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Enantioselective Synthesis of Cyclopropenes

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1.1 Introduction

Cyclopropene is the smallest unsaturated cyclic hydrocarbon. Its preparation is relatively tricky because it is an unstable compound that has a high ring strain. This strain energy of cyclopropene (228 kJ mol^{-1}) is basically double of the one of cyclopropane (115 kJ mol^{-1}), mainly because of the high angular strain present in the former [1, 2]. However, cyclopropenes containing one or two substituents on the aliphatic position are relatively stable and easily accessible compounds.

1.1.1 Synthesis of Cyclopropenes

The synthesis of the first cyclopropene was carried out by Demyanov and Doyarenko in 1922 via the thermal decomposition at high temperature (320°C) of trimethylcyclopropylammonium hydroxide under a carbon dioxide atmosphere. After the Hofmann elimination step, cyclopropene was obtained with low yield [3, 4]. An improved procedure was reported starting from allyl chloride and sodium bis(trimethylsilyl)amide that allowed to isolate cyclopropene in a better yield (40%) than in the previously published procedure [5]. An enantioenriched cyclopropene was prepared for the first time by Breslow and Douek via a resolution using cinchonine [6].

Cyclopropenes possessing various substitutions can be prepared: (i) by [2+1] cycloaddition between an alkyne and a free carbene or a metal carbene, most often resulting from the decomposition of diazo compounds; by cycle contraction, by retro-Diels–Alder reaction; from the nucleophilic attack on a previously synthesized cyclopropene; by isomerization; by rearrangement initiated by photochemistry; and finally, via elimination reactions induced by strong bases [7].

Diazo compounds have also been used in the development of asymmetric versions of cyclopropanations of alkynes. The various catalytic asymmetric methods are reviewed in this chapter.

1.1.2 Reactivity of Cyclopropenes

Cyclopropenes can be involved in a large variety of chemical transformations, whose driving force is the release of the ring strain. A few reviews highlighting the synthetic potential of cyclopropenes have been published [8–14].

The reactivity of cyclopropenes has been illustrated in various synthetically useful transformations. Releasing the strain energy enables cyclopropenes to undergo reactions that would be more challenging in other alkenes, e.g. hydrofunctionalization and cycloaddition reactions.

The catalytic stereoselective functionalization of cyclopropenes has been reported throughout various synthetic transformations (Scheme 1.1), i.e. carbocupration [15], carbozincation [16, 17], carbomagnesiation [18], Fe- [19] and Pd-catalyzed carbozincation [20], hydroboration [21], hydroformylation [22], hydroacylation [23], hydroalkylation [24], hydroalkynylation [25], and hydrosilylation [26, 27]. Also, chiral cyclopropylamines have been obtained via highly enantioselective Cu-catalyzed three-component cyclopropene alkenylamination [28]. Using these methods, a large diversity of enantioenriched cyclopropanes can be accessed. Getting high selectivities, i.e. ring-retention vs. ring-opening processes, is often a challenge. In this regard, Dong and coworkers elegantly demonstrated that the choice of a bisphosphine ligand could orient the hydrothiolation of cyclopropenes toward the formation of cyclopropyl sulfides or allylic sulfides [29]. The Pd-catalyzed selective alkynylallylation of the C—C σ bond of tetrasubstituted cyclopropenes has also been disclosed [30].

Cyclopropenes undergo a ring-opening process to generate rhodium carbenes due to the ring strain. This approach has been used in various synthetic transformations, e.g. the synthesis of dicarbonyl-functionalized 1,3-dienes by the reaction of enamines with cyclopropenes in the presence of a rhodium catalyst [31].

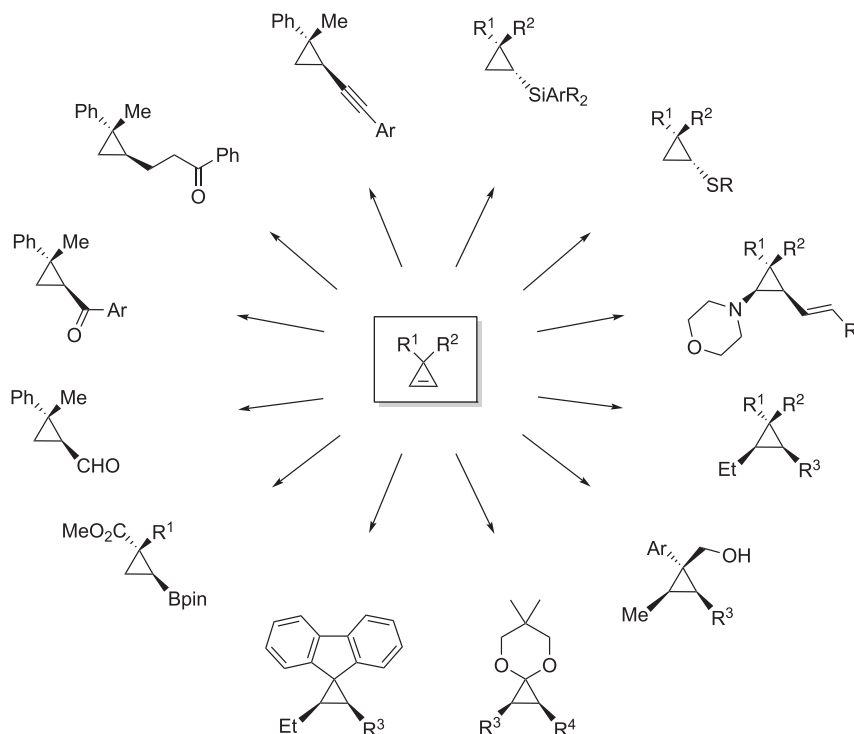
Cyclopropenes have been used in copper-catalyzed [3+2] cycloaddition reactions as dipolarophiles [32]. Donor–acceptor cyclopropenes have been used in [4+3]-cycloaddition reactions with benzopyrylium salts [33], and in Favorskii-type ring opening [34].

