CYCLIC BENZOXATHIAZINE 2,2-DIOXIDES: VERSATILE ELECTROPHILES FOR ASYMMETRIC CATALYSIS

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Lode De Muck, Carlos Vila and José R. Pedro

Department of Organic Chemistry, Facukty of Chenistry, University of València, Dr. Moliner 50, 46100 Burjassot, València, Spain

(e-mail: carlos.vila@uv.es; jose.r.pedro@uv.es)

Abstract. *Cyclic benzoxathiazine 2,2-dioxides are remarkable electrophiles that recently have attracted the attention of the synthetic organic community and became powerful electrophiles. In these imines the protecting group forms part of the cyclic structure of the compound, therefore they have lower conformational mobility and impossibility of E/Z isomerization of the double bond of the imine. Moreover, these imines are precursors of sulfamidates, a class of heterocyclic compounds with biological activities. Recently, several asymmetric reactions have been described in the literature using these cyclic imines. In this chapter, we will discuss about these reactions and the synthetic utility of the enantioselective methodologies.*

Contents

1. Introduction

In this chapter, we will described the use of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides as electrophiles in asymmetric catalysis. Recently, this kind of electrophiles has emerged as powerful electrophiles, because these sulfamate-derived cyclic imines are a kind of readily accessible and stable imines. The use of these cyclic imines has an important advantage, the protecting group forms part of the structure of the compound itself. Therefore, can be an alternative towards the *N*-protected imines, due to the lower conformational mobility and the impossibility of E/Z isomerization of the double bond of the imine (Figure 1).

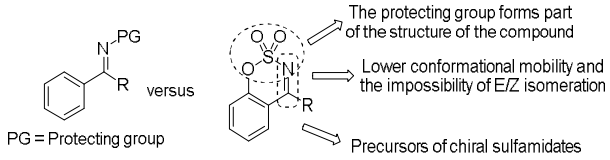


Figure 1. Comparison of protected imines and benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides.

On the other hand, benzoxathiazine 2,2-dioxides are precursors of the sulphamidate structure, which can be found in a considerable number of biologically and pharmacologically active compounds. This group can be found, for example, in artemisinin analogues, which are used in clinical treatment against malaria (Figure 2 **A**),[1] in oxazolidinones (Figure 2 **B**)[2] or Iβ-methylcarbapenes (Figure 2 **C**),[3] which are potent antibacterial drugs. The sulphamidates can also be used as building blocks in organic synthesis. An example

of this use can be found is the synthesis of *N*,*P*-ligands, used for the asymmetric addition of butyllithium to benzaldehyde.[4]

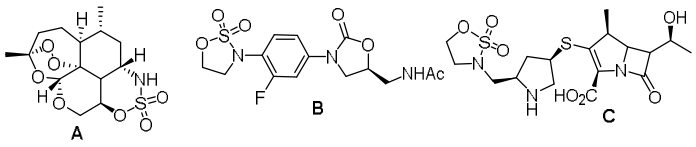
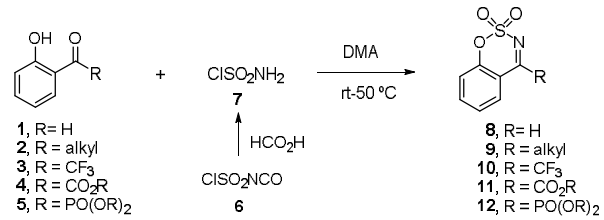


Figure 2. Different bioactive sulfamidate compounds (A) Analogous of artemisinin, (B) oxazolidinone derivative, (C) Iβ-methylcarbapene derivative.

As shown before, benzoxathiazine 2,2-dioxides are very interesting cyclic imines and have recently attracted considerable attention in organic synthesis and several catalytic enantioselective additions of nucleophiles have been described for the synthesis of chiral sulphamidates. Moreover, the corresponding chiral sulphamidates can be converted in interesting chiral heterocycles. This chapter will focus in the description of the asymmetric reactions of benzothiazine 2,2-dioxides and the application of the chiral sulphamidates for the synthesis of chiral heterocyclic compounds.

2. Preparation of benzoxathiazine 2,2-dioxides

Benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides (**8**-**12**) can be easily prepared by the reaction of *ortho*-hydroxy carbonyl compounds (**1**-**5**) and sulfamoyl chloride **7** using dimethyl acetamide (DMA) as a solvent (Scheme 1). Sulfamoyl chloride **7**, normally, is prepared *in situ* from the commercially available chlorosulfonyl isocyanate **6** ($ClSO_2NCO$) and formic acid using DMA as a solvent. Once that the solution of sulfamoyl chloride ($ClSO_2NH_2$) is freshly prepared, this reagent is added to a solution of the *ortho*-hydroxy carbonyl compound in DMA. When salicylaldehyde **1** is used as a carbonyl compound the reaction can be performed at room temperature. However, when an *ortho*-hydroxyketone (**2**-**5**) is used, the temperature of the reaction should be 50 ºC in order to have good conversions.



Scheme 1. Synthesis of benzoxathiazine 2,2-dioxides derivatives.

3. The use of benzoxathiazine 2,2-dioxides as electrophiles for asymmetric catalysis

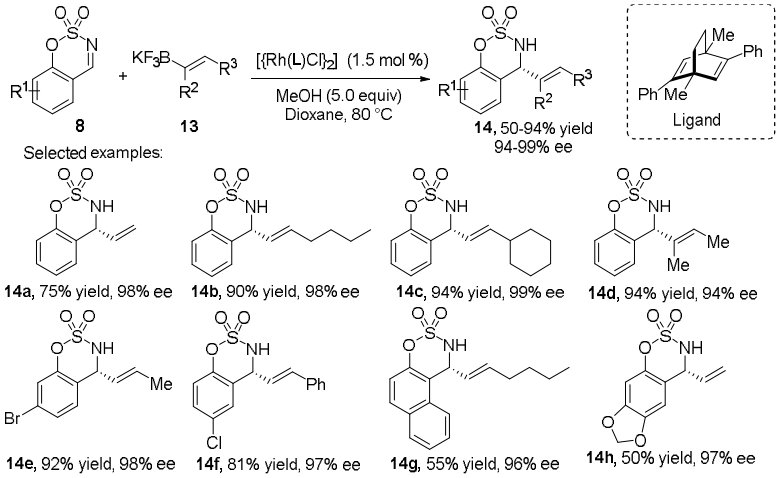
3.1. Addition reactions of organometallic reagents

The catalytic asymmetric addition reactions of organometallic reagents to imines[5] are a central processes in synthetic chemistry to prepare chiral amines. The enantioselective addition of organometallic reagents to acyclic imines have been extensively studied in the literature. However, the corresponding addition of organometallic reagents to cyclic imines is less studied, despite their great potential for the synthesis of chiral nitrogen containing heterocyclic compounds. In this context, only two kind of organometallic reagents, organoboron and organozinc reagents, have been used for the asymmetric nucleophilic addition to benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides.

3.1.1. Addition reaction of organoboron reagents

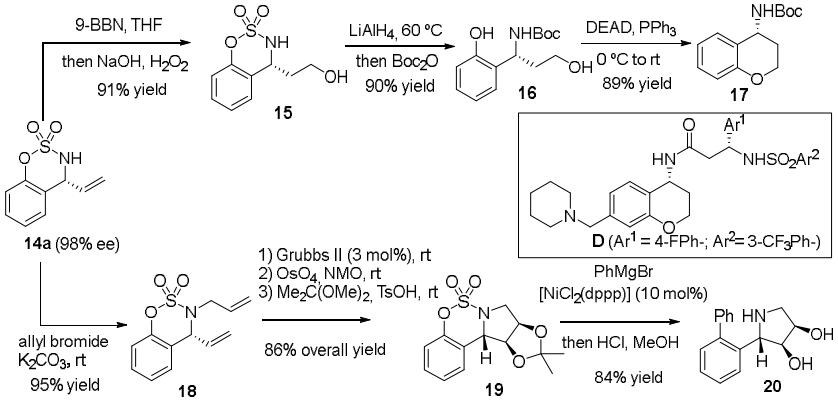
In 2012, Lam and collaborators described the first enantioselective Rh-catalyzed addition of alkenylboron compounds to cyclic aldimines (Scheme 2).[6] This is the first reaction described in which benzoxathiazine 2,2-dioxides function acts as electrophile in a catalytic enantioselective nucleophilic

addition. The authors proved the importance of the constrained *Z*-geometry of the C=N bond of these imines on the enantioselectivity, comparing with *N*,*N*-dimethylsulfamylimine which lead to the resulting product with a low enantioselectivity in the reaction with alkenylrhodium. According to the authors, this result could be due to the *E*/*Z*-isomerization, which they confirmed using a benzoxathiazine 2,2-dioxide (**8**) which doesn't allow the isomerization. With this substrate, they obtained the corresponding alkenylated amine **14a** with an excellent enantiomeric excess (98%) and with high yield in the presence of a diene as chiral ligand. Various alkenyltrifluoroborates (**13**) with alkyl or aryl substituents were tested, resulting all in high yields and excellent enantiomeric excesses (94-99%). They were also able to broaden the scope with differently substituted cyclic imines obtaining excellent results both in yield as in enantioselectivity (94-99% ee).



