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Manuel Barday, Pierre Bouillac, Yoann Coquerel, Muriel Amatore, Thierry Constantieux, et al.. Enantioselective Organocatalytic Syntheses and Ring-Expansions of Cyclobutane Derivatives. European Journal of Organic Chemistry, 2021, 2021 (21), pp.3023-3034. 10.1002/ejoc.202100405 . hal-03370300

HAL Id: hal-03370300

<https://hal.science/hal-03370300>

Submitted on 7 Oct 2021

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Enantioselective Organocatalytic Syntheses and Ring-Expansions of Cyclobutane Derivatives

Manuel Barday,^[a] Pierre Bouillac,^[a] Yoann Coquerel,^[a] Muriel Amatore,^{*,[a]} Thierry Constantieux,^{*,[a]} and Jean Rodriguez^[a]

Dedicated to Prof. Peter K. C. Vollhardt on the occasion of his 75th birthday.

The progress in enantioselective organocatalysis have enabled efficient and highly stereoselective syntheses of cyclobutane derivatives, through (2 + 2) annulation reactions, overcoming the geometrical constraints inherent to these small cyclic molecules. More importantly, and taking advantage of their strain-releasing fragmentation, some cyclobutane derivatives, especially cyclobutanones and cyclobutenones, can now be

regarded as versatile four-carbon atoms units amenable to the enantioselective construction of larger rings by (4 + n) annulation reactions to produce, five-, six-, seven- and eight-membered cyclic products. These recent developments concerning the enantioselective synthetic chemistry of cyclobutane derivatives under organocatalytic conditions are reviewed herein.

1. Introduction

Cyclobutane and cyclobutene are four-membered cyclic hydrocarbons that embed strain due to geometrical constraints.^[1] Nevertheless, these motifs are present in naturally occurring products,^[2] which has led organic chemists to develop numerous synthetic methodologies for their synthesis and use as molecular platforms to access more complex, or biologically relevant products.^[3] Taking advantage of the ring strain,^[4] progress in homogeneous catalysis with metal complexes have enabled the development of original synthetic approaches based on the selective cleavage of one of the C–C bonds, unlocking new opportunities for synthesis.^[5] Comparatively, enantioselective organocatalysis has only been used scarcely, and it is only recently that its potential was revealed. The objectives of this mini-review are to highlight selected representative recent organocatalytic methods, involving at least the formation/cleavage of one C–C bond, that allow i) for the enantioselective synthesis of cyclobutane derivatives, and ii) for the enantioselective, sometimes enantiospecific, ring-expansion reactions of cyclobutane derivatives towards five- to eight-membered rings.

2. Enantioselective organocatalytic synthesis of cyclobutane derivatives

Although recent advances have allowed efficient stereocontrol, the organocatalytic enantioselective synthesis of structurally diversified cyclobutanes is still challenging. By far, (2 + 2) annulation reactions represent the most straightforward strategy.^[6] For categorisation purpose, one can distinguish between organocatalytic methodologies involving covalent activation through iminium cation or enamine intermediates, and approaches relying on non-covalent activation such as hydrogen-bonds. Complementarily, dual catalysis based on the combination of organocatalysis and photoactivation also emerged as a highly enantioselective approach.

2.1. Covalent activation

2.1.1. via iminium cation intermediate

In this section, most of the organocatalytic enantioselective (2 + 2) annulations are initiated by FriedelCrafts-type processes. As pioneers, Ishihara's group described in 2007 the reaction between unactivated alkenes and α -acyloxyacroleins catalysed by an organoammonium salt derived from a chiral triamine, affording the desired cycloadducts in moderate yield, but with excellent diastereo- and enantioselectivity (Scheme 1).^[7] A stepwise mechanism involves *in situ* iminium activation of the acrolein derivative, triggering a Michael addition with the alkene followed by intramolecular trapping of the generated carbocation by the resulting enamine. To account for the observed absolute and relative stereochemistry, the authors postulated the crucial role of a hydrogen bond between the carbonyl group of the acyloxy moiety and the protonated form of the catalyst at the pyrrolidine ring, stabilizing the iminium cation in its (Z)-configuration.

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A related olefin (2+2) annulation approach, using diarylprolinol silyl ethers as catalysts, was developed in 2013 by Xu and co-workers for a highly enantioselective access to functionalised cyclobutanes from 2-vinylpyrroles and α,β -unsaturated aldehydes (Scheme 2).^[8] This domino reaction proceeds *via* the addition of the electron-rich 2-vinylpyrrole onto the conjugated iminium cation intermediate, leading to a transient enamine having a distal aza-fulvenyl cation. Rearomatisation by conjugate addition followed by reduction delivered the desired products in good yields and with excellent diastereo- and enantioselectivity. The overall process advantageously exploits the concept of organocatalysed domino reactions based on the iminium-enamine double activation of enals.^[9]

Another related domino approach was developed in 2016 by the group of McNulty, using an alkenylphenol as electron-rich alkene, *i.e.* a cinnamyl alcohol derivative in which the alkene is activated by mesomeric effect from the hydroxyl group in 4-position of the aryl (Scheme 3).^[10] As many naturally occurring cyclobutanes appear to be derived from the dimerisation of cinnamyl or coumaryl diene amides, this elegant methodology offers a stereoselective entry to the total synthesis of biologically active compounds with this strained carbocyclic core. From a mechanistic point of view, after conjugate addition of the activated alkene to the iminium cation intermediate, subsequent cyclisation occurs *via* enamine conjugate addition to the distal *p*-quinomethide cation.



Manuel Barday was born in Chalon-sur-Saône (France). After studying chemistry at the UPMC (Paris, France), he graduated in 2018 with a Ph.D. from the University of Liverpool (United Kingdom) under the supervision of Christophe Aïssa. He worked as a post-doctoral fellow at the IRCOF (Rouen, France) with Tatiana Besset and joined the group in 2020. His interests focus on organo- and organometallic catalysis.



Pierre Bouillac was born in Strasbourg, France, in 1993. He obtained his master's degree in 2018 in University of Bordeaux where he conducted research for Pr. Stéphane Quideau and Pr. Graham K. Murphy in Waterloo, Canada. He is now pursuing his Ph.D. under the guidance of Pr. Thierry Constantieux and Dr. Muriel Amatore in Aix-Marseille University. His main research interests focus on stereoselective NHC- and transition-metal-catalysed processes.



Yoann Coquerel received a Ph.D. degree from Grenoble-Alpes University with Prof. Jean-Pierre Deprés in 2001. After a post-doctoral appointment at Florida State University, he began his academic career as a CNRS researcher in 2003 at Aix-Marseille University with Prof. Jean Rodriguez, where he received his habilitation in 2009. In 2015, he was promoted Research Director at CNRS and became a "Junior Distinguished Member" of the French Chemical Society. Dr. Coquerel's research focuses on molecular chirality and the development of stereoselective methods for chemical synthesis, including applications with short-lived synthetic intermediates, in enantioselective organocatalysis, and more recently in the field of chiral polycyclic aromatic molecules.



