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ALQUINILACIÓN Y ALQUILACIÓN ENANTIOSELECTIVAS DE IMINAS CÍCLICAS

Tesis Doctoral

Lode De Munck

Directores

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Valencia, abril 2017

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Que la presente Tesis Doctoral, titulada "Alquinilación y alquilación enantioselectivas de iminas cíclicas" ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València por el licenciado en Farmacia **D. Lode De Munck** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Valencia, abril 2017

Fdo. José Ramón Pedro Llinares **Fdo. Carlos Vila Descals**

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ÍNDICE/INDEX

ABREVIATURAS/ABBREVIATIONS

[α]	Rotación específica/Specific rotation
Å	Ångström
Ac	Acetil/Acetyl
AcO	Acetato
Alk	Alquil/Alkyl
Ar	Aril/Aryl
BINOL	1,1´-Binaftil-2,2´-diol/1,1´-Binaphthyl-2,2´-diol
Bn	Bencil/Benzyl
Boc	*terc*-Butiloxicarbonil/*tert*-Butyloxycarbonyl
Box	Bisoxazolina/Bisoxazoline
Bu	Butil/Butyl
CAN	Nitrato cerico ammonico/Ceric ammonium nitrate
Cbz	Benciloxicarbonilo/Benzyloxycarbonyl
COD	Cyclooctadiene/Cyclooctadieno
d	Doblete/Doublet
DBDMH	Dibromodimetilhidantoina/Dibromodimethylhydantoin
DCE	Dicloroetano/Dichloroethane
DCM	Diclorometano/Dichloromethane
DEPT	Distortionless enahancement by polarization transfer
DFT	Density functional theory
DMA	Dimetilacetamida/Dimethylacetamide
DMF	Dimetilformamida/Dimethylformamide
dppp	Bis(diphenylphosphanyl)propane
E	Electrófilo/Electrophile
EDCI	1-Etil-3(3-dimetilaminopropil)carbodiimida/ 1-Ethyl-3(3-dimethylaminopropyl)carbodiimide
ee	Exceso enantiomérico/Enantiomeric excess
equiv	Equivalentes/Equivalents
ESI	Ionización por electrospray/Electrospray ionization
Et	Etil/Ethyl
h	Hora/Hour
HIV	Virus de inmunodeficiencia humana/Human immunodeficiency virus
HPLC	Cromatografía líquida de alta eficacia/High-performance liquid chromatography
HRMS	Espectrometría de masas de alta resolución/High resolution mass spectrometry
J	Constante de acoplamiento/Coupling constant
M	Molar
m	Multiplete/Multiplet
Me	Metil/Methyl
mg	Miligramo/Milligram
MHz	Megahercio/Megahertz
min	Minuto/Minute
mL	Mililitro/Milliliter
mmol	Milimol/Millimol
MOMCl	Clorometil metil éter/Chloromethyl methyl ether
MTBE	Metil *terc*-butil éter/Methyl *tert*-butyl ether

NMM	*N*-metilmorfolina/*N*-methylmorpholine
NMR	Resonancia magnética nuclear/Nuclear magnetic resonance
o	*Orto*/*Ortho*
p	*Para*
PEG	Polietilenglicol/Polyethylene glycol
Ph	Fenil/Phenyl
PMP	*Para*-metoxifenil/*Para*-methoxyphenyl
ppm	Partes por millón/Parts per million
Pr	Propil/Propyl
py	Piridina/Pyridine
q	Quadruplete/Quadruplet
R	Rendimiento/Yield
rt	Temperatura ambiente/Room temperature
s	Singlete/Singlet
t	Triplete/Triplet
ta	Temperatura ambiente/Room temperature
TBS	*Terc*-butil dimetilsilil/*Tert*-Butyl dimethylsilyl
TEMPO	(2,2,6,6-tetrametilpiperidin-1-il)oxidanil/ (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	Ácido trifluoroacético/Trifluoroacetic acid
TFE	Trifluoroetanol/Trifluoroethanol
THF	Tetrahidrofurano/Tetrahydrofurane
TIPS	Triisopropilsilil/Triisopropylsilyl
TLC	Cromatografía de capa fina/Thin layer chromatography
TMS	Trimetilsilil/Trimethylsilyl
Tol	Tolueno/Toluene
t_r	Tiempo de retención/Retention time
Ts	Tosil/Tosyl
UV	Ultravioleta/Ultraviolet
δ	Desplazamiento químico/Chemical shift
µ	Micro

CHAPTER 1

GENERAL INTRODUCTION AND OBJECTIVES

1.1. GENERAL INTRODUCTION

The search for methods focused on obtaining enantiomerically enriched compounds has been one of the biggest challenges is organic chemistry in the last decades. The significance of chirality can be seen in numerous natural compounds[1, 2] and in molecular receptors in biological systems.[3] The importance of chirality lies in the fact that enantiomers show different physiological and pharmacological properties.[4] The world became aware of the implications this fact had after the famous Thalidomide case.[5] Thalidomide (Figure 1.1) came on the market in 1957 in West Germany (and got approved in 46 countries) as a sedative and sleeping drug for pregnant women in a racemic mixture of (*R*)- and (*S*)-thalidomide. Tragically, after a few years, it became clear that the drug, besides being efficient for the indications described above, resulted also in malformations in fetuses. While the (*R*)-enantiomer was effective for sleeping problems, the (*S*)-enantiomer was teratogenic (a substance affecting the development of the fetus and causing structural or functional disability). This case showed the necessity of the development of procedures for the synthesis of enantiopure compounds.

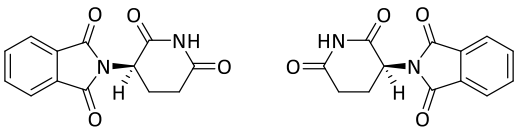

Figure 1.1. The two enantiomers of thalidomide.

Traditionally, the focus for getting enantiopure compounds lied on the use of natural sources of compounds coming from the so called “chiral-pool” (nature´s “off the shelf” enantiopure compounds such as amino acids and carbohydrates) and also the resolution of racemic mixtures (the separation of two enantiomers due to its different chemical properties in a reaction with another chiral molecule).[6] Another method that was frequently used was the one that uses “chiral auxiliaries”.[7] This methodology consists in the attachment of an achiral substrate to a chiral auxiliary which is followed by a stereoselective reaction and subsequent removal and recuperation of the chiral auxiliary. A chiral reagent, such as a chiral base, which selectively removes a proton out of two enantiotopic protons, can also induce enantioselectivity. However, in the modern organic synthesis, several new aspects have emerged as important factors, such as the efficiency of the synthesis, the consume of chirality or the necessity for more selectivity, which have led to the rise of asymmetric catalysis as a new synthetic methodology with a huge potential. The advantage of this method lies in obtaining the enantioenriched products with a high purity, with a low consume of chirality and with less residuals.

The asymmetric catalysis can be divided in two groups: asymmetric biocatalysis and chemocatalysis.[8, 9] Asymmetric biocatalysis is the chemical process in which enzymes or other biological catalysts perform asymmetric reactions in organic compounds. However, biocatalysis has several drawbacks: the development of biocatalysts is a slow process and does not follow a set of rules, the very limited range of stability (temperature, solvent, pH value, etc.) of the catalysts (enzymes) and finally the small amount of well characterized enzymes compared to chemical catalysts.[10] In chemocatalysis on the other hand, chiral molecules are used for inducing chirality in the chemical reactions. Asymmetric chemocatalysis can be separated into two sections. The first one is the transition metal asymmetric catalysis, in specific with organometallic catalysts. In these catalysts, the d-orbital of the transition-metal (Ni, Cu, Zn, Ag, Pd, Au, etc.) can activate substrates and accelerate the reaction rate by coordination, ligand exchange, insertion, etc. what results in the cleavage and the

formation of C-C bonds (also C-H and H-H bonds). A great advantage of this kind of catalysis is the diversity of ligands that can be used to change the reactivity and selectivity of the transition-metal catalysts.[11] A drawback is the possibility of residual (toxic) metals in the final products. A solution for this drawback is offered by the use of chiral organocatalysts. The term of organocatalysis was introduced in 2000 by Macmillan,[12] and has shown a big development in the last decade. Chiral organocatalysts are, in general, small organic molecules (for example chiral amines or thioureas) that are able to both coordinate and activate substrates, in order to catalyze a reaction in an asymmetric way, inducing chirality in the final product.[13, 14] An advantage of this method is the absence of, possible, toxic metals in the reaction mixture and the final product. A drawback is that the methodology is still very young and progress has still to be made. Also, the possible toxicity of the organocatalysts has not been investigated enough yet.

The importance of the asymmetric catalysis in the formation of carbon-carbon bonds lies in the possibility of obtaining stereogenic centers in structurally complex compounds, and asymmetric catalysis has been used in several reactions such as Friedel-Crafts, Diels-Alder, alkylation and alkynylation reactions, Henry reactions etc.[15-17] For this reason, this methodology has been used in the synthesis of numerous biologically and pharmacologically active compounds. In this context, chiral heterocyclic compounds are extremely important for chemical biology, which includes chiral cyclic amines.

Looking to the FDA database it can be noticed that nearly 60% of unique small-molecule drugs contain minimum one nitrogen heterocycle, which proofs the structural significance of the nitrogen heterocycle.[18] With this idea in mind, various compounds, with biological and pharmaceutical applications, can be found bearing a stereocenter (tertiary and quaternary), in the azomethine carbon. For example this is the case in compound **A**,[19] a HIV transcriptase, compound **B** (a derivative of Artemisinin),[20] which has proven activity against malaria and compound **C**,[21] a progesterone receptor agonist (Figure 1.2). Another drug that contains a stereocenter in the azomethine carbon is Flucloxacillin (**D**), a narrow-spectrum β-lactam antibiotic of the penicillin class.

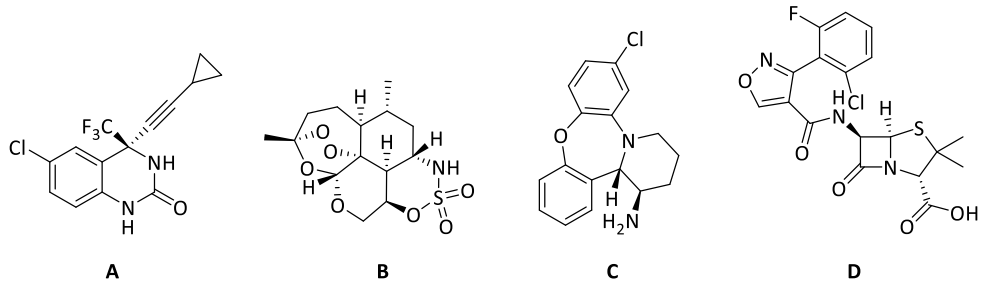

Figure 1.2. Heterocyclic compounds **A**-**D** containing stereocenters in the azomethine carbon.

As proven above, chiral heterocyclic amines have an importance in biological and pharmaceutical chemistry. One way to obtain this kind of compounds is by enantioselective nucleophilic addition of organometallic reagents to cyclic imines. For this reason, our attention in this thesis was focused on the development of new catalytic asymmetric additions to cyclic imines, leading to the synthesis of cyclic amines bearing a chiral center.

1.2. GENERAL OBJECTIVES

The nucleophile addition to C=N double bonds is one of the most used methods in the synthesis of nitrogenated derivatives. In this thesis we focused our attention to the nucleophilic enantioselective addition of organometallic reagents to cyclic imines, which is a challenge due to the low reactivity of the azomethine carbon.

Having this in mind, in this thesis we have proposed the following general objectives:

- Enantioselective alkynylation of benzo[*e*][1,2,3]oxathiazine 2,2-dioxides catalyzed by complexes of (*R*)-VAPOL-Zn
- Enantioselective alkynylation of benzo[*e*][1,2,3]oxathiazine 2,2-dioxides catalyzed by complexes of (*S*)-diarylprolinol-Zn
- Enantioselective alkylation of dibenzo[*b,f*][1,4]oxazepines catalyzed by complexes of (*R*)-VAPOL-Zn
- Catalytic enantioselective aza-Reformatsky reactions of benzo[*e*][1,2,3]oxathiazine 2,2-dioxides
- Catalytic enantioselective aza-Reformatsky reactions of dibenzo[*b,f*][1,4]oxazepines

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ENANTIOSELECTIVE ALKYNYLATION OF BENZO[*e*][1,2,3]OXATHIAZINE 2,2-DIOXIDES CATALYZED BY COMPLEXES OF (*R*)-VAPOL-Zn

CHAPTER 2

2.1. INTRODUCTION

Propargylic amines have emerged in the last years as versatile precursors in the synthesis of great variety of valuable compounds such as allylamines, pyrrolidines, oxazoles and pyrroles.[1] Their use has also been proved as building blocks in the synthesis of a wide range of fine chemicals, natural products, pharmaceuticals, herbicides and fungicides.[2-4]

Moreover, numerous compounds bearing the aminopropargylic structure can be found in the field of chemical biology and pharmacy.[5] For example, this particular motif is present in inhibitors of the enzyme monoamine oxidase B (MAO-B),[6] in antagonists of a subtype of the receptor of *N*-methyl-*D*-aspartate (NMDA) (Figure 2.1, **A**),[7] in inhibitors of platelet aggregation,[8] in inhibitors of the γ-aminobutyric acid (GABA) degradation,[9] in antibiotics,[10] in inhibitors of acetyl-CoA oxidase (Figure 2.1, **B**),[11] inhibitors of HIV transcriptase (Figure 2.1, **C**)[12] and in herbicides[13] among others.

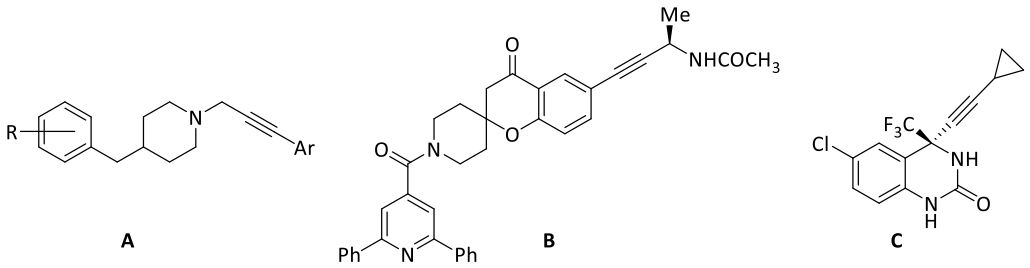
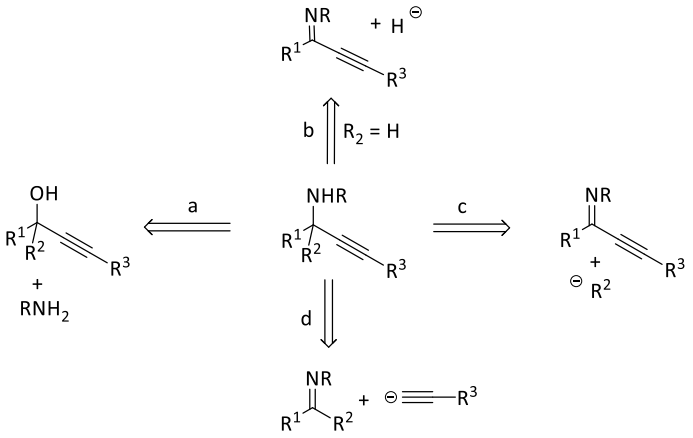


Figure 2.1. (**A**) Antagonist of the receptor of *N*-Methyl-*D*-aspartate (NMDA) (**B**) Inhibitor of acetyl-CoA oxidase (**C**) Inhibitor of HIV transcriptase.

The importance of the absolute stereochemistry on the biological activity of chiral compounds is well known. Due to this importance, the pharmaceutical industry and the synthetic organic chemists have focused their attention on developing new synthetic procedures that allow the synthesis of optically enriched compounds over the last years .

In general, four methodologies are used to obtain chiral propargylic amines. The first one consists in the nucleophilic substitution of propargylic alcohols with nitrogen containing nucleophiles (approximation a, Scheme 2.1).[14] The second method is the reduction of the C=N double bond in α,β-unsaturated ketimines (approximation b, Scheme 2.1).[15] Another way to obtain chiral propargylic amines is the 1,2-addition of carbon nucleophiles to imines with an α,β-triple bond (approximation c, Scheme 2.1).[16] The last methodology consists in the addition of nucleophilic alkynes to imines (approximation d, Scheme 2.1).[17] In this chapter, we will focus in the fourth approximation to prepare chiral propargylic amines.

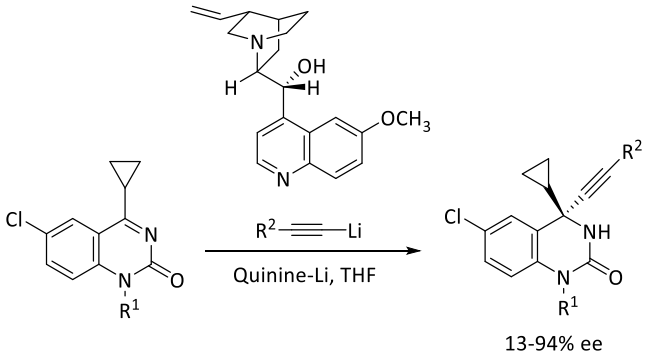
Whilst the asymmetric addition of terminal alkynes to carbonyl groups has been subject to various investigations, the asymmetric addition of terminal alkynes to imines has been less studied, due to the less reactive character of the azomethine carbon compared to the carbonyl of ketones and aldehydes. However, the reactivity of the C=N double bond can be increased by the use of nitrones, by the generation of iminium ions or by the introduction of electron-withdrawing groups on the nitrogen of the imine. The use of these strategies has permitted the synthesis of propargylic amines via the alkynylation reaction.



Scheme 2.1. General approximations for the synthesis of propargylic amines.