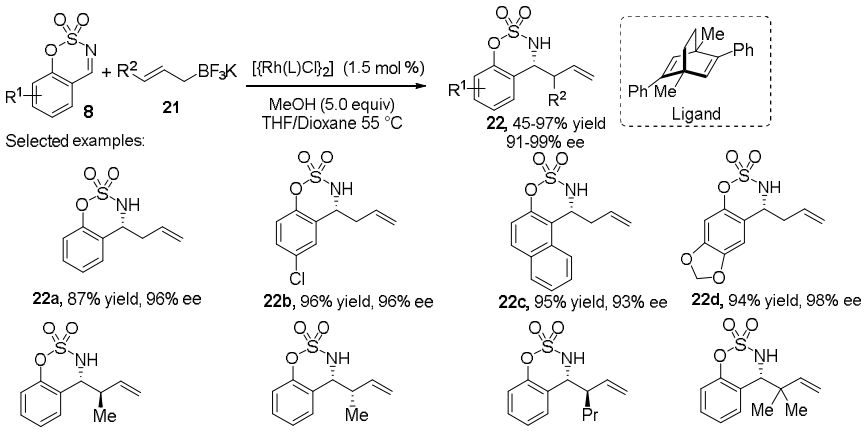
Scheme 2. Enantioselective rhodium-catalyzed additions of alkenylboron compounds to cyclic imines.

The utility of the final products was proven with various synthetic transformations (Scheme 3). For example, hydroboration/oxidation sequence from compound **14a** lead to a primary alcohol **15**. After reduction with $LiAlH_4$ and Boc protection the carbamate **16** was obtained which can be easily transformed to chiral chroman-4-amine **17**, a scaffold present in several drug candidates. Furthermore, a dihydroxylated 2-aryl pyrrolidine **20**, can be obtained after a sequence where a *N*-allylation, ring-closing metathesis using the second-generation Grubbs catalyst, dihydroxylation and a nickel-catalyzed Kumada coupling are involved.



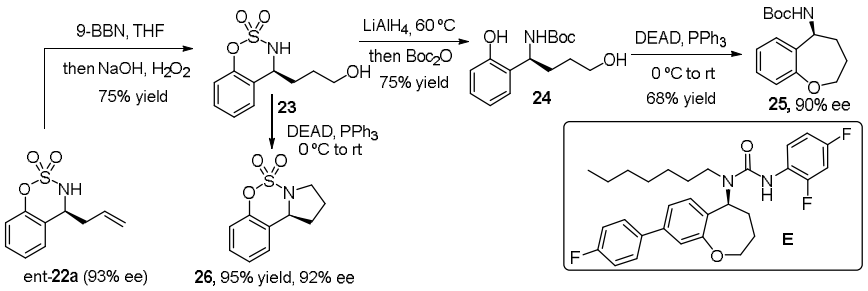
Scheme 3. Synthetic transformations of the chiral vinylic sulfamidates.

Also in 2012, the same research group described an enantioselective rhodium-catalyzed nucleophilic allylation of benzoxathiazine 2,2-dioxides **8** with allylboron reagents **21** (Scheme 4).[7] As already proven in the previous work, various acyclic imines were not useful in the reaction due to the low enantioselectivities obtained. However, the use of benzoxathiazine 2,2-dioxides **8** in the reaction with potassium allyltrifluoroborate **21** in the presence of a rhodium complex derived from a chiral diene resulted in the final product in a high yield (95%) and excellent enantiomeric excess (93% ee). It has to be noted that the use of potassium allyltrifluoroborate was necessary, whilst other allylboronic acids do not give satisfactory results. Differently substituted cyclic imines were tested in the optimized reaction conditions, as well as some highly substituted potassium allyltrifluoroborates, all resulting in good yields (45-97%) and excellent enantioselectivities (91-99% ee) and diastereoselective ratios (6:1-17:1). In 2013, the same research group published their further findings on the addition of highly substituted potassium allyltrifluoroborates to cyclic aldimines, obtaining similar results as described before.[8]



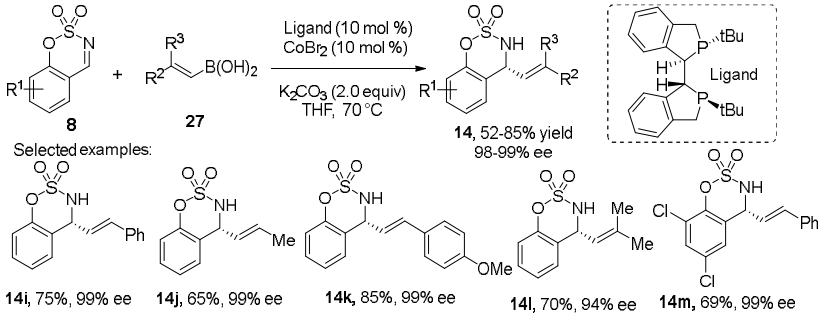
Scheme 4. Enantioselective rhodium-catalyzed nucleophilic allylation of cyclic imines with allylboron reagents.

The utility of the chiral allylic sulfamidates prepared was proven with various synthetic transformations (Scheme 5).[8] A hydroboration/oxidation sequence from the allylic sulfamidate *ent*-**22a** provided the primary alcohol **23**, which after reduction with $LiAlH_4$ followed by treatment with Boc_2O afforded the product **24**. Product **24** was converted in the tetrahydrobenzoxepine **25** by a Mitsunobu cyclization. Chiral amino-substituted tetrahydrobenzoxepine **25**, have the same core structure than compound **E**, a strong cholesterol *O*-acyltransferase inhibitor.[9] Moreover, the tricyclic sulfamidate **26**, was easily synthesized by Mitsunobu cyclization from **23**.



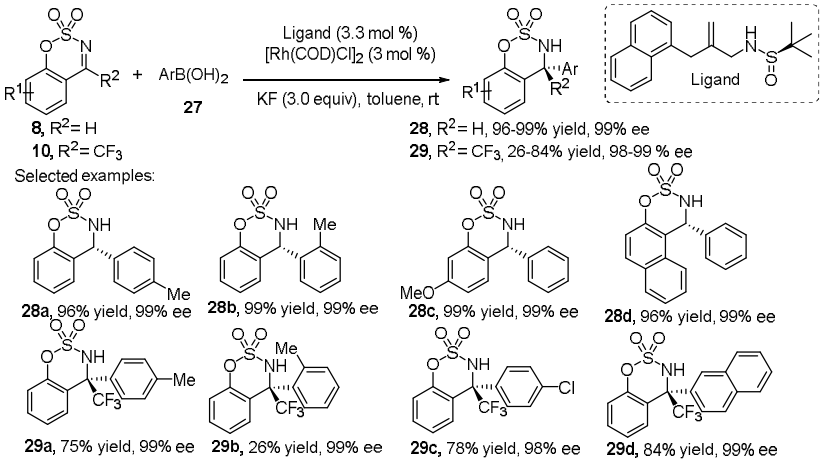
Scheme 5. Synthetic transformations of the chiral allylic sulfamidates.

In 2016, the Zhao group published their findings on the cobalt-catalyzed enantioselective vinylation of aldimines and activated ketones (Scheme 6).[10] The investigators applied both cyclic and acyclic imines in the reaction with 2-phenyl vinylboronic acid **27a**, promoted by $CoBr_2$. Only the benzoxathiazine 2,2-dioxide aldimine **8** resulted to be an optimum substrate, leading to the final product **14i** in high yield (75%) and excellent enantiomeric excess (99%), using a duanphos chiral ligand. The optimized reaction conditions were applied on different substituted cyclic imines and various vinyl boronic acids. All the reactions resulted in good yields (52-85%) and excellent enantiomeric excesses (98-99%).



Scheme 6. Cobalt-catalyzed enantioselective vinylation of benzoxathiazine 2,2-dioxide aldimines.

With regards to cyclic ketimines, in 2013, the Xu-group described a Rh-catalyzed highly enantioselective arylation of this kind of imines leading to the synthesis of tetrasubstituted carbon stereocenters (sulfamidates and sultams compounds) (Scheme 7).[11] They used sulfur-based olefin ligands to promote the enantioselectivity of the reaction. Xu and collaborators examined various, newly synthesized, ligands and under optimized reaction conditions $[Rh(COD)Cl]_2$ (3 mol %), ligand (3.3 mol %), KF (3.0 equiv) in toluene, the arylation reaction between arylboronic acid and benzoxatiazine 2,2-dioxide aldimines and ketimines bearing a CF_3 leads to the corresponding final products in variable yields (26-99%) and excellent enantioselectivities (98-99% ee).

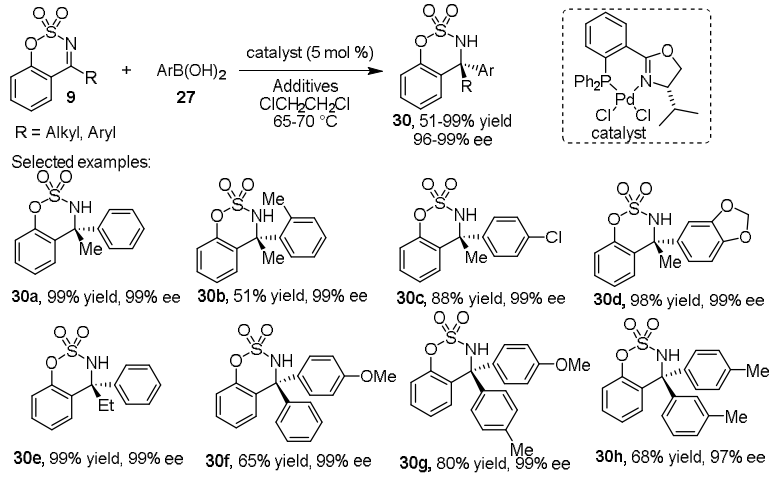


Scheme 7. Rhodium-catalyzed highly enantioselective arylation of cyclic imines.

