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Advanced Synthesis & Catalysis

Asymmetric Addition and Cycloaddition Reactions with Ylidene-Five-Membered Heterocycles

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Abstract: Five-membered heterocycles bearing an exocyclic double bond have been successfully used as substrates in asymmetric addition and cycloaddition reactions. Ylidene-heterocycles are attractive substrates due to their high functionalization and the presence of an electrophilic conjugated exocyclic double bound that can participate in nucleophilic addition reactions as well as cycloaddition reactions, which may be triggered by the formation of aromatic intermediates or products in many cases. During the last decades, catalytic methodologies have been developed using ylidene-heterocycles as substrates in order to synthesize useful optically active heterocyclic derivatives. 4-Ylidene-pyrazol-5-ones, isoxazolin-5-ones, 2,3-dioxopyrrolidines, rhodanines, oxazolidindiones, Erlenmeyer-Ploch azlactones and 5-ylidene-thiazolones have been successfully used as substrates in asymmetric reactions. This review collects the powerful research in asymmetric addition and cycloaddition reactions where ylidene-five-membered heterocycles have been used.

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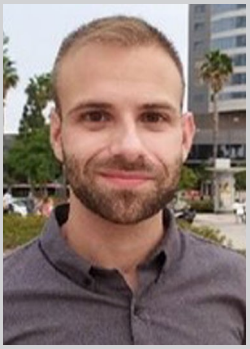
Keywords: asymmetric catalysis; addition reactions; cycloaddition reactions; ylidene-heterocycles; re-aromatization reactions



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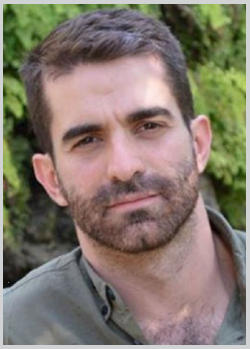

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1. Introduction

Asymmetric catalysis is one of the most powerful tools in organic chemistry to afford desired chiral compounds from simple achiral starting materials with high efficiency.[1] This field has received growing attention due to the high demand of enantiopure products in the pharmaceutical and agrochemical industry as well as in the materials chemistry area.[2] In this context, catalytic enantioselective methods for the formation of C–C and C–heteroatom bonds have represented an important challenge to organic chemists during the last decades.[3] Straightforward and useful synthetic approaches to this goal are the asymmetric addition of nucleophiles and cycloaddition reactions with electron-deficient alkenes, which constitute highly atom-economy processes. Accordingly, the development of new methodologies based on asymmetric conjugated addition or cycloaddition reactions has been broadly studied.[4] Commonly, these protocols play a pivotal role in the synthesis of natural products or in the preparation of important building blocks to be used in organic synthesis.

Among electrophilic double bonds, those occupying an exocyclic position with respect to a heterocycle result especially attractive in asymmetric catalysis giving rise to a variety of heterocycles decorated with a chiral chain. In many cases, these asymmetric reactions are triggered by the formation of intermediates or products with aromatic character. Chiral heterocycles have found a wide range of applications in medicinal and pharmaceutical chemistry and they are present in many natural products such as antibiotics, alkaloids or DNA.[5] For that reason, the use of heterocycles bearing exocyclic double bonds as electrophiles in asymmetric reactions represent an important approach to the synthesis of highly functionalized chiral heterocyclic products with potential use in many different fields.

In this review, we describe the efforts to develop efficient and useful enantioselective methodologies using five-membered heterocycles bearing exocyclic double bonds as electrophiles *via* asymmetric catalysis. This review identifies the ylidene-heterocycles most commonly used in asymmetric catalysis and review the most important reactions involving transformations on the exocyclic double bond, which in many cases are facilitated by re-aromatization processes (Figure 1).

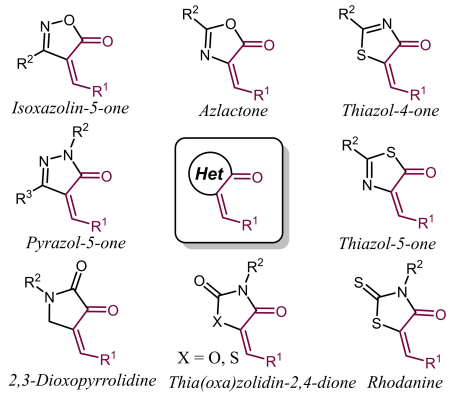


Figure 1. Ylidene-heterocycles commented in this review.

2. 4-Ylidene-Pyrazol-5-Ones

Pyrazol-5-ones are five membered heterocycles that can be found in a broad variety of bioactive compounds.[6] Some pharmaceutical uses include neuroprotector activity,[7] antitumor activity,[8] antioxidant activity[9] and anti-inflammatory activity.[10] Furthermore, agrochemical uses as antibacterials and insecticidals have been demonstrated.[11] Besides the biological uses, novel materials containing the pyrazolone scaffold have been developed, such as analytical detectors[12] and dyes[13] (Figure 2).

4-Ylidene-pyrazol-5-ones have shown to be very versatile substrates in asymmetric addition reactions obtaining novel attractive structures.[14] The exocyclic double bond can act as Michael acceptor, thus generating branched pyrazoles, commonly stabilized in the enol form of the pyrazol-5-one moiety. Furthermore, the 4-ylidene-pyrazolone scaffold contains two potential nucleophilic sites that, after the initial Michael addition step, can lead to fused pyrazoles or spiropyrazol-5-ones in formal cycloaddition reactions (Scheme 1). 3-Substituted 4-ylidene-pyrazol-5-ones prefer the more stable exocyclic double bond with the *Z*-configuration. A literature survey evidences that this stereochemistry is not always properly represented.

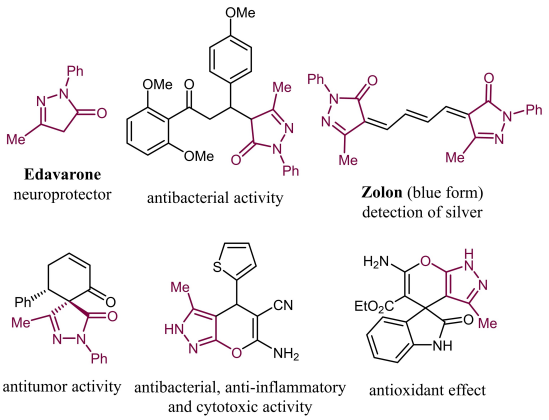
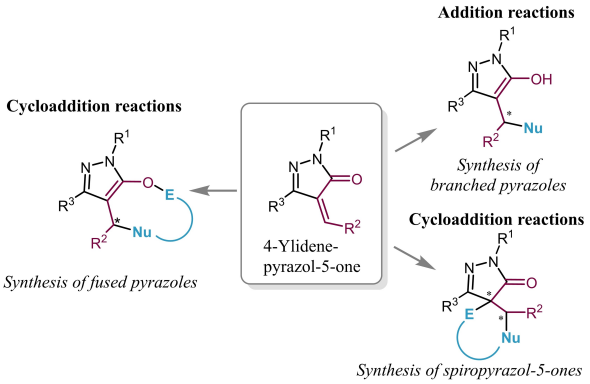


Figure 2. Selected bioactive compounds containing the pyrazol-5-one and pyrazole scaffolds.



Scheme 1. Reactivity of 4-arylidene-pyrazol-5-ones.

2.1. Organocatalytic Reactions with 4-Ylidene-Pyrazol-5-Ones

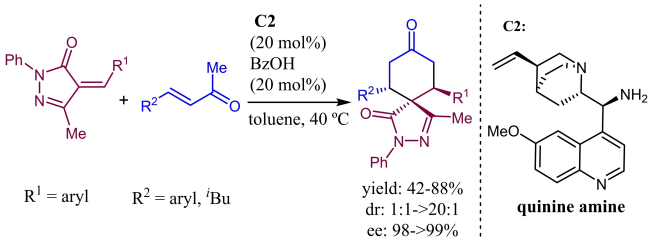
Most of the asymmetric reactions described with 4-ylidene-pyrazolones use organocatalytic methods. As shown below, enamine, *N*-heterocyclic carbene, phosphine and bifunctional catalysis have allowed the reaction of 4-ylidene-pyrazolones with a broad variety of pro-nucleophiles.

2.1.1. Reactions via Enamine Catalysis

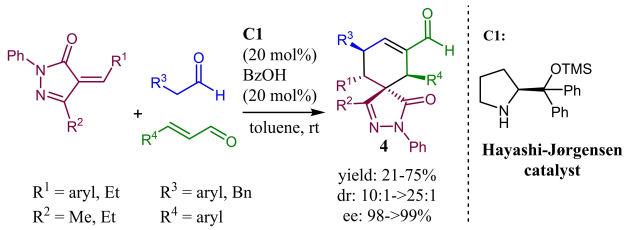
The first asymmetric reaction involving 4-ylidene-pyrazolones as electrophiles was described in 2011 by Rios et al. using enamine catalysis.[15] The authors described the synthesis of spiropyrazolones through a one pot tandem process involving two Michael additions and one aldol condensation followed by dehydration (Scheme 2). The Hayashi-Jørgensen catalyst **C1** and benzoic acid were selected as the optimal catalysts to afford the desired spiropyrazolones in moderate yields but excellent stereoselectivities. A variety of 4-ylidene-pyrazolones having aromatic and aliphatic substituents at the double bond as well as different functional groups in the aromatic ring were well supported. However, R^2 was limited to methyl or ethyl groups, as bulkier groups such as phenyl or *tert*-butyl hampered the reaction. The reaction showed applicability to a wide range of enolizable aldehydes. Finally, enals bearing aromatic substituents gave excellent stereoselectivities but aliphatic enals gave rise to complex reaction mixtures (Scheme 2).

In 2013, Wang and co-workers employed 4-arylidene-pyrazolones with enones to study the cascade double Michael addition catalyzed by quinine-derived amine **C2** (Scheme 3).[16] Benzoic acid played a pivotal role to obtain the spiropyrazolone-cyclohexanone adducts in high yields and excellent stereoselectivities. The study of the substrate scope revealed that identically substituted enones and 4-arylidene-pyrazolones (R^1=R^2) gave excellent diastereo- and enantioselectivity regardless of the electronic and steric characteristics of the substituents, although yields were slightly lower for reactants possessing electron-rich substituents. In contrast, the reaction with substrates having different substituents ($R^1 \neq R^2$) was complicated and displayed low dr values. However, when one of these substituents was an *ortho*-chlorophenyl group, the diastereoselectivity improved greatly and the spiropyrazolones with three consecutive stereogenic centers were obtained with excellent enantioselectivity, except with enones substituted with aliphatic groups R^2 that gave low diastereoselectivity. The authors noticed that if quinidine amine catalyst was used instead of **C2**, the opposite enantiomer of the product was obtained with similar results.

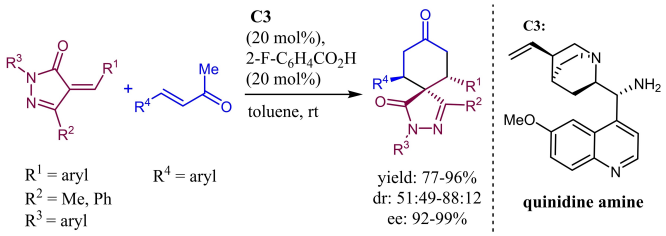
The synthesis of similar unsymmetrical diaryl-substituted spirocyclohexanone-pyrazolones was also described by the group of X.-W. Wang (Scheme 4).[17] This procedure was catalyzed by a quinidine amine catalyst **C3** and *ortho*-fluorobenzoic acid as co-catalyst, and provided the opposite enantiomers to



Scheme 3. Cascade asymmetric addition of enones to 4-arylidene-pyrazolones.



Scheme 2. One pot double Michael addition of aldehydes to 4-arylidene-pyrazolones.



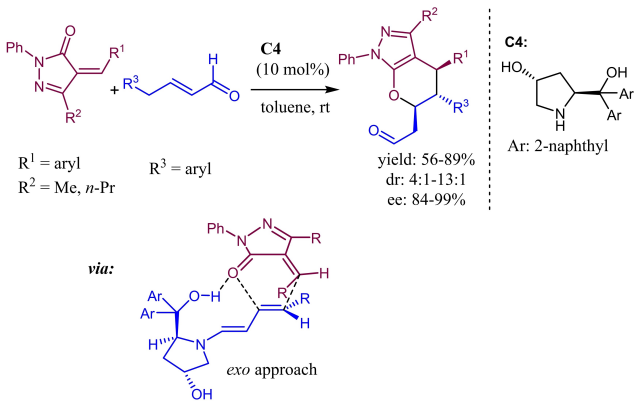
Scheme 4. Cascade asymmetric cycloaddition of enones and 4-arylidene-pyrazolones.

those obtained in the previous reaction. A broad variety of aromatic and heteroaromatic enones were tested obtaining high to excellent yields, high diastereoselectivities and excellent enantiomeric excesses.

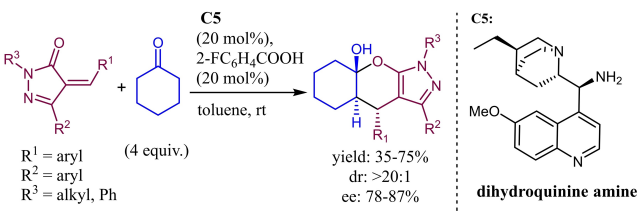
3-Methyl-4-arylidene-pyrazolones having aromatic substituents attached to both the *N* atom and the double bond (R^1 and R^3 = aryl) were evaluated obtaining excellent results. Remarkably, a 3-phenyl-4-arylidene-pyrazolone tested gave lower yield and diastereoselectivity, although excellent enantioselectivity.

In 2016, Pericàs *et al.* described an organocatalytic synthesis of tetrahydropyrano-pyrazoles using 4-hydroxydinaphthylprolinol **C4** as the catalyst.[18] In this case, the arylidene-pyrazolone reacted as a formal heterodiene in an inverse-electron demand hetero-Diels-Alder reaction. The hydroxyl group of the prolinol moiety demonstrated to be essential in the diastereo- and enantioselectivity induction (Scheme 5).

Under the optimal conditions, some 4-arylidene-pyrazolones were evaluated obtaining the best results with R^1 being a *para*-substituted phenyl ring, regardless of its electronic characteristics. A *n*-propyl group at R^2 was also tolerated but a higher reaction time was required. Aromatic enals (R^3 = aryl) were also evaluated obtaining in all cases high yields (72–88%), diastereoselectivities (up to 8:1) and enantioselectivities (84–90%).



Scheme 5. Asymmetric synthesis of tetrahydropyrano-pyrazoles from enals and 4-arylidene-pyrazolones.

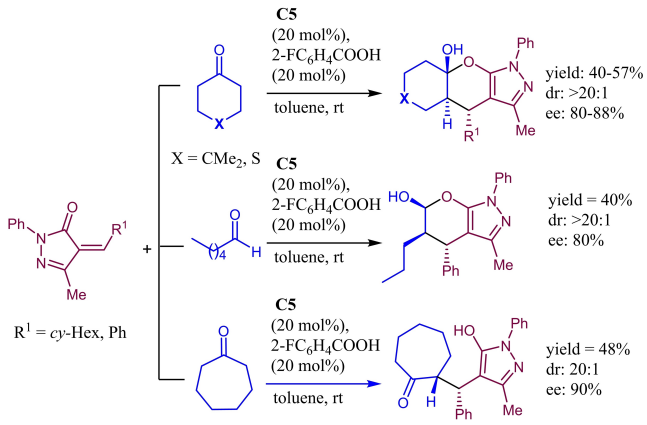


Scheme 6. Asymmetric addition of cyclohexanone to 4-arylidene-pyrazolones.

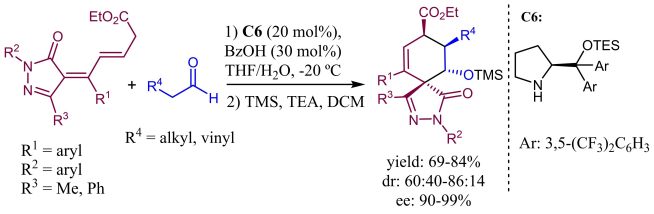
Tetrahydropyrano[2,3-*c*]pyrazoles were also synthesized by Pan *et al.* using 4-arylidene-pyrazolones and ketones.[19] The reaction proceeded via an asymmetric domino Michael/hemiacetalization reaction catalyzed by dihydroquinine-derived amine **C5** and 2-$FC_6H_4CO_2H$ (Scheme 6). Four equivalents of ketone were required to obtain the desired product in good yield, excellent diastereoselectivity and high enantiomeric excess. Good yields and excellent diastereoselectivities were obtained for a number of 4-arylidene-pyrazolones regardless of the electronic or steric features of the substituents R^1 and R^2. The enantiomeric excesses of the reaction products (*ca.* 80%) could be improved to >90% with a recrystallization process. Alkyl substituents such as ^{i}Pr or cyclohexyl at R^1 were also well tolerated. Furthermore, electron-rich and electron-poor aryl rings at R^3 gave higher yields than R^3=Ph.

A broad variety of enolizable ketones and aldehydes, including 4,4-dimethylcyclohexanone, tetrahydrothiopyran-4-one and pentanal were evaluated affording the corresponding cycloaddition products in moderate yield and high stereoselectivity. However, larger cyclic ketones such as cycloheptanone led to the single Michael addition product with fair yield but excellent stereoselectivity (Scheme 7).

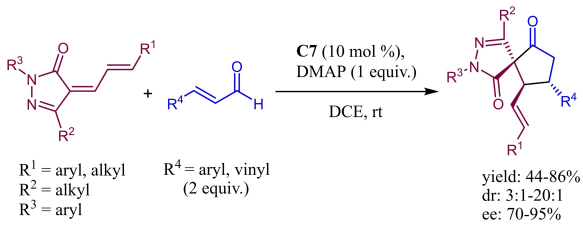
Vinylogous 4-ylidene-pyrazolones, bearing conjugated exocyclic double bonds, have also been employed in asymmetric catalysis. In 2019, Han, He and Peng developed an asymmetric formal [4+2] cycloaddition with enolizable aldehydes catalyzed by a proline derivative **C6**, related to the Hayashi-Jørgensen catalyst.[20] A triethylsilyl protecting group was required in the catalyst to afford the spiro compounds in good yields and diastereomeric ratios, and excellent enantiomeric excesses (Scheme 8). A broad range of vinylogous 4-arylidene-pyrazolones were studied, obtaining the desired spirocyclohexene-pyrazolones in high yields, good diastereoselectivities and excellent



Scheme 7. Asymmetric reaction of carbonyl compounds and 4-arylidene-pyrazolones catalyzed by amine **C5**.



Scheme 8. Asymmetric formal [4+2] cycloaddition of aldehydes and vinylogous 4-arylidene-pyrazolones.



Scheme 10. Asymmetric cycloaddition of enals and vinylogous 4-arylidene-pyrazolones.

enantiomeric excesses. Diastereoselectivity decreased when vinylogous 4-arylidene-pyrazolones were substituted with R^1 being a 2-naphthyl group or R^2 different of a phenyl group. 2-Alkyl and 2-vinyl substituted acetaldehydes also gave good yield, diastereoselectivity and enantiomeric excess (Scheme 8). Remarkably, the unprotected spirocyclohexene-pyrazolones (without TMS) demonstrated anticancer effect by inducing programmed cell death.

2.1.2. Reactions under NHC Catalysis

N-Heterocyclic carbene (NHC) catalysis is a powerful catalytic method widely employed in reactions involving aldehydes. This kind of catalysis is very efficient in asymmetric [4+2] annulation reactions involving 4-ylidene-pyrazolones. The first example of such reaction was described in 2013 by Ye[21] employing α-chloroaldehydes and 4-arylidene-pyrazolones catalyzed by Bode NHC catalyst (Scheme 9).[22]

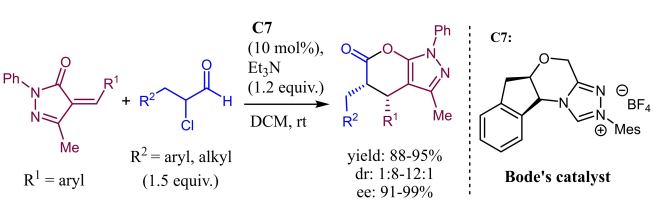
Aliphatic and aromatic α-chloroaldehydes gave the desired *cis*-dihydropyrano-pyrazolones in high yields, with good diastereo- and enantioselectivities. With elongated reaction times, epimerization of the *cis* cycloadduct to the *trans* isomer was observed, which could be avoided by reducing the base load. However, the *trans* isomer was favored when arylidene-pyrazolones with *o*-chlorophenyl or 1-naphthyl substituents were used, probably due to the larger steric hindrance of these groups.

The same NHC catalyst has been used by Enders in the asymmetric [4+2] annulation of enals and vinylogous 4-arylidene-pyrazolones to give chiral spirocyclopentane-pyrazolones (Scheme 10).[23] Enals containing *para*-substituted aromatic rings gave excellent results regardless of their electronic characteristics. Enals bearing heteroaryl and vinyl substituents were also tolerated. Substitution on the arylidene-pyrazolones was also evaluated obtaining the best results when R^2 was a ^{t}Bu group. On the other hand, aryl, heteroaryl and vinyl substituents R^1 at the side chain were tolerated, the reaction products being obtained with moderate yields and good stereoselectivities. The substituent at the nitrogen atom R^3 could be a substituted phenyl or benzyl group. However, when it was a *p*-chlorophenyl group, a slight decrease in the stereoselectivity was observed (Scheme 10).

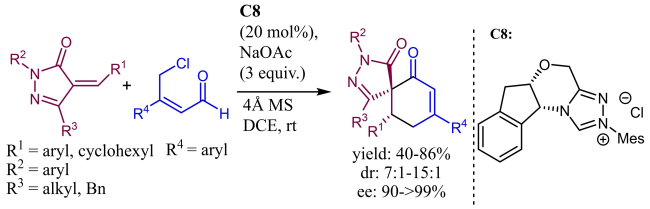
Two years later, Zhong and Yang described an asymmetric formal [4+2] annulation between γ-chloroenals and 4-arylidene-pyrazolones to construct spirocyclohexane-pyrazolones.[24] The reaction was catalyzed by the *N*-mesityl-substituted triazolium salt **C8** using NaOAc as base in the presence of 4 Å molecular sieves. These conditions were applied to a wide range of differently substituted 4-arylidene-pirazolones obtaining in all cases moderate to high yields, good diastereomeric ratios and enantiomeric excesses above 99% ee. Only when R^1 was a cyclohexyl group the enantiomeric excess decreased to 90%. Furthermore, γ-chloroenals bearing aryl or heteroaryl groups at the β position were well supported (Scheme 11).