2.1.1. Stoichiometric enantioselective alkynylations of imines

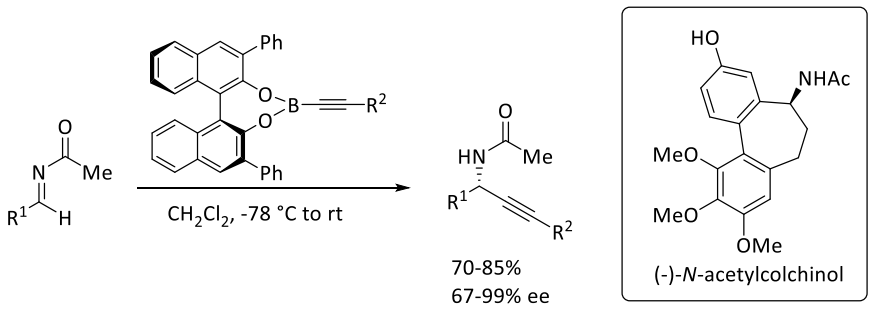
The first example of a non-catalytic enantioselective alkynylation of imines was described by Huffman in 1995.[12] In this work, they described the formation of an amine on a tertiary carbon in an asymmetric manner. The stereogenic center was formed by the addition of a lithium acetylide to a cyclic *N*-acyl ketimine (Scheme 2.2). In order to obtain the product in an enantioenriched way they used a quinine lithium alkoxide as a chiral additive (stoichiometric). The utility of this reaction was proven by the synthesis of a HIV reverse transcriptase inhibitor.



Scheme 2.2. Enantioselective alkynylation of a cyclic *N*-acyl ketimine.

As can be observed in the previous example, the processes developed for the synthesis of chiral propargylic amines require, in general, the deprotonation of the alkyne with strong bases in a previous step. On the other hand, the high reactivity of lithium, magnesium or aluminum acetylide results in a poor stereocontrol of the reaction, which on its turn influences negatively the enantioselectivity. A possible solution to these problems is the generation of acetylenic organometallic reagents *in situ* which allows the direct addition of the alkyne to imines under mild conditions compatible with other electrophilic groups. Alkynyl cuprates, boronates and alkynylzinc reagents have proven their utility.

In 2006, the research group of Wong described the asymmetric synthesis of *N*-protected propargylic amines by the alkynylation of *N*-acylimines using binaphthol-modified alkynylboronates (Scheme 2.3).[18] The best enantioselectivities and highest yields were obtained using 3,3'-disubstituted binaphthol with different aryl and alkyl alkynes. A restriction of this reaction is that only non-enolizable imines can be used. This methodology was used in the synthesis of (-)-*N*-acetylcolchinol (a selective vascular targeting agent with potential importance in cancer chemotherapy).

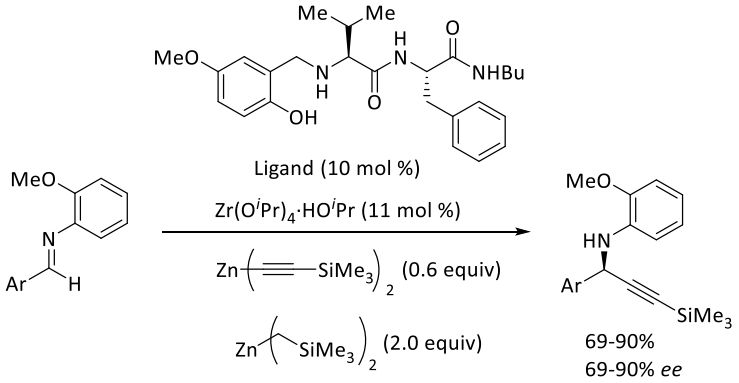


Scheme 2.3. Enantioselective alkynylation of *N*-acetylaldimines with alkynylboronates.

2.1.2. Catalytic enantioselective alkynylations of imines

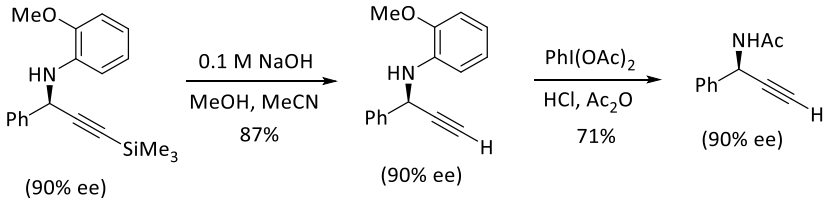
One way to generate the acetylene organometallic reagent is using dialkylzinc in order to deprotonate the alkyne. Dialkylzinc compounds have been extensively used in alkylation reactions of imines.[19] However, alkynylation reactions with dialkylzinc or alkylalkynylzinc are not that common, since the majority of the alkynylation of imines that are described in literature are performed using chiral copper complexes.[20] Next, a few selected examples of alkynylations with zinc reagents are presented.

In 2003, the group of Hoveyda presented the first catalytic enantioselective addition of alkynylzinc reagents to a variety of *o*-anisidyl imines.[21] The reaction was promoted by a chiral amino acid type ligand in the presence of $Zr(O^iPr)_4.HO^iPr$ (Scheme 2.4).



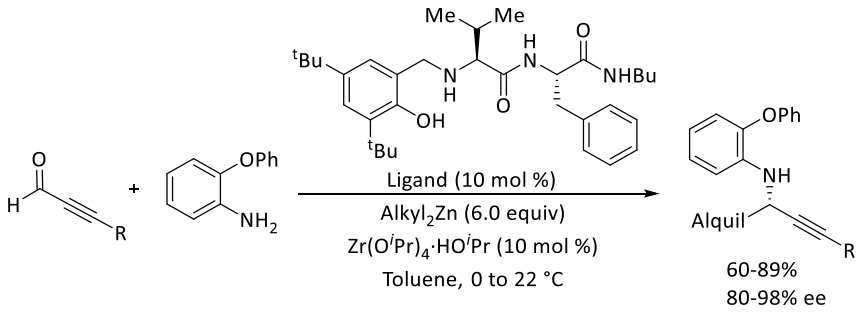
Scheme 2.4. Enantioselective addition of alkynylzinc to imines catalyzed by $Zr(O^iPr)_4.HO^iPr$

The authors were able to apply this protocol to different substituted *o*-anisidyl imines obtaining optically enriched secondary propargylic amines with enantioselectivities up to 90% ee and good yields. However, the presence of an *ortho* substituent in the aromatic ring, reduces the enantioselectivity to 69%. Trimethylsilylacetylene was used in the reaction, which led to terminal propargylic amines once eliminated the TMS group. The reaction was also performed with aliphatic and aromatic alkynylzinc, leading to moderate to good enantioselectivities. The obtained propargylic amines can be deprotected by oxidation using $PhI(OAc)_2$ resulting in the corresponding free amines (Scheme 2.5).



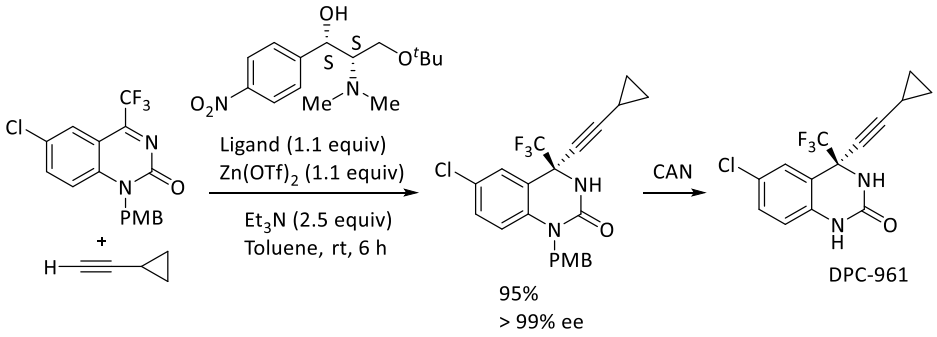
Scheme 2.5. Oxidative deprotection of the *o*-anisidyl group

The same research group also investigated the synthesis of propargylic amines via a three component reaction between α,β-unsaturated aldehydes, an *ortho*-phenoxy substituted primary aromatic amine and an alquilzinc reagent in the presence of $Zr(O^iPr)_4.HO^iPr$ and an chiral amino alcohol type ligand (Scheme 2.6).[22]



Scheme 2.6. Enantioselective synthesis of propargylic amines via the addition of dialkylzinc reagents to alkynyl imines.

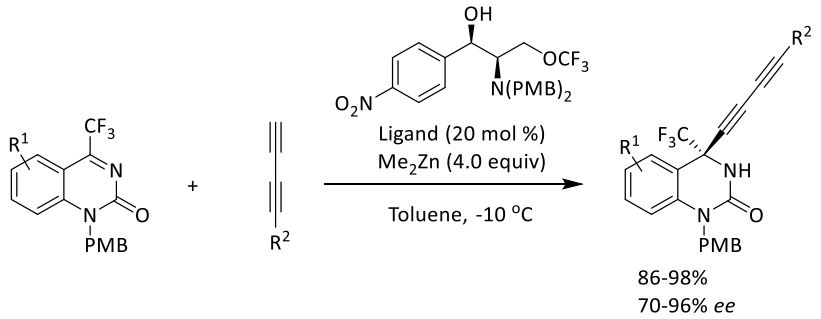
In 2004, Jiang and Si described the enantioselective alkynylation of a cyclic *N*-acyl ketimine using a stoichiometric amount of a chiral amino alcohol as ligand.[23] The cyclic imine is activated by a trifluoromethyl group and the reaction is performed in the presence of zinc triflate and triethylamine (Scheme 2.7). This reaction proved to be a key step in the synthesis of DPC-961, an analogue of Efavirenz (Sustiva®, Bristol-Myers-Squibb), a pharmaceutical used in the HIV therapy.[24] Various aromatic, allylic and silyl-substituted acetylenes were applied in the reaction leading to enantioselectivities up to 99.5% and yields higher than 63%.



Scheme 2.7. Enantioselective addition of cyclopropyl acetylene to a cyclic trifluoromethylimine.

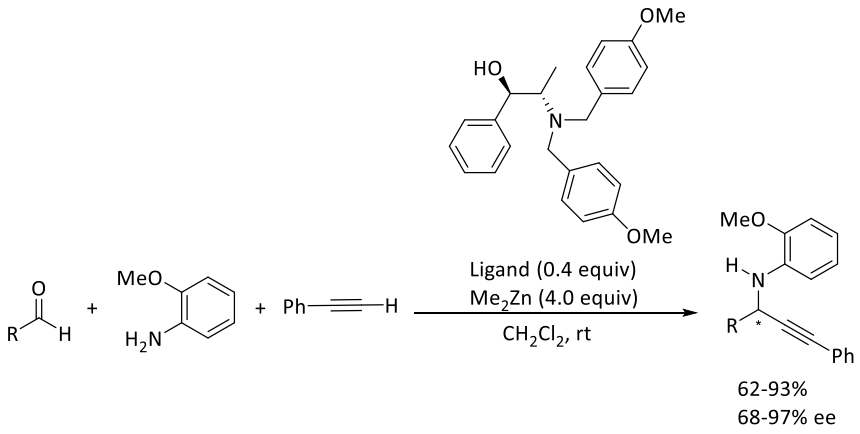
More recently, the research group of Ma published their results on the diynylation of cyclic *N*-acyl trifluoromethylimines using an amino alcohol like ligand and Me_2Zn (Scheme).[25] The reaction tolerates electron-withdrawing and electron-donating groups on the aromatic ring of the imine, as well as aromatic, alicyclic and aliphatic diynes, affording the chiral amines in high yields and enantioselectivities.

The authors also synthesized the opposite enantiomers of the diynylation products by using the chiral ligand shown in the scheme above (Scheme 2.8). They were also able to eliminate the *p*-methoxybenzyl group and reduce partially the triple bond without loss of enantioselectivity.



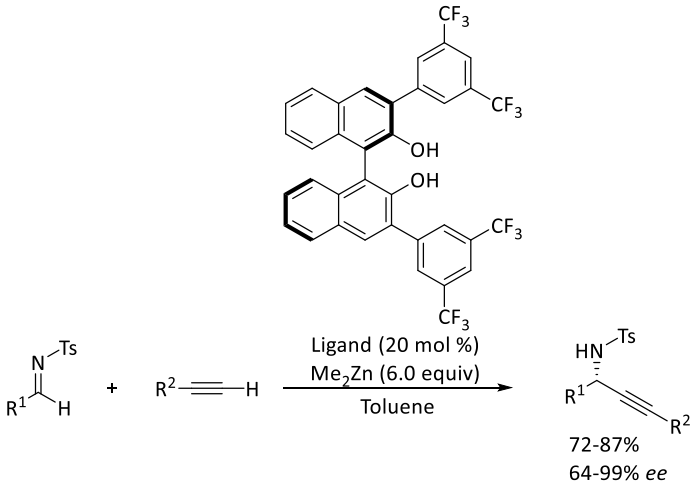
Scheme 2.8. Addition of diynes to *N*-acylimines catalyzed by an amino alcohol type ligand and Me_2Zn.

In 2007, the group of Bolm described a three component synthesis of propargylic amines using Me_2Zn with various aldehydes and *o*-methoxyaniline.[26] The efficiency of the methodology was improved by concentrating the reaction mixture using as only solvent the toluene of the Me_2Zn solution. In the same work the researchers developed also the enantioselective version of the reaction, using the same methodology, but performing the reaction in the presence of a (1*R*, 2*S*)-norepinephrine derivative as chiral inducer (Scheme 2.9). Aromatic, heteroaromatic and α-substituted aliphatic aldehydes, *o*-methoxyaniline and phenylacetylene were used to obtain the corresponding propargylic amines in moderate to good yields and with enantioselectivities between 68 and 97%. However, the reaction with aliphatic alkynes and with trimethylsilylacetylene resulted in lower enantiomeric excesses (13-53% *ee*).



Scheme 2.9. One-pot enantioselective synthesis of propargylic amines with an amino alcohol and Me_2Zn.

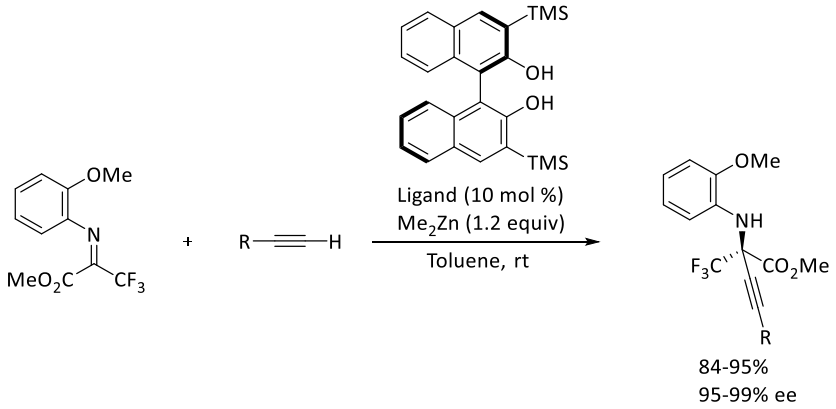
Taking in account that electron-withdrawing groups on the nitrogen atom increase the reactivity of the azomethine carbon of the C=N double bond, our group proposed the first dimethylzinc-mediated catalytic enantioselective alkynylation of *N*-sulfonyl imines using BINOL type ligands (Scheme 2.10).[17] As already observed by Bolm,[26] a reduction in the volume of the reaction resulted in an increase of the enantioselectivity; a reduction of 50% of the volume resulted in a slight increase of the enantioselectivity (96% to 98% *ee*).



Scheme 2.10. Enantioselective alkynylation of *N*-tosylimines promoted by Me_2Zn and BINOL type ligands.

With different *N*-tosylaldimines derived from aromatic and heteroaromatic aldehydes high enantioselectivities were obtained (up to ≥99% *ee*). On the other hand, the aliphatic imines showed less enantioselectivity (18-38% *ee*). Aliphatic alkynes were also applied in the reaction under the same reaction conditions, showing, depending the alkyne, enantioselectivities up to ≥99% *ee*. Moreover, the elimination of the tosyl group by SmI_2 was also carried out leading to free propargylic amines

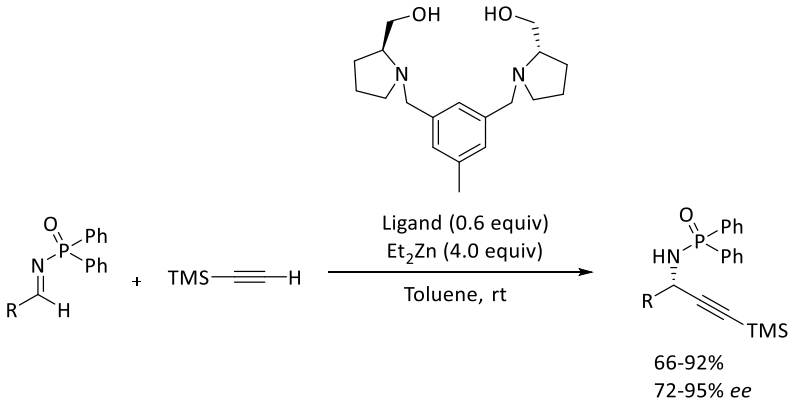
Zhang and collaborators also used a similar catalytic system, formed by Me_2Zn and a BINOL-type ligand.[27] They applied this catalytic system in the enantioselective alkynylation of α-trifluoromethyl ketimine esters (Scheme 2.11). Different types of alkynes (aliphatic, aryl and silyl-substituted) were tested in the reaction, obtaining in all of the cases excellent enantioselectivities (95-99% *ee*).



Scheme 2.11. Enantioselective alkynylation of α-trifluoromethyl ketimine esters catalyzed by BINOL-Zn.

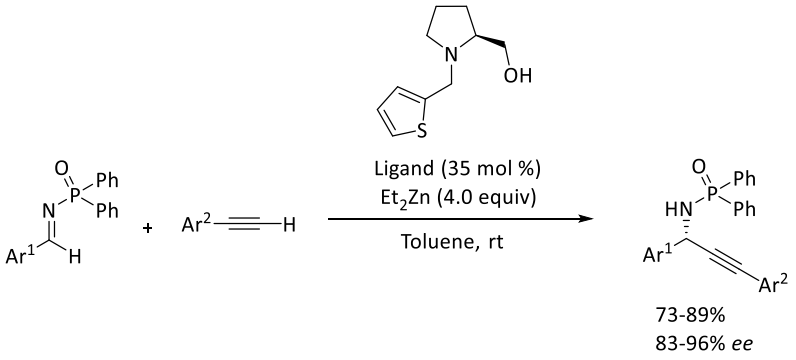
In 2009 the Wang group published their results on the first asymmetric addition of terminal alkynes to *N*-(diphenylphosphinoyl)imines promoted by a proline derived β-amino alcohol and Et_2Zn.[28] With substoichiometric amounts of ligand, they obtained a moderate enantioselectivity (68% *ee*) and only when they raised the ligand loading to a 100%, the alkynylation products were obtained in good yields and excellent enantioselectivities up to 95% *ee*. The same year they also described the nucleophilic addition of trimethylsilylacetylene to the same substrates (Scheme 2.12).[29] As chiral ligands they used different chiral amino alcohols. Different aryl, heteroaryl and alkyl imines were tested and moderate to good enantioselectivities (72-95% *ee*) were obtained. A drawback of this report is the amount of ligand needed in the reaction (60 mol %). They also applied the same

conditions to various *N*-(diethoxyphosphoryl)imines, obtaining good results, both in yield as in enantioselectivity.