In 2013, the same research group published their findings on the rhodium-catalyzed enantioselective addition of arylboronic acids to cyclic aldimines, a work in which the authors broadened the scope of the

arylation of cyclic aldimines discussed before.[11,12] The same reaction conditions were used and the products were obtained in excellent yields (96-99%) and enantioselectivities (97-99% ee).

In 2014, Hayashi and collaborators described an asymmetric arylation of ketimines derived from benzoxathiazine 2,2-dioxides using a palladium phosphinooxazoline catalyst (Scheme 8).[13] Taking into account the results of Xu and collaborators in 2013,[11,12] which described the arylation of *N*-sulfamidate aldimines and CF_3 substituted *N*-sulfamidate ketimines, Hayashi and coworkers proposed a new method for arylation of the less reactive alkyl and aryl cyclic ketimines **9**. Under optimized conditions, $PdCl_2$((*S*)-*i*Pr-phox) (5 mol %), $AgBF_4$ as additive in dichloroethane at 65-70 °C, the reaction between phenylboronic acid and benzoxathiazine 2,2-dioxide ketimine **9** led to excellent results both in yield as in enantiomeric excess (99%). These optimized reaction conditions were then applied to the reaction between different arylboronic acids **27** and *N*-sulfamidate ketimine (methyl), obtaining the corresponding products in high yields (51-99%) and excellent enantioselectivities (98-99% ee). Both the ethyl and the pentyl *N*-sulfamidate ketimines were also used in the reaction with phenylboronic acid leading to the reaction products in good yields and excellent enantioselectivities (99% ee). Finally, they also tested cyclic aryl ketimines, which are less reactive than the alkyl ketimines, obtaining satisfying results in the presence of a proton sponge both in yield as in enantioselectivity.



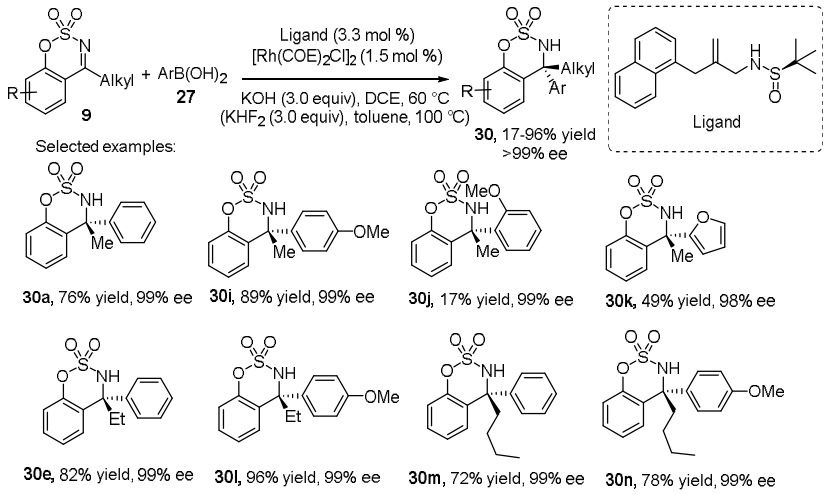
Scheme 8. Asymmetric arylation of cyclic ketimines using a palladium phosphinooxazoline catalyst.

A rhodium-catalyzed asymmetric arylation of cyclic alkyl ketimines in the synthesis of highly enantioenriched α-tertiary amines was described by Xu in 2015 (Scheme 9).[14] With the use of the sulfur-based olefin ligand, already applied in the arylation of cyclic ketimines **9**,[11] they were able to obtain α-alkylaryl-substituted benzosultams and benzosulfamidates with excellent enantioselectivities. After optimizing the conditions in the reaction between five membered *N*-sulfonyl ketimines and arylboronic acids, the researchers focused their attention on the enantioselective arylation of benzoxathiazine 2,2-dioxides alkylketimines. With a slight modification of the reaction conditions, they obtained, in the reaction between different substituted substrates **9** and different arylboronic acids **27**, good to variable yields (17-96%) and excellent enantioselectivities (≥99% ee).

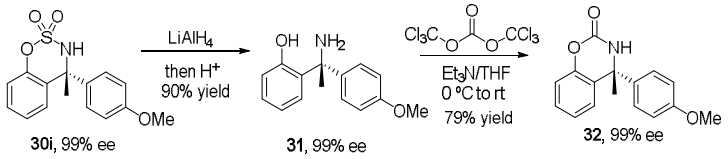
The authors highlighted the synthetic utility of the methodology performing several transformations (Scheme 10). The ring opening of benzosulfamidate **30i** by reduction with $LiAlH_4$ gave the corresponding phenolic methylamine compound **31**. This compound was reacted with triphosgene in the presence of Et_3N to afford the chiral benzoxazinone **32**.

Also in 2015, the Zhang group published their findings on the asymmetric addition of arylboronic acids to cyclic *N*-sufamidate ketimine esters **11** (Scheme 11).[15] The optimized conditions for the reaction [methyl (*S*)-6-(4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)nicotinate (7.5 mol %), $Pd(TFA)_2$ (5 mol %) in

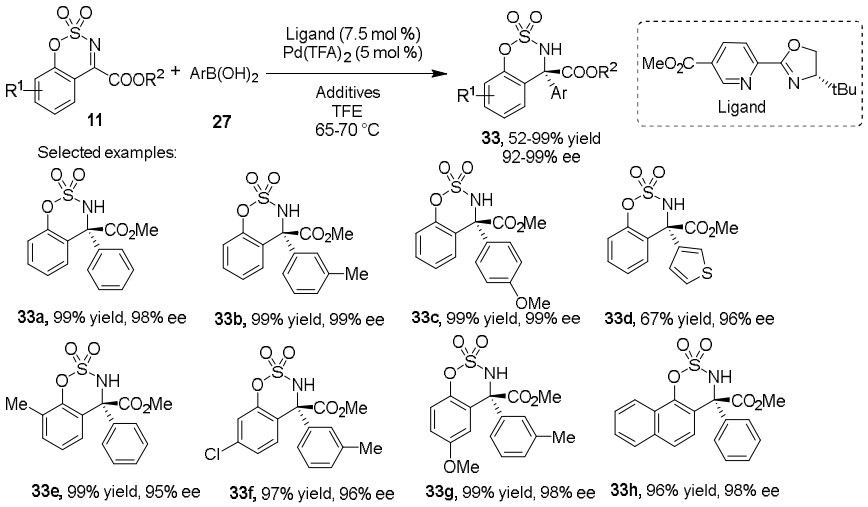
trifluoroethanol] allowed the reaction with phenylboronic acid obtaining the final product in good yield (90%) and excellent enantioselectivity (98% ee). The reaction conditions were applied to the reaction with various arylboronic acids and differently substituted cyclic *N*-sufamidate ketimine esters **11**, obtaining the α-aminoesters **33** in good yields (52-99%) and excellent enantioselectivities (92-99% ee).



Scheme 9. Rhodium-catalyzed asymmetric arylation of cyclic ketimines.



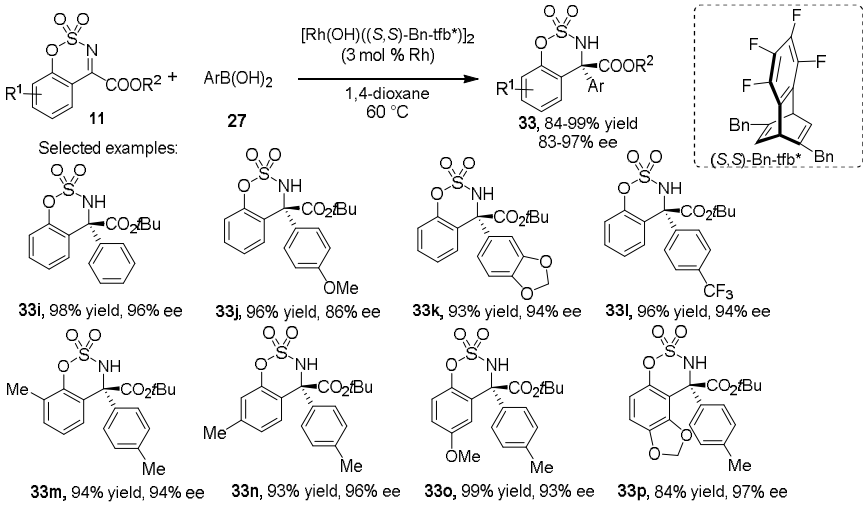
Scheme 10. Synthetic transformations of the chiral sulfamidates.



Scheme 11. Asymmetric addition of arylboronic acids to cyclic ketimine esters.

The researchers also performed a DFT calculation, which shows that both the rate determining step and the stereoselectivity determining step is the aryl transfer from the boride to the carbon atom of the cyclic ketimine.