2.1.3. Phosphine Catalysis

Phosphine catalysis has been commonly used in cycloaddition reactions that involve allenes or allenoates. In



Scheme 9. Asymmetric [4+2] cycloaddition of α-chloroaldehydes and 4-arylidene-pyrazolones.



Scheme 11. Formal [4+2] annulation of γ-chloroenals and 4-arylidene-pyrazolones.

2015, Guo and co-workers used this type of catalysis in the reaction of allenoates and 4-arylidene-pyrazolones to obtain chiral spiropyrazolones.[25] The racemic reaction proceeded with excellent yields when $MePPh_2$ in toluene at room temperature was used. The asymmetric version of the reaction was achieved with chiral phosphine **C9** in toluene at −10 °C obtaining in general fair diastereoselectivity and good enantioselectivity for a number of 4-arylidene-pyrazolones having aromatic rings attached to the double bond (Scheme 12).

2.1.4. Bifunctional Hydrogen-Bonding/Brønsted Base Catalysis

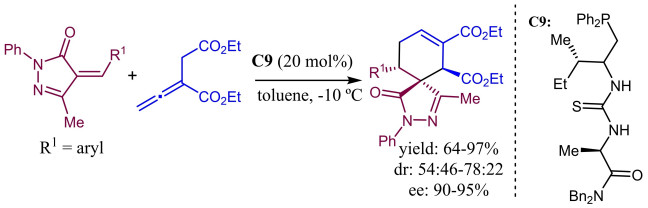
Bifunctional catalysis has been broadly studied in reactions with 4-arylidene-pyrazolones, being the most common organocatalytic method used. The first example described in 2012 by Wang and Jiang reported an asymmetric Michael/cyclization process using isothiocyanato imides as pronucleophiles (Scheme 13).[26] The reaction was catalyzed by a rosin-derived thiourea **C10** in dichloromethane achieving the spiropyrazolones in excellent yield and high stereoselectivity. Besides isothiocyanato imide, methyl isothiocyanato acetate (R^3=OMe) was tested giving the corresponding product with good yield but moderate stereoselectivity.

The same group reported a similar reaction using the same catalyst and isothiocyanato oxindoles as pronucleophiles to give bi-spirocyclic oxindole derivatives (Scheme 14).[27] Under these conditions, 4-arylidene-pyrazolones having a variety of aryl or heteroaryl groups R^1 (R^2=H) attached to the double bond gave excellent results. However, when dimethyl unsaturated pyrazolone (R^1=R^2=Me) was used the corresponding product was afforded in only 11% ee. One year later, the group of Yuan reported a quinine catalysis for the same reaction obtaining good yields, fair diastereoselectivity and good enantiomeric excesses (see Scheme 38).

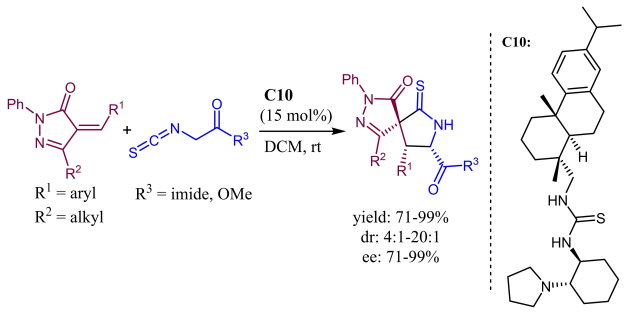
In 2013, Wang and Tao developed an asymmetric Michael/aromatization reaction of 4-arylidene-pyrazolones with oxazol-5-ones catalyzed by an isosteviol-derived thiourea **C11**.[28] Molecular sieves and low temperatures favored high enantiomeric excesses. Remarkably, the reaction occurs in a C4-regioselective fashion regarding the oxazolone giving masked amino acid structures containing a 3-hydroxypyrazole motif (Scheme 15).

A broad scope regarding 4-arylidene-pyrazolones was demonstrated and the products were obtained with high yields, good dr (>10:1) and high enantiomeric excesses regardless of the electronic features of the substituent attached to the double bond. Regarding the oxazol-5-one partner, the best results were obtained with those with a benzyl group attached to position 4 of the heterocyclic ring (R^3=Bn).

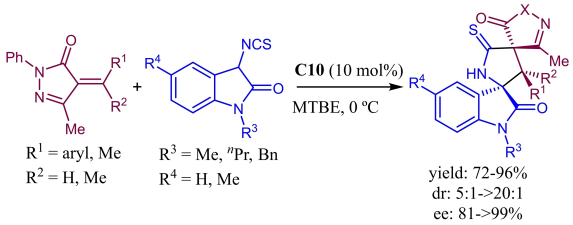
Isosteviol-derived thiourea catalyst **C11** was also used in the addition of diarylphosphine oxides to 4-arylidene-pyrazolones described by Wang and coworkers.[29] The reaction was first studied in a racemic



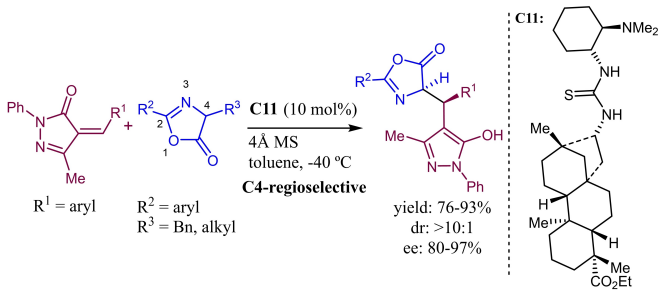
Scheme 12. Phosphine-catalyzed reaction of allenoates and 4-arylidene-pyrazolones.



Scheme 13. Asymmetric reaction of isothiocyanato imides and 4-arylidene-pyrazolones catalyzed by bifunctional thiourea **C10**.



Scheme 14. Asymmetric cycloaddition of isothiocyanato oxindoles and 4-arylidene-pyrazolones.

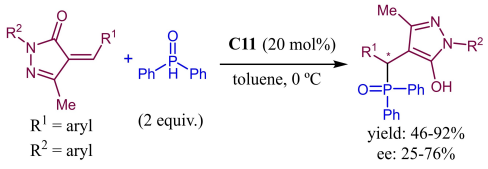


Scheme 15. Asymmetric C4-regioselective addition of oxazol-5-ones to 4-arylidene-pyrazolones.

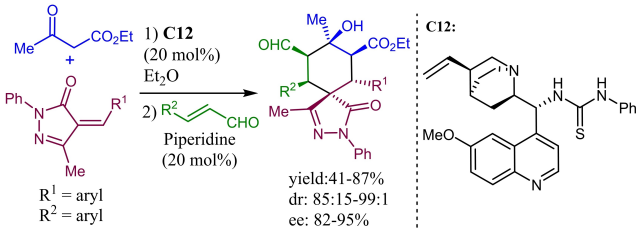
fashion, the desired products being obtained in very high yields in Et_2O at room temperature in the absence of catalyst. The asymmetric reaction was carried out at 0 °C to avoid the background reaction. The phosphorus-containing pyrazoles were obtained with fair to high yields and moderate enantiomeric excesses. No significant differences were observed with substrates having either electron-donating or electron-withdrawing groups attached to the double bond. The best results were obtained with bulky substituents such as 2-naphthyl (Scheme 16).

In 2014, the group of Xie developed the synthesis of chiral spirocyclohexane-pyrazolones through a one-pot sequential Michael/Michael/Aldol reaction of 1,3-dicarbonyl compounds with ylidene-pyrazolones and *α,β*-unsaturated aldehydes (Scheme 17).[30] The reaction was sequentially catalyzed by a *Cinchona* alkaloid thiourea **C12** and piperidine, providing the spirocyclic compounds with high yield and stereoselectivity for a number of pyrazolones and aldehydes. A notable feature of this reaction is the formation of up to six consecutive stereogenic centers, one of them being quaternary and five tertiary.

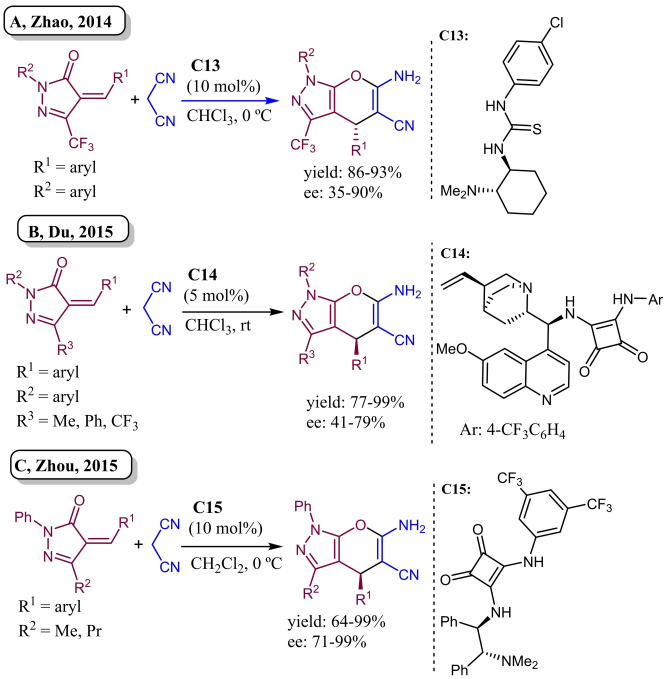
Since 2014, a number of organocatalytic procedures for the synthesis of dihydropyrano[2,3-*c*]pyrazoles from malononitrile and 4-arylidene-pyrazolones through a cascade Michael addition/cyclization have been developed. A bifunctional diaminocyclohexane-thiourea catalyst **C13** was employed by Zhao to furnish the reaction products with excellent yields and fair to good enantiomeric excesses (Scheme 18,A).[31] In this example, 3-trifluoromethyl-4-arylidene-pyrazolones bearing aromatic groups attached to the nitrogen and the double bond were used as electrophiles. In 2015,



Scheme 16. Asymmetric addition of diarylphosphine oxides to 4-arylidene-pyrazolones.



Scheme 17. Asymmetric sequential Michael/Michael/Aldol reaction of 1,3-dicarbonyl compounds with 4-arylidene-pyrazol-5-ones and *α,β*-unsaturated aldehydes.

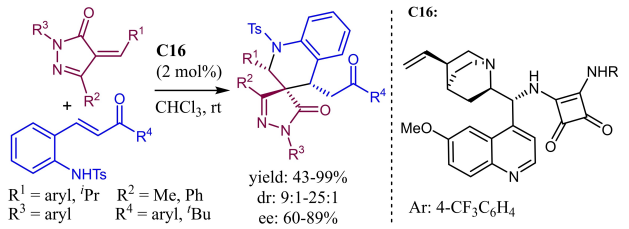


Scheme 18. Asymmetric cycloaddition of malononitrile and 4-arylidene-pyrazol-5-ones under different conditions.

Du and co-workers used a quinine-derived squaramide **C14** as catalyst. The reaction was tested with 3-methyl-, 3-phenyl- and 3-trifluoromethyl- arylidene-pyrazolones having different aromatic groups attached to the double bond and the heterocyclic *N* atom.[32] The reaction products were obtained in excellent yields but only fair enantiomeric excesses (Scheme 18,B). Finally, a squaramide derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **C15** was used by Zhou as catalyst.[33] With this catalyst both the yield and the enantiomeric excesses were excellent for a number of substrates bearing aromatic and heteroaromatic groups at the double bond (Scheme 18,C).

An organocatalyzed cascade *aza*-Michael/Michael addition of 2-tosylamino enones and 4-arylidene-pyrazol-5-ones has been described by Du.[34] The reaction, catalyzed by a quinidine-derived squaramide **C16**, led to highly functionalized spiropyrazolone-tetrahydroquinolines in excellent yields, excellent diastereomeric ratios and good enantiomeric excesses (Scheme 19).

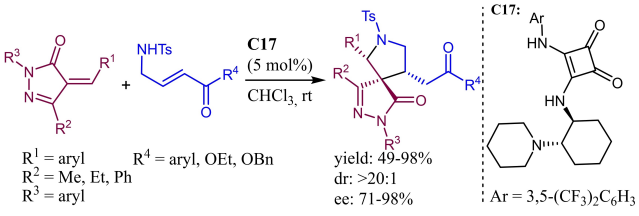
Later, the same group described another *aza*-Michael/Michael reaction with *N*-tosyl-aminomethyl enones to obtain chiral spiropyrrolidine-pyrazolones.[35] The reaction was catalyzed by a 1,2-diaminocyclohexane-derived squaramide **C17** obtaining excellent yields and stereoselectivities. 3-Methyl-4-arylidene-pyrazolones gave the best results. Ethyl and phenyl substitution at position 3 was also tolerated although the yield and ee slightly decreased. Pyrazolones that have



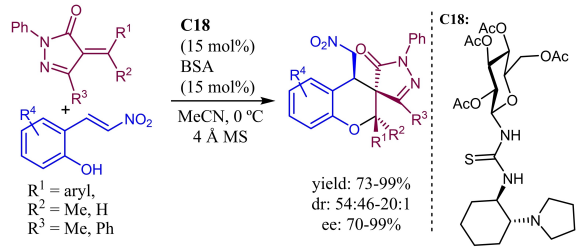
Scheme 19. Cascade *aza*-Michael/Michael addition of 2-tosylaminoenones and 4-arylidene-pyrazol-5-ones.

electron-withdrawing groups attached to the double bond gave higher yields but lower enantiomeric excesses, and similarly happened when this was an *ortho*-substituted phenyl group. Remarkably, not only arylketones but also esters were suitable aminoalkene substrates in this reaction (Scheme 20).

In 2015, a related asymmetric *oxa*-Michael/Michael cascade reaction between 4-arylidene-pyrazolones and 2-nitrovinylphenols was described by Miao.[36] The products containing the spiro[chroman-3,3′-pyrazol] scaffold were obtained in excellent yields and enantiomeric excesses when carbohydrate/cyclohexane-1,2-diamine thiourea **C18** was employed as catalyst. The use of benzenesulfonic acid (BSA) contributed to improve the diastereoselectivity. Under the optimal conditions, some 2-nitrovinylphenols were tested achieving high to excellent results. Aryl rings bearing electron-donating and electron-withdrawing groups in R^1 were well tolerated while a furyl substituent gave lower stereoselectivity. Furthermore, the nitrostyrene



Scheme 20. Asymmetric synthesis of chiral spiropyrrolidine-pyrazolones.



Scheme 21. Asymmetric *oxa*-Michael/Michael cascade reaction of 4-arylidene-pyrazolones and 2-nitrovinylphenols.

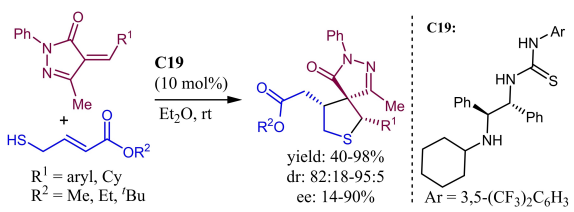
partner tolerated groups of different electronic nature on the aromatic ring (Scheme 21).

A related organocatalytic *thia*-Michael/Michael reaction was developed by Lattanzi in 2017.[37] The reaction between *tert*-butyl (*E*)-4-mercapto-2-butenoates and 4-arylidene-pyrazolones using the (*R*,*R*)-ethylendiamine-derived thiourea **C19** as catalyst provided highly functionalized spiro[pyrazolone-4,3′-tetrahydrothiophenes] bearing three consecutive stereocenters in good yields and fairly good diastereo-and enantioselectivities. The *tert*-butyl ester moiety was required to obtain high enantiomeric excesses. The reaction worked well with 4-arylidene-pyrazolones bearing *meta*- or *para*-substituted phenyl rings attached to the double bond (except *p*-CN) (Scheme 22).

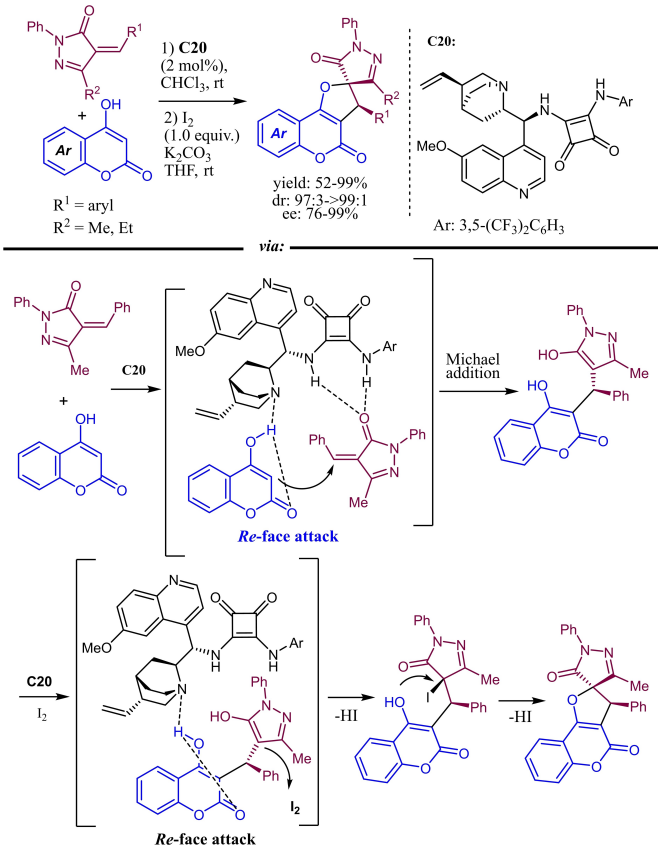
Later this year, 4-hydroxycoumarins were used as dinucleophiles in an asymmetric Michael addition/I_2-mediated cyclization reaction with 4-arylidene-pyrazolones reported by Xu.[38] Spiro[dihydrofurocoumarin/pyrazolone] compounds were obtained in moderate to excellent yields with excellent diastereoselectivities and good to excellent enantioselectivities in the presence of a quinine-derived squaramide **C20** as catalyst. Generally, 4-arylidene-pyrazolones having electron-rich aryl rings attached to the double bond gave better enantioselectivities than those bearing electron-withdrawing groups. Additionally, an ethyl group in R^2 instead of methyl produced a slight decrease in the ee of the product. Moreover, C7-substituted 4-hydroxycoumarins provided better yields than their C6-substituted analogues (Scheme 23).

The authors suggested a plausible mechanism as depicted in Scheme 23. In the first Michael addition step, the 4-hydroxycoumarin would be activated by hydrogen-bonding between the catalyst protonated amine and the two oxygen atoms at the time that the pyrazolone would be activated by the squaramide moiety, driving the approach of the coumarin to the *Re*-face of the pyrazolone double bond. The catalyst also directed the approach of I_2 in the cyclization step, which after an electrophilic/nucleophilic substitution sequence driven by HI loss would give the spirocyclic product.

The reaction also worked with 4-hydroxy-6-methyl-2-pyrone, which was evaluated with different 4-



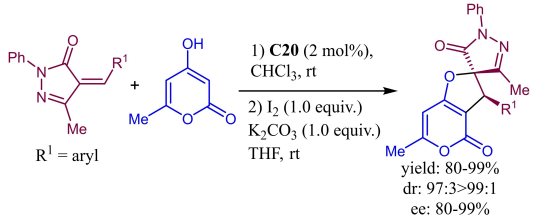
Scheme 22. Asymmetric *thia*-Michael/Michael reaction between (*E*)-4-mercapto-2-butenoates and 4-arylidene-pyrazolones.



Scheme 23. Asymmetric Michael addition/I_2-mediated cyclization reaction of 4-hydroxycoumarins and 4-arylidene-pyrazolones.

arylidene-pyrazolones. The desired products were achieved in high yields (80-90%), high to excellent enantiomeric excesses (80–96%) and excellent diastereomeric ratios (97:3 to >99:1) (Scheme 24).

An extension of this one-pot methodology using 1,3-diketones was reported by the same group catalyzed by a related squaramide **C21**.[39] Spiropyrazolones were obtained in excellent yields, diastereoselectivities and enantiomeric excesses. 3-Methyl- and 3-ethyl-4-arylidene-pyrazolones substituted at the double bond with aryl groups of different character were



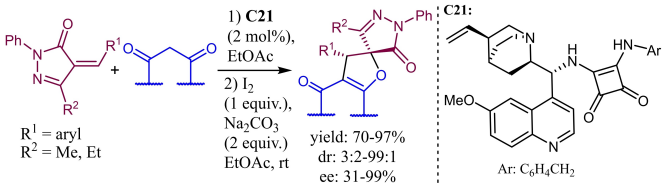
Scheme 24. Asymmetric Michael addition/I_2-mediated cyclization reaction of 4-hydroxy-6-methyl-2-pyrone and 4-arylidene-pyrazolones.

suitable substrates. Cyclic 1,3-diketones gave excellent results unlike acetylacetone that furnished the product with good yield but low stereoselectivity (Scheme 25).

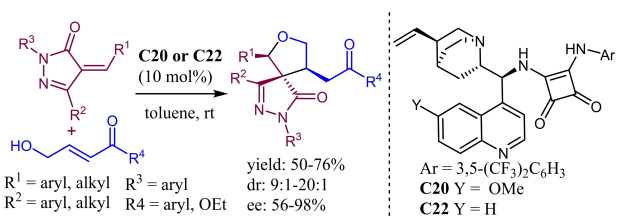
In 2018, Pan developed an asymmetric *oxa*-Michael/Michael reaction between 4-arylidene-pyrazolones and γ-hydroxyenones to construct chiral spirotetrahydrofuran-pyrazolones.[40] Two different squaramides **C20** and **C22** were used as optimal catalysts, depending on the substituents of both reaction partners. A number of γ-hydroxyenones having aryl or alkyl groups attached to the ketone gave excellent results with catalyst **C20**. Moreover, γ-hydroxyesters could also participate in the reaction although with modest enantioselectivity. On the other hand, squaramide **C22** was employed for the study of differently substituted 4-arylidene-pyrazolones with the phenyl ketone (R^4=Ph) to give the reaction products with excellent enantiomeric excesses (Scheme 26).

