Recent Advances in Catalytic Enantioselective Synthesis of Pyrazolones with a Tetrasubstituted Stereogenic Center at 4-Position†

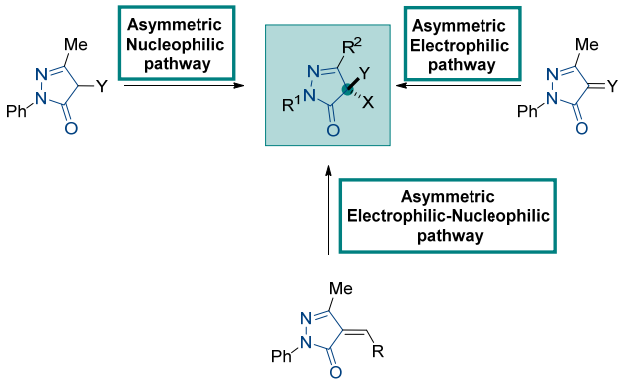
Laura Carceller-Ferrer[a]
Gonzalo Blay[a]
José R. Pedro*[a]
Carlos Vila*[a]

[a] Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain).

* indicates the main/corresponding author.

jose.r.pedro@uv.es; carlos.vila@uv.es

† Dedicated to the memory of Prof. Dieter Enders



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Abstract Pyrazolone represents one of the most important five membered nitrogen heterocycles which is present in numerous pharmaceutical drugs and molecules with biologically activities. Recently, many catalytic methodologies for the asymmetric synthesis of chiral pyrazolones have been established with great success, specially, for the synthesis of pyrazolones bearing a tetrasubstituted stereocenter at C-4. This review summarizes these excellent research studies since 2018, including representative examples and some mechanistic pathways explaining the observed stereochemistry.

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2 Catalytic enantioselective synthesis of chiral pyrazolones with a full carbon tetrasubstituted stereocenter at 4 position.
3 Catalytic enantioselective synthesis of chiral pyrazolones with a quaternary carbon stereocenter at 4 position bearing a heteroatom.
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Key words asymmetric catalysis; pyrazolones; organocatalysis; tetrasubstituted stereogenic centers; nitrogen heterocycles

1 Introduction

Nitrogen heterocycles are ubiquitous in nature.[1] This kind of heterocycles are extremely important for medicinal chemistry and pharmaceutical industry, as well as material science. Between the different types of nitrogen heterocycles, pyrazol-3-ones[2] represent one of the most important class of nitrogen containing five membered heterocyclic compounds that have attracted enormous attention in recent years due to wide range of biological activities and applications as pharmaceutical agents. In this context, 4,4-disubstituted-pyrazol-3-ones represent a common scaffold present in a wide range of biological active compounds (Figure 1) such as compound **A** with tolomerase activity,[3] compound **B** with antibacterial activity,[4] compound **C** with analgesic activity,[5] compounds **D**[6]-**E**[7] with phosphodiesterase activity, compound **F** with inotropic activity,[8] compound **G** with acetyl-CoA carboxylase activity,[9] compound **H** with PPARα activity[10] and compound **I** with RaIA activity,[11] among others.[12]

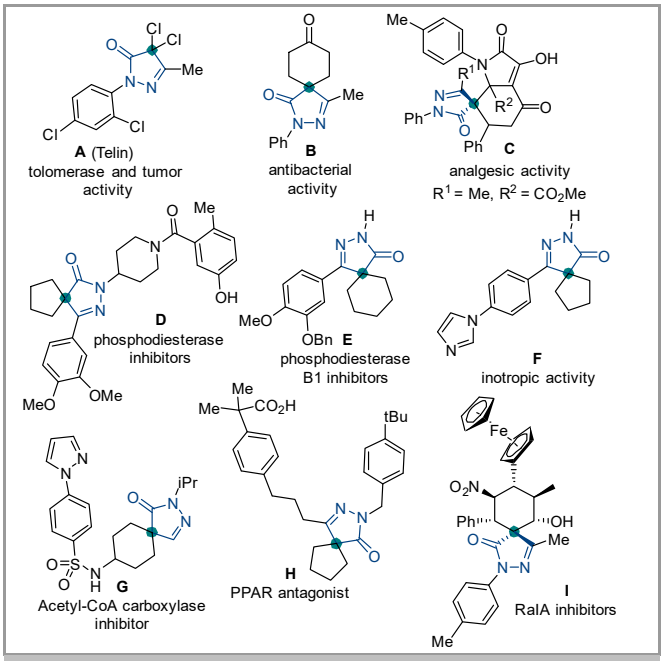
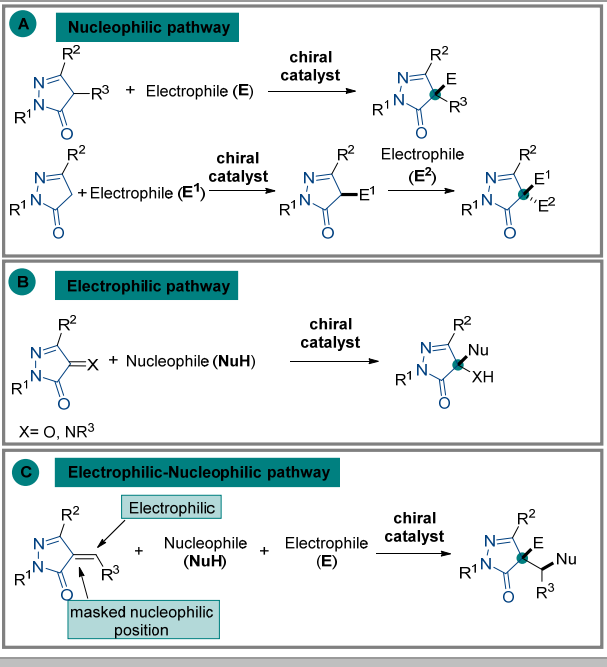


Figure 1 Pyrazolone drugs and bioactive compounds bearing a tetrasubstituted carbon at 4 position.

Therefore, new synthetic methodologies for the preparation and functionalization of pyrazolones derivatives have appeared in the literature in the last decade. In this sense, enantioselective catalysis has been used extensively for the synthesis of chiral 4,4-disubstituted-pyrazol-3-ones. However, the construction of chiral quaternary carbon stereocenters is a difficult task in asymmetric catalysis and has been a synthetic challenge for the chemistry community for many decades,[13] particularly in the area of medicinal chemistry and pharmaceutical industry. For many years, medicinal chemists have focused attention on achiral planar (hetero)aromatic compounds as potential drug

candidates. However, the lack in these compounds of a three dimensional structures provokes a number of drawbacks such as occupation of small fraction of chemical space, limitation of their interactions with target proteins (which have a three-dimensional structure) and low solubility and bioavailability because polyaromatic molecules tend to interact strongly by π-stacking. One of the solutions to these drawbacks is the incorporation of sp^3-hybridized carbon stereocenters into the molecule. In particular, quaternary stereocenters offers an excellent chemical shape by the three-dimensional orientation of the substituents and, usually, a better chemical stability. Therefore, the synthesis of chiral molecules bearing a quaternary stereocenters are extremely important for synthetic chemistry.

In this review, we focus on the recent advances in the synthesis of chiral pyrazol-3-ones bearing a quaternary stereocenter at 4-position. Recently, the asymmetric synthesis of pyrazolones has been the subject of two excellent reviews by Enders[14] and Wang,[15] although several important advances and reports have been made in this topic in the last 3 years. There are several methodologies described for the catalytic synthesis of pyrazol-3-ones bearing a quaternary stereocenter at 4-position (Scheme 1). The first strategy is the electrophilic substitution (Scheme 1A), where the pyrazolone, with a nucleophilic position at C-4, reacts with an electrophile in the presence of a chiral catalyst, affording the chiral 4,4-disubstituted pyrazolone. In some of the examples reported, the nucleophilic pyrazolones reacted sequentially with two electrophiles in order to generate the quaternary stereocenter. The second strategy is the nucleophilic addition (Scheme 1B) introduced elegantly by Enders,[16] where a pyrazolone bearing a ketimine/ketone at the C-4 position suffers an 1,2-addition of a nucleophile. Finally, the third strategy consists in the tandem nucleophilic 1,4-addition/electrophilic substitution of α,β-unsaturated pyrazolones assisted by a chiral catalyst, affording chiral pyrazolone bering two stereocenters (Scheme 1C).

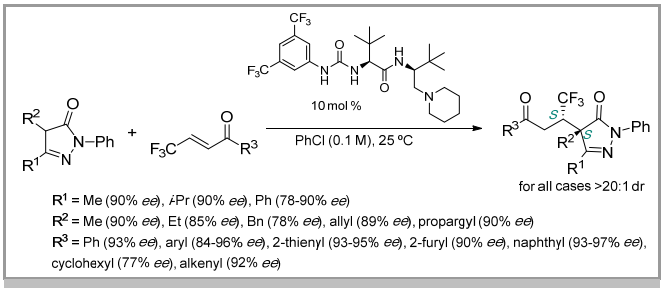


Scheme 1 Main strategies for catalytic asymmetric synthesis of pyrazolone derivatives bearing a tetrasubstituted stereocenter at 4-position

In this review, we consider the asymmetric synthesis of pyrazolones bearing a tetrasubstituted center at C-4 reported in the past three years. The review is divided into three parts, depending on the structural characteristics of the tetrasubstituted stereocenters at C-4 of the pyrazolones. These three parts are: asymmetric synthesis of pyrazolones with a full carbon tetrasubstituted stereocenter at C-4, asymmetric synthesis of pyrazolones with a quaternary carbon stereocenter bearing a heteroatom at C-4 and asymmetric synthesis of chiral spiropyrazolones.

2 Catalytic enantioselective synthesis of chiral pyrazolones with a full carbon tetrasubstituted stereocenter at 4 position.

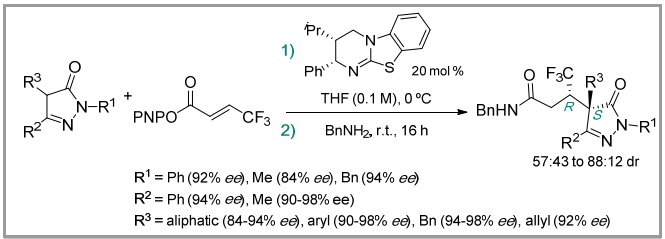
The Michael addition reaction represents one of the most powerful methods for the formation of carbon–carbon bonds in organic synthesis.[17] Therefore, the asymmetric Michael reaction[18] has proven to be one of the most efficient tools for the synthesis of chiral compounds, and in particular the synthesis of compounds with full carbon tetrasubstituted stereogenic centers. Several catalytic asymmetric Michael additions of 4-substituted pyrazolones to α,β-unsaturated carbonyl compounds to form a quaternary stereocenter has been studied in the literature. For example, the enantioselective bifunctional urea-catalyzed conjugate addition of pyrazolones to β-trifluoromethyl-α,β-unsaturated ketones have been reported by Zhu, Chang and co-workers in 2020 (Scheme 2).[19] This reaction constitutes a successful example of stereoselective introduction of trifluoromethyl group into organic molecules, highly important in pharmaceutical industry,[20] using β-trifluoromethyl-α,βunsaturated ketones as Michael acceptors.[21] In this report, the corresponding trifluoromethylated products bearing two vicinal stereocenters (one of them quaternary) were obtained with good to excellent yields (up to 95%) and enantioselectivities (up to 97% ee) and excellent diastereoisomeric ratios (>20:1 dr). The authors have widely studied the effect of different substituents in the enone. So, phenyl substituent as well as *ortho*-, *meta*- and *para*- substituted phenyl ring with groups of any electronic character are well tolerated. Also, heteroaromatic rings, such as thiophene or furan, or alkenyl groups as substituents do not produce a significant variation in the enantioselectivity. However, cyclohexyl group lead to a decrease of enantiomeric excess to 77% *ee*. With regard to the pyrazolone, a wide range of different substituents (aliphatic, allyl, propargyl, benzyl and aromatic) are well tolerated.



Scheme 2 Enantioselective Michael addition of 4-substituted pyrazolones to β-trifluoromethyl-α,β-unsaturated ketones described by Chang.

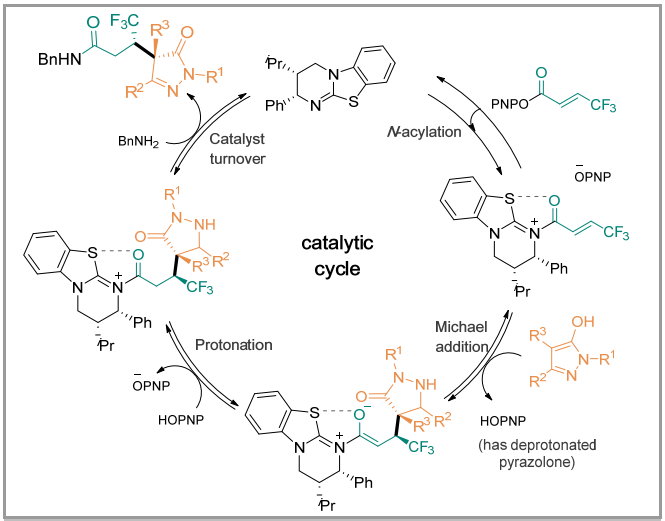
The same year, Smith research group developed another example of synthesis of trifluoromethylated organic molecules bearing a pyrazolone scaffold (Scheme 3).[22] The authors described the

asymmetric organocatalytic conjugated addition of pyrazolones (among other *N*-heterocyclic compounds) to β-trifluoromethyl-α,β-unsaturated aryl esters to afford the desired products bearing two contiguous stereocenters in low to good yields (up to 89%) and diastereoselectivities and high enantioselectivities using a isothiourea organocatalyst.[23] With this strategy, aryl, benzyl and allyl substituents in any position of the 4-substituted pyrazolone do not have a big effect on enantiomeric excess while aliphatic substituents can lightly decrease the enantioselectivity in some cases.



Scheme 3 Enantioselective Michael addition of 4-substituted pyrazolones to β-trifluoromethyl-α,β-unsaturated aryl esters described by Smith.