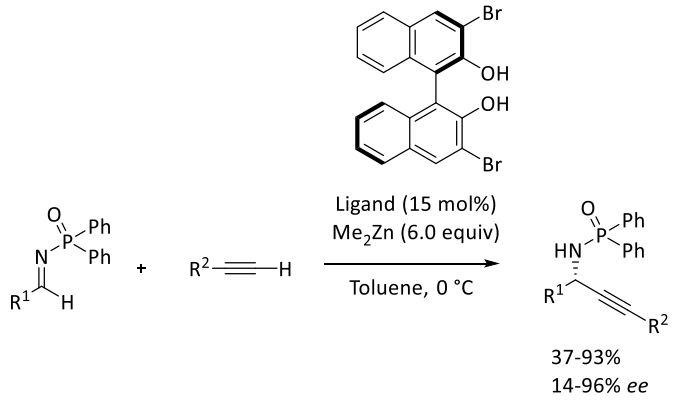
Scheme 2.12. Enantioselective addition of trimethylsilylacetylene to *N*-(diphenylphosphinoyl)imines promoted by Et_2Zn and a β-amino alcohol like ligand.

In 2010, the same group described the design and application of amino alcohol like tridentate ligands derived from prolinol (Scheme 2.13).[30] These ligands were applied in the enantioselective addition of phenylacetylene, 2-thienyl- and 3-thienylacetylene to aromatic *N*-(diphenylphosphinoyl)imines resulting in good yields and good enantioselectivities using less amount of chiral ligand (35 mol %).



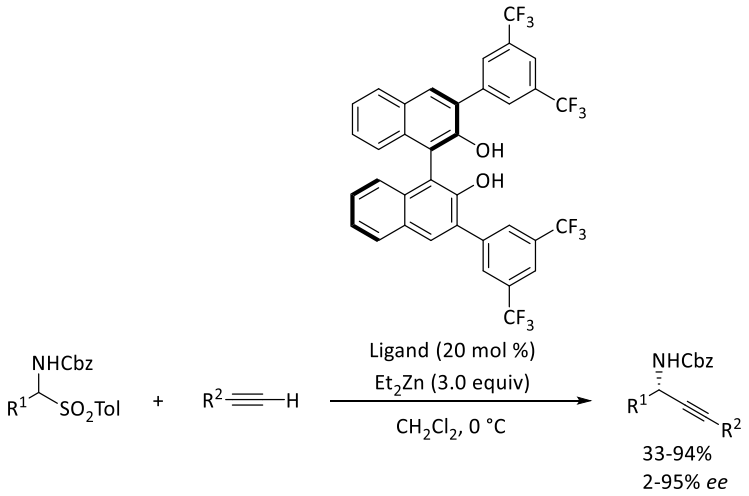
Scheme 2.13. Enantioselective addition of alkynes to *N*-(diphenylphosphinoyl)imines.

In 2012 our research group published their results on the enantioselective addition of terminal alkynes to *N*-(diphenylphosphinoyl)imines (Scheme 2.14).[31] The catalytic system formed by Me_2Zn and a BINOL type ligand, 3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol, leads to the best enantioselectivities. The optimized reaction conditions were applied on one hand on differently substituted *N*-(diphenylphosphinoyl)imines leading to good yields up to 86% and enantioselectivities up to 96%, and on the other hand with different aromatic, heteroaromatic and aliphatic alkynes obtaining the corresponding products in good yields (up to 93%) and enantioselectivities (up to 93% *ee*).



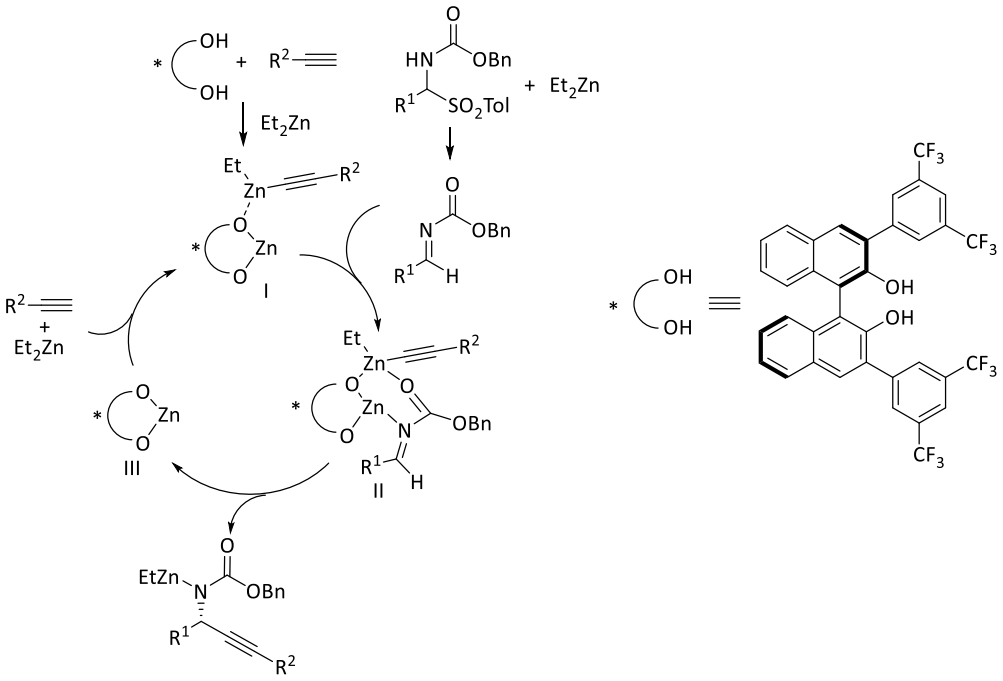
Scheme 2.14. Enantioselective addition of terminal alkynes to *N*-(diphenylphosphinoyl)imines.

One year later, in 2013, our research group developed an enantioselective Zn-BINOL catalyzed alkynylation of aldimines generated *in situ* from α-amido sulfones (Scheme 2.15).[32] The advantage of using α-amido sulfones lies in the fact that they are stable solids that can be readily obtained in one-step fashion by condensation of carbamates and sodium aryl sulfinates with the desired aldehydes, and form easily *N*-carbamoyl imines in basic medium by deprotonation of the carbamate and elimination of the sulfinate group. The best results were obtained with 3,3'-bis(3,5-bis(trifluoromethyl)phenyl)- [1,1'-binaphthalene]-2,2'-diol and Et_2Zn as catalytic system. Various differently substituted aromatic α-amido sulfones were tested in the reaction conditions obtaining good yields and enantioselectivities. Different terminal aromatic and aliphatic alkynes were also tested leading to good yields and high enantioselectivities.



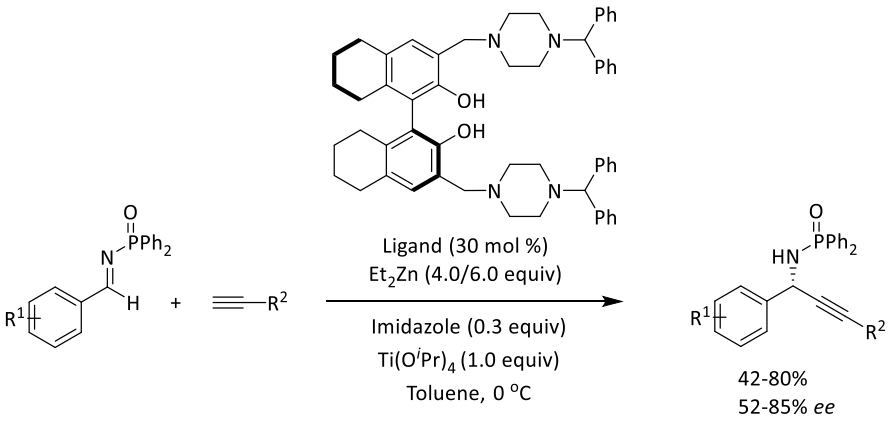
Scheme 2.15. Enantioselective alkynylation of aldimines generated *in situ* from α-amido sulfones.

In the same publication, a possible catalytic cycle was proposed for the reaction (Scheme 2.16). Deprotonation of the BINOL and acetylene by diethylzinc leads to the formation of the BINOL zincate-ethylalkynylzinc complex catalyst **I**. A reaction between another diethylzinc molecule and the α-amido sulfone leads to the formation of the *N*-Cbz-protected imine, which coordinates to the catalyst complex **I** to give the intermediate **II**. In a next step, a transfer of the alkynylide from the ethylalkynylzinc moiety to the imine takes place. This leads to the release of the reaction product and BINOL-zincate **III**, which after coordination with another ethylalkynylzinc molecule regenerates the complex catalyst, to reinitiate the catalytic cycle.



Scheme 2.16. Proposed catalytic cycle for the enantioselective alkynylation of aldimines generated *in situ* from α-amido sulfones in presence of BINOL-Zn complexes.

In 2016, an asymmetric alkynylation reaction using *N*-(diphenylphosphinoyl)imines as electrophiles in the presence of Et_2Zn and a BINOL type ligand was described by Pu and collaborators (Scheme 2.17).[33] The researchers used 3,3'-di(1-diphenylmethylpiperazinyl)methyl H_8BINOL as chiral ligand, in the presence of 1 equivalent $Ti(O^iPr)_4$ and 0.3 equivalents of imidazole. The ligand was prepared from the Mannich type reaction of (*S*)-H_8BINOL with paraformaldehyde and 1-(diphenylmethyl)piperazine. The alkynylation reaction conditions allow the use of different alkyl and aryl alkynes, leading to good yields and enantioselectivities, especially for alkyl alkynes, with enantioselectivities up to 85% *ee*.



Scheme 2.17. Asymmetric alkynylation reaction to *N*-(diphenylphosphinoyl)imines in the presence of Et_2Zn and a BINOL type ligand.

2.1.3. Catalytic enantioselective reactions of benzoxathiazine 2,2-dioxides

In this chapter, we want to explore the use of cyclic imines as electrophiles. More concretely benzoxathiazine 2,2-dioxides, which have never been used as electrophiles in enantioselective

alkynylation reactions. The use of these cyclic imines in which the protecting group forms part of the structure of the compound can be an alternative towards the *N*-protected imines, due to the lower conformational mobility and the impossibility of E/Z isomeration of the double bond of the imine.

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 2.2, **A**),[34] in oxazolidinones (Figure 2.2, **B**)[35] or Iβ-methylcarbapenes (Figure 2.2, **C**),[36] 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.[37]

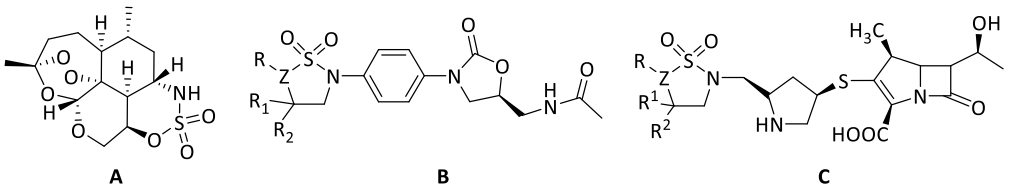
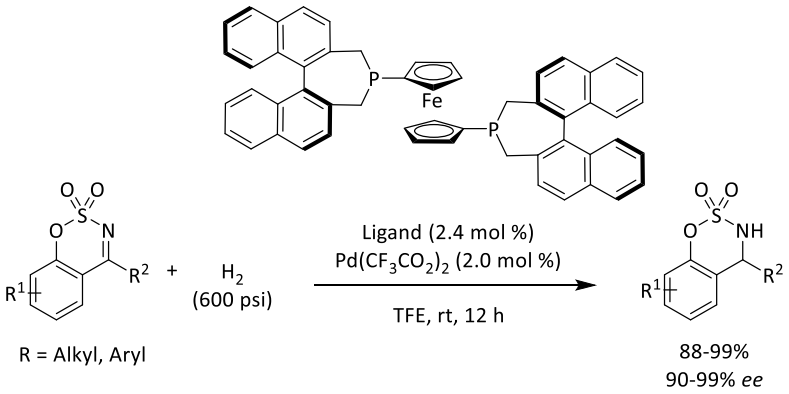


Figure 2.2. (**A**) Analogue of artemisinin, (**B**) oxazolidinone derivate, (**C**) Iβ-methylcarbapene derivative.

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.

2.1.3.1. Catalytic enantioselective hydrogenation reactions of benzoxathiazine 2,2-dioxides

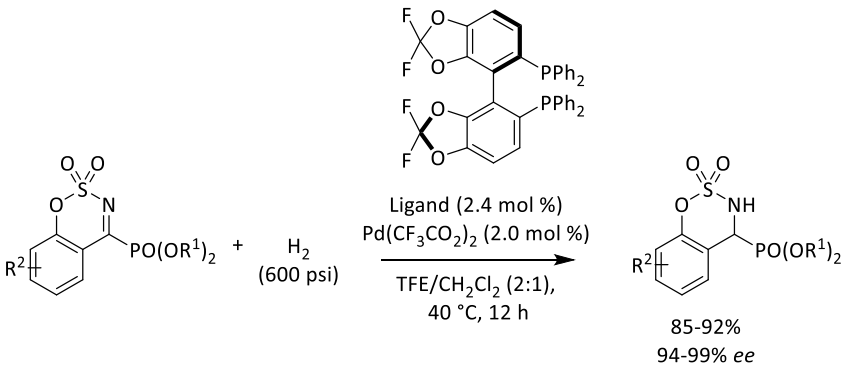
In 2008, Zhou and collaborators published their findings on the hydrogenation of cyclic cetimines using palladium as catalyst in the synthesis of cyclic sulphamidates (Scheme 2.18).[38] Optimized conditions were obtained and then applied to a series of ketone derived substituted benzoxathiazine-2,2-dioxides. 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, arylated substrates lead to better enantioselectivities (97-99% *ee*) than alkylated substrates (90-94% *ee*) in this enantioselective hydrogenation.



Scheme 2.18. Pd catalyzed enantioselective hydrogenation of benzoxathiazine-2,2-dioxides.

In 2016, the same research group published their findings on the enantioselective synthesis of α-aminophosphonates through Pd catalyzed hydrogenation of cyclic ketimine phosphonates (Scheme 2.19).[39] In a first stage, the researchers used a *N*-tosyl α-ketiminephosphonate, from which

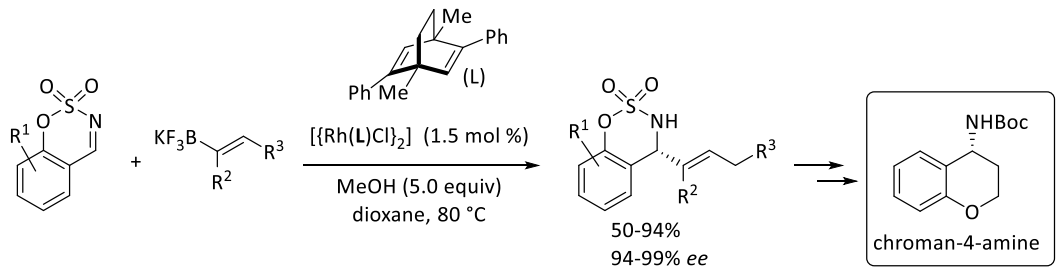
they carried out an easy synthesis of α-aminophosphonates. The hydrogenation of this kind of imine gives the best results under the following reaction conditions: $Pd(OCOCF_3)_2$/(*R*)-DifluorPhos as catalyst, trifluoroethanol/dichloromethane in a 2:1 proportion as solvent at 40 °C. These reaction conditions were then applied on differently substituted cyclic α-ketiminephosphonates derived from benzoxathiazine 2,2-dioxides, leading to excellent results both in yield (85-92%) as in enantioselectivity (94-99% *ee*).



Scheme 2.19. Enantioselective synthesis of α-aminophosphonates through Pd catalyzed hydrogenation.

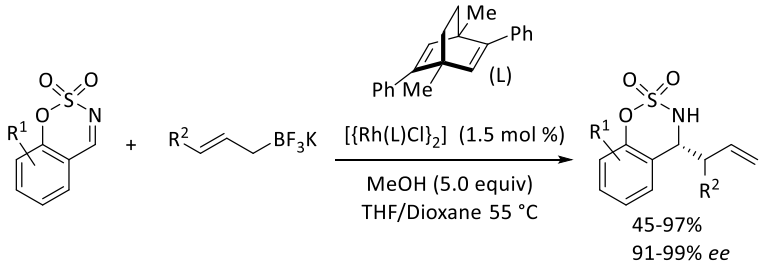
2.1.3.2. Catalytic enantioselective addition reactions of boron organometallic reagents to benzoxathiazine 2,2-dioxides

In 2012, Lam and collaborators described the first enantioselective Rh-catalyzed additions of alkenylboron compounds to cyclic imines (Scheme 2.20).[40] This is the first reaction described in which benzoxathiazine 2,2-dioxides function acts as electrophile in an asymmetric catalytic enantioselective reaction. The authors proved the importance of the constrained *Z*-geometry of the C=N bond of these imines on the enantioselectivity, testing *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 which does not allow the isomerization. With this substrate, they obtained the corresponding alkenylated amine with an excellent enantiomeric excess (98%) and with high yield in the presence of a diene as chiral ligand. Various alkenyltrifluoroborates 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*). A cyclic *N*-sulfonyl ketimine also proved to be an excellent substrate providing the corresponding chiral sultam in 68% yield and 90% *ee*. The utility of the final products was proven with various synthetic transformations such as a hydroboration/oxidation sequence leading to an alcohol. After treatment with $LiAlH_4$ and Boc protection a carbamate was obtained which can easily be transformed to chiral chroman-4-amine, a scaffold present in several drug candidates.