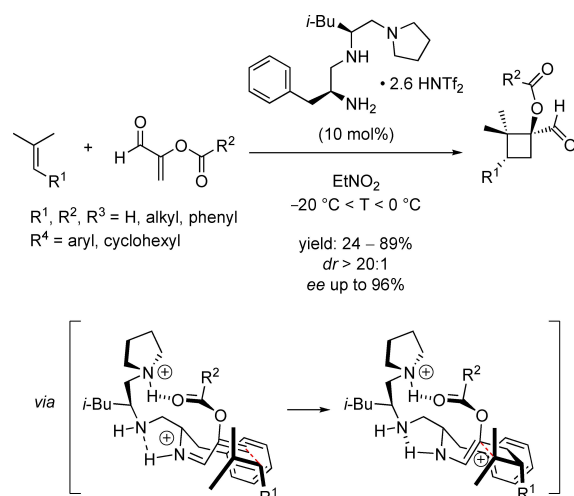
Muriel Amatore was born in Paris in 1979 and obtained her Ph.D. in 2006 with Dr. C. Gosmini (UPEC, France). She carried out three post-doctoral research stays in enantioselective organocatalysis (Princeton University, Prof. D. W. C. MacMillan) and organometallic catalysis (Ecole Polytechnique, Dr C. Gosmini/Université Pierre et Marie Curie, Dr. Corinne Aubert) before achieving a permanent position as assistant professor at UPMC (2010). In 2018, she moved to Aix-Marseille Université to join the group of Prof. Thierry Constantieux (iSm2, STeRéO). Her current research interests center on the development of transition metal-catalysed and organocatalysed processes for their application in stereoselective synthesis.



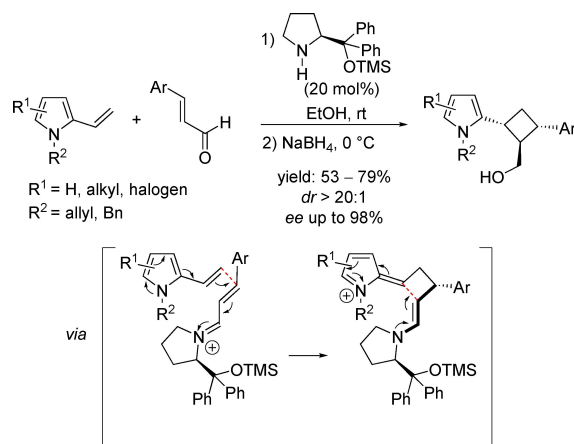
Thierry Constantieux was born in Pau, France, in 1968. After studying chemistry at the University Bordeaux I (France), he received a Ph.D. degree in 1994. He completed his Habilitation in 2004, at Aix-Marseille Université (France), where he is currently Professor, and Director of the Doctoral School of Chemical Sciences. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially organocatalytic enantioselective domino and multi-component reactions from 1,3-dicarbonyl compounds, and their applications in heterocyclic chemistry.



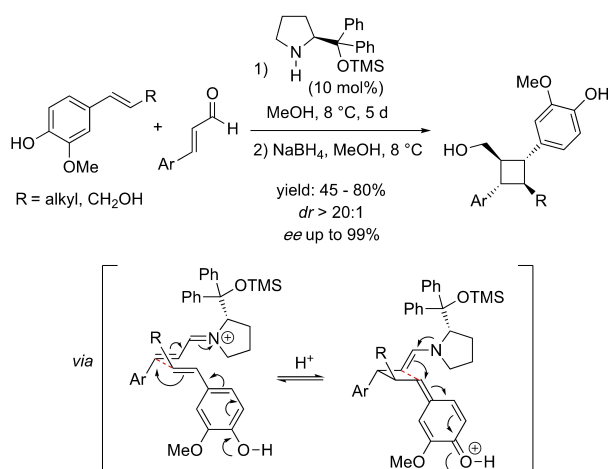
Jean Rodriguez was born in Cieza (Spain) in 1958, and in 1959 his family emigrated to France. After studying chemistry at the University of Aix-Marseille (France), he completed his Ph.D. as a CNRS researcher in 1987, and his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-7313-iSm2. His research interests include the development of multiple bond-forming transformations, including domino and multicomponent reactions, and their application in stereoselective organocatalysed synthesis. In 1998, he was awarded the ACROS prize in Organic Chemistry, and in 2009 the prize of the Division of Organic Chemistry from the French Chemical Society (SCF). In 2013, he became "Distinguished member" of the French Chemical Society.



Scheme 1. Pioneering results from Ishihara's group.



Scheme 2. (2+2) Annulation of enals and 2-vinylpyrroles.

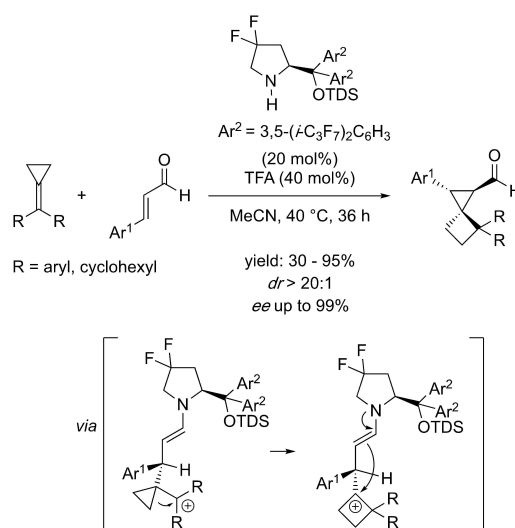


Scheme 3. (2+2) Annulation of enals and electron-rich styrenes.

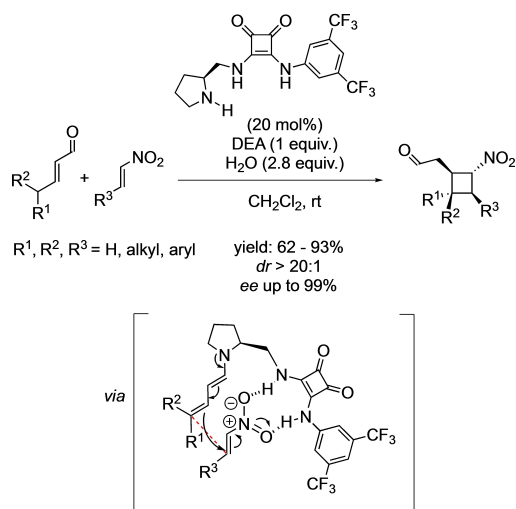
More recently, Xu and co-workers reported a highly enantioselective access to very strained and relatively unexplored spiro[2.3]hexane derivatives, by introducing methylene-cyclopropanes as electron-rich alkenes in a formal (2+2) annulation operating by a domino Michael addition/ring expansion/cyclisation reaction (Scheme 4).^[11] Compared to the above-mentioned reports, one of the key points for the success of this transformation is the modification of the organocatalyst that activates the enal, by using a difluoro-substituted diaryl-silylprolinol ether (TDS = thexyldimethylsilyl). After Michael addition of the alkene to the β position of the conjugated iminium cation, rearrangement of the cyclopropane intermediate by ring expansion of the cyclopropane occurs to install the new four-membered core. Finally, a new cyclopropane is formed by cyclisation of the resulting enamine with the rearranged carbocation. The reaction can be scaled up easily and the products can be selectively post-functionalised, offering an interesting route to more complex skeletons present in natural products and compounds of pharmaceutical interest.