Cyclopropenes have also been used in radical chemistry. Waser has reported the radical azidation of cyclopropenes leading to alkenyl nitriles and polycyclic aromatic compounds [35]. A visible-light-promoted addition of α -bromoacetophenones onto the cyclopropene π -system in the presence of the *fac*-Ir(ppy)₃ has been described by Landais and coworkers [36].

The synthesis of difluoro- and trifluoromethylated derivatives of cyclopropenes has been disclosed using diazo compounds [37–39]. Continuous-flow methods have been reported for the difluorocyclopropenation of alkynes using trimethylsilyl trifluoromethane (TMSCF₃) [40] and for the photochemical cyclopropenation of alkynes using trifluoromethyl diazirines [41].

Cyclopropenes have appeared to be key intermediates in various total syntheses. The intramolecular Pauson–Khand reaction of a cyclopropene with an alkyne has been used in the synthesis of (–)-pentalene and (–)-spirochensilide A [42, 43].

The polymerization of cyclopropenes, in particular the well-developed ring-opening metathesis polymerization, takes advantage of their high strain



Scheme 1.1 Catalytic stereoselective functionalization of cyclopropenes.

energy [44]. Recent uses of cyclopropene units have recently emerged in the study of biological systems. Cyclopropenes can react quickly in tetrazine and photoclick ligation reactions [43].

1.2 Metal-Catalyzed Enantioselective Syntheses of Cyclopropenes

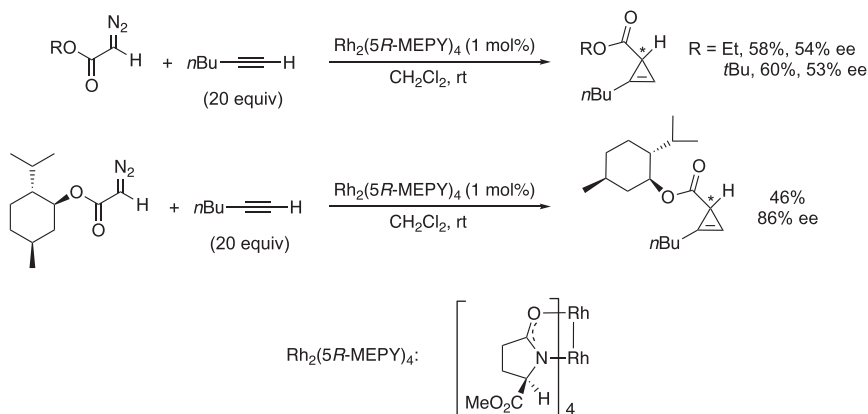
The [2+1] cycloaddition between an alkyne and a metal carbene is the main enantioselective approach to prepare cyclopropenes. The metal carbene usually results from the decomposition of a diazo compound using a chiral metal catalyst.

A practical non-enantioselective method was first published by Teyssié and coworkers using a Rh-catalyzed [2+1] cycloaddition of methyl diazoacetate with alkynes [45].

1.2.1 Rhodium Catalysis

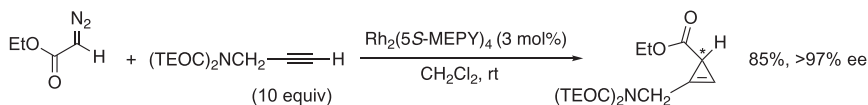
Asymmetric versions of these transformations came out with pioneering work of Doyle and coworkers and Müller with the use of chiral complexes based on rhodium [46–61]. Doyle and coworkers focused their work on the cyclopropenation

of terminal alkylated alkynes with the use of chiral dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*R*)-carboxylate] $\text{Rh}_2(5R\text{-MEPY})_4$. This method was applied to various diazoacetates and was even extended to chiral diazo possessing auxiliaries derived from menthol (Scheme 1.2) [46, 47]. Using a significant excess of alkyne (20 equiv), cyclopropenes were obtained in high enantioselectivities.



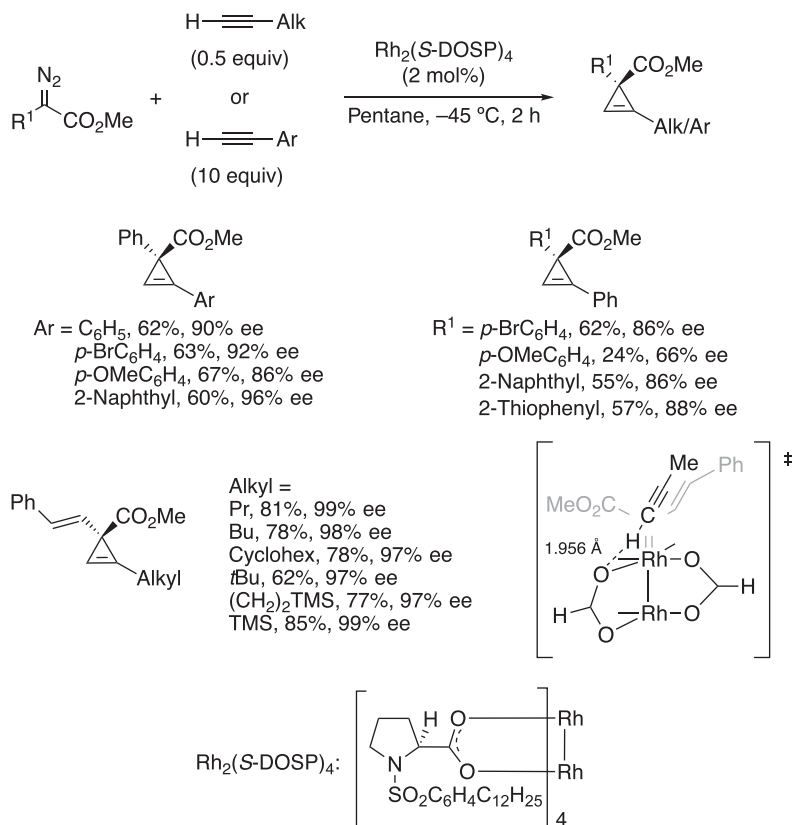
Scheme 1.2 Asymmetric cyclopropenation of terminal alkynes with $\text{Rh}_2(5R\text{-MEPY})_4$ catalyst.