Some months later, Nishimura and collaborator described a rhodium catalyzed asymmetric addition of arylboronic acids to similar substrates (cyclic ketimine esters), directed towards the synthesis of α,α-diaryl-α-amino acid derivatives (Scheme 12).[16] The initial study focused on the addition of phenylboronic acid to the cyclic ketimine ethylester. It was observed that in the presence of [Rh(OH)((*S*,*S*)-Bn-tfb*)]2 (tfb=tetrafluorobenzobarrelene) the final product was obtained in excellent yield (99%) and enantioselectivity (96% ee). The scope of the reaction was extended to a wide variety of cyclic ketimine esters **11** and arylboronic acids **27** obtaining the corresponding products **33** in excellent yields (84-99%) and enantioselectivities (83-97% ee).

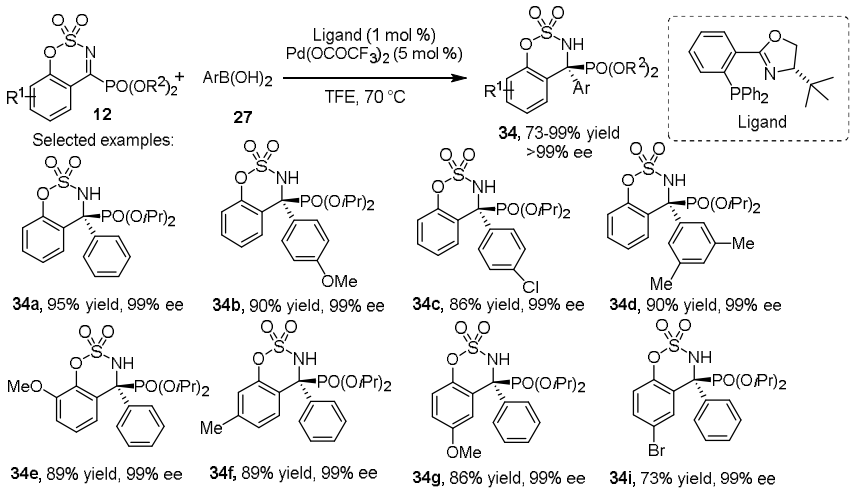


Scheme 12. Rhodium catalyzed asymmetric addition of arylboronic acids to cyclic ketimine esters.

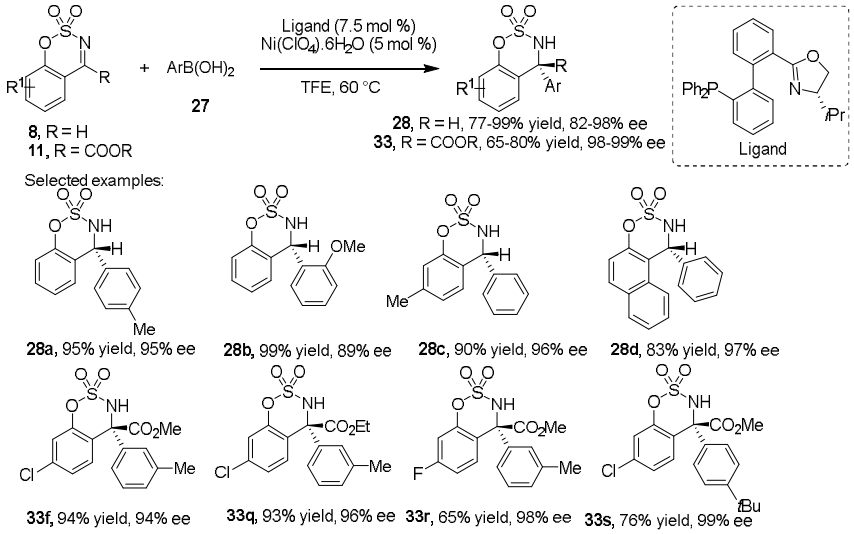
Recently, the Zhou group published their results on the Pd-catalyzed enantioselective arylation of cyclic α-ketiminephosphonates **12** with arylboronic acids **27** (Scheme 13).[17] The investigators used a cyclic α-ketiminephosphonate as model substrate in the addition reaction with phenylboronic acid. They obtained excellent results both in yield (95%) and enantioselectivity (99% ee) using a palladium phosphinooxazoline complex, with only a 1 mol % of ligand being required, in trifluoroethanol (TFE) as solvent. These conditions were used in reactions with differently substituted cyclic α-ketiminephosphonates derived from benzoxathiazine-2,2-dioxides and various arylboronic acids, all of which led to the corresponding products **34** with good yields (73-99%) and excellent enantioselectivities (>99% ee).

Very recently, Zhang and collaborators described a Ni(II)-catalyzed asymmetric addition of arylboronic acids to benzoxathiazine 2,2-dioxides (Scheme 14).[18] Under optimized conditions ($Ni(ClO_4)_2.6H_2O$/tropos phosphine-oxazoline biphenyl complex in trifluoroethanol as solvent at 60 °C), various arylboronic acids were tested in the reaction with cyclic aldimines, with excellent yields (77-99%) and enantioselectivities (82-98% ee). Furthermore, the authors broadened the scope by testing various aldimines and aryl ketimine esters, all resulting in good yields (65-80%) and excellent enantioselectivities (98-99% ee).

With regards to propargylation reactions, in 2015, the Jarvo group described a silver-catalyzed enantioselective reaction of *N*-sulfonyl ketimines.[19] Upon optimization of the reaction conditions, they were able to obtain a homopropargylic amine in a good yield and excellent enantiomeric excess (98%) through the reaction between allenylboronic acid pinacol ester **35** and a cyclic five membered *N*-sulfonyl ketimine using silver in the presence of a Walphos ligand as catalyst.



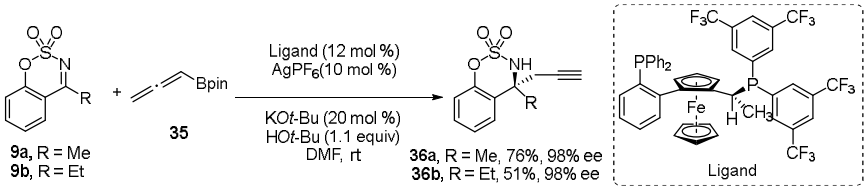
Scheme 13. Palladium-catalyzed enantioselective arylation of cyclic α-ketiminephosphonates.



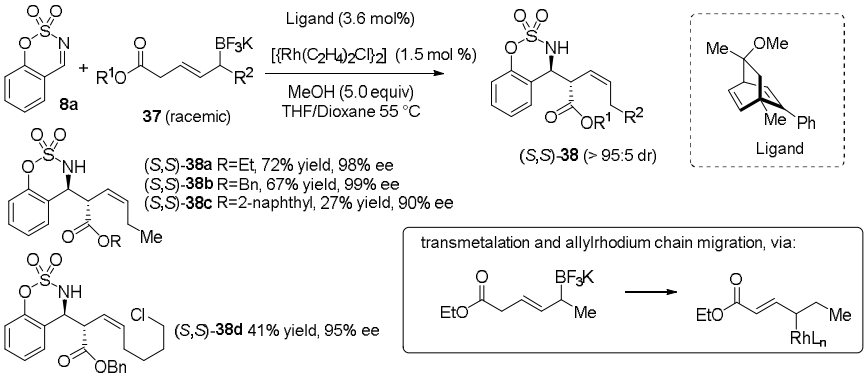
Scheme 14. Nickel-catalyzed asymmetric addition of arylboronic acids to benzoxathiazine 2,2-dioxides.

The same reaction conditions were applied on the reaction between allenylboronic acid pinacol ester **35** and different cyclic alkyl ketimines **9** derived from benzoxathiazine 2,2-dioxides, which are less reactive, obtaining the corresponding products **36** in good yields (51-76%) and excellent enantiomeric excesses (98% ee) (Scheme 15).

In 2016, Lam described a chain walking of an allylrhodium species towards esters during a rhodium catalyzed allylation of benzoxathiazine 2,2-dioxides.[20] The authors observed the chain walking to the ester moiety in a δ-trifluoroboryl β,γ-unsaturated esters **37** in the presence of a rhodium catalyst. The resulting allyl rhodium species react with the cyclic imine affording the corresponding products **38**, containing 2 chiral centers and a *Z*-alkene, with moderate to good yields and high diastereoselectivities and enantioselectivities (Scheme 16).



Scheme 15. Silver-catalyzed enantioselective propargylation reaction of benzoxathiazine 2,2-dioxide ketimines.