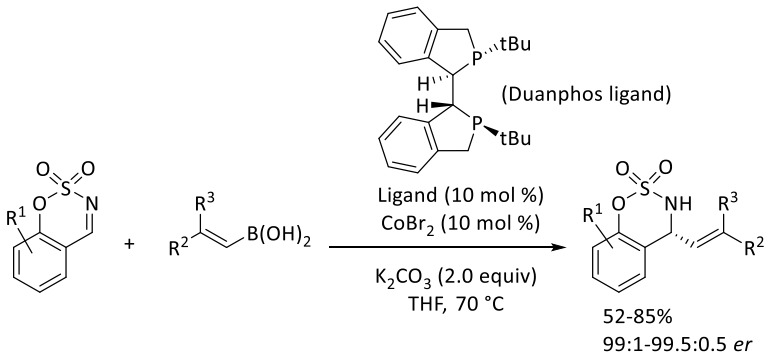
Scheme 2.20. Enantioselective Rh-catalyzed additions of alkenylboron compounds to cyclic benzoxathiazine 2,2-dioxides.

In the same year, the same research group described an enantioselective rhodium-catalyzed nucleophilic allylation of benzoxathiazine 2,2-dioxides with allylboron reagents (Scheme 2.21).[41] As already proven in the previous work, various acyclic imines did not proof to be useful in the reaction due to the low enatioselectivities obtained. However, the use of benzoxathiazine 2,2-dioxides in the reaction with potassium allyltrifluoroborate 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, resulting in good yields (45-97%) and excellent diastereoselective ratios (6:1-17:1) and enantioselectivities (91-99% *ee*). In 2013, the same research group published their further findings on the addition of highly substituted potassium allyltrifluoroborates on cyclic aldimines, obtaining similar results as described before.[42]



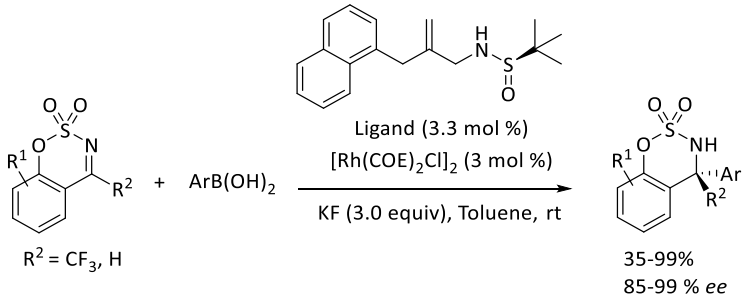
Scheme 2.21. Enantioselective rhodium-catalyzed nucleophilic allylation of benzoxathiazine 2,2-dioxides with allylboron reagents

In 2016, the Zhao group published their findings on the cobalt-catalyzed enantioselective vinylation of activated ketones and imines (Scheme 2.22).[43] The investigators used both cyclic and acyclic imines in the reaction with 2-phenyl vinylboronic acid, promoted by $CoBr_2$. Only the benzoxathiazine 2,2-dioxide aldimines resulted to be optimum substrates, leading to the final product in high yield (75%) and excellent enantiomeric ratio (99.5:0.5), using as the chiral ligand a duanphos ligand. The optimized reaction conditions were applied on different substituted cyclic imines and various vinyl boronic acids. The reactions resulted in good yields (52-85%) and excellent enantiomeric ratios (99:1-99.5:0.5).



Scheme 2.22. Cobalt-catalyzed enantioselective vinylation of benzoxathiazine 2,2-dioxide aldimines.

In 2013, the Xu group described a Rh-catalyzed highly enantioselective arylation of cyclic ketimines leading to the synthesis of tetrasubstituted carbon stereocenters (both sultams and sulfamidates) (Scheme 2.23).[44] They use sulfur-based olefin ligands to promote the enantioselectivity of the reaction. Xu and collaborators examined various new ligands and under optimized reaction conditions [$Rh(COE)_2Cl_2$ (3 mol %), ligand (3.3 mol %), KF (3.0 equiv) in toluene], the arylboronation reaction between *p*-anisylboronic and benzoxatiazine 2,2-dioxide aldimines and ketimines bearing a CF_3 leads to the corresponding final products in good yields (35-99%) and excellent enantioselectivities (85-99% *ee*).

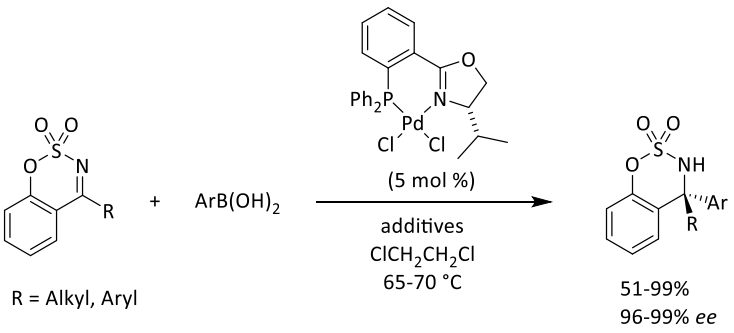


Scheme 2.23. Rh-catalyzed highly enantioselective arylation of cyclic imines.

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.[44, 45] The same reaction conditions were used and the products were obtained in excellent yields (96-99%) and enantioselectivities (97-99% *ee*).

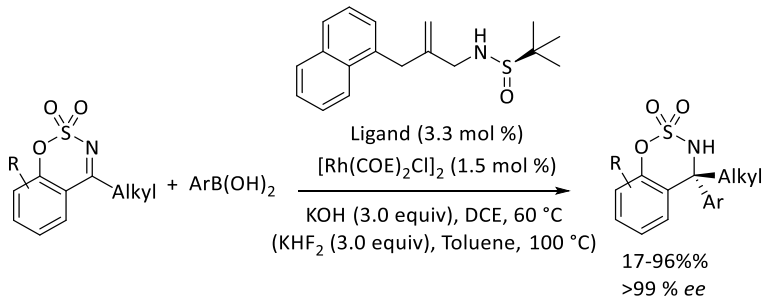
In 2014, Hayashi and collaborators described an asymmetric arylation of ketimines derived from benzoxathiazine 2,2-dioxides using a palladium phosphinooxazoline catalyst (Scheme 2.24).[46] Taking into account the results of Xu and collaborators in 2013,[44, 45] which described the arylation of *N*-sulfamidate aldimines and CF_3 substituted *N*-sulfamidate ketimines, Hayashi and coworkers proposed a new method for arylation of the less reactive alkyl and aryl *N*-sulfonyl ketimines. 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 *N*-sulfonyl aldimines and *N*-sulfonyl ketimines (methyl) led to excellent results both in yield as in enantiomeric excess (99% and 99.5% respectively). These optimized reaction conditions were then applied in the reaction between different arylboronic acids and *N*-sulfamidate ketimine (methyl), obtaining the corresponding products in good to high yields (51-99%) and excellent enantioselectivities (98-99% *ee*). Both the ethyl and the pentyl *N*-sulfamidate ketimines were used in the reaction with phenylboronic acid leading to the reaction products in good

yields and excellent enantioselectivities (99% *ee*). Finally, they also tested several aryl *N*-sulfonyl ketimines, which are less reactive than the alkyl ketimines, obtaining satisfying results both in yield as in enantioselectivity in the presence of a proton sponge.



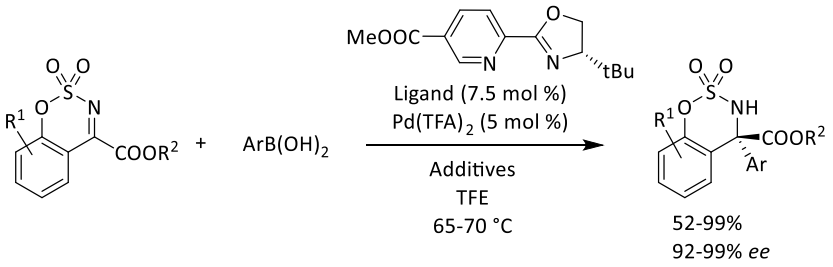
Scheme 2.24. Asymmetric arylation of cyclic ketimines using a palladium phosphinooxazoline catalyst.

A rhodium-catalyzed asymmetric arylation of cyclic alkyl ketimines in the synthesis of highly enantioriched tertiary amines was described by Xu in 2015 (Scheme 2.25).[47] With the use of the sulfur-based olefin ligand, already applied in the arylation of cyclic ketimines,[44] they were able to obtain α-aryl α-alkyl disubstituted benzosultams and benzosulfamidates with excellent enantioselectivities. After optimizing the reaction 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-dioxide alkylketimines. With a slight modification of the reaction conditions, they obtained, in the reaction between different substituted substrates and different arylboronic acids, variable yields (17-96%) and excellent enantioselectivities (≥99% *ee*).



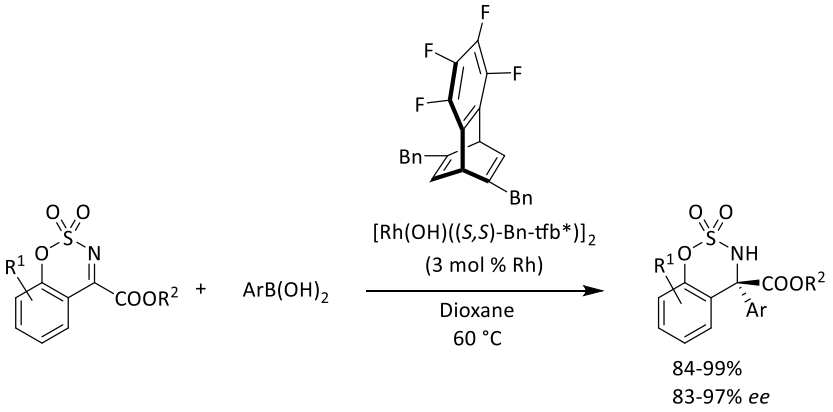
Scheme 2.25. Rhodium-catalyzed asymmetric arylation of cyclic ketimines.

The Zhang group published, in 2015, their findings on the asymmetric addition of arylboronic acids to cyclic *N*-sufamidate ketimine esters (Scheme).[48] 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 in the reaction with various arylboronic acids and differently substituted cyclic *N*-sufamidate ketimine esters, obtaining the α-aminoesters in good yields (52-99%) and excellent enantioselectivities (92-99% *ee*). 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.



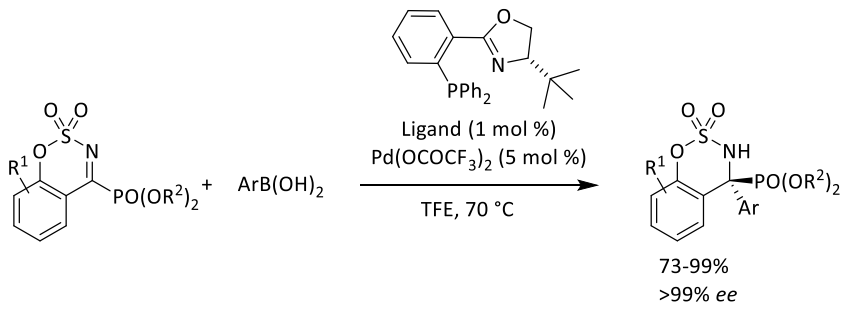
Scheme 2.26. Asymmetric addition of arylboronic acids to cyclic ketimine esters.

Some months later, Nishimura and Takedi 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 2.27).[49] The initial study focused on the addition of phenylboronic acid to the cyclic ketimine ethyl ester. 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 and arylboronic acids obtaining the corresponding products in excellent yields (84-99%) and enantioselectivities (83-97% *ee*).



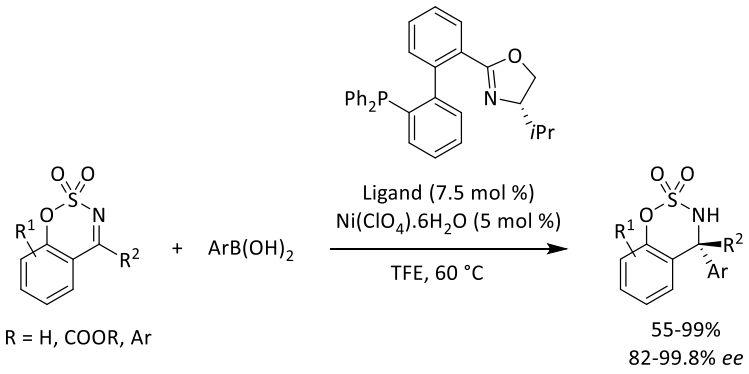
Scheme 2.27. Rhodium catalyzed asymmetric addition of arylboronic acids to cyclic ketimine esters

Recently, the Zhou group published their results on the Pd-catalyzed enantioselective arylation of cyclic α-ketiminephosphonates with arylboronic acids (Scheme 2.28).[50] 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, in trifluoroethanol (TFE) as solvent. These optimized reaction conditions were used in reactions with differently substituted cyclic α-ketiminephosphonates derived from benzoxathiazine-2,2-dioxide and various arylboronic acids, all of which led to the corresponding products with good yields (73-97%) and excellent enantioselectivities (>99% *ee*).



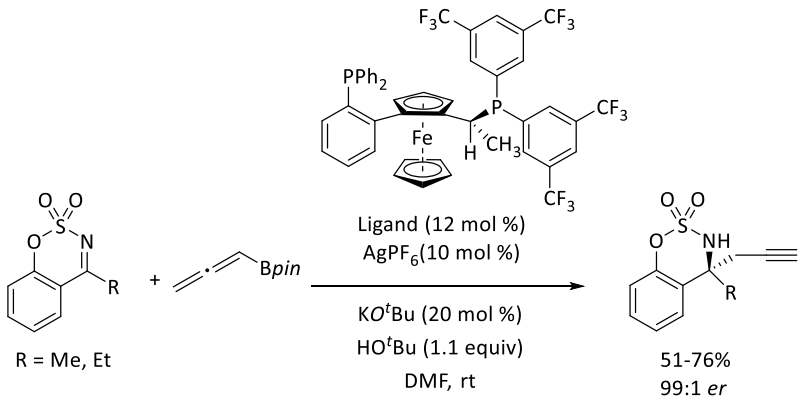
Scheme 2.28. Pd-catalyzed enantioselective arylation of cyclic α-ketiminephosphonates with arylboronic acids.

Very recently, Zhang and collaborators described a Ni(II)-catalyzed asymmetric addition of arylboronic acids to benzoxathiazine 2,2-dioxides (Scheme 2.29).[51] Under optimized conditions ($Ni(ClO_4)_2.6H_2O$/*tropos* phosphine-oxazoline biphenyl complex in trifluoroethanol as solvent at 60 °C), various arylboronic acids are tested in the reaction with cyclic aldimines, with excellent yields (77-99%) and enantioselectivities (82-97% *ee*). Furthermore, the authors amplified the scope by testing various aldimines and ester and aryl ketimines, resulting in good yields (55-99%) and excellent enantioselectivities (92-99.8% *ee*).



Scheme 2.29. Ni(II)-catalyzed asymmetric addition of arylboronic acids to benzoxathiazine 2,2-dioxides

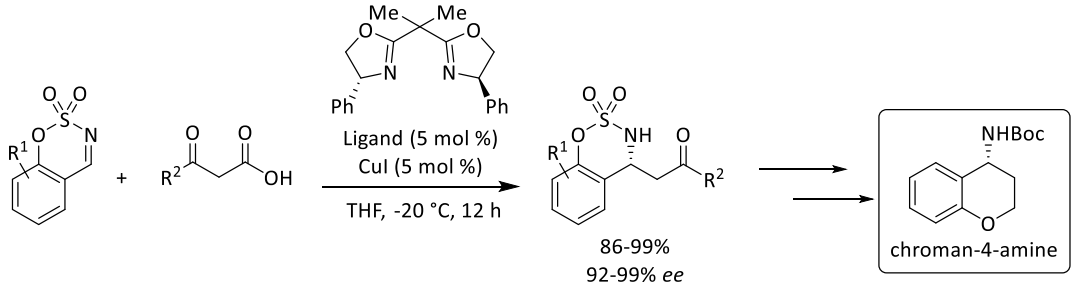
In 2015, the Jarvo group described a silver-catalyzed enantioselective propargylation reaction of *N*-sulfonyl ketimines (Scheme 2.30).[52] Upon optimization of the reaction conditions, they were able to obtain a homopropargylic amine in a good yield and excellent enantiomeric ratio (99:1) through the reaction between allenylboronic acid pinacol ester and a cyclic five membered *N*-sulfonyl ketimine using silver in the presence of a Walphos ligand as catalyst. The same reaction conditions were applied on the reaction between allenylboronic acid pinacol ester and different cyclic alkyl ketimines derived from benzoxathiazine 2,2-dioxides, which are less reactive, obtaining the corresponding products in good yields (51-76%) and excellent enantiomeric ratios (99:1).



Scheme 2.30. Silver-catalyzed enantioselective propargylation reaction of *N*-sulfonyl and sulfamidate ketimines.

2.1.3.3. Catalytic enantioselective Mannich reactions of benzoxathiazine 2,2-dioxides

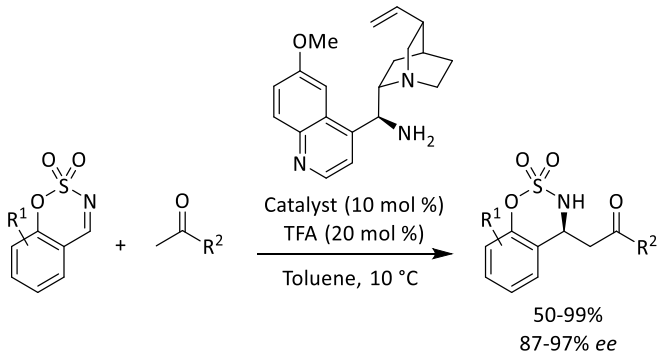
In 2014, Ma and collaborators published their findings on the Cu-catalyzed decarboxylative Mannich reaction of β-ketoacids with benzoxathiazine-2,2-dioxides as electrophiles (Scheme 2.31).[53] This decarboxylative Mannich reaction is an alternative pathway to the synthesis of β-aminoketones. Upon optimization, 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 reation to various differently substituted benzoxathiazine 2,2-dioxides and various aromatic and aliphatic β-ketoacids, led to excellent yields (86-99%) an enantioselectivities (92-99% *ee*). Through a series of synthetic transformations, the obtained products can lead to chroman-4-amines without loss of optical purity.