The reaction of 4-arylidene-pyrazolones with α-nitroketones has been reported by Pan in 2017. 3-Acyloxypyrazoles were obtained with excellent yields and enantiomeric excesses through a Michael/hemiketalization/retro-aldol reaction in the presence of a *tert*-leucine-derived bifunctional thiourea **C23** in $PhCF_3$.[41] Good results were obtained with 4-arylidene-pyrazolones substituted at the double bond with aromatic rings of different electronic features. Moreover, a wide variety of α-nitroketones were well tolerated (Scheme 27). The nitro group could be successfully reduced to the corresponding amine using $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ in methanol without loss of enantiomeric excess.

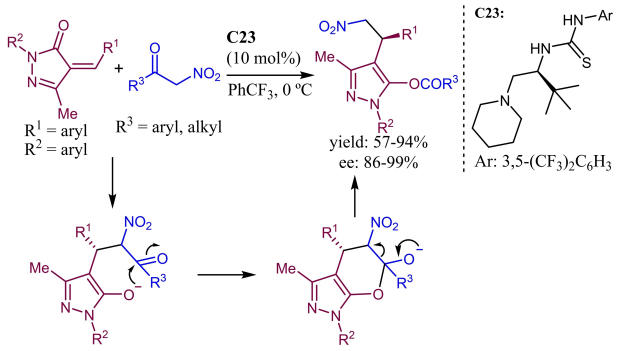
The asymmetric Weitz – Scheffer epoxidation of 4-arylidene-pyrazolones using *tert*-butyl hydroperoxide as oxidant has been reported (Scheme 28).[42] Lattanzi



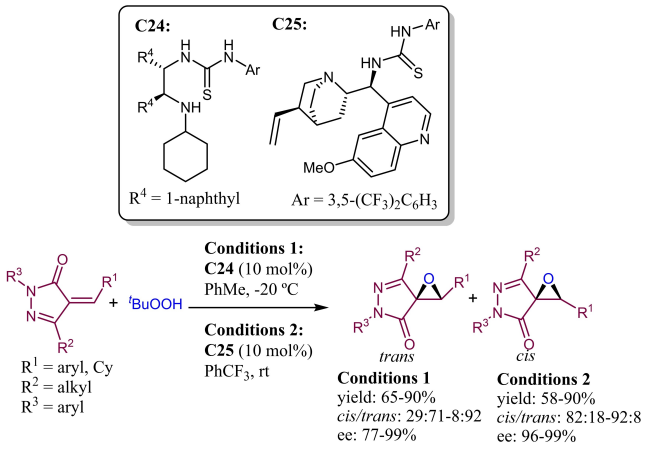
Scheme 25. Asymmetric reaction of 1,3-diketones and 4-arylidene-pyrazolones.



Scheme 26. Synthesis of spirotetrahydrofuran-pyrazolones via an *oxa*-Michael/Michael reaction.



Scheme 27. Asymmetric addition of α-nitroketones to 4-arylidene-pyrazolones.



Scheme 28. Asymmetric epoxidation of 4-arylidene-pyrazolones.

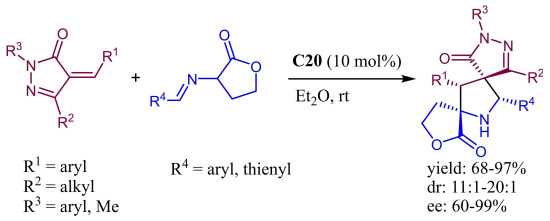
and co-workers developed this organocatalyzed reaction involving an *oxa*-Michael/ring closure sequence. Herein, the ratio of *cis*/*trans* epoxides is controlled by the ring closure step where the organocatalyst plays a critical role.

The *trans* epoxide was obtained as the major isomer when ethylendiamine derived catalyst **C24** was employed. On the other hand, *Cinchona* alkaloid-derived thiourea **C25** led mostly to the *cis* epoxide. In both cases, the desired epoxides were obtained in high yields and stereoselectivities regardless of the electronic and steric features of the pyrazolone substituents. DFT studies demonstrated that the organocatalyst played a pivotal role in the reaction mechanism and that the *oxa*-Michael addition step was the enantioselectivity and rate-determining step.

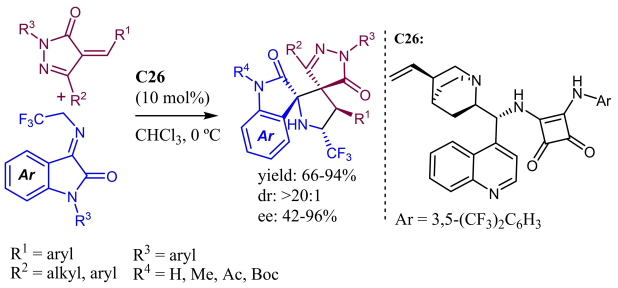
Bifunctional catalyst **C20** was also effective in the synthesis of tricyclic compounds with the bispiro[γ-butyrolactone-pyrrolidin-4,4′-pyrazolone] scaffold through an asymmetric formal 1,3-dipolar cycloaddition between α-imino-γ-lactones and 4-arylidene-pyrazolones reported by Cai.[43] Under mild conditions, the desired products were obtained with excellent results, supporting a broad variety of 4-arylidene-pyrazolones and α-imino-γ-lactones. Short aliphatic chains in R^2 gave the best results and substitution in R^1 and R^3 did not affect the reactivity. Unfortunately, α-imino-γ-lactones with bulky R^4 substituents gave diminished diastereo- and enantioselectivity (Scheme 29).

The 1,3-dipolar cycloaddition of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 4-arylidene-pyrazolones was developed by the group of Yan to obtain trifluoromethylated spirooxindole-pyrrolidine-pyrazolone compounds. Again a *Cinchona* alkaloid squaramide **C26** was used as catalyst.[44] Some isatin ketimines were evaluated obtaining the best results with those bearing electron-donating groups on the aromatic ring and a methyl group at the nitrogen atom. Furthermore, a variety of 4-arylidene-pyrazolones were tested observing that the substitution in R^1, R^2 and R^3 did not affect significantly the stereoselectivity (Scheme 30).

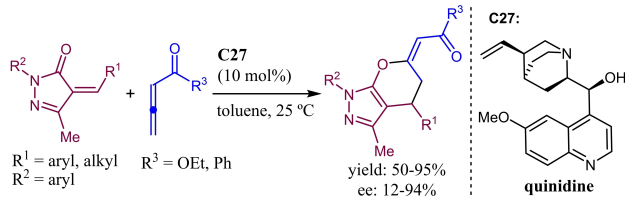
Chandra reported in 2019 the asymmetric cycloaddition of allenoates with 4-arylidene-pyrazolones. The reaction took place through a cascade Michael addition/*oxa*-Michael cyclization catalyzed by easily accessible quinidine (**C27**).[45] The reaction afforded the desired tetrahydropyrano-pyrazoles in moderate to high yields. The enantioselectivity of the reaction was highly dependent on the substituent attached to the double bond of the pyrazolone, with the ee dropping when this was an electron-poor aryl group. Allenyl ketones could be also employed (Scheme 31).



Scheme 29. Asymmetric formal 1,3-dipolar cycloaddition of α-imino-γ-lactones and 4-arylidene-pyrazolones.

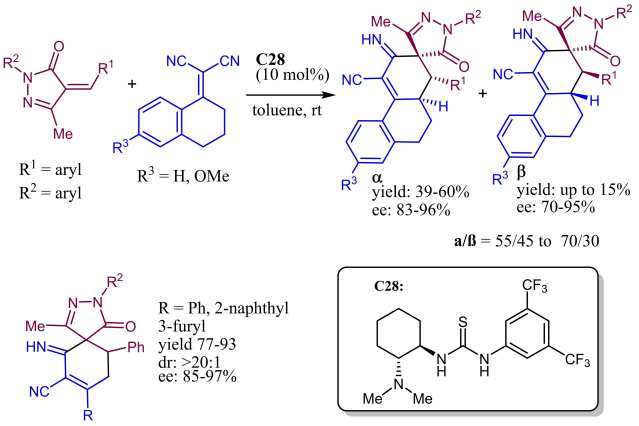


Scheme 30. Asymmetric cycloaddition of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 4-arylidene-pyrazolones.

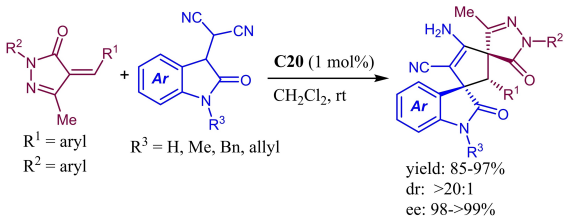


Scheme 31. Asymmetric cascade Michael addition/*oxa*-Michael cyclization of allenoates and 4-arylidene-pyrazolones.

Later that year, Lattanzi and co-workers developed an asymmetric synthesis of fused pyrazolone-spirocyclohexeneimines using Takemoto thiourea **C28** as catalyst.[46] The reaction of (dihydronaphthalen-1(2*H*)-ylidene) malononitriles with arylidene-pyrazolones took place via a vinylogous Michael/cyclization cascade process under mild conditions to give the corresponding products with good yields and enantioselectivities but with poor diastereoselectivity. The best results were obtained with 4-arylidene-pyrazolone having *p*-substituted aryl groups attached to the double bond. Remarkably, α,α-dicyanoalkylidene-s derived from acyclic aromatic and heteroaromatic methyl ketones provided the spirocyclic products also with high diastereoselectivity (Scheme 32).



Scheme 32. Synthesis of fused pyrazolone-spirocyclohexeneimines from benzylidene-malononitriles and 4-arylidene-pyrazolones.

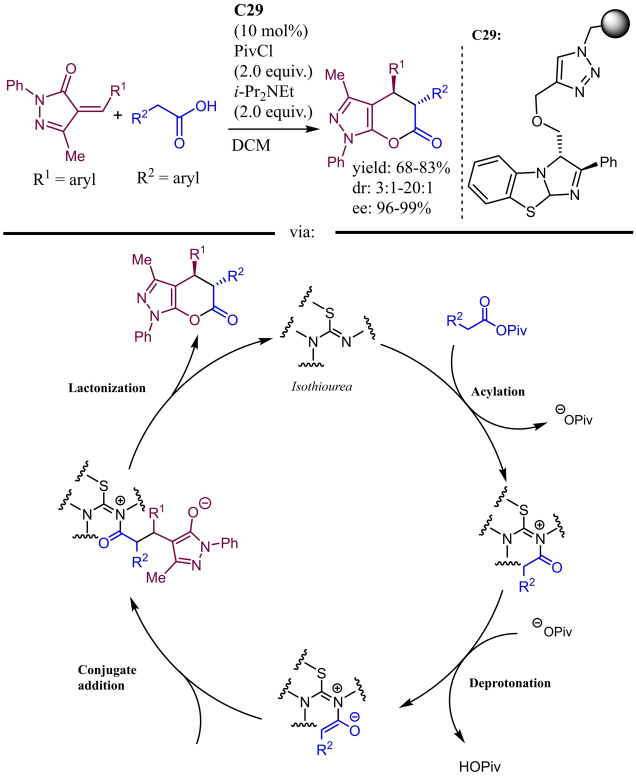


Scheme 33. Asymmetric formal [3+2] cycloaddition of 2-(2-oxoindolin-3-yl)malononitriles and 4-arylidene-pyrazolones.

The reaction of 2-(1-methyl-2-oxoindolin-3-yl) malononitriles with 4-arylidene-pyrazolones has been developed by Du to obtain spirooxindole-spiropyrazolones.[47] The reaction, catalyzed by the quinine-derived squaramide **C20**, gave the reaction products with high to excellent yields and excellent stereoselectivities with diastereomeric ratios above 20:1 and enantiomeric excesses above 98%. Furthermore, 4-aryliedene-pyrazolones substituted with electron-withdrawing and electron-donating groups in either R^1 or R^2 gave excellent results regardless of the substitution pattern (Scheme 33).

2.1.5. Isothiourea-Catalyzed Reactions

Isothiourea catalysis is another powerful enantioselective organocatalytic method to promote reactions with carboxylic acid derivatives via acyl activation. Using this kind of catalysis Pericàs developed a synthesis of functionalized dihydropyrano-pyrazolones through a formal [4+2] cycloaddition of arylacetic acids and 4-arylidene-pyrazolones. The reaction also worked with 5-arylidene-thiazol-4-ones to give the corresponding spirothiazolones (Scheme 34).[48] A polystyrene-supported isothiourea **C29** was used and the reaction could be performed in batch or flow conditions. A wide range of 4-arylidene-pyrazolones and substituted phenylace-



Scheme 34. Asymmetric [4+2] cycloaddition of arylacetic acids and 4-arylidene-pyrazolones.

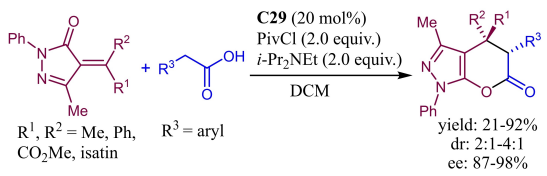
tic acid derivatives was tested obtaining in all cases high yields and diastereomeric ratios and excellent enantiomeric excesses. Furthermore, a range of substituted aromatic arylacetic acids gave excellent results regardless of the electronic character of the substituent.

The proposed catalytic cycle involves the initial formation of a mixed anhydride from the arylacetic acid and pivaloyl chloride, followed by formation of an acyl ammonium species with the thiourea catalyst. This is deprotonated by the pivalate to generate an enolate, which undergoes stereoselective conjugate addition, followed by lactonization to give the reaction product and release the catalyst (Scheme 34).

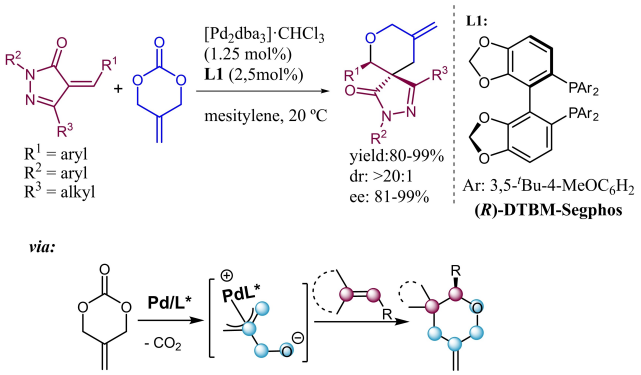
Disubstituted 4-arylidene-pyrazolones, which would provide a quaternary stereocenter, were also evaluated although higher catalytic load (20 mol%) was required. Although most disubstituted alkylidene pyrazolones did not engage in the reaction or gave low yields under these conditions, the less sterically demanding isatin-derived 4-arylidene-pyrazolones gave the best results giving rise to the spirocyclic oxindoles with high yield, moderate diastereoselectivity and excellent enantioselectivity (Scheme 35).

2.2. Palladium-Catalyzed Reactions with 4-Ylidene-Pyrazolones

Although most of the reactions with 4-ylidene-pyrazolones have been carried out under organocatalytic conditions, recently, Guo and co-workers reported a palladium-catalyzed asymmetric [4+2] cycloaddition of 5-methylene-1,3-dioxan-2-one with 4-arylidene-pyrazolones and other cyclic alkenes.[49] With 4-arylidene-pyrazolones the best results were achieved with $[Pd_2dba_3]\cdot CHCl_3$ in mesitylene using (*R*)-DTBM-Segphos as ligand. Under these conditions, a broad variety of 4-arylidene-pyrazolones were studied, obtaining in all cases excellent yields and stereoselectivities. 4-Arylidene-pyrazolones substituted at C3 with methyl or ethyl groups gave excellent results. A *n*-propyl group at this position was also tolerated. Remarkably, indandione and barbiturate-derived alkenes were also studied under modified conditions (changing the amount of palladium and ligand), obtaining high to excellent yields and excellent enantiomeric excesses (Scheme 36).



Scheme 35. Asymmetric [4+2] cycloaddition of arylacetic acids and disubstituted 4-arylidene-pyrazolones.



Scheme 36. Asymmetric [4+2] cycloaddition of 5-methylene-1,3-dioxan-2-one with 4-arylidene-pyrazolones.

3. 4-Ylidene-Isoxazolin-5-Ones

Isoxazolin-5-ones are versatile five-membered heterocycles that can be found in natural products isolated from bacteria,[50] fungi,[51] insects[52] or seedlings.[53] This moiety an its derivate 4-ylidene-isoxazolin-5-one are present in some biologically active compounds including anti-fungal agents,[54] PTP_1B inhibitors with anti-obesity activity,[55] antimicrobial agents[56] or anti-cancer agents.[57] Moreover, the 4-ylidene-isoxazolin-5-one core is present in new photoluminescent materials[58] and donor-acceptor molecules that can act as dyes (Figure 3).[59]

Furthermore, the isoxazol-5-one ring is a useful building block, which can be converted into different

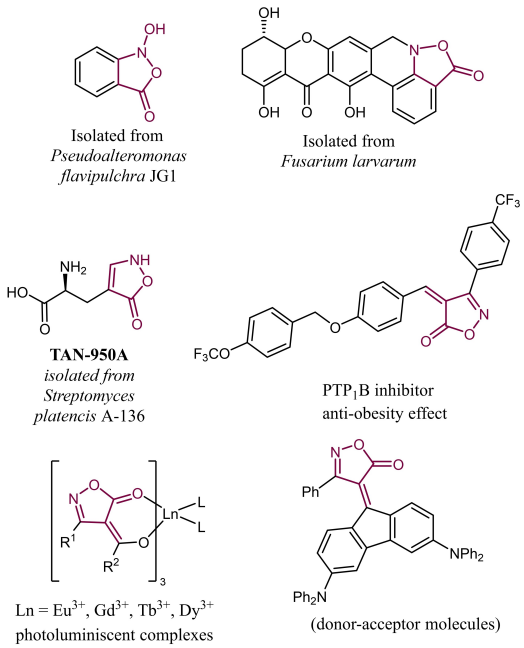


Figure 3. Selected examples of interesting compounds containing the isoxazolin-5-one scaffold.

structural motifs.[60] Asymmetric addition reaction to 4-ylidene-isoxazolin-5-one followed by a nitrosative cleavage allows the synthesis of branched alkynes. Further, taking the advantage of the weak N – O bond strength, a reductive protocol using iron can selective transforms the isoxazol-5-one ring into a ketone (Scheme 37).[61] Due to their potential applications, 4-ylidene-isoxazolin-5-ones have emerged as powerful 1,4-acceptors in asymmetric additions. Nucleophilic addition to the double bond is favored by resonance stabilization of the resulting carbanion, which is delocalized to the imine and carbonyl groups. The nucleophilic character of this carbanion allows the development of formal cycloaddition reactions in domino processes, normally with formation of a quaternary stereogenic center at C-4.[62] Participation of the carbonyl oxygen in these domino processes is hampered because the charge in the carbanion intermediate is concentrated on the C-4 and N atoms of the heterocycle. Hence, 4-arylidene-isoxazolin-5-ones do not often participate as heterodienes in cycloaddition reactions unlike 4-ylidene-pyrazol-5-ones and other ylidene-heterocycles presented in this review. Finally, as 4-ylidene-pyrazol-5-ones, 4-ylidene-isoxazolin-5-ones also prefer the exocyclic double bond with the *Z*-configuration despite being represented sometimes with the *E*-configuration.

3.1. Organocatalytic Reactions with 4-Ylidene-Isoxazolin-5-Ones

3.1.1. Brønsted Base and Bifunctional Hydrogen-Bonding/Brønsted Base Catalysis

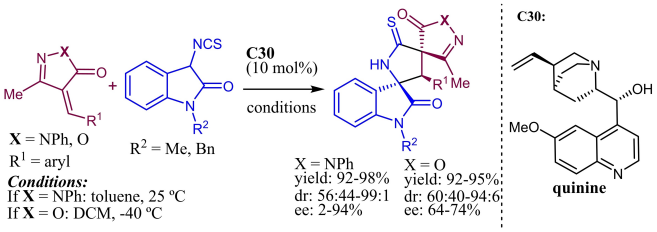
To the best of our knowledge, only organocatalytic methodologies have been applied in asymmetric reactions involving 4-ylidene-isoxazolin-5-ones. Bifunctional catalysis and enamine catalysis have been the most frequently applied approaches in these cases.

In 2014, the group of Yuan reported the quinine-catalyzed synthesis of spirocyclic oxindoles with three consecutive stereocenters via an asymmetric Michael/cyclization reaction with 3-isothiocyanato oxindoles as formal dipoles. 4-Arylidene-pyrazol-5-ones and 4-arylidene-isoxazolin-5-ones were used as dipolarophiles.[63] In both cases, the reaction products were obtained with good yields moderate diastereoselectivities and fair to good enantiomeric excesses, that were higher with pyrazolones than with isoxazolinones (Scheme 38).

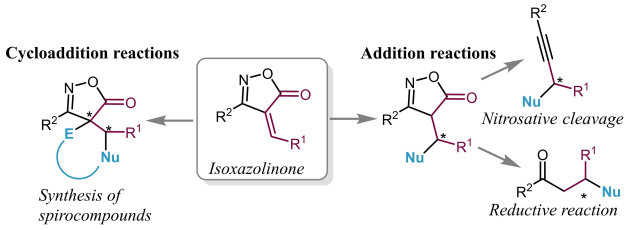
Recently, our group developed an asymmetric [3 + 2] cycloaddition between 4-ylidene-isoxazolinones and isocyanoacetates esters catalyzed by a chiral squaramide **C30** and silver oxide.[64] This cooperative system gave functionalized diazaspirocycles with high to excellent yields and high stereoselectivities. A broad variety of 4-ylidene-isoxazolinones were evaluated obtaining excellent results regardless of the electronic and steric effect of the substituents in the R^2 aromatic rings. Moreover, a R^2 cyclopropyl group was well tolerated. The highest enantiomeric excesses were obtained with 5-methyl-4-arylidene-isoxazolinones (R^1=Me). Benzyl isocyanoacetate performed similarly to the methyl ester (Scheme 39). During this research, it was noticed that 4-ylidene-isoxazolinones decomposed in dichloromethane solution, an issue that could be alleviated by reducing the concentration of the reaction mixture.