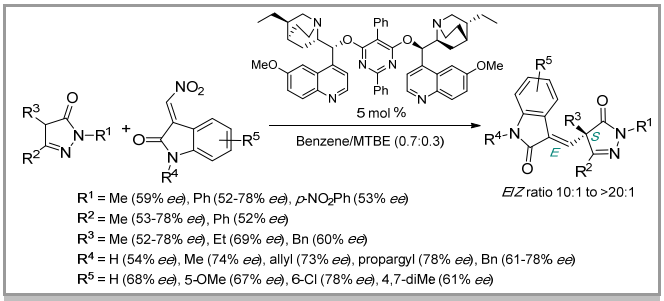
In the first step of the mechanism proposed by the authors, the isothiourea catalyst binds to the electrophile providing an activated electrophile and the chiral environment. Follows a Michael addition of the enolate of the pyrazolone (formed via deprotonation by the ⁻OPNP alkoxide) to the activated electrophile. Finally, the resulting enolate is protonated by the alcohol HOPNP and the catalyst is released and ready to begin a new catalytic cycle (Scheme 4).



Scheme 4 Proposed mechanism pathway for the Michael addition reported by Smith.

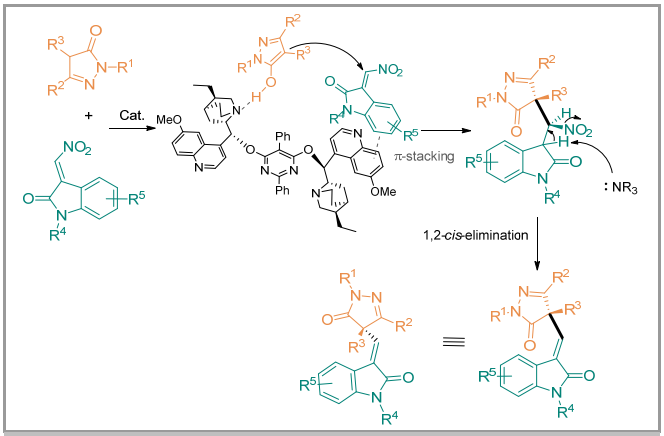
Another example of enantioselective conjugate addition of 4-substituted pyrazolones to α,β-unsaturated compounds was reported by our research group in 2019.[24] In this report, we described the regio- and stereoselective addition of pyrazolones to isatin-derived nitroalkenes to synthesize 2-oxindole-derived compounds bearing a pyrazolone moiety with a quaternary stereocenter. The reaction conditions afford selectively the *E* isomer of the alkylidene-2-oxindoles products with good yields, excellent regio- and diastereoselectivities and moderate enantioselectivities using $(DHQ)_2Pyr$ as organocatalyst (Scheme 5). The stereoselective synthesis of 3-alkylidene-2-oxindoles bearing a pyrazolone scaffold was explained through a nucleophilic vinylic substitution (S_NV)[25] of (*E*)-3-(nitromethylene)indolin-2-one derivatives. (*E*)-3-(nitromethylene)indolin-2-one is a challenging electrophile,[26] due to the nucleophile can attack the β-position of the nitroolefin or the α-position and consequently the regioselectivity of the addition step should be controled. Moreover, if the nucleophile attacks the α-position of the nitroalkene, the addition product can progress through a nitrous acid elimination reaction, leading to a double bond where the stereoselectivity should also be controlled.

The analysis of the products shows that the reaction gives a complete regioselective transformation, with high levels of stereoselectivity in the formation of the double bond, but moderate enantioselectivities (up to 78% ee). The methodology tolerates substituents with both electron-donating and electron-withdrawing character in the 2-oxindole aromatic ring. *N*-substituted isatine-ketimines lead to better enantioselectivity than non-protected isatin ketimine (78% vs 54% *ee*). Different substitution in pyrazolone moiety bring about moderate enantiomeric excess affording the best result with *N*-aryl and C-4-aliphatic substitution.



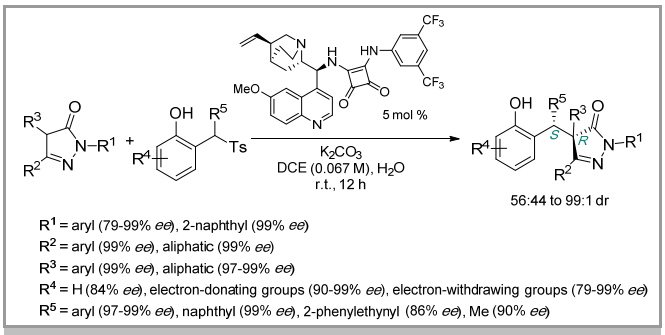
Scheme 5 Enantioselective addition of 4-substituted-pyrazolones to isatin-derived nitroalkenes described by Pedro and Vila.

In the mechanistic proposal both substrates are coordinated to the $(DHQ)_2Pyr$ catalyst, and then the enol form of the pyrazolone attacks the α-position of nitroalkene and finally the tertiary amine of the catalyst acts as a base and forces the 1,2-*cis*-elimination to achieve the final products in an enantiomerically enriched way (Scheme 6).



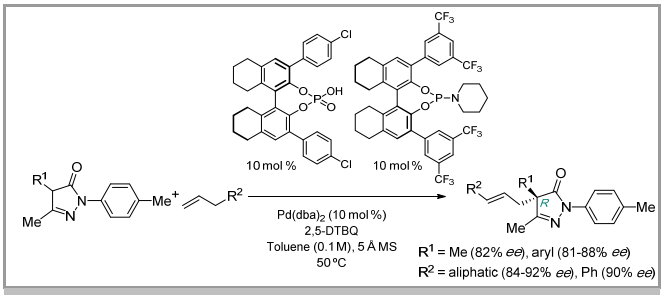
Scheme 1 Proposed mechanistic pathway for the enantioselective nucleophilic vinylic substitution reported by Pedro and Vila.

Ortho-quinone methides[27] are highly reactive and versatile intermediates in asymmetric synthesis, which allow the construction of benzylic stereogenic centers through 1,4-addition reaction.[28] Wang and Xu reported, in 2019, the enantioselective Michael addition of 4-substituted-pyrazolone to *ortho*-quinone methides generated *in situ* using a quinine-derived squaramide (Scheme 7).[29,30] As in the previously described reactions involving *ortho*-quinone methides, a biphasic system is necessary to obtain excellent enantioselectivities since the inorganic base and catalyst are solubilized in two different phases. All substituents tested afford an excellent enantiomeric excess (all above 90% *ee*) with few exceptions such as *ortho*-substituted electron-withdrawing groups in the phenol moiety which slightly decrease the enantioselectivity to 88% *ee* for *o*-F and to 79% *ee* for *o*-CF_3. Regarding the diastereoselectivity of the reaction, in order to reach an excellent dr (above 95:5), is necessary the presence of substituents (electron-donating or electron-withdrawing) tethered to the *ortho* position of the phenol moieties. The authors showed the practicality of the described methodology, by carrying out a gram scale reaction with good results.



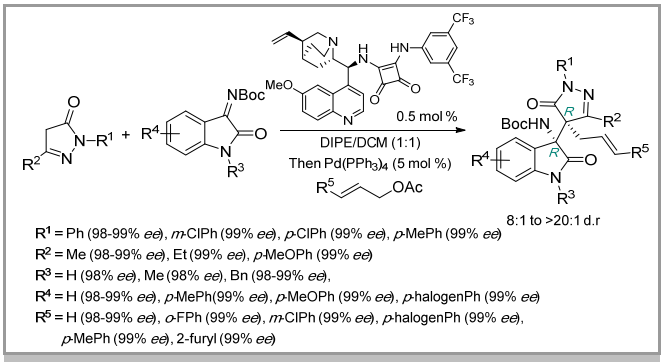
Scheme 7 Enantioselective organocatalytic conjugated addition of 4-substituted pyrazolones to *ortho*-quinone methides described by Wang and Xu.

The asymmetric allylic alkylation[31] has proven to be an exceptionally powerful method for the efficient construction of stereogenic centers, particularly chiral quaternary carbon centers. In this context, the palladium catalyzed asymmetric allylic alkylation (Tsuji-Trost reaction) has been widely used in the synthesis of natural products and drug molecules.[32] 4-substituted pyrazolones represent an excellent type of nucleophile in palladium asymmetric allylic alkylations, and have been used successfully in the past using allylic alcohols as electrophiles.[33] In addition, there are several examples in the literature for the construction of quaternary stereocenters at 4-position of pyrazolones using palladium catalysis and chiral phosphoric acids (CPA) using terminal alkenes by Wang.[34] In 2019, his research group extended a previous methodology for the asymmetric allylic C–H alkylation of pyrazolones with unactivated alkenes using a catalytic system formed by $Pd_2(dba)_3$, a chiral phosphoramidite ligand and a chiral phosphoric acid (Scheme 8). The desired products bearing a quaternary center are synthesized in moderate to good yields and good enantioselectivities (up to 90% ee). This methodology tolerates several unactivated alkenes bearing a variety of functional groups, such as ether, ester, silyl ether, amide and alkyl chloride, tethered to terminal alkenes obtaining good yields and stereoselectivities.



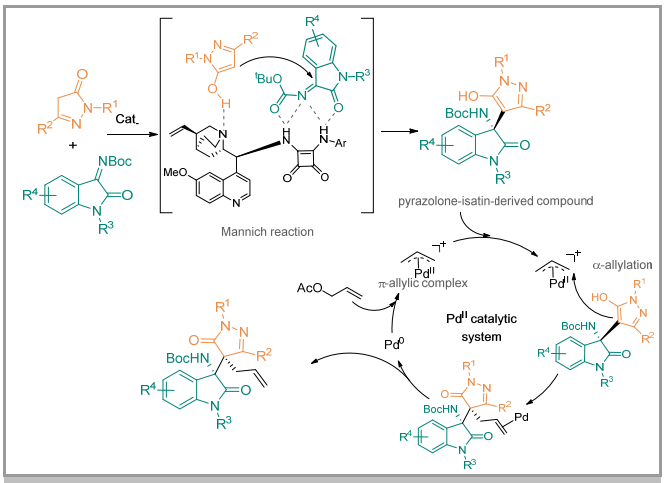
Scheme 8 Palladium-catalyzed asymmetric allylic C–H alkylation of unactivated alkenes with 4-substituted pyrazolones reported by Wang.

Another example of palladium catalyzed allylic alkylation involving pyrazolones was described by Huang and co-workers (Scheme 9).[35] They reported an asymmetric *one-pot* tandem reaction in which an organocatalyzed Michael addition of 4-unsubstituted pyrazolones to isatin-derived ketimines was followed by a Pd^{II}-catalyzed α-allylation with allylic acetates, affording the corresponding products bearing two contiguous quaternary centers with moderate to high yields and diastereoselectivities but excellent enantioselectivities (up to 99% ee). With a low catalytic load (only 0.5 mol %), the authors have developed a robust methodology. Different alkyl and aromatic substituents are perfectly tolerated as substituents of the pyrazolone ring as well as benzyl and alkyl *N*-substituents of the isatin ketimine. Moreover, electron-donating and electron-withdrawing groups are permitted for the aromatic substitution of both substrates, obtaining in all cases good results. The authors showcase the practicability of their method with a scale-up experiment to gram scale reaction.



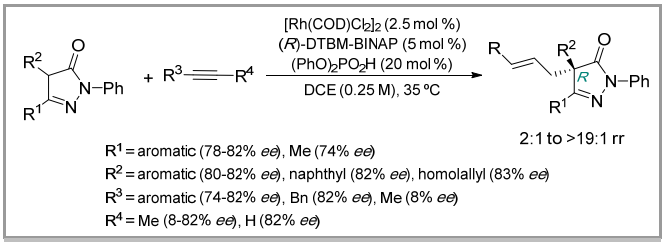
Scheme 9 Enantioselective Mannich/α-allylation sequential reactions using pyrazolones as nucleophiles described by Huang.

According to the proposed mechanism by the authors, the reaction starts with a nucleophilic addition of pyrazolone to the isatin-derived ketimine, where both substrates are activated by the quinine-derived squaramide catalyst (Scheme 10). Then, when the allylic acetate and the palladium reagent are added a Pd^{II}-allylic complex is formed, which reacts with the pyrazolone-isatin-derived compound. A final reductive elimination of Pd^{II} forms the desired product in a diastereo- and enantiocontrolled path. Therefore, the first enantioselective Mannich reaction controls the diastereoselectivity of the second C-C bond formig reaction.



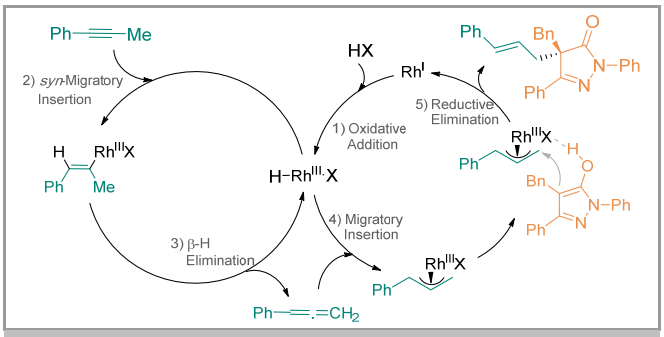
Scheme 10 Proposed mechanistic pathway for the asymmetric allylic alkylation reported by Huang.

This year, Chen's group reported the regioselective and asymmetric addition of pyrazolones to alkynes using a chiral rhodium(III) complex as catalyst (Scheme 11).[36] The corresponding products bearing a quaternary center were obtained with generally good yields (up to 91%) and regio- and enantioselectivies (up to >19:1 rr and 82% *ee*). Regarding the scope of the reaction, aliphatic and aromatic substituents with a great variety of electronic and steric characteristics are perfectly tolerated at the pyrazolone. Howewer, aromatic or benzylic alkynes are essential for the enantiocontrol of the reaction, since the use of 2-butyne decreases significantly the enantiomeric excess (8% ee) and regioselectivity (2:1 rr). Among the aromatic substituents for the alkyne, electron-donating and electron-withdrawing substituents as well as naphthyl and 2-thienyl substituents (76-83%*ee*) are perfectly supported without bigger variations in the enantiomeric excess.



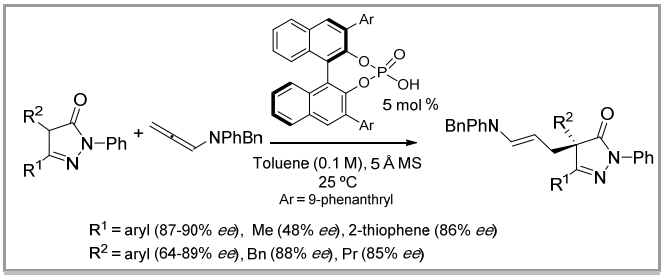
Scheme 11 Asymmetric allylic alkylation of 4-substituted pyrazolones with allenamides reported by Chen.