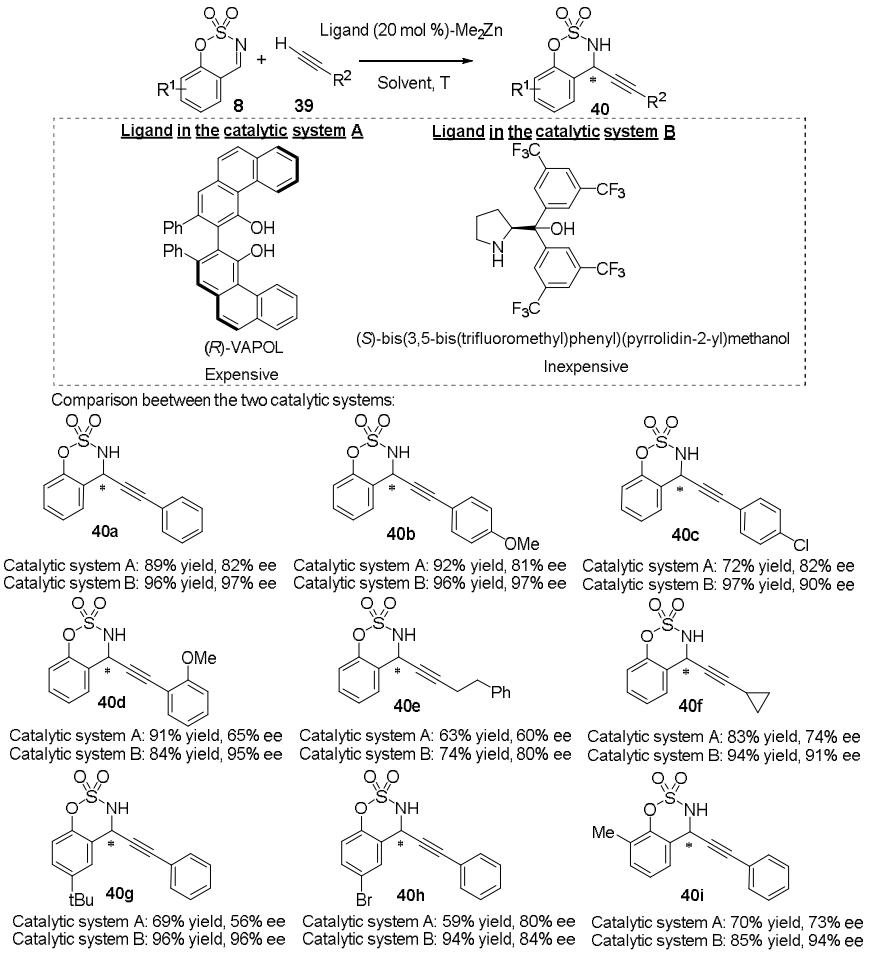
Scheme 16. Enantioselective rhodium-catalyzed nucleophilic allylation of benzoxathiazine 2,2-dioxides with a chain walking of the allylrhodium species towards the ester.

3.1.2. Addition reactions of organozinc reagents

The enantioselective alkynylation of imines is one of the most useful carbon-carbon bond-forming reactions for the preparation of chiral propargylic amines,[21] which are versatile building blocks for the synthesis of fine chemicals, pharmaceuticals, agrochemicals and natural products. Two examples of this kind of reaction have been described by the same group using two different catalytic systems (Scheme 17). In 2015 Pedro and coworkers,[22] developed the enantioselective alkynylation of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides catalysed by (*R*)-VAPOL-Zn(II) complexes. This approach provided a new methodology to synthesize optically active propargylic sulfamidates **40** with high yields (up to 93% yield) and good enantioselectivities (up to 87% ee). Recently, the same group developed an enhanced methodology by using a more simple and economical ligand that could afford better enantioselectivities. In this communication,[23] they report a highly efficient catalytic system for the alkynylation of cyclic benzoxathiazine 2,2-dioxides **8** using a diarylprolinol-Zn(II) complex as catalyst, affording the corresponding chiral propargylic sulfamidates **40** with higher enantiomeric excesses than with the previously described catalytic system (Scheme 17). If we compare both catalytic systems, we can see that when diaryl prolinol ligand is used the results in terms of yield and enantioselectivity are superior to those obtained when (*R*)-VAPOL is used as a ligand. The catalytic system B is more robust with higher enantiocontrol for the synthesis of the chiral propargylic sulfamidates. In general, when this catalytic system is used with aromatic and aliphatic alkynes **39**, chiral sulfamidates **40** are obtained with enantiomeric excesses around around 90% ee.

Another asymmetric addition of organozinc reagents to benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides, was described by Pedro and Vila in 2016 and consists on the enantioselective Reformatsky reaction with ethyl iodo acetate.[24] Catalytic enantioselective Reformatsky[25,26] reaction using imines as electrophiles provides a suitable methodology for the synthesis of chiral β-amino esters, which are a significant class of building blocks in synthetic chemistry, due to they have been used for the synthesis of optically pure γ-amino alcohols or β-amino acids.[27] The authors described a methodology where a readily available diaryl prolinol is used as a chiral ligand, $ZnMe_2$ as a zinc source and ethyl iodoacetate **41** as reagent in the presence of air atmosphere (Scheme 18). In their methodology, cyclic aldimines **8** and ketimines **9** can be used as

electrophiles obtaining chiral β-amino esters **42** and **43**, respectively, with excellent enantiomeric excesses. This approach represents the first catalytic enantioselective aza-Reformatsky reaction with ketimines, leading to β-amino esters bearing a quaternary stereocenter.

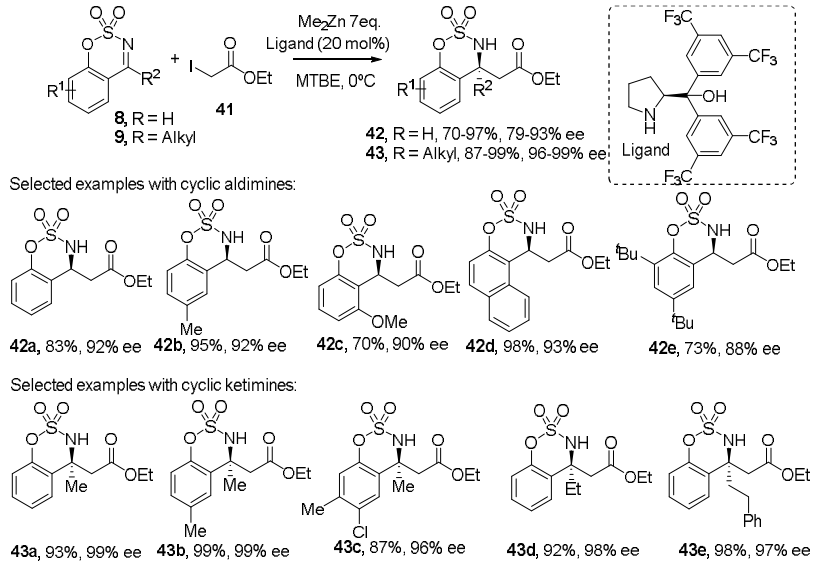


Scheme 17. Enantioselective alkynylation of benzoxatiazine 2,2-dioxides.

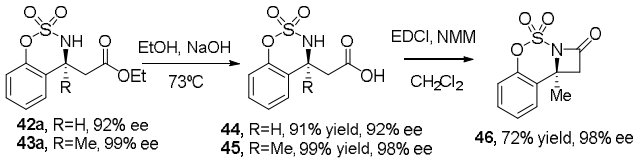
To highlight the synthetic utility, the authors have applied several chemical transformations for the synthesis of interesting chiral compounds (Scheme 19). The β-amino acids **44** and **45** were prepared by simple saponification with good yields and without loss of enantiomeric purity. Furthermore, the chiral β-lactam **46** with three fused cycles and a quaternary stereocenter was prepared from the β-amino acid **45**, in 72% yield and 98%ee.

3.2. Cycloadditions reactions

Cycloadditions reactions using imines as electrophiles are fundamental reactions for the synthesis of nitrogen heterocycles, and have been used extensively in the literature. In the context, of cyclic benzoxathiazine 2,2-dioxides, although several examples of enantioselective cycloadditions have been described, the synthetic potential of this kind of reactions with these cyclic imines is still in its infancy.



Scheme 18. Enantioselective Reformastky reaction with benzoxathiazine 2,2-dioxides.



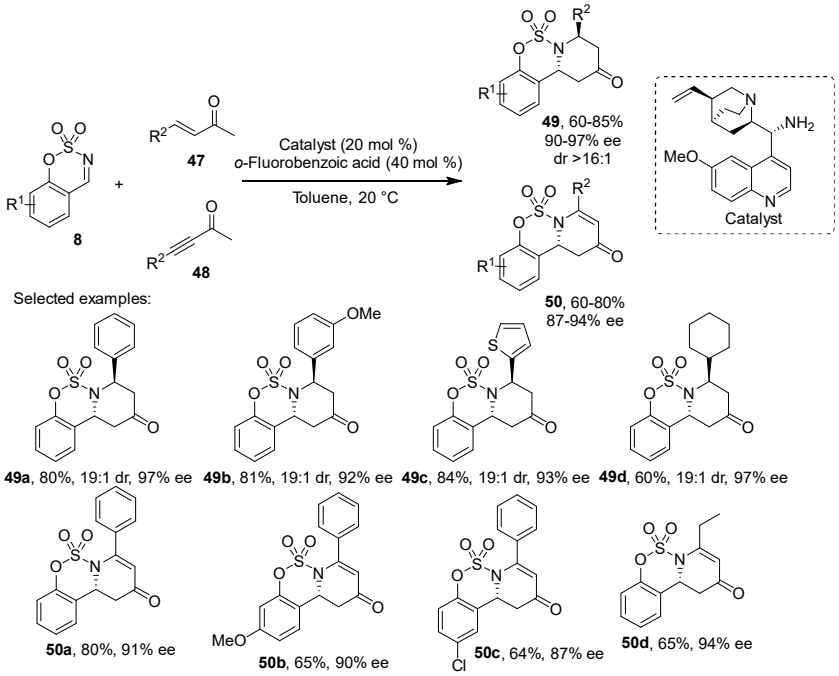
Scheme 19. Synthetic transformations of the chiral sulfamidates.