The ability of 4-arylidene-isoxazolinones to participate in asymmetric formal [3 + 2] cycloadditions has been also demonstrated by Du.[65] The authors reported a squaramide-catalyzed tandem Michael/Michael reaction between 3-((2-oxoindolin-3-yl)oxy)acrylates and 4-arylidene-isoxazolinones obtaining isoxazolone-spirooxindoles with excellent results (Scheme 40).

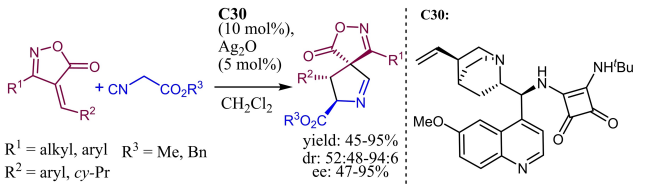
The reaction tolerated a broad variety of allyl and aromatic substituents in R^2. Unfortunately, only examples featuring a methyl or ethyl group at position 3 in the isoxazolinone ring were reported. On the other



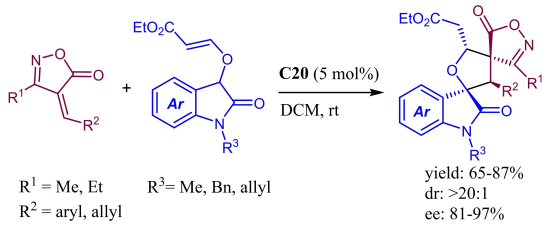
Scheme 38. Domino Michael/cyclization reaction between 3-isothiocyanato oxindoles and 4-arylidene-pyrazolones or 4-arylidene-isoxazolinones.



Scheme 37. Reactivity of 4-ylidene-isoxazolin-5-ones.



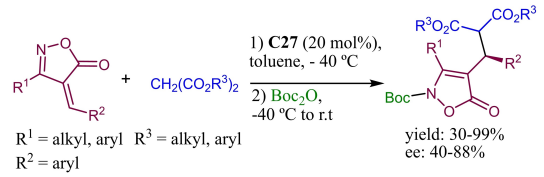
Scheme 39. Asymmetric [3 + 2] cycloaddition between 4-ylidene-isoxazolinones and isocyanoacetates esters.



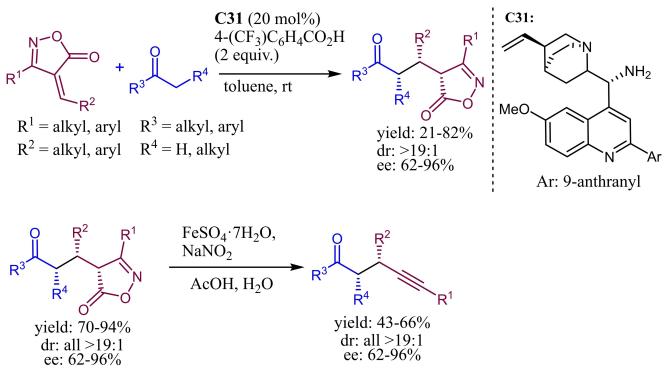
Scheme 40. Asymmetric [3+2] cycloaddition between 4-ylidene-isoxazolinones and 3-((2-oxoindolin-3-yl)oxy)acrylates.

hand, a wide range of 3-((2-oxoindolin-3-yl)oxy) acrylates bearing different substitution at the aromatic ring were also well tolerated (Scheme 40).

Besides these formal cycloaddition reactions, the single asymmetric addition of malonates to 4-ylidene-isoxazolin-5-ones was studied by Massa using quinidine as catalyst (Scheme 41).[66] Once the adduct is formed, a purification challenge appeared due to the rapid isomerization of the isoxazolinone ring that led to a mixture of all the possible isomers. So, a *N*-trapping method was also developed founding Boc_2O as the best trapping agent. With these conditions in hand, a good number of 4-arylidene-isoxazolinones was studied obtaining the best results with bulkier substituents in R^1. Conversely, small alkoxy groups in the malonate ester led to better yields and enantiomeric excesses.



Scheme 41. Asymmetric addition of malonates to 4-arylidene-isoxazolinones.



Scheme 42. Enamine-catalyzed addition of ketones to 4-ylidene-isoxazolinones.

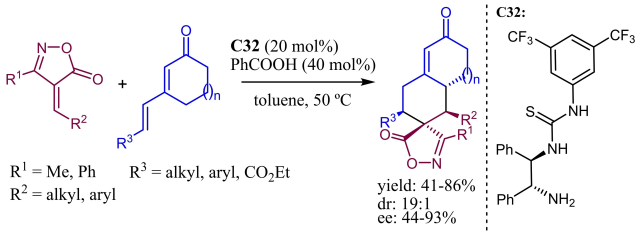
3.1.2. Reactions via Enamine Catalysis

Enamine catalysis using a chiral primary amine is especially useful when starting materials bearing a carbonyl group in their structures are used. In 2017, Jurberg described an asymmetric Michael addition of ketones to 4-ylidene-isoxazolinones using a Cinchona alkaloid-derived amine **C31** as the catalyst (Scheme 42).[67] The *p*-trifluoromethylbenzoic acid co-catalyst was needed to increase both the yield and the enantiomeric excess. The reaction worked with a number of cyclic and acyclic ketones, usually with good diastereo-and enantioselectivity. With non-symmetrical ketones, the reaction took place by the least substituted α-carbon. Cyclohexanone was tested with several 4-ylidene-isoxazolinones observing good tolerance regarding the substituents in both the imine and the double bond. The isoxazolinone ring was transformed into an alkyne by a nitrosative cleavage using $FeSO_4 \cdot 7H_2O$, $NaNO_2$ and $AcOH/H_2O$, thus obtaining the corresponding alkyne with two consecutive stereocenters.

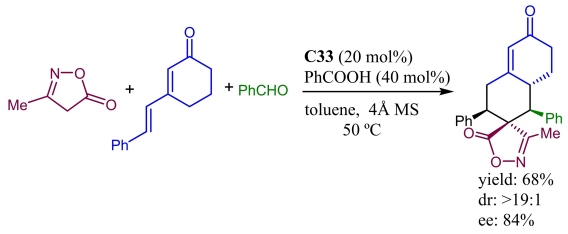
One year later, Chen and Ouyang studied a regio- and diastereodivergent [4+2] cycloaddition of cyclic 2,4-dienones catalyzed by a bifunctional amine-thiourea **C32**.[68] In this work, a wide variety of heterocyclic electrophiles is studied, but, paying attention to 4-ylidene-isoxazolinones three important types of reaction were developed. The addition of 2,4-dienones to 4-ylidene-isoxazolinones was first studied. The reaction was carried out in the presence of benzoic acid as co-catalyst, obtaining fair to good yields of spirotricyclic compounds with excellent diastereoselectivities and enantiomeric excesses (Scheme 43).

Furthermore, the authors found that the same catalytic system allowed the three-component reaction between 3-methylisoxazolin-5-one, 2,4-dienones and benzaldehyde. In this case, the 4-ylidene-isoxazolinones are generated *in situ.* 4 Å Molecular sieves was needed to increase the yield and the enantiomeric excess (Scheme 44).

Going further, a four component cascade reaction involving the *in situ* formation of both, the 4-arylidene-isoxazolinone and the 2,4-dienone was studied. In this case, a *Cinchona* alkaloid amine was also



Scheme 43. Asymmetric formal [4+2] cycloaddition of 2,4-dienones and 4-arylidene-isoxazolinones.

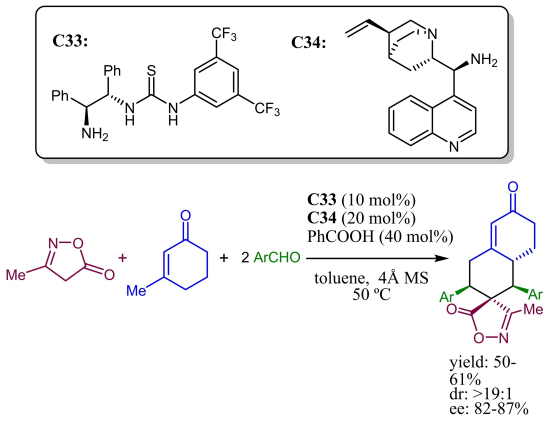


Scheme 44. Three-component reaction between isoxazolinones, 2,4-dienones and benzaldehyde.

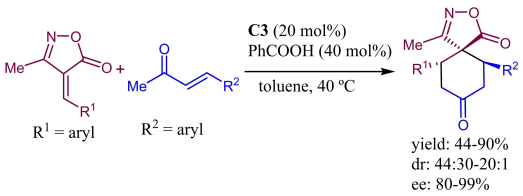
required to form the 2,4-dienone. The reaction occurs in moderate yields, excellent diastereoselectivities and good enantiomeric excesses (Scheme 45).

Recently, a novel formal [4+2] cycloaddition leading to chiral spiroisoxazol-5-ones has been developed by Jurberg through enamine catalysis.[69] Quinidine amine **C3** and benzoic acid catalyzed the cyclization reaction between methyl vinyl ketones and 4-arylidene-isoxazolin-5-ones. Remarkably, a methyl group at the C3 position of the 4-arylidene-isoxazolinone was required to obtain exclusively the 6,10-*trans*-spiroisoxazol-5-ones, while compounds having an aryl or isopropyl group at this position gave the *cis*-isomers, either achiral or in a racemic form. DFT calculations demonstrated that apolar solvents and short reaction times favored the 6,10-*trans*-spiroisoxazol-5-one (kinetic control) while polar solvents and larger reaction times favored the 6,10-*cis*-spirisoxazol-5-one (thermodynamic control) in a racemic fashion. In the enantioselective reaction, a number of 4-arylidene-isoxazolinones and methyl arylvinyl ketones were tested obtaining high yields and excellent enantiomeric excesses (Scheme 46).

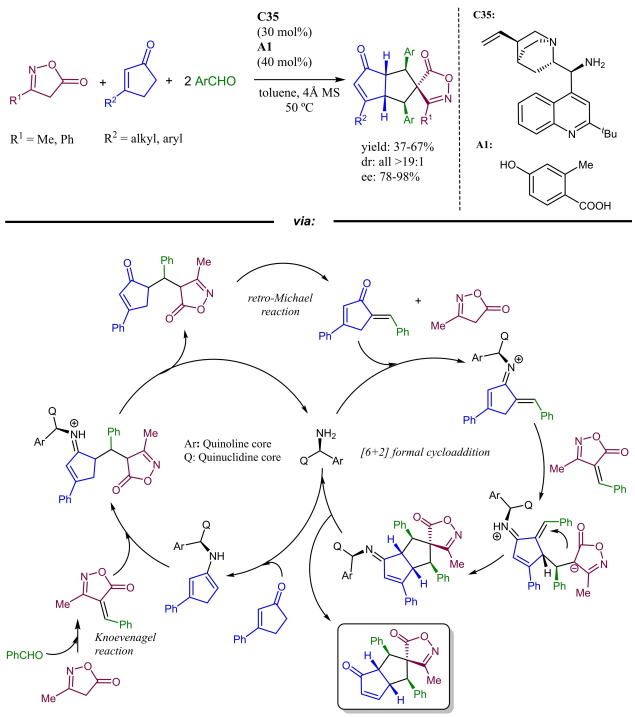
An asymmetric four component cycloaddition involving the *in situ* formation of 4-arylidene-isoxazolinones and α'-arylidene-3-substituted 2-cyclopentenones has been reported by Du and Chen.[70] This [5+1+1+1] formal cycloaddition was catalyzed by a chiral amine **C35** in the presence of *p*-methylsalicylic acid (**A1**) as co-catalyst (Scheme 47). 3-Methylisoxazolinone and 3-phenylisoxazolinone were used together with 3-substituted 2-cyclopentenones and aldehydes as starting materials. The spirocyclic products were obtained in fair to good yields, excellent diastereoselectivities and good to excellent enantioselectivities. The authors proposed a mechanism where the enamine of the 2-cyclopentenone would attack the 4-arylidene-isoxazolinone (generated *in situ)* in a Michael addition fashion, which after a retro-Michael reaction would give an α′-arylidene-3-substituted 2-cyclopentenone and recover the initial isoxazolinone. Then, the formed cyclopentadienone would react, via enamine catalysis with another molecule giving the cycloaddition product.



Scheme 45. Asymmetric four-component reaction.



Scheme 46. Asymmetric cycloaddition between methyl arylvinyl ketones and 4-arylidene-isoxazolinones.



Scheme 47. Asymmetric four-component cycloaddition between isoxazolinones, 3-cyclopentanones and aldehydes.

4. 4-Ylidene-2,3-Dioxopyrrolidines

Five-membered ring lactams also named γ-lactams or 2-oxopyrrolidines can be found in natural products[71] and some drugs as *piracetam*.[72] When a carbonyl group is incorporated in position 3 of the ring, a new biologically active moiety named 2,3-dioxopyrrolidine appears. These heterocycles can be found in natural products,[73] and compounds that are used as anticoagulants,[74] antitumor[75] or glucokinase activators to regulate the type II diabetes mellitus.[76] Moreover, these compounds have been used in the synthesis of novel antifungals (Figure 4).[77]

The 4-ylidene-2,3-dioxopyrrolidines have different reactive sites, which allows the synthesis of diverse structures through different addition and cycloaddition reactions. These compounds can react as monoenes in Michael addition reactions, and as 4π *oxa*-dienes or 2π dienophiles in cycloaddition reactions that can be initiated by nucleophilic addition to the double bond. In these cases, the C3-carbonyl enolate carbonyl is stabilized by conjugation of the double bond with the amide carbonyl, rendering the oxygen at C3 very nucleophilic and, hence favoring the the *oxa*-diene-like behavior (Scheme 48). Both, transition metal catalysis and organocatalysis have been used in asymmetric reactions involving these compounds as substrates.

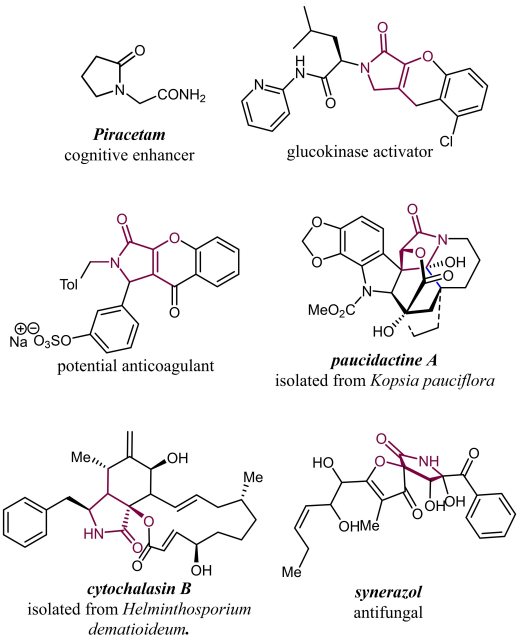
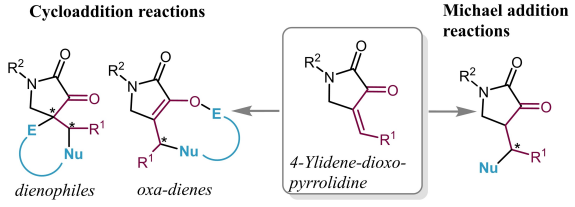


Figure 4. Examples of bioactive compounds containing the 2-oxopyrrolidine and 2,3-dioxopyrrolidine motif.



Scheme 48. General reactivity of 2,3-dioxopyrrolidines.

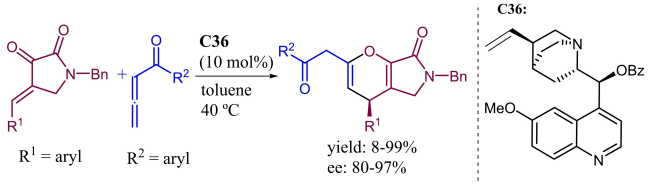
4.1. Organocatalytic Reactions with 4-Ylidene-2,3-Dioxopyrrolidines

4.1.1. Brønsted Base and Bifunctional Hydrogen Bonding/Brønsted Base Catalysis

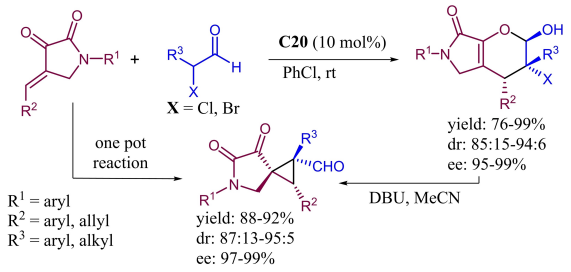
The first asymmetric organocatalytic reaction with 4-ylidene-dioxopyrrolidines was described by Xu in 2015.[78] Quinine benzoyl ester **C36** catalyzed the asymmetric formal [4+2] cycloaddition between allenyl ketones and 4-arylidene-2,3-dioxopyrrolidines to give fused 4*H*-pyran-pyrrolin-2-one derivatives, which were obtained in high yields and good enantioselectivities. The steric rather than the electronic characteristics of the aryl group R^1 determined the enantioselectivity of the reaction, the best results being obtained with *meta*-and *para*-substituted 2,3-dioxopyrrolidines. Alkyl allenones or allene esters gave poor yields (Scheme 49).

In 2018, Li reported the asymmetric cycloaddition of α-haloaldehydes and 4-arylidene-2,3-dioxopyrrolidines catalyzed by squaramide **C20**.[79] The key intermediate in this reaction, an α-halogenated enolate susceptible to dehalogenation, is stabilized and stereochemically controlled using bifunctional tertiary amines. The bicyclic dihydropyrans bearing a halogenated quaternary stereocenter were afforded in excellent yields, high diastereoselectivities and excellent enantiomeric excesses. Furthermore, the bicyclic compounds could be transformed into valuable densely functionalized spirocyclopropanes, which possess two contiguous all-carbon quaternary stereocenters, using DBU in acetonitrile (even in a one-pot fashion) with good to excellent yields and stereoselectivities (Scheme 50).

Later in 2020, Du reported a related reaction using this time 3-chlorooxindoles as pronucleophiles. Again, the reaction was catalyzed by a bifunctional squaramide derivative of quinine **C14**.[80] The authors found that the presence of one equivalent of NH_4HCO_3 was



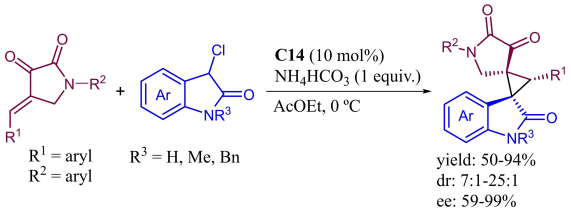
Scheme 49. Asymmetric [4+2] cycloaddition between allenyl ketones and 2,3-dioxopyrrolidines.



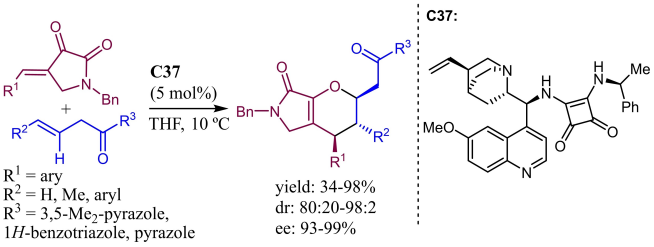
Scheme 50. Asymmetric cyclopropanation of 4-alkylidene-2,3-dioxopyrrolidinones with α-haloaldehydes.

crucial to obtain the desired bi-spirocyclic products in high yields, diastereoselectivities and enantiomeric excesses (Scheme 51). A broad variety of 4-arylidene-pyrrolidinones were studied obtaining the bispirocyclic products bearing three adjacent chiral centers with excellent results (Scheme 51).

In 2019, Huang reported a regiodivergent reaction between 3-butenyl *N*-acylpyrazoles and 4-arylidene-2,3-dioxopyrrolidines catalyzed by a squaramide **C37** derived from quinine.[81] The reaction with 4-aryl-3-butenyl *N*-acylpyrazoles provided tetrahydropyrano-pyrolone adducts with excellent results through a vinylogous Michael addition/*oxa*-Michael reaction. Excellent yields, diastereo- and enantioselectivities were obtained for a range of 4-arylidene-2,3-dioxopyrrolidines having aromatic or heteroaromatic rings (R^1) attached to the double bond. The β,γ-unsaturated amide also tolerated aromatic and heteroaromatic groups R^2.



Scheme 51. Asymmetric cyclopropanation of 4-arylidene-2,3-dioxopyrrolidines with 3-chlorooxindoles.



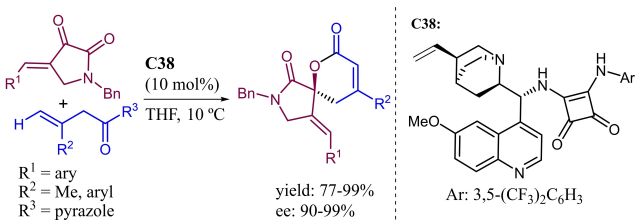
Scheme 52. Asymmetric vinylogous Michael addition/*oxa*-Michael reaction between 4-aryl-3-butenyl *N*-acylpyrazoles and 4-arylidene-2,3-dioxopyrrolidines.

The best results were obtained with amides derived from 3,5-dimethylpyrazole (Scheme 52).