Müller used $\text{Rh}_2(5R\text{-MEPY})_4$ for the cyclopropenation of propargylamines bearing two carboxyl or sulfonyl protecting groups using ethyl diazoacetate [48, 49]. The cycloaddition reaction proceeds smoothly at room temperature in CH_2Cl_2 with a slow addition of the diazo compounds via a syringe pump to 10 equiv of the alkyne. This method employing 3–7% of rhodium affords high yields and excellent enantioselectivities in the range of 90–97% ee (Scheme 1.3). Further derivatizations via selective deprotection of the TEOC derivatives (*N,N*-di-(2-trimethylsilyl ethoxycarbonyl)) could be illustrated by the synthesis of γ -aminobutyric acid (GABA) analogues containing the cyclopropene ring.



Scheme 1.3 Asymmetric cyclopropenation of terminal alkynes with $\text{Rh}_2(5S\text{-MEPY})_4$.

These transformations were initially conducted with diazoesters, i.e. ethyl diazoacetate. As shown in Scheme 1.4, Davies' work with dirhodium tetrakis (*S*)-*N*-(dodecylbenzenesulfonyl) proline $\text{Rh}_2(\text{S-DOSP})_4$ demonstrated that the catalyst was efficient for this transformation to get high enantioselectivities of the cyclopropenes via the asymmetric cyclopropenation of terminal alkynes using aryl or vinyl diazoacetates [62, 63]. A large excess of aromatic alkynes is used vs. the aliphatic ones, showing an improved reactivity of the latter. Computational studies



Scheme 1.4 Asymmetric cyclopropanation of terminal alkynes with $\text{Rh}_2(\text{S-DOSP})_4$.

demonstrated that the chiral induction of the process is governed by the specific orientation of the alkyne as it approaches the metal carbene. Specific orientation occurs due to the presence of a binding interaction between the alkyne hydrogen and the carboxylate ligand on the dirhodium catalyst.

A closely related observation was made by Hashimoto and coworkers with dirhodium carboxylate catalyst $[\text{Rh}_2(\text{S-tbptl})_4]$ emerging as a catalyst of choice for enantioselective cyclopropanation reactions of terminal alkynes with various alkyl-diazoacetates, in which high levels of asymmetric induction (up to 99% ee) as well as high chemoselectivities have been achieved [64]. In addition to the binding interaction between the alkyne hydrogen and the carboxylate ligand, the alkene formation through a 1,2-hydride shift was highlighted.

Corey and coworkers developed a new chiral rhodium catalyst $\text{Rh}_2(\text{OAc})_x(\text{DPTI})_y$ (DPTI: diphenyltriflylimidazolidinone) capable of affording excellent yields and enantioselectivities of various C1- and C3-substituted cyclopropenes [50–53]. This route involved mild reaction conditions with the use of 0.05–0.5 mol% of catalyst (Scheme 1.5). A rationale for understanding the chirality induction was provided with the help of X-ray structural data. A mechanistic model in which one of the

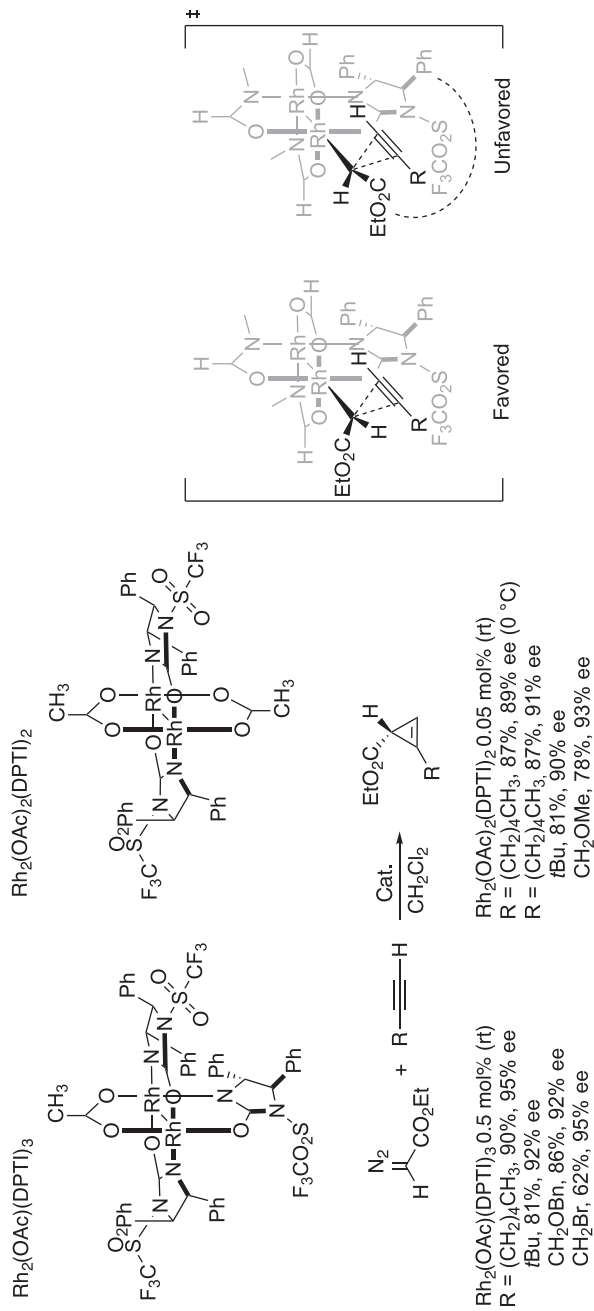
ligand bridges is broken in the intermediate Rh–carbene complex was disclosed. The synthetic results led to conclusions regarding kinetically and thermodynamically favored pathways for the synthesis of mixed acetate–DPTI complexes. Experimental ^{13}C KIEs were investigated by Singleton and compared to calculated ones to establish the mechanism of the cyclopropanation reaction [65]. The plane geometry of the carbenoid carbon is oriented perpendicular to donating proximal Rh–N bonds. The alkyne approach *anti* to the Rh–N bond remains unobstructed. The chirality is determined by the orientation of the carboalkoxy group on the carbenoid which is affected by the proximal phenyl group from the DPTI ligand.

