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Advances in the catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes

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Chiral cyclobutanes with quaternary stereogenic centers are motifs frequently found in various natural products and bioactive compounds. In addition, they are also useful intermediates for chemical synthesis, as they could undergo ring-expansion or ring-cleavage reactions to deliver various cyclic and acyclic chiral molecules. Therefore, the development of efficient catalytic methods for the highly enantioselective construction of chiral quaternary carbon containing cyclobutanes is of great synthetic value and has broad application prospects. The current review provides a summarization on the advances in catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes.

1. Introduction

Chiral cyclobutanes with quaternary stereogenic carbon centers are important structural motifs frequently found in various bioactive natural products (Fig. 1).[1] Due to their structural rigidity and defined spatial arrangement of their substituents, a feature that is often favorable in drug discovery, cyclobutanes bearing quaternary centers are identified as privileged structural motifs in structure-based drug design.[2] In addition, quaternary carbon containing cyclobutanes are useful intermediates for chemical synthesis, as they could undergo ring-expansion or ring-cleavage reactions to deliver a variety of cyclic or acyclic chiral molecules bearing quaternary carbon centers.[3] Therefore, the development of catalytic methods for the highly enantioselective construction of chiral quaternary carbon containing cyclobutanes is of great synthetic value and has broad application prospects.

In this context, the last decades have witnessed rapid progress in this area and many novel synthetic methods have been reported. These methods could be classified into four major categories (Fig. 2): (a) asymmetric [2 + 2] cycloaddition reaction of 1,1-disubstituted alkenes with another multiply carbon–carbon bond; (b) enantioselective ring-expansion rearrangement of prochiral cyclopropanol derivatives; (c) catalytic desymmetrization of prochiral substrates, such as cyclobutanes and cyclobutanones; and (d) enantioselective alkylation of cyclobutenolate.

To date, the enantioselective construction of chiral 4-membered carbon ring has been the topic of many nice reviews.[4] Early in 2003, Lee-Ruf *et al.* introduced the synthesis of enantiomerically pure cyclobutane derivatives and their use in organic synthesis.[3a] The groups of Butenschön, Brown and Bach summarized the application of [2 + 2] cycloaddition reactions in the synthesis of cyclobutanes in 2008, 2015 and 2016, respectively.[4a–c] Secci and co-workers reviewed the stereocontrolled synthesis and functionalization of cyclobutanes and cyclobutanones.[4d] Lu and Ding reviewed the recent advances in the total synthesis of cyclobutane-containing natural products in 2018 and 2020, respectively.[1] Very interestingly however, and to the best of our knowledge, no survey focusing on the construction of quaternary carbon containing cyclobutanes has been documented. In view of this, the current review aims to give a summary of the advances in the catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes and is organized according to the above-mentioned four major strategies (Fig. 2).

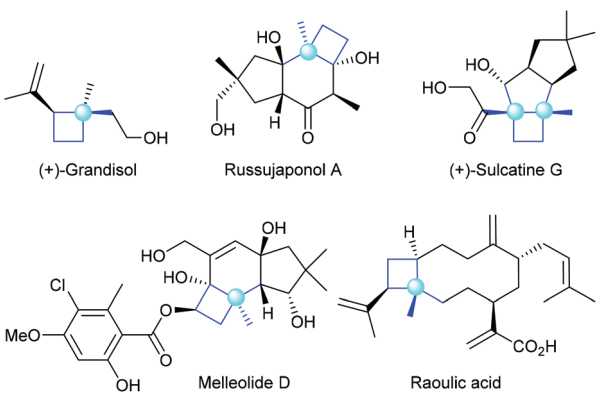

Fig. 1 Selected natural products bearing quaternary carbon containing cyclobutanes.

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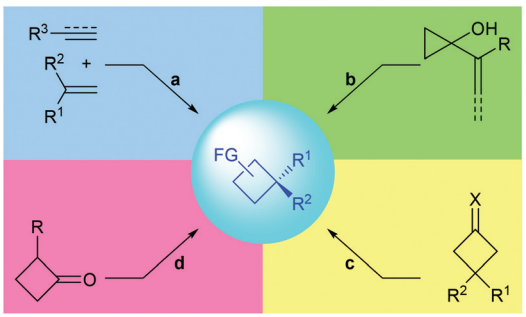


Fig. 2 Synthetic strategies to quaternary carbon containing cyclobutanes.

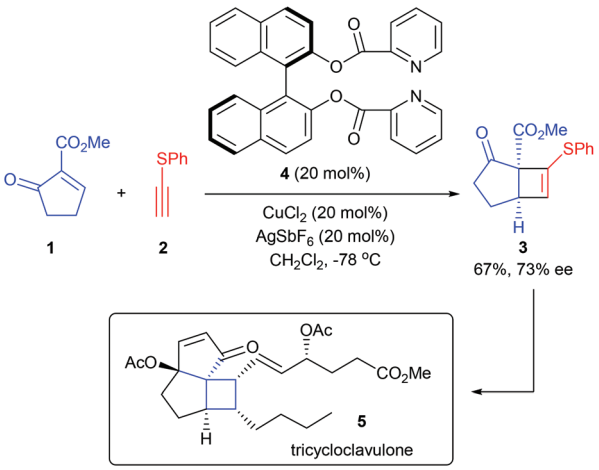
2. Asymmetric [2 + 2] cycloaddition

Catalytic asymmetric [2 + 2] cycloadditions are the most extensively studied and widely used strategies in the synthesis of cyclobutanes and their derivatives, as they could deliver cyclobutane scaffolds from simple and readily available alkene and alkyne starting materials and are completely atom-economical. As for the construction of quaternary carbon containing cyclobutanes, the reaction requires the use of 1,1-disubstituted alkenes. Since both of the substituents on the C=C bond of 1,1-disubstituted alkenes are non-hydrogen substituents, the steric difference between these two substituents is relatively small, thus making stereoselectivity control more challenging. Though challenging, the last decade still witnessed the development of a series of highly enantioselective methods to construct quaternary carbon containing cyclobutanes.

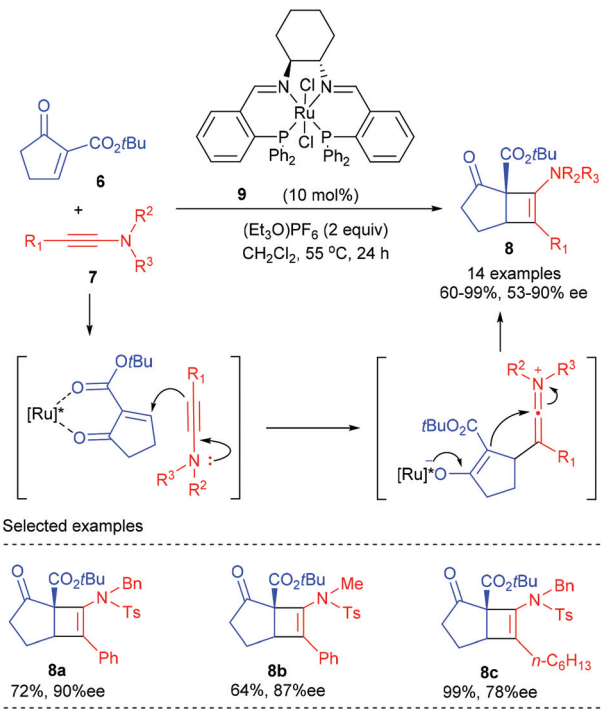
2.1. Asymmetric Lewis acid catalysis

2.1.1. Sigma Lewis acid catalysis. Early in 2004, in their efforts to achieve the total synthesis of (+)-tricycloclavulone (**5**), Iguchi and co-workers disclosed a catalytic enantioselective [2 + 2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one **1** with thioacetylene **2** for the construction of chiral bicyclic systems containing chiral quaternary carbon centers (Scheme 1).[5a,b] In the presence of 20 mol% Cu(II) complex derived from ligand **4**, which was easily synthesized from BINOL and picolinic acid, the desired cycloaddition product **3** could be obtained in up to 67% yield and with 73% ee value at −78 °C. It should be mentioned that this newly developed catalyst is more effective than the known chiral catalysts, such as Ti-TADDOL and Cu-BOX. In a following report from the same group, this reaction was further utilized for the enantioselective formal synthesis of (+)-precapnelladiene.[5c]

In 2011, the Mezzetti group reported the first enantioselective Ficini reaction to construct amidocyclobutenes bearing quaternary chiral centers (Scheme 2).[6] In the presence of 10 mol% dicationic ruthenium/PNNP complex **9** as the catalyst, together with 2.0 equivalents of $(Et_3O)PF_6$ as the activator, the [2 + 2] reaction of α-methylene β-keto ester **6** with a number of dienes **7** proceeded smoothly to deliver the desired amidocyclobutenes in 64–99% yield and with 53–90% ee values. The



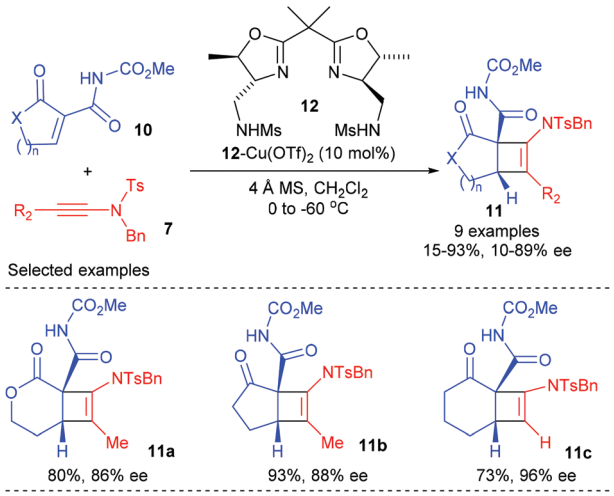
Scheme 1 [2 + 2]-Cycloaddition reaction of cyclopenten-1-one with thioacetylene.



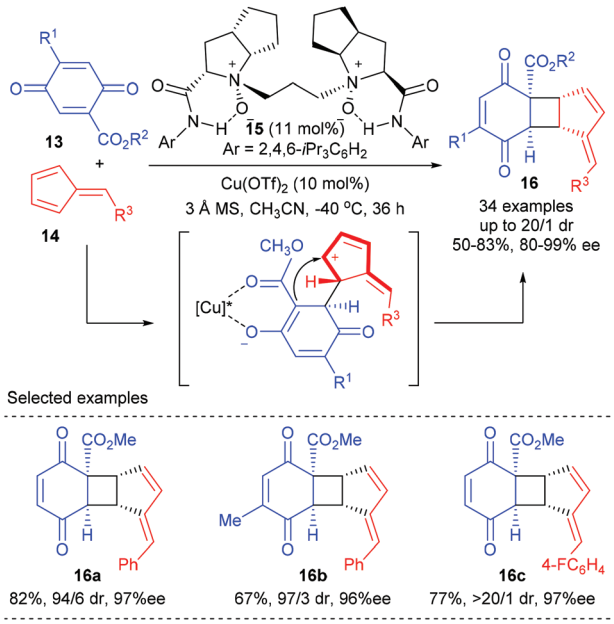
Scheme 2 Ruthenium catalyzed [2 + 2] cycloaddition of ynamides with cyclic enones.

reaction showed a good functional group tolerance. By and large, bulky substituents at the α position of ynamides are required for high enantioselectivity, and good electron donating substituents afforded higher yields (**8c**). Although the reaction is formally a [2 + 2] cycloaddition process, it is believed to occur stepwise by nucleophilic attack of the β-carbon atom of the ynamide onto the electrophilic position of the enone, which was originally suggested by Ficini for enamines.

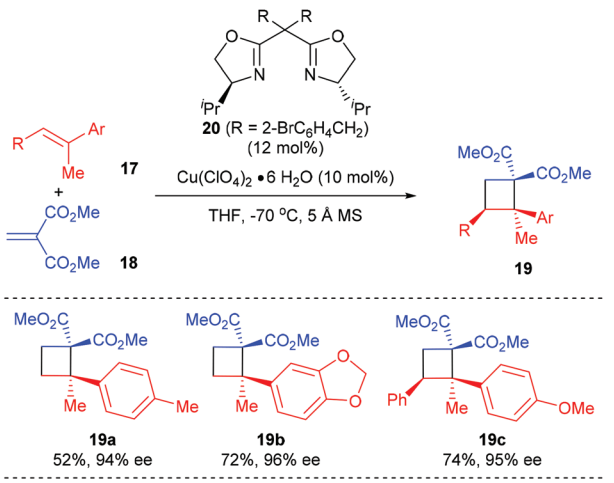
Later in 2015, the Nakada group extended this ynamide participated catalytic enantioselective [2 + 2] cycloadditions to



Scheme 3 [2 + 2]-Cycloadditions of cyclic α-alkylidene β-oxo imides with ynamides.



Scheme 4 Asymmetric [2 + 2] cycloaddition between quinones and fulvenes.