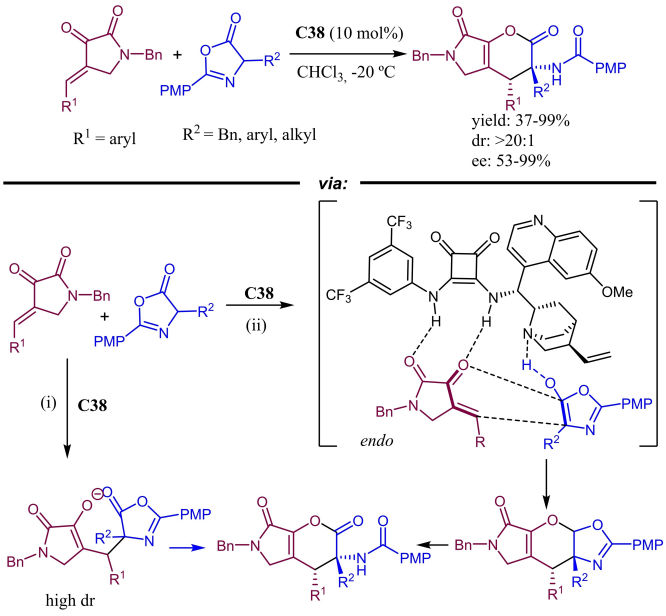
On the other hand, when 3-aryl-3-butenyl *N*-acylpyrazoles were used, spiropyrrolidinone-dihydro-pyranones were obtained in excellent yields and enantiomeric excesses via a 1,2-selective γ-addition to the ketone carbonyl of the dioxopyrrolidine ring followed by cyclization. The 3-substituted-3-butenyl *N*-acylpyrazoles did not perform as β,γ-regioselective dienophiles, because of the formation of a demanding steric hindered quaternary stereogenic carbon at position 3. In this case, the steric hindrance of the substituent in R^1 had a slightly negative effect in the enantiocontrol, although both electron-poor and electron-rich substituents were well tolerated. In addition, good results were obtained with 3-butenyl *N*-acylpyrazoles bearing different aryl rings or a methyl group at position 3 (Scheme 53).

Using this catalyst, the same authors also developed an asymmetric formal [4+2] cycloaddition of 4-arylidene-2,3-dioxopyrrolidines and azlactones.[82] The reaction proceeded well with 2,3-dioxopyrrolidines containing different aromatic substituents in R^1 and azlactones having benzyl, alkyl or halophenyl groups at R^2 and a *para*-methoxyphenyl ring (PMP) attached to the imine carbon, other aromatic rings at this position were tolerated but led to lower enantiomeric excesses. The corresponding pyrano[2,3-*c*]pyrrole products were obtained in high yields and excellent diastereoselectivities (>20:1). Two plausible mechanisms were also proposed: (i) involving a conjugate addition of the azlactone to the 4-arylidene-dioxopyrrolidinone followed by an intramolecular cyclization, and (ii) involving an inverse-electron-demand hetero-Diels-Alder reaction that proceeds in an *endo* way followed by ring opening (Scheme 54).

A modularly designed organocatalyst, self-assembled *in situ* from a thiourea derived from quinine **C25** and *L*-proline, was developed by Huang for the synthesis of a series of fused tricyclic pyrano[3′,2′:5,6]pyrano[2,3-c]pyrrolones.[83] The reaction involved 4-arylidene-2,3-dioxopyrrolidines and aldehydes featuring a properly positioned enone moiety in their structure, leading to the reaction products through a Michael addition/acetalation/*oxa*-Michael process. The



Scheme 53. Asymmetric 1,2-γ-addition/cyclization between 3-aryl-3-butenyl *N*-acylpyrazoles and 4-arylidene-pyrrolidinones.



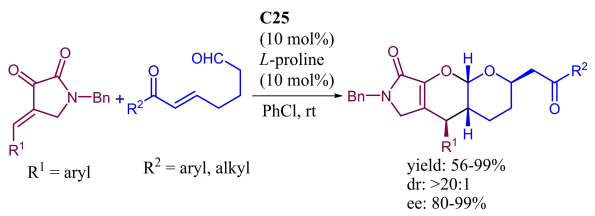
Scheme 54. Asymmetric synthesis of pyrano[2,3-*c*]pyrroles from azlactones and 4-arylidene-dioxopyrrolidines.

tricyclic compounds were obtained in excellent yields, diastereoselectivities and enantiomeric excesses (Scheme 55).

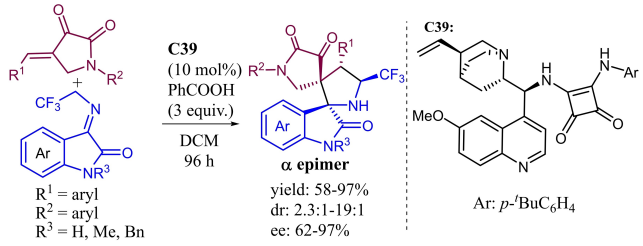
A diastereodivergent and enantioselective formal [3 + 2] cycloaddition reaction between *N*-(2,2,2-trifluoroethyl)isatin ketimines and 4-alkylidene-dioxopyrrolidinones has been developed by the group of Jiang.[84] Initial studies demonstrated that a quinine derived squaramide **C39** was the best catalyst and benzoic acid was needed to increase both chemical yield and enantiomeric excess. Furthermore, it was found that the reaction time and the ratio catalyst/benzoic acid played an essential role in the formation of one or another epimer. Thus, long reaction times (96 h), 10 mol% of catalyst and three equivalents of benzoic acid led to preferential formation of the **α** epimer (Scheme 56).

On the other hand, when a 30 mol% of **C39**, 1.5 equivalents of benzoic acid and shorter reaction times (9 h) were used, the **β** epimer was obtained as the major isomer. In both cases, the reaction allowed the use of different *N*-(2,2,2-trifluoroethyl)isatin ketimines as well as 4-arylidene-2,3-dioxopyrrolidines, and the bi-spirocyclic oxindoles were obtained in moderate to excellent yields, diastereoselectivities and enantiomeric excesses (Scheme 57).

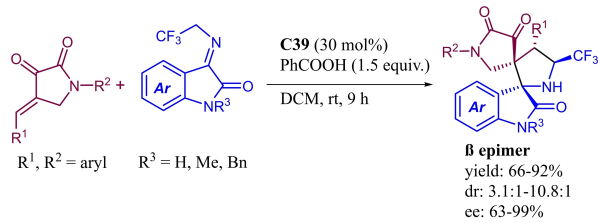
Finally, an asymmetric conjugate addition of nitroalkanes to 4-arylidene-2,3-dioxopyrrolidines and 4-arylidene-dihydrofuran-2,3-diones catalyzed by bifunctional squaramide **C20** has been recently published by Bugaut and co-workers.[85] The authors found better results with 4-arylidene-2,3-dioxopyrrolidines than with 4-arylidene-dihydrofuran-2,3-diones. The reaction was tested with differently substituted nitroalkanes, obtaining the highest yields and enantiomeric excesses with nitroethane, although diastereoselectivities were, in general, low (Scheme 58). When 2-nitro-1-phenylethanone (R^2=PhCO) was used, the Michael addition was followed by C-to-O benzoyl migration in a similar manner as in the reaction with pyrazolones (see Scheme 27).



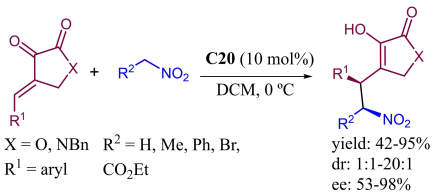
Scheme 55. Synthesis of fused tricyclic acetals.



Scheme 56. Asymmetric diastereodivergent [3 + 2] cycloaddition of isatin ketimines and 4-arylidene-pyrrolidinones (**α** epimer).



Scheme 57. Asymmetric diastereodivergent [3 + 2] cycloaddition of isatin ketimines and 4-arylidene-pyrrolidinones (**β** epimer).



Scheme 58. Asymmetric addition of nitroalkanes to 4-arylidene-2,3-dioxopyrrolidines and 4-arylidene-dihydrofuran-2,3-diones.

4.1.2. Reactions via Enamine Catalysis

2,3-Dioxopyrrolidines have been used as heterodienes in the inverse-electron-demand *oxa*-Diels-Alder reaction with enolizable aldehydes via enamine catalysis by Gou and Peng.[86] Fused bicyclic dihydropyrans were obtained in good yields with good diastereoselectivities and high enantiomeric excesses using the Hayashi-Jørgensen catalyst **C1** and benzoic acid as co-catalyst. The reaction could be carried out with a variety of aliphatic aldehydes and with a good number of *N*-benzyl 4-arylidene-2,3-dioxopyrrolidines bearing differently substituted aromatic and heteroaromatic groups R^1 attached to the double bond (Scheme 59).

Remarkably, the authors could adjust the reaction conditions to carry out the reaction with aqueous acetaldehyde. An acetylation-chlorination reaction of the resulting bicyclic *trans*-dihydropyranones was then performed giving chloro-substituted products with configurational retention (Scheme 60).

4.1.3. Phosphine and Phosphonium Salt Catalyzed Reactions

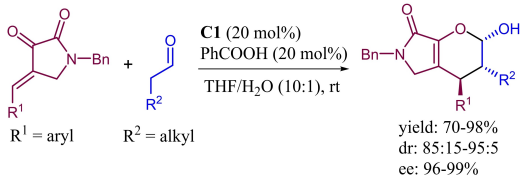
Asymmetric cycloaddition reactions using 4-ylidene-2,3-dioxopyrrolidines have been also achieved with phosphine catalysis. In 2017, Guo reported the asymmetric [4+2] cycloaddition of α-substituted allenoates with 4-arylidene-pyrrolidine-2,3-diones catalyzed by an amino acid-derived chiral phosphine **C40**.[87] The reaction required 4 Å molecular sieves as additive to obtain the desired products in high yields and good enantiomeric excesses. Fused pyrrolidinone-dihydropyran derivatives were afforded in moderate to good yields and excellent enantioselectivities (Scheme 61). A broad variety of 4-arylidene-2,3-dioxopyrrolidines having aromatic rings attached to the double bond were supported, observing a slight decrease in the yield with those being *ortho* or *meta* substituted. On the other hand, a benzylic substituent at the α-position of the allenoate was required, no reaction being observed when this was a methyl group (R^2=H)

In 2019, a new C_2-symmetric chiral phosphine **C41** was employed to catalyze the highly enantioselective domino process involving 4-arylidene-2,3-dioxopyrrolidines and γ-substituted allenoates to afford tricyclic γ-lactams with five contiguous stereogenic centers.[88] A variety of 4-arylidene-dioxopyrrolidines were good substrates for the reaction. The R^2 substituent on the allenoate could be either an aryl, alkyl or an ester group. In this reaction, the phosphine catalyst generates a δ-anion that undergoes a Michael addition to the 2,3-dioxopyrrolidine. Once the Michael addition occurs, a H-shift allows the intramolecular addition over the carbonyl group of the 2,3-dioxopyrrolidine heterocycle. Then, an intramolecular *oxa*-cycloaddition delivers the desired tricyclic γ-lactam (Scheme 62).

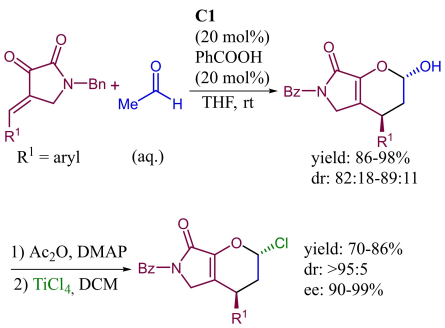
Recently, Wang and Gao have studied the asymmetric 1,3-dipolar cycloaddition of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 4-alkenyl-2,3-dioxopyrrolidines.[89] This reaction was successfully catalyzed by a dipeptide-derived phosphonium salt **C42** under phase-transfer conditions (PTC), and provided CF_3-substituted 3,2'-pyrrolidinyl spirooxindoles. A good number of 4-arylidene-pyrrolidinones and substituted isatin ketimines were tested to give the desired products in high yields, as a single diastereomer with high enantiomeric excesses (Scheme 63).

Mechanistic study experiments revealed that the stereocontrol of the reaction is due to a hydrogen-bonding coordination of the peptide NH with the carbonyl oxygen atoms of the dioxopyrrolidine core and ion pairing between the phosphorous cation and the isatin ketimine anion.

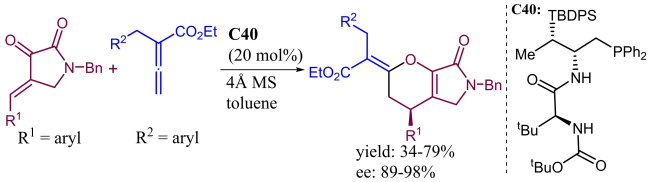
The same group also reported enantioselective PTC in the reaction of 4-bromopyrazolones and 4-arylidene-dioxopyrrolidines using another dipeptide-derived



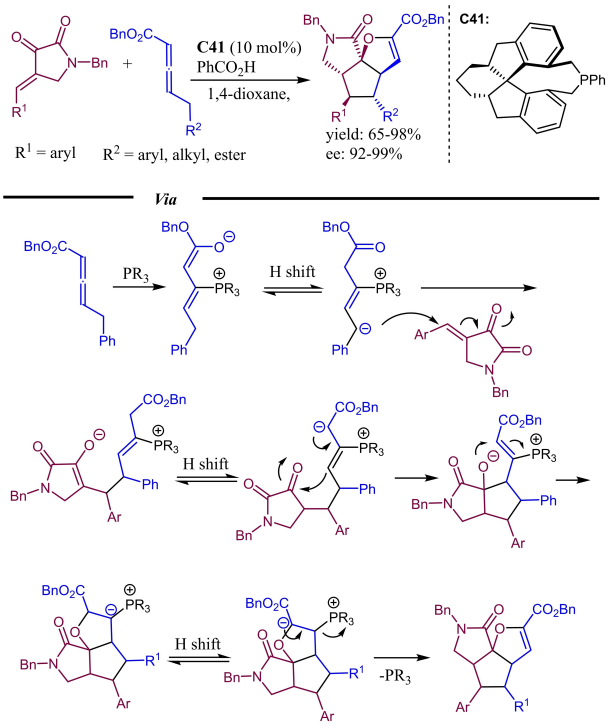
Scheme 59. Asymmetric inverse-electron-demand *oxa*-Diels-Alder between enolizable aldehydes and 4-yliene-2,3-dioxopyrrolidines.



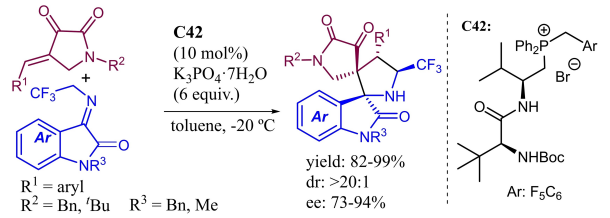
Scheme 60. Asymmetric inverse-electron-demand *oxa*-Diels-Alder between aqueous acetaldehyde and 2,3-dioxopyrrolidines.



Scheme 61. Asymmetric [4+2] cycloaddition of α-substituted allenoates with 4-arylidene-2,3-dioxopyrrolidines.



Scheme 62. Asymmetric cycloaddition between 4-arylidene-dioxopyrrolidines and allene esters.

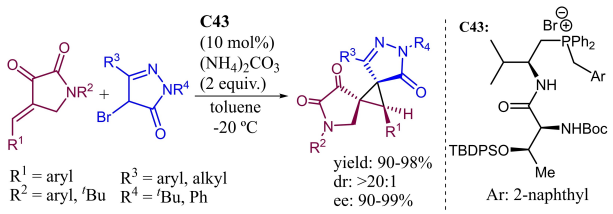


Scheme 63. 1,3-Dipolar cycloaddition between isatin ketimines and 4-arylidene-dioxopyrrolidines under PTC.

phosphonium salt **C43**.[90] The reaction involved a Michael addition of the pyrazolone enolate to the arylidene-dioxopyrrolidine followed by intramolecular S_N2 to give the formal [2+1] cycloaddition product containing a cyclopropylspirocyclic moiety. The reaction could be applied to a wide range of 4-arylidene-2,3-dioxopyrrolidines, and pyrazolones, obtaining in all the cases excellent yields, diastereoselectivities and enantioselectivities (Scheme 64).

4.1.4. Reactions via NHC Catalysis

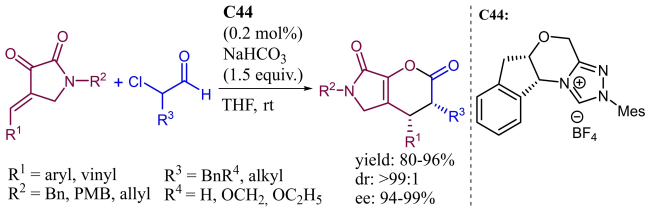
Peng and Shen have reported the asymmetric NHC-catalyzed formal [4+2] cycloaddition of 4-arylidene-dioxopyrrolidines and α-haloaldehydes.[91] Bicyclic dihydropyranones were obtained in high yields and excellent enantioselectivities. Both electron-donating and electron-withdrawing groups on the aromatic ring



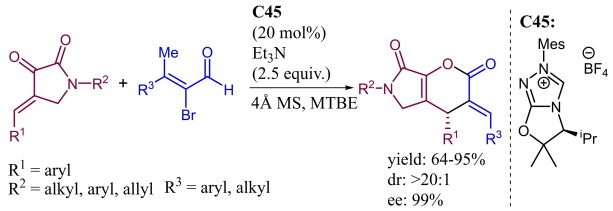
Scheme 64. Asymmetric cyclopropanation of 4-arylidene-2,3-dioxopyrrolidines with of 4-halopyrazolones.

attached to the double bond of the arylidene-dioxopyrrolidine were accepted. Moreover, linear aliphatic or benzyloxy substituted aldehydes produced the corresponding dihydropyranones with excellent results (Scheme 65). Remarkably, the substituents on the lactone ring showed a *cis* disposition, in contrast with the *trans* disposition observed in a related reaction described by the same group under enamine catalysis (see Scheme 59).[86]

Another synthesis of these bicyclic dihydropyranones has been described by Wang in 2020.[92] This asymmetric NHC-catalyzed [4+2] annulation of α-bromoenals and 2,3-dioxopyrrolidines showed broad substrate scope and gave the bicyclic products in good to high yields and excellent enantioselectivities. *N*-Bn protected 2,3-dioxopyrrolidines gave the best results allowing aromatic rings of different substitution pattern and electronic character attached to the double bond. Furthermore, α-bromoenals could contain a methyl, aryl or heteroaryl group R^3 on the double bond (Scheme 66).



Scheme 65. Asymmetric [4+2] cycloaddition of α-chloroaldehydes to 4-arylidene-dioxopirrolidines.



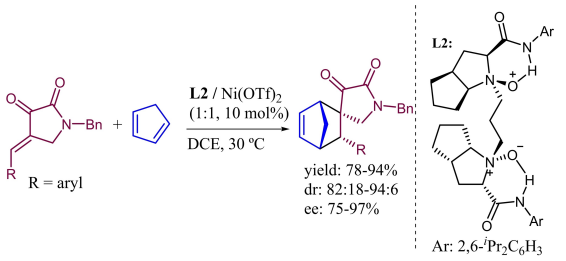
Scheme 66. Asymmetric [4+2] annulation between α-bromoenals and 4-arylidene-2,3-dioxopyrrolidines.

4.2. Metal-Catalyzed Reactions with 4-Ylidene-2,3-Dioxopyrrolidines

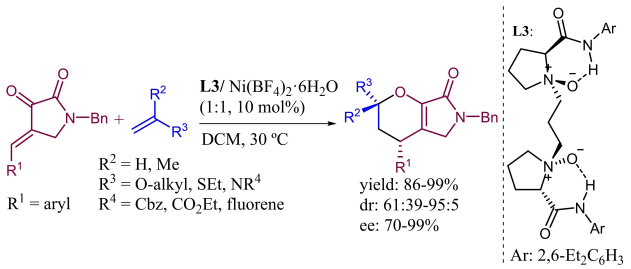
The first metal-catalyzed enantioselective reaction involving the 4-ylidene-2,3-dioxopyrrolidine motif was described in 2016 by Feng.[93] In this paper, a Diels-Alder reaction between 4-arylidene-2,3-dioxopyrrolidines and cyclopentadiene was achieved using a complex of $Ni(OTf)_2$ with a *N,N'*-dioxide ligand **L2** as catalyst. In general, high yields, diastereoselectivities and enantiomeric excesses of spirocyclic compounds were obtained with a variety of arylidene-dioxopyrrolidine derivatives bearing aromatic groups attached to the double bond (Scheme 67).

Two years later, a similar Ni catalyst complex with a *L*-proline-derived dioxide ligand **L3** was used by the same authors to carry out an inverse-electron-demand hetero-Diels – Alder reaction.[94] 4-Arylidene-2,3-dioxopyrrolidines reacted as heterodienes with hetero-substituted alkenes to give the corresponding fused pyrano-pyrroles with excellent yields and stereoselectivities, regardless of the electronic or steric features of the substituents on the exocyclic double bond. Besides monosubstituted vinyl ethers, *N*-vinyl carbamates reacted to give the expected products with good yields, fair to good diastereoselectivities and high enantioselectivities. A vinyl sulfide as well as disubstituted vinyl ethers also reacted but with moderated diastereo- and enantioselectivity (Scheme 68).

In 2020, the conjugate addition of nitroalkanes to 4-arylidene-2,3-dioxopyrrolidines was reported by Wang



Scheme 67. Asymmetric Diels-Alder reaction between 4-arylidene-2,3-dioxopyrrolidine and cyclopentadiene.



Scheme 68. Asymmetric inverse-electron-demand hetero-Diels – Alder reaction.

using a copper complex with a proline-derived ligand **L4** in aqueous media.[95] The reaction needed the use of *N*-ethylmorpholine as a base and sodium lauryl sulfate (SLS) as surfactant. A series of nitro-containing pyrrolidones were prepared in high yields, excellent diastereoselectivities, and enantiomeric excesses. The reaction tolerated aromatic rings of diverse nature attached to the double bond of the arylidene-dioxopyrrolidine. On the other hand, the reaction worked better with nitroethane and nitropropane than with nitromethane (Scheme 69).

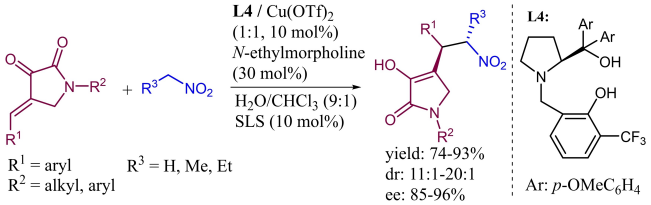
5. Reactions with Rhodanine and Oxazolidindione Derivatives

Rhodanine-based compounds have become very important in drug discovery because of their varied biological activities.[96] Some of these compounds have been reported to possess antibacterial,[97] antiviral,[98] pesticide,[99] antimalarial,[100] antitumor[101] or anti-inflammatory activity.[102] Furthermore, they can potentially be used in the treatment of diabetes[103] and Alzheimer,[104] among others. On the other hand, the oxazolidin-2,4-dione motif can be found in herbicides,[105] antiepileptic agents,[106] and anti-inflammatory drugs.[107] Moreover, this motif is also being studied for the development of novel photosensitive dyes (Figure 5).[108]

The oxazolidindione and rhodanine scaffolds bearing exocyclic double bonds have emerged as powerful substrates in asymmetric cycloaddition reactions providing highly functionalized spirocompounds.[109] While organocatalysis has been the most frequently used with rhodanine derivatives, metal-ligand catalysis has been also used with oxazolidindione derivatives, despite examples of organocatalytic asymmetric Michael additions with these substrates are also known (Scheme 70).