Scheme 2.31. Cu-catalyzed decarboxylative Mannich reaction of β-ketoacids with benzoxathiazine-2,2-dioxides

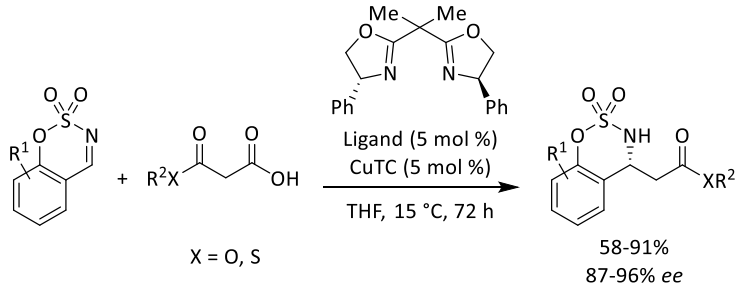
In the same year, Zhang and collaborators described an organocatalytic direct Mannich reaction of alkyl methyl ketones with cyclic benzoxathiazine 2,2-dioxides (Scheme 2.32).[54] The reaction conditions were optimized in the reaction between acetone and benzoxathiazine-2,2-dioxide and the best results were obtained when the reaction was catalyzed by a 10 mol % of a *Cinchona* alkaloid 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-dioxide and different alkyl methyl ketones, leading to 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 with cyclic imines with *Cinchona* alkaloid based primary amines.[55] 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 imines and various aryl methyl ketones leading to the corresponding products with good yields (32-99%) and enantioselectivities (89-98% *ee*).



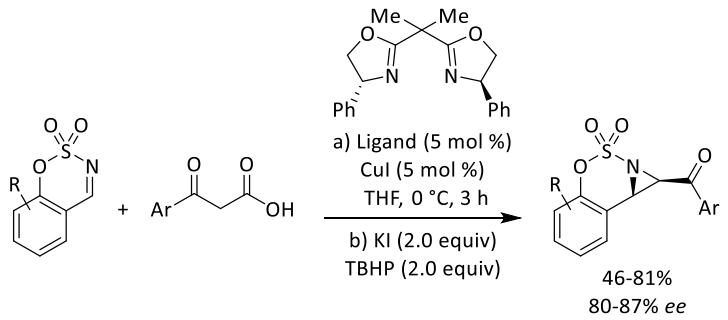
Scheme 2.32. Organocatalytic Mannich reaction of alkyl methyl ketones with cyclic benzoxathiazine 2,2-dioxides

Also in 2016, Ma and collaborators described a catalytic asymmetric decarboxylative Mannich reaction of malonic acid half esters with cyclic aldimines derived from benzoxathiazine 2,2-dioxides (Scheme 2.33).[56] As a model reaction, the authors used the reaction between benzoxathiazine 2,2-dioxides and a malonic acid half ester. 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, leading to an extended scope with good yields (72-91%) and enantioselectivities (87-96% *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*).



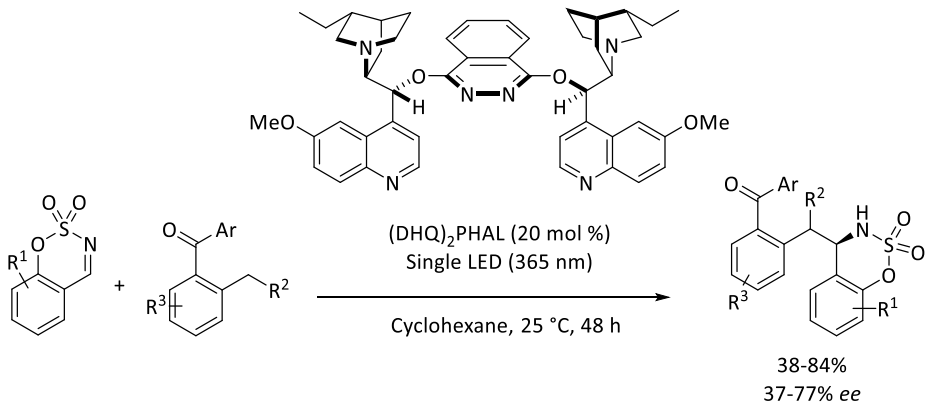
Scheme 2.33. Catalytic asymmetric decarboxylative Mannich reaction of malonic acid half esters with cyclic aldimines.

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 of cyclic imines with β-ketoacids (Scheme 2.34).[57] The researchers observed that the reaction between cyclic imines derived from benzoxathiazine 2,2-dioxides and β-ketoacids in the presence of KI and TBHP (*tert*-butylhydroperoxide) in THF at room temperature gives rise to the synthesis to racemic fused aziridines in moderate to good yields (46-78%). The researchers were able to make this reaction also in an enantioselective way, however the treatment of an enantiopure intermediate product (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 was obtained in moderate to good yield (46-81%) and good enantioselectivity (80-87% *ee*).



Scheme 2.34. One-pot enantioselective synthesis of fused aziridines.

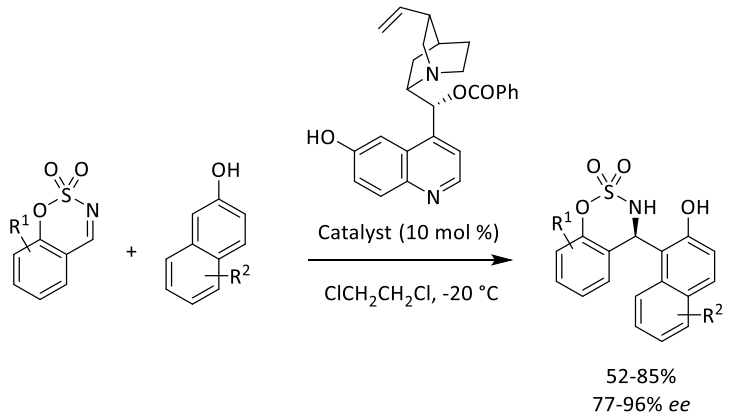
Recently, Melchiorre and collaborators have described a light-triggered enantioselective organocatalytic Mannich type reaction with cyclic imines derived from benzoxathiazine 2,2-dioxides (Scheme 2.35).[58] By photochemical reaction of 2-alkylbenzophenones, a hydroxy-*o*-quinodimethane was generated, which would react with cyclic imines in the presence of an organocatalyst to give rise to a [4+2] cycloaddition. However, the researchers observed only a Mannich type reaction. The presence of a dimeric *Cinchona* alkaloid derivative $(DHQ)_2PHAL$ (after optimization), led to the Mannich product in good yield (82%) and enantioselectivity (72% *ee*). The optimized reaction conditions were applied to the reaction between differently substituted cyclic imines and various 2-alkylbenzophenones leading to the corresponding products in moderate to good yields (38-84%) and enantioselectivities (37-77% *ee*).



Scheme 2.35. Light-triggered enantioselective organocatalytic Mannich type reaction with cyclic imines.

2.1.3.4. Catalytic enantioselective aza-Friedel-Crafts reactions of benzoxathiazine 2,2-dioxides

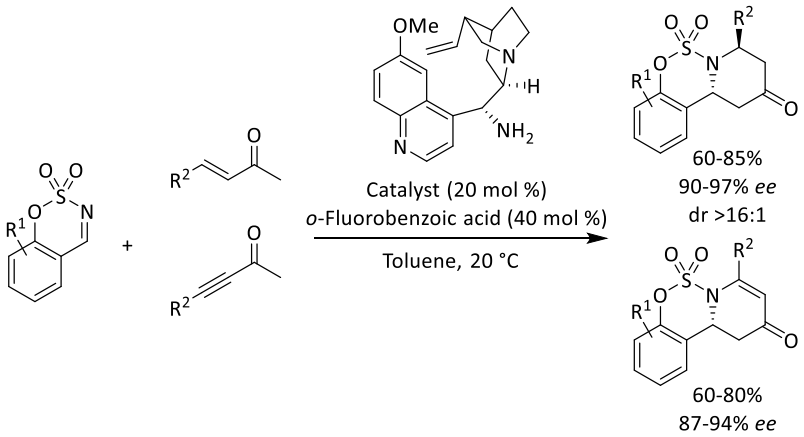
In 2014, our research group described an organocatalytic enantioselective aza-Friedel-Crafts reaction of 2-naphthols with cyclic imines derived from benzoxathiazine-2,2-dioxides (Scheme 2.36).[59] The optimized conditions of the reaction were the following: addition of 2-naphthols in the presence of 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-naphthol and sesamol to differently substituted benzoxathiazine-2,2-dioxides, leading to the corresponding products with good yields (52-85%) and enantioselectivities (77-96% *ee*).



Scheme 2.36. Organocatalytic enantioselective aza-Friedel-Crafts reaction of 2-naphthols with cyclic imines.

2.1.3.5. Catalytic enantioselective [4+2] cycloaddition reactions of benzoxathiazine 2,2-dioxides

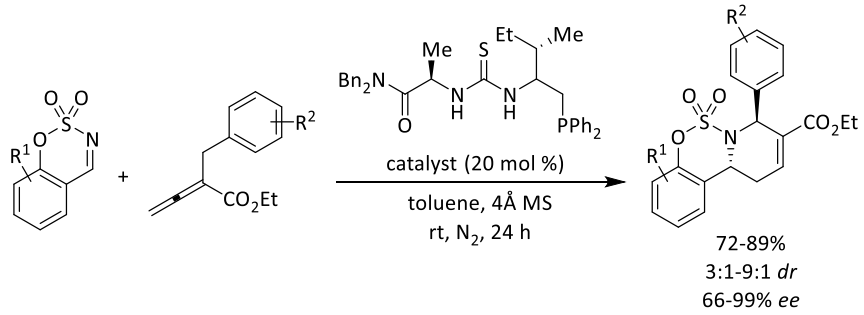
In 2013, Kang and collaborators described the enantioselective [4+2] cycloaddition of cyclic imines with acyclic enones or ynones leading to sulfamidate-fused 2,6-disubstituted piperidin-4-ones (Scheme 2.37).[60] The reaction conditions were optimized in the reaction between benzoxathiazine 2,2-dioxide 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 and various enones, leading to the [4+2] cycloaddition products 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 and ynones, leading to 2,6-disubstituted 2,3-dihydropyridin-4(1*H*)-ones in good yields (60-80%) and enantioselectivities (87-94% *ee*).



Scheme 2.37. Enantioselective [4+2] cycloaddition of cyclic imines and acyclic enones or ynones.

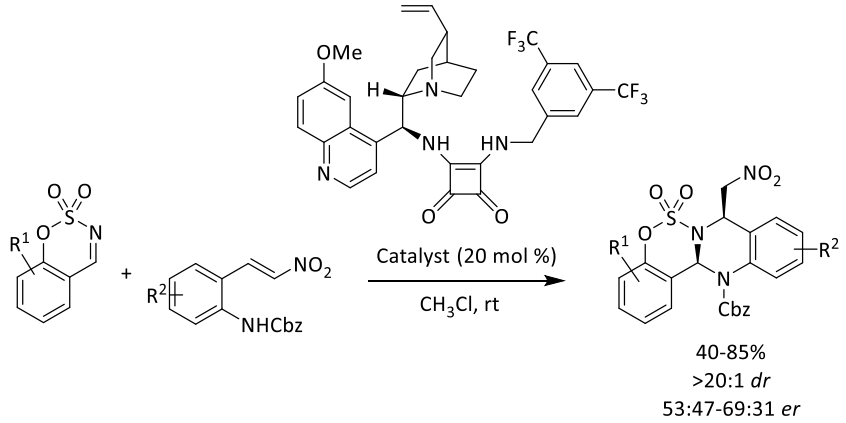
In the same year, Guo and collaborators described the phosphine catalyzed [4+2] cycloaddition of cyclic imines with allenoates (Scheme 2.38).[61] In the first part of the publication, the researchers focused on the non-enantioselective [4+2] cycloaddition with PPh_3 of various α-substituted allenoates and differently substituted benzoxathiazine 2,2-dioxides, obtaining the cycloaddition products in good to excellent yields (45-98%). In the second part, the researchers

investigated 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 with good yields (72-89%), moderate diastereomeric ratio (3:1-9:1) and good to excellent enantioselectivities (66-99% *ee*).



Scheme 2.38. Phosphine catalyzed [4+2] cycloaddition of cyclic imines with allenoates.

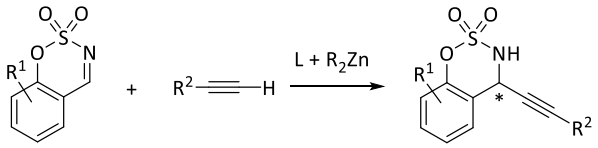
In 2016, Kim and collaborators described the stereoselective synthesis of a benzosulfamidate-fused tetrahidroquinazoline scaffold via an organocatalytic [4+2] cycloaddition of 2-amino-β-nitrostyrenes with cyclic imines (Scheme 2.39).[62] At first , the investigators performed the non-enantioselective 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 ligand, leading to the corresponding products in good yields (40-85%), excellent diastereomeric ratios (>20:1) and low enatiomeric ratios (53:47-69:31).



Scheme 2.39. Organocatalytic [4+2] cycloaddition of 2-amino-β-nitrostyrenes with cyclic imines.

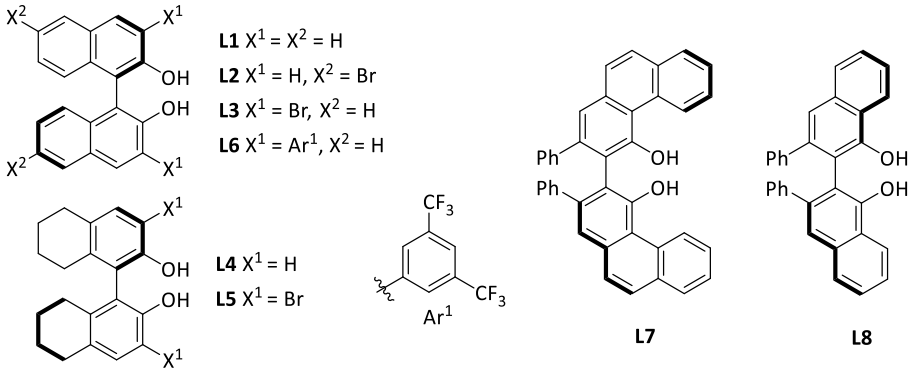
2.2. OBJETIVOS

El objetivo general de este capítulo es el desarrollo de un método catalítico y enantioselectivo de adición de alquinos terminales a aldiminas cíclicas derivadas de salicilaldehidos (2,2-dióxido benzoxatiazinas) que transcurra con buenos rendimientos y excesos enantioméricos.



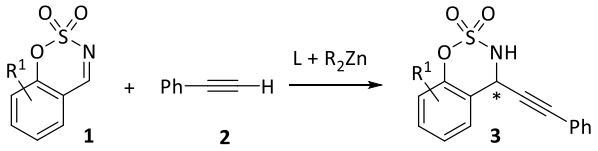
En el estudio de este primer proyecto se considerarán los siguientes aspectos:

1. Influencia de la estructura de diversos ligandos de tipo (*R*)-BINOL (**L1**-**L6**), (*R*)-VAPOL (**L7**) y (*R*)-VANOL (**L8**) sobre el rendimiento y la enantioselectividad de la reacción.

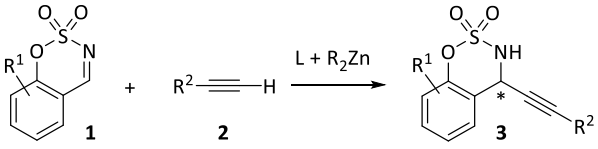


2. La influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn), número de equivalentes de dialquilzinc, disolvente, temperatura de reacción y número de equivalentes de alquino.

3. Evaluación de diversas aldiminas cíclicas del tipo 2,2-dióxido benzoxatiazina con diferente naturaleza electrónica y estérica en la reacción de alquinilacion con fenilacetileno.



4. Evaluación de distintas aldiminas cíclicas del tipo 2,2-dióxido benzoxatiazina en la reacción con diferentes alquinos terminales que presentan sustituyentes con distinta naturaleza electrónica y estérica.



5. Evaluación de distintas transformaciones sintéticas basadas en la reactividad del triple enlace y del grupo sulfamidato presente en los productos de alquinilación sin pérdida de pureza óptica.

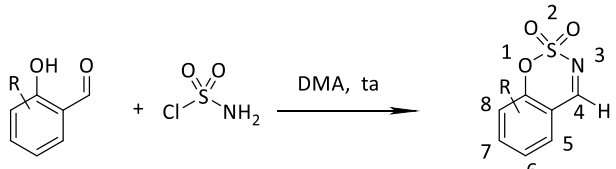
6. Determinación de la configuración absoluta del centro estereogénico presente en las aminas propargílicas quirales obtenidas.

2.3. RESULTADOS Y DISCUSIÓN

2.3.1. Síntesis de 2,2-dióxido benzoxatiazinas

Las iminas cíclicas con esqueleto de 2,2-dióxido benzoxatiazina han sido preparadas a partir de aldehídos salicílicos comerciales y clorosulfonilamina, preparada *in situ* a partir de isocianato de clorosulfonilo, a temperatura ambiente utilizando como disolvente *N,N*-dimetilacetamida (DMA). Los resultados se encuentran recogidos en la tabla 1. Este procedimiento fue descrito por el grupo de Lam en 2012.[40] Como se puede apreciar en la tabla, todas las iminas se obtuvieron con rendimientos moderados, excepto la imina **1a** la cual se obtuvo con un 85% de rendimiento. Las iminas se pueden purificar mediante cromatografía de columna, sin experimentar descomposición por hidrólisis.

Tabla 2.1. Síntesis de 2,2-dióxido benzoxatiazinas.



4 **5** **1**

Entrada	4	R	t (h)	1	R (%)[a]
1	**4a**	H	18	**1a**	85
2	**4b**	6-Me	18	**1b**	41
3	**4c**	6-^{t}Bu	18	**1c**	49
4	**4e**	6-Br	18	**1e**	60
5	**4f**	8-Me	18	**1f**	53
6	**4g**	8-^{t}Bu	18	**1g**	42

[a] Rendimiento tras purificación por cromatografía de columna.