According to the mechanism, the authors propose the following combined catalytic cycles (Scheme 12). First, the allene intermediate is formed from the alkyne, by migratoy insertion of the rhodium hydride followed by a β-elimination process. After, this allene forms the π-allyl rhodium complex in the presence of the rhodium hydride which reacts with the enol form of the pyrazolone to achieve the desired product and a Rh(I) species which is regenerated into the Rh(III) hydride species in the presence of the Brønsted acid.



Scheme 12 Proposed mechanistic pathway for the asymmetric allylic alkylation reported by Chen.

The use of chiral phosphoric acids (CPAs) in organocatalysis has become a potent strategy to construct quaternary centers in the last decades.[37] In particular, they have been used extensively in asymmetric allylic alkylation in combination with metal catalysts. However, metal free allylic alkylation using CPA have also been reported. In this context, Wang's research group reported in 2018 the enantioselective allylic alkylation of 4-substituted pyrazolones with allenamides, affording the corresponding chiral pyrazolones bearing a tetrasubstituted center with mostly great yields and moderate to high enantioselectivities (Scheme 13).[38] Regarding the scope of the reaction, it tolerates any kind of substitution in the aryl group at C-5 without great variations of enantioselectivity. However, when a methyl group is present in that position the enantiomeric excess decreases to 48% *ee*. At C-4 position, aliphatic groups (such as propyl) and also benzyl substituent are well tolerated. Electron-donating groups in the aryl group at C-4 do not affect enantiomeric excess but electron-withdrawing substituents slightly decreases it. A mention has to be made regarding the mechanism. In the first place the allenamide is activated by the protonation of its nitrogen atom and then this protonated species and the enol form of the pyrazolone are coordinated to the CPA catalyst, thus making the enantiocontrol possible.

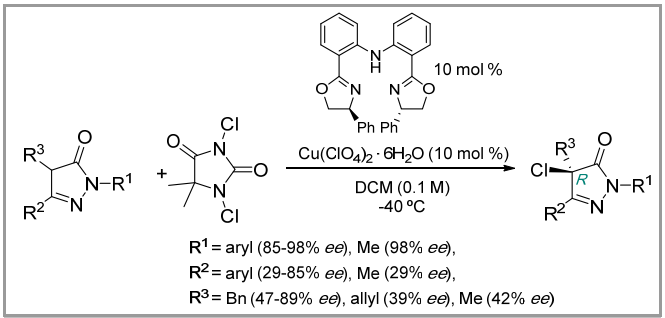


Scheme 13 Asymmetric allylic alkylation of 4-substituted pyrazolones with allenamides reported by Wang.

3 Catalytic enantioselective synthesis of chiral pyrazolones with a quaternary carbon stereocenter at 4 position bearing a heteroatom

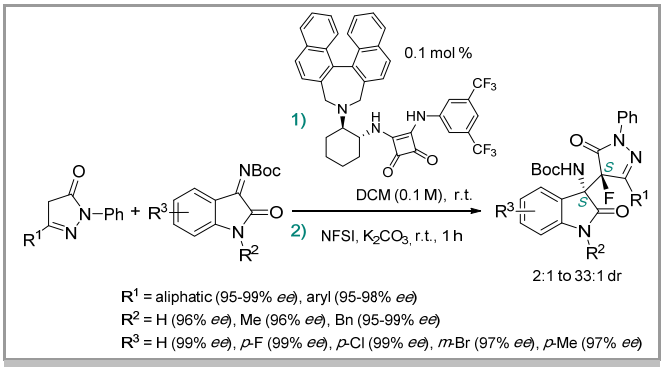
As we have exposed in the introduction, there are two general approaches for the synthesis of pyrazolones bearing a tetrasubstituted stereocenter at C-4 with a heteroatom. One is the electrophilic substitution of 4-substituted pyrazolones. This strategy has been used for the formation of C-X or C-S bonds. However, this approach for the preparation of chiral 4-heteroatom-substituted pyrazolones is less explored.

The organocatalytic enantioselective electrophilic halogenation of 4-substituted pyrazolones have been described previously in the literature.[39] Recently, Wang's group has reported the asymmetric chlorination of 4-substituted pyrazolones (Scheme 14), using chiral bis(oxazoline)–copper complexes,[40] affording the corresponding products with high to excellent yields (up to 98%) and low to excellent enantioselectivities (up to 98% ee).[41] The aforementioned procedure admits a large number of substituents in the pyrazolone scaffold. Accordingly, aryl and benzylic substituents are generally well tolerated except in the case with a *p*-Br substituted phenyl as R^2 (29% *ee*). When there is an allyl substituent at C-4 of the pyrazolone, the enantiomeric excess is moderate. Regarding the methyl substituents, the presence of a Me at the nitrogen of the pyrazolone, does not affect to the reactivity and enantioselectivity. However, when R^2 or R^3 is a methyl substituent, the enantioselectivity of the reaction decreases.



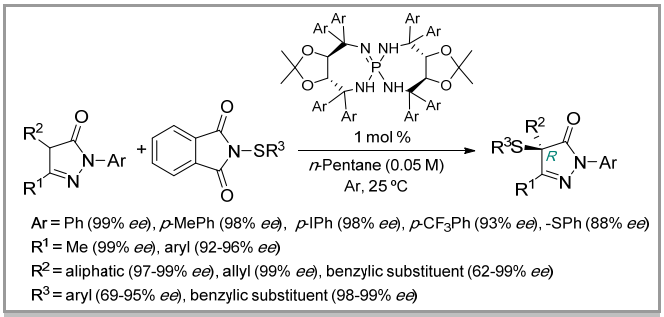
Scheme 14 Asymmetric chlorination of 4-substituted pyrazolones reported by Wang.

Kim and co-workers described in 2018 the asymmetric Mannich addition of pyrazolones to isatin-derived ketimines catalyzed by a bifunctional squaramide followed by the fluorination of the C-4 position with NFSI generating a quaternary center (Scheme 15). The desired products are obtained with good yields, high diastereoselectivities (up to 33:1 dr) and excellent enantioselectivities (up to 99% ee).[42] This reaction was described previously by Wang,[43] however a highlight of the work of Kim is that the catalytic loading used is only 0.1 mol % of the chiral bifunctional catalyst. Therefore, this report is the most efficient methodology to prepare such compounds that has been published. As shown in the scheme below, aliphatic and aryl substituents in the pyrazolone moiety are perfectly well tolerated obtaining the reactions product with excellent enantiomeric excesses. Same trend is observed for the *N*-substitution of the isatin ketimine. Regarding the aromatic ring substitution, electron-donating and electron-withdrawing groups do not have a significant effect in the enantioselectivity of the reaction.



Scheme 15 Asymmetric Mannich addition/Fluorination of pyrazolones to isatin-derived ketimines reported by Kim.

In order to obtain a tetrasubstituted center bearing a C-S bond, the asymmetric electrophilic sulfenylation is one of the best aproaches.[44] Few examples have been reported for the synthesis of enantiomerically enriched pyrazolone derivatives bearing sulfur-substituted quaternary stereocenters. In this context, Wong's research group developed in 2019 the asymmetric organocatalytic sulfenylation of pyrazolones under permanent solvation catalyzed by a chiral iminophosphorane (Scheme 16).[45] This methodology is highly enantioselective and proceeds with very good yields using only 1 mol % of catalyst. According to the reaction scope study carried out (37 examples), this asymmetric reaction tolerates a wide range of substituents (aryl, benzyl, aliphatic) in the pyrazolone moiety as well as in the *N*-(substituted-thio)phthalimide reagent. All starting materials (except the *ortho*-substituted sulfur reagent) gave the corresponding reaction products with high to excellent enantiomeric excess. Remarkably, gram scale sulfenylation reaction was performed, obtaining a quantitative yield of the corresponding product with excellent 99% ee.

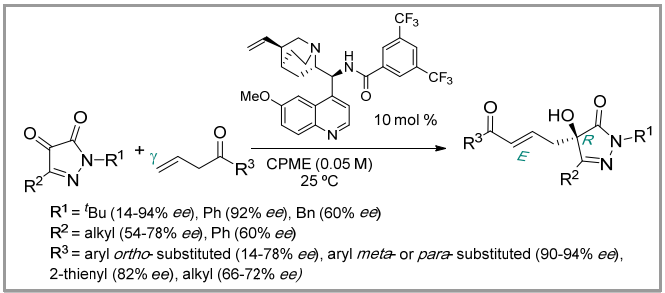


Scheme 16 Asymmetric organocatalytic sulfenylation of 4-substituted pyrazolones reported by Wong.

Another strategy to generate a quaternary stereocenter in the C-4 position of pyrazolone bearing a heteroatom, is the nucleophilic 1,2-addition. So, the enantioselective nucleophilic addition to pyrazole-4,5-diones affords a stereocenter bearing a hydroxy group. The main difference with the previous strategies is that in this substrate the C-4 position is an electrophilic center.

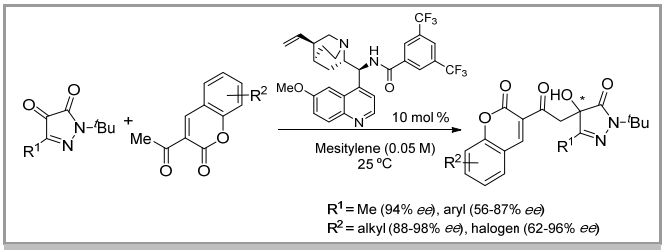
Three enantioselective synthesis to access to enantiomerically enriched 4-hydroxypyrazol-5-ones have been reported since 2018. Mukherjee's research group described the first regio- (γ) and stereoselective (*E*-selective and enantioselective) vinylogous nucleophilic addition of allyl ketones to pyrazol-4,5-diones catalyzed by a quinine-derived bifunctional catalyst (Scheme 17).[46] Vinylogy is the extension of the electronic behaviour due to

the conjugation in a molecule, and sometimes it is challenging to control the regioselectivity in vinylogous reactions.[47] In this report, the authors have solved this problem of regioselectivity (α- and γ- mixtures) using a bulky substituent (^{t}Bu) attached to the nitrogen atom of the pyrazolone. Furthermore, this reaction is completely *E*-selective. With allyl aryl ketones, excellent enantioselectivities are obtained when *meta*- and *para*-substituents are present but, in contrast, the enantiomeric excess is considerably decreased when there is an *ortho*- substituent. Allyl alkyl ketones are also tolerated albeit the enantioselectivities of the reaction are moderated. Alkyl or aryl substituents in C-3 o N-1 of the pyrazole-4,5-dione lead to enantiomeric excesses from 60 to 92% ee. The authors performed the reaction at 1 mmol scale obtaining the reaction product with 72% yield, >20:1 *E/Z* ratio and 92% ee. Moreover, several transformations of the product were carried out such as the hydrogenation and the epoxidation of the double bond.



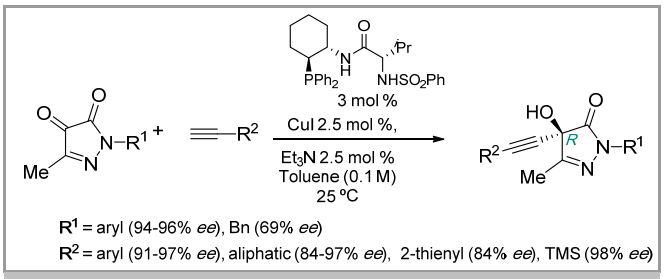
Scheme 17 Asymmetric organocatalytic vinylogous aldol reaction of allyl ketones to pyrazole-4,5-diones reported by Mukherjee.

In the early 2019s, the same group reported the enantioselective aldol reaction of 3-acetylcoumarins to pyrazole-4,5-diones with the same quinine-derived bifunctional catalyst used in the previous example, affording the corresponding products with high yields and medium to excellent enantioselectivities (Scheme 18).[48] It is important to note that the reaction through the enol/enolate of the ketone which is formed by the tertiary amine moiety of the bifunctional catalyst. In this reaction, the activation of the ketone is produced by the acid-base interaction of the Brønsted and not by an enamine mechanism. This methodology tolerates a wide range of substituents in the coumarin moiety without significant variability in the enantiomeric excess which is, generally, very high (62-98% ee). If the C-3 substituent of the pyrazole-4,5-dione is changed from a methyl substituent to an aryl substituent (Ph, 4-ClPh or 4-MePh) the enantioselectivities are lower (56-87% ee).



Scheme 18 Asymmetric organocatalytic vinylogous aldol reaction of 3-acetylcoumarins to pyrazole-4,5-diones reported by Mukherjee.

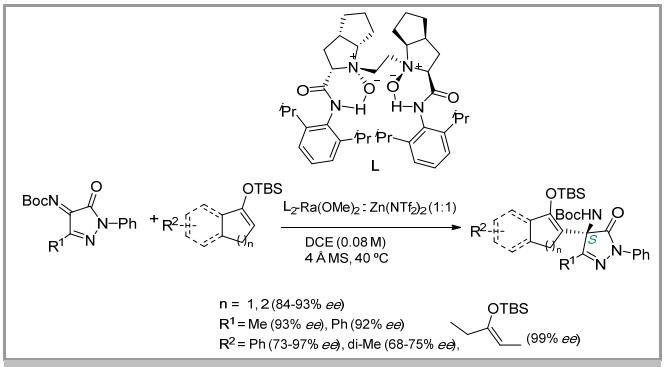
Also in 2019, Wu's group used the well-known strategy of enantioselective alkynylation of carbonyl compounds[49] applied to pyrazole-4,5-diones to obtain an stereogenic center bearing a propargylic alcohol (Scheme 19).[50] Thus, the authors described the enantioselective alkynylation using a copper (I) complex with chiral phosphine, achieving the corresponding tertiary alcohols in good to excellent yields (83-98%) and excellent enantioselectivities (69-98% ee). This robust method is compatible with a great variety of substituents. For example, excellent enantiomeric excesses were obtained whether electron-withdrawing or electron-donating groups are present in *para*-, *ortho*- or *meta*- position of the phenyl substituent in the acetylene. Aliphatic substituents such as butyl or cyclopropyl are also well tolerated in the acetylene leading to moderate to excellent enantioselectivities. Furthermore, TMS and 2-thienyl substituents are good admitted leading to high and excellent enantiomeric excess. The scope of the reaction regarding the electrophile is narrower, and only 4 different pyrazole-4,5-diones were reported. Furthermore, the authors also demonstrate the synthetic utility of their methodology, performing a gram scale reaction obtaining the reaction product with 95% yield and 96% ee. They also performed several transformations such the protection of the tertiary alcohol and the reduction of the triple bond.