2.1.2. via dienamine intermediate

The reaction between a secondary amine with an α,β-unsaturated aldehyde bearing an aliphatic group on the γ-position results in the formation of a dienamine product.^[12] In this way, amino-catalysis offers effective solutions to the functionalisation of unsaturated aldehydes, either in α-position or in γ-position. The latter usually results in a more difficult stereocontrol due to the greater distance between the catalyst and the reacting carbon atom. In this context, Jørgensen and co-workers addressed in 2012 the highly challenging development of an enantioselective (2+2) annulation between the remote double bond of a dienamine and a nitroolefin (Scheme 5).^[13] This methodology offers a direct access to polysubstituted cyclo-



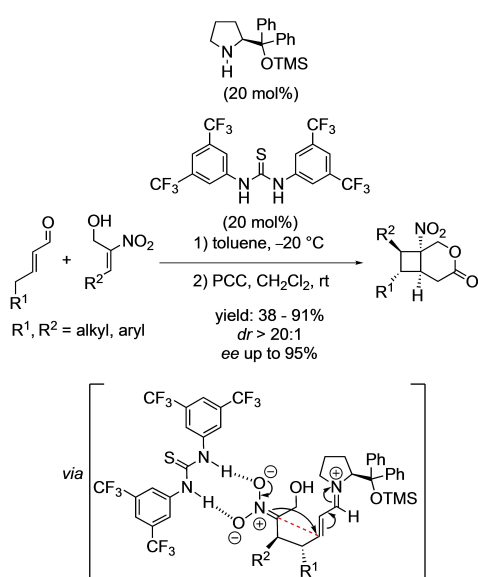
Scheme 4. Synthesis of very strained spiro[2.3]hexanes. TFA = trifluoroacetic acid



Scheme 5. (2+2) Annulation via dienamine activation with bifunctional catalyst (DEA: *N,N*-diethylacetamide)

butanes with excellent diastereo- and enantioselectivity. The key point of this strategy was the use of a bifunctional catalyst bearing both a secondary amine for generation of the dienamine intermediate and a squaramide moiety to control the orientation of the electrophile by hydrogen-bond in the approach to the transition state, resulting in high regio- and stereocontrol.

Shortly after, Vicario's group reported a conceptually similar (2+2) annulation based on a dual catalysis approach combining a diarylprolinol silyl ether and an achiral thiourea catalysts (Scheme 6).^[14] The former covalently activates the enal and the latter activates the α -hydroxymethylnitrostyrene derivative



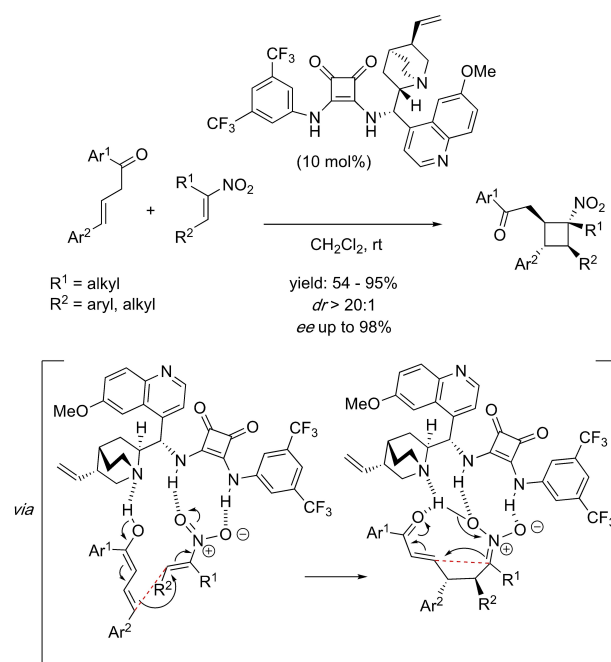
Scheme 6. (2+2) Annulation via dual catalysis

through hydrogen bonding. A Michael/Michael/hemiacetalisation domino sequence, followed by an oxidation step, results in the formation of cyclobutane-containing bicyclic lactones with excellent diastereo- and enantioselectivity. These pioneering results, together with subsequent contributions from Wang^[15] and Jørgensen,^[16] illustrate the high potential of cooperative dienamine/hydrogen-bonding activation.

2.2. Non-covalent activation

Another major activation strategy within enantioselective organocatalysis is based on the use of chiral hydrogen-bond donors,^[17] including essentially Cinchona alkaloid derivatives, diols, ureas, thioureas, squaramides and phosphoric acids. Among them, bifunctional catalysts possessing both H-bonding function and basic/nucleophilic moiety have emerged as platforms capable of simultaneously activating electrophilic and nucleophilic reaction partners, respectively. In many cases, the non-covalent interactions allowed reaching nearly perfect spatial organisation in the approaches to the transition states, leading to excellent regio- and stereoselectivity.^[18]

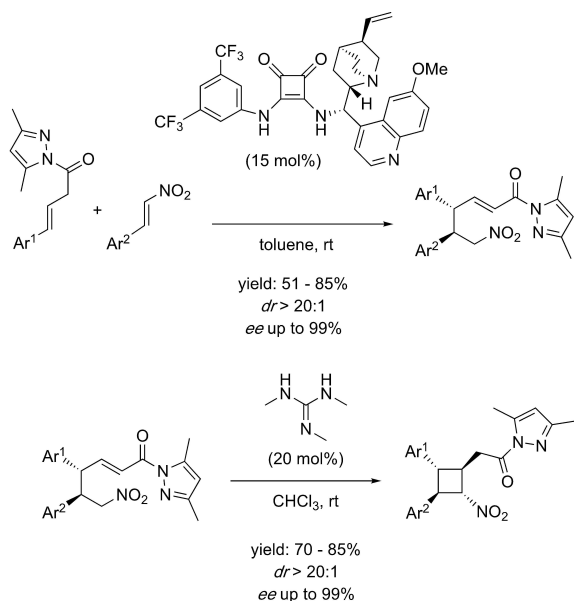
In this context, Hong's group showed in 2018 that a bifunctional catalyst of the squaramide/cinchona alkaloid family could promote the (2+2) annulation between nitroolefins and β,γ -unsaturated ketones in a highly regio-, diastereo- and enantioselective manner (Scheme 7).^[19] This Michael/Michael domino sequence provides diversely functionalised cyclobutanes with four contiguous stereogenic carbon atoms, including a quaternary one. In this formal annulation, the nitroolefin is activated by H-bonding interactions with the squaramide



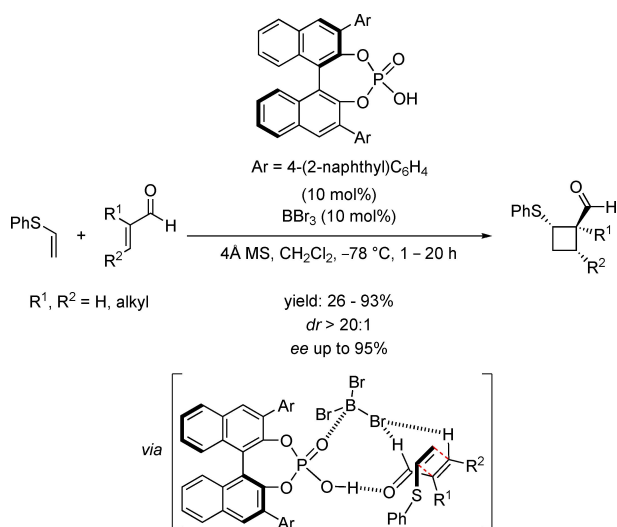
Scheme 7. Cooperative dienolate/H-bonding activation.

moiety and the vinylogous ketone enolate is generated by the basic part of the organocatalyst. A conjugate addition/nitro-Michael cyclisation sequence afforded the four-membered core in excellent diastereo- and enantioselectivity.