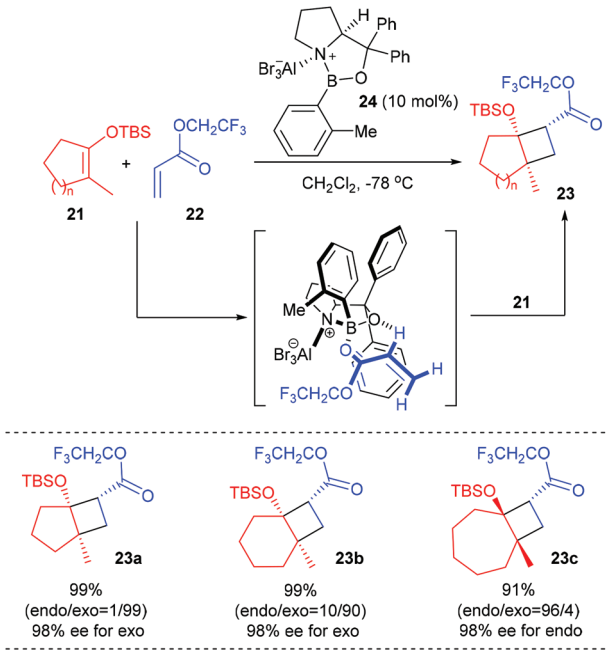
Scheme 5 Cu(II)/SaBOX-catalyzed [2 + 2] reaction of alkenes with methylidenemalonate.

cyclic α-alkylidene-β-oxo imides (Scheme 3).[7] Under the catalysis of 10 mol% bisoxazoline ligand **12** derived Cu(II) complex, the reaction of terminal ynamide and α-methyl ynamide with various cyclic α-alkylidene β-oxo imides **10** could give the desired bicyclic products **11a–c** with good to high yields and ee values at low temperature, whereas the reaction of α-phenyl ynamide resulted in significantly decreased yield and ee values, likely because of the steric effect of the substituents at the alkyne terminal. The current catalytic asymmetric [2 + 2] cycloaddition is highly useful for natural product synthesis, as the imide group in the resulting products could be successfully transformed into amide, nitrile, and ester groups.

Feng and co-workers achieved the first catalytic asymmetric [2 + 2] cycloaddition between quinones and fulvenes using their chiral *N*,*N*′-dioxide ligand derived Cu(II) complex in 2017 (Scheme 4).[8] After efforts toward optimization of the chiral catalysts, ligand **15** was identified as the optimal choice, with which the targeted [6,4,5]-tricyclic cyclobutane derivatives **16** could be obtained with good yields and excellent regio- and stereoselectivities, whereas the use of a BOX ligand led to substantial polycondensation of quinine and trace adducts were obtained. In addition, the thus obtained cyclobutane **16** can be easily converted into cyclopenta[*b*]benzofuran structures diastereo- and enantioselectively under the catalysis of In $(OTf)_3$.

Besides using electron deficient cyclic alkenes as the π-components, the Tang group reported the first asymmetric [2 + 2] cycloaddition of dimethyl methylidenemalonate with polysubstituted olefins for the synthesis of chiral quaternary carbon containing cyclobutanes, using their SaBOX (side-arm-modified BOX) **20** derived Cu(II) complex as the catalyst (Scheme 5).[9] Under optimized conditions, the reaction of acyclic methylidenemalonate **18** with 1,1-disubstituted alkenes **17a and b** afforded quaternary carbon containing cyclobutanes **19a and b** in 52–72% yields and with 94–95% ee values. Moreover, trisubstituted alkene **17c** was also a compatible substrate for this reaction, giving product **19c** in 74% yield and with excellent enantioselectivity.

Based on their finding that the oxazaborolidine–$AlBr_3$ complex **24** is an exceedingly effective chiral catalyst for cycloaddition reactions of achiral components, Corey and co-workers developed a new and useful methodology for the synthesis of chiral cyclobutanes bearing a quaternary carbon stereocenter starting from vinyloxysilanes and α,β-unsaturated esters (Scheme 6).[10] In the presence of the chiral aluminum bromide complex **24** (10 mol%) as the Lewis acid catalyst, a series of cyclic TBS enolate silyl ethers **21** could react with trifluoroethyl acrylate **22** to give [2 + 2]-cycloaddition products

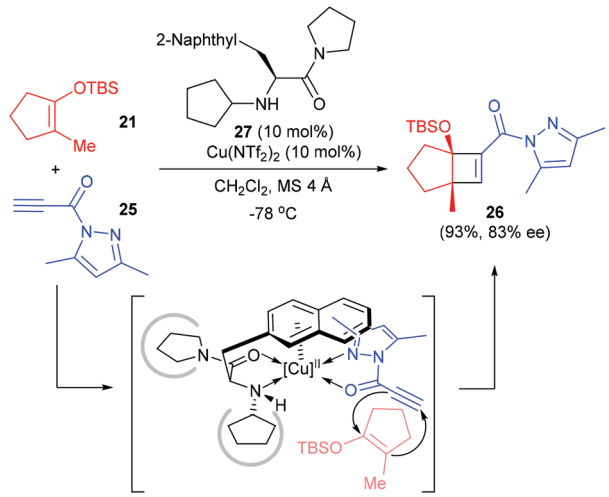


Scheme 6 Chiral $AlBr_3$ complex catalyzed enantioselective [2 + 2]-cycloaddition reactions.

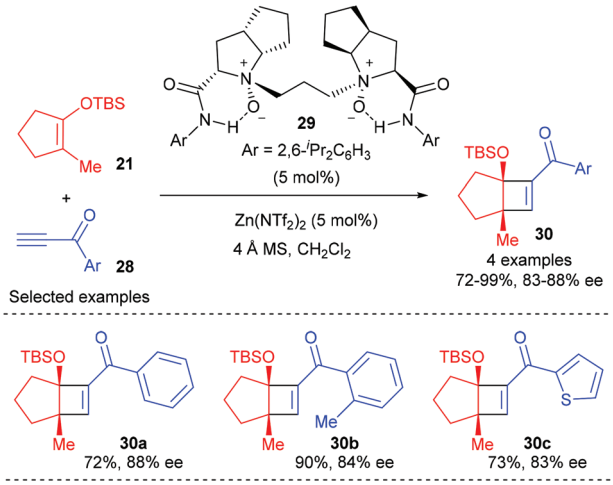
23a–c, which are very useful chiral intermediates for further synthetic elaboration, with up to 99% yields and 98% ee values at −78 °C. It is hypothesized that the [2 + 2] cycloaddition occurs by an asynchronous process involving the α-C–H hydrogen-bonded complex of catalyst **24** and trifluoroethyl acrylate.

Besides electron deficient alkenes, the electron deficient alkynes are also viable counterparts for enantioselective [2 + 2] cycloaddition reactions with cyclic enolate silyl ethers. Early in 2008, Ishihara and co-workers reported a catalytic and highly enantioselective [2 + 2] cycloaddition reaction of cyclic enolate silyl ethers with electron-deficient propiolamide derivatives **25** (Scheme 7).[11] Under the catalysis of the 3-(2-naphthyl)-L-alanine amide **27** derived Cu(II) complex (10 mol%), **25** could react with 2-methyl 1-silyloxy-1-cyclopentenes **21** to give quaternary cyclobutenecarboxamide **26** in 93% yield and with 83% ee value, but the scope of this reaction is yet to be explored.

More recently, Feng and co-workers have achieved a highly efficient enantioselective [2 + 2] cycloaddition between alkynones and cyclic enol silyl ethers using a chiral *N*,*N*′-dioxide–zinc(II) complex as the catalyst.[12] A variety of terminal alkynes and internal alkynes were well tolerated to react with cyclic enol silyl ethers to give good to excellent enantioselectivity. Although the authors focused their attention mainly on 1,2-disubstituted cyclic enol silyl ethers, the reaction of β-methyl substituted enol silyl ether **21** with a range of terminal alkynones (**28**) with different substituted aryl groups was also explored, affording cyclobutenes (**30**) with two contiguous stereocenters in 72–99% yields and with 83–88% ee values (Scheme 8).

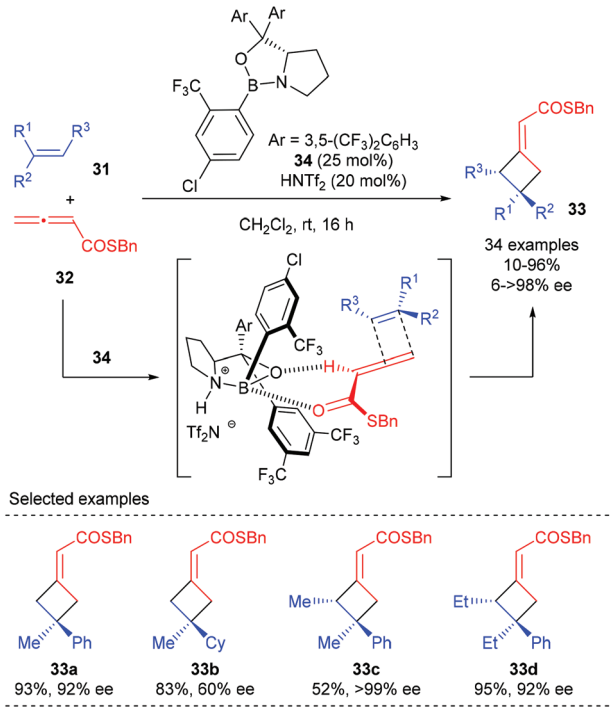


Scheme 7 [2 + 2] Cycloaddition of cyclic enolate silyl ether with propiolamide derivatives.



Scheme 8 Enantioselective [2 + 2] cycloaddition between alkynones and cyclic enol silyl ethers.

All the reactions discussed above involve the Lewis acid activation of unsaturated carbonyl compounds and cycloaddition *via* a stepwise process. The Brown group has recently disclosed a catalytic enantioselective [2 + 2] cycloaddition of allenoates and alkenes that is proposed to proceed *via* a concerted mechanism (Scheme 9).[13] Using Brønsted acid $HNTf_2$ as the activator for chiral oxazaborolidine **34**, the [2 + 2] cycloaddition reaction of α-alkyl styrenes **31** with allenoates **32** could give the corresponding products (**33a**) with high enantioselectivity. Replacement of the aryl group with a cyclohexyl group resulted in a substantial decrease in the ee value (**33b**), demonstrating that the aryl group is necessary to obtain high ee value. Acyclic trisubstituted alkenes are also compatible substrates to give cyclobutanes **33c and d** bearing adjacent stereocenters in a highly stereospecific and enantioselective fashion.

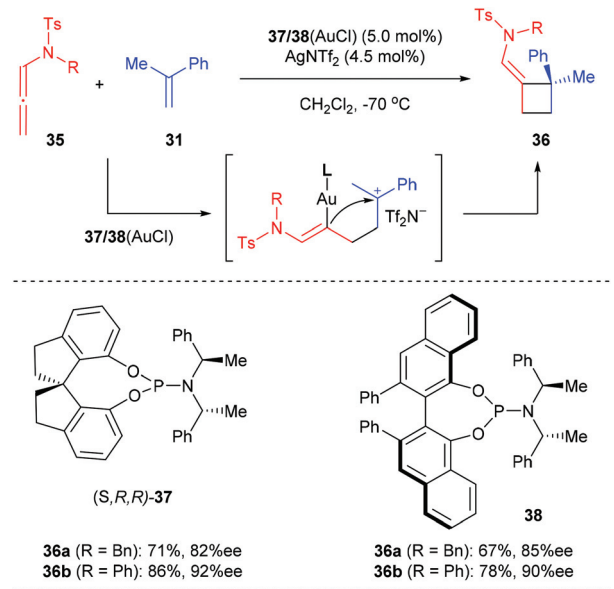


Scheme 9 Enantioselective [2 + 2] cycloaddition of alkene with allenoates.

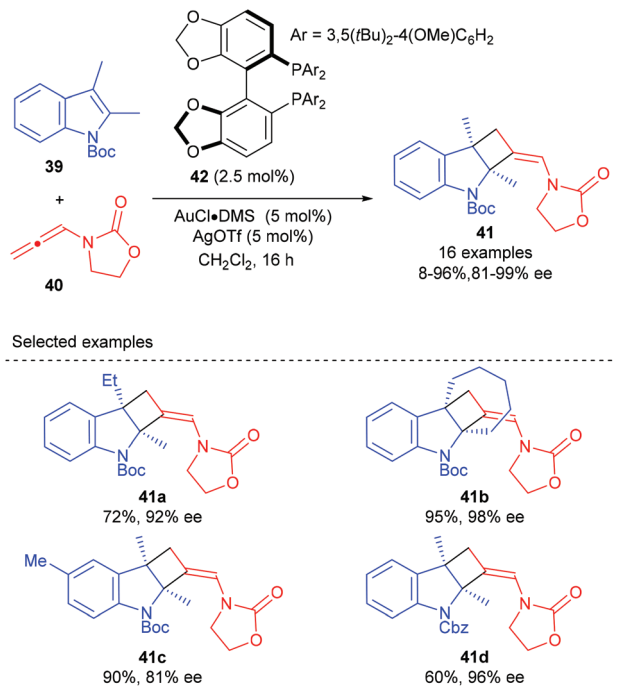
2.1.2. π-Philic Lewis acid catalysis. González *et al.* reported the first asymmetric gold-catalyzed intermolecular [2 + 2] cycloaddition of readily available sulfonylallenamides and vinylarenes to provide a straightforward entry into optically active cyclobutanes in 2012 (Scheme 10).[14] After several trials, they found that when ligands **37**/**38** derived from (*R*,*R*)-bis(1-phenylethylamine) and (*S*)-1,1′-spirobiindane-7,7′-diol or (*R*)-VANOL were used, the reaction of *N*-benzyl sulfonylallenamides **35a** with α-methylstyrene **31** could afford the desired chiral cyclobutane **36a** with 82–85% ee values, whereas the reaction of *N*-phenyl sulfonylallenamides **35b** with **31** generally afforded cycloadduct 36b with higher ee values (90–92%). This reaction is believed to proceed *via* a stepwise pathway including the activation of the allene by the gold(I) catalyst to facilitate a subsequent attack on the olefin followed by the evolution of the cationic vinyl gold intermediate to give the cyclobutane product. The current reaction also represents one of the first uses of an allene in an intermolecular gold catalyzed process involving enantioselective carbon–carbon bond formation.

As a continuation of their research interest on the [Au(I)]-mediated functionalization of indoles, the Bandini group reported the first enantioselective gold catalyzed dearomative [2 + 2] cycloaddition between indoles and allenamide for the construction of densely functionalized 2,3-indoline-cyclobutanes (Scheme 11).[15] The merger of commercially available (*R*)-DTBM-segphos (**42**) and AuCl·DMS was identified as the best catalyst, in the presence of which a series of methylenecyclobutane-fused indolines, featuring two consecutive quaternary carbon centers, could be accessed with excellent stereochemical control (>20 : 1 dr and up to 99% ee).