5.1. Organocatalytic Reactions with 5-Ylidene-Rhodanines

5-Ylidene-rhodanines have been successfully employed as substrates in asymmetric cycloaddition reactions. Organocatalytic methods such as enamine



Scheme 69. Asymmetric addition of nitroalkanes to 4-arylidene-2,3-dioxopyrrolidines.

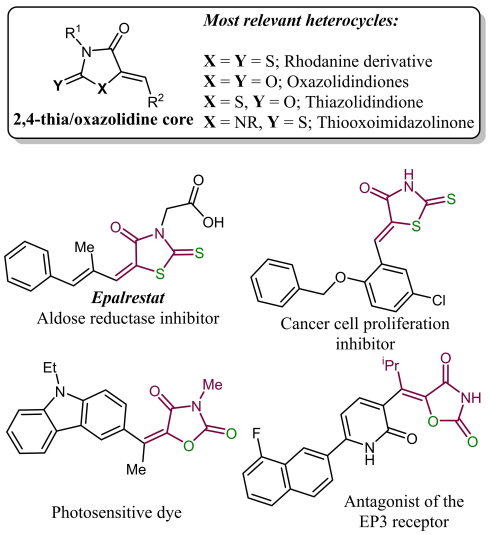
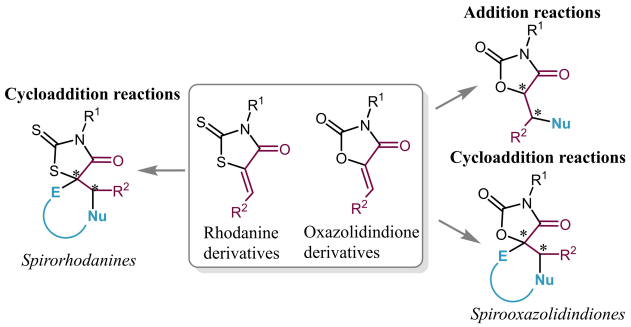


Figure 5. Examples of bioactive compounds containing the rhodanine and oxazolidin-2,4-dione motifs.

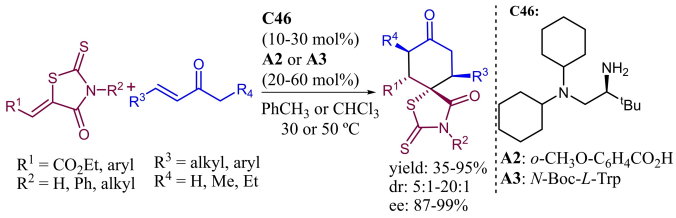


Scheme 70. General reactivity of ylidene-derivatives of rhodanine and oxazolidindiones.

and *Cinchona* alkaloid bifunctional catalysis have been shown extremely efficient to perform these reactions.

5.1.1. Reactions via Enamine Catalysis

Ye described the first asymmetric reaction involving 5-ylidene-rhodanines in 2012.[110] A tandem double Michael addition between 4-ylidene-rhodanines and enolizable enones was performed using a chiral primary amine **C46** as catalyst in the presence of an acid additive such as *ortho*-methoxybenzoic acid or *N*-Boc-*L*-Trp. The substituents on the N atom and double bond of the rhodanine derivative were amenable to modification as well as the substituent on the double bond of the enone. Rhodanine spirocyclic compounds bearing three (R^4=H) or four (R^4=Me) stereogenic centers were obtained with good yields, fair to high diastereoselectivities and excellent enantiomeric excesses (Scheme 71).



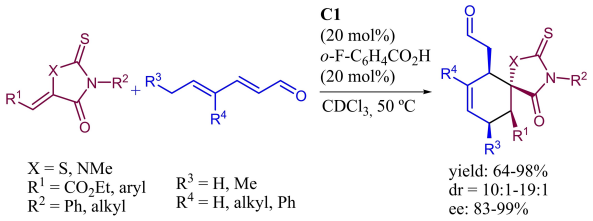
Scheme 71. Asymmetric double Michael addition of enolizable enones to 5-ylidene-rhodanines.

The same group also described a Diels-Alder reaction between 2,4-dienals and 5-ylidene-rhodanines catalyzed by the Hayashi-Jørgensen catalyst **C1** and *o*-fluorobenzoic acid as co-catalyst.[111] The reaction was carried out in $CDCl_3$ as the solvent, which apparently provided the best solubility for the rhodanine and favored higher yields. The scope and limitations of the reaction were investigated using first some 5-ylidene-rhodanines, observing that the substituent R^1 has a high influence in the reaction rate. Long reaction times (72-96 h) were needed when R^1 was an aromatic ring while shorter reaction times were required when R^1 was CO_2Et. Remarkably, the structure of R^1 had very limited influence on the stereoselectivity of the reaction, which afforded the spirocyclic products with high diastereoselectivities (10:1) and excellent enantiomeric excesses (>90%). Furthermore, the authors assayed differently substituted 2,4-dienals obtaining in all cases high to excellent yields, diastereoselectivities and enantiomeric excesses (Scheme 72).

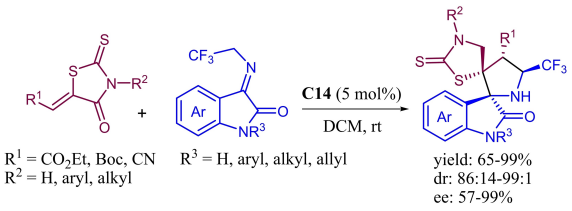
5.1.2. Bifunctional Hydrogen-Bonding/Brønsted Base Catalysis

Cinchona alkaloid derivatives have shown to be powerful catalysts in asymmetric addition reactions to rhodanine derivatives. Du and co-workers reported in 2018 an asymmetric formal [3+2] cycloaddition reaction of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 5-ylidene-rhodanines involving a domino Michael/Mannich process (Scheme 73).[112]

The bifunctional squaramide **C14** was found as the best catalyst. An electron-withdrawing group R^1 (ester,



Scheme 72. Asymmetric Diels-Alder reaction between 2,4-dienals and 5-ylidene-rhodanines.

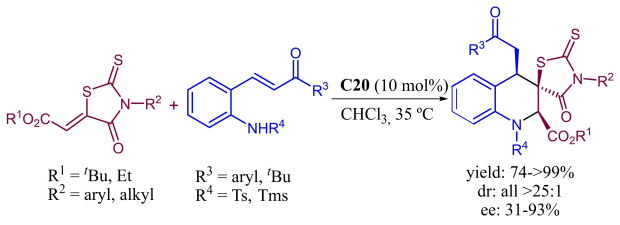


Scheme 73. Asymmetric formal [3+2] cycloaddition of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 5-arylidene-rhodanines.

CN) attached to the exocyclic double bond of the rhodanine was required as rhodanines having a phenyl group did not react. However, a diversity of alkyl and aryl groups R^2 attached to the N atom were tolerated. On the other hand, the isatin ketimines permitted different substituents on either the aromatic ring or N1. In general, the bi-spirocyclic oxindoles were obtained with high yields, diastereo-and enantioselectivities.

The same authors also studied an asymmetric cascade *aza*-Michael/Michael addition reaction between rhodanine derivatives and β-(2-tosylaminophenyl)enones to afford spirothiazolidinone-tetrahydroquinolines.[113] In this case, squaramide **C20** was the best performing catalyst providing the reaction products with good yields excellent diastereoselectivities and fair to good enantiomeric excesses. An ester group attached to the exocyclic double bond and substitution at the *N* atom of the rhodanine were required. On the other hand, the enone required a non-enolizable group (aryl or *tert*-butyl) attached to the carbonyl, as methyl ketone did not react (Scheme 74).

In 2020, the asymmetric [3+3] annulation between pyrazolones and novel rhodanine ketoesters catalyzed by the chiral squaramide **C20** was described by Xu.[114] The rhodanine ketoesters played as bis-electrophiles, and featured two potential hydrogen-bonding activation sites to favor the reaction and promoting the stereoselectivity. A variety of aromatic groups attached to the N atom of the rhodanine, and to the N atom and azomethinic carbon of the pyrazolones were permitted. The 2′-thioxo-5,6-dihydrospiro[pyrano[2,3-c]pyrazole-4,5′-thiazolidin]-4′-ones were obtained in high yields, and excellent diastereomeric ratios and enantiomeric excesses (Scheme 75).



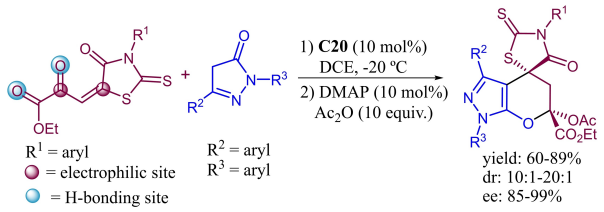
Scheme 74. Asymmetric cascade *aza*-Michael/Michael addition reaction between rhodanine derivatives and β-(2-aminophenyl) enones.

5.2. Asymmetric Organocatalytic Reactions with Oxazolidindione and Thiazolidindione Derivatives

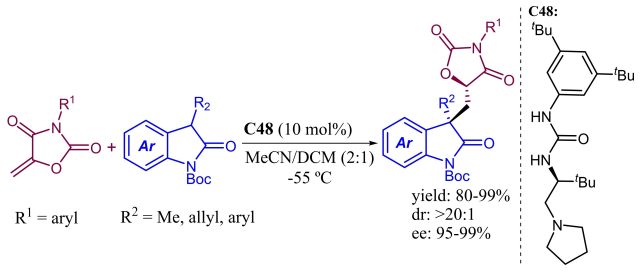
In 2017, an asymmetric tandem conjugated addition/protonation reaction of 3-substituted oxindoles and 1,3-oxazolidin-2,4-diones using a chiral bifunctional urea/Brønsted base catalyst **C48** was reported by Jiang.[115] The reaction allowed to construct a quaternary and a secondary C–O stereogenic centers. The *N*-Boc protecting group of the oxindole was required to obtain good results. Methylene-1,3-oxazolidine-2,4-diones having a phenyl, 4-Cl–, 4-MeO– or 3-F phenyl groups attached to the N atom were successfully employed. A variety of oxindoles having different substitution at the aromatic ring, and benzyl or aryl groups at position 3 reacted to give the corresponding products with high to excellent yields, and excellent diastereo- and enantioselectivities (Scheme 76).

Inspired by these results, the authors also studied the addition of thiols using a related catalyst **C49**. In this case, 5 Å molecular sieves and NaCl were needed as additives (Scheme 77). A few thiols of different nature (benzyl, aryl and alkyl) were studied, obtaining high to excellent yields and enantioselectivities. The ee of the reaction products could be increased above 99% after crystallization.

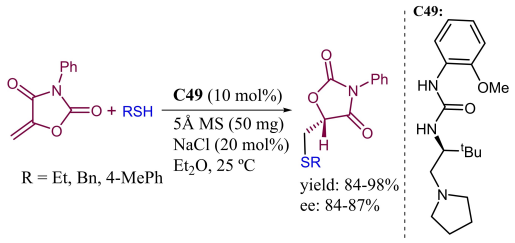
Later, in 2019, Zhu and Chang employed azlactones as nucleophiles for a similar asymmetric conjugate addition/protonation reaction.[116] Again, a bifunctional



Scheme 75. Asymmetric [3+3] annulation between pyrazolones and novel rhodanine ketoesters.

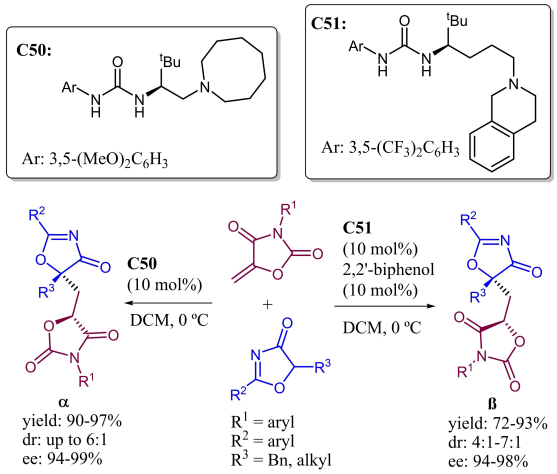


Scheme 76. Asymmetric addition of 3-substituted oxindoles to methylene-1,3-oxazolidine-2,4-diones.

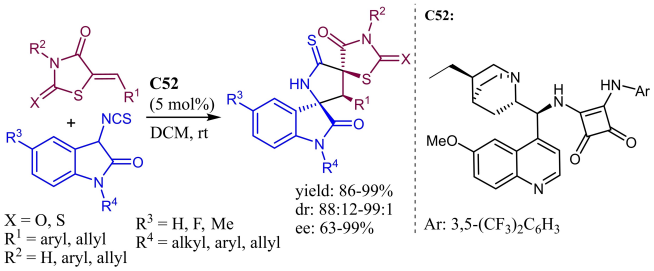


Scheme 77. Asymmetric addition of thiols to *N*-phenyl methylene-1,3-oxazolidine-2,4-dione.

urea/Brønsted base was used as catalyst. The ring size linked to the tertiary amine of the catalyst played an important role in the reaction, obtaining the best results with an eight-membered ring **C50**. Different azlactones and a wide variety of methylene 1,3-oxazolidine-2,4-diones were studied obtaining in all cases the α-diastereomer with excellent results. Moreover, when 2,2′-biphenol was used as additive and **C51** as catalyst, a diastereoselectivity switch was observed affording the β diastereomer (Scheme 78).



Scheme 78. Asymmetric diastereodivergent addition of azlactones to methylene-1,3-oxazolidine-2,4-diones.

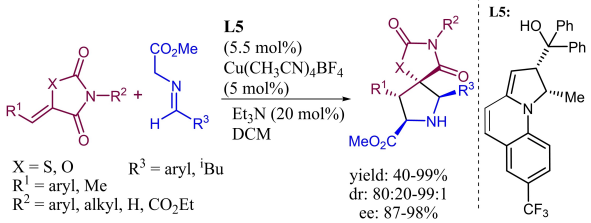


Scheme 79. Asymmetric addition of 3-isothiocyanato oxindoles to 5-arylidene-thiazolidine-2,4-diones.

Besides these conjugate addition reactions, Du and Song described a formal [3 + 2] cycloaddition involving a cascade Michael/cyclization reaction of unsaturated thiazolidinones and isothiocyanato oxindoles catalyzed by bifunctional squaramide **C52**.[117] A variety of *N*-protected 5-ylidene-thiazolidine-2,4-diones and isothiocyanato oxindoles were studied, affording oxindole-pyrrolidone-thiazolidinone bi-spirocyclic heterocycles in high yields and excellent diastereo- and enantioselectivities. The authors also tested a rhodanine derivate as electrophile obtaining an excellent yield (95%), good diastereoselectivity (88:12) and moderate enantiomeric excess (62%) due to the lower electronegativity of the substrate (Scheme 79).

5.3. Asymmetric Metal-Catalyzed Reactions with Oxazolidindione and Thiazolidindione Derivatives

Despite the prevalence of organocatalytic procedures, the first asymmetric reaction with 5-ylidene-thiazolidine-2,4-diones was reported by Deng and Yu in 2015 using metal catalysis.[118] These compounds reacted as dipolarophiles in the asymmetric 1,3-dipolar cycloaddition with azomethine ylides catalyzed by a chiral copper complex with the chiral amino alcohol ligand **L5**. The corresponding spirocyclic pyrrolidine-thiazolidindione products containing a spiro-heteroquaternary stereogenic center were obtained in good to excellent yields, with excellent levels of diastereo- and enantioselectivity. Imines derived from aromatic or heteroaromatic aldehydes worked efficiently in the reaction. Imines derived from 3-methylbutanal also were adequate substrates, although the diastereomeric ratio obtained in these cases was lower than with aromatic imines. The thiazolidine-2,4-dione partner allowed different aromatic or alkyl groups attached to the N atom and the exocyclic double bond. The authors also tested a few 5-ylidene-oxazolidine-2,4-diones (X=O) bearing haloaromatic rings on the double bond that reacted similarly to their sulfur analogues (Scheme 80).



Scheme 80. Asymmetric 1,3-dipolar cycloaddition of azomethine ylides and 5-ylidene-thiazolidine-2,4-diones.

6. 4-Ylidene-Azlactones

Olefinic 2-oxazolones, so-called Erlenmeyer azlactones, were synthesized in 1893 by Erlenmeyer through a Perkin condensation of *N*-acetyl glycine with acetic anhydride and sodium acetate.[119] These compounds are very attractive in the synthesis of novel heterocycles.[120] Furthermore, ring opening reactions lead to the corresponding amino acid derivatives, for example *L*-cyclohexylalanine[121] and *L*-phenylalanine.[122] The phytotoxic tetrapeptide Tentoxin can be also synthesized using an azlactone as starting material.[123] Furthermore, the azlactone moiety itself can be found in some biologically active compounds including antibacterials and antifungals,[124] HCMV and HSV-2 proteases inhibitors[125] and anti-inflammatory agents.[126] Also, these heterocycles have been used as titrant agents for the analysis of hydrolases[127] (Figure 6).

Condensation of azlactones with aldehydes gives 4-ylidene-azlactones (Erlenmeyer-Ploch azlactones) bearing an exocyclic double bond that can participate as Michael acceptors or in cycloaddition reactions generating spirocyclic compounds. Moreover, in absence of an external electrophile the Erlenmeyer-Ploch azlactones can undergo a double nucleophilic attack involving addition to the exocyclic double bond followed by nucleophilic attack to the lactone carbonyl in an inter- or intramolecular fashion with cleavage of the azlactone ring. Cleavage of the azlactone ring is favored by the formation of a stable amide gorup or amide anion and is the driving force of many of the reactions involving this kind of compounds. This dielectrophilic behavior allows the synthesis of privileged amino acid derivatives with two continuous stereocenters (Scheme 81). In general, Erlenmeyer-Ploch azlactones are obtained as the more thermodynamically stable *Z* isomers, although sometimes they are obtained as a mixture of isomers that can be separated by crystallization.

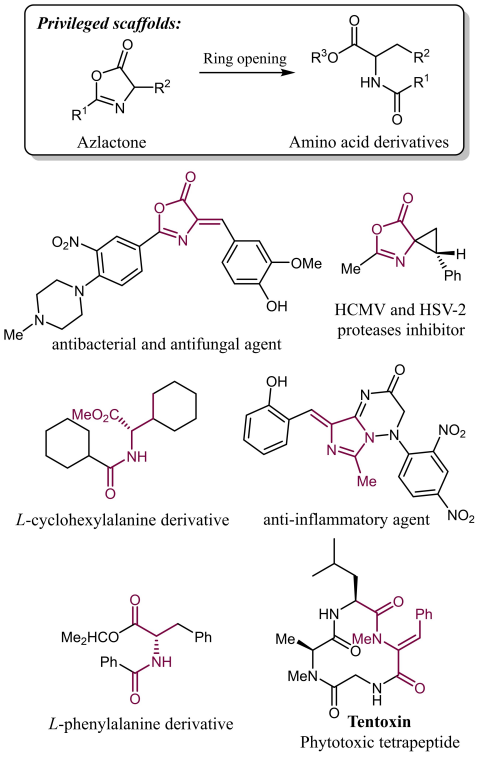


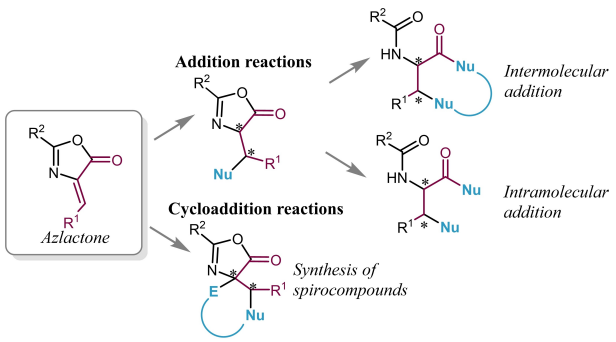
Figure 6. Selected compounds derived from Erlenmeyer azlactones.

6.1. Organocatalytic Reactions with 4-Ylidene-Azlactones

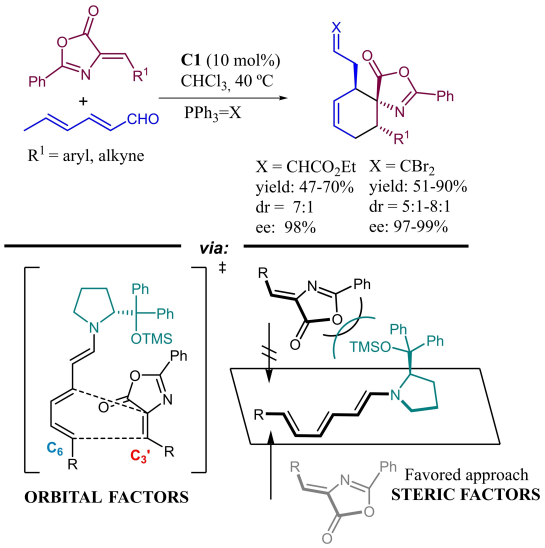
In the last years, organocatalytic asymmetric conjugate additions to Erlenmeyer-Ploch azlactones have gained relevance. Several protocols have been developed using enamine, phosphine or phosphoric acid catalysis.

6.1.1. Reactions via Enamine Catalysis

As early as 2011, the group of Jørgensen described the first asymmetric reaction involving 4-ylidene-azlactones The authors developed an enamine-catalyzed Diels-Alder reaction of 2,4-dienals with 4-ylidene-azlactones (Scheme 82).[128] The reaction takes place through a trienamine intermediate formed from the dienal and the catalyst, and allows the synthesis of rigid carbocyclic α,α-disubstituted amino acid derivatives in a regio- and stereoselective way. To improve the stability of the products and determine the enantiomeric excesses, a homologation using a stabilized phosphonium ylide (Wittig reaction) was done achieving moderate yields and diastereoselectivities and excellent enantiomeric excesses. The use of a Ramirez olefination[129] (with $PPh_3{=}CBr_2$) instead of the Wittig reaction improved both the yield and diastereoselectivity. Apparently, the shorter reaction time required for the Ramirez olefination reduced the



Scheme 81. General reactivity of Erlenmeyer-Ploch azlactones.



