**Stereocontrolled Synthesis and Functionalization of Cyclobutanes and Cyclobutanones**

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**Abstract:** In the last decade a certain number of new cyclobutane and cyclobutanone synthesis and functionalization protocols have been published. Organo- and biocatalyzed eco-friendly approaches to cyclobutane-containing molecules have been developed with interesting results. Also, successful new total synthesis of bioactive compounds and drugs have been recently reported where a four membered ring represented the key intermediate. Therefore, the rising interest in this field represents a great point of discussion for the scientific community, disclosing the synthetic potential of strained four membered ring carbocyclic compounds. Herein we report a critical survey on the literature concerning the enantiocontrolled synthesis and functionalization of cyclobutane derivatives, with particular attention to metal-free, low impact methodologies, published during the period 2000–2013.

**Keywords:** cyclobutanone; cyclobutane; stereocontrol; ring enlargement; alkylation; organocatalysis; cycloaddition; biocatalysis; stereochemistry; oxidation

1. Introduction

Strained carbocyclic molecules have emerged in the past decades as highly useful synthetic tools [1]. In this class of compounds cyclopropane and cyclobutane derivatives certainly represent the most studied and versatile organic molecules [2]. Due to their inherent ring strain, the selective modification of their structures can be strategically used in organic synthesis [3]. Ring enlargement and ring
contraction can be obtained regio- and stereoselectively by using a certain number of reaction conditions [4,5]. Moreover carbocyclic ring opening is possible and it represents an advantageous synthetic route to acyclic compounds [6]. Cyclobutane and cyclobutanone derivatives can be easily prepared by reliable synthetic methods [7] such as [2+2] cycloadditions, [8,9] cyclopropanol- [10,11], cyclopropylphenylthio- [12–15] and selenium-carbinols ring expansions [16–18] or ring enlargement of oxaspiropentanes [19–21]. A large number of papers and patents have been published in this area. Cyclobutanones have been employed as key starting materials [22] for a wide number of total syntheses [23,24] (examples are the syntheses of compounds 4–8 [25–28], Figure 1) and as building blocks for the preparation of bioactive molecules and drugs such as the cyclobutane nucleosides 1 and 2 [29–32]. An example of the versatility of this class of molecules is well represented by the squaric acid derivatives, which are involved in a large number of synthetic applications as demonstrated by Moore and co-workers [33–38]. Moreover chiral cyclobutane compounds have been recently isolated independently by Seebach [39] and Blackmond [40], as key intermediates 3, in the organocatalyzed conjugated addition of nitrostyrenes to different carbonyl compounds. Again, cyclobutane core skeletons are frequently identified in alkaloids [41] and secondary plant metabolites such as compound 9 [42,43].

**Figure 1.** Cyclobutane containing natural products and synthetic intermediates.

![Figure 1](image-url)
Among the different transformations of the cyclobutane system, the \( \alpha \)-functionalization in most cases [44] involves the use of organometallic-based reactions or metal catalyzed transformations [45–48].

The growing attention to ecofriendly procedures, accompanied by the use and the development of new high-performing chiral organic catalysts has changed certain paradigms about the functionalization and transformation of organic compounds. Moreover, organocatalyzed and biosynthetic procedures have deeply influenced the development of new synthetic approaches. As a consequence of this new sensibility, the synthesis and transformation of strained carbocyclic compounds have been revisited and investigated with the aim of achieving green routes for the preparation of these important synthetic tools. Therefore a, remarkable number of procedures have been recently published, showing a rising interest on the development of stereo- and enantioselective metal free methodologies for the synthesis and functionalization of cyclobutanes [49,50].

Based on these considerations, this review will highlight some of the most important and recent achievements in this field. The reader of this review should not expect a complete compendium but rather a selection of papers that report the development of new eco-friendly procedures, mainly organocatalyzed transformations, highlighting applications in the synthesis of biologically active molecules and natural products where cyclobutanone derivatives appear as key starting materials. In graphical schemes, essential precursors or transition states for the relevant cyclobutane derivatives are placed in parentheses whereas non-isolated intermediates are marked with square brackets. As the synthetic application is emphasized, the reader is referred to the original literature for detailed mechanistic considerations. This review is organized according to the following classes of key steps:

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2. Stereoselective [2+2] Cycloaddition Synthesis of Cyclobutane Derivatives

2.1. Stereoselective Synthesis of Cyclobutane Amino Acids

Thermal [2+2] stereoselective cycloaddition, involving 2-acylaminoacrylates 10, as electron-poor acceptor alkenes has been performed by Peregrina and co-workers [51]. This reaction involves a Michael-Dieckmann-type process that allows access to the substituted cyclobutane skeleton 11. Finally, deacylation and hydrolysis reactions were performed to isolate the 2-hydroxycyclobutane-(R)-amino acid serine analogues (c4Ser) 12 as reported in Scheme 1.