The use of mixed ligands on paddlewheel complexes was also tackled by Fox and coworkers. They showed that this route offers a versatile handle for diversifying catalyst structure and reactivity for cyclopropanation of terminal alkynes and cyclopropanation reactions [66].

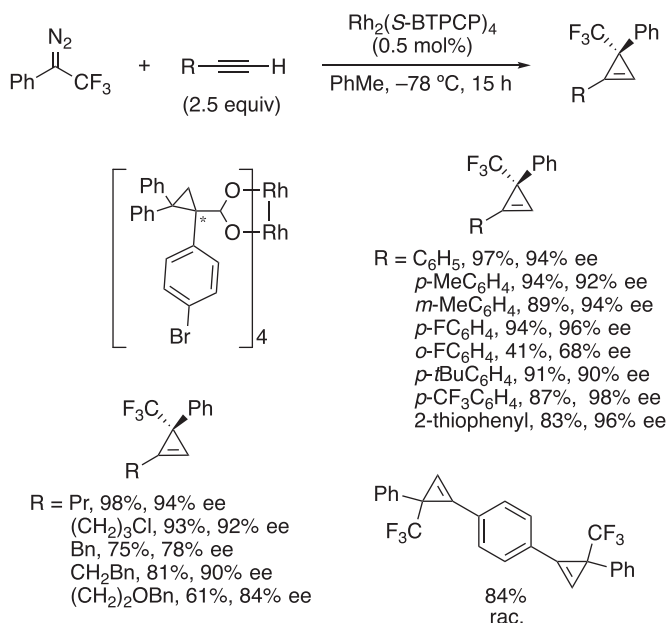
In the same category of donor–acceptor diazo compounds, Koenigs' work with the use of trifluoromethyl diazo compounds further demonstrates the potential of a rhodium chiral catalyst for the enantioselective synthesis of cyclopropenes [38]. Up to 97% yield with 98% ee of trifluoromethylcyclopropenes using aliphatic terminal alkynes but also aromatic alkynes have been obtained (Scheme 1.6). The method was also tested on oligo-alkynes, thus making it possible to generate a subclass of rare racemic oligo-cyclopropenes with excellent yields.

Charette and coworkers developed a simple and highly stereoselective method of cyclopropanation of alkynes catalyzed by rhodium(II) with diacceptor-type diazo compounds [67]. This route represents a very efficient method to access cyano-phosphonate cyclopropenes with high yields and enantioselectivities (Scheme 1.7). Mild conditions and a normal addition of diazo compounds by avoiding the use of a syringe pump afforded excellent results with an easy and practical protocol. Given the reactivity of the cyano-carbene intermediates generated *in situ*, the scope of the substrates was also extended to the use of substituted allenes. This study highlighted the first enantioselective method for the synthesis of cyclopropane alkylidene diacceptors. Scheme 1.6 illustrates the results obtained for the cyclopropanation of alkynes.

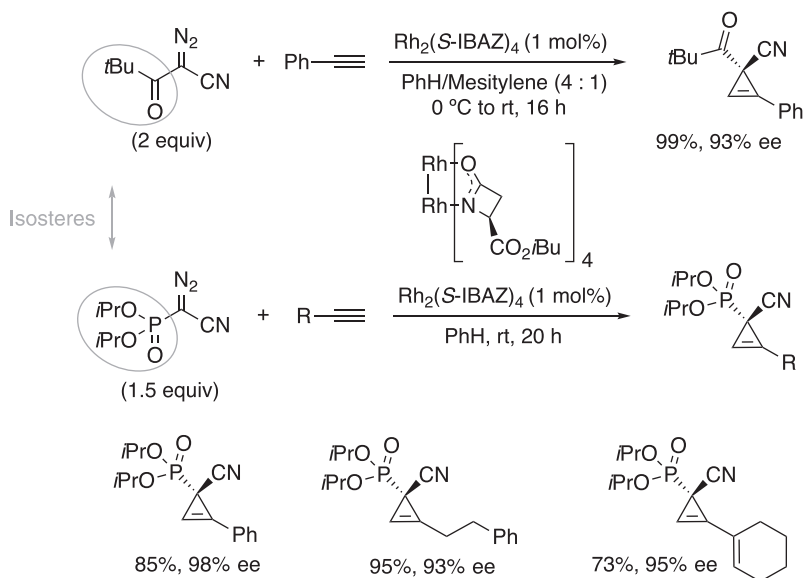
Early work to incorporate a fluorine motif on the chiral cyclopropene unit was reported by Marek and coworkers (Scheme 1.8) [37]. This motif is incorporated through the use of difluorodiazethane, obtained via diazotization of the corresponding amine. This study offers a wide range of enantioenriched difluoromethylated cyclopropenes (40 examples, up to 99% yield, 97% ee) within a short reaction time. Disubstituted alkynes have been mainly employed with an excess of the difluorinated diazo compound. Indeed, the use of terminal alkyne did not give them satisfactory results (no enantioselectivity obtained or no conversion). This cyclopropanation reaction is carried out at low temperature with a reaction time of 40 minutes allowing for total conversions. The synthetic utility of the difluorinated cyclopropenes obtained was demonstrated with subsequent applications, such as cross-coupling reactions, hydrogenation, Diels–Alder cyclization, and Pauson–Khand reaction.