More recently, a stepwise related (2 + 2) annulation between nitroolefins and β,γ -unsaturated pyrazolyl amides, leading to the same family of cyclobutanes, has been reported by Huang and co-workers (Scheme 8).^[20] The strategy involves first a chiral squaramide-catalysed vinylogous Michael addition, delivering the corresponding adducts with high diastereo- and enantioselectivity.



Scheme 8. Base-mediated enantiospecific cyclisation toward cyclobutanes.



Scheme 9. Dual chiral Brønsted acid/Lewis acid catalysis for (2 + 2) annulation.

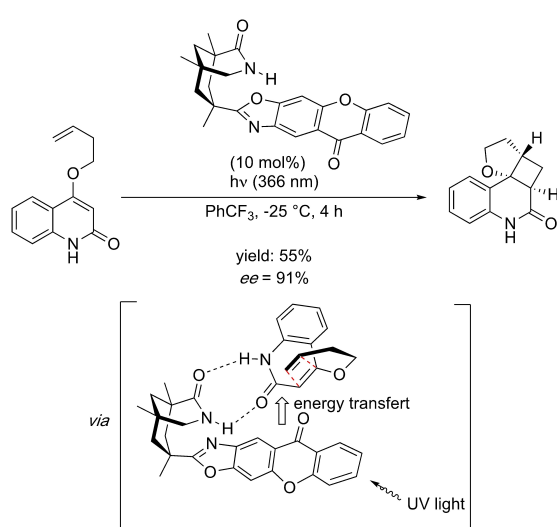
lectivity, which are then enantiospecifically cyclised by action of a catalytic amount of trimethylguanidine.

Chiral phosphoric acids are alternative popular organocatalysts operating by non-covalent interactions.^[21] However, their application to the formation of cyclobutane derivatives through (2 + 2) annulations has only been reported once, in combination with a Lewis acid, by Ishihara and co-workers. They developed the reaction between phenyl vinyl sulfide and various α - and/or β -substituted acroleins to lead to the synthesis of cyclobutane adducts with high enantiomeric excesses (Scheme 9).^[22] To explain the regio- and the enantioselectivity, the authors proposed a transition state in which the acrolein derivative is activated, on the one hand, by hydrogen bonding with the proton of the Brønsted acid catalyst, and on the other hand by additive hydrogen bonds developed by one of the bromine atoms of the boron tribromide Lewis acid catalyst, itself coordinated to the oxo group of the phosphoric acid catalyst (catalytic Lewis pair).

2.3. Dual photo- and organocatalytic activation

2.3.1. via non-covalent activation

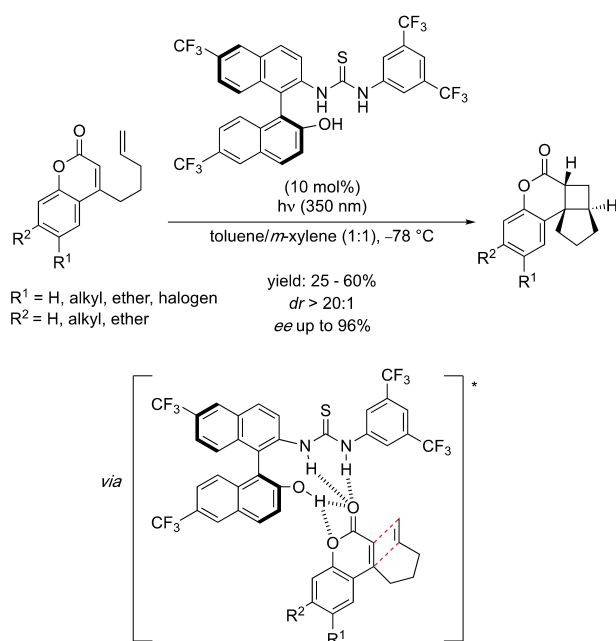
[2 + 2] Cycloadditions are suitable for photochemical activation,^[23] but their stereochemical control remained challenging until Bach and co-workers demonstrated in 2009 the first highly enantioselective organocatalytic photocycloaddition.^[24] They designed a chiral sensitizer combining a chromophore from the xanthone family and an amide moiety able to develop hydrogen-bonding type interactions. Using 10 mol% of this new dual activator, the intramolecular [2 + 2] photocycloaddition of a simple prochiral quinolone proceeded with excellent regio- and enantiocontrol (Scheme 10). This agrees with the catalyst-substrate complex



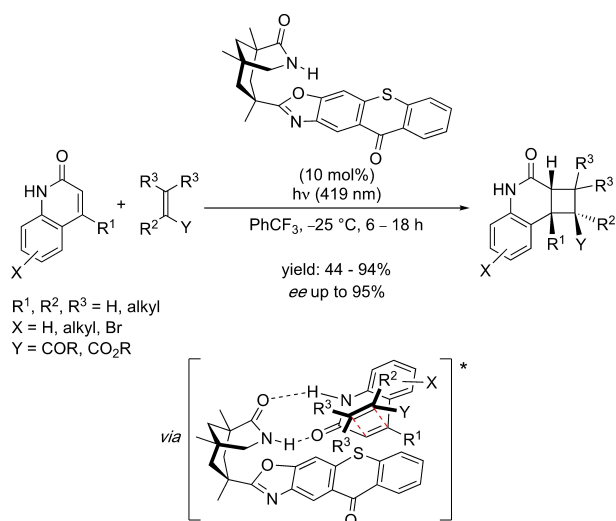
Scheme 10. First organo-photocatalytic enantioselective [2 + 2] cycloaddition.

absorbing UV light at longer wavelength than the free substrate. These pioneering results, together with subsequent contributions from the same group,^[25] perfectly fulfil the requirements of a chiral triplet sensitizer for enantioselective photoreactions.

Contemporarily, Sibi, Sivaguru and co-workers demonstrated that atropisomeric binaphthyl-based thiourea organocatalysts can efficiently absorb photons and promote similar intramolecular transformations in the coumarin series, with good enantiocontrol (Scheme 11).^[26] Under UV irradiation and with relatively low catalyst loading, the reaction gives access to



Scheme 11. Organo-photocatalytic enantioselective [2 + 2] cycloaddition.



Scheme 12. Intermolecular [2 + 2] photocycloaddition.

fused four-membered ring frameworks with good to excellent enantioselectivities. In this transformation, the photon-excited thiourea catalyst activates the coumarin carbonyl moiety through hydrogen-bonding, and the generated exciplex results in the formation of the desired photo-cycloadduct.