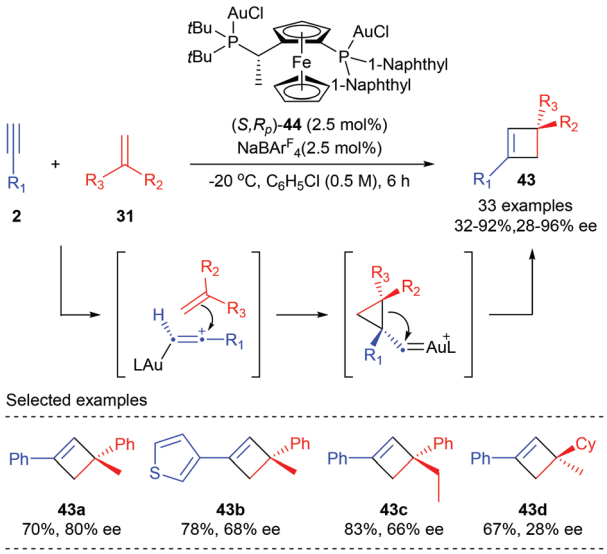
Unlike the above examples using activated alkenes and alkynes, Echavarren *et al.* have recently reported the first general enantioselective intermolecular [2 + 2] cycloaddition of terminal alkynes with alkenes for the synthesis of cyclobutanes (Scheme 12).[16] After evaluation of about 90 chiral ligands, the chiral non-C_2 symmetrical Josiphos derived digold(I) complex



Scheme 10 Au(I)-Catalyzed intermolecular [2 + 2] cycloaddition.



Scheme 11 Enantioselective [2 + 2] cycloaddition reaction between indoles and allenamides.



Scheme 12 Gold-(I)-catalyzed [2 + 2] cycloaddition of terminal alkynes with alkenes.

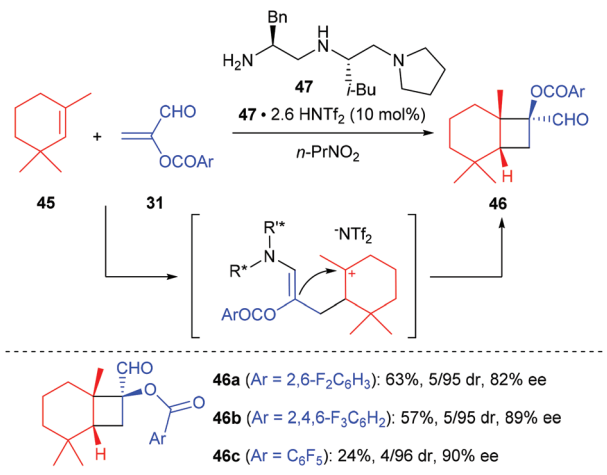
(S,R_P)-**44** turned out to be the optimal choice. In the presence of only 2.5 mol% **44**, together with 2.5 mol% $NaBAr^F_4$ as the chloride scavenger, the reaction of terminal aromatic alkynes with various 1,1-disubstituted alkenes could afford quaternary carbon containing cyclobutanes **43** with moderate to high yields and enantioselectivities. Generally, satisfactory results could be expected from aryl alkynes bearing electron rich substituents. Good ee values were obtained with α-alkyl styrenes. However, 1,1-dialkyl substituted alkenes or simple styrenes resulted in a significant loss of enantioselectivity (**43d**).

2.2. Asymmetric organocatalysis

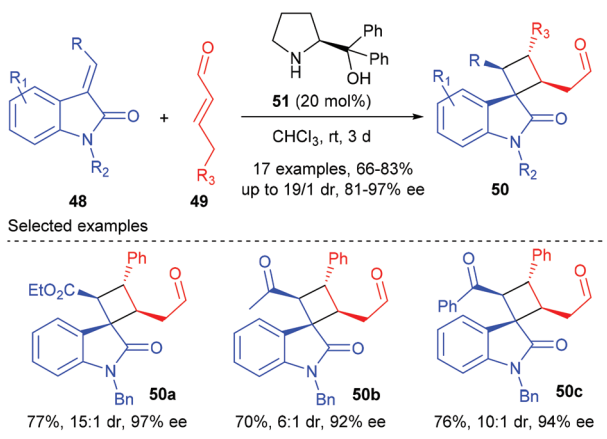
The first organocatalytic enantioselective [2 + 2] cycloaddition reaction of unactivated alkenes with α-acyloxyacroleins was reported by Ishihara and Nakano in 2007 (Scheme 13).[17] This reaction was proposed to proceed *via* a stepwise enantioselective Michael addition of alkenes to a (*Z*)-iminium intermediate and intramolecular cyclization of a carbocation intermediate. Under optimized conditions, using the organosalt of a chiral secondary amine **47** (10 mol%) as the catalyst, the reaction of α-(fluorobenzoyloxy)acroleins **31** with 1,3,3-trimethylhexene **45** gave bicyclic cyclobutanecarbaldehydes **46** in moderate to good yields and with high ee values. In addition, acyclic alkenes, such as α-methylstyrene, are also compatible substrates for this reaction, giving the desired products with slightly lower enantioselectivities.

After Ishihara's pioneering work, the groups of Jørgensen, Vicario and Xu also reported their efforts in organocatalytic [2 + 2] cycloaddition reactions, but not for the construction of chiral quaternary carbon containing cyclobutanes.[18] Later in 2014, Wang and co-workers achieved the first organocatalytic formal [2 + 2] cycloaddition reaction of ethyleneindolinones with α,β-unsaturated aldehydes *via* the H-bond-directing dienamine activation strategy (Scheme 14).[19] In the presence of α,α-diphenylprolinol **51** (20 mol%) as the catalyst, the reaction could afford the structurally complex spirocyclobutyloxindole products **50** in good yields and with up to >19 : 1 dr and 97% ee values at room temperature. A variety of substituents on both the oxindole benzene ring and the nitrogen atom were well tolerated. Furthermore, when the ester group was replaced by an acetyl or a benzoyl group, the reactions also proceeded smoothly with excellent stereocontrol to give products **50b and c**.

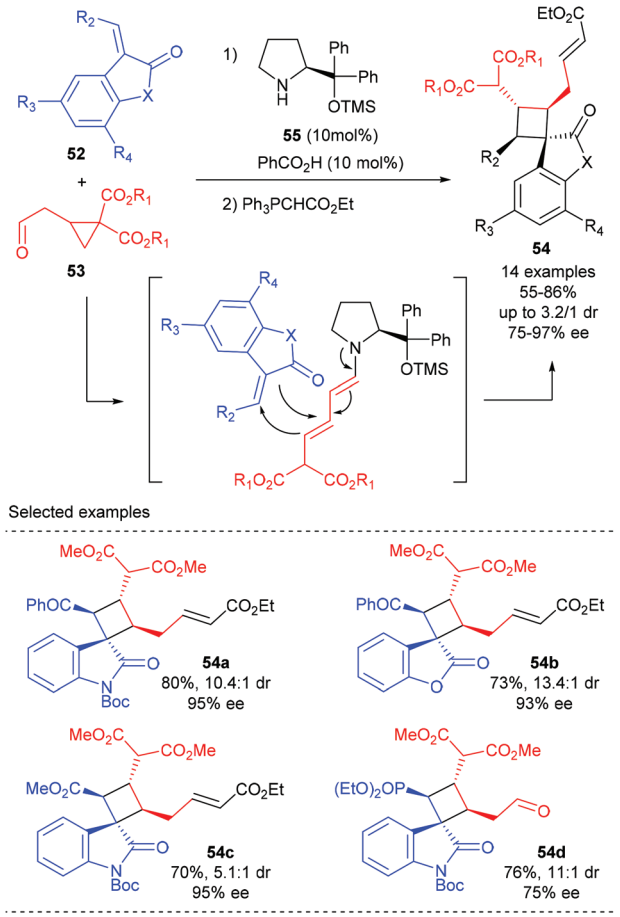
Jørgensen and co-workers described a novel organocatalytic activation mode of cyclopropane and its application in the synthesis of spirocyclobutane derivatives (Scheme 15).[20] It is proposed that the treatment of cyclopropylacetaldehyde **53** with aminocatalyst **55** could lead to the ring-opening of cyclopropyl functionality and form a dienamine intermediate, which could then react in a formal [2 + 2]-cycloaddition with benzoyl 3-olefinic oxindoles and benzofuranone to form the desired products **54a and b** in good yields and with high dr and ee values. Oxindoles carrying an ester or a phosphonate on the olefinic



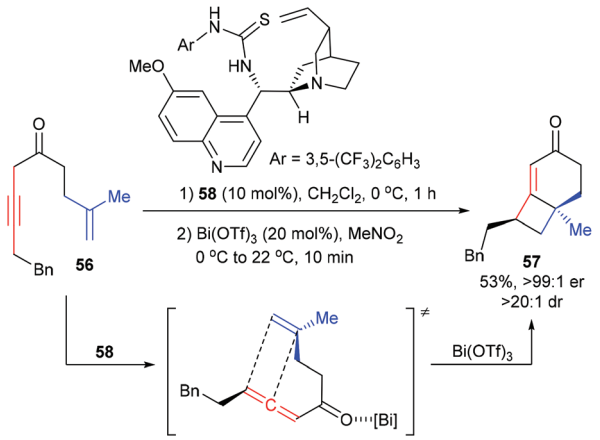
Scheme 13 First organocatalytic enantioselective [2 + 2] cycloaddition reaction.



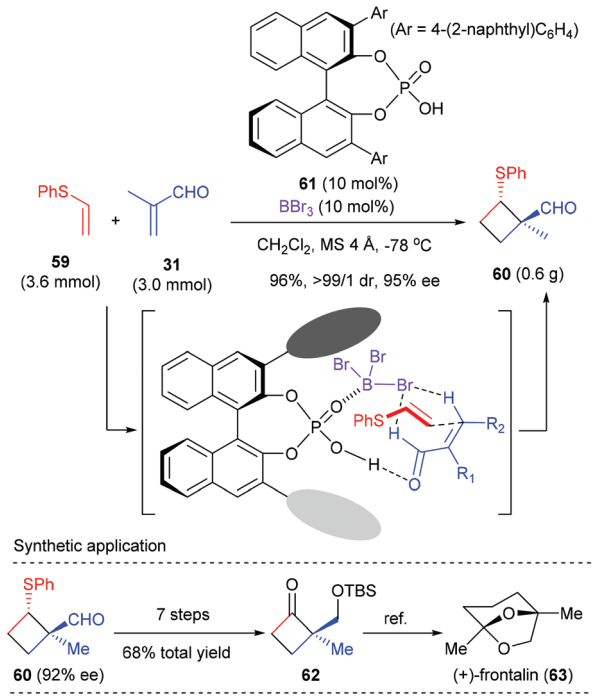
Scheme 14 Organocatalytic [2 + 2] cycloaddition for the synthesis of spirocyclobutyloxindole.



Scheme 15 Enamine-activation of cyclopropanes for highly stereoselective synthesis of cyclobutanes.



Scheme 16 Chirality transfer [2 + 2] cycloadditions of allenic ketones with alkenes.



Scheme 17 BBr_3-assisted chiral phosphoric acid catalysts for asymmetric [2 + 2] cycloaddition.

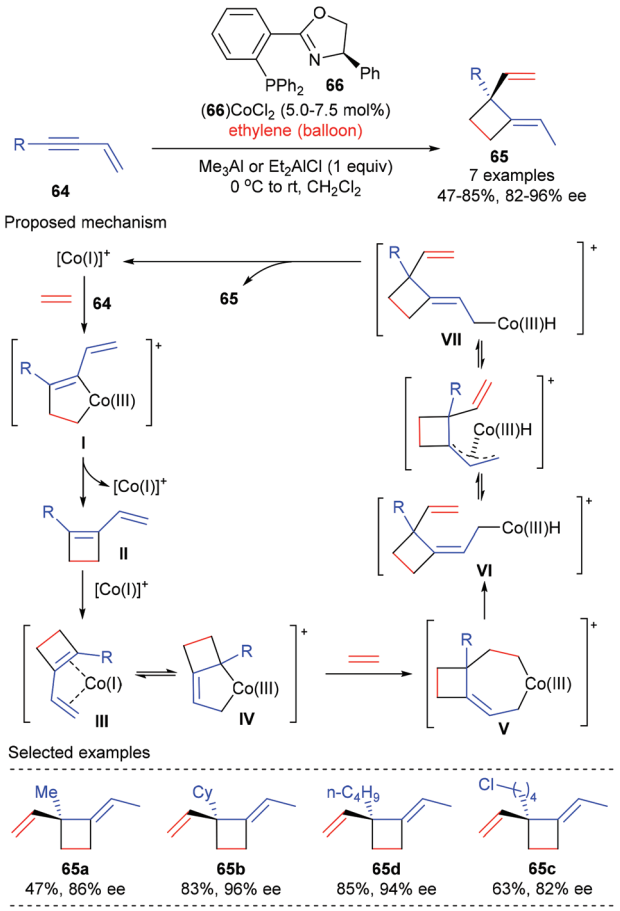
moiety are also well tolerated, albeit gave diminished diastereoselectivity (**54c**) or enantioselectivity (**54d**), respectively.

The Brown group reported a chirality transfer [2 + 2] cycloaddition of allenic ketone with tethered alkene for the enantioselective synthesis of [4.2.0]-fused bicycles (Scheme 16).[21] Under the catalysis of 10 mol% thiourea catalyst **58**, the achiral β,γ-alkynyl ketone **56** was first enantioselectively isomerized to provide a chiral allene intermediate. After adding $Bi(OTf)_3$ (10 mol%), the chiral allene moiety could directly undergo chirality transfer [2 + 2] cycloaddition with the tethered 1,1-disubstituted alkene to form product **57**, which contains a quaternary carbon center, with good yield and enantioselectivity.