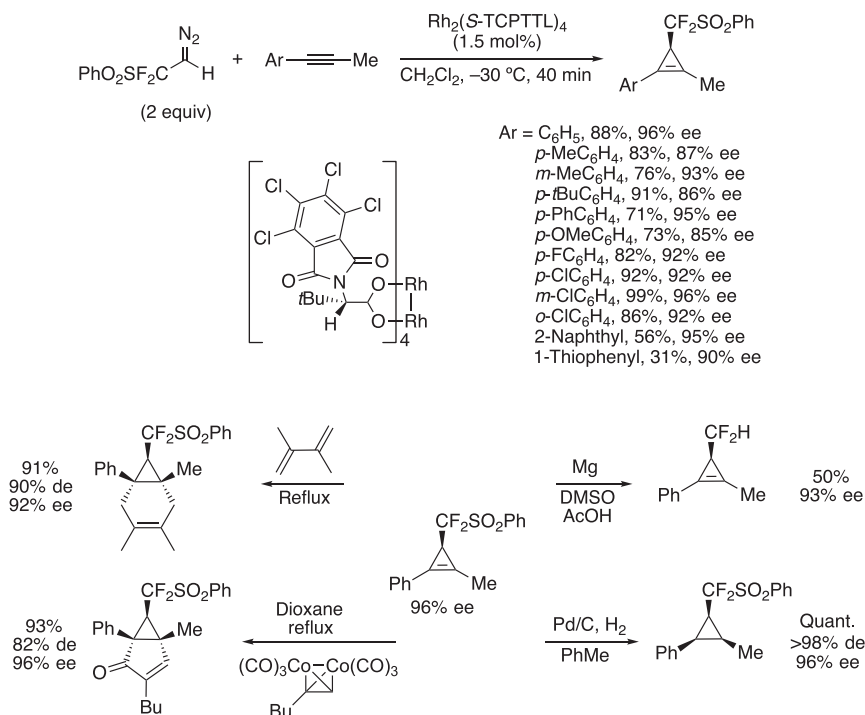
Scheme 1.5 Enantioselective [2+1]-cycloaddition reactions of ethyl diazoacetate and terminal acetylenes using mixed-ligand Rh(II) complexes.



Scheme 1.6 Asymmetric cyclopropenation of terminal alkynes using $\text{Rh}_2(\text{S-BTPCP})_4$.



Scheme 1.7 $\text{Rh}_2(\text{S-IBAZ})_4$ -catalyzed cyclopropenation of terminal alkynes with diaceptor diazo compounds.



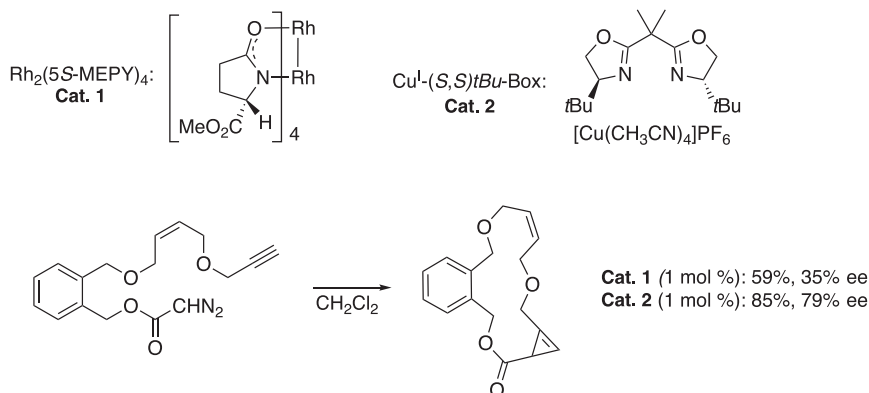
Scheme 1.8 First enantioselective synthesis of fluorinated cyclopropenes and their applications. Source: Zhang et al. [37]/John Wiley & Sons.

1.2.2 Copper Catalysis

Unlike rhodium catalysis, copper catalysis is underused. Indeed, only one example in the literature illustrates this cyclopropanation of alkynes with diazo compounds (Scheme 1.9) [56, 68]. Two intramolecular cyclopropanations allowing the formation of macrocycles were carried out using Cu^I and bis-oxazoline as chiral ligand. Poor results compared to rhodium were generally observed except for the synthesis of a macrocycle where a yield of 85% and 79% ee was obtained.