Scheme 19 Asymmetric alkynylation of pyrazole-4,5-diones reported by Wu.

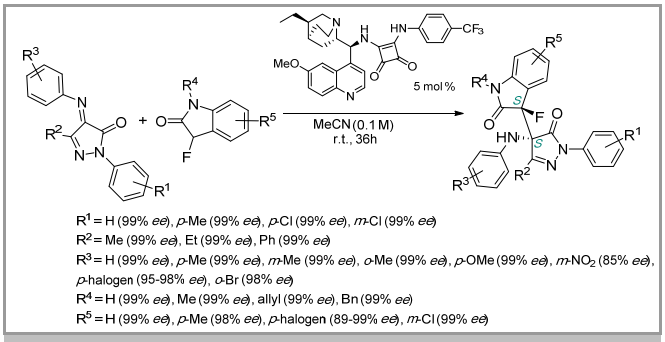
Just as the aforementioned strategy, the use of pyrazolinone ketimine reactions represent another straightforward method for constructing quaternary center in the pyrazolone motif. Again, as it happened with pyrazole-4,5-diones, the natural polarity of C-4 position of the pyrazolone have been reversed.

In 2019, Feng and co-workers reported the first asymmetric Zn(II)-catalyzed alkenylation reaction of pyrazolinone ketimines using silyl enol ethers while the expecting Mukaiyama–Mannich reaction, which is a competitive process in these conditions (Scheme 18).[51] The desired products were obtained in low to excellent yields (21-98%) and good to excellent enantioselectivities (up to 99% ee) using chiral *N*,*N*'-dioxide metal complexes developed widely by the group of Feng.[52] This methodology achieves excellent enantiomeric excess whether the pyrazolone substituent at C-3 is a methyl or aryl group (92% ee and 93% *ee*, respectively). On the other hand, the cycle size (n= 1 or 2) of the nucleophile does affect to enantioselectivity: five-member cycle leads to better results than six-member one (93% *vs* 84% *ee*). In addition, an aromatic ring fused to these cycles increases the enantiomeric excess in the smallest cycle (97% *ee*) while decreases enantioselectivity in the biggest cycle (73% *ee*). Aliphatic substituents result in a reduction of enantioselectivity for both cycle sizes (68% and 75% *ee*). Anyway, the best enantiomeric result is obtained with the acyclic silyl enol ether derived of pentan-3-one (99% *ee*).



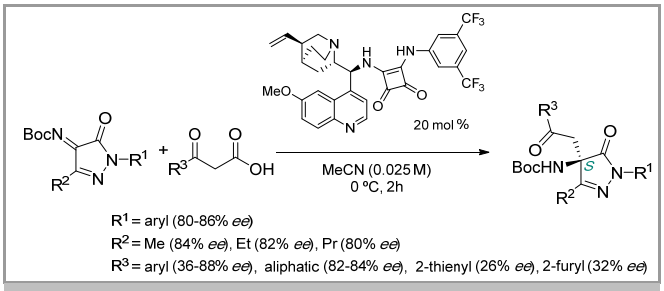
Scheme 20 Enantioselective addition of silyl enol ethers to pyrazolinone-derived ketimines reported by Feng.

Also in 2019, Du's research group reported the diastereo- and enantioselective Mannich reaction of 3-fluorooxindole to pyrazolinone-derived ketimines using a dihydroquinine-derived squaramide as organocatalyst (Scheme 21).[53] The corresponding products bear two vicinal quaternary centers and incorporate the widely known benefits of fluorine atoms in its final structure. In general, the corresponding Mannich products are obtained in high to excellent yields, excellent diastereomeric ratio and great to excellent enantioselectivities (up to 99% ee). This catalytic system tolerates electron-withdrawing substituents (F, Cl, Br, CF_3 and NO_2) as well as electron-donor substituents (MeO, Me) in both aromatic rings of the pyrazolone moiety without any loss of enantiomeric excess (99% *ee* for all cases), with the only exception of NO_2 substituent in *para*- position (85% *ee*). Aliphatic and aryl substituents as R^2 are also allowed maintaining excellent enantioselectivity. Regarding to the nitrogen bond substituent in the 3-fluorooxindole, with aliphatic, allylic and benzylic substituents excellent enantiomeric excess were also obtained. Halogen substituents were perfectly tolerated in *para*- and *meta*-position of the aromatic ring of 3-fluorooxindole. The reaction was scale up to 2.5 mmol, obtaining 1.04 gr of the corresponding product and maintaining the excellent stereoselectivity of the reaction (94% yield, >20:1 dr, 99% ee).



Scheme 21 Enantioselective Michael reaction between 3-fluorooxindoles and pyrazolinone-derived ketimines reported by Du.

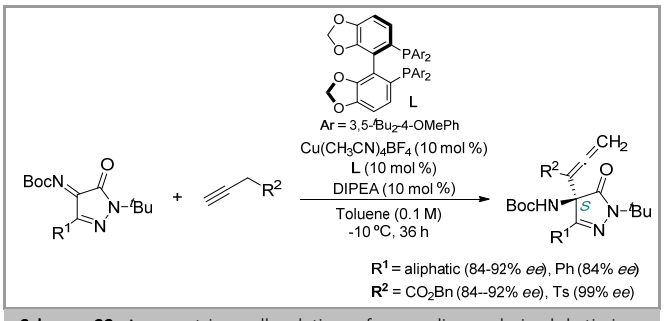
Another strategy using pyrazolinone-derived ketimines was described by Yuan's group in 2019.[54] This report consists in an asymmetric decarboxylative Mannich reaction of β-ketoacids to pyrazolinone-derived ketimines catalyzed by a quinine-derived squaramide (Scheme 22). The corresponding chiral pyrazolones bearing a tetrasubstituted center at C-4 position are obtained in excellent yields and, generally, good enantioselectivities (up to 88% ee). The substituents in the pyrazolone moiety does not affect the enantiomeric excess of the reaction product which is around 80% *ee* for all the substituents studied. Thus, electron-donating or electron-withdrawing groups in *para*- position of the aromatic ring attached to the nitrogen of the pyrazolone do not trigger a significant change in enantioselectivity (80-86% *ee*) neither the aliphatic chain length (Me, Et, Pr) in C-3 (80-84% *ee*). Regarding the nucleophile, the substituents in the β-ketoacids have a more varied effect on the stereoselectivity. Aliphatic substituents (Me, Et, Pr) as R^3 do not affect the enantioselectivity (82-84% *ee*). Aromatic substituents, such as a *para*-halogen substituted aryl group, *meta* and *ortho*-substituted aryl group (76-88% ee) or naphthyl group (80%) don not change the enantiomeric excess significantly. However, the presence of a MeO group at *para* position of the aryl group implies a huge decrease in the enantioselectivity of the reaction (36% ee). Similarly, heteroaromatic substitutents such as 2-thienyl and 2-furyl, led to the formation of the products with poor enantiomeric excesses (26% and 32% *ee*, respectively).



Scheme 22 Organocatalyzed decarboxylative Mannich reaction of β-ketoacids with pyrazolinone-derived ketimines reported by Yuan.

Additionally, the authors apply these reaction conditions using pyrazole-4,5-diones as electrophiles. The corresponding chiral tertiary alcohols were obtained in good yields, but moderate enantioselectivities (up to 64% *ee*).

Recently, Chen, Du and coworkers described the enantioselective addition of benzyl 3-butynoates to pyrazolinone ketimines using a chiral Cu(I) complex as catalyst obtaining the desired products bearing an allenyl moiety in good to high yields (64-89%) and high enantioselectivities (up to 92% *ee*).[55] This methodology tolerates aromatic and different aliphatic chains as the olefinic substituents for the pyrazolone moiety maintaining the enantioselectivity of the reaction and the authors only observed the α-allelylation product (Scheme 23). Furthermore, when a propargyl sulfone is used as nucleophile with the same optimized conditions, the corresponding amine is obatined with good yield and excellent enantiomeric excess (82% and 99% *ee*).



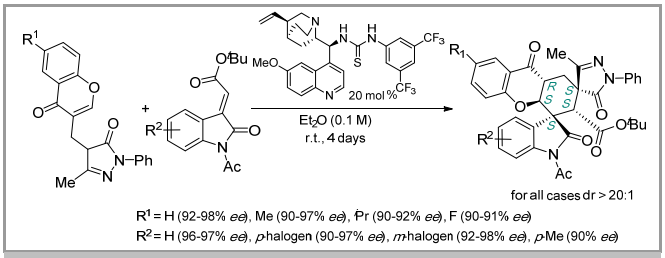
Scheme 23 Asymmetric α-allenylation of pyrazolinone-derived ketimines reported by Du and Chen.

4 Catalytic enantioselective synthesis of chiral spiropyrazolones

According to the IUPAC a spiro compound is a molecule having one atom (usually a quaternary carbon) as the only common member of two rings. This special feature confers a peculiar rigidity to the whole structure which have positioned chiral spirocyclic scaffold in a distinguished place in different areas, such as medicinal chemistry where can you find many biological active compounds with this motif in its skeleton. Moreover, spiro compounds are present in a plethora of natural products. Very recently, special efforts have been made in the challenging asymmetric synthesis of spirocyclic compounds.[56] Hence, the construction of a quaternary spirocyclic center in pyrazolone-derivatives results in an interesting combination of structural features due to the well-known pharmaceutical uses of pyrazolone structures.

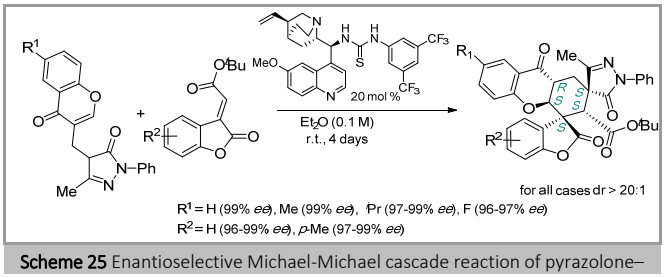
4.1 Asymmetric synthesis of chiral spiropyrazolones bearing a full carbon stereogenic spirocyclic center.

Since 2018, several publications in this area have been published. Spiropyrazolones are generally obtained by tandem reactions of 4-substituted pyrazolones with different starting materials bearing two reactive centers. Zhou's group developed in 2018 the asymmetric and organocatalytic double Michael addition of a bifunctional pyrazolone–chromone compounds to 3-substituted methyleneoxindoles to construct an hexahydroxanthones-derived structure with five contiguous stereocenters (two of them quaternary centers and spirocenters) in good yields and excellent diastereo- (all above 20:1 dr) and enantioselectivity (all above 90% *ee*) (Scheme 24).[57] These conditions allow electron-donating and electron-withdrawing substituents in the aromatic ring of pyrazolone as well as in its oxindole-derived partner.



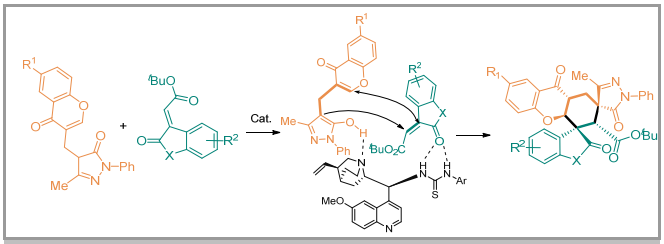
Scheme 24 Enantioselective tandem Michael-Michael cascade reaction of pyrazolone–chromone compounds and methyleneoxindoles reported by Zhou and Liu.

In addition, the authors extended their methodology to different methylene benzofuranones, obtaining moderate yields but excellent diastereoselectivities and extraordinary enantiomeric excesses (all above 96% *ee*) (Scheme 25). Aliphatic and halogen substituents are perfectly tolerated without any significant change in enantioselectivity.



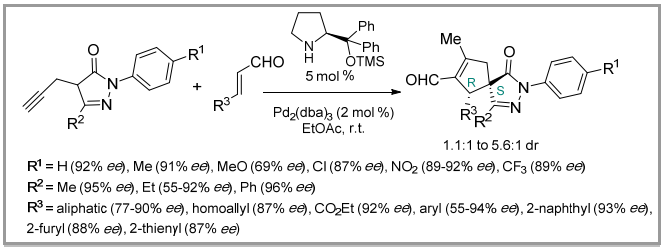
Scheme 25 Enantioselective Michael-Michael cascade reaction of pyrazolone–chromone compounds and methylene benzofuranones reported by Zhou and Liu.

The authors proposed a possible mechanism for this reaction in which both reactants are coordinated to the bifunctional catalyst in a fixed spatial order (Scheme 26). At this point, a Michael addition of the enol of the pyrazolone moiety to the α,β-unsaturated amide is produced. Then the α-carbon to that amide lead a second Michael addition to the chromone to achieve the final product in an enantiocontrolled pathway.



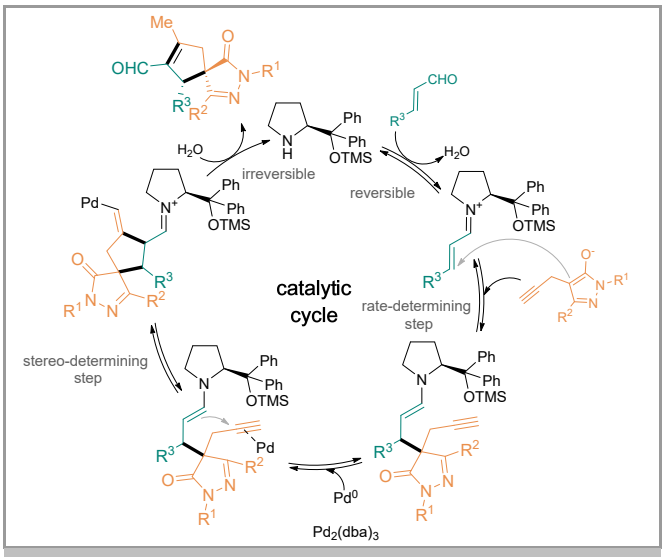
Scheme 26 Proposed mechanistic pathway for the reaction for the enantioselective Michael-Michael cascade reaction reported by Zhou and Liu.