As a continuation of their interest in Lewis acid-activated chiral Brønsted acid (LBA) catalysis,[22] Ishihara *et al.* developed BBr_3-assisted chiral phosphoric acid catalysts for enantioselective [2 + 2] cycloaddition. Using phosphoric acid **61** as the catalyst, together with equal amount of BBr_3 as the Lewis acid activator, the reaction of phenyl vinyl sulfide **59** with α-methyl acrolein **31** proceeded smoothly to deliver [2 + 2] cycloadduct **60** with high ee value (Scheme 17).[23] The thus obtained **60** was a synthetically useful chiral cyclobutane, as is exemplified by the transformation to a key intermediate **62** for the total synthesis of (+)-frontalin (**63**), a pheromone in Asian elephants. It should be mentioned that this reaction represents the first chiral Brønsted acid catalyzed enantioselective [2 + 2] cycloaddition reaction.

2.3. Transition metal catalysis

Based on their interest on transition metal catalyzed enantioselective coupling reaction of alkenes, RajanBabu and Pagar achieved a catalytic asymmetric tandem coupling of ethylene and enynes to functionalized quaternary carbon containing cyclobutanes (Scheme 18).[24] Starting from 1,3-enynes and



Scheme 18 Asymmetric tandem coupling of ethylene and enynes to quaternary carbon containing cyclobutanes.

ethylene, using the phosphinooxazoline ligand **66** derived Co(II) complex as the chiral catalyst, an initial oxidative dimerization of ethylene and enyne **64** delivered a metallacyclopentene **I**, which could undergo reductive elimination to afford a cyclobutene intermediate **II**. Another oxidative dimerization between **II** and ethylene gave a metallacycloheptene **V**, which then underwent β-hydrogen elimination to form a Co(III)–hydride intermediate **VI**. The sterically encumbered **VI** could undergo (*Z*)/(*E*)-isomerization to produce the (*E*)-4-isomer **VII** as the major product. A further reductive elimination of **VII** could deliver cyclobutanes **65**, bearing an all-carbon quaternary center, as the (*E*)-isomer in generally very good yield and with excellent enantioselectivity. This process is highly efficient and desirable, as three highly selective carbon–carbon bonds were formed in one pot using a single chiral cobalt catalyst from simple precursors.

2.4. Photochemical [2 + 2] cycloadditions

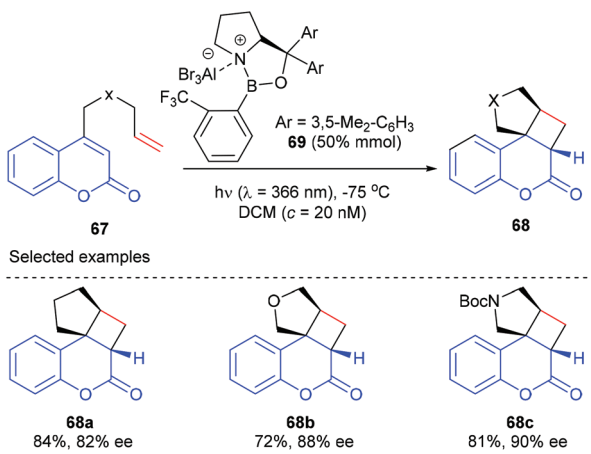
2.4.1. Lewis acid catalysis. Early in 2010, the Bach group reported that the oxazaborolidine–$AlBr_3$ complex could also serve as a chiral catalyst for a photocycloaddition reaction. In order to compete with an achiral background reaction, a catalyst loading of 50 mol% was required to achieve a good level of enantioselectivity. When the cationic oxazaborolidine–$AlBr_3$ complex **69** was used, the intramolecular [2 + 2] photocycloaddition reaction of 4-alkenyl-substituted coumarins **67a** could proceed smoothly to give product **68a** in 84% yield and with 82% ee value (Scheme 19).[25a]

In a following report, they further demonstrated that the above-mentioned catalytic system is also applicable to the [2 + 2] photocycloaddition of heteroatom analogues to give products **68b and c** with good to high yields and ee values.[25b] A mechanism study using UV/Vis spectra indicated that the coordination of the oxazaborolidine–$AlBr_3$ complex **69** to coumarins **67** leads to a bathochromic absorption shift, which in turn facilitates their excitation at λ = 366 nm.

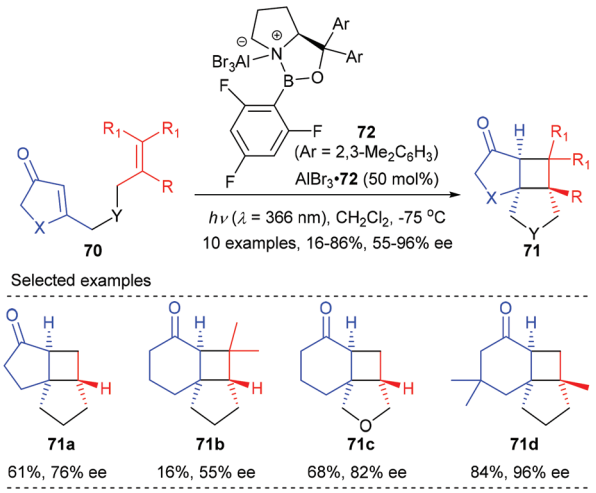
In a recent report, they have further achieved an $AlBr_3$-activated oxazaborolidine catalyzed intramolecular [2 + 2] photocycloaddition of 3-alkenyl-2-cycloalkenones (Scheme 20).[25c] After extensive screening, oxazaborolidine **72** that bears two 2,3-dimethylphenyl groups on the prolinol and a 2,4,6-trifluorophenyl group on the boron atom was identified as the optimal choice. Upon irradiation at λ = 366 nm, the first asymmetric intramolecular [2 + 2] cycloaddition of both 3-alkenyl 2-cyclohexenones and 2-cyclopentenones proceeded well to give the desired products **71** in 16–86% yields and with up to 96% ee values in the presence of 50 mol% $AlBr_3$-activated **72**.

Intermolecular [2 + 2] photocycloaddition reactions were also achievable using the $AlBr_3$-activated oxazaborolidine complex as the Lewis acid catalyst.[26] As shown in Scheme 21, the intermolecular [2 + 2] photocycloaddition of typical cyclic α,β-unsaturated enones **73** with 1,1′-disubstituted olefins **31** could deliver products **74** in moderate to good yields and with high enantioselectivity under the catalysis of 50 mol% **72**. The synthetic potential of this methodology was illustrated by the enantioselective total synthesis of monoterpene (−)-grandisol in 6 steps with an overall yield of 13%.

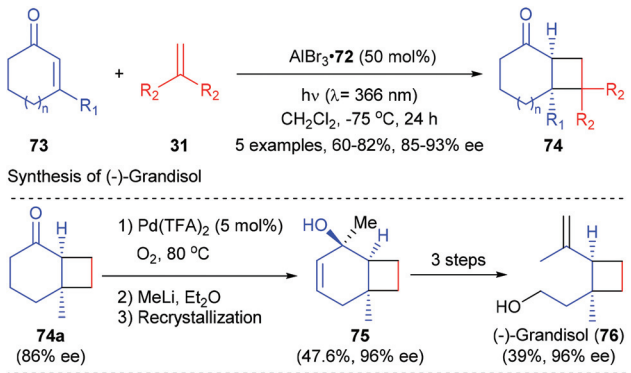
In addition to cyclic α,β-unsaturated enone substrates, Bach *et al.* further showed that the chiral $AlBr_3$ complex could also activate phenanthrene-9-carboxaldehydes **77** to enable their



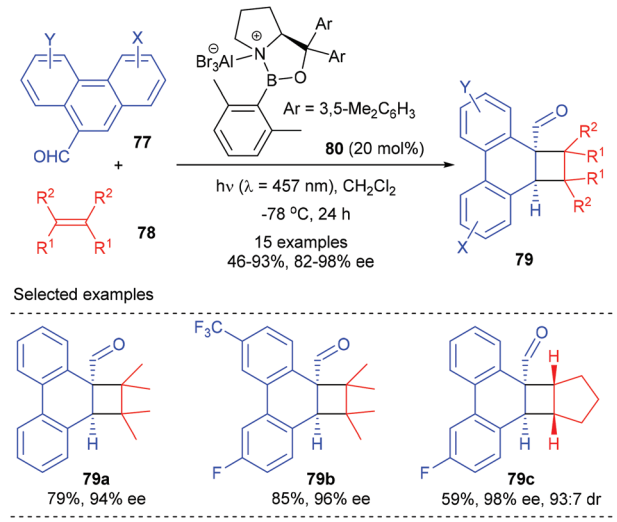
Scheme 19 Chiral $AlBr_3$ complex catalyzed enantioselective [2 + 2]-cycloaddition reactions.



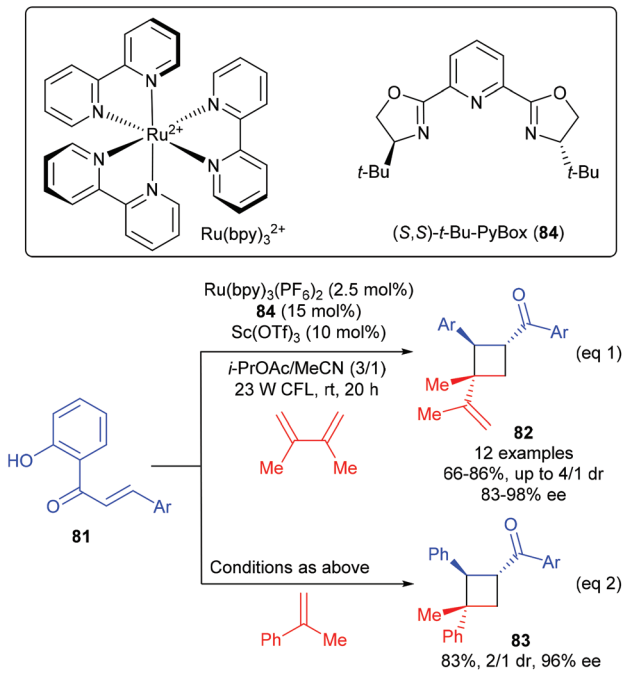
Scheme 20 Chiral $AlBr_3$ complex catalyzed enantioselective [2 + 2]-cycloaddition reaction of 3-alkenyl-2-cycloalkenones.



Scheme 21 Asymmetric intermolecular [2 + 2] photocycloaddition reaction of cyclic enones.



Scheme 22 Enantioselective photocycloaddition of olefins with phenanthrene-9-carboxaldehydes.



Scheme 23 Asymmetric [2 + 2] photocycloaddition through Lewis acid–catalyzed triplet energy transfer.

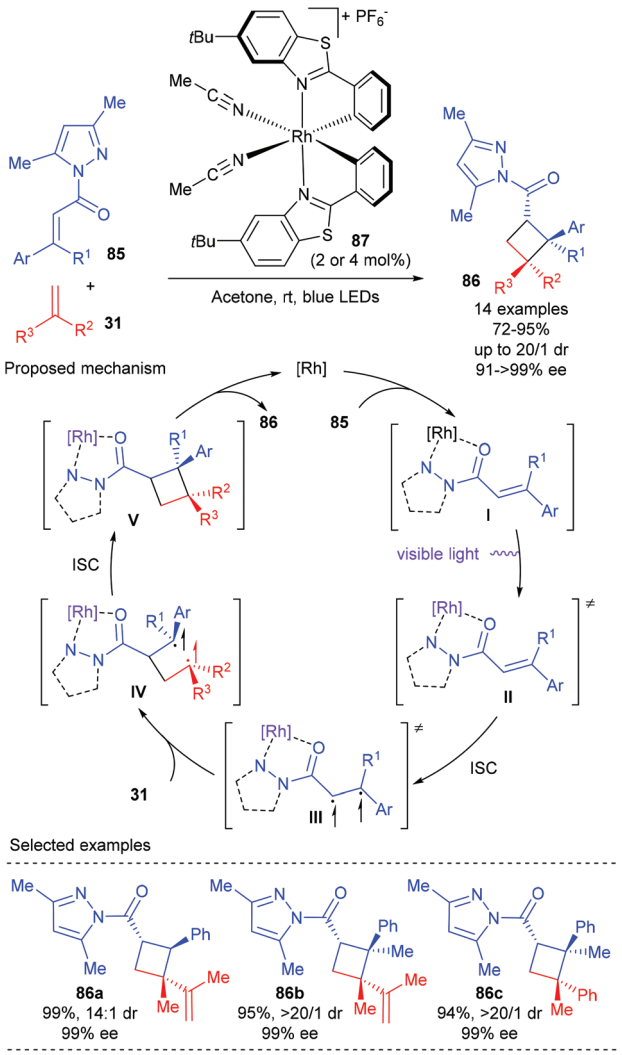
enantioselective *ortho* photocycloaddition with olefins under visible-light irradiation conditions (Scheme 22).[27] Upon coordination to a Lewis acid, **77** would undergo an extensive bathochromic shift to stretch beyond the absorption bands of uncoordinated phenanthrene-9-carboxaldehydes, thus enabling a selective excitation of the Lewis acid complex and alleviating the achiral background reaction. Therefore, the loading of the chiral oxazaborolidine–$AlBr_3$ complex **80** could be lowered to 20 mol%. A series of substituted phenanthrene-9-carboxaldehydes reacted smoothly with 2,3-dimethyl-2-butane and cyclopentene to give products **79** with 46–93% yields and 82–98% ee values.