Scheme 1. Stereoselective synthesis of (cis/trans)-2-hydroxycyclobutane amino acids.

\[
\begin{align*}
\text{COOMe} & \quad \text{OEt} \\
\text{NHAc} & \quad \text{OEt} \\
10 & \quad 11 \\
& \quad \text{trans-12} \\
\text{HO}_\text{R} & \quad \text{COOMe} \\
\text{NHAc} & \quad \text{HO} \\
\end{align*}
\]

2.2. Stereoselective Diels-Alder Reactions using Cyclobutenones

Cyclobutenone 14 was employed as dienophile for the first time by Danishesfsky to promote a Diels-Alder cycloaddition reaction with functionalized dienes 13 (Scheme 2). This reaction provides diverse and complex cycloadducts 15 in good yields. Cycloadducts bearing a strained cyclobutanone moiety were able to undergo regioselective ring expansions to produce the corresponding cyclopentanones, lactone, and lactams 16a–c, through a straightforward synthetic approach [52].

Scheme 2. Cyclobutenone as a highly reactive dienophile in Diels-Alder reactions.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
13 & \quad 14 \\
\text{Et}_3\text{N} & \quad -30^\circ\text{C} \\
15 & \quad \text{46-90 % yield} \\
16 & \quad \text{a-c} \\
16a & \quad X = \text{C} \\
16b & \quad X = \text{N} \\
16c & \quad X = \text{O} \\
\end{align*}
\]
3. Enantioselective Stoichiometric Synthesis of Cyclobutane Derivatives

3.1. Enantioselective Stoichiometric [2+2] Cycloadditions

Photochemical, Diels-Alder reactions and [2+2] ketene cycloadditions represent the most common and efficient routes to cyclobutane or cyclobutanone derivatives. However, a big effort has been made in the last years to combine together the possibility to synthetize chiral substituted cyclobutane compounds with high stereo- and enantioselectivity by using chiral auxiliaries or chiral catalysts increasing the atom economy of the synthetic processes.

In 2002 Ghosez and co-workers developed an excellent two-step sequence for the asymmetric vicinal acylation of olefins by a [2+2+1] strategy [53]. The key reaction of this methodology is a [2+2] cycloaddition of an olefin 19 to a chiral keteniminium salt 18 derived from N-tosylsarcosinamide 17 yielding stereoselectively only cis-α-aminocyclobutanones 20 with good enantioselectivity (68%–98% ee) through the intermediate 18. In the original paper, this reaction is followed by a m-CPBA regioselective Baeyer-Villiger oxidation providing the lactol derivative 21 in good yields. However, the oxidation step occurs without any detrimental effect on the stereochemistry and enantiopurity of cyclobutanones (Scheme 3).

Scheme 3. [2+2] Cycloaddition of chiral keteniminium salts in the synthesis of cyclobutanones.

A similar approach was utilized by the same group for the development of another [2+2] ketene mediated cycloaddition reaction between the α-chloroacetyl chloride 22 and a chiral oxazolidine 23 affording α-chloro-α'-aminocyclobutanones 24. The bicyclic cyclobutane derivative 24 was subsequently converted in the enantiopure cyclobutane aminoacid 25 after few synthetic steps [54] as reported in Scheme 4.

Scheme 4. Synthesis of enantiopure α-chlorocyclobutanones.
(−)-Esermthole (28 [55]) has been synthetized in 2013 by Shishido and co-workers, through a key [2+2] cycloaddition reaction that simultaneously generated the tricyclic unit 27 in one single synthetic step [56]. The stereochemistry of the fused cyclobutane 27, has been controlled by the introduction of a dioxolane chiral auxiliary in the starting material 26, thus obtaining the chiral scaffold in >95% de. Further functionalization of the cyclobutane moiety allowed to afford the fused bispyrrolidine natural product (−)-28 with high enantio- and diastereoselectivity (Scheme 5).

Scheme 5. Enantioselective access to pyrrolidinoindoline alkaloids.

Aitken and co-workers reported the [2+2] cycloaddition of ethylene with chiral unsaturated γ-lactam 29. The so obtained cyclobutane derivative 30 was transformed in few synthetic steps in the corresponding Boc-2-aminomethylcyclobutanecarboxylic acids 31 [57]. This synthetic protocol has been modified in a second time by the same group with the aim to improve its efficiency [58]. The synthetic pathway to access to racemic cis-cyclobutane γ-amino acid core 30, reported in Scheme 6, was simplified and the yields were improved [58] Racemic 2-aminocyclobutanecarboxylic acids 32 were diastereoisomerically separated, giving the advantage to afford both of the enantiomers through a non-destructive cleavage of the chiral auxiliary either by hydrolysis or by amonolysis, thus providing an efficacious access to N-protected derivatives \((R,S)-31\) and \((S,R)-31\) and their corresponding γ-aminoacids 32.

