycloaddition of oxygen-diester substituted cyclobutanes.

Three-donor-substituted cyclobutanones were introduced by Matsuo and co-workers for their use in formal [4+2] cycloaddition in 2008 (Scheme 7.35).[216] In the case of bicyclic cyclobutanones, cleavage of the less substituted C-C bond was observed, leading to stable bicyclic acetals as products (**A**). For acyclic cyclobutanones, the regioselectivity of the reaction was dependent from the temperature (**B**). At -45°C, cleavage of the less substituted C-C bond was observed. In contrast, if the temperature was raised to room temperature, the reversed regiochemistry and elimination of ethanol was observed. This is probably due to the higher stability of the more substituted zwitterion intermediate. In 2012, Matsuo and co-workers also reported the use of cobalt octacarbonyl alkyne complexes as donor on cyclobutanones.[217]
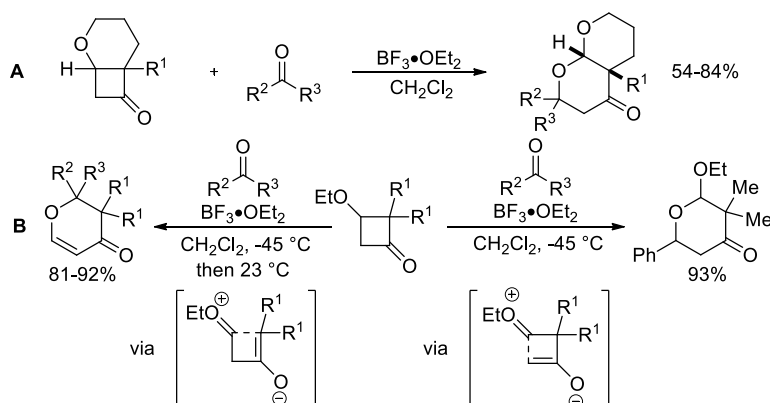
Scheme 7.35: Formal [4+2] cycloaddition of 3-oxo-cyclobutanones.

7.3.2 Reactions with Other Four-Membered Rings

Most of the cycloadditions involving other four-membered rings are based on reactions between oxetanes and azetidines and carbon monoxide or cumulenes. Baba and co-workers first reported that tetraphenylstibonium iodide was also a good catalyst for the cycloaddition of oxetanes and cumulenes.[163, 218] Alper and co-workers then studied the activation of both oxetanes and azetidines with cobalt and palladium catalysts (Scheme 7.36). Cobalt octacarbonyl was a good catalyst for the carbonylation of azetidines with carbon monoxide (**A**).[219] Cleavage of the more substituted C-N bond was observed in the case of aryl substituents on the azetidine. For alkyl substituents, the other regioselectivity was observed. Reaction under milder conditions could be achieved using a palladium catalyst and vinyl azetidines or oxetanes.[220-222] This reaction proceeds via π-allyl palladium intermediates and was successful in the case of isocyanates, isothiocyanates, carbodiimides, ketenes and ketimines as cumulenes. Finally, Mann and co-workers reported the reaction of tosyl azetidines and electron-rich olefins promoted by boron trifluoride etherate.[223] In this case, a mixture of [4+2] cycloaddition and further elimination products was obtained.
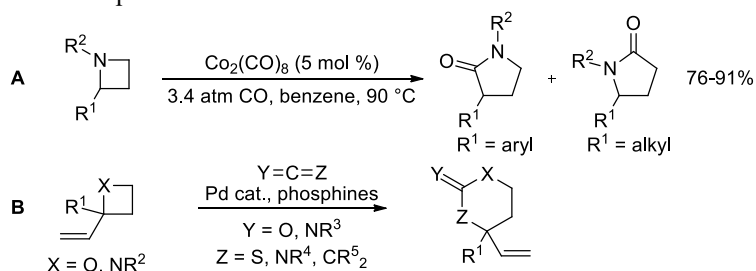
Scheme 7.36: Formal [4+2] cycloaddition of azetidines and oxetanes with carbon monoxides and cumulenes.

7.4 Reactions with Larger Rings

Up to now, there are only very few studies on formal cycloaddition reactions involving C-C bond cleavage of larger rings which gives saturated heterocycles. This is probably due to the lack of ring strain, which makes these reactions less favorable. An interesting example has nevertheless been reported by Zhou and Alper, who developed the palladium-catalyzed formal [5+2] cycloaddition of vinyl pyrrolidines and isocyanates to give diazepin-2-ones (Equation 7.13).[224]
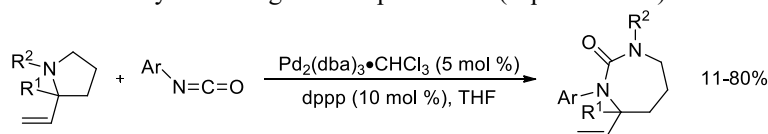
Equation 7.13: Formal [5+2] cycloaddition of vinylpyrrolidines with isocyanates.

7.5 Conclusions

Formal cycloadditions proceeding by C-C bond cleavage are important synthetic tools, as they give access to more saturated heterocycles than "classical" cycloadditions involving π-systems. However, the activation of C-C bond is difficult, and the use of ring strain or strong polarized bonds has been necessary to develop efficient processes. During the last two decades, broadly applicable methods have appeared that build on the earlier pioneering work in this area. Cycloaddition of donor-acceptor cyclopropanes and two or three-atom π systems, as well as reactions of epoxides and aziridines with carbon monoxide or cumulenes are now burgeoning fields of research in organic chemistry. They have found important applications both in the synthesis of natural products or the large scale synthesis of commodity chemicals. Nevertheless, the field is still in its infancy when considering the nearly endless possible combinations of partners for formal cycloaddition reactions. Furthermore, only few successes have been reported for the simultaneous control of diastereo- and enantioselectivity. There is consequently a huge potential for both applications and further methodological developments in the field of formal cycloaddition reactions for saturated heterocycle synthesis.

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