Scheme 82. Trienamine catalysis in the Diels-Alder reaction of 2,4-dienals and 4-ylidene-azlactones.

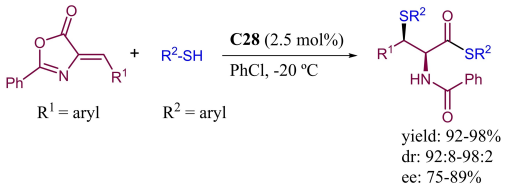
decomposition of the intermediate aldehyde, which affected more the major diastereomer.

The results indicated that an aryl substituent on the azlactone ring was vital for the reaction. Electron-withdrawing and electron-donating as well as heteroaryl or even alkynyl substituents in the azlactone exocyclic double bond were well tolerated affording the desired products in moderated yields, good diastereoselectivities and excellent enantiomeric ratios. The authors propose that regioselectivity is determined by maximized orbital overlap between the HOMO of C6 of the aldehyde and C3′ in the ylidene-azlactone. *Endo* selectivity was favored by secondary orbital interactions including possible π-π interactions (Scheme 82).

6.1.2. Bifunctional Hydrogen-Bonding/Brønsted Base Catalysis

Bifunctional catalysts have been widely applied in enantioselective reactions with 4-arylidene-azlactones. In 2012, Wang and co-workers developed an organocatalytic cascade *thia*-Michael/ring opening reaction between arylthiols and 4-arylidene-azlactones.[130] The corresponding β-thio-α-amino acids resulting from *thia*-Michael addition and thiolysis of the azlactone were obtained with excellent yields and diastereoselectivities and good enantiomeric excesses using Takemoto thiourea **C28** as catalyst. Electron-donor and electron-withdrawing substituents at the exocyclic double bond of the 4-arylidene-azlactones were suited. Substituted arylthiols reacted similarly regardless of the characteristics of the substituent (Scheme 83).

One year later, an organocatalytic Michael/cyclization reaction between 3-isothiocyanato oxindoles and 4-arylidene-azlactones was studied by Yuan.[131] A

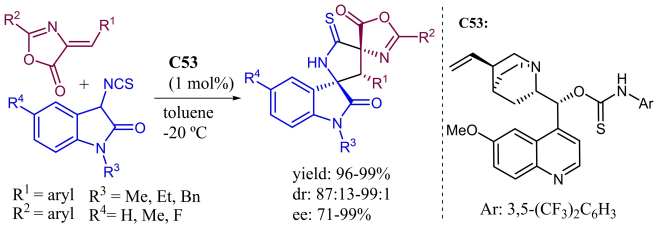


Scheme 83. Cascade *thia*-Michael/ring opening between arylthiols and 4-arylidene-azlactones.

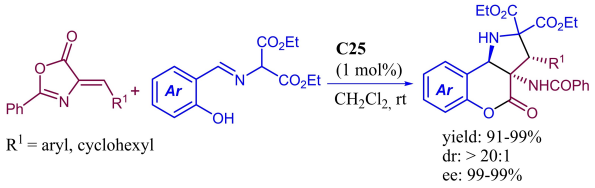
quinine thiocarbamate **C53** catalyzed the formal [3+2] cycloaddition to give bi-spirocyclic thiopyrrolidine-oxindoles in excellent yields and stereoselectivities. A broad variety of 4-arylidene-azlactones containing electron-withdrawing, electron-donating, bulky aryl or heteroaryl substituents in R^1 or R^2 were tolerated giving in all cases excellent results. Some 3-isothiocyanato oxindoles were also studied obtaining the best result with *N*-Me protected ones (Scheme 84).

In 2014, Xu developed a cascade [3+2] cycloaddition/transesterification reaction between *o*-salicylaldehyde imines and 4-ylidene-azlactones catalyzed by thiourea **C25**.[132] A good number of 4-ylidene-azlactones bearing aryl, heteroaryl or cyclohexyl groups were studied obtaining the corresponding polysubstituted chromeno[4,3-b]pyrrolidines with excellent yields and stereoselectivities. Imines of substituted salicylic aldehydes were also suitable substrates for the reaction (Scheme 85). Remarkably, a gram scale reaction was performed giving the desired product with excellent results.

Recently, Du studied the organocatalytic asymmetric formal [3+2] cycloaddition involving a domino Michael/Mannich process of *N*-(2,2,2-trifluoroethyl)



Scheme 84. Organocatalytic Michael/cyclization reaction between 3-isothiocyanato oxindoles and 4-ylidene-azlactones.



Scheme 85. Cascade [3+2] cycloaddition/transesterification between *o*-salicylaldehyde imines and 4-ylidene-azlactones.

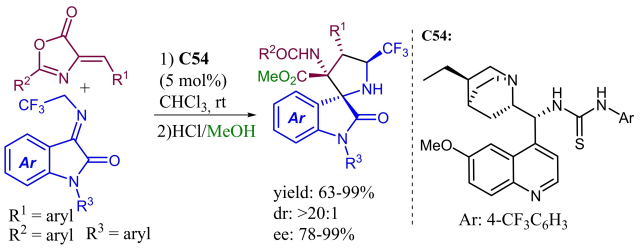
isatin ketimines and 4-arylidene-azlactones catalyzed by a dihydroquinine-derived thiourea **C54**.[133] Due to the instability of the resulting tricyclic products, a one pot hydrolysis was carried out to obtain the corresponding 3,2′-pyrrolidinyl spirooxindoles bearing four vicinal stereogenic centers. A variety of isatin ketimines were studied obtaining excellent results regardless of the electronic characteristics of the substituents on the aromatic ring. 4-Arylidene-azlactones were also evaluated founding that electron-withdrawing and electron-donating groups in R^1 and R^2 were well tolerated, although when R^1 was an heteroaryl or bulky aryl group lower yields and enantiomeric excesses were obtained (Scheme 86).

Nazarov reagents (γ,δ-unsaturated β-ketoesters) can react with Erlenmeyer-Ploch azlactones to synthesize highly functionalized spirocycles. Thus, in 2014, a double Michael addition between Nazarov reagents and 4-arylidene-azlactones catalyzed by a bifunctional thiourea-tertiary amine **C55** was described by Yuan (Scheme 87).[134]

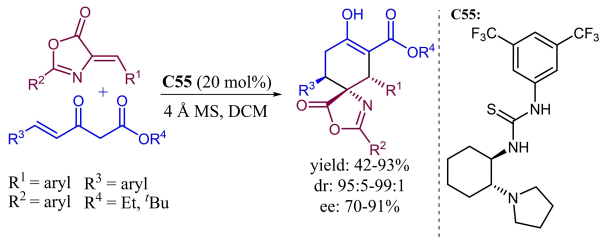
4Å Molecular sieves was needed to improve the chemical yield. *tert*-Butyl Nazarov esters gave better results than ethyl esters and electron-poor or *p*-Me substituted aryl rings in R^3 produced a decrease in yield and enantiomeric excess. Conversely, different 4-arylidene-azlactones were suitable substrates independently of the electronic characteristics of the substituents on the aryl ring (Scheme 87).

In 2016, Zhou reported what they described as an asymmetric [3 + 3] annulation between indolin-2-thiones and 4-benzylidene-azlactones.[135] The reaction, catalyzed by the chiral squaramide **C56**, proceeded via a tandem Michael addition/thiolactonization process. Cyclic tryptophan derivatives were prepared in acceptable yields and excellent diastereoselectivities for several 4-benzylidene-azlactones bearing electron-donating or electron-withdrawing substituents in R^1 and a number of substituted *N*-methylindolin-2-thiones (Scheme 88).

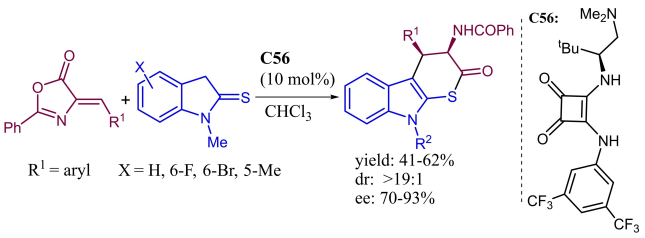
Like indolin-2-thiones, cyclohexane-1,3-diones can also participate in formal [3 + 3] cycloadditions with 4-ylidene-azlactones as Shi and Tu reported in 2016.[136] The reaction was catalyzed by the chiral thiourea **C57** affording structurally diverse 3-aminohexahydrocoumarin derivatives with high stereoselectivity. The addition of 5Å molecular sieves was needed to avoid hydrolysis of the azlactone and improve the chemical yield. A broad variety of 4-ylidene-azlactones having aromatic or heteroaromatic groups attached to the exocyclic double bond or to the azomethinic carbon reacted with 5,5-dimethylcyclohexane-1,3-dione to give the expected products with fair to good yields, excellent diastereoselectivities and fair to good enantioselectivities. 4-Ylidene-azlactones bearing an aliphatic group at either position did not react. Cycloheptane-1,3-dione was also reactive, while cyclopentane-1,3-dione did not react and acyclic pentane-2,4-dione required higher temperature and provided an almost racemic product, but with high diastereoselectivity (Scheme 89).



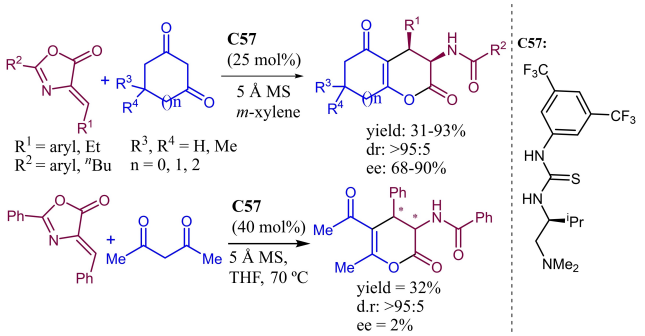
Scheme 86. Domino Michael/Mannich cycloaddition of isatin ketimines and 4-arylidene-azlactones.



Scheme 87. Double Michael addition with ketoesters and 4-arylidene-azlactones.



Scheme 88. Asymmetric [3 + 3] cycloaddition between indolin-2-thiones and 4-benzylidene-azlactones.



Scheme 89. Organocatalytic [3 + 3] cycloaddition of diketones and 4-ylidene-azlactones.

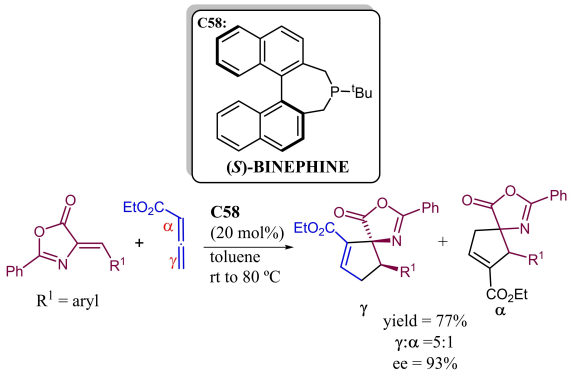
6.1.3. Phosphine Catalysis

In 2012, Jørgensen and co-workers developed a [3+2] cycloaddition between allenoates and 4-arylidene-azlactones catalyzed by (*S*)-BINEPHINE (Scheme 90).[137] The reaction was performed under a temperature gradient from room temperature to 80 °C to give the γ-addition product as the major isomer (γ/α = 5:1) with high enantiomeric excess (93% ee).

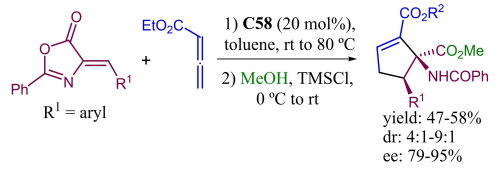
The authors then envisioned a one-pot [3+2] cycloaddition/methanolysis procedure directly accessing *N*-protected amino acid derivatives with a variety of 4-arylidene-azlactones. The reaction crude was treated with MeOH/TMSCl and the γ-addition-derived aminoacids were isolated as the major products in moderate yields and regioselectivities, but excellent enantiomeric excesses (Scheme 91).

A modification of the phosphine catalyst and reaction conditions allowed Shi to perform the same reaction with almost full regioselectivity favoring the γ-isomer.[138] By using the chiral phosphine **C59** in the presence of 4Å molecular sieves the corresponding spiro compounds were obtained in good to high yields and excellent stereoselectivities for a number of different 4-ylidene-azlactones regardless of the electronic character of the substituent in R^1. Heteroaryl and aliphatic substituents were also well tolerated. Benzyl and alkyl allenoates reacted properly with similar results (Scheme 92).

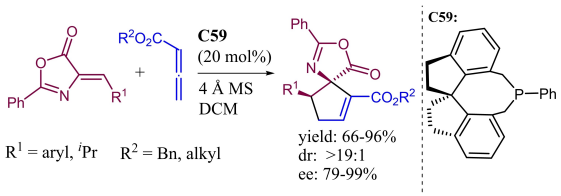
Remarkably, the phosphine-catalyzed reaction of allenoate esters with arylidene-azlactones leads to the [3+2] cycloaddition product in contrast with the [4+2] product obtained with arylidene-dioxopyrrolidines (see Scheme 61), which indicates the different character of the carbonyl group in both heterocycles.



Scheme 90. [3+2] Cycloaddition between allenoates and 4-arylidene-azlactones.



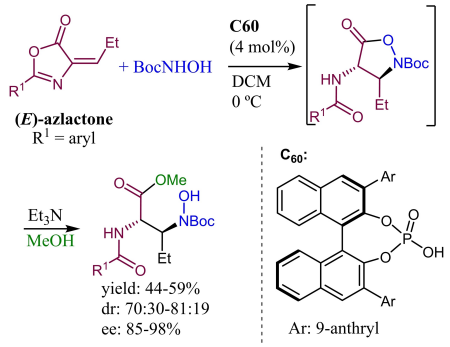
Scheme 91. One pot [3+2] cycloaddition/methanolysis between allenoates and 4-arylidene-azlactones.



Scheme 92. [3+2] Cycloaddition between allenoates and 4-arylidene-azlactones.

6.1.4. Phosphoric Acid Catalysis

In 2016, Takemoto and co-workers developed a tandem *aza*-Michael/ring opening reaction between *N*-Boc hydroxylamine and 4-ethylidene-azlactones catalyzed by a phosphoric acid **C60**.[139] The authors found that the use of catalysts bearing a tertiary amine, i.e. bifunctional thiourea/amine catalysts, promoted the undesired *O*-1,2-addition with cleavage of the azlactone ring owing to activation of the more acidic OH group of the hydroxylamine by the tertiary amine. The *aza*-Michael products obtained upon acid catalysis with **C60** were unstable and therefore transformed into diamino esters by methanolysis. The authors found that the *E* and *Z* isomers of the azlactone provided opposite enantiomers, with the *E* isomer reacting faster and with higher enantioselectivity. Initially the *E* isomer was chosen as starting material and, since both diastereomers equilibrate in solution, conditions were set to minimize the reaction of the formed *Z*-isomer. The diamino compounds were obtained in moderate yields and diastereoselectivities but high enantiomeric excesses for a few examples of aryl substituted (*E*)-azlactones (Scheme 93).



Scheme 93. Tandem *aza*-Michael/ring opening reaction between *N*-Boc hydroxylamine and (*E*)-azlactones.

Due to the difficulty to prepare the (*E*)-azlactones, a method for the *in situ* isomerization of (*Z*)-azlactones was developed. For this purpose, triphenylphosphine was used as co-catalyst to promote isomerization of the ylidene-azlactone. In this way, the *anti*-α,β-diaminoacids were obtained with similar or slightly higher yields, similar diastereoselectivity but lower enantiomeric excesses than when starting from the *E* isomer (Scheme 94).

6.2. Metal-Catalyzed Reactions

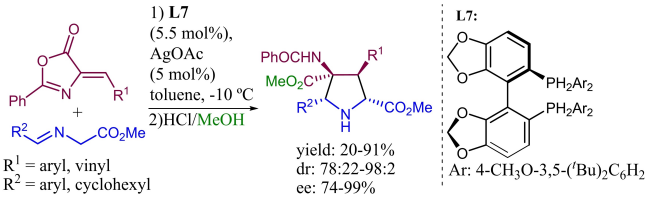
In 2011, Trost and Morris developed a formal [3+2] cycloaddition of vinyl cyclopropanes with 4-ylidene-azlactones catalyzed by a palladium complex with chiral ligand **L6** (Scheme 95).[140]

The reaction involves the participation of a π-allyl Pd-complex dipole formed from the vinylcyclopropane diester. Trifluoroethyl esters were used in this case to stabilize the dipole intermediate. The synthesis of spirocyclopentane-azlactones was achieved in moderate yield and excellent stereoselectivity with different 4-arylidene-azlactones bearing *meta*- and *para*- substituted phenyl rings attached to the double bond, while 4-alkylidene- azlactones provided the corresponding spiro compounds in lower yield and stereoselectivity (Scheme 95).

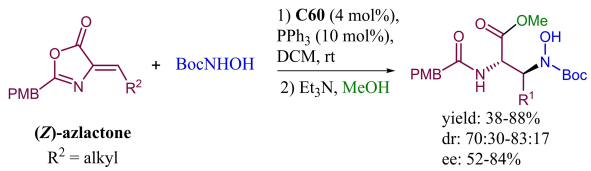
In 2013, Carretero and Adrio described the 1,3-dipolar cycloaddition of azomethine ylides and 4-ylidene-azlactones catalyzed by a silver/DTBM-Segphos (**L7**) complex.[141] Due to the instability of the resulting spirocyclic pyrrolidines, a one-pot methanolysis was carried out obtaining the corresponding pyrrolidine dicarboxylate derivatives. A broad variety of aromatic azomethine ylides were studied obtaining good to moderate yields and excellent stereoselectivities. Unfortunately, the cyclohexyl-substituted ylide did not react under the optimized conditions. Azlactones substituted at the double bond with phenyl groups bearing either electron-withdrawing or electron-donating groups or with heteroaromatic rings were well tolerated. Alkenyl azlactones gave moderate yields and excellent enantioselectivities (Scheme 96).

7. 5-Ylidene-Thiazolones

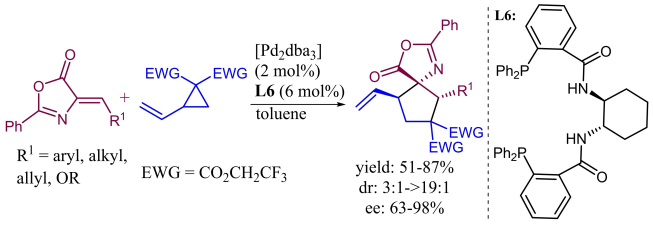
Thiazoles are five-membered heterocycles containing nitrogen and sulfur atoms that can be found in a broad variety of biologically active compounds.[142] Furthermore, thiazoles are privileged scaffolds in drug discovery.[143] Some examples include anti-HIV-drugs,[144] insecticides,[145] antiparasitic,[146] antiulcer,[147] and antineoplastic agents.[148] Otherwise, the thiazol-4-one moiety plays a crucial role in the synthesis of bioactive compounds too. Antiobesity,[149] antimicrobial[150] and antiviral[151] agents are some of the examples containing this scaffold (Figure 7).



Scheme 96. 1,3-Dipolar cycloaddition of azomethine ylides and 4-ylidene-azlactones.



Scheme 94. Tandem isomerization/*aza*-Michael/ring opening reaction between *N*-Boc hydroxylamine and (*Z*)-azlactones.



Scheme 95. Formal [3+2]-cycloaddition of vinyl cyclopropanes with 4-ylidene-azlactones.

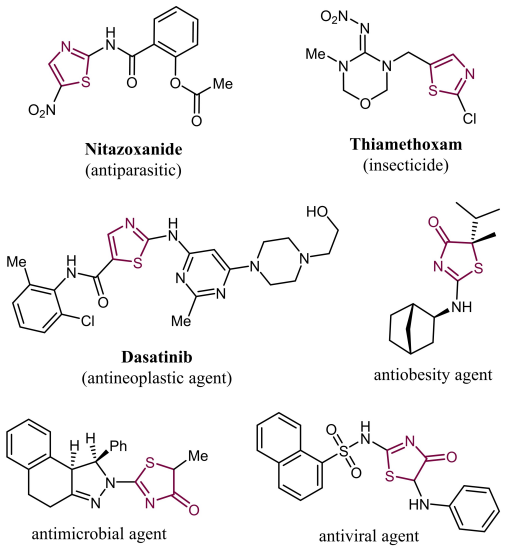


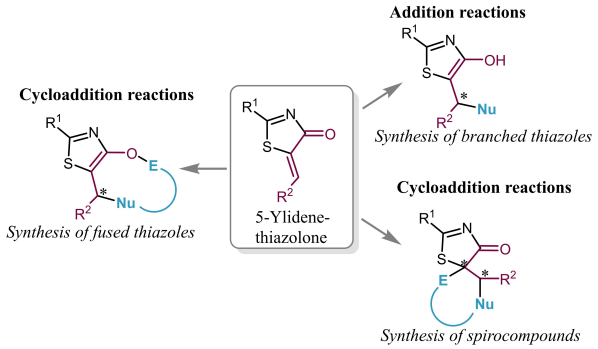
Figure 7. Selected bioactive compounds containing the thiazole and thiazol-4-one moieties.

7.1. Organocatalytic Reactions with 5-Ylidene-Thiazolones

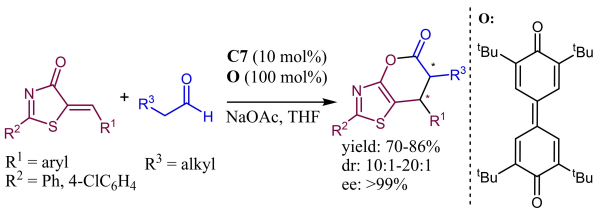
5-Ylidene-thiazolones[152] have been used in a broad variety of organocatalytic asymmetric reactions due to their versatility. Chiral branched thiazoles can be synthesized by Michael addition, and fused thiazoles can be obtained through cascade Michael/*oxa*-cycloaddition reactions. Moreover, spirocompounds containing the thiazolone moiety can be obtained through Michael/cyclization reactions (Scheme 97).