In 2019, Herrera, Rios, Veselý and coworkers described a tandem reaction of pyrazolones bearing a propargylic moiety at C-4 with α,β-unsaturated aldehydes (Scheme 27).[58] In particular, this example consists in a Michael addition catalyzed by the Jørgensen-Hayashi catalyst[57] followed by a Pd(II)-catalyzed Conia-ene cyclization. The corresponding spirocyclic products were obtained in low to moderate diastereoselectivities (up to 5.6:1 dr), low to high yields (up to 93%) and excellent enantiomeric excesses (up to 96% ee). Electron-donating and electron-withdrawing substituents are tolerated at the *N*-aryl substituent of the pyrazolone, although the presence of a methoxy group decreases the enantioselectivity to 69% *ee*. A great variety of substituents (aliphatic, aryl, heteroaryl, homoallyl, esters, ...) are well tolerated in the α,β-unsaturated aldehyde, without modifying the enantioselectivity of the reaction. Only when 4-nitrocinnamaldehyde was used, the enantiomeric excess obtained was 55% *ee* for the major diastereoisomer (if R^2 = Et).



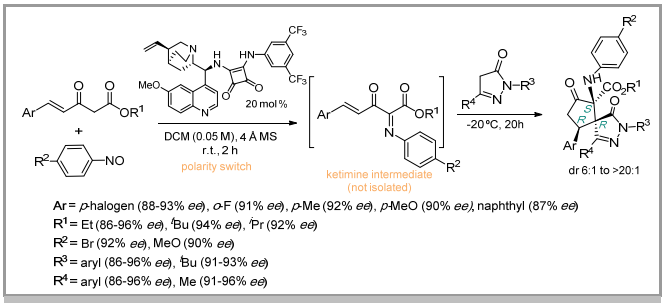
Scheme 27 Enantioselective Michael/Conia-ene reaction between pyrazolones and α,β-unsaturated aldehydes described by Herrera, Rios and Veselý.

The authors have proposed a mechanism based on kinetic studies. First the prolinol catalyst condenses with the carbonyl group of the enal to form the corresponding electrophilic chiral iminium intermediate which is attacked by the C-4 nucleophilic position of the pyrazolone. Then, the alkyne presents in this adduct is coordinated to the palladium (0) and the resulting complex is regioselectively attacked by the enamine leading to the construction of a five-membered ring. The final hydrolysis of the iminium achieves the final product (Scheme 28).



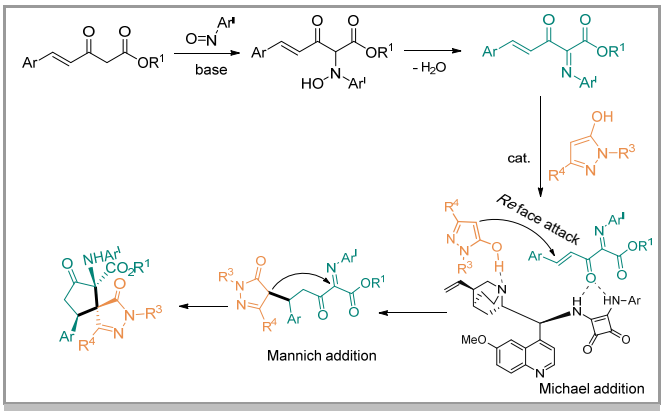
Scheme 28 Proposed mechanism pathway for the enantioselective Michael/Conia-ene reaction described by Herrera, Rios and Veselý.

Recently, Xu and co-workers have reported the enantioselective and organocatalyzed formal [4+1] cyclization of pyrazolones with an *in situ* formed imine to obtain the corresponding annulation products with three contiguous stereocenters (two of them quaternary) in moderate to good yields and stereoselectivities (Scheme 29).[60] The present methodology is a robust protocol considering that electron-withdrawing or electron-donating groups are well tolerated in the three components of the reaction, obtaining the reaction products with high enantioselectivities, although the diastereoselectivities are affected in some cases. Furthermore, the authors described the transformation of one chiral spirocyclopentanone compound into a spirocyclohexamide pyrazolone product using the Lawesson reagent, maintaining the stereointegrity of the compound.



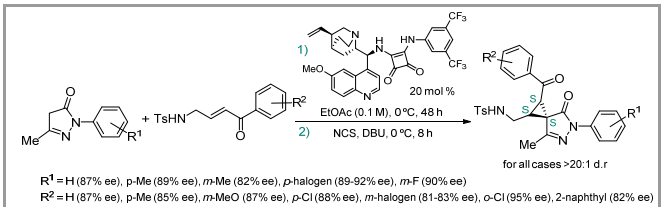
Scheme 29 Asymmetric [4+1] cyclization of pyrazolones reported by Xu

According to the proposed mechanism by the authors, the reaction starts with the *in situ* formation of the imine in the active methylene position of the α,β-unsaturated ketoester via the reaction with nitrosobenzene and subsequent water elimination. Next, a Michael addition of the enol form of the pyrazolone to the α,β-unsaturated ketone occurs by the *Re* face which is more favourable than the *Si* face attack due to the spatial distribution of both reactants coordinated to the bifunctional catalyst. Later, a second nucleophilic attack of the pyrazolone, but this time, to the ketimine affords the enantiomerically enriched desired cyclopentanone-spiropyrazolone adduct (Scheme 30).



Scheme 30 Proposed mechanistic pathway for the reaction asymmetric [4+1] by Xu

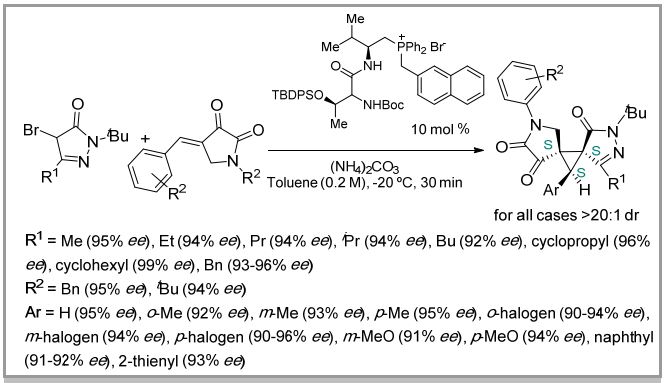
The cyclopropyl ring is a particular carbocyclic ring present in natural and pharmaceutical compounds, that has constantly fascinated organic chemists due to the highly strained structure and bonding properties of this ring.[61] The asymmetric synthesis of such compounds is a challenging task, as well as the synthesis of spirocyclic compounds containing a cyclopropyl ring. Xu and coworkers in 2019, described the enantioselective synthesis of spiropyrazolones with a cyclopropane ring. The methodology consists in an asymmetric cascade cyclization reaction (conjugate addition/chlorination/nucleophilic substitution) of pyrazolones with *N*-tosyl aminomethyl enones using a quinine-derived squaramide as organocatalyst (Scheme 31).[62] In this reaction, the nucleophilic C-4 position of the pyrazolone triggers a conjugated addition to the α,β-unsaturated ketone to form the corresponding chiral Michael adduct by the action of the chiral squaramide catalyst. A subsequent diastereoselective chlorination at the C-4 position of the pyrazolone scaffold, switches its nucleophilic polarity to electrophilic. In this way, the enolate, generated by the DBU, provokes a nucleophilic substitution at the C-4 position of the pyrazolone to construct a cyclopropyl scaffold. These final products bearing three contiguous stereocenters (one of them quaternary and spirocyclic) are obtained with low to good yields, high enantioselectivities and excellent diastereoselectivities. Regarding the scope, electron-donating and electron-withdrawing substituents in both aromatic rings are tolerated. Although, substituents at meta position as well as 2-naphthyl group, lead to a slightly decrease of enantiomeric excesses of the reaction products.



Scheme 31 Enantioselective synthesis of spiropyrazolones by a sequential reaction reported by Xu.

Another example of spirocyclopropyl construction bearing a pyrazolone scaffold was reported in 2020 by Wang's research group. The authors reported the enantioselective cyclization of 2,3-dioxopyrrolidines with 4-bromopyrazolones, affording highly substituted chiral cyclopropanes (Scheme 32).[63] The

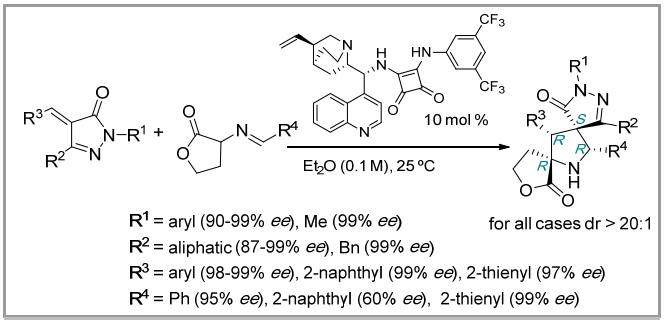
reaction starts with the nucleophilic Michael addition of 4-bromopyrazolone derivatives to 2,3-dioxopyrrolidines. After, the resulting enolate attacks the 4-position of the pyrazolone through a nucleophilic substitution generating the bis-spiro-cyclopropane-pyrazolone derivatives. This reaction is catalyzed by a chiral dipeptide-based phosphonium salt which acts as a bifunctional catalyst coordinating both substrates to achieve the final enantiomerically enriched products bearing three contiguous stereocenters in very high yields and stereoselectivities. This study has a broad scope and shows that cyclic and acyclic aliphatic chains as well as benzyl substituents are well tolerated in the pyrazolone moiety. Regarding the 2,3-dioxopyrrolidines, ^{t}Bu and benzyl groups for the *N*-substitution maintain the enantiomeric excess and electron-donating and electron-withdrawing substituents at the aromatic ring are also perfectly admitted.



Scheme 32 Asymmetric [2+1] cyclization of 4-halogen pyrazolones and 2,3-dioxopyrrolidines reported by Wang.

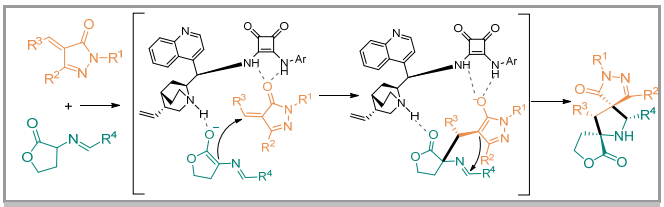
An alternative strategy to construct a quaternary center at C-4 position of the pyrazolone is the employment of alkylidene pyrazolones as electrophiles in formal [3+2] and [4+2] cycloaddition reactions.[64] Besides, this approach constitutes a straightforward access to pyrazolone-derived spirocylic compounds. These examples are remarkable due to the high functionalization of the structures obtained as well as the high stereoselectivity of the several stereogenic centers formed.

Since 2018, several elegant examples of formal [3+2] cycloadditions using alkylidene pyrazolones have been reported. A first example is the enantioselective 1,3-dipolar cycloaddition of α-imino γ-lactones using a quinine-derived squaramide as organocatalyst reported by Cai's group (Scheme 33).[65] The corresponding products bearing four stereocenters (two of them quaternary spirocentres) were obtained with good yields and, overall, excellent diastereo- and enantioselectivities. With regard to the scope of the reaction, enantiomeric excesses above 90% *ee* were achieved with almost all substituents tested. Thus, aliphatic, aryl, heterocyclic and benzyl groups are tolerated in the pyrazolone moiety. On the other hand, on α-imino γ-lactone derivatives, phenyl and thienyl substituents are permitted without modifications of enantioselectivity, but the presence of a 2-naphthyl group decreases enantiomeric excess to 60% *ee*.



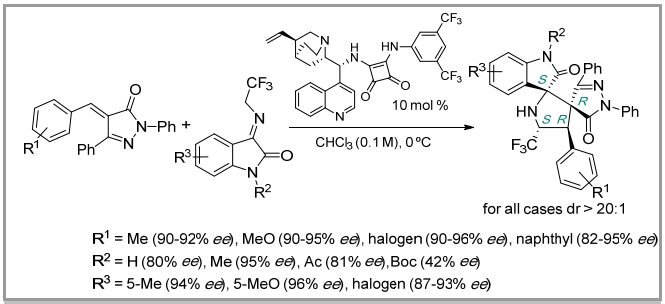
Scheme 33 Enantioselective [3+2] cycloaddition of alkylidene pyrazolones and α-imino γ-lactones reported by Cai.

Regarding the proposed mechanism, the authors postulate that both substrates are coordinated to the bifunctional organocatalyst, so that a Michael addition of the α-imino γ-lactones enolate (formed by deprotonation with the catalyst) to the alkylidene pyrazolone can occurs. After that, the resulting pyrazolone enolate can add to the electrophilic imine to generate the desired spirocyclic compound (Scheme 34).



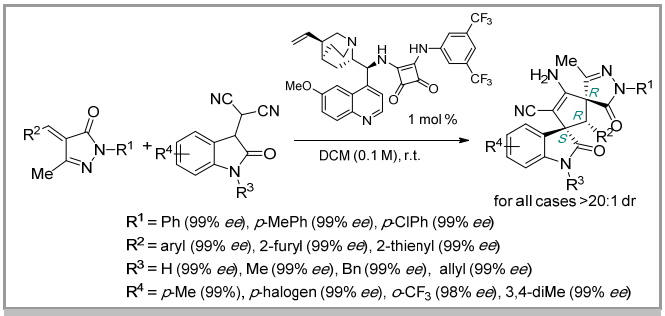
Scheme 34 Proposed mechanism pathway for the asymmetric [3+2] cycloaddition reported by Cai.

Another elegant example of 1,3-dipolar annulation using alkylidene pyrazolones was reported by Yan and co-workers in 2019. The authors developed the enantioselective organocatalytic 1,3-dipolar annulation of *N*-2,2,2-trifluoroethylisatin ketimines with alkylidene pyrazolones to synthesize the corresponding double spirocyclic products bearing four stereogenic centers (two of them quaternary and spirocyclic) with good yields and enantioselectivities and excellent diastereoselectivities (>20:1) (Scheme 35).[66] This strategy was compatible with electron-donating and electron withdrawing groups in the aromatic ring of the pyrazolone moiety as well as in the aromatic ring of the isatin-derived ketimine. In relation to *N*-substitution of the isatin derivatives, the methyl group leads to the best results in terms of enantioselectivity (95% *ee*), while acetyl and Boc protected groups decreases the enantioselectivity of the reaction (81% and 42% *ee*, respectively). Thereby, it is demonstrated that the cinchonine-derived squaramide catalyst is basic enough to generate the carbanion of the *N*-2,2,2-trifluoroethylisatin ketimines in α-position to CF_3.