In 2013, Kang and collaborators described the enantioselective [4+2] cycloaddition of cyclic imines **8** with acyclic enones **47** or ynones **48** leading to sulfamidate-fused 2,6-disubstituted piperidin-4-ones (**49** and **50**) (Scheme 20).[28] The reaction conditions were optimized in the reaction between benzoxathiazine 2,2-dioxide and (*E*)-4-phenylbut-3-en-2-one in the presence of a *Cinchona* alkaloid derivative (primary amine) and *o*-fluorobenzoic acid in toluene at 20 °C, leading to the cycloaddition product with a yield of 80% and an enantioselectivity of 97% ee (dr >19:1). These reaction conditions were then applied to the reaction between differently substituted cyclic aldimines **8** and various enones **47**, leading to the [4+2] cycloaddition products **49** in good yields (60-85%) and excellent enantioselectivities (90-97% ee, dr >16:1). The same reaction conditions were also applied in the reaction between various cyclic aldimines **8** and ynones **48**, leading to 2,6-disubstituted 2,3-dihydropyridin-4(1*H*)-ones **50** in good yields (60-80%) and enantioselectivities (87-94% ee).

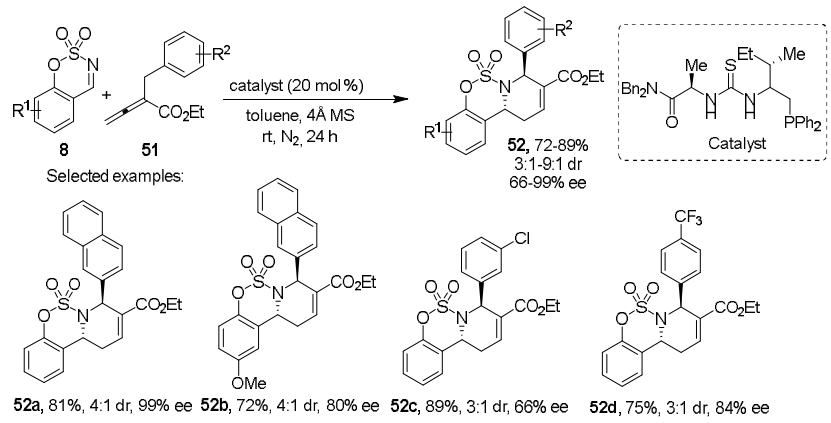
In the same year, Guo and collaborators described the phosphine catalyzed [4+2] cycloaddition of benzoxathiazine 2,2-dioxides **8** with allenoates **51** (Scheme 21).[29] In the first part of the publication, the researchers focused on the non-enantioselective [4+2] cycloaddition with PPh_3 of various α-substituted alkylallenoates and differently substituted benzoxathiazine 2,2-dioxides **8**, obtaining the cycloaddition products in good to excellent yields (45-98%). In the second part, the researchers developed the enantioselective version of this reaction. They used an amino acid based bifunctional chiral phosphine in the presence of 4Å molecular sieves, leading to the corresponding products **52** with good yields (72-89%), moderate diastereomeric ratio (3:1-9:1) and good to excellent enantioselectivities (66-99% ee).

In 2016, Kim and collaborators described the stereoselective synthesis of a benzosulfamidate-fused tetrahidroquinazoline scaffold via an organocatalytic [4+2] cycloaddition of 2-amino-β-nitrostyrenes **53** with benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides **8** (Scheme 22).[30] At first, the investigators performed the non-

enantioselective version of the reaction with various cyclic imines, promoted by imidazole, resulting in moderate to good yields (27-77%). The enantioselective version of the reaction was then tested with a squaramide catalyst, leading to the corresponding products in good yields (40-85%), excellent diastereomeric ratios (>20:1) but low enantiomeric ratios (53:47-69:31).



Scheme 20. Enantioselective [4+2] cycloaddition of benzoxathiazine 2,2-dioxides and acyclic enones or ynones.

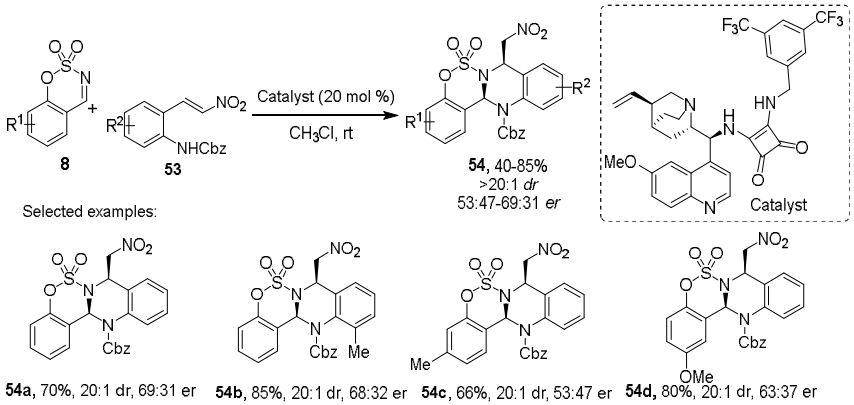


Scheme 21. Phosphine catalyzed [4+2] cycloaddition of benzoxathiazine 2,2-dioxides with alkyl allenoates.

3.3. Mannich reactions

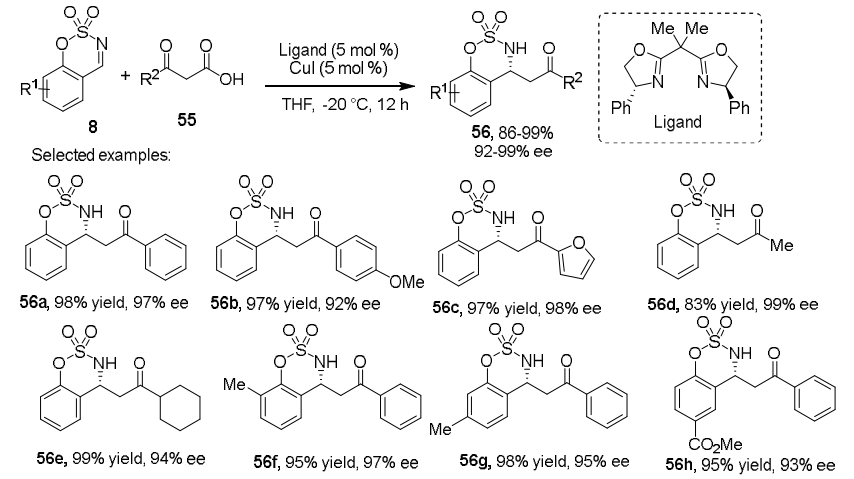
Another methodology that have been used for prepare chiral amines, is the asymmetric Mannich reaction.[31] This reaction is a powerful methodology for the synthesis of chiral β-amino-carbonyl compounds,

an important building blocks for the synthesis of fine chemicals. Several examples have been described using benzoxathiazine 2,2-dioxides as electrophiles.

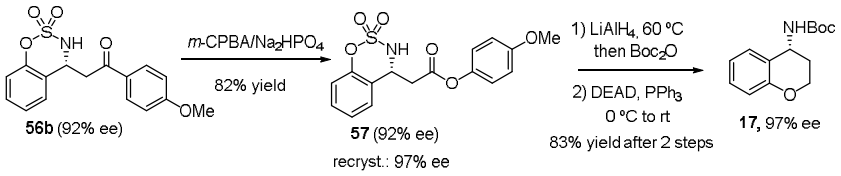


Scheme 22. Organocatalytic [4+2] cycloaddition of benzoxathiazine 2,2-dioxides with 2-amino-β-nitrostyrenes.

In 2014, Ma and collaborators published their findings on the Cu-catalyzed decarboxylative Mannich reaction of β-ketoacids **55** with benzoxathiazine 2,2-dioxides **8** as electrophiles (Scheme 23).[32] This decarboxylative Mannich reaction is an alternative pathway to the synthesis of β-aminoketones **56**. Upon optimization, the researchers concluded that all Cu(I) salts tested gave good results in combination with a bisoxazoline ligand, whereas the Cu(II) salts tested gave lower enantioselectivities. They were also able to decrease the ligand loading to a 1 mol % maintaining a good enantioselectivity. With the optimized conditions in hand, the researcher extended the scope of the reaction to various differently substituted benzoxathiazine 2,2-dioxides **8** and various aromatic and aliphatic β-ketoacids **55**, obtaining the corresponding products **56** with excellent yields (86-99%) and enantioselectivities (92-99% ee). Through a series of synthetic transformations, the obtained products can lead to chroman-4-amines without loss of enantiomeric purity (Scheme 24).

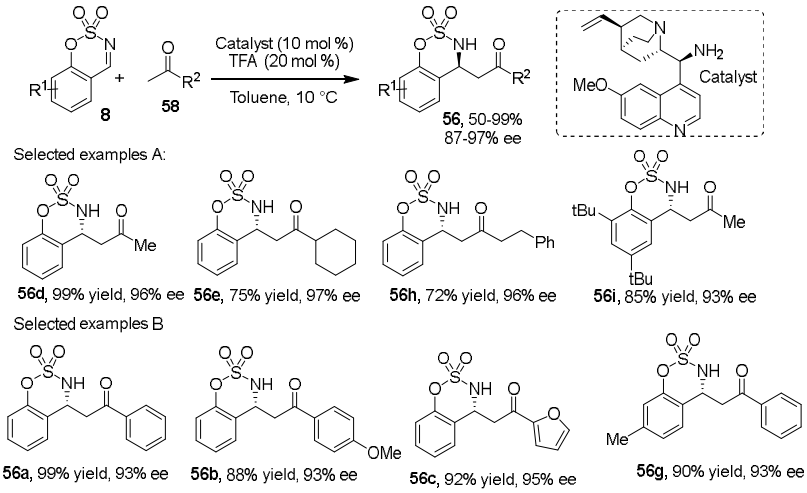


Scheme 23. Copper-catalyzed decarboxylative Mannich reaction of benzoxatiazine 2,2-dioxides with β-ketoacids.