Scheme 6. Stereoselective synthesis of cis- and trans-γ-cyclobutane amino acids.
3.2. Chiral Allene-Based [2+2] Asymmetric Cycloadditions

Endocyclic allene 33, has been used by Ogasawara and co-workers in the synthesis of chiral cyclobutenone 34 through a [2+2] regio- and stereoselective cycloaddition with dichloroketene. The reaction smoothly proceeds with good stereospecificity affording the scalemic cycloadduct 34 with complete transfer of the optical purity (Scheme 7) [59].

Scheme 7. Use of a chiral allene in the synthesis of substituted cyclobutenones.

![Scheme 7](image)

3.3. Organocatalyzed Enantioselective [2+2] Cycloadditions

Corey and co-workers reported in 2007 a straightforward organocatalyzed [2+2] enantioselective vinylogous cycloaddition of esters 36 with dihydrofuran 35 using oxazaborolidine-aluminum bromide complex 38, conveniently generated in situ by the addition of a commercially available solution of aluminum bromide in CH$_2$Br$_2$ to a cold −20 °C CH$_2$Cl$_2$ solution of oxazaborolidine (Scheme 8). This procedure afforded the exo-[2+2]-cycloadduct 32 in 87% yield and with 99% ee [60].

Scheme 8. [2+2] enantioselective vinylogous cycloaddition of esters with dihydrofuran.

![Scheme 8](image)

3.4. Iminium-Ion Intermediated [2+2] Cycloaddition of Enals

An enantioselective organocatalytic vinylogous formal [2+2] cycloaddition has been successfully developed based on a tandem iminium–enamine activation of enals [61]. Reactions carried out in the presence of catalysts 43 or 44 and HNTf$_2$ gave the enantioselective [2+2] cycloaddition reaction of alkenes 39 and functionalized benzoyloxyacrolein 40 yielding optically active 1-acyloxycyclobutanecarbaldehydes 41, presumibly through the one of the transition states TS 45. In the same paper, cyclobutane aldehyde 41a was also used as chiral intermediate for the synthesis of (−)-taiwaniaquinol B (42, [62]) as reported in Scheme 9.
Scheme 9. Enantioselective [2+2] cycloaddition of unactivated alkenes with α-acyloxyacroleins.

A [2+2] organocatalytic cycloaddition protocol, has been recently reported by Jørgensen and co-workers [63]. This procedure was efficiently used for the construction of nitrocyclobutanes 48 with four contiguous stereocenters achieving complete diastereo- and enantiomeric control.

This new concept is based on a simultaneous dual activation of α,β-unsaturated aldehydes 46 and nitroolefins 47 via amino- and hydrogen-bonding catalysis. For this purpose, new bifunctional squaramide-based aminocatalyst 49 was synthesized with the idea to enable such an activation strategy.

The authors reported also an exhaustive computational study that rationalizes the stereochemical outcome of this methodology through the formation of the TS 50 reported in Scheme 10.

Scheme 10. Asymmetric formal [2+2] cycloadditions via bifunctional dienamine catalysis.
Another vinylogous organocatalyzed enantioselective [2+2] cycloaddition based on a similar concept has been reported by Vicario [64], by using diphenyltrimethylsilyloxypyrrolidine 54 and thiourea derivatives co-catalyst 55 as nitrostyrene hydrogen bonding activator (Scheme 11). The procedure, represent a good way to access, from enals 51, to interesting cyclobutalactols 53 with the creation of four new stereocentres with high ee values (85%–94%) and satisfactory yields.

Scheme 11. Asymmetric formal [2+2] cycloadditions via enamine catalysis.

Catalyst 54 was also employed in an iminium-intermediated cycloaddition of enals 57 and 2-vinylpyrroles 56 [65]. The methodology, developed by Xu and co-workers represent an interesting variation of the above mentioned vinylogous [2+2] cycloaddition wherein the nitroalkene was replaced by the use of enals, accessing to chiral pyrrole-cyclobutane derivatives 58 with high stereocontrol of the three new formed stereocentres and accompanied by satisfactory yields as reported in Scheme 12.

Scheme 12. Asymmetric vinylogous formal [2+2] cycloadditions via enamine catalysis.