Yoon and workers discovered that chiral Lewis acids could also work cooperatively with a photosensitizer to facilitate the first asymmetric [2 + 2] photocycloadditions of acyclic excited-state 2′-hydroxychalcones with alkenes (Scheme 23).[28] In the presence of the PyBox (**84**) derived Sc(III) complex (15 mol%) as the Lewis acid catalyst, together with 2.5 mol% $Ru(bpy)_3(PF_6)_2$ as the photosensitizer, a series of 2′-hydroxychalcones **81** reacted with 2,3-dimethylbuta-1,3-diene to afford vinyl cyclobutanes **82** in 66–86% yields and with 83–98% ee values (eqn (1)), whereas the reaction of **81** with α-methyl styrene could give product **83** in 83% yield and with 96% ee (eqn (2)). After a variety of mechanistic studies, they ruled out substrate activation by means of photo-induced electron transfer and proposed an unprecedented mechanism, *i.e.* Lewis acid coordination could lower the triplet energy of the chalcone substrate and the photosensitizer is responsible for absorbing visible light and the subsequent energy transfer to the substrate–Lewis acid complex.

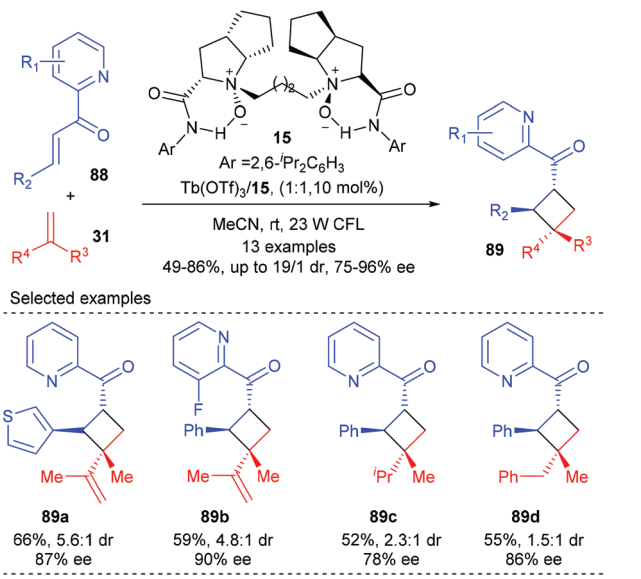
In 2017, Meggers *et al.* reported that their bis-cyclometalated chiral-at-metal complexes could serve as bifunctional catalysts, combining visible-light-induced electronic activation and reaction stereocontrol, for asymmetric [2 + 2] photocycloadditions. Using 2–4 mol% Δ-RhS (**87**) as the single catalyst, a variety of α,β-unsaturated imidazoles **85** could react smoothly with 1,1-disubstituted alkene **31** to deliver [2 + 2] addition products **86** in good to excellent yields and with up to 16 : 1 dr and up to >99% ee values (Scheme 24).[29] It is worth noting that cyclobutanes (**86b–c**) with three contiguous stereogenic centers and vicinal all-carbon quaternary stereocenters can be constructed in a single step using this new methodology in high yields and with excellent dr and ee values. The authors proposed that the complex of **85** and the catalyst were directly excited by visible light to give its lowest singlet state (**II**). A subsequent intersystem crossing (ISC) of **II** could give an excited triplet state (**III**), which then reacted with alkene **31** under control of the stereochemistry by the chiral catalyst to generate a rhodium-bound 1,4-diradical intermediate (**IV**). The desired [2 + 2] cycloaddition product **86** was obtained after an ISC followed by cyclization and chiral catalyst dissociation.

Feng and Liu showed that their chiral *N*,*N*′-dioxide derived Tb(III) complexes alone could catalyze the direct visible-light-excited asymmetric [2 + 2] cycloaddition of 2-alkenoylpyridines with various alkenes (Scheme 25).[30] In the presence of the chiral *N*,*N*′-dioxide **15** coordinated Tb(III) complex (10 mol%), together with 23 W CFL as the irradiator, 1,1-disubstituted alkenes and diene could react smoothly with 2-alkenoylpyridines **88** to deliver products **89** in 52–66% yields and with 78–90% ee and moderate dr values. It was believed that the 2-alkenoylpyridine bounded *N*,*N*′-dioxide–Tb(III) complex itself could absorb visible light to reach its excited state and provide facial selectivity of the bound enone, thus enabling the generation of chiral cyclobutane derivatives in the absence of an additional photosensitizer. Additionally, 2′-hydroxychalcones are also compatible substrates for this reaction using a chiral *N*,*N*′-dioxide–Sc(III) complex.

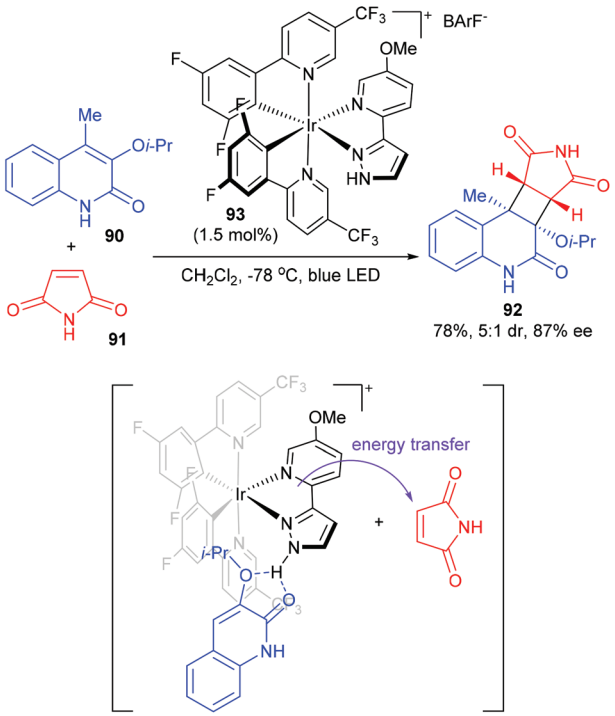
The Yoon group achieved a chiral hydrogen-bonding iridium photosensitizer catalyzed intermolecular [2 + 2] cycloaddition of 3-alkoxyquinolones (Scheme 26).[31] In the presence of only 1.5 mol% chiral Ir complex **93**, 4-methyl-3-isopropoxyquinolone **90** reacted with maleimide to afford product **92** in 78% yield and with 5/1 dr and 87% ee values. After a series of mechanistic studies, the authors proposed that photocatalyst **93** and quinolone could form a hydrogen-bonded complex to realize stereocontrol. Upon photoexcitation of this complex, energy transfer sensitization of maleimide rather than quinolone is preferred. Then, the sensitized maleimide reacted with the quinolone–photocatalyst complex to afford the enantioenriched cycloadduct.



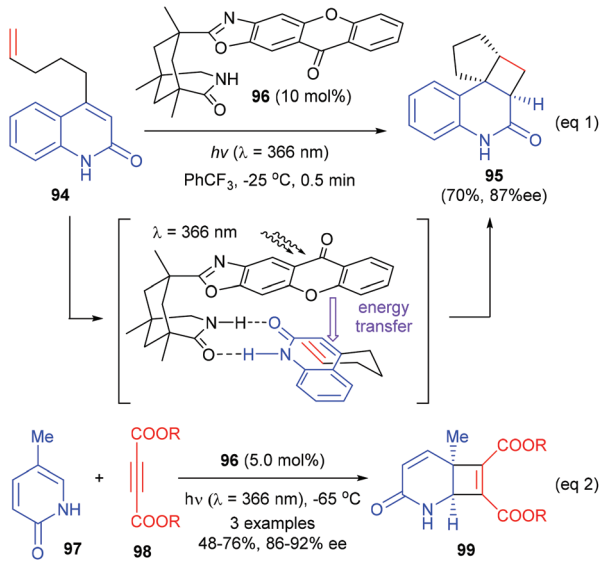
Scheme 24 Chiral-at-metal complex catalyzed intermolecular [2 + 2] photocycloaddition.



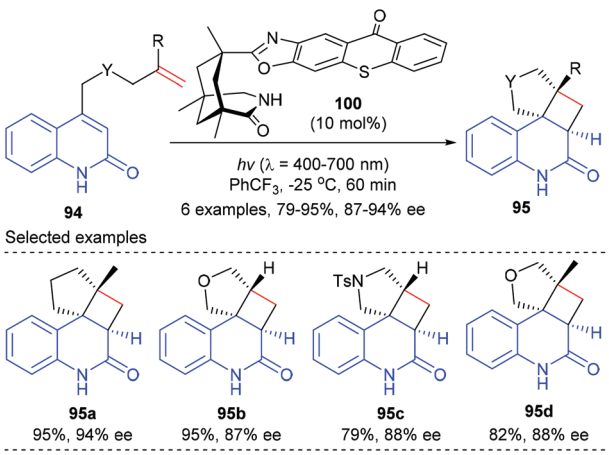
Scheme 25 Asymmetric [2 + 2] photocycloaddition reactions of enones with olefins.



Scheme 26 Intermolecular [2 + 2] cycloaddition of maleimide with 3-alkoxyquinolones.



Scheme 27 [2 + 2]-Photocycloaddition reactions catalyzed by xanthone-based organocatalyst.

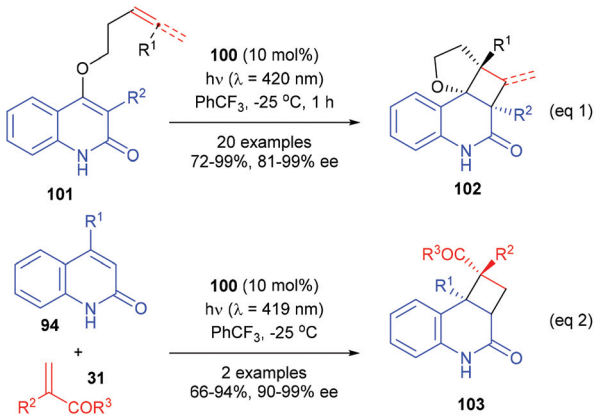


Scheme 28 Chiral thioxanthone catalyzed [2 + 2] photocycloaddition reactions of 4-tethered quinolones.

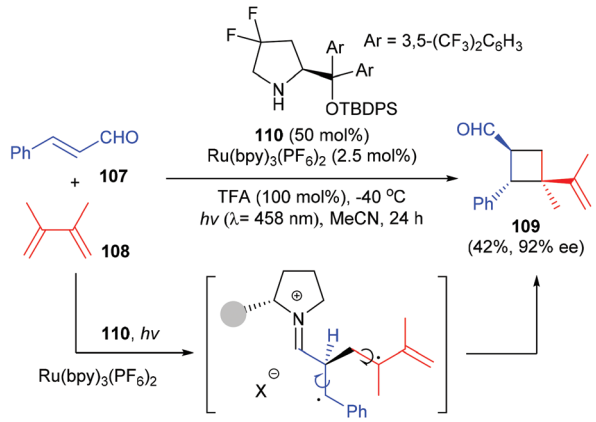
2.4.2. Organocatalytic [2 + 2]-photocycloaddition. Besides using Lewis acid catalysts, the [2 + 2]-photocycloaddition could also be achieved using organocatalysts as the chiral sources. Early in 2011, Bach and co-workers reported the synthesis of a series of organic chiral sensitizers and their application in asymmetric intramolecular [2 + 2] photocycloaddition reactions (Scheme 27).[32] The authors proposed that when quinolone substrate **94** associated with the chiral catalyst, the xanthone moiety could in one hand act as the light-harvesting antenna to transmit energy of the absorbed photon to quinolone and shield the top face of the substrate, so that the tethered alkene moiety could attack the quinolone double bond enantioselectively from the bottom face. On irradiation at λ = 366 nm, **96** could catalyze the intramolecular [2 + 2] reaction of pent-4-enyl quinolone **94** to give the desired product **95** in 70% yield and with 87% ee value (eqn (1)). This catalyst is also effective in catalyzing an intermolecular [2 + 2] photocycloaddition to form enantioenriched quaternary carbon containing cyclobutanes, as is demonstrated by the reaction between 2-pyridones **97** and acetylenedicarboxylates **98**, giving products **99** in 48–76% yields and with 86–92% ee values (eqn (2)).

Based on the above success, the Bach group further synthesized a chiral thioxanthone that is capable of processing visible light for a highly enantioselective photochemical reaction (Scheme 28).[33] With a visible source, thioxanthone **100** (10 mol%) facilitated the intramolecular [2 + 2] reaction of 4-(pent-4-enyl) quinolone **94a** to deliver tetracyclic product **95a** in 95% yield and with 94% ee at −25 °C. The enantioselectivities obtained for the heteroatom analogues **95b**, **95c** and **95d** were slightly lower (87–88%).

In a most recent report, Bach *et al.* have further used the chiral thioxanthone catalyst for intramolecular [2 + 2] photocycloaddition reactions of 3-alkylquinolones with 4-*O*-tethered alkenes and allenes (eqn (1), Scheme 29).[34] These reactions could form up to four defined stereogenic centers, including two quaternary carbon centers, in a single step. The alkyl group in the 3-position of **101** could significantly decrease the triplet energy, and it is therefore crucial for the success of the reaction. The intermolecular [2 + 2] reaction of 2(1*H*)-quinolones **94** with electron-deficient olefins **31** were also possible using **100** as the catalyst, but only two examples of the synthesis of quaternary chiral cyclobutanes were explored (eqn (2)).



Scheme 29 Chiral thioxanthone catalyzed intra- and intermolecular [2 + 2] photocycloaddition reactions.