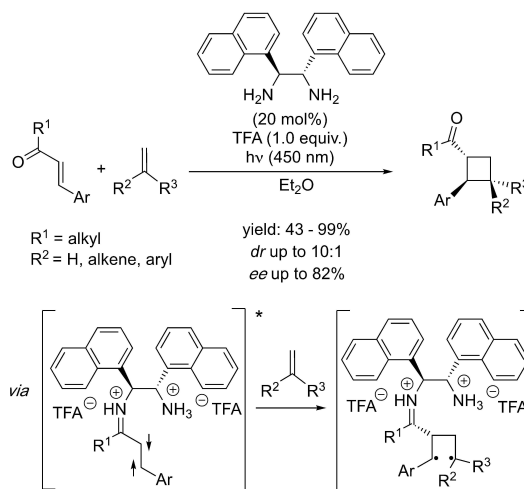
Although UV irradiation is frequently used in photochemistry, the energy associated to the corresponding photons may be, in some cases, significantly higher than the triplet energy of many photochemical substrates. This limitation prompted researchers to move towards more suitable photocatalysts active under visible-light irradiation. Along these lines, Bach and his team modified their previously designed chiral sensitizer, switching the chromophore part from the xanthone to the thioxanthone series.^[27]

By this way, they were able, in particular, to perform a highly enantioselective intermolecular [2 + 2] photocycloaddition between 2(1*H*)-quinolones and electron-deficient olefins, with excellent regio-, diastereoselectivity, and enantiomeric excesses (Scheme 12).^[28]

Alternatively, the same group also developed a dual catalytic system, combining the use of a chiral bis-thiourea as a template for H-bonding activation of the substrate and an achiral thioxanthone as triplet sensitizer for enantioselective intramolecular [2 + 2] photocycloaddition of dihydropyridones, however with lower enantioselectivity.^[29]

2.3.2. via covalent activation

Recently, Alemán and co-workers reported an original visible-light photo- and aminocatalysed strategy to obtain highly enantioenriched cyclobutane derivatives through [2 + 2] cycloaddition between enones and olefins (Scheme 13).^[30] They postulated that the *in situ* generation of an iminium ion-based charge transfer complex allows its preferential light excitation over the carbonyl species, thus avoiding any racemic background reaction. In the presence of the alkene partner, the [2 +



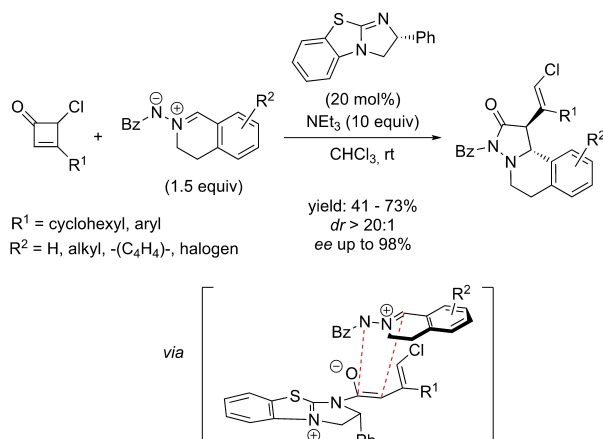
Scheme 13. Photo- and aminocatalysed [2 + 2] cycloaddition.

2] photocycloaddition gives a biradical intermediate, that evolves to the final product after hydrolysis of the resulting transient cyclobutyl iminium ion. Supported by DFT calculations, this approach was validated leading to the desired four-membered cyclic compounds in high yields, with good diastereomeric ratios and enantiomeric excesses.

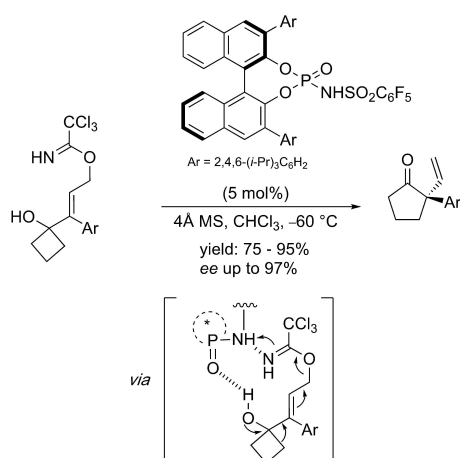
3. Enantioselective ring-expansion to five-membered ring systems

3.1. Using cyclobutenones

In 2015, the highly regio- and stereoselective 1,3-dipolar annulation of monosubstituted γ -chlorocyclobutenones with azomethine imines affording original heterocyclic compounds has been reported by Chi and co-workers (Scheme 14).^[31] Using a chiral isothiurea organocatalyst, the formation of a reactive dienolate intermediate is favoured by rupture of a weakened



Scheme 14. Lewis base-catalysed 1,3-dipolar annulation.



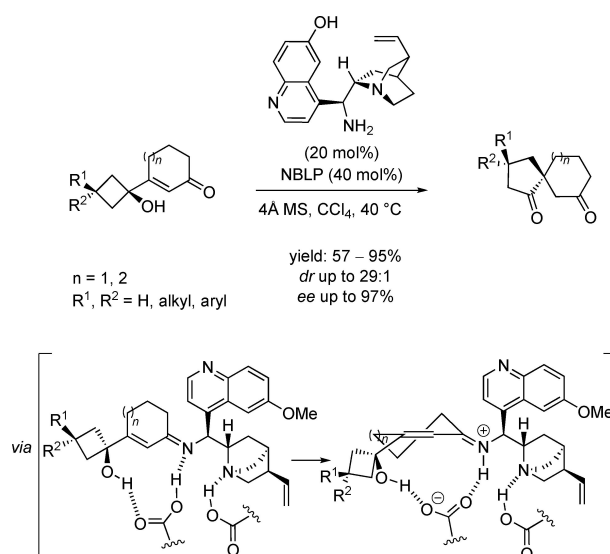
Scheme 15. Semipinacol rearrangement of allylic cyclobutanols.

C–C bond in the zwitterionic adduct obtained by addition of the Lewis base catalyst to the ketone group in the substrate. The catalytic dienolate species then undergoes α -selective addition to the 1,3-dipole followed by cyclisation. Optimisation studies have revealed that the presence of a chlorine atom at the γ -position of the cyclobutenone partner was crucial for the reaction to occur.^[32] The corresponding 1,3-dipolar annulation products were obtained in moderate to good yields and high enantioselectivities.

3.2. Using cyclobutanol derivatives

The semipinacol rearrangement of strained allylic cyclobutanols bearing a trichloroacetimidate moiety as potential leaving group can furnish the corresponding α -vinyl cyclopentanones in an efficient manner with high enantioselectivity through organocatalytic activation (Scheme 15).^[33] In the presence of a chiral Brønsted acid, the substrate undergoes a semipinacol rearrangement leading to optically active cyclopentanones with a quaternary carbon atom.

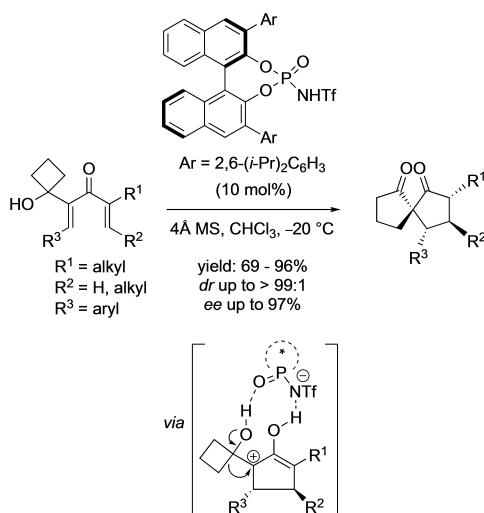
This methodology has been previously developed with cyclic vinylogous γ -ketols to furnish spirocyclic diketones featuring a quaternary stereogenic carbon atom with good to excellent yields under dual catalysis in the presence of a primary amine chiral organocatalyst and a chiral acid co-catalyst (*N*-Boc-*L*-phenylglycine, NBLP, Scheme 16).^[34] Several cyclic enones having a cyclobutanol substituent at C3 were subjected to the reaction conditions and afforded the corresponding spiro-1,4-diketones via a semipinacol-type 1,2-migration in the chiral intermediate. Both diastereomers of the cyclobutanol substrates were amenable to the transformation with comparable rates (no kinetic resolution observed), and in most of the reported examples, the R^1 and R^2 substituents were identical, avoiding match/mismatch issues. However, with either R^1 or R^2