3.5. Hydrogen-Bonding Mediated [2+2] Asymmetric Cycloaddition

The first examples of enantioselective intermolecular [2+2] photocycloadditions of isoquinolone 59 with EWG-functionalized alkenes has been reported very recently by Bach and co-workers [66]. Photoreactions were carried out at low temperature via a chiral hydrogen-bonding template 61. This supramolecular complex, is able to shield one face of the isoquinolone 59, thus directing the stereochemistry of the [2+2] photocycloadditions. Functionalized tricyclic cyclobutane derivatives 60, were obtained in excellent yields (86%–98%) and with outstanding regio-, diastereo-, and enantioselectivity as reported in Scheme 13.
Scheme 13. Intermolecular [2+2] cycloaddition of isoquinolone via a chiral H-bonding template.

4. Desymmetrization of Cyclobutane and Cyclobutanone Derivatives

4.1. Organocatalyzed Bronsted Acids based Desymmetrizations

In 2010 List and co-workers reported the design and the successful implementation of a new class of chiral binaphthylphosphoric acids-pyridinamides [67] which were used as powerful catalysts in the enantioselective desymmetrization of meso anhydrides directing the enantioselective anidride cleavage and the selective esterification of a carboxylic unit yielding compounds in high yields and ee.

This desymetrization protocol was also used for the synthesis of the boll weevils Anthonomus grandis Boheman pheromone (+)-grandisol as shown in Scheme 14.

Scheme 14. Bifunctional Brønsted acids based desymmetrization of meso cyclobutaneanidrides.

4.2. Organocatalyzed Aldol based Desymmetrization Reactions

The enantio- and diastereoselective desymetrization of 3-substituted cyclobutanones has been recently achieved by Frongia and Piras, by using a N-phenylsulfonyl-(S)-proline catalyzed aldol reaction, affording the corresponding 2,3-functionalized cyclobutanones in good yield and with excellent diastereo- and enantioselectivity [69] as described in Scheme 15.
Scheme 15. Desymmetrization of 3-substituted cyclobutanones via organocatalyzed aldol reactions.

\[
\text{Scheme 15}
\]

4.3. Enaminocatalyzed Reactions of Cyclobutanones with Nitrosobenzene

The same group reported another original organocatalyzed enantioselective desymmetrization reaction of 3-substituted cyclobutanones 66 [70]. This desymetrization procedure is based on a tandem O-nitrosobenzene alkylation-cyclobutanone ring expansion, mediated by proline derivative catalysts and in particular from the tetrazole derivative 70, as reported in Scheme 16. In this conditions, cyclobutanones 66 were converted into 4-substituted-5-hydroxy-\(\gamma\)-lactams 69 [71,72] through the TS 71. The synthetic protocol provides enantiomerically enriched nitrogen containing five-membered ring systems in good yields and \(ee\) with the generation of two new stereogenic centers.

Scheme 16. Organocatalyzed synthesis of chiral 4-substituted \(\gamma\)-lactams.

5. Biocatalytic Resolution of Cyclobutanes

5.1. Biocatalytic PPL based Cyclobutanol Resolution by Esterification and Hydrolysis

Biocatalytic methods for the regio- and enantioselective resolution of cyclobutane derivatives have been recently developed by Fadel and co-workers [73]. Porcine pancreatic lipase PPL is able to discriminate between the two (\(\pm\))-alcohols rac-72, affording the optically pure ester 73 and allowing to isolate the cyclobutane alcohol (\(S\))-74 as pure enantiomer as showed in Scheme 17.
Another PPL-based cyclobutane resolution has been published by Lee-Ruff [74]. Diole 75 can be efficiently resolved in toluene/vinylacetate to afford the ester 76 as pure compound. Also, cyclobutane diacetate 77 was selectively hydrolyzed from PPL at pH 7.0, in absence of the acetate source, yielding the monoacetate (+)-78 in 97% yield as reported in Scheme 18. The so obtained derivatives have been afterward used for the synthesis of important key intermediates in the synthesis of chiral cyclobutane nucleosides [30] and aminoacids [31,75–77].

6. Cyclobutanone α-Functionalization

The past few years have witnessed notable breakthroughs in the development of asymmetric intermolecular α-alkylations of carbonyl compounds whereas synthetic applications of cyclobutanones other than ring expansion and fragmentation reactions are rare [2,3].

6.1. α-Functionalization of Cyclobutanones via SOMO Catalysis

In 2010 the McMillan’s group published the first enantioselective organocatalytic α-allylation of cyclic ketones [78] via singly occupied molecular orbital catalysis (SOMO) [79,80]. Geometrically constrained radical cations, generated from the one-electron oxidation of transiently generated enamines, readily undergo allylic alkylation with a variety of allyl silanes.
In this procedure, cyclobutanone 79 was α-functionalized using a new oxidatively stable class of imidazolidinone catalysts, such as compound 82, and allylsilane 80 in presence of CAN (Scheme 19) to enantioselectively afford cyclobutanone 81 in 66% yield.