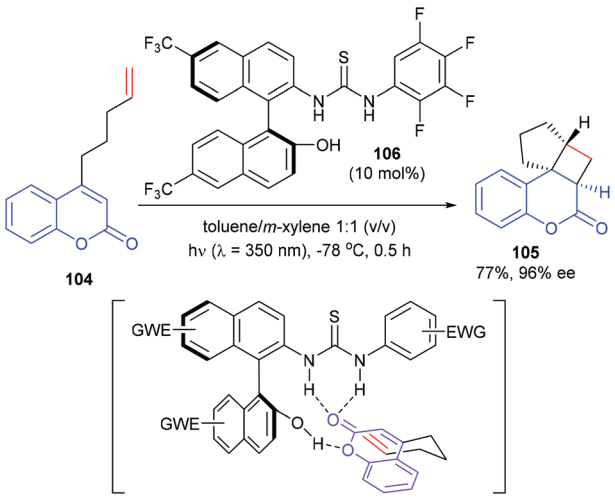


Scheme 31 Intermolecular [2 + 2] photocycloaddition of olefins with α,β-unsaturated aldehydes.

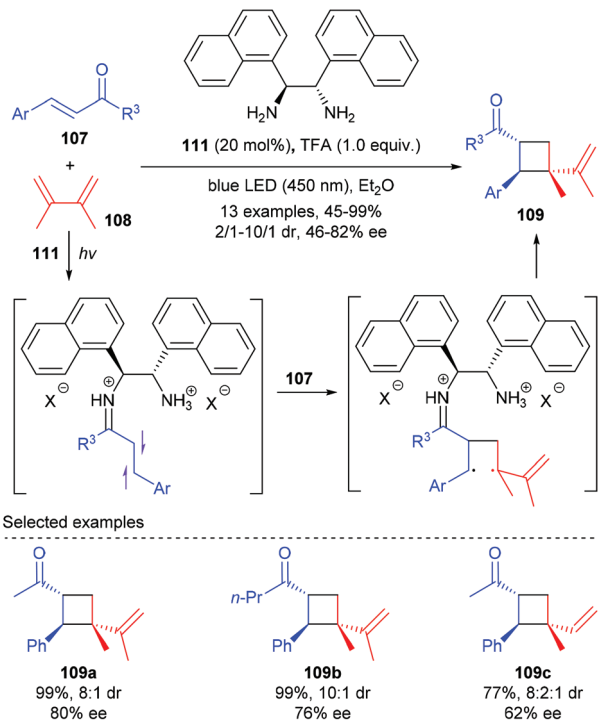
Sivaguru and co-workers reported that a series of chiral binaphthyl-based thiourea derivatives were also efficient organocatalysts for a [2 + 2] photocycloaddition (Scheme 30).[35] Among these newly designed catalysts, **106** was found to be the most promising in terms of both yield and enantioselectivity. In the presence of **106** (10 mol%), the intramolecular [2 + 2] reaction of 4-alkenyl-substituted coumarins **104** could afford product **105** with 77% yield and high enantioselectivity. With the aid of hydrogen bonding, the catalyst and the substrate could form a complex, which could be excited efficiently at λ = 350 nm and react to form the desired photoproduct.

Besides hydrogen bond recognition, the organocatalysts could also mediate a [2 + 2] photocycloaddition by covalent activation. In a very recent work, Bach *et al.* have found that a chiral Proline derived secondary amine catalyst could activate α,β-unsaturated aldehydes to undergo an intermolecular [2 + 2] photocycloaddition with olefins to afford quaternary carbon containing cyclobutane derivative **109** in 42% yield and with 92% ee, upon irradiation with visible light using a ruthenium (2.5 mol%) complex as the photocatalyst (Scheme 31).[36]

Soon after that, Alemán reported a chiral diamine catalyzed enantioselective [2 + 2] photocycloaddition of α,β-unsaturated ketones (Scheme 32).[37] Unlike the above catalytic system, the current reaction does not require the use of any external photocatalyst, and the loading of diamine catalyst **111** could be lowered to 20 mol%. Under blue LED irradiation, together with naphthyl substituted chiral ethane-1,2-diamine **111** as the single catalyst and TFA as an acid promoter, the reaction of enones **107** with 2,3-dimethylbuta-1,3-diene **108** could deliver



Scheme 30 Atropisomeric thiourea derivative catalyzed asymmetric [2 + 2] photocycloaddition.



Scheme 32 Enantioselective aminocatalytic [2 + 2] cycloaddition through visible light excitation.

chiral quaternary carbon containing cyclobutane **109** with good enantiomeric and diastereoisomeric ratios and high yields. The authors proposed that upon condensation with the enone substrate, the diamine catalyst could form an iminium ion intermediate that absorbs in the visible light region. The direct excitation of such an intermediate leads to a charge transfer excited state that unlocks the desired asymmetric [2 + 2] photocycloaddition.

3. Ring-expansion rearrangement

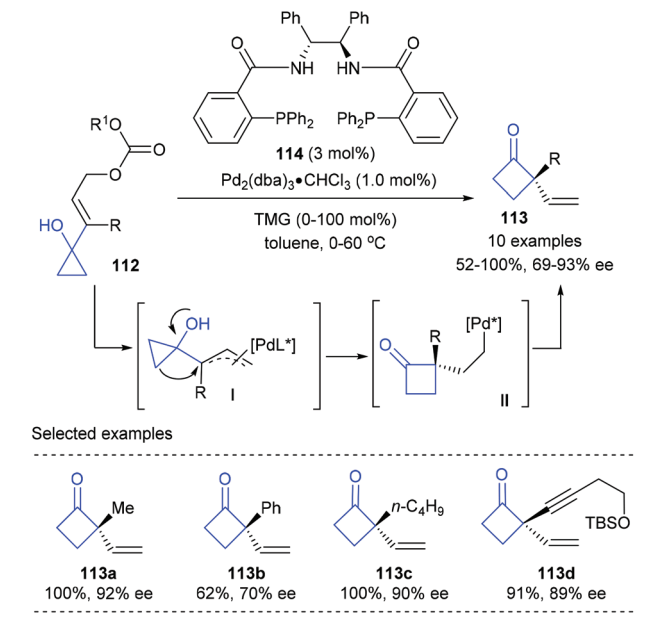
The high ring strain energy associated with the three-membered ring allows cyclopropane derivatives to undergo a variety of synthetically useful ring-expansion reactions to deliver cyclic products that are less strained. For example, the cyclopropylcarbinyl-cyclobutyl rearrangement of cyclopropanols offered efficient methods for the construction of chiral quaternary cyclobutanones.[38]

Early in 2001, Trost and co-workers reported the first catalytic enantioselective Wagner–Meerwein rearrangement of prochiral vinylcyclopropanols for the synthesis of cyclobutanones bearing quaternary carbon centers (Scheme 33).[39] In the presence of only 1 mol% chiral Pd(0) complex derived from Trost ligand **114** as the catalyst, the targeted quaternary vinylcyclobutanones **113** could be obtained in 52–100% yields and with 69–93% ee values. The current reaction was believed to be initiated by the formation of an π–allylpalladium intermediate (**I**) *via* the reaction of the chiral Pd(0) complex with allyl carbonate **112**, which is proposed to be the enantio-discriminating step; then a subsequent 1,2-migration and reductive elimination resulted in the final product.

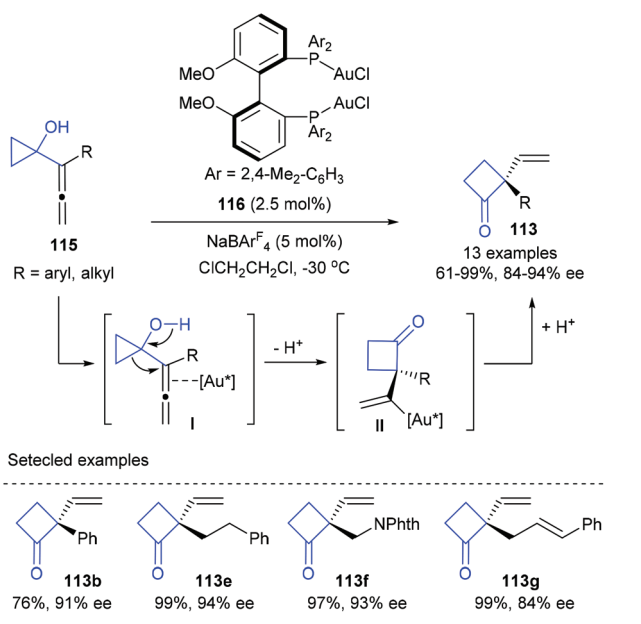
Besides Pd(0) catalysis, cationic Au(I) catalysis has also shown its potential in the desymmetric ring-expansion of prochiral cyclopropanols. In 2009, a enantioselective Wagner–Meerwein rearrangement of 1-allenylcyclopropanols **115** to form cyclobutanones **113** possessing a vinyl-substituted quaternary stereogenic centre in 61–99% yields and with 84–94% ee values was developed by Toste and Kleinbeck, using 2.5 mol% MeO-DM-BIPHEP derived Au(I) complex **116** and 5 mol% $NaBAr^F_4$ as the catalyst (Scheme 34).[40] The cationic gold(I) catalyst was proposed to coordinate with the internal double bond of the allene moiety (**I**) and trigger ring-expansion by a Wagner–Meerwein rearrangement to generate a vinylgold intermediate (**II**), which could then undergo a protodemetalation to deliver the final product **113**. It should be noted that this work was also the first report of enantioselective gold-catalyzed 1,2-alkyl migration reactions.

In addition, such ring-expansion reactions could also be initiated by enantioselective halogenations. The Alexakis group described that the fluorination and iodination initiated ring-expansion reaction of allylic cyclopropanols could be achieved using the chiral-counterion catalysis strategy (Scheme 35).[41] In the presence of 5 mol% chiral phosphoric acid **117** as the chiral source, Na_3PO_4 as base and Selectfluor as the fluorinating reagent, the fluorination/ring-expansion reaction of tetralone based allylic cyclopropanols **119** could give the desired β-fluoro spirocyclobutanones **121** with up to 96% yields, >20/1 dr and 94% ee values (eqn (1)). The chiral phosphoric acid counterion is believed to control the facial selectivity and activate the hydroxyl moiety of the substrate *via* deprotonation.

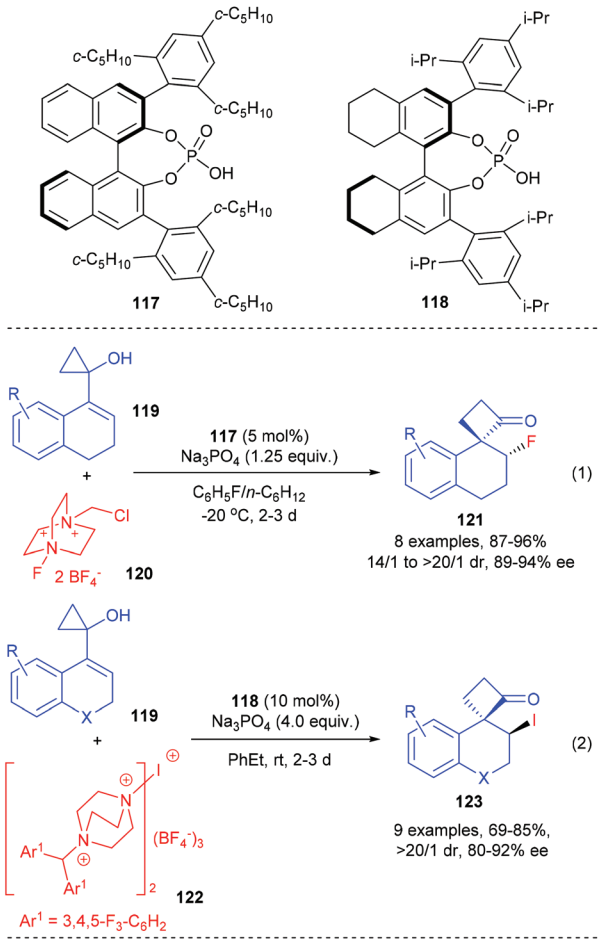
A similar phosphoric acid catalyst **118** was found to be an efficient catalyst for the electrophilic iodination initiated ring-expansion rearrangement of strained allylic cyclopropanols



Scheme 33 First catalytic asymmetric Wagner–Meerwein rearrangement.



Scheme 34 Asymmetric ring expansion of allenylcyclopropanols.

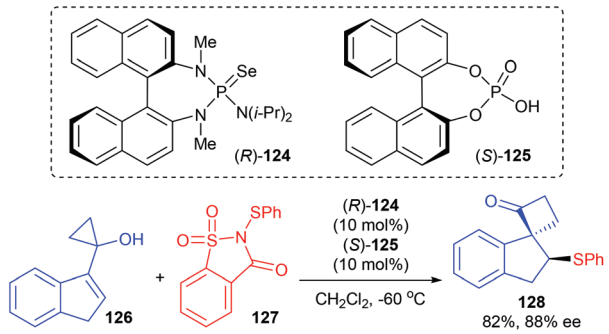


Scheme 35 Halogenation initiated ring-expansion reaction.

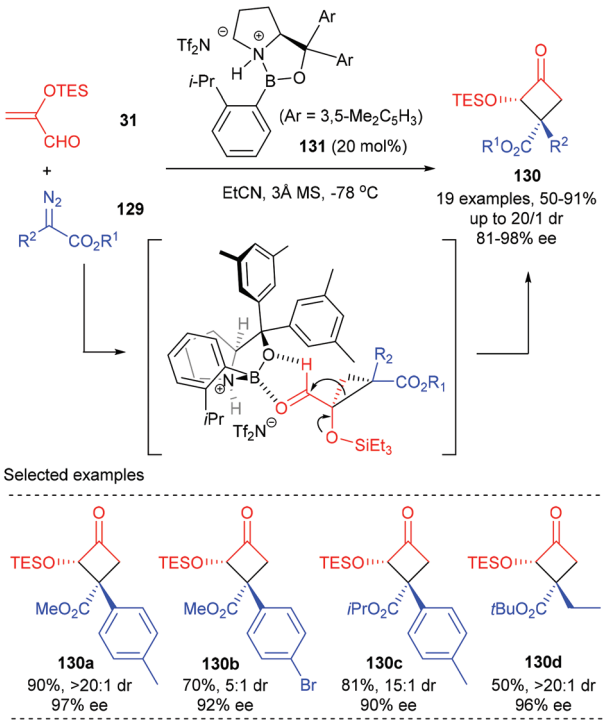
119 to give β-iodo spirocyclobutanones **123** (eqn (2)). After screening a variety of iodinating reagents, a bulky and insoluble cationic iodinating reagent **122** was identified as the optimal choice, with which the desired product **123** could be obtained with up to 92% ee values and 69–85% yields.