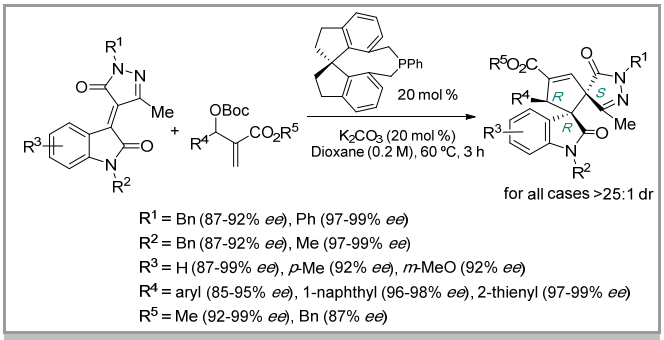
Scheme 35 Enantioselective [3+2] cycloaddition of alkylidene pyrazolones and *N*-2,2,2-trifluoroethylisatin ketimines reported by Yan.

Another interesting source of nucleophilic reagents in cycloaddition reactions are the malononitrile oxindole derivatives. Thus, Du's research group reported in 2019 the asymmetric [3+2] cycloaddition of 2-(1-methyl-2-oxoindolin-3-yl)malononitriles to alkylidene pyrazolones using a quinine-derived squaramide, affording the corresponding double-spirocyclic products with high yields and extraordinary enantio- and diastereoselectivities (Scheme 36).[67] The reaction products of this cycloaddition as well as of the reaction described above are very interesting since they present two bioactive scaffolds such as pyrazolone and oxindole moieties. The wide reaction scope study carried out shows that this spiroannulation is very robust as the enantioselectivity is maintained above 98% *ee* for all the substituents tested in pyrazolone and the malononitrile derivatives.



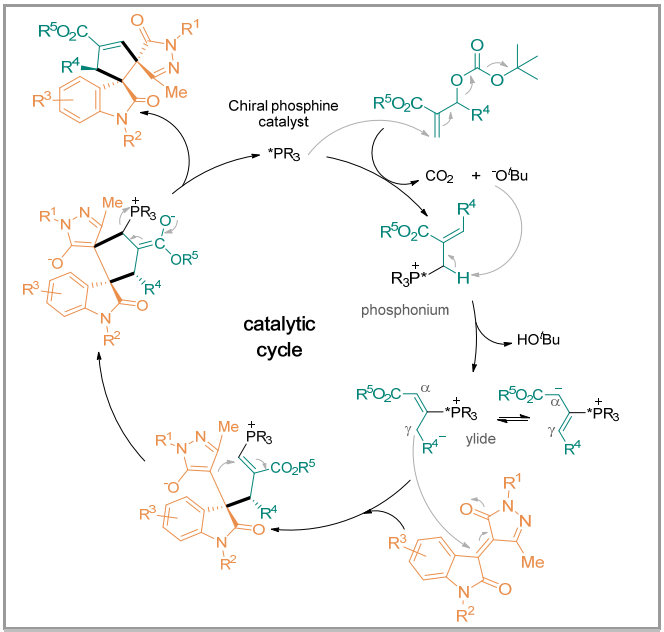
Scheme 36 Asymmetric [3+2] cycloaddition of alkylidene pyrazolones and 2-(1-methyl-2-oxoindolin-3-yl)malononitriles reported by Du.

As we said before, compounds bearing pyrazolone and oxindole moieties are very interesting for pharmaceutical and medicinal chemistry, because these particular scaffolds are present in numerous biological active compounds. In the previous examples the pyrazolone and the oxindole scaffolds were present in each of the two partners. However, these two scaffolds can be present in one of the partners of the [3+2] cycloaddition reaction. With this idea in mind, in 2019 Ullah, Lu and coworkers described the use of a pyrazolonyldiene oxindoles as electrophiles with Morita-Baylis-Hilman (MBH) carbonates as nucleophiles. A successfully asymmetric phosphine-catalyzed [3+2] annulation was accomplished. The desired spirocyclic products bearing three contiguous stereocenters (two of them quaternary and spirocyclic) were achieved in high to excellent yields and enantioselectivities and excellent diastereoselectivities (Scheme 37).[68] Enantiomeric excesses are above 85% *ee* regardless of the nature of substituent. Thus, aliphatic, benzyl and aryl substituents are well admitted in this catalytic system. However, it must be indicated that *ortho*-substituted aromatic ring in the MBH carbonate lead to enantioselectivities under 90% *ee*.



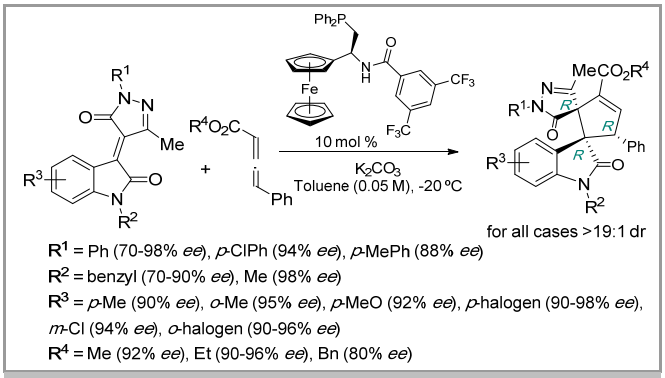
Scheme 37 Enantioselective [3+2] cyclization of pyrazolonyldiene oxindoles and MBH carbonates reported by Ullah and Lu.

In this example, the authors postulate a mechanism, in which the formation of the ylide by the reaction of the achiral catalyst *PR_3 with the MBH carbonate is the first step (attack of phosphine on the terminal olefinic carbon atom followed by deprotonation by the *tert*-butoxide formed *in situ*). Then, a γ-addition to the pyrazolonyldiene oxindole occurs and the subsequent intramolecular Michael addition of the enolate of the pyrazolone followed by the release of the catalyst achieve the final product in an enantiocontrolled pathway (Scheme 38).



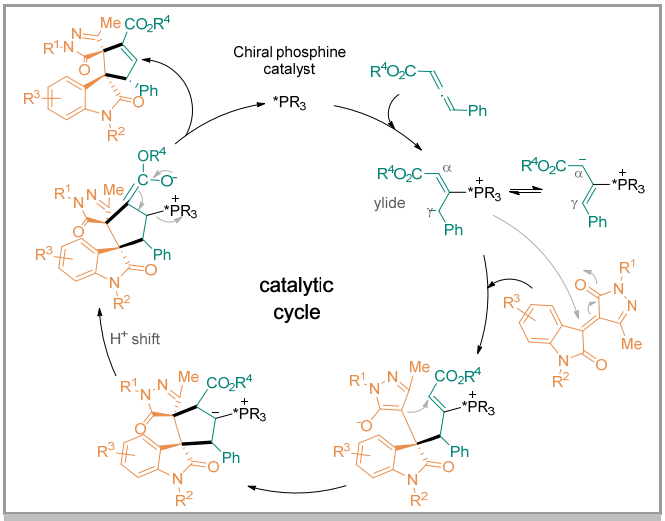
Scheme 38 Proposed mechanism pathway for the [3+2] cycloaddition reported by Ullah and Lu.

Curiously, an epimer of the previous product can be obtained using the methodology reported by Zong in 2020.[69] His group described the enantioselective [3+2] cycloaddition of allenes (ethyl 4-phenylbuta-2,3-dienoate) with a pyrazolonyldiene oxindole using a chiral phosphine as catalyst. The corresponding dispirocyclic products were obtained in high yields and enantioselectivities and excellent diastereoselectivities (Scheme 39). Great variability of substituents is tolerated, electron-donating and electron-withdrawing groups can be present in any of the aromatic rings maintaining high values of enantiomeric excess. Furthermore, aliphatic chains are also suitable as substituents in the allene and for the *N*-substitution of the oxindole motif.



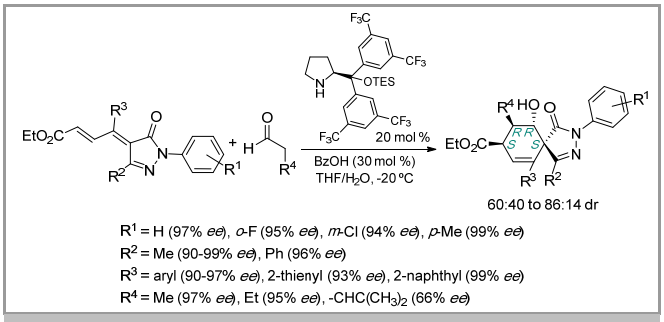
Scheme 39 Asymmetric [3+2] annulation of pyrazolonyldiene oxindoles and allenes reported by Zhong.

According to the proposed mechanism by the authors, first, the allene is attacked by the chiral phosphine catalyst (*PR_3) to form the ylide (zwitterionic intermediate) which trigger a conjugated γ-addition to the pyrazolonyldiene oxindole. The enolate formed in the pyrazolone moiety allows the cyclization and the subsequent H^+ shift and elimination of the catalyst lead to the formation of the desired product (Scheme 40).



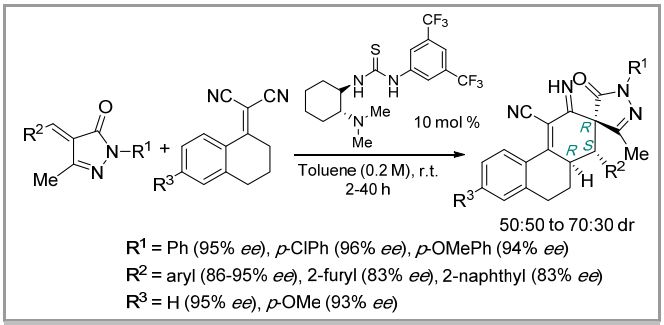
Scheme 40 Proposed mechanism pathway for enantioselective [3+2] annulation reported by Zhong.

Other enantioselective formal [4+2] cycloaddition reactions using alkylidene pyrazolone has been described. In 2019, He and Han described the stereoselective 1,6-addition of aldehydes to α,β,γ,δ-unsaturated pyrazolones using the Hayashi-Jørgensen organocatalyst to afford the corresponding chiral [4+2] annulation products with good yields and diastereoselectivities and generally high enantiomeric excesses (Scheme 41).[70] Aliphatic and aromatic substituents are well tolerated in the pyrazolone motif as well as in the aldehyde, being the enantiomeric excesses of all the reaction products above 90% *ee* with the only exception of the 4-methyl-2-pentenal which lead to the corresponding reaction product with a moderate enantioselectivity (66% *ee*). Moreover, the authors tested the biological activity of the chiral pyrazolone derivatives, and they found that some compounds suppressed proliferation in a panel of cancer cell lines.



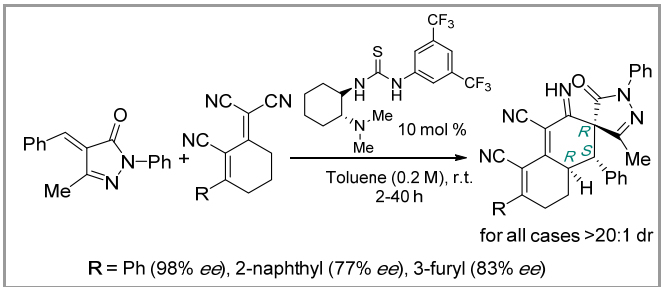
Scheme 41 Enantioselective formal [4+2] cycloaddition of α,β,γ,δ-unsaturated pyrazolones and aldehydes reported by He and Han.

Another example of [4+2] cycloaddition using alkylidene pyrazolones was reported by Lattanzi in 2019.[71] The authors describe the enantioselective vinylogous addition of dicyanoalkylidenes to α,β-unsaturated pyrazolones followed by a cyclization reaction using the Takemoto's organocatalyst,[72] obtaining the corresponding pyrazolone-fused spirocyclohexenimines bearing three stereocenters with low to moderate yields but high enantioselectivities (Scheme 42). The reaction tolerates electron-donating an electron-withdrawing groups in the aromatic rings of the alkylidene pyrazolones, obtaining high enantiomeric excess. In contrast, 2-furan and *ortho*-methylphenyl substituents as R^2 in pyrazolone causes a decrease in the enantioselectivity (83% and 86% *ee*, respectively).



Scheme 42 Asymmetric [4+2] cyclization of alkylidene pyrazolones and dicyanoalkylidenes reported by Lattanzi.

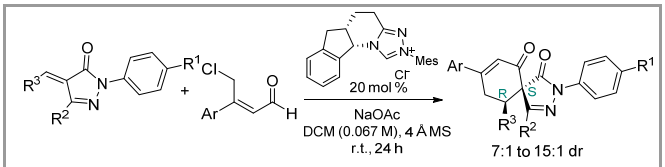
Furthermore, the authors also tested several dicyanoalkylidenes that did not share a fused aromatic ring achieving excellent diastereoselectivities (Scheme 43).



Scheme 43 Asymmetric [4+2] cyclization of alkylidene pyrazolones and dicyanoalkylidenes reported by Lattanzi.

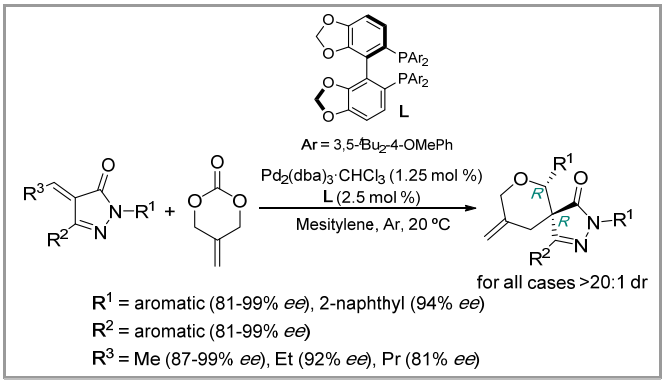
In 2019, Yang and Zhong described another example of enantioselective [4+2] cyclization. In this case, the authors described the annulation reaction of γ-chloroenals and alkylidene pyrazolones using *N*-heterocyclic carbenes (NHC) as

catalysts. The corresponding products were obtained in good yields and diastereoselectivities and excellent enantiomeric excesses (Scheme 44).[73] The extensive study of the reaction scope revealed that this methodology is extremely robust maintaining a 99% *ee* for all substituents tested except when a cyclohexyl group is present as R^3 (90% *ee*) or when naphthyl or thiophene-derived γ-chloroenals are used (92% and 96% *ee*, respectively). Thus, aliphatic and aryl substituents with different electronic character are perfectly tolerated in both substrates. Two interesting examples of diastereoselective [4+2] cycloadditions using α,β-unsaturated pyrazolones and nitrofunctionalized organic compounds were reported by Singh recently. However, the development of enantioselective versions of these reactions was unsuccessfully.[74]



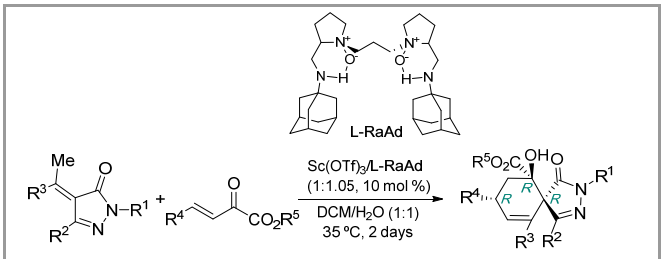
Scheme 44 Asymmetric organocatalytic [4+2] cyclization of alkylidene pyrazolones and γ-chloroenals reported by Yang and Zhong.