**Scheme 19.** Enantioselective α-alkylation of cyclobutanone via SOMO catalysis.

6.2. Asymmetric SN1 Alkylation of Cyclobutanones

Cyclobutanone carbocation alkylation, has been recently achieved by Zhang and co-workers [81]. The strategy developed by this group consists in a Brønsted acid *in situ* carbocation generation, using highly polar and ionic liquids and benzoimidazolium derivatives 84 as catalysts. In these experiments, cyclobutanone 79 was reacted with diphenylmethanol, using phthalic acid as additive affording α-functionalized cyclobutanone 83 in good yields and satisfactory enantiomeric excess. FCILs might provide a favorable catalytic sphere for direct α-alkylation of ketones, in which ionic intermediates, such as 86, are involved through an asymmetric SN1 alkylation [82] as reported in Scheme 20.

**Scheme 20.** Asymmetric SN1 α-alkylation of cyclobutanone catalyzed by chiral ionic liquids.

6.3. Organocatalyzed Aldol Reactions

Cyclobutanone aldol reactions were explored for the first time by Ley and co-workers in 2005 using (S)-proline-N-phenylsulfonamide organocatalysts 68 and the pyrrolidinetetrazole derivative 70 [83]. These catalysts were developed as valid alternative to (S)-proline based catalysis, overcoming, solubility and solvent problems [84,85]. Good results were obtained when catalyst 68 was used in the direct aldol reaction between cyclobutanone 79 and p-nitrobenzaldehyde affording the corresponding syn/anti adducts 86 in high enantiomeric excess and reasonable diastereoselectivity (Scheme 21).
Scheme 21. Enantioselective organocatalyzed synthesis of cyclobutanone aldol derivatives.

[Chemical structures and reactions]

Similar results were achieved by Ma’s group using catalytic systems made up of primary amine organocatalysts, derived from natural primary amino acids 88, in combination with 2,4-dinitrophenol (DNP) as additive [86]. Catalyst 88 have proven to be an efficient catalyst in the direct aldol reactions of cyclobutanone 79 with different aromatic aldehydes, in brine without further addition of organic solvents (Scheme 22), affording the corresponding aldol adducts 87 in good yields and high ee (d.r. up to 1:99).

Scheme 22. Enantioselective organocatalyzed synthesis of cyclobutanone aldol derivatives.

[Chemical structures and reactions]

Interesting results have also been achieved by Maruoka and co-workers [87] in the alkylation of cyclic ketones using primary amine catalysts 91 through a scrupulous screening of additives. Reaction of cyclic ketones including cyclobutanone 79 (Scheme 23) with α-oxoalkyl esters 89 in the presence of bifunctional primary amine catalyst 91 and achiral acid additives afforded syn-aldol adduct 90 with good yields and excellent enantiomeric excess.

Scheme 23. Enantioselective organocatalyzed synthesis of cyclobutanone aldol derivatives.

[Chemical structures and reactions]
Enantioselective aldol reaction between 2-hydroxycyclobutanone 92 and aromatic aldehydes in DMF has been achieved using (S)-tryptophan 94 by Frongia and Ollivier. The reaction is completely regioselective and gives the 2,2-disubstituted cyclobutanone 93 in up to 80% yield [88]. The major adduct was obtained in 67% ee, with an anti-relative configuration in contrast with the selectivity of organocatalysed aldol reactions conducted on acyclic hydroxyketone substrates [89]. anti-Configuration was assigned by X-ray analysis and rationalized on the basis of an hydrogen-bonding interaction between the N–H and the cyclobutanone-alcohol function in the enamine intermediate (Figure 2 TS_{A}). In this assumption, the approach of the aldehyde in the transition state is facilitated by the carboxylate function, which is preferentially oriented to minimize steric repulsion, leading to an anti-configuration of the aldol product anti-93 (Scheme 24).

Scheme 24. Enantioselective organocatalyzed synthesis of syn- and anti-cyclobutanone diols.

Analogous reactions carried out in solvent-free conditions, using (S)-threonine, were investigated by the same group [90]. Deracemized aldol adducts featuring a chiral quaternary center were obtained in up to 72% yield, with syn-selectivity up to 85:15 dr and ee up to 84%. Switch on anti/syn configuration of compounds 93 were rationalized by the formation of a stabilizing hydrogen bonding network between the enamine-specie and the aldehyde acceptor as described in Figure 2 (TS_{B}).

Figure 2. Rationalized transition states A and B for the L-Thr (TS_{A}) and L-Trp (TS_{B}) catalyzed aldol reaction of hydroxycyclobutanone 92 with aromatic aldehydes.