Scheme 24. Synthetic transformations of the chiral sulfamidates.

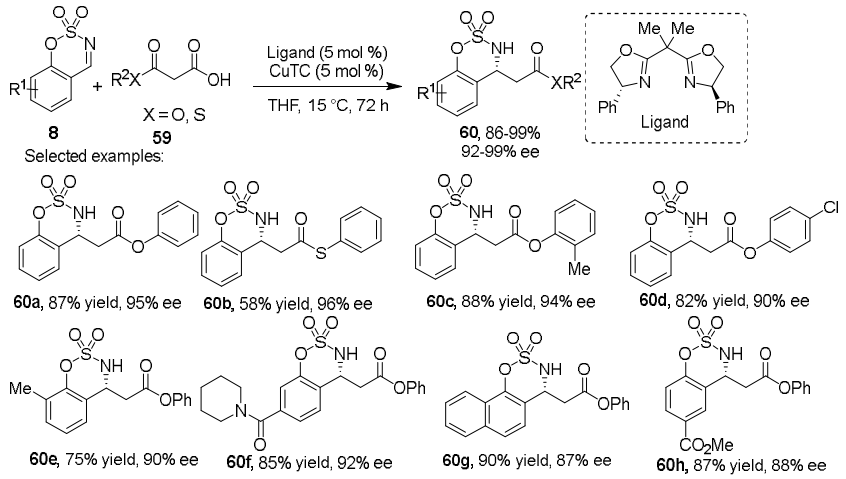
In the same year, Zhang and collaborators described an organocatalytic direct Mannich reaction of alkyl methyl ketones with benzoxathiazine 2,2-dioxides (Scheme 25, examples A).[33] The reaction conditions were optimized in the reaction between acetone and benzoxathiazine-2,2-dioxide and the best results were obtained when the reaction was catalyzed by a 10 mol % of a *Cinchona* alkaloid based primary amine in the presence of a 20 mol % of a Brønsted acid (trifluoroacetic acid) in toluene at 10 °C. At first, various cyclic aldimines were tested under the reaction conditions with acetone, obtaining the corresponding products in high yields (76-99%) and enantioselectivities (91-97% ee). In order to extend the scope of the reaction, the researchers applied the same conditions in the reaction between benzoxathiazine 2,2-dioxides **8** and different alkyl methyl ketones **58**, leading to the products **56** with good results (50-99%, 87-97% ee). However, when the alkyl group was voluminous, no reaction was observed, probably due to steric hindrance. In 2016, the same research group described the organocatalytic enantioselective Mannich reaction of aryl methyl ketones (Scheme 25, examples B) with benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides with *Cinchona* alkaloid based primary amines.[34] They used the same catalyst that was used in the publication in 2014 (however the reaction was performed in *p*-xylene) in the reaction between differently substituted cyclic imines and various aryl methyl ketones leading to the corresponding products with good yields (32-99%) and enantioselectivities (89-98% ee).



Scheme 25. Organocatalytic Mannich reaction of alkyl methyl ketones and aryl methyl ketones with benzoxathiazine 2,2-dioxides.

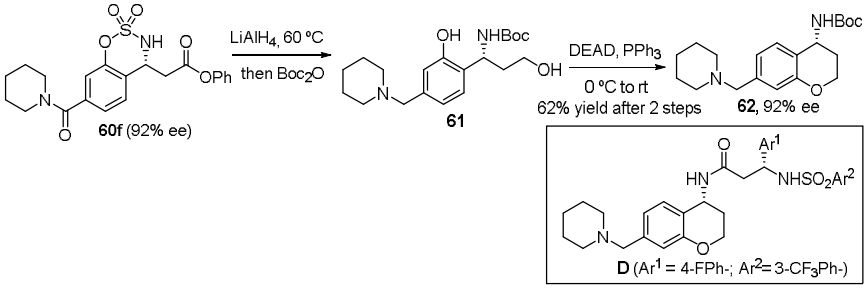
Also in 2016, Ma and collaborators described a catalytic asymmetric decarboxylative Mannich reaction of malonic acid half esters with benzoxathiazine 2,2-dioxides (Scheme 26).[35] As a model reaction, the authors used the reaction between benzoxathiazine 2,2-dioxides **8** and a malonic acid half ester **59**. The best result in the addition reaction were obtained in the presence of CuTC [copper(I)-thiophene-2-carboxylate] and a bisoxazoline ligand in THF at 15 °C. These reaction conditions are applied in the reaction between different cyclic aldimines and various malonic acid half esters **59**, leading to a wide scope with

good yields (86-99%) and enantioselectivities (92-99% ee). The reaction can also be carried out with a malonic acid half thioester leading to the corresponding product with a moderate yield (58%) and an excellent enantioselectivity (96% ee).



Scheme 26. Catalytic asymmetric decarboxylative Mannich reaction of malonic acid half esters with benzoxathiazine 2,2-dioxides.

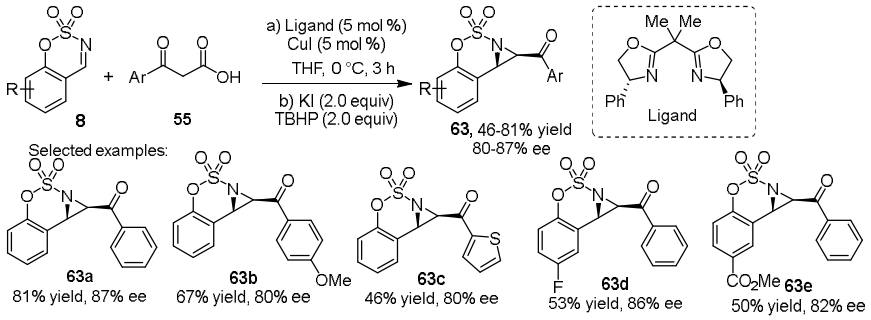
To demonstrate the potential application of their protocol, the authors performed a short-step chemical transformation of the decarboxylative Mannich adduct **60f** in order to prepare the chiral chroman-4-amine **62**, which is a key intermediate of the human Bradykinin B1 receptor antagonist **D** (Scheme 27). Direct reduction of sulfonamidate, amide, and ester groups present in **60f** with $LiAlH_4$, followed by protection with Boc_2O, furnished the intermediate **61**. This compound was directly subjected to the Mitsunobu cyclization to afford product **62** in 62% total yield without losing of enantiomeric purity.



Scheme 27. Synthetic transformations of the chiral sulfamidates.

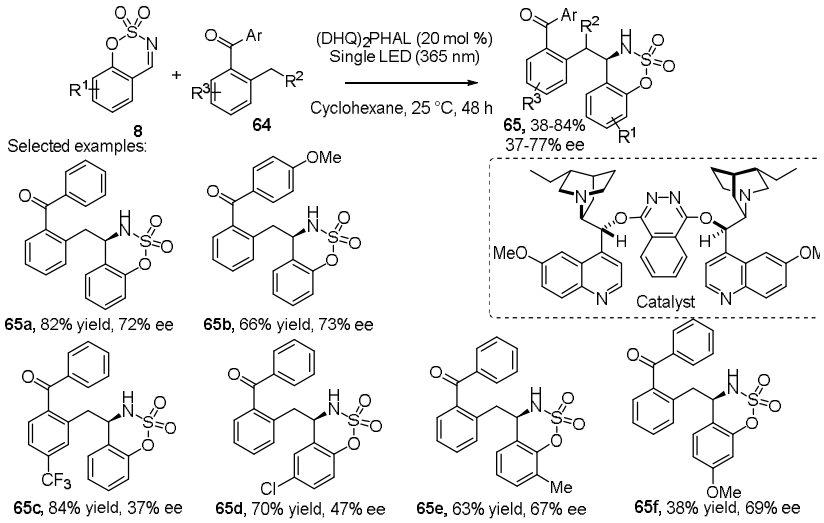
In the same year, the same research group described a one-pot enantioselective synthesis of fused aziridines, through a decarboxylative Mannich reaction followed by an oxidative C-H amination starting from benzoxathiazine 2-2-dioxides and β-ketoacids (Scheme 28).[36] The researchers observed that the reaction between cyclic imines derived from benzoxathiazine 2,2-dioxides **8** and β-ketoacids **55** in the presence of KI and TBHP (*tert*-butylhydroperoxide) in THF at room temperature gives rise of the synthesis to racemic fused aziridines in moderate to good yields (46-78%). The researchers were also able to make this reaction in an enantioselective way, however the treatment of an enantiopure intermediate product (resulting of the reaction between benzoxathiazine 2,2-dioxide and β-ketoacid) with KI and TBHP led to the racemic fused aziridine. Strikingly, when the reaction was performed in an one-pot manner, first the enantioselective

decarboxylative Mannich reaction in the presence of a CuI/Ph-Box complex and then addition of KI and TBHP to the same reaction mixture, the final product **63** was obtained in moderate to good yield (46-81%) and good enantioselectivity (80-87% ee).