1.2.3 Iridium Catalysis

Katsuki and coworkers developed a synthesis of a chiral iridium (Ir(salen)) complex suitable to efficiently catalyze the cyclopropanation reaction of alkynes with two families of diazo compounds [69]. This cyclopropanation method can be carried out using donor–acceptor-type diazo compounds, but also using acceptor–acceptor-type diazo compounds (Scheme 1.10). The latter are less reactive toward metal-catalyzed decomposition. However, once decomposition by a metal takes place, the resulting metal carbenes are highly electrophilic and their reactions are less selective. This is why, in order to counterbalance this reactivity, a large excess of alkyne was used. The reactions provided highly enantioenriched cyclopropenes in excellent yields. Alkylated alkynes and terminal aryls were employed to show the selectivity of



Scheme 1.9 Macrocyclization via cyclopropanation of alkynes using copper catalysis.

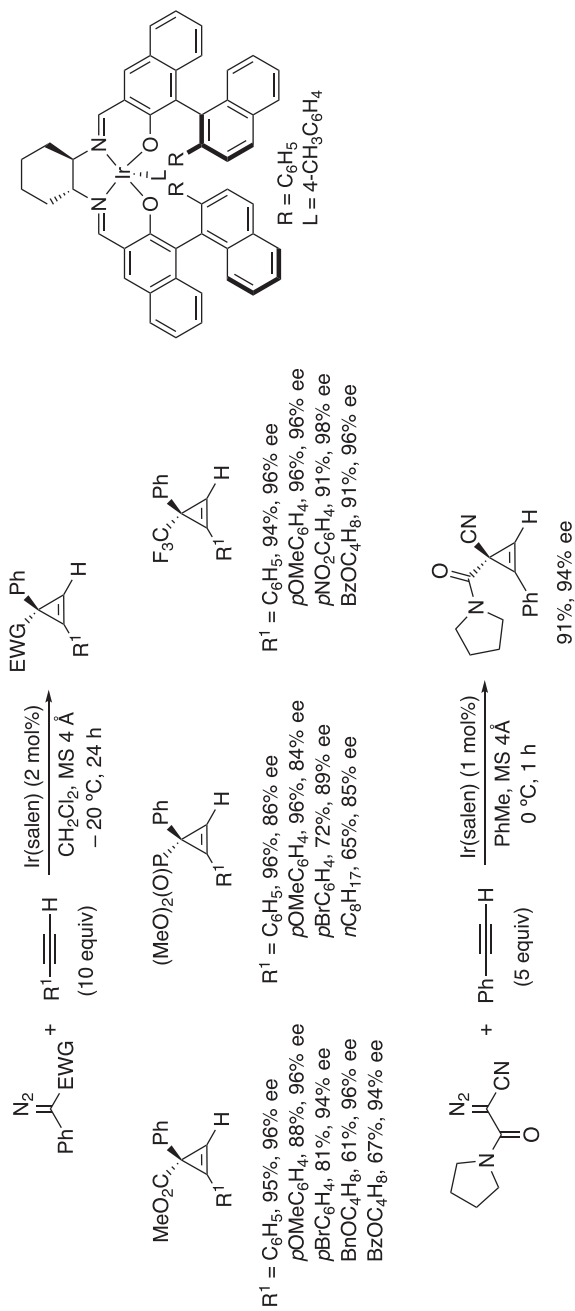
this transformation into a cyclopropene. In general, the yields are higher for the cyclopropanation of arylated alkynes than for alkylated ones. Moreover, the levels of enantioselectivities remain unchanged between the various families of alkynes, being more dependent on the nature of the electron withdrawing group (EWG) present on the diazo substrate.

1.2.4 Cobalt–Chiral Porphyrin Catalysis

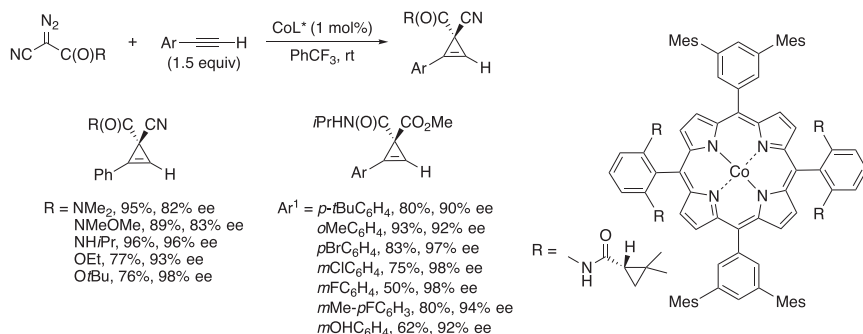
Cobalt(II) complex with a chiral D_2 -symmetrical porphyrin ligand was found to be a highly efficient chiral catalyst for the enantioselective cyclopropanation of alkynes with diazo compounds bearing acceptor–acceptor groups, such as cyanodiazoacetamides and cyanodiazoacetates (Scheme 1.11) [70]. Metal catalysts based on a Co^{II} –porphyrin were shown by Zhang and coworkers to be very effective in asymmetric cyclopropanation of a wide range of olefinic substrates with diazo compounds [71]. This cobalt(II)–porphyrin complex also catalyzes the cyclopropanation reaction of a large variety of terminal aromatic and conjugated alkynes possessing various steric and electronic properties, providing tri-substituted cyclopropenes with high yields and excellent enantioselectivities (up to 99% ee). Only terminal alkynes were used. In addition to the mild reaction conditions, this catalytic transformation exhibits a high degree of tolerance for the presence of functional groups around the alkyne. The consecutive diastereoselective addition of thiols on generated cyclopropenes allowed the synthesis of several cyclopropanes retaining 98% ee.