6.4. Organocatalyzed Mannich Addition of Cyclobutanones to Glycolates

Furthermore, (S)-pyrrolidinetetrazole 70 well catalyzed the Mannic reaction of cyclobutanone 79 with PMP-ethylglyoxylate imine affording the corresponding α-aminoacilecyclobutanone 96 in good yields [83,91,92] and ee as reported in Scheme 25.
Scheme 25. Enantioselective organocatalyzed Mannich reaction of cyclobutanone with glycolates.

\[
\begin{align*}
\text{cat. 70, 5 mol %} & \quad \text{DCM} \\
\text{EtOOC} & \quad \text{EtOOC} \\
\text{NHPMP} & \quad \text{NHPMP} \\
\text{79} & \quad \text{96}
\end{align*}
\]

19:1 d.r.
94% ee
74 % yield

Supported (S)-proline catalysts 97 were used by Rodriguez-Escrich and co-workers in the enantioselective Mannich reaction of different carbonyl compounds, including cyclobutanone 79 and N-PMP-ethylglyoxylate imine in the presence of the supported catalyst 97 [93]. In this investigation, the effect of the proline-support linker were studied; and 1,2,3-triazole linker constructed from azidomethyl polystyrene and O-propargyl hydroxyproline turned out to be optimal catalyst, both in terms of catalytic activity and enantioselectivity. With this protocol, compound 79, was converted into the corresponding α-aminoacylcyclobutanone 96 in moderated yield, accompanied by high ee and excellent dr as reported in Scheme 26.

Scheme 26. Enantioselective organocatalyzed Mannich reaction of cyclobutanone with glycolates.

\[
\begin{align*}
\text{cat. 97, 20 mol %} & \quad \text{DMF} \\
\text{EtOOC} & \quad \text{EtOOC} \\
\text{NHPMP} & \quad \text{NHPMP} \\
\text{79} & \quad \text{96}
\end{align*}
\]

97:3 d.r.
99% ee
45 % yield

6.5. Organocatalyzed Michael addition of Cyclobutanones to Nitrostyrenes

Reaction of cyclobutanone 79 with nitrostyrene in presence of catalyst 99 and ionic liquids-[bmim]PF₆ and [hmim]BF₄ gave the racemic corresponding cyclobutanone-nitroadduct 98 in 43% yield [94] as described in Scheme 27.

Scheme 27. Organocatalyzed Michael reaction of cyclobutanone with nitrostyrenes.

\[
\begin{align*}
\text{cat. 99, 5 mol %} & \quad \text{ionic liquid} \\
\text{EtOOC} & \quad \text{EtOOC} \\
\text{NHPMP} & \quad \text{NHPMP} \\
\text{79} & \quad \text{98}
\end{align*}
\]

Rodriguez and co-workers published in 2012 a straightforward, highly efficient diastereo- and enantioselective organocatalytic Michael additions of 2-substituted cyclobutanone derivatives 100 and nitroalkenes, affording the stereocontrolled creation of α-2,2-disubstituted cyclobutanone quaternary
centers [95]. The approach relies on both the use of Brønsted base/hydrogen-bonding donor bifunctional organocatalysts 102, based on cinchona alkaloids and importantly, the specific stabilization and activation of cyclobutanone with a secondary amide moiety. The reaction was found to nicely accommodate a broad scope of substrates, allowing the control of up to three contiguous stereogenic centers yielding the corresponding cyclobutanone derivatives 101 (Scheme 28) in excellent yields and ee.

**Scheme 28.** Enantioselective functionalization of 2-substituted cyclobutanones via Michael reaction.

6.6. **Cyclobutanone α-Heteroatom Functionalization**

Toma and co-workers reported the addition of cyclobutanone 79 to diethyl azodicarboxylate in ionic liquids-[bmim]PF₆ and [hmim]BF₄ in the presence of (S)-proline 99 [96]. The procedure afforded α-N-functionalized cyclobutanone 103 in moderate yields but no ee value was reported (Scheme 29).

**Scheme 29.** Heteroatom functionalization of cyclobutanone with azodicarboxylates.

Better results were achieved when the same reaction was extended to different cyclic ketones or aldehydes.

7. **Cyclobutane Ring Enlargement**

7.1. **Chiral Non Racemic Cyclobutanes Ring Expansion**

Acid-catalyzed ring expansion of chiral cyclopropyl and cyclobutyl derivatives was reported from Piras and co-workers for the synthesis of strained carbo- and heterocyclic compounds [97]. Chiral adducts 105 were prepared using (S)-proline catalyzed direct asymmetric aldol reactions of 1-phenylthiocyclobutane carboxaldehydes 104 with different ketones. The aldol compounds were diastereoselectively reduced to diols 106 and transformed in the corresponding spirocyclic cyclobutane derivatives 108 using catalytic amounts of PTSA. Also, diol-adducts 106 were transformed into oxaspiroexanes by using Me₃OBF₄ which undergo ring expansion to chiral cyclopentanones 107 in high yields and ee values up to 99% as shown in Scheme 30.
Scheme 30. Enantiomerically enriched cyclobutane diols ring enlargement and spiranization.