Scheme 28. Cu-catalyzed decarboxylative Mannich reaction and oxidative C–H amination of benzoxathiazine 2,2-dioxides with β-ketoacids.

Recently, Melchiorre and collaborators have described a light-triggered enantioselective organocatalytic Mannich type reaction with benzoxathiazine 2,2-dioxides (Scheme 29).[37] By photochemical reaction of 2-alkylbenzophenones **64**, a hydroxy-*o*-quinodimethane was generated, which would react with the cyclic imines in the presence of an organocatalyst to give rise to a [4+2] cycloaddition. However, the researchers observed only the Mannich type reaction. The presence of a dimeric *Cinchona* alkaloid derivative $(DHQ)_2PHAL$ (after optimization), led to the Mannich product **65a** in good yield (82%) and enantioselectivity (72% ee). The optimized reaction conditions were applied to the reaction between differently substituted cyclic imines **8** and various 2-alkylbenzophenones **64** leading to the corresponding products in moderate to good yields (38-84%) and enantioselectivities (37-77% ee).

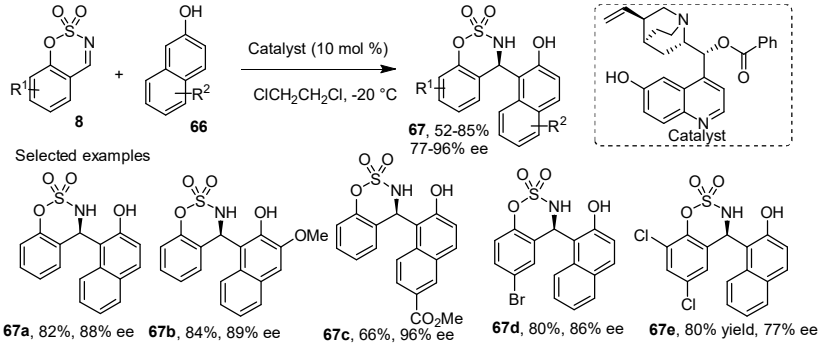


Scheme 29. Light-triggered enantioselective organocatalytic Mannich type reaction with benzoxathiazine 2,2-dioxides.

3.4. Friedel-Crafts reactions

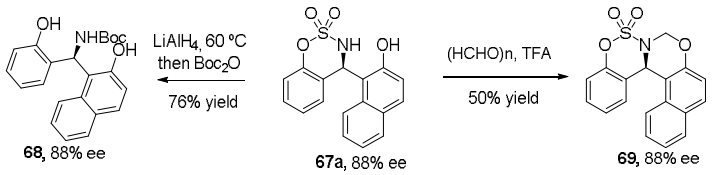
The enantioselective addition of aromatic compounds to imines (aza-Friedel–Crafts reaction) is an important strategy for the synthesis of enantioenriched benzylic amines, which are present in a wide variety of natural products. There are an enormous number of examples of asymmetric Friedel-Crafts reactions using acyclic imines. Nevertheless, the number of examples of aza-Friedel-Crafts with cyclic imines is scarce. For example, only one example of enantioselective Friedel-Crafts reaction using benzoxathiazine 2,2-dioxides as electrophiles have been described in the literature.[38]

In 2014, Pedro and coworkers described an organocatalytic enantioselective aza-Friedel-Crafts reaction of 2-naphthols **66** with benzoxathiazine-2,2-dioxides **8** (Scheme 30). The optimized conditions of the reaction were the following: addition of 2-naphthols in the presence of 10 mol % of an organocatalyst derived from cupreine in dichloroethane at -20 °C and addition of the imine via a syringe pump during 12 hours. The authors were able to demonstrate the effectiveness of their system in the reaction with various 1-naphthols, 2-naphthols and sesamol to differently substituted benzoxathiazine 2,2-dioxides, leading to the corresponding products **67** with good yields (52-85%) and enantioselectivities (77-96% ee).



Scheme 30. Organocatalytic enantioselective aza-Friedel-Crafts reaction of 2-naphthols with benzoxathiazine 2,2 dioxides.

The synthetic utility of the methodology was highlighted by performing several transformations (Scheme 31). The reduction of the sulfamidate group using $LiAlH_4$ afforded the corresponding aminomethylphenol, which was protected as its Boc derivative **68** in a one pot procedure, in good yield and without loss of enantiomeric purity. Additionally, pentacyclic compound **69** was obtained in 50% yield after acidic treatment of product **67a** in the presence of paraformaldehyde.



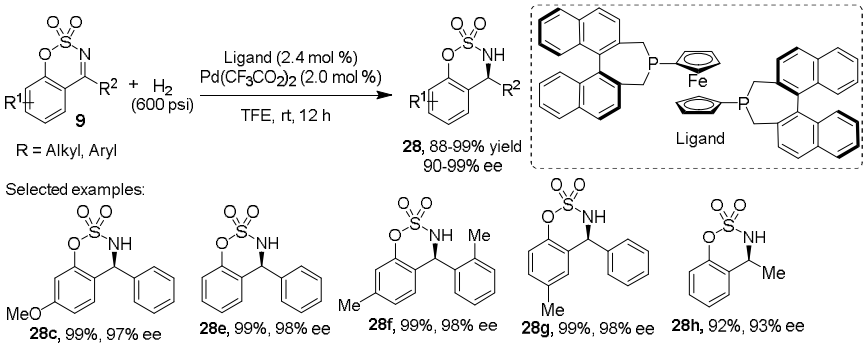
Scheme 31. Synthetic transformations of the chiral sulfamidates.

3.5. Hydrogenation reactions

The asymmetric hydrogenation of cyclic imines is a straightforward methodology for the synthesis of chiral nitrogen heterocycles.[39] In this context, the asymmetric hydrogenation reactions of benzoxathiazine 2,2-dioxides lead to the synthesis of chiral cyclic sulfamidates. Only two examples have been described in the literature using a chiral palladium catalysts.

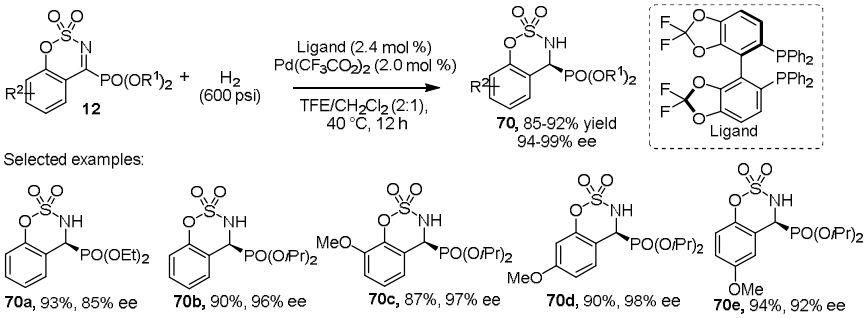
In 2008, Zhou and collaborators published their findings on the hydrogenation of cyclic ketimines using palladium as catalyst in the synthesis of cyclic sulfamidates (Scheme 32).[40] Optimized conditions were obtained and then applied to a series of ketone derived substituted benzoxathiazine-2,2-dioxides. The

optimized conditions consist in the use of a $Pd(CF_3CO_2)_2$/(*S*,*S*)-f-binaphane catalyst in trifluoroethanol at room temperature under H_2 atmosphere. Excellent results were obtained, both in yield (88-99%) as in enantioselectivity (90-99% ee). In general, aryl substituted ketimines lead to better enantioselectivities (97-99% ee) than alkyl substituted ketimines (90-94% ee) than alkyl substituted ketimines (90-94% ee) in this enantioselective hydrogenation.



Scheme 32. Palladium-catalyzed enantioselective hydrogenation of substituted benzoxathiazine 2,2-dioxides.

In 2016, the same research group published their findings on the enantioselective synthesis of α-aminophosphonates through palladium-catalyzed hydrogenation of cyclic phosphonate substituted ketimines (Scheme 33).[41] In a first stage, the researchers used a *N*-tosyl α-ketiminephosphonate, from which they carried out an easy synthesis of α-aminophosphonates. The hydrogenation of this kind of imine gives the best results under the following reaction conditions: $Pd(OCOCF_3)_2$/(*R*)-DifluorPhos as catalyst, trifluoroethanol/dichloromethane in a 2:1 proportion as solvent at 40 °C. These reaction conditions were then applied on differently substituted cyclic α-ketiminephosphonates **12** derived from benzoxathiazine 2,2-dioxides, leading to excellent results both in yield (85-92%) as in enantioselectivity (94-99% ee).



Scheme 33. Palladium-catalyzed enantioselective hydrogenation of substituted benzoxathiazine-2,2-dioxides.

7. Conclusions

As summarized in this chapter, the benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides (**8-12**) are highly interesting electrophiles, where the protecting group forms part of the structure of the compounds and consequently have lower conformational mobility than the acyclic imines. These facts made that these six membered cyclic imines are perfect electrophiles for a several asymmetric transformations, leading to the corresponding chiral sulfamidates with high levels of enantioselectivity. Although significant progress has been made in the development of catalytic asymmetric methodologies over the last 5 years, the use of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides as electrophiles has not been exploited to its full potential and there

is still plenty of room for major improvement for developing new reactions using these electrophiles. Moreover, the application of this kind of electrophiles for the synthesis of interesting medicinal and biological active compounds is still in its infancy with a lot of opportunities. All these facts made that these cyclic imines are interesting substrates to study in the field of asymmetric catalysis.

Acknowledgements

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