In 2020, Guos's research group developed the first enantioselective [4+2] cyclization of alkylidene pyrazolones with methylidenetrimethylene carbonates using palladium catalysis (Scheme 45).[75] The corresponding products bearing two contiguous stereocenters (one of them spirocyclic) were obtained in high to excellent yields and enantioselectivities (83-99% and 81-99% *ee*) and with excellent diastereoisomeric ratios (>20:1 for all examples). Regarding the scope of the reaction, for the *N*-substitution as well as for the β-position in the pyrazolone electron-donating and electron-withdrawing substituents in any position at the phenyl group are perfectly tolerated. Aliphatic substituents have not been tested for these positions. For the olefinic subsituent in the pyrazolone, a methyl or ethyl group have no impact on the enantioselectivity, but a propyl group decreases the enantiomeric excess to 81% *ee*.



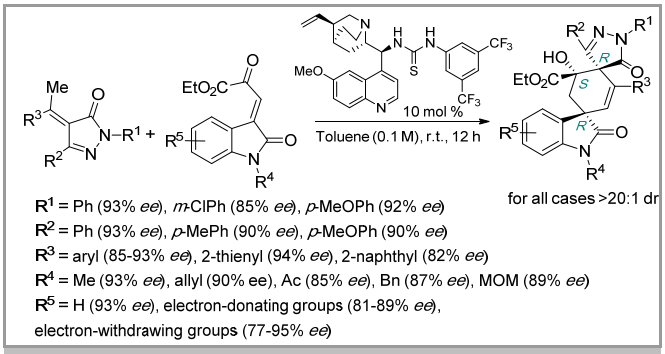
Scheme 45 Enantioselective [4+2] cyclization of alkylidene pyrazolones with methylidenetrimethylene carbonates reported by Guo.

Besides of the previous [4+2] cycloaddition reactions using alkylidene pyrazolones as electrophiles, several examples of asymmetric [4+2] annulations reactions using a vinylogous strategy have also been described. In this context, Feng's research group described in 2019 the asymmetric tandem reaction of β,γ-unsaturated-α-ketoesters and alkylidene pyrazolones in aqueous phase using a chiral Sc(III) complex as catalyst.[76] The desired spirocyclohexene pyrazolones bearing three stereocenters were obtained in good diastereoselectivities and high yields and enantioselectivities (Scheme 46). Focusing on the reaction scope, an aromatic ring seems to be necessary for the *N*-substitution of the pyrazolone while aliphatic groups can be tolerated in any of the other two positions tested for the nucleophile (R^2 and R^3). Regarding the electrophile, aromatic and aliphatic rings are permitted in γ-position of the β,γ-unsaturated α-ketoester, while aliphatic alkoxy groups can be cyclic and acyclic.



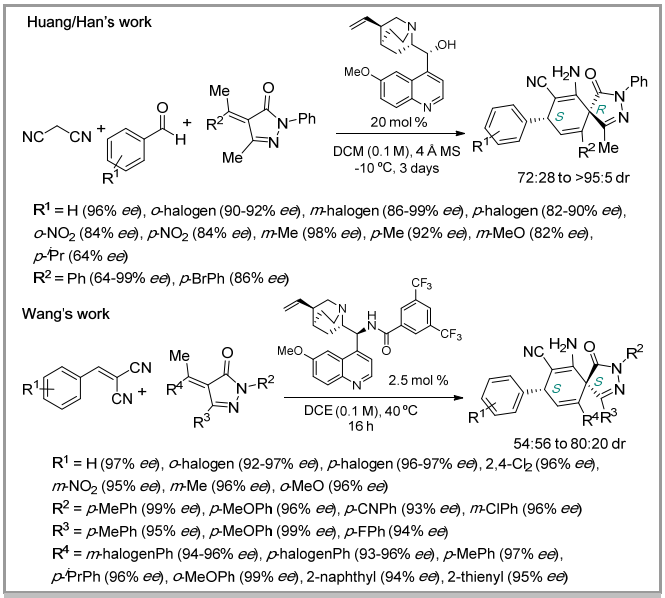
Scheme 46 Asymmetric cascade reaction between alkylidene pyrazolones and β,γ- unsaturated-α-ketoesters reported by Feng.

Another example of asymmetric [4+2] cycloaddition using α-arylidene pyrazolones as vinylogous reagents has recently been reported by Wang. The authors described the tandem reaction (Michael/cyclization) of alkylidene pyrazolones to β,γ-unsaturated α-ketoesters oxindoles using a cinchonine-derived thiourea catalyst to obtain the corresponding products bearing three quaternary centers (two of them spirocenters) with excellent diastereoselectivities (> 20:1 for all cases) and high yields and enantioselectivities (Scheme 47).[77] According to the scope of the reaction, electron-donating and electron-withdrawing groups are well tolerated in the aromatic ring of the oxindole (R^1 and R^2). Regarding the substituents of the alkylidene pyrazolone, only aromatic substituents were tolerated at the nitrogen and at C-5, as well as R^3. The reaction is very sensitive to steric effects, and low conversion was observed when the pyrazolinone derived from 2′-methoxyacetophenone was employed as a substrate. The authors could scale up the reaction, obtaining 1.02 g of the product (76% yield) with 83% ee and >20:1 dr.



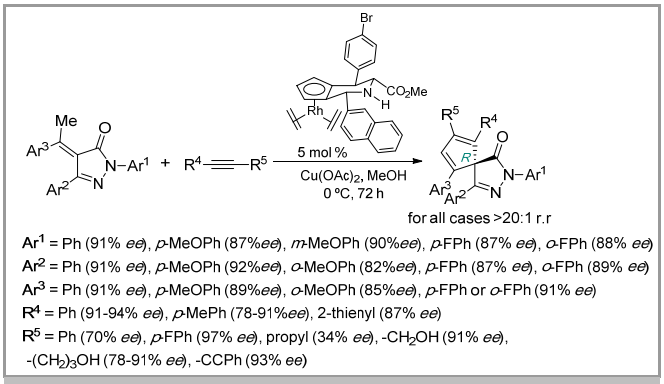
Scheme 47 Asymmetric formal [4+2] annulation of alkylidene pyrazolones and β,γ-unsaturated α-ketoesters oxindoles reported by Wang.

In 2019, Huang and Han described the quinine catalysed stereoselective tricomponent sequence reaction of malononitrile, benzaldehyde and α-arylidenepyrazolone including Knoevenagel reaction followed by a vinylogous addition to synthesize the corresponding spirocyclic compounds in good to excellent diastereoselectivities and high yields and enantiomeric excesses (Scheme 48).[78] This example represents an organocatalytic [1 + 2 + 3] annulation reaction, and is very similar to a [3+3] cycloaddition of α-arylidene pyrazolinones and 2-benzylidenemalononitriles reported by Wang the same year.[79] In the report by Huang, the organocatalyst is simple quinine and the diastereoselectivities are superior than the report of Wang, in which a quinine-derived squaramide is used as catalyst. Moreover, the yields of the report of Huang are better than the reported by Wang. Although, Huang uses 20 mol% of catalysts, while Wang only 2.5 mol%. The reaction tolerates a variety of substituents at the aromatic ring of the benzaldehyde as well as in the pyrazolone. Wang reported more examples of chiral spirocyclohexadiene-pyrazolone products than Huang.



Scheme 48 Asymmetric vinylogous formal cycloaddition reaction of α-arylidene-pyrazolones and 2-benzylidenemalononitriles reported by Huang and Wang

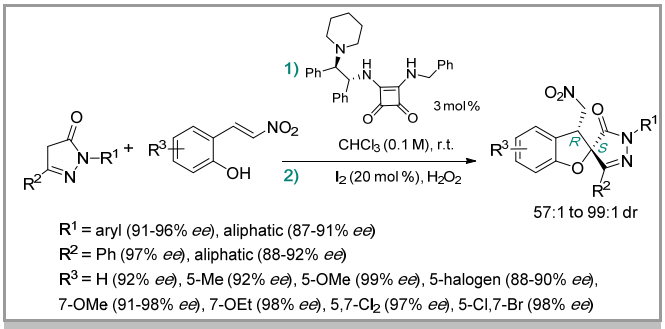
Alkynes have also been used as reagents in enantioselective cycloaddition reactions of alkylidene pyrazolones as in the example reported by Waldmann and Antonchick in 2019.[80] The authors reported the regio- and enantioselective vinylogous addition of α,β-unsaturated pyrazolones to internal alkynes (symmetric and asymmetric) using as catalyst a chiral rhodium(III) complex (Scheme 49). The pyrazolone-derived spirocyclic products are obtained as only one regioisomer (>20:1 r.r.) in good to high yields and high enantioselectivities. Regarding the reaction scope, electron with-drawing and electron-donating groups are tolerated in any of the three aromatic substituents of the α-arylidenepyrazolone. In the alkyne reagent, aromatic, alkynyl and aliphatic chains bearing a hydroxyl group are well tolerated, while aliphatic substituents such as propyl decreases the enantioselectivity to 34% *ee*.



Scheme 49 Regio- and stereoselective vinylogous addition of α-arylidene pyrazolones to alkynes reported by Waldmann and Antonchick.

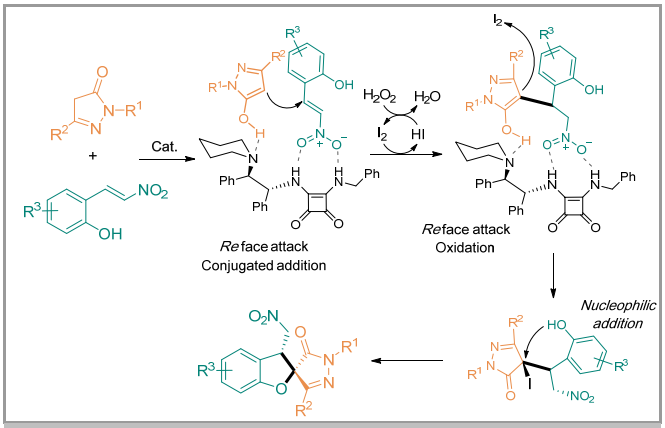
4.2 Asymmetric synthesis of chiral spiropyrazolones bearing a heteroatom in the spirostereogenic center.

Some strategies that combine the generation of an spiropyrazolone derivative with the formation of a quaternary centre bearing a heteroatom have been described in the literature. In 2018, Xia and Xu described the one-pot reaction of pyrazolones and 2-hydroxy-β-nitrostyrene using the combination of organocatalysis and iodine catalysis to synthesize dihydrobenzofuran and pyrazolone-derived spirocyclic products in moderate to good yields, excellent diastereoselectivities (>99:1 in almost all cases) and high enantiomeric excesses (up to 98% ee) (Scheme 50).[81] This strategy allows aryl and aliphatic substituents in the pyrazolone moiety without big changes of enantiomeric excess. It would be worth highlighting that when the substituent on the olefinic carbon of pyrazolone is a phenyl group the enantiomeric excess rises up to 97% *ee*. Regarding the nitrostyrene, electron-donating and electron-withdrawing substituents are perfectly tolerated in the aromatic ring, the best results being obtained when methoxy groups are accommodated at *ortho*- and *para*- positions of the aromatic ring. While in the pyrazolone derivatives, the reaction tolerates several substituents such as Me, Et, Pr, ^{i}Pr, cyclopropyl and Ph at the 5-position of the pyrazolone. Different aliphatic and aromatic groups as substituents at the nitrogen atom of the pyrazolone lead to excellent results in all cases.



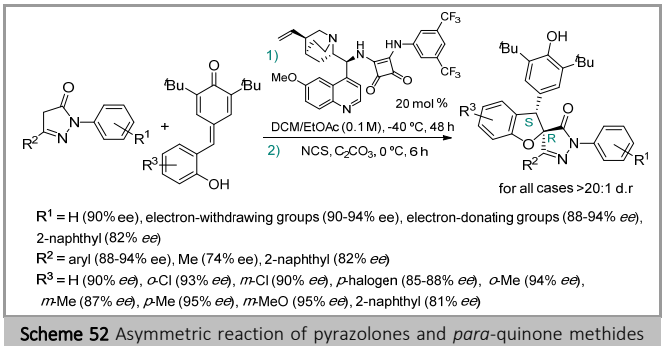
Scheme 50 Asymmetric one-pot reaction of pyrazolones and 2-hydroxy-β-nitrostyrenes reported by Xia and Xu.

According to the authors the mechanism of this reaction is a cascade reaction in which a conjugated addition takes place first, followed by an iodination and a nucleophilic substitution reaction (SN2). Hydrogen peroxide is used to reoxidize the hydrogen iodide to iodine so it can be used in a catalytic amount (Scheme 51).



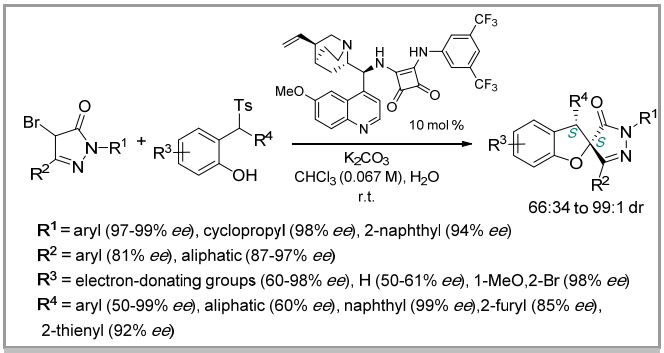
Scheme 51 Proposed mechanism pathway for the reaction of pyrazolones and 2-hydroxy-β-nitrostyrenes reported by Xia and Xu.