Geminal 2,2-dimethyl and 2,2-dialkylcyclopentanone 111 was prepared by acid catalyzed ring expansion of isopropenylcyclobutanol 109 by Piras and co-workers [98]. The stereochemical behaviour of this 1,2-sigmatropic shift clearly showed that, the pinacol-type rearrangement, occurred through carbocationic specie intermediate 110 without any detrimental effect on the optical purity of the starting allylic alcohols. The reaction was found to nicely accommodate a broad scope of substrates, allowing the control of the new stereogenic centers yielding the corresponding cyclopentanone derivatives (Scheme 31) in excellent yields and ee. The method was extended to differently substituted aryl cyclobutanols such as 112 that once submitted to acid-catalyzed ring expansion allowed to access to the family of sesquiterpene (+)-cuparenone (113, [99]) in good yields.

Scheme 31. Acid catalyzed ring expansion of enantiomerically enriched cyclobutanols.
7.2. Chiral Non Racemic Oxa Spirohexanes Ring Enlargement

Asymmetric epoxidation of benzylidencyclobutane 114 and subsequent rearrangement, was performed by Shi and co-workers [100]. The synthetic protocol is based on a catalytic epoxidation of benzylidene derivatives 114 using fructose oxazolidinone 117 and oxone® [101–103], affording the corresponding oxa spirohexanes 115 in high ee and good to excellent yields.

The so obtained chiral oxyranes were sucessfully transformed into the corresponding cyclo-pentanones (R)-116 and (S)-116 by using Lewis acids, such as Et₂AlCl and LiI [104], achieving the enantiocontrolled ring expansion with the possibility to obtain the two enantiomerically enriched cyclopentanone enantiomers (Scheme 32).

Scheme 32. Enantioselective synthesis of 2-aryl cyclopentanones.

7.3. Organocatalyzed Enantioselective Cyclobutane Ring Expansions

The formation of quaternary stereogenic carbons results an attractive challenge in many stoichiometric and catalytic transformation. Tu and co-workers [105] have, very recently developed a straightforwardring expansion, based on a 1,2-sigmatropic semipinacolic rearrangement. This enantioselective transformation has been performed with vinylogous ketones 118 using a combination of N-Boc-L-phenylglycine 121 and a cinchona alkaloid as catalyst 120 (Scheme 33) leading to chiral spirocyclic dienones 119 in good to excellent yields and high enantioselectivity.

Scheme 33. Enantioselective construction of chiral quaternary stereocentres in spirocyclic diketones.

Cinchona catalyst 120 has been used by the same group, in the synthesis of chiral spiroderivatives 122, starting from cyclobutanols 118 [106]. This straightforward achievement has been obtained by
using Brønsted acids (TFA) and hydrogen peroxide through a tandem enone epoxidation-cyclobutanol ring expansion, affording the spiroketoalcohols 122 in high yields and up to 99% ee (Scheme 34).

**Scheme 34.** Synthesis of spirocycloalkanediones by organocatalytic asymmetric epoxidation.

Tu and co-workers, also developed an interesting enantioselective organocatalyzed semipinacolic rearrangement of cyclobutanol allylic alcohols 123 [107]. This reaction represents a catalytic Paquette-type [108, 109] cyclobutanol ring expansion, through the enantioselective protonation of dihydropyranyl- or furanyl double bonds, followed by a cyclobutanol sigmatropic 1,2-shift [110].

Bulkly di-(2,4,6-triisopropylphenyl)-substituted phosphoric acid 125, afforded the corresponding spirocompounds 124 with good enantioselectivity 74%–98% and good to excellent yields 51%–98%. Further modification of this protocol, involving silver phosphate 126 as catalyst, gave similar results as shown in Scheme 35.

**Scheme 35.** Enantioselective acid catalyzed ring expansion of cyclobutanols.

7.4. Organocatalyzed Enantioselective Fluorination-Induced Cyclobutanes and Cyclopropanes Ring Expansion

Alexakis and co-workers developed an enantioselective organocatalyzed fluorination-induced Wagner-Meerwien rearrangement of allylic cyclopropanols 127 and cyclobutanols 131 [111]. This tandem fluorination-ring enlargement reaction was achieved by using binol-derived phosphoric acids 130 in the presence of the fluorinating agent 128. Phosphoric acids 130 were used as a privileged source of chiral anions, able to induce asymmetry through an interaction between the strained allylic alcohols 131 (or 127) and 128 as reported in the mechanistic rationale 133 (Scheme 36). β-Fluoro spirocyclic ketones 129 and 132 were isolated in high yields and ee, also accompanied by excellent levels of diastereoselection.
Scheme 36. Enantioselective fluorination-induced cyclopropane and cyclobutane ring expansion.