2.3.2. Optimización de las condiciones de la reacción

Para abordar el proceso de optimización de la reacción de alquinilación de aldiminas cíclicas se escogió la reacción entre la 2,2-dióxido benzoxatiazina (**1a**) y fenilacetileno (**2a**). Inicialmente se tomaron como referencia las condiciones optimizadas para la alquinilación enantioselectiva de *N*-tosiliminas publicada previamente por nuestro grupo.[17] Este procedimiento consiste en la adición de una disolución de Me_2Zn 2 M en tolueno sobre fenilacetileno. Tras una hora de agitación, se adiciona una disolución de (*R*)-BINOL (**L1**) en tolueno y, transcurridos 15 minutos, se añade la aldimina cíclica **1a** (Procedimiento A, Figura 2.3). No obstante, el producto de alquinilación se obtuvo con rendimiento moderado (61%) y prácticamente racémico (4% *ee*). Por ello, decidimos modificar el procedimiento experimental y para ello nos basamos en el procedimiento descrito por nuestro grupo en 2012 para la alquinilación enantioselectiva de α-amido sulfonas.[32] El nuevo procedimiento (Procedimiento B, Figura 2.3) consistía en añadir la disolución de Et_2Zn sobre una disolución de fenilacetileno y (*R*)-BINOL (**L1**) en diclorometano. Tras una hora de agitación se añadía la aldimina cíclica a 0 °C. El producto de alquinilación se obtuvo con un rendimiento inferior (41%), pero una enantioselectividad más elevada (30% *ee*).

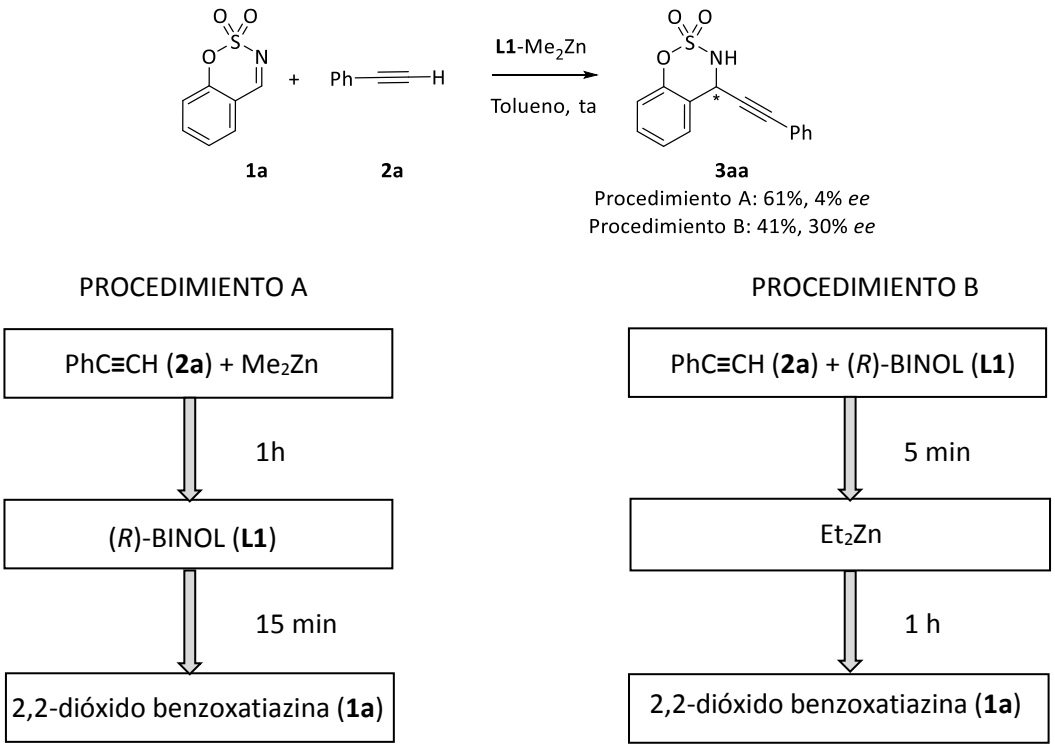
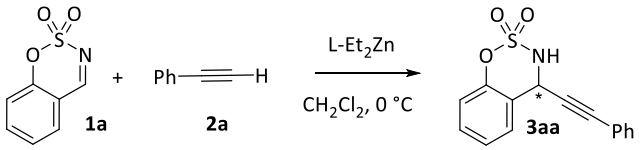


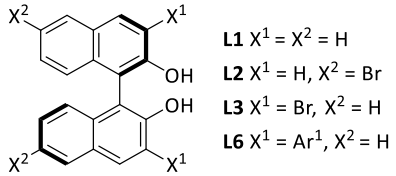
Figura 2.3. Procedimientos experimentales A y B.

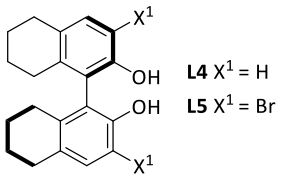
Debido a que la aplicación de este último procedimiento condujo a una enantioselectividad más elevada que la obtenida en el procedimiento A, comenzamos el proceso de optimización ensayando un conjunto de ligandos en presencia de 3 equivalentes de Et_2Zn (1 M en hexano) empleando diclorometano como disolvente a 0 °C (Tabla 2.2).

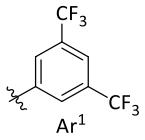
Los resultados revelaron que la utilización de ligandos de tipo BINOL con átomos de bromo en las posiciones 3,3' (**L2**) o 6,6' (**L3**), así como los ligandos octahidrogenados **L4** y **L5** proporcionaron enantioselectividades muy bajas (Tabla 2.2, entradas 2-5). Además, un mayor incremento de impedimento estérico de los sustituyentes en las posiciones 3,3' condujo a un exceso enantiomérico del 15% (Tabla 2.2, entrada 6). Debido a que la utilización de ligandos de tipo BINOL no condujo a resultados satisfactorios, ensayamos la reacción en presencia de un ligando de tipo VAPOL (**L7**), con el cual se obtuvo el correspondiente producto de alquinilación con un rendimiento moderado, pero una enantioselectividad del 78% *ee* (Tabla 2.2, entrada 7). Por último, se evaluó la utilización de (*R*)-VANOL (**L8**) (Tabla , entrada 8) obteniéndose un rendimiento mayor pero una enantioselectividad inferior (Tabla , entrada 8).

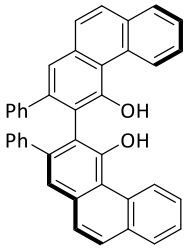
Tabla 2.2. Adición enantioselectiva de fenilacetileno (**2a**) a 2,2-dióxido benzoxatiazina (**1a**) utilizando Et_2Zn en diclorometano a 0 °C. Evaluación de diferentes ligandos de tipo BINOL.[a]



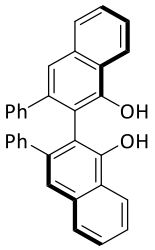








L7



L8

Entrada	Ligando	t (h)	R (%)[b]	*ee* (%)[c]
1	**L1**	3	41	30
2	**L2**	2	57	3
3	**L3**	2	60	6
4	**L4**	4	32	4
5	**L5**	2	61	3
6	**L6**	2	68	15
7	**L7**	3	38	-78
8	**L8**	2	65	-54

[a] **1a** (0,090 mmol), **2a** (0,650 mmol), 2 M Et_2Zn en hexano (0,270 mmol), **L1-L8** (0,018 mmol). [b] Rendimiento tras la cromatografía de columna. [c] Determinado mediante HPLC usando fases estacionarias quirales.

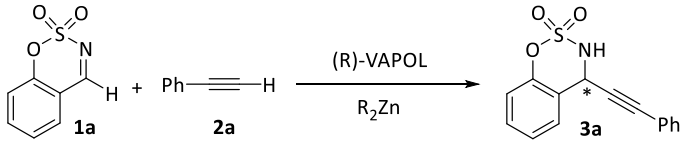
Una vez identificado el ligando **L7** como el que proporcionaba los mejores resultados entre los ligandos examinados, continuamos el proceso de optimización ensayando la reacción con diferentes reactivos de dialquilzinc y disolventes a varias temperaturas (Tabla 2.3).

La utilización de Me_2Zn en lugar de Et_2Zn dio lugar a un valor de exceso enantiomérico similar, pero se incrementó el rendimiento de la reacción hasta el 84% (Tabla 2.3, entrada 2). A continuación evaluamos el efecto de varios disolventes sobre el rendimiento y la enantioselectividad (Tabla 2.3, entrada 2-4). Se observó que la utilización de tolueno como disolvente proporcionó el producto de alquinilación con un 73% de rendimiento y 80% de exceso enantiomérico (Tabla 2.3, entrada 3). El uso de dicloroetano condujo a los mejores resultados en términos de rendimiento (88%) y enantioslectividad (82% *ee*) (Tabla 2.3, entrada 4). Por ello, continuamos el proceso de optimización utilizando dicloroetano como disolvente.

Cuando redujimos la cantidad de Me_2Zn hasta 1,5 equivalentes, observamos un aumento del rendimiento de la reacción, pero la enantioselectividad disminuyó notablemente (Tabla 2.3, entrada 5). Por otra parte, un aumento hasta 4 equivalentes condujo a una ligera mejora de la enantioselectividad (Tabla 2.3, entrada 6). Por último, la adición de 6 equivalentes de Me_2Zn dio lugar a un valor de exceso enantiomérico de 85%; sin embargo, se observó un descenso del rendimiento de la reacción (Tabla 2.3, Entrada 7).

En cuanto a la temperatura, una disminución a -20 °C resultó en un detrimento del rendimiento y la enantioselectividad, mientras que cuando se llevó a cabo la reacción tanto a 10 °C como a temperatura ambiente, se observaron resultados comparables a los obtenidos a 0 °C (Tabla 2.3, entradas 9-10). Así pues, decidimos escoger la temperatura ambiente como temperatura óptima de reacción. Finalmente, conseguimos reducir la cantidad de fenilacetileno de 7,2 a 4 equivalentes manteniendo tanto el rendimiento como la enantioselectividad de la reacción (Tabla 2.3, Entrada 11).

Tabla 2.3. Adición enantioselectiva de fenilacetileno (**2a**) a 2,2-dióxido benzoxatiazina (**1a**). Evaluación de reactivos de dialquilzinc, equivalentes de dialquilzinc, disolvente, temperatura de reacción y equivalentes de alquino.[a]



1a **2a** **3a**

Entrada	R_2Zn	Equiv	Equiv 2a	Disolvente	t (h)	T (°C)	R (%)[b]	*ee* (%)[c]
1	Et_2Zn	3	7,2	CH_2Cl_2	4	0	38	78
2	Me_2Zn	3	7,2	CH_2Cl_2	2	0	84	75
3	Me_2Zn	3	7,2	Tolueno	3	0	73	80
4	Me_2Zn	3	7,2	$ClCH_2CH_2Cl$	2	0	88	82
5	Me_2Zn	1,5	7,2	$ClCH_2CH_2Cl$	2	0	95	59
6	Me_2Zn	4	7,2	$ClCH_2CH_2Cl$	2	0	84	83
7	Me_2Zn	6	7,2	$ClCH_2CH_2Cl$	3	0	62	85
8	Me_2Zn	4	7,2	$ClCH_2CH_2Cl$	3	-20	62	77
9	Me_2Zn	4	7,2	$ClCH_2CH_2Cl$	2	10	86	83
10	Me_2Zn	4	7,2	$ClCH_2CH_2Cl$	2	ta	89	83
11	Me_2Zn	4	4	$ClCH_2CH_2Cl$	2	ta	89	82

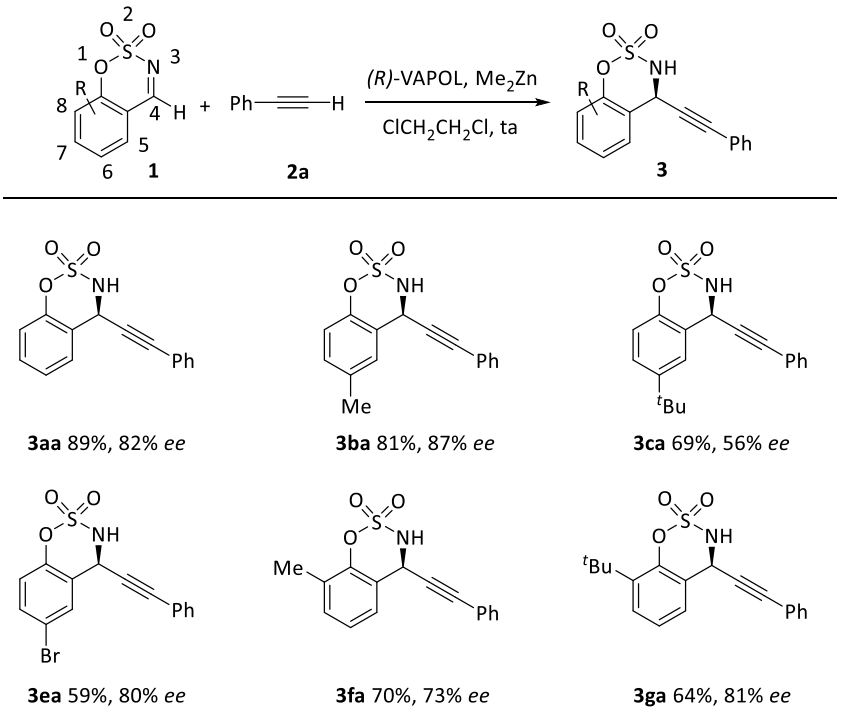
[a] **1a** (0,090 mmol), (*R*)-VAPOL (0,018 mmol). [b] Rendimiento tras purificación por cromatografía de columna. [c] Determinado mediante HPLC usando fases estacionarias quirales.

2.3.3. Alcance y limitaciones de la reacción

En el estudio del alcance y limitaciones de la reacción, se aplicaron las condiciones optimizadas para la reacción entre 2,2-dióxido benzoxatiazina (**1a**) y fenilacetileno (**2a**) a distintas 2,2-dióxido benzoxatiazinas y alquinos terminales.

2.3.3.1. Evaluación de distintas 2,2-dióxido benzoxatiazinas

En primer lugar se evaluó la reacción entre varias 2,2-dióxido benzoxatiazinas diferentemente sustituidas (**1a**-**1c**, **1e**-**1g**) y fenilacetileno (**2a**). Los resultados se pueden observar en el esquema 2.40.



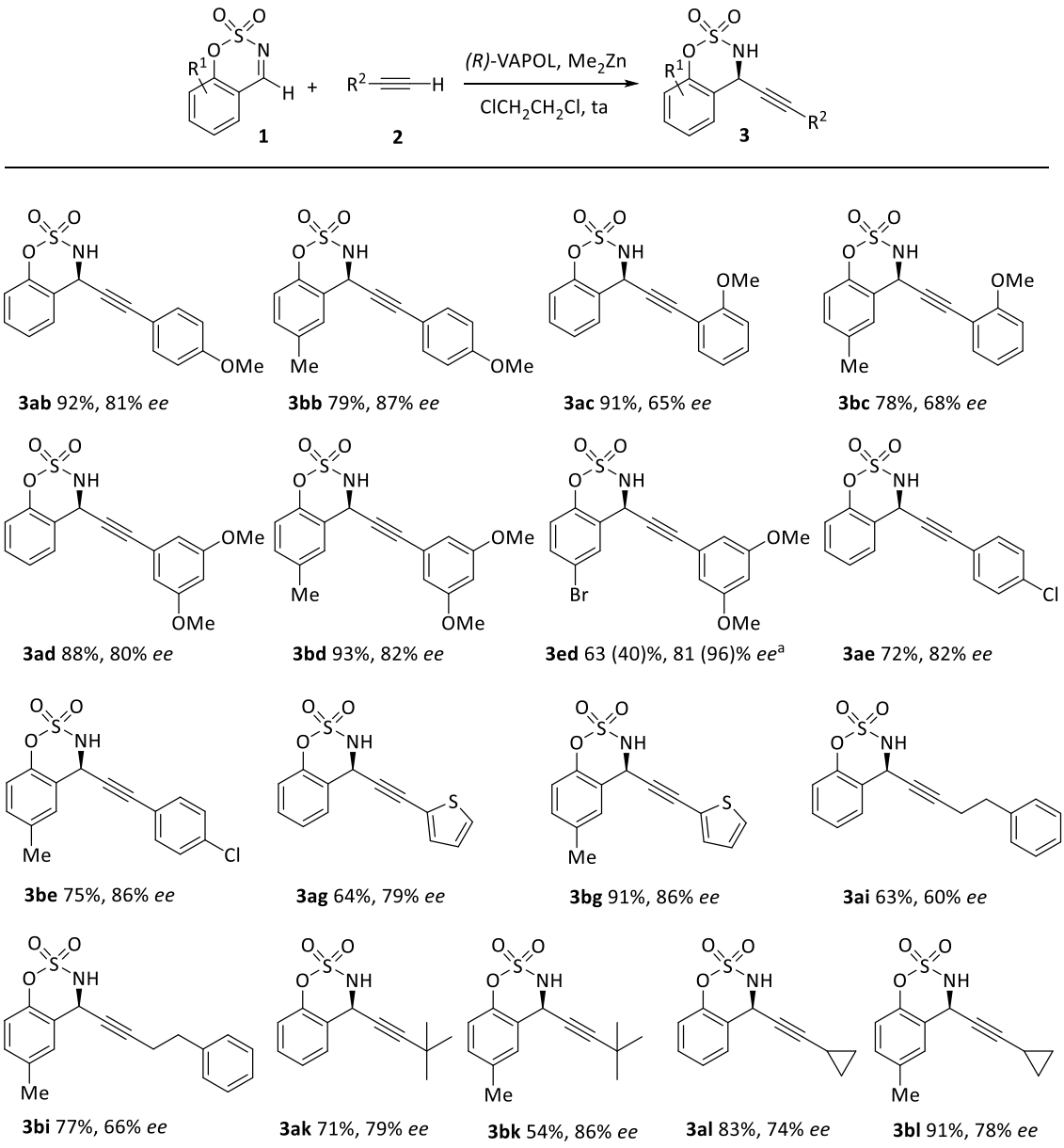
Esquema 2.40. Adición enantioselectiva de fenilacetileno (**2a**) a 2,2-dióxido benzoxatiazinas con (*R*)-VAPOL y Me_2Zn. **1** (0,090 mmol), **2a** (0,360 mmol), 2 M Me_2Zn en tolueno (0,360 mmol), (*R*)-VAPOL (0,018 mmol). Rendimiento tras la cromatografía de columna. Exceso enatiomérico determinado mediante HPLC usando fases estacionarias quirales.