7.1.1. Reactions via NHC Catalysis

N-heterocyclic carbene catalysis was used in the first enantioselective reaction employing 5-arylidene-thiazol-4-ones as substrates. In 2015, Wang developed an oxidative annulation of aldehydes and 5-arylidene-thiazol-4-ones to afford functionalized chiral thiazolopyrones.[153] The *N*-heterocyclic carbene **C7** was used as catalyst together with a stoichiometric amount of 3,3′,5,5′-(^{t}Bu)$_4$-diphenoquinone (**O**) as oxidant. Also, an inorganic base was required to form the aldehyde enolate, NaOAc being the optimal choice. A number of 5-arylidene-thiazol-4-ones bearing differently substituted phenyl or heteroaromatic rings attached to the double bond reacted with butanal and other aliphatic aldehydes to give the reaction products in high yields and excellent diastereo- and enantioselectivities (Scheme 98).



Scheme 97. General reactivity of 5-ylidiene-thiazolones.



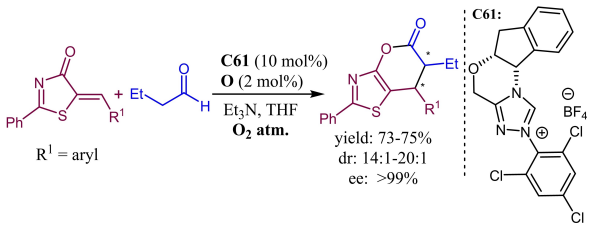
Scheme 98. Oxidative annulation of aldehydes and 5-arylidene-thiazol-4-ones.

A modification of the reaction conditions was developed to permit the use of a catalytic amount of 3,3′,5,5′-(^{t}Bu)$_4$-diphenoquinone (**O**) and molecular oxygen as terminal oxidant. In this case, the combination of NHC **C61** and Et_3N as the base provided the best results (Scheme 99).

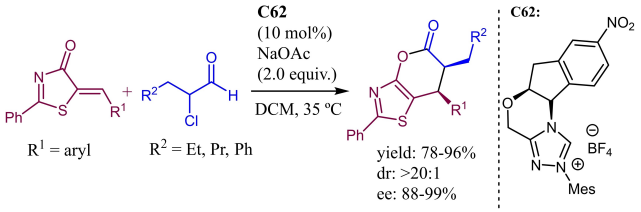
On the other hand, α-chloroaldehydes were used by Enders in a [4 + 2] annulation with 5-arylidene-thiazol-4-ones to give the same compounds under non-oxidative conditions (Scheme 100).[154]

In this reaction, NHC **C62** and NaOAc were chosen as the optimal catalyst and base, respectively. Several α-chloroaldehydes reacted with 5-arylidene-thiazol-4-ones bearing electron-donating and electron-withdrawing groups, affording the products in excellent yields and stereoselectivities regardless of the substitution pattern (Scheme 100).

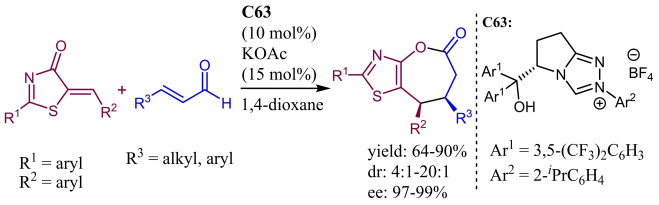
In 2016, Ye developed an asymmetric synthesis of thiazole-fused ε-lactones through an NHC-catalyzed [3 + 4] cycloaddition of enals and 5-arylidene-thiazol-4-ones.[155] The reaction occurs through a homoenolate equivalent formed from the enal and the catalyst without oxidation. The base played an important role in the reaction, as the use of cesium carbonate or DBU instead of KOAc decreased the yield because of formation of the competitive [3 + 2] cycloadduct as side product. A broad variety of 5-arylidene-thiazol-4-ones having aromatic rings of different electronic nature reacted with enals substituted with short and long alkyl groups to give exclusively the *cis* product with good yields and enantioselectivities. Cinnamaldehyde derivatives also worked in this reaction, although in this case the diastereoselectivity was lower, still favoring the *cis* isomer (Scheme 101).



Scheme 99. Oxidative annulation of aldehydes and 5-arylidene-thiazol-4-ones with oxygen as terminal oxidant.



Scheme 100. [4 + 2] Annulation of α-chloroaldehydes and 5-arylidene-thiazol-4-ones.



Scheme 101. [3+4]-Cycloaddition of enals with 5-arylidene-thiazol-4-ones.

7.1.2. Brønsted Base and Bifunctional Hydrogen-Bonding/Brønsted Base Catalysis

Bifunctional hydrogen-bonding/Brønsted base catalysis was used in 2016 by Zhou in an asymmetric formal [2+4] cycloaddition of malononitrile and 5-ylidene-thiazol-4-ones.[156] The reaction was catalyzed by a chiral squaramide **C64** derived from *L-tert*-leucine and led to 7*H*-pyrano[2,3-*d*]thiazole derivatives via a Michael addition/alkoxide addition to nitrile. The yield and enantioselectivity of the reaction were highly influenced by the substituents R^1 and R^2 (Scheme 102).

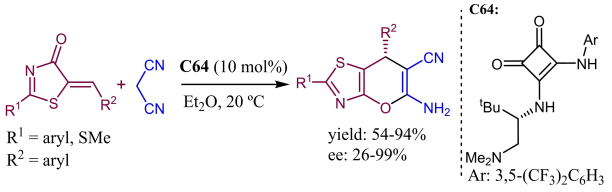
In 2019, an organocatalytic [3+2] cycloaddition between CF_3-containing azomethine ylides and 5-arylidene-thiazol-4-ones was described by Yan and Wang.[157] Rigid chiral tertiary amine *β*-isocupreidine catalyst **C65** gave the desired CF_3-containing spiro-thiazolone-pyrrolidines (Scheme 103).

A wide range of 2-phenylthiazolones having substituted phenyl rings with either electron-withdrawing or electron-donating groups at different positions reacted to give the expected products with good yields and excellent enantioselectivities. The aryl group attached to the azomethinic carbon was also amenable to variation permitting substituents of different electronic character.

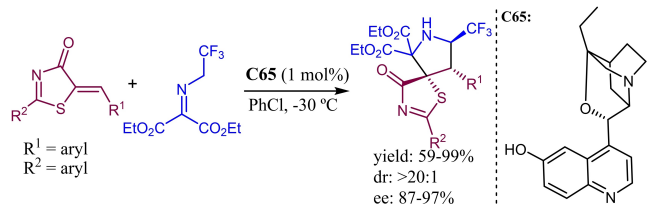
In 2020, Li, Peng and Jiang studied another organocatalytic formal 1,3-dipolar cycloaddition between *N*-(2,2,2-trifluoroethyl)isatin ketimines and 5-ylidene-thiazol-4-ones to obtain pyrrolidinyl spirooxindoles.[158] The best results were obtained with the basic catalyst $(DHQD)_2PYR$ **C66**. The reaction supported a variety of 5-arylidene-thiazol-4-ones having aromatic or heteroaromatic rings of different substitution and electronic character at R^1 and R^2, as well as substituents on the aromatic ring and N1 of the isatin derivative (Scheme 104). The reaction products were obtained in good yields as only one diastereomer (**α**) with high enantiomeric excesses. It is worth mentioning that when the reaction was carried out in the presence of squaramide **C67** the epimer at one of the spiranic carbons was obtained as the major diastereomer (**β**), albeit almost racemic (see Scheme 105).

Moreover, the authors found that, upon acidic treatment, the enantioenriched **α** diastereomer or the racemic **β** diastereomer could be isomerized to another diastereomer (**γ**) via a cascade ring-opening/retro-Mannich reaction followed by a carbon-carbon bond-reforming event driven by thermodynamic preferences. Notably, when starting from enantioenriched **α** this transformation occurred without loss of the enantiomeric excess (Scheme 105).

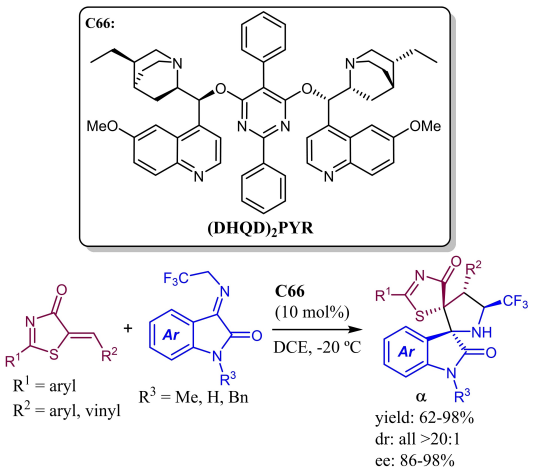
An organocatalytic formal [2+1] Michael addition/alkylation reaction between 3-chlorooxindoles and 5-arylidene-thiazol-4-ones catalyzed by Takemoto thiourea **C28** was reported by Sheng in 2019 to give bi-spirocyclic oxindoles containing a cyclopropane ring and three stereogenic centers.[159] The stereoselectivity of the reaction showed a notable dependence on the base and the solvent employed, selecting Et_3N and



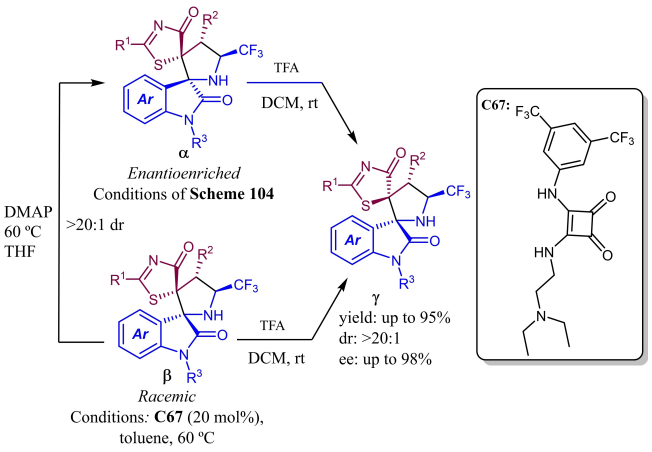
Scheme 102. Formal [2+4] cycloaddition of malononitriles with 5-ylidene-thiazol-4-ones.



Scheme 103. Formal [3+2]-cycloaddition between CF_3-containing azomethine ylides and 5-arylidene-thiazol-4-ones.



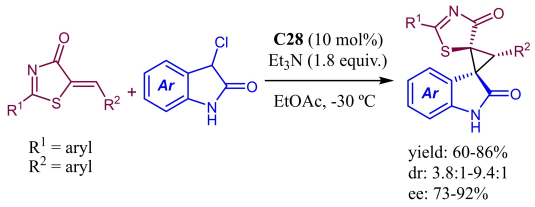
Scheme 104. Formal 1,3-dipolar cycloaddition between *N*-(2,2,2-trifluoroethyl)isatin ketimines and 5-ylidene-thiazol-4-ones.



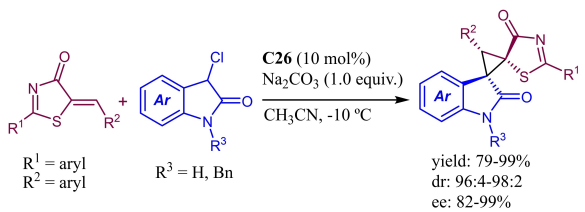
Scheme 105. Isomerization of spirocyclic oxindoles.

EtOAc as the best candidates. Aromatic 3-chlorooxindoles were tested obtaining the best results with C5 and C6 substituted ones, regardless of the electronic features of the substituents. Different substitution in R^1 or R^2 of the 5-arylidene-thiazol-4-ones was possible. The reaction products were obtained with fair to good yields and diastereoselectivities and high enantiomeric excesses (Scheme 106).

The same reaction was reported by Du using the quinine-derived squaramide **C26** as catalyst and Na_2CO_3 as base in acetonitrile at −10 °C.[160] These conditions provided the reaction products in higher yield, and better diastereoselectivity and enantioselectivity than those reported by Sheng. Regarding the reaction scope, C6-substituted 3-chlorooxindoles gave the best results. Moreover, *N*-benzyl substituted 3-chlorooxindoles were suited. In addition, some 5-arylidene-thiazol-4-ones were studied, observing that electronic changes in R^1 only affected slightly the chemical yield. Electron-poor, electron-rich, heteroaryl and bulkier substituents in R^2 gave excellent results (Scheme 107).



Scheme 106. Synthesis of fused spirooxindole-spirothiazolones described by Sheng.



Scheme 107. Synthesis of fused spirooxindole- spirothiazolones described by Du.

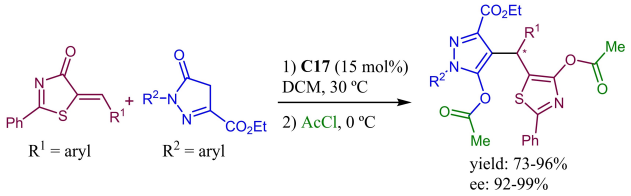
A single Michael addition of pyrazolones to 5-ylidene-thiazol-4-ones using the bifunctional squaramide **C17** as catalyst was described in 2018 by Shen.[161] Due to the high polarity of the products an acylation step was required to facilitate the purification process. 5-Arylidene-thiazol-4-ones were evaluated, founding that methyl and halogenated substitution in *meta-* and *ortho-* positions gave the best results. Disubstituted or bulky aryl rings in R^1 were also studied obtaining the desired products in high yields and excellent enantiomeric excesses. Unfortunately, 5-alkylidene-thiazol-4-ones (R^1 = alkyl) were not suitable substrates (Scheme 108).

Du developed a synthesis of 4-acyloxythiazole derivatives through an asymmetric cascade Michael addition/hemiketalization/retro-aldol reaction between α-nitroketones and 5-arylidene-thiazol-4-ones catalyzed by the bifunctional squaramide **C17** (Scheme 109).[162]

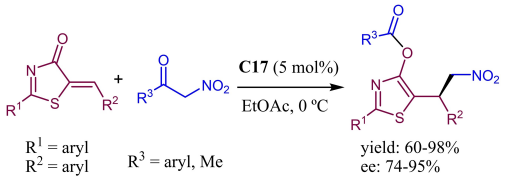
A variety of aromatic and heteroaromatic groups at R^1 and R^2 were tolerated. Furthermore, different aryl, heteroaryl and methyl groups attached to the carbonyl group of the nitroketones were possible and did not affect seriously the yield and stereoselectivity of the reaction (Scheme 109).

7.1.3. Phosphine and Phosphonium Salt Catalyzed Reactions

The first example of a phosphine-catalyzed reaction involving 5-arylidene-thiazol-4-ones appeared in



Scheme 108. Michael addition of pyrazolones to 5-ylidene-thiazol-4-ones.



Scheme 109. Cascade Michael/hemiketalization/retro-aldol reaction between α-nitroketones and 5-arylidene-thiazol-4-ones.

2016.[163] In this report by Xiao, a [2+4] annulation of allenoates with 5-arylidene-thiazol-4-ones to give 6,7-dihydro-5*H*-pyrano[2,3-d]thiazoles was described. First, the authors developed the racemic version of this reaction, using PMe_2Ph as catalyst obtaining moderate to high yields. Motivated by these results, the enantioselective version of the reaction was studied founding Kwon phosphine **C68** as the best catalyst. Only four examples were studied of the asymmetric version, obtaining in all cases high yields and excellent enantioselectivities. Unfortunately, the absolute configuration of the reaction products could not be determined (Scheme 110).

In 2020, the group of Wang studied the formal [2+4] annulation between 5-arylidene-thiazol-4-ones and *o*-hydroxyphenyl substituted *p*-quinone methides catalyzed by a bifunctional phosphonium salt **C69**.[164] Spiro[chroman-thiazolones] were synthesized in excellent yield and stereoselectivity from 5-arylidene-thiazol-4-ones bearing *para*-substituted rings with either electron-withdrawing or electron-donating groups in R^1. Unfortunately, *ortho*-substitution gave lower enantiomeric excesses. Heteroaryl and bulkier substituents as naphthyl in the 5-arylidene-thiazol-4-ones were well tolerated. Furthermore, a number of *o*-hydroxyphenyl substituted *p*-quinone methides was tested, obtaining excellent results in all cases (Scheme 111).

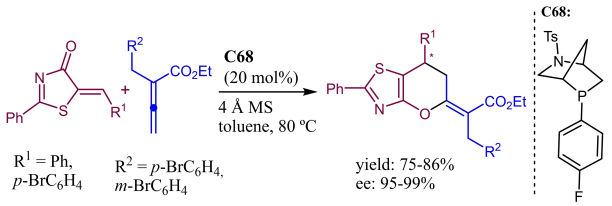
7.1.4. Reactions via Enamine Catalysis

Enamine catalysis is also present in enantioselective reactions involving 5-arylidene-thiazol-4-ones. In 2018, Li et al. developed a formal *oxa*-Diels-Alder reaction between aliphatic aldehydes and 5-arylidene-thiazol-4-ones catalyzed by the Hayashi-Jørgensen catalyst (**C1**).[165] The use of benzoic acid and aqueous solvent was required to increase the yield of the reaction. The initial hemiacetals were reduced with Et_3SiH to give thiazole-fused dihydropyran derivatives as a single diastereomer. Aliphatic aldehydes and phenylpropanal reacted with 5-arylidene-thiazol-4-ones containing aromatic groups of different electronic nature and substitution to give the reaction products in high yields and enantioselectivities (Scheme 112).

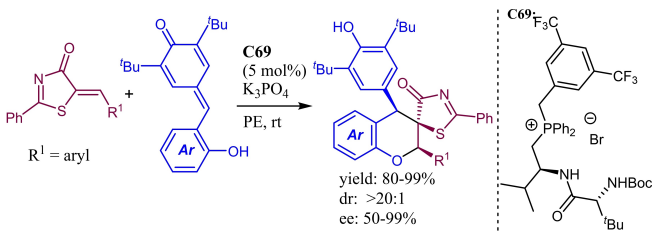
Moreover, this methodology was extended to the use of more challenging aqueous acetaldehyde. The bicyclic heterocycles were obtained in outstanding yields with good diastereoselectivity and excellent enantioselectivity (Scheme 113).

7.1.5. Isothiourea-Catalyzed Reactions

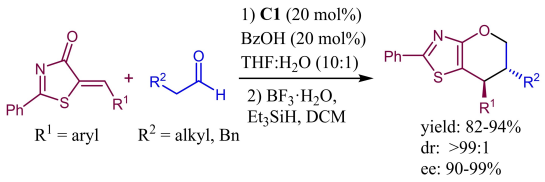
As mentioned above, Pericàs developed an immobilized isothiourea catalyst that was used in the formal [4+2] cycloaddition of arylacetic acids and different ylidene-heterocycles such as 4-ylidene-pyrazolones (Scheme 34).[48] As a part of this work, the reaction of 5-benzylidene-2-phenylthiazol-4(5*H*)-one with several arylacetic acids was also studied obtaining in all cases



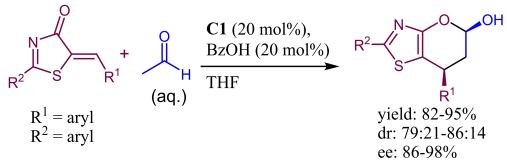
Scheme 110. [2+4] Annulation of allenoates with 5-arylidene-thiazol-4-ones.



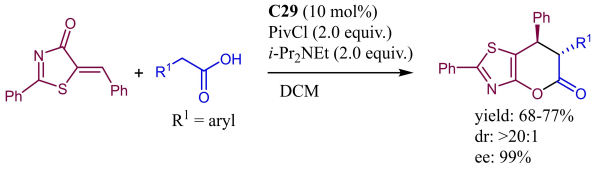
Scheme 111. Formal [2+4] annulation of *o*-hydroxyphenyl-substituted *p*-quinone methides with 5-arylidene-thiazol-4-ones.



Scheme 112. Formal *oxa*-Diels-Alder reaction between aliphatic aldehydes and 5-arylidene-thiazol-4-ones.



Scheme 113. Formal *oxa*-Diels-Alder reaction between aqueous acetaldehyde and 5-arylidene-thiazol-4-ones.



Scheme 114. Formal [4+2] cycloaddition of arylacetic acids and 5-arylidene-thiazol-4-ones.

the reaction product as a single stereoisomer (Scheme 114).

8. Conclusion

The ylidene-five-membered heterocycles reviewed in this article have shown an enormous potential as substrates in asymmetric catalysis for the synthesis of a vast diversity of chiral heterocyclic compounds. Simple conjugate addition to the exocyclic bond, many times favored by aromatization, have permitted the preparation of aromatic heterocycles decorated with chiral pendant chains. These compounds have also shown the ability of the exocyclic double bond to participate as dienophile or dipolarophile in formal cycloaddition reactions leading to spirocyclic compounds. On the other hand, the presence of an unsaturated carbonyl group permits this kind of compounds to participate in a number of formal cycloadditions leading to bi- or poly- cyclic fused heterocycles by reacting as heterodienes in [4+n] cycloadditions or as bis-electrophiles. Furthermore, the presence of two electrophilic sites, the exocyclic double bond and the heterocyclic carbonyl group, confers a bis-electrophilic character that has been profited in the synthesis of fused heterocycles by reacting with reaction partners with bis-nucleophilic character. These reactions have been made possible in an enantioselective fashion with different catalysts, especially organocatalysts, that operate by different activation modes. Bifunctional hydrogen-bonding/Brønsted base and enamine catalysis have resulted especially powerful, but other catalysis; i.e. nucleophilic phosphine, phosphoric Brønsted acid or NHC catalysis; have been also efficient depending on the reaction partner. Besides, some metal-catalyzed reactions have been described. Despite these results, reactions involving single conjugate additions have been little explored. Studies addressed to developing new conjugate addition reactions of new nucleophiles are foreseen. Furthermore, given the rich chemistry of these compounds, further development will involve new reaction patterns in cycloaddition reactions with new substrates through different activation modes.

Acknowledgements

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