1.2.5 Gold and Silver Catalysis

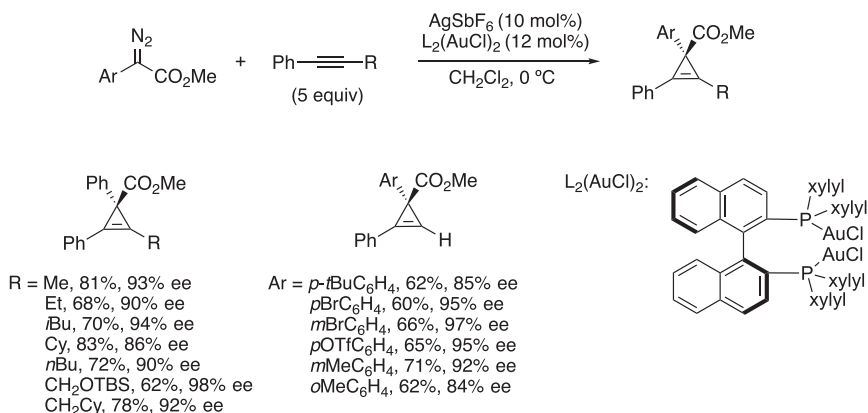
Davies and coworker developed a gold catalyst ((*S*)-xylylBINAP(AuCl)₂ dimer), which, once activated by silver hexafluoroantimonate (AgSbF_6), enables highly enantioselective cyclopropanation reactions of internal alkynes with aryldiazoacetates [72]. Enantioselective cyclopropanation of terminal alkynes with Rh^{II} ,



Scheme 1.10 Iridium-catalyzed enantioselective cyclopropanation of terminal alkynes.

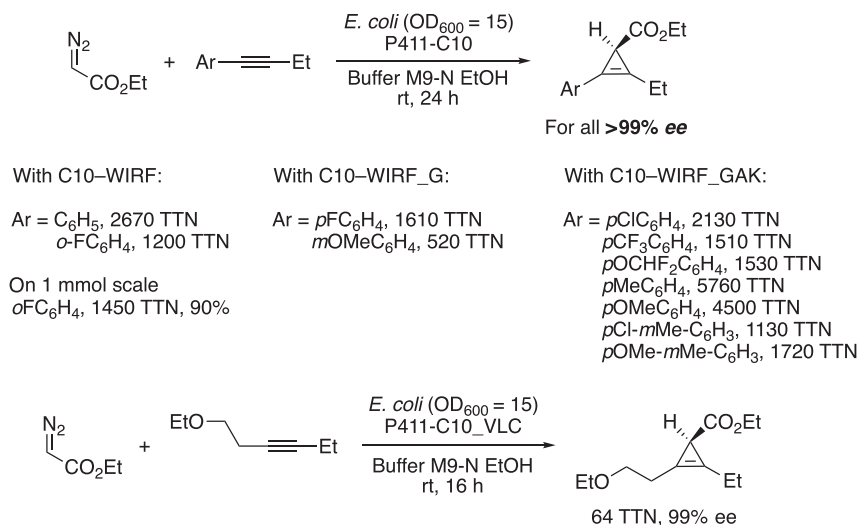


Scheme 1.11 Enantioselective cyclopropenation with a cobalt–porphyrin complex.
Source: Cui et al. [70]/American Chemical Society.



Scheme 1.12 Enantioselective cyclopropenation reaction catalyzed by a gold–silver chiral complex.

Co^{II}, and Ir^{III} catalysts is well established as previously seen. Despite this progress, extending asymmetric cyclopropenation reactions to disubstituted alkynes remains a challenge. Reactivity of gold carbenes and silver carbenes appears to be similar, where gold carbenes have a very different reactivity profile from that of rhodium carbenes. Indeed, these carbenic species are much less sensitive to steric effects, thus allowing an easier approach to disubstituted alkynes. Different disubstituted alkynes in slight excess have been used with various aryl diazoacetates under mild reaction conditions (Scheme 1.12). Yields around 80% have been obtained with high enantioselectivities. The joint use of AgSbF₆ is essential for the gold catalyst to initiate the cyclopropenation reaction. However, the exact structure of the active catalyst has not been determined. Hypotheses have nevertheless been proposed, such as mass spectrometry data of L₂Au₂AgCl₂ catalyst, suggesting the possibility of the presence of a mixed gold–silver complex. Indeed, it is well known that combining a silver salt with a gold pre-catalyst leads to a more complex structure than a simple phenomenon of ligand exchange by halide removal.



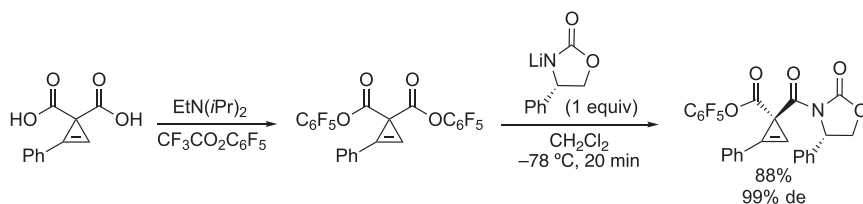
Scheme 1.13 Directed evolution catalysis for enantioselective synthesis of cyclopropenes.

1.2.6 Biocatalysis

Arnold demonstrated the directed evolution catalysis for the enantioselective synthesis of cyclopropenes. She developed a biocatalytic system based on cytochrome P411 in the form of *Escherichia coli* whole-cell catalysts able to provide access to a range of cyclopropenes by transferring carbene from ethyl diazoacetate with disubstituted alkynes in equimolar mixture [73, 74]. This evolutionary biocatalytic system provides high total turnover number (TTN) and cyclopropenes with unprecedented stereoselectivities (>99% ee for all, Scheme 1.13). This enzyme platform is also adaptable for the production of cyclopropenes on large scale (1 mmol), with even higher yields, which is notorious in the field of biocatalysis. Enantioselective cycloprope-nation of internal aliphatic alkynes has also been shown possible, but catalytically much less efficient [74].