Como se puede observar en el esquema 2.40, la presencia de un grupo electrón-donante poco voluminoso (Me) en la posición 6 de la benzoxatiazina conduce al producto de alquinilación con buen rendimiento y una enantioselectividad elevada del 87% *ee* (**3ba**). Sin embargo, la presencia del mismo grupo en posición 8 del anillo aromático produce una disminución de la enantioselectividad (73% *ee*, **3fa**). La presencia de un grupo alquilo voluminoso (*terc*-butilo) en la posición 6 del anillo da lugar al producto de alquinilación con un buen rendimiento, pero un moderado exceso enantiomérico del 56% (**3ca**), mientras que la presencia del mismo grupo voluminoso en posición 8 conduce al producto de adición con buen rendimiento y con buena enantioselectividad de 81% *ee* (**3ga**). Es decir, se observa una gran influencia estérica de los sustituyentes situados en la posición 6 del anillo.

También se ensayó la reacción de alquinilación con una benzoxatiazina con un grupo electrón-aceptor en posición 6 (Br), con la que se obtuvo un 59% de rendimiento y 80% *ee* (**3ea**)

2.3.3.2. Evaluación de distintos alquinos terminales

La aplicabilidad de esta reacción se ensayó también con distintos alquinos aromáticos, heteroaromáticos y alifáticos proporcionando buenos rendimientos y excesos enantioméricos elevados (Esquema 2.41). Este estudio se llevó a cabo con tres 2,2-dióxido benzoxatiazinas **3a**,**3b** y **3e**.



Esquema 2.41. Adición enantioselectiva de diferentes alquinos terminales **2** a varias 2,2-dióxido benzoxatiazinas **1** con (*R*)-VAPOL y Me_2Zn. **1** (0,090 mmol), **2** (0,360 mmol), 2 M Me_2Zn en tolueno (0,360 mmol), (*R*)-VAPOL (0,018 mmol). Rendimiento tras la cromatografía de columna. Determinado mediante HPLC usando fases estacionarias quirales. [a] Exceso enatiomérico tras cristalización.

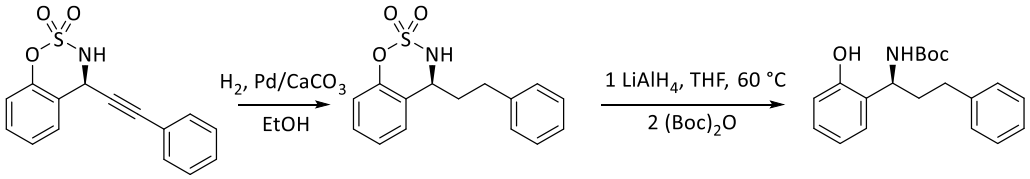
Se examinaron diferentes alquinos aromáticos terminales con sustituyentes electrón-donantes y aceptores (Esquema 2.41). La presencia de grupos electrón-donantes (MeO) da lugar a los productos de alquinilación con rendimientos elevados al torno al 90%. Se puede observar que la presencia del grupo MeO en las posiciones *para* (**3ab** y **3bb**) o *meta* (**3ad**, **3bd** y **3ed**) del anillo aromático del alquino conduce a los productos resultantes con buenas enantioselectividades (80-82% *ee*). Sin embargo, la presencia del mismo grupo en *orto* (**3ac** y **3bc**) provoca una disminución de la enantioselectividad (65-68% *ee*). También se ensayó un alquino con un grupo electrón-aceptor (Cl) en la posición *para* del anillo aromático, obteniéndose los productos correspondientes (**3ae** y **3be**) con buenos rendimientos (72-75%) y buenas enantioselectividades (82-86% *ee*).

Cuando se llevó a cabo la reacción utilizando un alquino heteroaromático, se obtuvieron los productos de alquinilación (**3ag** y **3bg**) con buenas enantioselectividades (79-86% *ee*) y buenos rendimientos (64-91%).

Por último, se evaluaron tres alquinos alifáticos (**2i**, **2k**, **2l**). La adición de un alquino unido a carbono primario dio lugar a los correspondientes productos de alquinilación con enantioselectividades moderadas (60-66% *ee*). La adición de ciclopropilacetileno condujo a una enantioselectividad superior (74-78% *ee*) y, finalmente, la reacción con 3,3-dimetil-1-butino dio lugar a los correspondientes productos de alquinilación (**3ak**, **3bk**) con excesos enantioméricos del 79% *ee* y del 86% *ee* respectivamente.

2.3.4. Transformaciones sintéticas

Con el producto de alquinilación **3aa** llevamos a cabo distintas transformaciones sintéticas. En primer lugar se llevó a cabo una hidrogenación del triple enlace con $Pd/CaCO_3$ obteniéndose el producto **6** con un buen rendimiento de 93% y con mantenimiento de la pureza óptica (Esquema 2.42). Además tratamos el producto **6** con $LiAlH_4$ seguido de una protección en forma de Boc (*terc*-butiloxicarbonilo), lo cual nos permitió obtener el producto **7** con un buen rendimiento y sin pérdida de pureza óptica.[42]



3aa 83% *ee* **6** 93%, 80% *ee* **7** 84%, 80% *ee*

Esquema 2.42. Transformaciones sintéticas del producto de alquinilación **3aa**.

2.3.5. Determinación de la configuración absoluta

Por cristalización del compuesto **3ed** pudimos obtener una muestra adecuada para el estudio por difracción de Rayos X de monocristal, lo cual nos permitió determinar su configuración absoluta. El carbono esterogénico presenta configuración *(S)* (parámetro de Flack: 0.010(8)) (Figura 2.4). La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

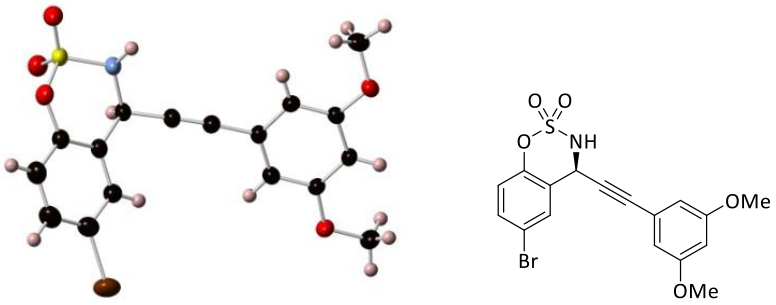
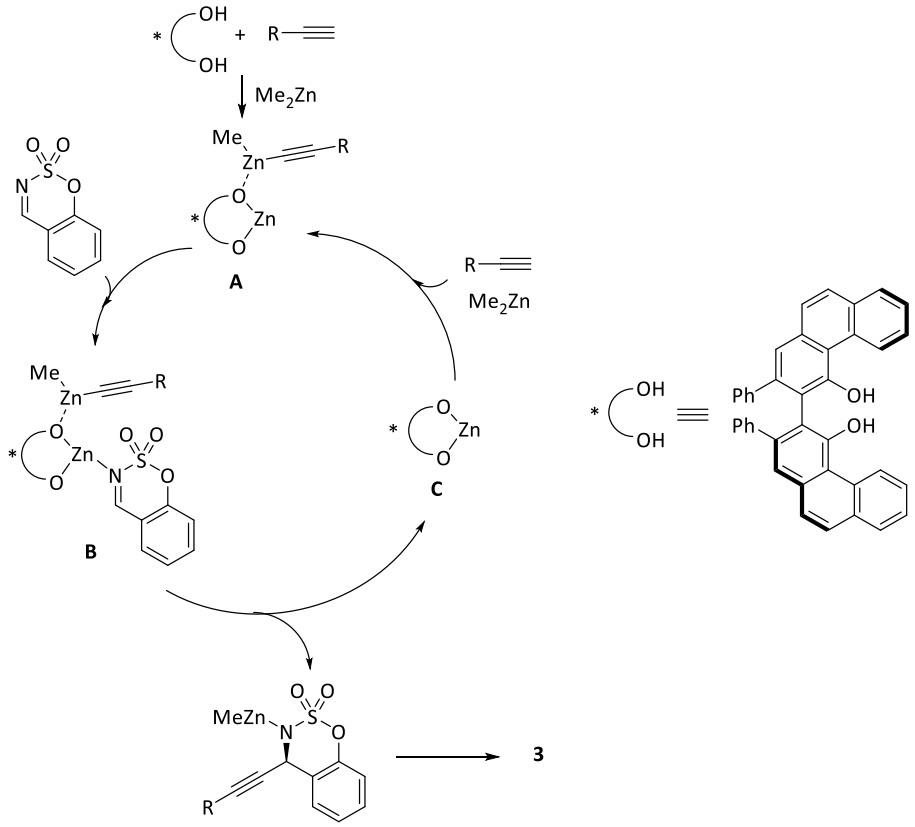


Figura 2.4. Configuración absoluta determinada por difracción de rayos X del compuesto **3ed**.

2.3.6. Propuesta mecanística para la alquinilación de 2,2-dióxido benzoxatiazinas catalizada por complejos de (*R*)-VAPOL-Zn

El esquema 2.43 muestra un posible mecanismo para la reacción de alquinilación de 2,2-dióxido benzoxatiazinas catalizada por complejos de (*R*)-VAPOL-Zn. En primer se produce la desprotonación del ligando VAPOL y del acetileno por parte del dimetilzinc, lo cual da lugar al complejo **A** (VAPOL zincato-metilalquinilzinc). Este complejo **A** se coordina con la imina cíclica (2,2-dióxido benzoxatiazina) formando el complejo **B**. En este complejo tiene lugar la transferencia del alquiniluro desde el metilalquinilzinc al carbono azometínico la imina, lo cual libera el producto de reacción y el VAPOL-zincato **C**. Se completa el ciclo catalítico tras la coordinación de una nueva molecula de metilalquinilzinc al complejo **C**, generando el complejo **A**.[32]



Esquema 2.43. Propuesta mecanística para la alquinilación de 2,2-dioxido benzoxatiazinas catalizada por complejos de (*R*)-VAPOL-Zn.

2.4. CONCLUSIONES

1. Se ha diseñado un método enantioselectivo de adición de alquinos terminales a aldiminas cíclicas de tipo 2,2-dióxido benzoxatiazina catalizada por un sistema formado por (*R*)-VAPOL y Me_2Zn a temperatura ambiente utilizando $ClCH_2CH_2Cl$ como disolvente.

2. Se ha estudiado la reacción con diferentes ligandos de tipo BINOL, obteniéndose los productos de alquinilación con enantioselectividades muy bajas. La reacción con (*R*)-VANOL condujo a un buen exceso enantiomérico, pero la reacción transcurrió con mejor enantioselectividad cuando se utilizó *(R*)-VAPOL.

3. Los sustituyentes sobre el anillo aromático de la aldimina cíclica afectan a la enantioselectividad y al rendimiento de la reacción con fenilacetileno. La presencia de un grupo electrón-donante o electrón-aceptor poco voluminoso en la posición 6 de la imina conduce a enantioselectividades mayores, mientras que un grupo electrón-donante voluminoso en esta posición disminuye la enantioselectividad de la reacción. Benzoxatiazinas sustituidas con un grupo electrón-donante en la posición 8 dan lugar a buenas enantioselectividades.

4. Se han ensayado seis alquinos aromáticos con grupos electrón-donantes y electrón-aceptores en la reacción con diferentes 2,2-dióxido benzoxatiazinas con rendimientos y enantioselectividades elevadas. La presencia de sustituyentes en la posición *orto* del anillo aromático del alquino disminuye la enantioselectividad. La reacción con alquinos heteroaromáticos y alifáticos dio lugar a los correspondientes productos de alquinilación con enantioselectividades de moderadas a buenas.

5. Se ha podido realizar la hidrogenación del triple enlace del alquino y la reduci'on del sulfamidato con $LiAlH_4$ seguido por protección en forma de Boc dando lugar a la amina protegida **7** sin pérdida de pureza óptica.

6. Se ha podido determinar la configuración absoluta del carbono estereogénico (*S*) del compuesto **3fd** mediante difracción de Rayos X. Al resto de productos se les asignó la misma configuración absoluta asumiendo que la reacción sigue el mismo curso estereoquímico.

7. Se ha propuesto un posible mecanismo para la alquinilación de 2,2-dióxido benzoxatiazinas con un complejo de Me_2Zn-VAPOL.

2.5. EXPERIMENTAL SECTION

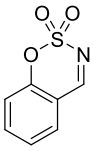
2.5.1. General experimental methods

Reactions were carried out under nitrogen in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel. Commercially available alkynes were used as received.

2.5.2. General synthetic procedure and characterization data for compounds 1

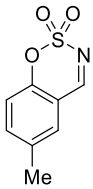
Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of salicylaldehyde **4** (10 mmol) in DMA (15 mL) at 0 °C. After addition, the reaction was placed at room temperature and stirred for 18 h. After, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography obtaining product **1**. The products previously described in literature, are only characterized with ^{1}H and ^{13}C NMR.

Benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1a)[40, 41]



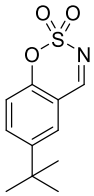
White solid; 92-94 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.76 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.69 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.43 (td, *J* = 7.6, 1.0 Hz, 1H), 7.32 – 7.27 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (CH), 154.3 (C), 137.6 (CH), 130.7 (CH), 126.1 (CH), 118.6 (CH), 115.4 (C) ppm.

6-Methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1b)[40, 41]



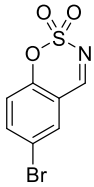
White solid; 73-74 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 0.4 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.46 (dd, *J* = 1.5, 0.6 Hz, 1H), 7.17 (dd, *J* = 8.7, 0.3 Hz, 1H), 2.44 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (CH), 152.2 (C), 138.4 (CH), 136.4 (C), 130.6 (CH), 118.3 (CH), 115.1 (C), 20.6 (CH_3) ppm.

6-(*tert*-Butyl)benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1c)[40, 41]



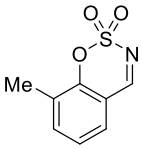
White solid; 56-58 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 0.6 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.64 (d, *J* = 2.5 Hz, 1H), 7.26 – 7.21 (m, 1H), 1.36 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2 (CH), 152.0 (C), 149.7 (C), 135.2 (CH), 127.3 (CH), 118.0 (CH), 114.8 (C), 34.7 (C), 31.0 (CH_3) ppm

6-Bromobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1e)[40, 41]



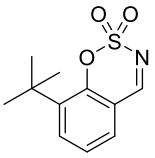
White solid; 131-133 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.24 – 7.20 (m, 1H) ppm. **^{13}C NMR** (75 MHz, CDCl3) δ 166.2 (CH), 153.2 (C), 140.2 (CH), 132.9 (CH), 120.5 (CH), 118.7 (C), 116.5 (C) ppm.

8-Methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1f)[40, 41]



White solid; 89-91 °C; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.54 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.49 (ddd, *J* = 7.7, 1.6, 0.5 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 2.30 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2 (CH), 152.1 (C), 139.1 (CH), 128.6 (CH), 128.0 (C), 125.5 (CH), 114.9 (C), 14.2 (CH_3) ppm.

8-(*tert*-Butyl)benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1g)[40, 41]



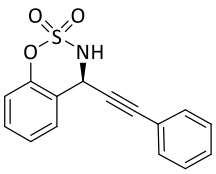
White solid; 70-72 °C; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.75 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 153.0 (C), 140.2 (C), 135.3 (CH), 129.2 (CH), 125.9 (CH), 116.0 (C), 34.8 (C), 29.5 (CH_3).

2.5.3. General synthetic procedures and characterization data for compounds 3

General procedure for the enantioselective alkynylation reaction: A 2 M Me_2Zn solution in toluene (0.18 mL, 0.36 mmol) was added dropwise on a solution of **L7** (9.7 mg, 0.018 mmol) and alkyne **2** (0.36 mmol) in dichloroethane (0.3 mL) at room temperature under nitrogen. After stirring 1 hour, a solution of benzoxathiazine 2,2-dioxide **1** (0.09 mmol) in dichloroethane (1.0 mL) was added via syringe. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded compound **3**.

General procedure for the non-enantioselective alkynylation reaction: A 1 M Et_2Zn solution in hexane (0.30 mL, 0.30 mmol) was added dropwise on a solution of racemic BINOL (5.7 mg, 0.02 mmol) and alkyne **2** (0.72 mmol) in dichloroethane (0.4 mL) at room temperature under nitrogen. After stirring 1 hour, a solution of benzoxathiazine 2,2-dioxide **1** (0.10 mmol) in dichloroethane (1.0 mL) was added via syringe. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded the racemic compound **3**.

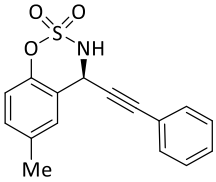
(*S*)-4-(Phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3aa)



The enantiomeric excess (82%) was determined by chiral HPLC (Chiralpak ODH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 15.82 min, minor enantiomer t_r = 13.68 min.

Oil; $[\alpha]_D^{20}$ = -32.6 (c 1.0, $CHCl_3$, 82% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (ddd, J = 7.8, 1.6, 1.1 Hz, 1H), 7.50 (dd, J = 7.8, 1.8 Hz, 2H), 7.44-7.33 (m, 4H), 7.28 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.3 Hz,1H), 5.94 (d, *J* = 10.0 Hz, 1H), 4.93 (d, *J* = 9.6 Hz, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.6 (C), 132 (CH), 130.4 (CH), 129.5 (CH), 128.5 (CH), 127.6 (CH), 125.6 (CH), 121.1 (C), 119.6 (C), 118.7 (CH), 87.7 (C), 82.3 (C), 50.3 (CH); **HRMS** (ESI) *m/z*: 284.0376 $[M - H]^-$, $C_{15}H_{10}NO_3S$ requires 284.0381.

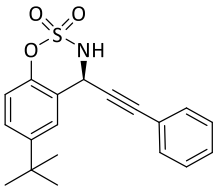
(*S*)-6-Methyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ba)



The enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 16.46 min, minor enantiomer t_r = 25.98 min.