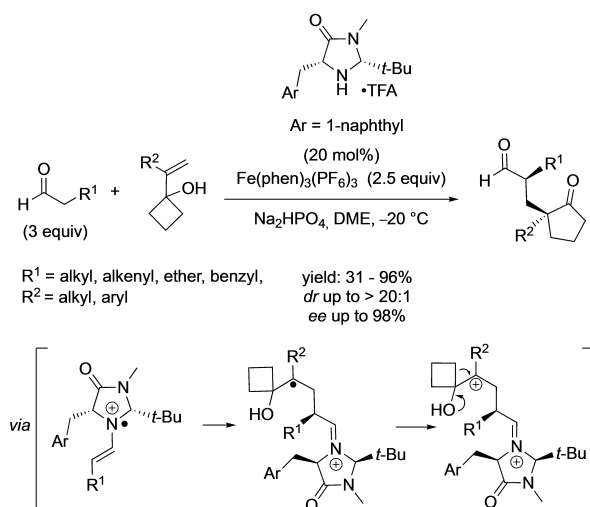
Scheme 16. Semipinacol rearrangement of cyclic vinylogous γ -ketols.

being a hydrogen atom, it was demonstrated that the match diastereomer is with $R^2 < C = > H$ (*cis* isomer). Recent computational studies provided some mechanistic insights and confirmed that intrinsic steric repulsions in the catalytic chiral iminium cation were at the origin of enantioselectivity.^[35] The chiral carboxylic acid additive was found necessary to control the conformation of the cyclohexene core in the approach to the transition state and to serve as a proton shuttle, resulting in an increased enantiocontrol.

The access to valuable spiro[4.4]nonane-1,6-dione cores has been investigated using a Nazarov cyclisation/semipinacol rearrangement sequence.^[36] Contrary to tedious multi-step approaches generally described for the synthesis of such compounds, the proposed methodology advantageously offers a one-step procedure and allows the construction of four controlled stereogenic carbon atoms, with high yields and



Scheme 17. Domino Nazarov cyclisation/semipinacol rearrangement.



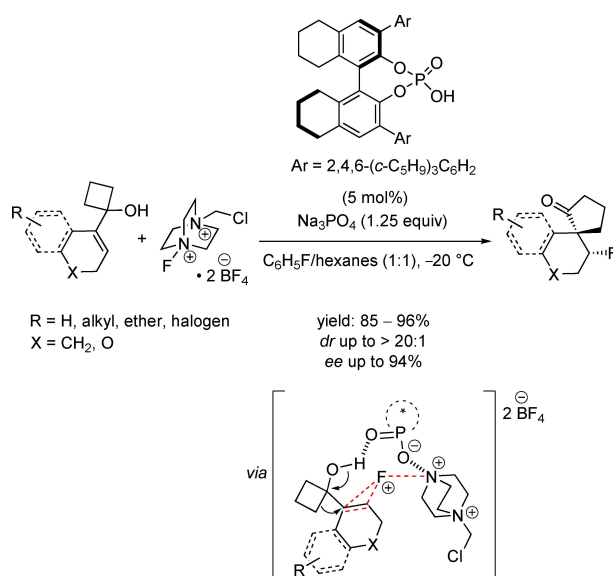
Scheme 18. Domino α -alkylation/semipinacol rearrangement.

enantioselectivities (Scheme 17). Mechanistically, a chiral *N*-triflylphosphoramidate Brønsted acid is able to trigger the enantioselective Nazarov cyclisation of unactivated racemic substrates (no kinetic resolution was observed). At this point, the cationic oxyallyl intermediate induces a stereocontrolled semipinacol rearrangement to furnish the spiro[4.4]nonane-1,6-diones.

Another ring-expansive semipinacol rearrangement was developed using the SOMO organocatalytic activation mode.^[37] In this case, strained allylic cyclobutanols were appropriate SOMO-nucleophiles affording a new carbocation intermediate amenable to the rearrangement (Scheme 18).^[38] According to this strategy, a large panel of 1,5-dicarbonyl compounds bearing a quaternary stereogenic carbon atom have been obtained with satisfactory results in terms of yield and stereo-selectivity. Some intramolecular versions of this reaction afforded the corresponding bicyclic products, which are valuable synthetic platforms as illustrated with an elegant enantioselective total synthesis of (+)-cerapiccol.

The semipinacol rearrangement of cyclobutanols induced by the formation of a halonium cation intermediate has been described by Alexakis and co-workers as an elegant approach to tricyclic β -fluorospiroketones.^[39] Excellent yields and stereo-selectivities have been reported using a chiral BINOL-based phosphoric acid sodium salt and Selectfluor as the cationic fluorinating agent (Scheme 19).

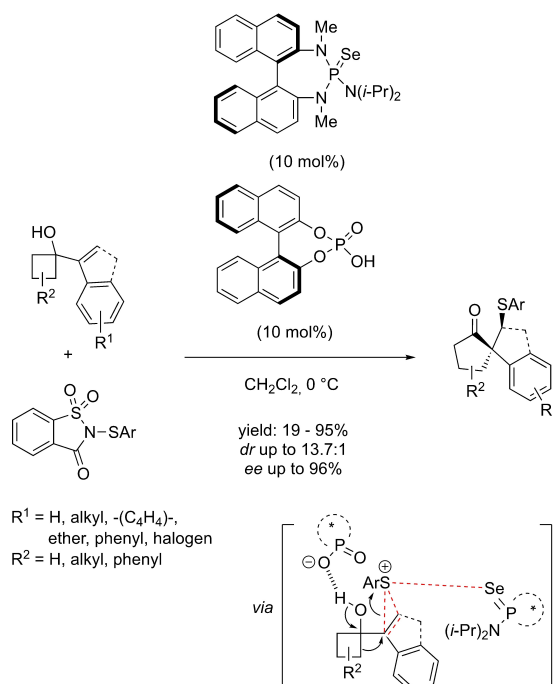
In the course of their optimisation studies, the authors confirmed that the chiral organocatalyst was responsible for both the stereocontrolled transfer of fluorine atom and the alkyl migration step through an ion-pairing mechanism. Moreover, reactions were conducted in a basic mixture of non-polar solvents in which the chiral phosphoric acid anion behaved as a homogeneous anionic phase-transfer catalyst for insoluble cationic Selectfluor, producing a catalytic soluble chiral fluori-