1.3 Other Synthetic Routes and Derivatizations of Enantioenriched Cyclopropenes

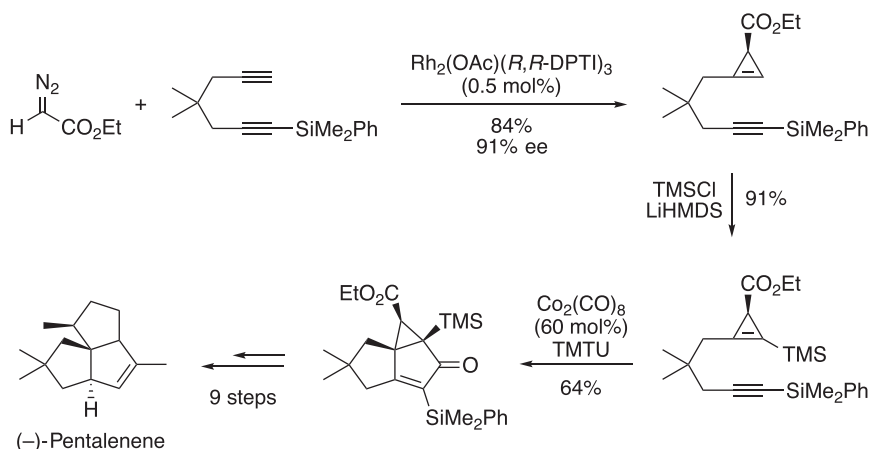
Another approach that could be envisioned for the preparation of chiral cyclopropenes involves the enantioselective desymmetrization of previously generated cyclopropenes [32, 75]. Scheme 1.14 illustrates an easy and stereoselective synthesis of an enriched cyclopropene. Subsequent acyl transfer with azide and Curtius rearrangement provides protected α -amino acid derivatives, which are shown to be stable to harshly acidic and basic reaction conditions. Starting achiral cyclopropenes are generated via the cycloprope-nation of the corresponding terminal alkyne with diazomalonate.



Scheme 1.14 Enantioselective desymmetrization of bis-pentafluorophenylesters.

Marek and coworkers have described the preparation of enantiomerically pure cyclopropenyl carbinols by kinetic resolution via Sharpless epoxidation of racemic cyclopropene alcohols [76]. Only one enantiomer is epoxidized leading to a hypothetical unstable chiral 2-oxabicyclobutane. The remaining non-epoxidized enantiomer is obtained with high enantiomeric excess.

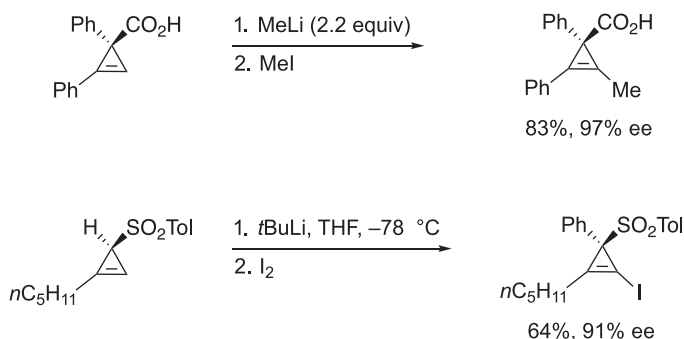
Fox and coworker reported on the first enantioselective synthesis of (–)-pentalenene via the Pauson–Khand cycloaddition involving enantioenriched cyclopropenes (Scheme 1.15) [42]. This enantioselective synthesis has been described with an overall yield of 9% from the known diyne. The key to success for this synthesis was the use of enantiopure cyclopropene for the Pauson–Khand step leading to the desired quaternary center using 0.6 equiv $\text{Co}_2(\text{CO})_8$ and TMTU (tetramethylthiourea). This cyclopropene was synthesized via the cyclopropenation of the corresponding terminal alkyne with ethyl diazoacetate using a chiral dirhodium complex.



Scheme 1.15 Synthesis of (–)-pentalenene via Pauson–Khand cycloaddition involving enantioenriched cyclopropenes. Source: Pallerla and Fox [42]/American Chemical Society.

Starting with a camphene compound has also been used for the diastereoselective synthesis of cyclopropene derivatives [77].

The preparation of enantiomerically enriched 1,2-disubstituted cyclopropenes remains challenging. A convenient way to access these kinds of cyclopropenes is a post-functionalization of enantioenriched mono-substituted cyclopropenes (Scheme 1.16). These derivatizations include palladium catalysis or the trapping of nucleophilic chiral cyclopropenyl metal species with electrophiles [51, 78, 79].



Scheme 1.16 Post-functionalization of enantioenriched mono-substituted cyclopropenes.

1.4 Summary and Prospect

The synthesis of enantioenriched cyclopropenes has been reviewed with the focus on the cyclopropenation of alkynes involving metal-catalyzed decomposition of diazo compounds. Various chiral catalysts are known for the enantioselective cyclopropenation of terminal alkynes. Tremendous work has been done with the use of chiral dirhodium paddlewheels catalysts. Synthetic methods involving other metals have been highlighted. Few reports involve the cyclopropenation of disubstituted alkynes, one of them being the use of enzymatic directed evolution. Enantioselective desymmetrization is one alternative in the synthesis of chiral cyclopropenes, as well as further functionalizations of enantioenriched cyclopropenes.

An interest for the design of new reactions is emerging from the atypical three-membered unit of cyclopropenes. The high angular strain and relative stability of cyclopropenes containing one or two substituents on the aliphatic position will be undoubtedly exploited in the development of new stereoselective reactions.

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