As a continuation of efforts in developing an asymmetric semipinacol rearrangement reaction for synthetic application, Tu and co-workers presented a chiral Lewis base **124** and chiral Brønsted acid **125** co-catalyzed asymmetric sulfenylation/semipinacol rearrangement reaction of 1,1-disubstituted and trisubstituted allylic alcohols for the synthesis of β-arylthio ketones. Although they focused their attention mainly on allylic cyclobutanol substrates, a cyclopropanol substrate **126** was also tried and 82% yield and 88% ee were obtained for product **128** (Scheme 36).[42]

Ryu *et al.* achieved the first Lewis acid catalyzed asymmetric cyclopropanation/semipinacol rearrangement tandem process to produce quaternary cyclobutanones (Scheme 37).[43] Under optimized conditions, using the chiral oxazaborolidinium ion **131** as the catalyst, various α-silyloxycyclobutanones **130** possessing a chiral β-quaternary centre were obtained with up to 91% yields and excellent enantio- and diastereoselectivities (up to 98% ee and >20 : 1 dr values). Such a process was proposed to start from asymmetric cyclopropanation between α-silyloxyacrolein **31** and diazoester **129** to form a donor–acceptor cyclopropane intermediate, which was further activated by a Lewis acid catalyst to undergo a concerted 1,2-alkyl shift of C_1 with an electron-withdrawing group, leading to the formation of α-silyloxycyclobutanones **130** after the subsequent silyl group migration.



Scheme 36 Asymmetric sulfenylation/semipinacol rearrangement.



Scheme 37 Tandem cyclopropanation/semipinacol rearrangement.

4. Desymmetrization

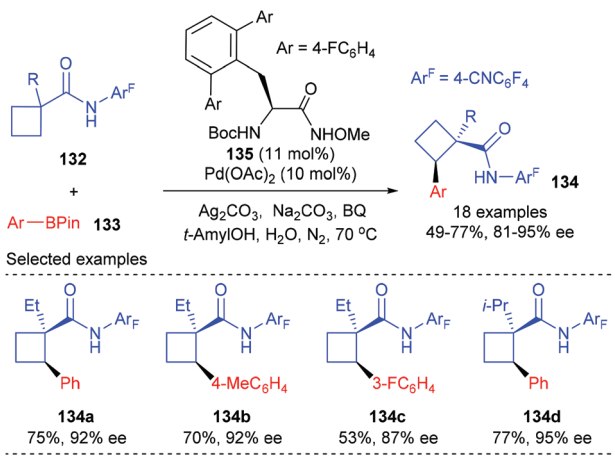
The desymmetrization strategy allows the chiral determining step to proceed at the tethered functionality rather than at the prochiral carbon centre, which could alleviate the unfavourable steric repulsion to some extent during the formation of

quaternary carbon centers. On the other hand, the reaction site is at least one covalent bond away from the existing quaternary carbon, thus making it more difficult to control the stereoselectivity. Therefore, catalytic desymmetrization reactions are highly potential, but also challenging, for the construction of chiral quaternary carbon containing cyclobutanes.[44]

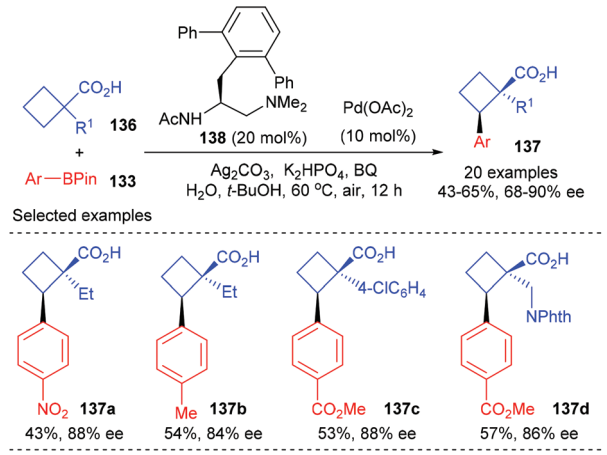
In 2014, Yu and co-workers reported that a Pd(II)-catalyzed desymmetric methylene C(sp^3)–H bond reaction of prochiral cyclobutanecarboxylic acid derivatives with arylboron reagents can provide an alternative approach for the enantioselective synthesis of cyclobutane carboxylates containing α-chiral quaternary stereocenters (Scheme 38).[45] Under the catalysis of 10 mol% Pd(II) complex derived from newly developed chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid **135**, the intermolecular cross-coupling reaction could give the desired optical active cyclobutanecarboxylates **134** in 49–77% yields and with 81–95% ee values.

In a more recent work of the same group, they have described that the above-mentioned desymmetric Pd(II)-catalyzed enantioselective C(sp^3)–H cross-coupling reaction could be extended to simpler free cyclobutanecarboxylic acids (Scheme 39).[46] In the presence of 10 mol% $Pd(OAc)_2$ as the metal catalyst and 20 mol% mono-protected amino ethyl amine **138** as the chiral ligand, prochiral cyclobutanecarboxylic acid could be desymmetrized to afford cyclobutanecarboxylic acids **137** containing quaternary stereocenters in up to 65% yields and with 90% ee values.

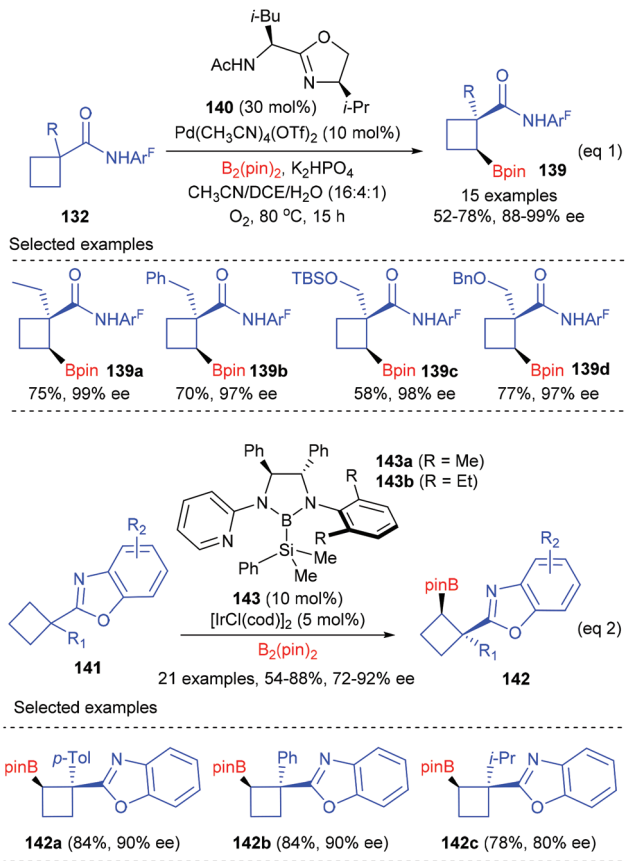
Besides enantioselective C(sp^3)–H bond arylation, the desymmetrization of cyclobutanecarboxylic acid derivatives could also be achieved *via* enantioselective C(sp^3)–H bond borylation reactions (Scheme 40).[47a] After evaluation of a diverse group of newly designed bidentate oxazoline ligands, Yu *et al.* found that the merger of (*S*,*R*)-**140** (30 mol%) and Pd$(CH_3CN)_4(OTf)_2$ (10 mol%) was the best catalyst, which could facilitate the cross-coupling reactions of cyclobutanecarboxylic amides **132** and $B_2(pin)_2$ to give chiral cyclobutanecarboxylate



Scheme 38 Enantioselective C(sp^3)–H activation of prochiral cyclobutanecarboxylic acid derivatives.



Scheme 39 Enantioselective C(sp^3)–H activation of free prochiral cyclobutanecarboxylic acids.



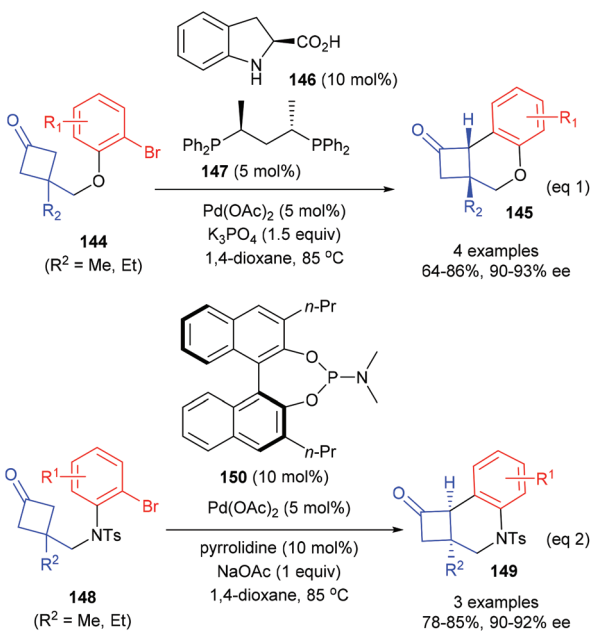
Scheme 40 Desymmetrization of cyclobutanes *via* enantioselective C(sp^3)–H borylation.

products **139** in up to 78% yields and with 88–99% enantioselectivities (eqn (1)). Most recently, Shen and Xu have reported the first benzoxazoline-directed C(sp^3)–H borylation of prochiral cyclobutane to give cyclobutylboronates (eqn (2)).[47b] In the presence of the chiral bidentate boryl

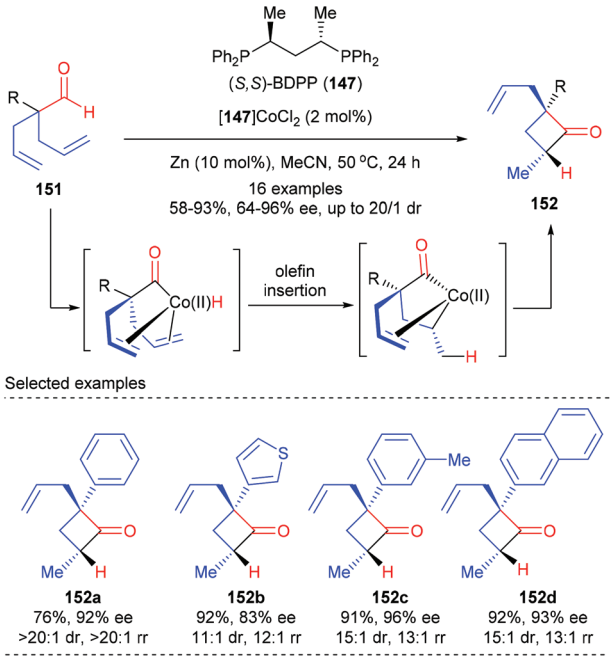
ligand **143** coordinated Iridium complex (10 mol%), a variety of functionalized prochiral cyclobutanes could be enantioselectively desymmetrized to afford products **142** with good to excellent ee values, which are synthetically useful intermediates to provide optically active trisubstituted cyclobutane derivatives.

In 2018, Lu and co-workers described that the catalytic enantioselective desymmetrization of cyclobutanones is also an effective route for the synthesis of quaternary carbon containing cyclobutanes (Scheme 41).[48] Two different enantioselective control strategies were developed according to the types of substrates. As for the reaction of cyclobutanone substrates bearing *O*-tethered aryl bromides **144**, the merger of (*S*)-indoline-2-carboxylic acid **146** (10 mol%) as the enamine catalyst and (*S*,*S*)-BDPP **147** derived Pd(II) complex (5 mol%) could enable the intramolecular arylation reaction to afford chiral cyclobutanones **145** in 64–86% yields and with 90–93% ee values (eqn (1)), whereas the reaction of substrates bearing *N*-tethered aryl bromides **144** only requires a chiral phosphoramidite ligand **150** as the chiral source and the targeted products **149** could be obtained with 78–85% yields and up to 92% ee values (eqn (2)).

Besides prochiral 4-membered ring substrates, Dong and co-workers have recently reported an alternative cobalt catalyzed intramolecular hydroacylation of acyclic α-aryl dienyl aldehydes to prepare chiral cyclobutanones (Scheme 42).[49] In the presence of the (*S*,*S*)-BDPP **147** derived Co(II) complex as the optimal catalyst, together with 10 mol% zinc as the reducing agent, a variety of α-aryl dienyl aldehydes **151** underwent intramolecular hydroacylation to afford cyclobutanones **152** as the major product with excellent regio-, diastereo-, and



Scheme 41 Enantioselective desymmetrization of cyclobutanones bearing a tethered aryl bromide.



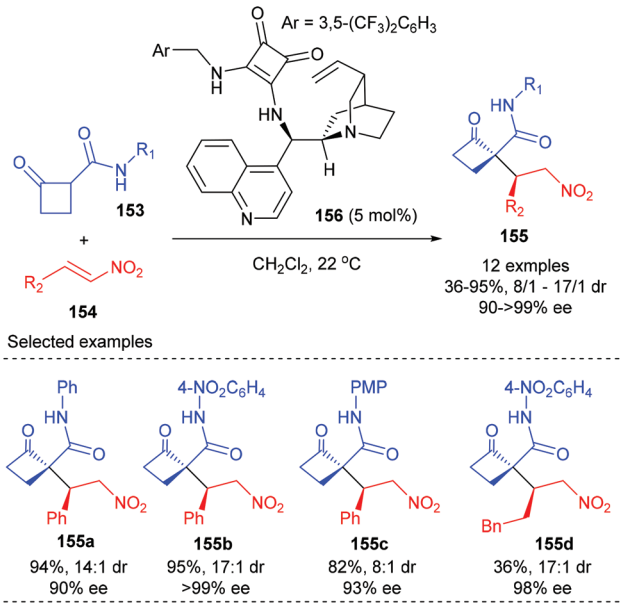
Scheme 42 Cobalt catalyzed intramolecular hydroacylation of prochiral α-aryl dienyl aldehydes.

enantiocontrol. The authors proposed that this cyclization was initiated by oxidative addition of Co(0) to the aldehyde C–H bond to form an acyl-Co-hydride intermediate, which underwent subsequent olefin insertion and reductive elimination to construct the strained ring.