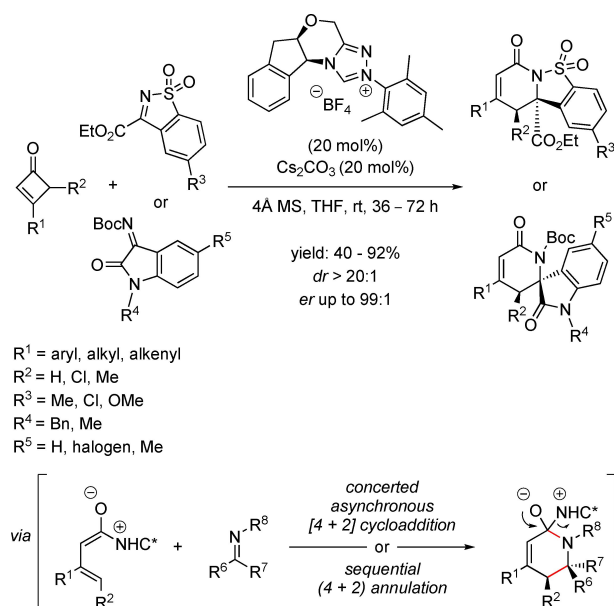
Scheme 19. Fluorination/semipinacol rearrangement of allylic cyclobutanols.

nating reagent.^[40] Later, alongside mechanistic studies, the substrate scope of this reaction was extended and successfully applied to the deracemisation of chiral substrates.^[41]

The synthesis of valuable chiral organosulfur compounds has also been investigated based on a similar strategy with excellent results (Scheme 20).^[42] A catalytic combination of



Scheme 20. Sulfenylation/semipinacol rearrangement of allylic cyclobutenols.



Scheme 21. NHC-catalysed (4 + 2) annulation of cyclobutenones with imines.

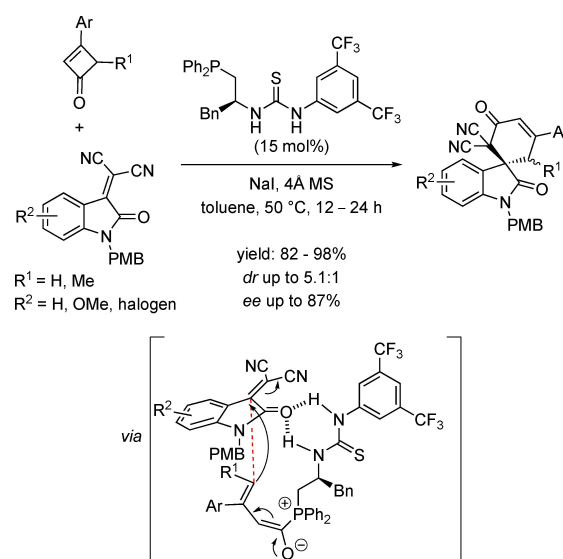
chiral Lewis base selenide and chiral phosphoric acid was used for the stereocontrolled transfer of an electrophilic sulfur atom released from *N*-phenylthiosaccharin. Under these conditions, a catalytic chiral sulfenylating agent was generated *in situ* and the chiral phosphate directed the allylic alcohol substrate for the formation of the favored thiiranium ion intermediate and subsequent semipinacol rearrangement.

4. Enantioselective ring-expansion to six-membered ring systems

4.1. Using cyclobutenones

Chi and his group reported in 2015 the first example of *N*-heterocyclic carbenes (NHC)-catalysed stereoselective ring-expansion reaction of cyclobutenones (Scheme 21).^[43] Some computational mechanistic investigations showed that a concerted asynchronous process takes place with isatin imines (true aza-Diels-Alder cycloaddition), while a stepwise 1,2-addition/lactamisation is preferred in the case of cyclic sulfonylimines (formal aza-Diels-Alder cycloaddition).^[44]

The same year, Zhang and co-workers developed another Lewis base-catalysed ring opening of cyclobutenones, now using an amino-acid derived phosphine-based catalyst bearing a thiourea moiety in a (4 + 2) annulation (Scheme 22).^[45] According to the authors, activation of the dienophile *via* hydrogen-bonding allows the reaction to proceed through the topicity depicted in scheme 22. The use of sodium iodide as an additive is believed to stabilize the zwitterionic dienolate intermediate.



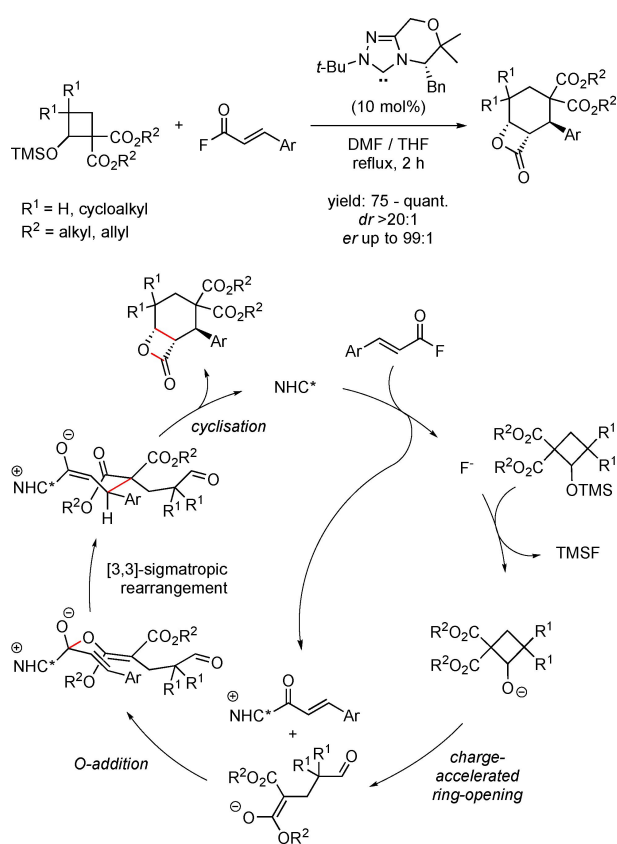
Scheme 22. Phosphine-catalysed formal (4 + 2) annulation of cyclobutenones (PMB: *para*-methoxybenzyl)

4.2. Using cyclobutanol silyl ethers

As a unique example, the Lupton group developed a highly stereoselective NHC-catalysed, indirect fluoride-induced ring-opening/aldolisation/lactonisation cascade from some cyclobutanol trimethylsilyl ethers to form bicyclic six-membered products in excellent yields (Scheme 23).^[46] The cascade process is initiated upon addition of the NHC catalyst onto the α,β -unsaturated acyl fluoride which liberates the required catalytic fluoride anion needed for the deprotection of the cyclobutanol substrate. A charge-accelerated ring-opening step occurs to generate the corresponding acyclic stabilised ester enolate having a distal aldehyde moiety amenable to further cyclisation by aldolisation. Mechanistic studies have demonstrated that *O*-addition takes place leading to the ketal intermediate which undergoes a [3,3]-sigmatropic rearrangement. Subsequent aldolisation/lactonisation regenerates the NHC-catalyst and releases the desired product.

4.3. Using cyclobutanones

Our group recently published the organocatalysed enantiospecific ring opening of α -disubstituted cyclobutanones



Scheme 23. NHC-catalysed ring-opening/aldolisation/lactonisation sequence.