In a similar way, Wei and Xu described the enantioselective 1,6-addition of pyrazolones to *para*-quinone methides, followed by chlorination with NCS and nucleophilic substitution to achieve the spiropyrazolones in high yields and enantioselectivities and excellent diastereoselectivities (Scheme 52).[62] Substituents with different electronic characteristics are well tolerated in both aromatic rings at N-2 and C-5 of the pyrazolone, although 2-naphthyl substituent slightly decreases the enantiomeric excess. With regard to the *para*-quinone methides, electron-donating and electron-withdrawing substituents at the fenolic aromatic ring are perfectly tolerated, although 2-naphthyl substituent also slightly decreases the enantiomeric excess.



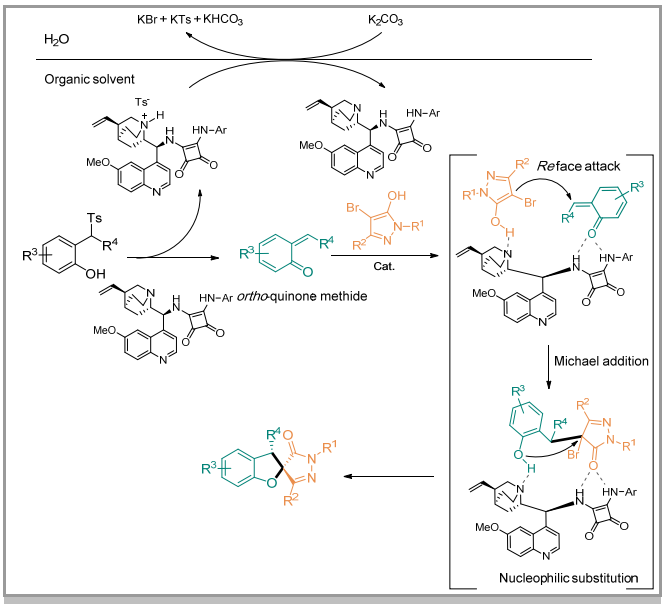
Scheme 52 Asymmetric reaction of pyrazolones and *para*-quinone methides reported by Wei and Xu.

Another example of the use of pyrazolone and quinona methides was reported by Wang and Xu in 2019.[82] These authors developed an enantioselective organocatalytic tandem reaction (Michael addition plus nucleophilic substitution) of 4-bromopyrazolones to *ortho*-quinone methides generated *in situ* in a biphasic organic solvent:H_2O system to obtain the corresponding spiro-derived compounds with two vicinal stereocenters in good to great yields and excellent stereoselectivities (up to 99:1 dr and 99% *ee*) (Scheme 53). This [1+4] formal cycloaddition constitutes a robust methodology since it tolerates a high variety of substituent with different electronic characteristics in the aromatic ring of the pyrazolone as well as in the 2-[phenyl (tosyl)methyl]phenols. However, in order to reach enantioselectivities over 90%, the presence of a methoxy group at *ortho* position of the phenolic hydroxyl is necessary.



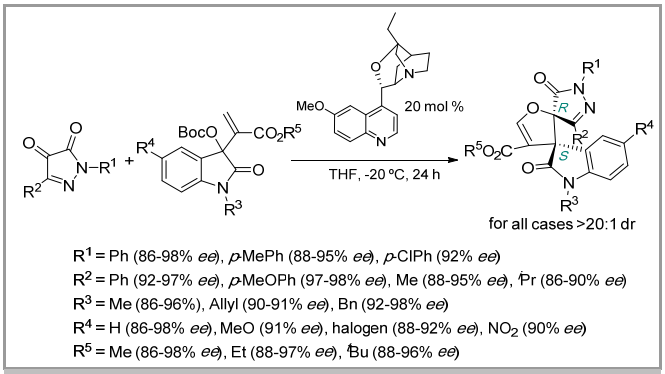
Scheme 53 Tandem [1+4] annulation of 4-halopyrazolones with *ortho*-quinone methides reported by Wang and Xu.

The biphasic system organic solvent:H_2O has been shown to be necessary for the correct enantiocontrol of the reaction. According to the mechanism (Scheme 54), the inorganic base is solubilized in water and is necessary to recover the catalyst into its active form. As shown, the tertiary amine of the quinine-derived squaramide forms the *ortho*-quinone methide *in situ* by deprotonating the phenolic hydroxyl followed by elimination of the tosyl group. Then, the nucleophilic C-4 position of the pyrazolone attacks the β-position of the *ortho*-quinone methide and the oxygen atom of the newly formed phenolic hydroxyl compound is involved in a nucleophilic substitution reaction to construct the desired spiropyrazolone product in a stereocontrolled process.



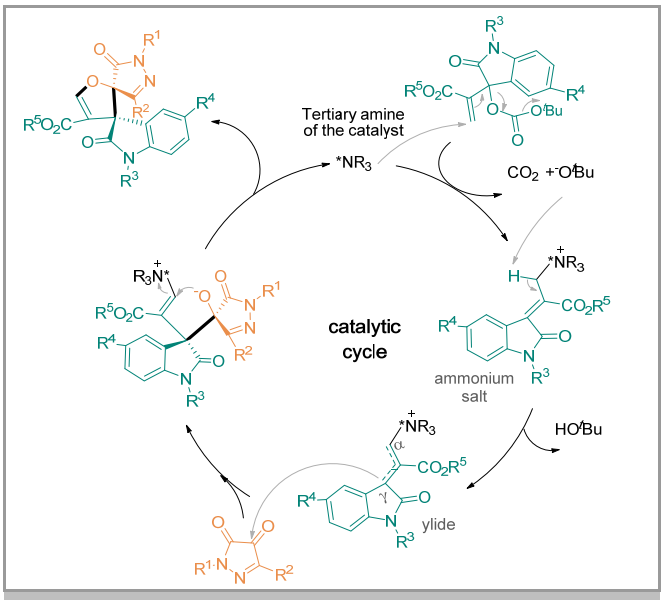
Scheme 54 Proposed mechanism pathway for the tandem [1+4] annulation reported by Wang and Xu.

Morita-Baylis-Hillman (MBH) carbonates have been described as useful scaffolds in the formation of highly functionalized products.[83] The use of this kind of nucleophiles, in concrete isatin derived Morita-Baylis-Hillman carbonate, in the asymmetric and β-isoquinidine-catalyzed [3+2] cycloaddition with pyrazole-4,5-diones described by Bhat and co-workers in 2020 allows the construction of the corresponding di-spirocyclic product with a pyrazolone moiety bearing one of the spirocenters (Scheme 55).[84] The corresponding [3+2] cycloadducts are obtained in high yields and enantioselectivies and with excellent diastereoisomeric ratios (>20:1 in all cases). Regarding the scope, electron-donating and electron-withdrawing groups are well tolerated in the *N*-aryl substitution of pyrazole-4,5-dione and in the aromatic ring of the oxindole moiety. Several substituents (Me, ^{i}Pr, Ph and *p*-MeOPh) are also tolerated at the C-3 position of the pyrazole-4,5-dione.



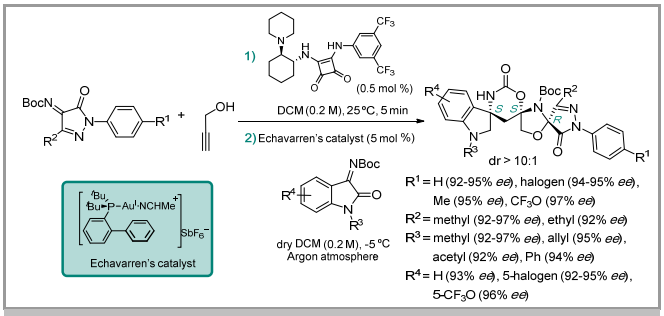
Scheme 55 Enantioselective [3+2] cycloaddition with pyrazole-4,5-diones and isatin derived MBH carbonate reported by Bhat.

The authors proposed a mechanism in which, in first place, the tertiary amine of the β-isoquinidine catalyst attacks to the MBH carbonate leading to a chiral ammonium salt which is deprotonated by the *tert*-butoxide (formed *in situ*) to achieve the corresponding ylide. The γ-position of this ylide attacks to the carbonyl group of the pyrazole-4,5-dione and the adduct undergoes an intramolecular reaction leading to the formation of the final product in an enantiocontrolled pathway (Scheme 56).



Scheme 56 Proposed mechanistic pathway for the [3+2] cycloaddition reported by Bhat.

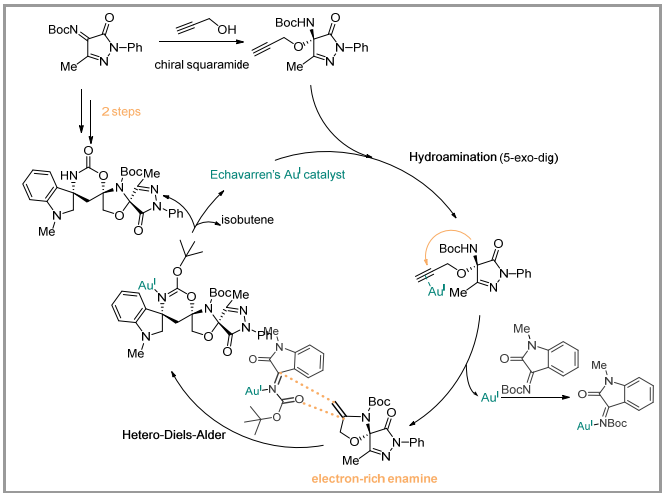
Other example of the construction of spiropyrazolones bearing a heteroatom was reported by Li's group in 2018. The authors developed an enantioselective organocatalytic 1,2-addition of propargylic alcohols to pyrazolone-derived *N*-Boc ketimines catalyzed by a chiral bifunctional squaramide, followed by a diastereoselective base-Au^{I}-catalyzed cascade hydroamination/hetero-Diels-Alder and elimination of the protecting groups as isobutene using isatin-derived ketimine as electrophile and the Echavarren's catalyst.[85] This sequential methodology, allows the synthesis of spirocycles bearing three tetrasubstituted stereogenic centers with good yields and excellent enantioselectivities (92-97% *ee*) (Scheme 57).[86] This sequential synthesis allows great variability in the substituents of both ketimines. Excellent enantiomeric excesses are obtained when substituents with different electronic characteristics (Me, F, Cl, Br, OCF_3) are present in the aromatic ring bonded to the nitrogen of the pyrazolinone ketimine. Great results are achieved when electron-withdrawing (F, Cl, Br, I) or electron-donating substituents (OCF_3) are present in the aromatic ring of the isatin-derived ketimines.



Scheme 57 Enantioselective cascade reaction with pyrazolone ketimines and propargylic alcohols reported by Li.

The authors have suggested a feasible mechanism for this sequential reaction (Scheme 58). Firstly, the oxygen atom of in

the propargylic alcohol attacks the ketimine in the pyrazolone in an asymmetric 1,2-addition reaction to form the corresponding aminal in an enantiomerically controlled path by the chiral squaramide. Then, reaction mixture is filtrated over silica gel pad to remove the organocatalyst because the tertiary amine is not compatible with the cationic gold(I) catalyst. Once the bifunctional catalyst is removed, Echavarren's gold catalyst can be added to activate the triple bond of the propargylic ether, which will be attacked diastereoselectively by the *N*-protected amine to form the corresponding electron-rich enamine as only isomer by a 5-exo-digonal cyclization. The double bond of the recently formed exocyclic enamine will act as dienophile of a hetero-Diels-Alder reaction with the *N*-Boc isatin-derived ketimine as diene. Elimination of the protecting group as isobutene achieves the final chiral product with excellent stereoselectivity.



Scheme 58 Proposed mechanism pathway for the reaction of pyrazoloneketimines and propargylic alcohols reported by Li.

5 Conclusion

Pyrazolone skeleton have proven to be a privileged scaffold in medicinal chemistry and pharmaceutical industry. Recently, the examples describing the asymmetric synthesis of chiral pyrazolones have grown exponentially in the scientific community. In the last three years, many research groups have reported the synthesis of chiral pyrazolone derivatives bearing a tetrasubstituted stereogenic center at C-4 position using several catalytic enantioselective methodologies. Using chiral metal or organocatalysts, various C–C, C-O, C-S, C-N and C–X bond formation reactions as well as cascade sequences affording chiral spirocycles have been described with excellent results both in yields, regioselectivities and stereoselectivities. However, the research groups have paid more attention in the development of asymmetric methodologies for the synthesis of chiral pyrazolones rather than studying their applications. Nevertheless, we believe that further applications of chiral pyrazolones derivatives will be reported soon, as well as new methodologies for the synthesis of such heterocyclic compounds.

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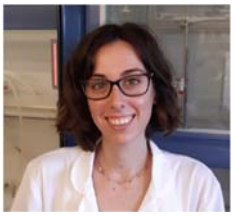
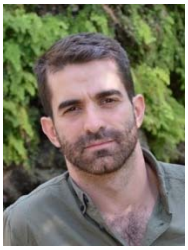
Biosketches

	Laura Carceller-Ferrer received her degree in Chemistry in 2018 and her master degree in Organic Chemistry in 2019 (both from Universitat de València). Currently, she is working in her PhD about the enantioselective functionalization of pyrazolones and the synthesis of nitrogen-containing heterocyclic compounds under the supervision of Dr. Carlos Vila and Prof. Dr. José Ramón Pedro at the same university.
	Gonzalo Blay (Real de Gandia, Valencia, 1964) received his degree in chemistry (1987) and his Ph.D. (1992) from the University of Valencia. He has been a Marie Curie postdoctoral fellow at the Agricultural University of Wageningen, The Netherlands, with Professor A. de Groot (1993–94) and visiting researcher at Aarhus University, Denmark, with Professor K. A. Jørgensen (2005). In 1996, he became Associate Professor at the Department of Organic Chemistry of the University of Valencia and was appointed Full Professor in 2012. His research interest includes organic synthesis and the development of catalytic methodologies, in particular asymmetric catalysis.
	José R. Pedro graduated in chemistry from Valencia University, Spain, in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at Valencia University. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at Valencia University (AsymCat, GIUV13).
	Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from Valencia University. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling reactions with organolithium reagents and asymmetric catalysis. In 2017, he was appointed as a 'Ramón y Cajal' researcher at the Organic Chemistry Department, Valencia University. His current research interests are asymmetric catalysis and photocatalysis.

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