5. Asymmetric alkylation and miscellaneous

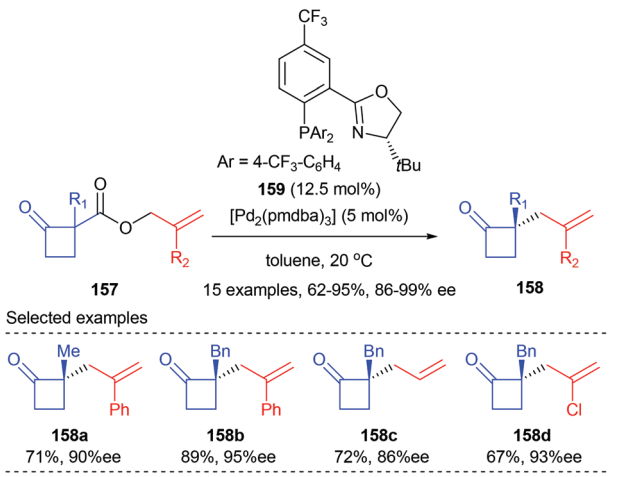
Asymmetric alkylation of *in situ* generated enolates is one of the most important synthetic routes to α-quaternary carbonyl compounds and has become a fundamental transformation in organic synthesis. As expected, this strategy has also found its application in the synthesis of enantiomerically enriched cyclobutanes bearing quaternary carbon centers.

In 2012, Rodriguez and co-workers reported efficient and stereoselective Michael addition reactions of 2-substituted cyclobutanones with nitroalkenes for the construction of densely functionalized cyclobutanones, which are versatile building blocks for further elaboration (Scheme 43).[50] Under the catalysis of 5 mol% squaramide-containing organocatalyst **156**, the addition of various cyclobutanones **153** to 2-phenyl nitroalkenes **154** could deliver products **155** in good to excellent yields and with >90% ee values. The reaction of 2-alkyl-substituted nitroolefin also gave product **155d** with excellent ee value, but with poor yield. It should be mentioned that this work represents the first enantioselective route to cyclobutanones displaying a chiral quaternary carbon center adjacent to an additional controlled stereocenter.



Scheme 43 Enantioselective Michael addition of cyclobutanones to nitroalkenes.

Later in 2013, the Stoltz group demonstrated that the asymmetric alkylation of cyclobutenolates could also be achieved by transition metal catalysis. In the presence of 12.5 mol% PHOX ligand **159** and 5 mol% [Pd_2(pmdba)$_3$], allyl cyclobutanecarboxylate **157** could undergo asymmetric decarboxylative allylic alkylation reactions to give the corresponding chiral cyclobutanone products **158** with up to 92% yields and 86–99% ee values (Scheme 44).[51] A wide range of substituents are tolerated at both the α-keto and 2-allyl positions. The synthetic utility of the resultant chiral cyclobutanones was demonstrated by transforming into a variety of enantioenriched derivative compounds, such as dialkyl γ-lactams, dialkyl γ-lactones, and α-quaternary cyclopentanones.

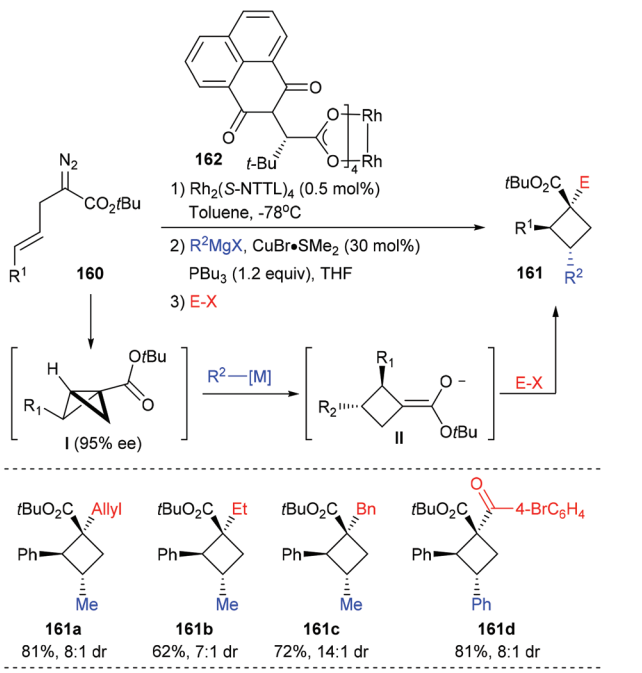


Scheme 44 Catalytic asymmetric allylic alkylation of cyclobutanones.

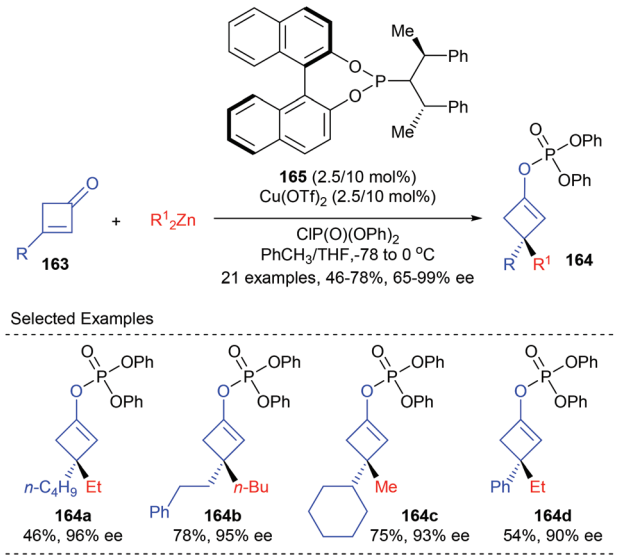
In the same year, Fox *et al.* reported the construction of chiral quaternary carbon containing cyclobutanes *via* a 3-component, 2-catalyst, single-flask process (Scheme 45).[52] Using 0.5 mol% Rh_2(*S*-NTTL)$_4$ as the catalyst, (*E*)-2-diazo-5-arylpent-4-enoates **160** first underwent an intramolecular cyclopropanation to afford an enantiomerically enriched bicyclobutane intermediate **I**, which could then undergo a Cu-catalyzed homo conjugate addition to give exocyclic enolate **II**. The desired cyclobutanes **161** could be obtained in up to 81% yields after the addition of electrophiles. This process has high potential as many versatile chiral cyclobutanes could be obtained by altering any of the reaction components.

As a part of their ongoing effort to construct enantioenriched cyclobutanes, Lu and co-workers envisioned that the 1,4-addition/trapping reaction of 3-substituted cyclobutenones may offer a direct route to 3,3-disubstituted cyclobutene derivatives (Scheme 46).[53] It was found that using the phosphoramidite ligand **165** coordinated Cu(II) complex as the catalyst, dialkyl zinc could react with 3-substituted cyclobutenones **163** to give a chiral metal enol intermediate, which was then *in situ* trapped by diphenyl chlorophosphate to furnish chiral 3,3-disubstituted cyclobutene derivatives **164** in 46–78% yields and with 65–99% ee values.

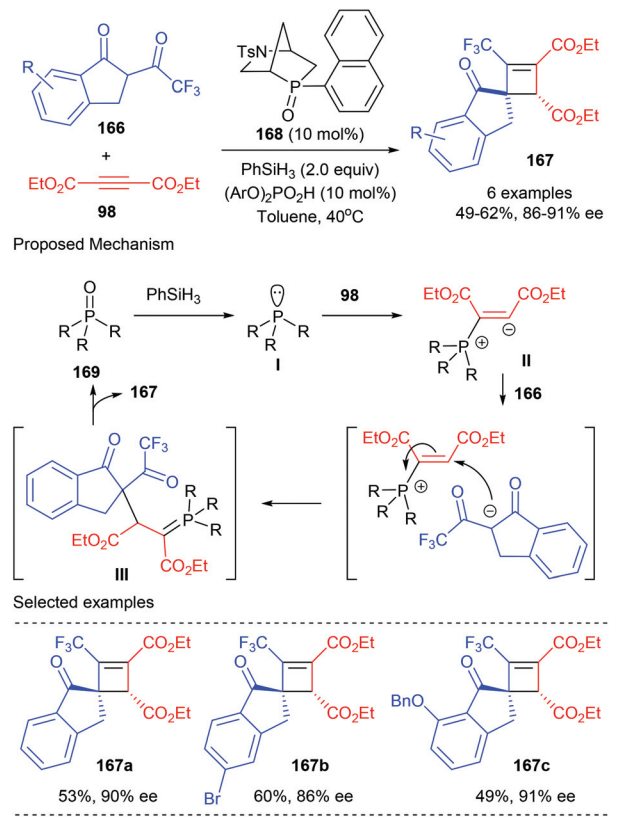
In 2019, the Voituriez group developed the first catalytic asymmetric Michael addition/Wittig reaction to synthesize highly functionalized CF_3-substituted spirocyclobutene **167** bearing two contiguous stereogenic centers (Scheme 47).[54] This process started from the reduction of the phosphine oxide catalyst **168** to afford chiral phosphine **I**, which could then add to dialkyl acetylene dicarboxylate **98** to form the



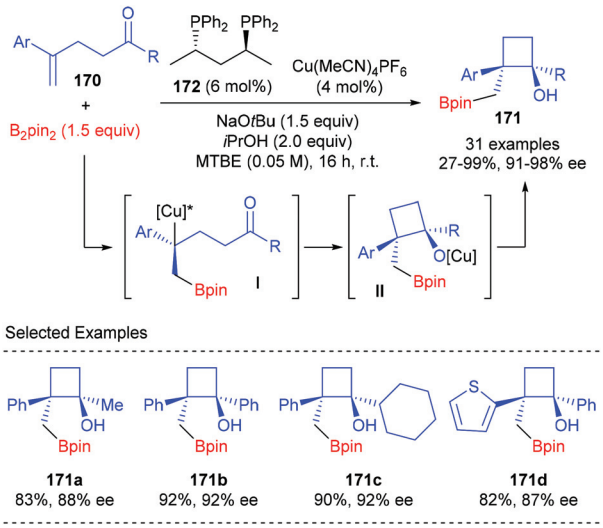
Scheme 45 Synthesis of enantiomerically enriched cyclobutanes by a three-component process.



Scheme 46 Enantioselective 1,4-addition/trapping reaction of 3-substituted cyclobutenones.



Scheme 47 Michael addition/Wittig olefination reaction of CF_3-substituted spirocyclobutene.



Scheme 48 Asymmetric synthesis of functionalized cyclobutanols *via* borylcupration.

zwitterionic species **II**. Intermolecular proton transfer that occurred between **II** and CF_3-dihydro-1*H*-indenone **166** and the subsequent addition reaction could form *in situ* ylide intermediate **III**. After an intramolecular Wittig olefination reaction, the desired chiral cyclobutene product **167** could be obtained with the regeneration of the catalyst. In the presence of bicyclic chiral phosphine oxides HypPhos **168** (20 mol%), developed by Ohyun Kwon,[55] together with phenyl silane as the reducing agent, good isolated yields and up to 91% ee values could be obtained for products **167**. Different substituents in different positions of the indenone backbone were well tolerated.

Lautens *et al.* described a chiral Cu(I) complex catalyzed asymmetric approach to construct boryl-functionalized monocyclic cyclobutanols using 1,1-disubstituted styrenes tethered with a ketone moiety (Scheme 48).[56] The reaction was believed to start with the enantioselective borylcupration of 1,1-disubstituted styrenes **170** to generate a chiral benzylic copper intermediate **I**, which underwent an intramolecular addition with the tethered ketone to form quaternary monocyclic cyclobutanols. In the presence of the (*S*,*S*)-BDPP derived Cu(I) complex (4 mol%) as the transition metal catalyst, sodium *tert*-butoxide as the Lewis base promoter, and isopropanol as an additive, this sequence could afford products **171** in 27–99% yields and with 91–98% ee values.

6. Conclusions and perspectives

Due to the wide existence of enantiomerically active quaternary carbon containing cyclobutane moieties in natural products and bioactive compounds, substantial efforts have been made to develop highly efficient and enantioselective catalytic asymmetric strategies to construct these useful structures. Up to now, four major synthetic routes, including [2 + 2] cycloaddition, ring-expansion, desymmetrization and asymmetric alkylation, have been developed and the asymmetric [2 + 2] cycloaddition reaction is the most widely utilized route. Despite the impressive progress, a number of problems remain to be overcome.

Firstly, catalytic systems that could facilitate a highly enantioselective [2 + 2] cycloaddition between two acyclic alkenes to construct monocyclic cyclobutanes are still rare and the scope of the reported methodologies are relatively limited. Secondly, desymmetrization and ring expansion have emerged as highly potential strategies to obtain chiral quaternary carbon containing cyclobutanes, but the types of substrates used in these reactions are still very limited. In addition, the number of applications of these reactions remains limited compared with the numerous catalytic systems that have already been developed. Therefore, the development of new synthetic strategies to enable the highly enantioselective construction of structurally-unique quaternary carbon containing cyclobutanes and identification of new types of substrates of known strategies are required and these would undoubtedly benefit the total synthesis of related natural products and the development of new drugs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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