8. Enantioselective Bayer-Villiger Oxidation of Cyclobutanones

8.1. Enantio- and Diastereoselective Bayer-Villiger Oxidation of Chiral Cyclobutanones

Enantiomerically enriched oxaspiropentane 134 were transformed into the corresponding cyclobutanone derivatives 135 [6,7] using Lil [104]. This investigation, allowed for the first time to understand the Lil intermediacy in the semipinacolic C3-C4 ring expansion through a double inversion of configuration process leading to the formation of the corresponding chiral cyclobutanones in high yields and ee. This strategy, was subsequently used by the same group for the synthesis of the enantiomerically enriched (−)-grandisol (64, [112]) and (−)-muricatacin (137, [113]) pheromones as reported in Scheme 37.

Scheme 37. Enantio- and diastereoselective Bayer-Villiger oxidation of cyclobutanones.
8.2. Organocatalyzed Enantioselective Cyclobutanone Bayer-Villiger Oxidation

Enantioselective Bayer-Villiger oxidation has been performed by different groups in the last years and a certain number of chiral ligands and catalysts have been synthesized and explored (Figure 3). Cyclobutanone moiety, is relatively easy to oxidize, due to the ring strain of the carboyclic system [1,2] and attempts to catalyze this oxidation reaction are well documented [114–119]. Thiourea based catalysts 55 and 138 [120], are able to catalyze efficiently the oxidation of 3-substituted cyclobutanones 143, affording the corresponding lactone derivatives 144 in good yields.

Figure 3. chemo- and enantioselective cyclobutanone Bayer-Villiger metal-free catalysts.

More recently, good results were achieved using chiral flavine derivatives 139 [121] and 140 [122] (Figure 2) in association with hydrogen peroxide, affording the corresponding lactones in good yields and ee (61%–74% ee). Better results were obtained using chiral phosphoric acids 141 and hydrogen peroxide isolating the corresponding lactones 143 in high yields and good ee (55%–93%) [123,124].

Moreover, bis-pyrrolidineoxide ligand 142 was used in this reaction obtaining straightforward cyclobutanone oxidation to 144 in high yields and high ee (80%–91%) [125]. Results of these investigations are reported in Scheme 38.

Scheme 38. Organocatalyzed enantioselective cyclobutanone Bayer-Villiger oxidation.
8.3. Biocatalytic Enantioselective Cyclobutanone Bayer-Villiger Oxidation

An interesting microbial Baeyer–Villiger oxidations of fused bicyclic ketones 145 with a cyclobutanone structural motif has been reported. Enantioselective cyclobutanone oxidation catalyzed by recombinant Escherichia coli cells was performed using monoxygenases from Brevibacterium, CHMObrev1 and CHMObrev2 [126] leading to γ-lactones as reported in Scheme 39.

Interestingly, the two CHMO forms allowed to achieve different regiochemical results, obtaining the conventional Bayer-Villiger lactone 146 through the migration of the more substituted carbon atom. However, once CHMObrev2 was used, lactones 147, were isolated, resulting from the migration of the less substituted carbon atom.

Scheme 39. Biocatalytic enantioselective cyclobutanone Bayer-Villiger oxidation.

Phenylacetone Monoxygenase PAMO mutants were also screened as potential Bayer-Villiger oxidation biocatalysts in the transformation of cyclobutanone 148 in the corresponding lactone 149 [127].

This unusually thermostable enzyme, is a promising candidate for catalyzing enantioselective Baeyer-Villiger reactions in organic chemistry. Unfortunately, however, its substrate scope is very limited, reasonable reaction rates being observed essentially only with phenylacetone and similar linear phenyl-substituted analogs. The oxidation of substrate 148 proceeds with the preferential formation of lactone (1S,5R)-149, whereas the mutants lead to a reversal of enantioselectivity (Scheme 40).

Scheme 40. PAMO-mutants biocatalytic cyclobutanone Bayer-Villiger oxidation.
9. Conclusions

Cyclobutane and cyclobutanone are easily accessible and useful synthetic tool that still represent a challenging target for organic chemists. Enantioselective stoichiometric and catalytic approaches have been developed with successful results, giving to this class of compounds a relevant role as key intermediate in a large number of asymmetric synthetic applications. Based on these findings, it is reasonable to expect that new interesting methodologies focused on the use of this versatile family of compounds will soon be developed.

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Conflicts of Interest

The authors declare no conflict of interest.

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