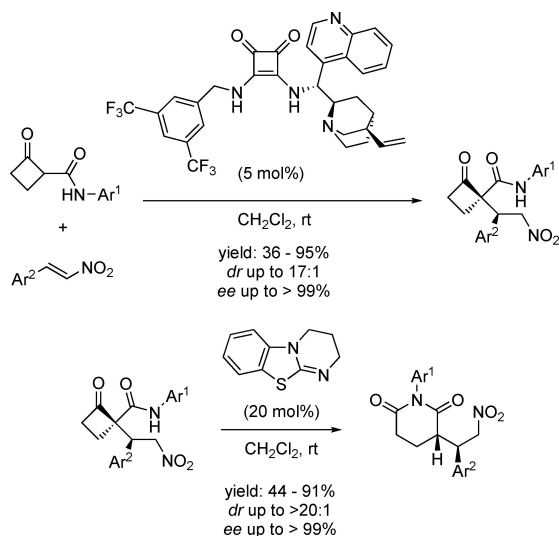
(Scheme 24).^[47] Relying on a previously reported methodology in which we were able to access α -disubstituted cyclobutanones enantioselectively,^[48] those substrates were reacted with the Okamoto isothiourea catalyst to trigger the ring opening. A series of highly enantioenriched glutarimides was thus isolated in moderate to excellent yields. Excellent enantiospecificity was observed though with low diastereoselectivities in some cases. A cross-experiment showed that with alternative basic catalysts, some retro-Michael/Michael processes occur at significant rate, leading to partial racemisation in the products. A computational mechanistic study was performed in order to fully elucidate the reaction pathway.

5. Enantioselective ring-expansion to medium size ring systems

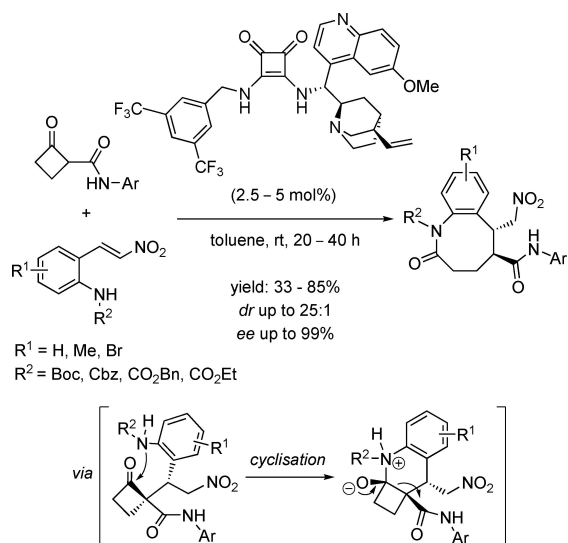
In 2019, Coquerel, Rodriguez, and co-workers reported a Michael/cyclisation/fragmentation domino reaction from cyclobutanones, which allowed preparing benzo-fused eight membered lactams through an original four-atom ring expansion approach (Scheme 25).^[49]

The benzazocinone derivatives were obtained in moderate to good yields with high enantioselectivities and good diastereoselectivities. Interestingly, it was demonstrated that diastereoselectivity, *i.e.* the relative configuration of the carbon atom bearing the secondary amide substituent, is governed by thermodynamic factors.

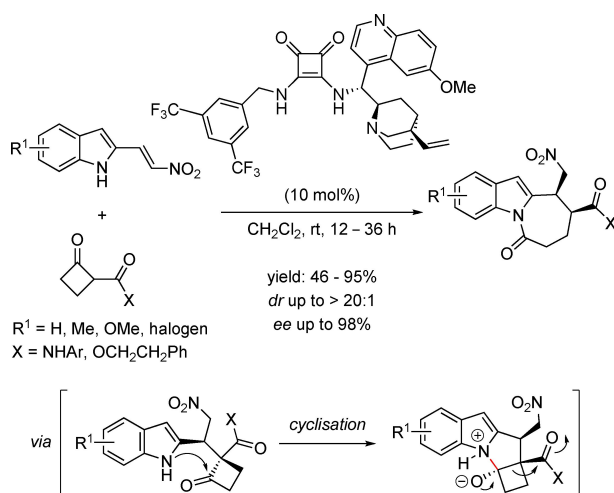
Inspired by this work, Yang, Deng, and co-workers have recently reported a related original three-atom ring expansion of cyclobutanones based on similar Michael/cyclisation/fragmentation domino reaction, now using 2-nitrovinyl indoles instead of the previously employed *ortho*-aminonitrostyrenes (Scheme 26).^[50] It resulted in an elegant and efficient synthetic



Scheme 24. Enantiospecific two-atom ring-expansion of cyclobutanones.



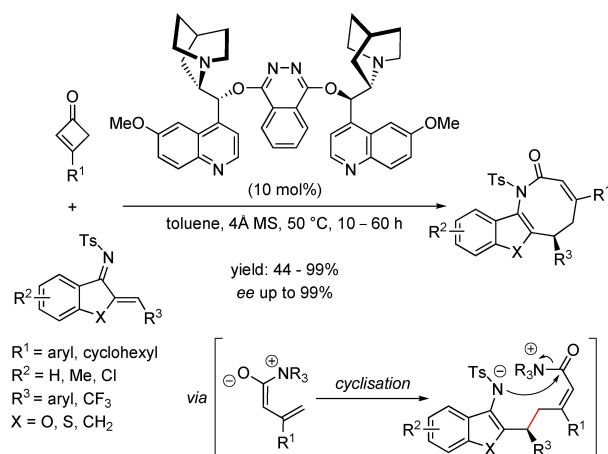
Scheme 25. Four-atom ring expansion to benzazocinones.



Scheme 26. Three-atom ring expansion to azepino[1,2-*a*]indoles.

approach to highly enantioenriched azepino[1,2-*a*]indole derivatives.

Following a different approach, Jiang *et al.* have reported recently an original four-atom ring expansion of cyclobutenones with 1-azadienes (Scheme 27).^[51] Using a nucleophilic organocatalyst the reaction is initiated by fragmentation of the cyclobutenone substrate into a chiral zwitterionic dienolate that can then undergo (4+4) annulation through a Michael addition/cyclisation sequence. The products are obtained in high yields with excellent enantioselectivities. Remarkably, this is a unique example for a bulky tertiary amine catalyst to promote the catalytic fragmentation of cyclobutenones (see above for examples with other nucleophilic catalysts).



Scheme 27. Four-atom ring expansion to azocinones.

6. Summary and Outlook

Recent progress in the enantioselective organocatalytic syntheses and reactions of cyclobutane derivatives are highlighted in this mini-review. The synthesis of cyclobutane derivatives usually involves stepwise processes, typically Friedel-Crafts initiated (2+2) annulations, or photochemically-promoted concerted [2+2] cycloadditions. Cyclobutane derivatives have been successfully used in efficient ring expansion reactions. For one-atom ring-expansion reactions, the most productive approach has been the semipinacol rearrangement of cyclobutanol derivatives using either aminocatalysts operating by iminium ion activation or Brønsted acid catalysts providing hydrogen-bonding interactions. For two-or-more-atom ring-expansion reactions, two promising approaches emerged to realize (4+n) annulations: one relies on the fragmentation of cyclobutenones using nucleophilic catalysts to produce zwitterionic dienolate intermediates amenable to add to electrophilic moieties followed by cyclisation, and the other involves Michael addition-initiated processes of cyclobutanones followed by cyclisation and fragmentation. Taking full advantage of the ring strain, it can reasonably be anticipated that more of these enantioselective organocatalytic ring expansive (4+n) annulation reactions will be discovered soon.

Acknowledgements

M. B. thanks the Fondation de la Maison de la Chimie for a post-doctoral fellowship. P. B. thanks the French government for a doctoral studentship (2018–2021). Financial support from Aix-Marseille University, Centrale Marseille and the CNRS is also gratefully acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Medium-ring compounds · Organocatalysis · Ring expansion · Small ring systems · Strained molecules

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