Oil; $[\alpha]_D^{20}$ = -76.73 (c 1.0, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.41-7.33 (m, 4H), 7.19-7.15 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.90 (d, *J* = 9.9 Hz, 1H), 4.88 (d, *J* = 9.9 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.5 (C), 135.5 (C), 132.0 (CH), 130.9 (CH), 129.5 (CH), 128.52 (CH), 127.7 (CH), 121.1 (C), 119.1 (C), 118.5 (CH), 87.6 (C), 82.5 (C), 50.3 (CH), 20.8 (CH_3); **HRMS** (ESI) *m/z*: 298.0532 $[M - H]^-$, $C_{16}H_{12}NO_3S$ requires 298.0538.

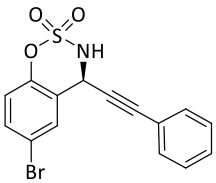
(*S*)-6-(*tert*-Butyl)-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ca)



The enantiomeric excess (56%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 8.16 min, minor enantiomer t_r = 9.15 min.

Oil; $[\alpha]_D^{20}$ = -77.26 (c 1.0, $CHCl_3$, 56% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 2.4, 1.1, 1H), 7.55-7.45 (m, 2H), 7.43-7.30 (m, 4H), 6.98 (d, *J* = 8.7 Hz, 1H), 5.93 (d, *J* = 10 Hz, 1H), 4.83 (d, *J* = 10,0 Hz, 1H), 1.34 (s, 9H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.8 (C), 148.3 (C), 131.9 (CH), 129.4 (CH), 128.6 (CH), 127.4 (CH), 124.3 (CH), 121.2 (C), 118.7 (C), 118.1 (CH), 87.7 (C), 82.7 (C), 50.51 (CH), 34.6 (C), 31.3 (CH_3); **HRMS** (ESI) *m/z*: 340.1007 $[M - H]^-$, $C_{19}H_{18}NO_3S$ requires 340.1007.

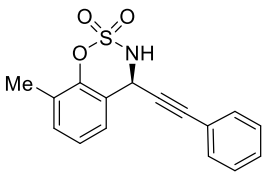
(*S*)-6-bromo-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ea)



The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 10.63 min, minor enantiomer t_r = 12.47 min.

Oil; $[\alpha]_D^{20}$ = -114.82 (c 1.0, $CHCl_3$, 80% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 2.4, 1.1 Hz, 1H), 7.58-7.46 (m, 3H), 7.45-7.33 (m, 3H), 6.94 (d, *J* = 8.8Hz, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 149.6 (C), 133.4 (CH), 132.1 (CH), 130.4 (CH), 129.7 (CH), 128.6 (CH), 121.5 (C), 120.7 (C), 120.4 (CH), 118.3 (C), 88.4 (C), 81.4 (C), 49.9 (CH); **HRMS** (ESI) *m/z*: 361.9472 $[M - H]^-$, $C_{15}H_9BrNO_3S$ requires 361.9487.

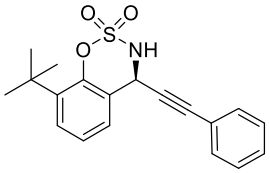
(*S*)-8-Methyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3fa)



The enantiomeric excess (73%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 12.22 min, minor enantiomer t_r = 21.42 min.

Oil; $[\alpha]_D^{20}$ = -6.00 (c 1.0, $CHCl_3$, 73% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H), 7.48 – 7.42 (m, 1H), 7.41 – 7.32 (m, 3H), 7.26 – 7.22 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.92 (d, *J* = 10.2 Hz, 1H), 4.84 (d, *J* = 10.0 Hz, 1H), 3.30 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 149.1 (C), 131.9 (CH), 131.8 (C), 129.4 (CH), 128.5 (CH), 128.1 (C), 125.0 (CH), 121.1 (C), 119.5 (CH), 87.8 (C), 82.6 (C), 50.3 (CH), 15.4 (CH_3); **HRMS** (ESI) *m/z*: 298.0545 $[M - H]^-$, $C_{16}H_{12}NO_3S$ requires 298.0538.

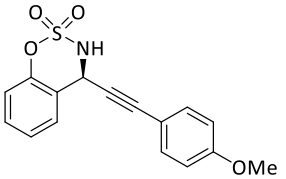
(*S*)-8-(*tert*-Butyl)-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ga)



The enantiomeric excess (81%) was determined by chiral HPLC (Chiralpak OD-H), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 10.08 min, minor enantiomer t_r = 8.42 min.

Solid; mp 118-119 °C; $[\alpha]_D^{20}$ = +8.08 (c 1.0, $CHCl_3$, 81% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 3H), 7.42-7.34 (m, 4H), 7.20 (t, *J* = 7.8Hz, 1H), 5.90 (d, *J* = 10.1Hz, 1H), 4.86 (d, *J* = 10.1Hz, 1H), 1.44 (s, 9H); **^{13}C NMR** (75.5 MHz, CDCl3) δ 149,9 (C), 140.1 (C), 131.9 (CH), 129.4 (CH), 128.5 (CH), 128.0 (CH), 125.4 (CH), 125.1 (CH), 121.3 (C), 121.2 (C), 87.8 (C), 82.6 (C), 50.1 (CH), 35.0 (C), 30.0 (CH_3); **HRMS** (ESI) *m/z*: 342.1159 $[M + H]^+$, $C_{19}H_{20}NO_3S$ requires 342.1164.

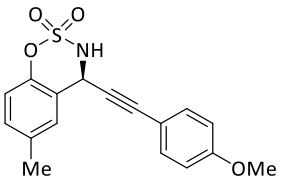
(*S*)-4-((4-Methoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ab)



The enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 23.85 min, minor enantiomer t_r = 32.73 min.

Oil; $[\alpha]_D^{20}$ = -26.13 (c 1.0, $CHCl_3$, 83% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.37 (ddd, *J* = 8.3, 1.7, 0.8Hz, 1H), 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.87 (dt, *J* = 9.2, 2.7 Hz, 2H), 5.92 (d, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.5 (C), 150.6 (C), 133.5 (CH), 130.3 (CH), 127.6 (CH), 125.6 (CH), 119.9 (C), 118.7 (CH), 114.2 (CH), 113.0 (C), 87.9 (C), 81.1 (C), 55.35 (CH), 50.40 (CH_3); **HRMS** (ESI) *m/z*: 316.0638 $[M + H]^+$, $C_{16}H_{14}NO_4S$ requires 316.0644.

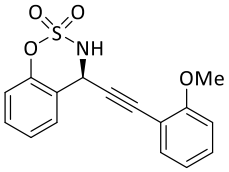
(*S*)-4-((4-Methoxyphenyl)ethynyl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bb)



The enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 29.96 min, minor enantiomer t_r = 40.36 min.

Oil; $[\alpha]_D^{20}$ = -47.60 (c 1.0, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.36 (dt, *J* = 2.1, 0.9 Hz, 1H), 7.17 (ddt, *J* = 8.4, 2.2, 0.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.92 – 6.83 (m, 1H), 5.88 (d, *J* = 9.9 Hz, 1H), 4.78 (d, *J* = 9.9 Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.5 (C), 148.5 (C), 135.5 (C), 133.6 (CH), 130.9 (CH), 127.7 (CH), 119.3 (C), 118.4 (CH), 114.2 (CH), 113.1 (C), 87.6 (C), 81.3 (C), 55.4 (CH_3), 50.4 (CH), 20.8 (CH_3); **HRMS** (ESI) *m/z*: 330.0793 $[M + H]^+$, $C_{17}H_{16}NO_4S$ requires 330.0800.

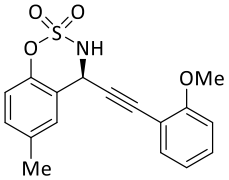
(*S*)-4-((2-Methoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ac)



The enantiomeric excess (65%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 19.21 min, minor enantiomer t_r = 28.89 min.

Solid; mp 103-105 °C; $[\alpha]_D^{20}$ = -25.47 (c 1.0, $CHCl_3$, 65% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.26 (td, *J* = 7.5, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.96 – 6.90 (m, 2H), 5.99 (d, *J* = 10.1 Hz, 1H), 4.91 (d, *J* = 10.1 Hz, 1 H), 3.89 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.5 (C), 150.6 (C), 133.7 (CH), 130.9 (CH), 130.2 (CH), 127.8 (CH), 125.5 (CH), 120.5 (CH), 119.8 (C), 118.5 (CH), 110.8 (CH), 110.3 (C), 86.2 (C), 84.2 (C), 55.7 (CH_3), 50.5 (CH); **HRMS** (ESI) *m/z*: 316.0638 $[M + H]^+$, $C_{16}H_{14}NO_4S$ requires 316.0644.

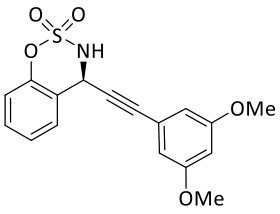
(*S*)-4-((2-Methoxyphenyl)ethynyl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bc)



The enantiomeric excess (68%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 25.23 min, minor enantiomer t_r = 41.05 min.

Solid; mp 157-159 °C; $[\alpha]_D^{20}$ = -58.26 (c 1.0, $CHCl_3$, 68% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.40 – 7.32 (m, 1H), 7.19 – 7.15 (m, 1H), 6.98 – 6.88 (m, 3H), 5.94 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 3.90 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.6 (C), 148.5 (C), 135.5 (C), 133.7 (CH), 130.9 (CH), 130.8 (CH), 129.0 (CH), 120.5 (CH), 119.4 (C), 118.3 (CH), 110.7 (CH), 110.4 (C), 86.3 (C), 84.2 (C), 55.7 (CH_3), 50.5 (CH), 20.9 (CH_3); **HRMS** (ESI) *m/z*: 330.0804 $[M + H]^+$, $C_{17}H_{16}NO_4S$ requires 330.0800.

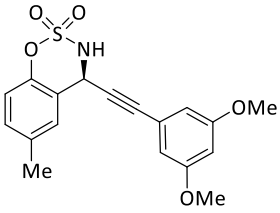
(*S*)-4-((3,5-Dimethoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ad)



The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 12.32 min, minor enantiomer t_r = 19.33 min.

Solid; mp 126-128 °C; $[\alpha]_D^{20}$ = -25.50 (c 1.0, $CHCl_3$, 80% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 1H), 7.42 – 7.36 (m, 1H), 7.27 (td, *J* = 7.6, 1.3 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 2H), 6.48 (dt, *J* = 10.1, 2.3 Hz, 1H), 5.92 (d, *J* = 9.87 Hz, 1H), 4.96 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 6H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.6 (C), 150.5 (C), 130.4 (CH), 127.6 (CH), 125.6 (CH), 122.3 (C), 119.5 (C), 118.7 (CH), 109.8 (CH), 102.6 (CH), 87.6 (C), 81.8 (C), 55.5 (CH_3), 50.2 (CH); **HRMS** (ESI) *m/z*: 346.0757 $[M + H]^+$, $C_{17}H_{16}NO_5S$ requires 346.0749.

(*S*)-4-((3,5-Dimethoxyphenyl)ethynyl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (3bd)

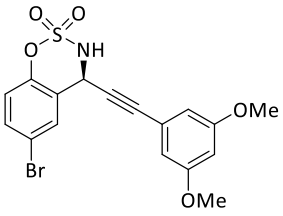


The enantiomeric excess (82%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r =12.10 min, minor enantiomer t_r = 19.93 min.

Solid; mp 135-136 °C; $[\alpha]_D^{20}$ = -65.18 (c 1.0, $CHCl_3$, 82% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 1H), 7.20 – 7.15 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 2H), 6.50 (t, *J* = 2.3 Hz, 1H), 5.87 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 6H), 2.37 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.6 (C), 148.4 (C), 135.5 (C), 130.9 (C), 127.6

(CH), 122.4 (C), 119.0 (C), 118.4 (CH), 109.8 (CH), 102.6 (CH), 87.4 (C), 82.0 (C), 55.5 (CH_3), 50.2 (CH), 20.8 (CH_3); **HRMS** (ESI) *m/z*: 360.0905 $[M + H]^+$, $C_{18\,h18}NO_5S$ requires 360.0906.

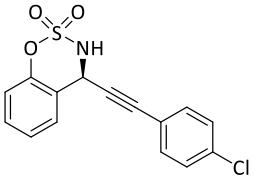
(*S*)-6-Bromo-4-((3,5-dimethoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (3ed)



The enantiomeric excess (82%) (96% ee after crystalization) was determined by chiral HPLC (Chiralpak ODH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 22.01 min, minor enantiomer t_r = 39.14 min.

Oil; $[\alpha]_D^{20}$ = -109.36 (c 1.0, $CHCl_3$, 82% *ee*); **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 2.5, 1.2 Hz, 1H), 7.49 (dd, J = 8.8, 2.4 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 6.64 (d, J = 2.2 Hz, 2H), 6.51 (t, J = 2.3 Hz, 1H), 5.88 (d, J = 7.0 Hz, 1H), 4.97 (d, J = 8.0 Hz, 1H), 3.80 (s, 6H); **^{13}C** (75,5 MHz, $CDCl_3$) δ 160.6 (C), 149.6 (C), 133.4 (CH), 130.4 (CH), 121.9 (C), 121.4 (C), 120.4 (CH), 118.3 (C), 109.9 (CH), 102.8 (CH), 88.3 (C), 81.0 (C), 55.5 (CH_3), 49.9 (CH); **HRMS** (ESI) *m/z*: 423.9851 $[M + H]^+$, $C_{17}H_{15}BrNO_5S$ requires 422.9854.

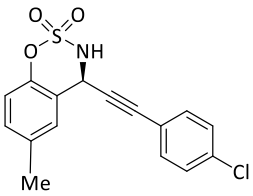
(*S*)-4-((4-Chlorophenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ae)



The enantiomeric excess (81%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 11.95 min, minor enantiomer t_r = 19.02 min.

Solid; mp 93-95 °C; $[\alpha]_D^{20}$ = -26.41 (c 1.0, $CHCl_3$, 81% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.37 – 7.32 (m, 2H), 7.27 (td, *J* = 7.8, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.93 (d, *J* = 9.9 Hz, 1H), 4.98 (d, *J* = 9.9 Hz, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.5 (C), 135.7 (C), 133.2 (CH), 130.4 (CH), 128.9 (CH), 127.5 (CH), 125.6 (CH), 119.5 (C), 119.4 (C), 118.8 (CH), 86.5 (C), 83.4 (C), 50.2 (CH); **HRMS** (ESI) *m/z*: 317.9993 $[M - H]^-$, $C_{15}H_9ClNO_3S$ requires 317.9992.

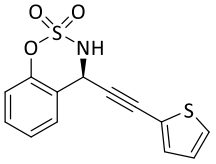
(*S*)-4-((4-Chlorophenyl)ethynyl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3be)



The enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 14.06 min, minor enantiomer t_r = 20.77 min.

Oil; $[\alpha]_D^{20}$ = -46.06 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.36 – 7.33 (m, 3H), 7.20 – 7.16 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.88 (d, *J* = 9.6 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 2.37 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.4 (C), 135.7 (C), 135.6 (C), 133.2 (CH), 131.0 (CH), 128.9 (CH), 127.6 (CH), 119.6 (C), 118.9 (C), 118.6 (CH), 86.4 (C), 83.6 (C), 50.2 (CH), 20.9 (C); **HRMS** (ESI) *m/z*: 332.0141 $[M - H]^-$, $C_{16}H_{11}ClNO_3S$ requires 332.0148.

(*S*)-4-(Thiophen-2-ylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ag)

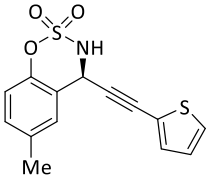


The enantiomeric excess (79%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 8.82 min, minor enantiomer t_r = 11.89 min.

Oil; $[\alpha]_D^{20}$ = -13.4 (c 1.0, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.46 – 7.34 (m, 1H), 7.35 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.32 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.27 (td, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 4.93 (d, *J* = 9.9 Hz, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.5 (C), 133.7 (CH), 130.4 (CH), 128.7 (CH),

127.6 (CH), 127.2 (C), 125.7 (CH), 120.7 (C), 119.3 (C), 118.8 (CH), 86.2 (C), 81.2 (C), 50.5 (CH); **HRMS** (ESI) *m/z*: 289.9946 $[M - H]^-$, $C_{13}H_8NO_3S_2$ requires 289.9946.

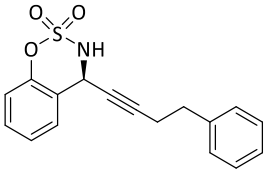
(*S*)-6-Methyl-4-(thiophen-2-ylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bg)



The enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 17.86 min, minor enantiomer t_r = 24.74 min.

Oil; $[\alpha]_D^{20}$ = -24.1 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.33 (dt, *J* = 3.7, 1.2 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.91 (Br s, 1H), 4.84 (br s, 1H), 2.37 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.4 (C), 135.6 (C), 133.7 (CH), 131.0 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 120.9 (C), 118.8 (C), 118.5 (CH), 86.4 (C), 81.0 (C), 50.4 (CH), 20.8 (CH_3); **HRMS** (ESI) *m/z*: 304.0107 $[M - H]^-$, $C_{14}H_{10}NO_3S_2$ requires 304.0102.

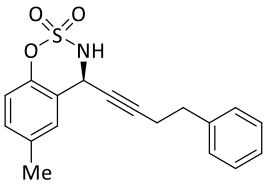
(*S*)-4-(4-Phenylbut-1-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ai)



The enantiomeric excess (60%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 14.04 min, minor enantiomer t_r = 16.72 min.

Oil; $[\alpha]_D^{20}$ = -30.34 (c 1.0, $CHCl_3$, 60% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H), 7.24 – 7.15 (m, 4H), 7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.64 (d, *J* = 8.2 Hz, 1H), 4.64 (d, 8.3 Hz, 1H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.61 (td, *J* = 7.2, 2.2 Hz, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.4 (C), 139.9 (C), 130.1 (C), 128.5 (CH), 127.6 (CH), 126.6 (CH), 125.4 (CH), 119.9 (C), 118.5 (CH), 88.1 (C), 74.9 (C), 49.9 (CH), 34.4 (CH_2), 20.7 (CH_2) **HRMS** (ESI) *m/z*: 312.0689 $[M - H]^-$, $C_{17}H_{14}NO_3S$ requires 312.0694.

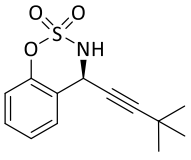
(*S*)-6-Methyl-4-(4-phenylbut-1-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bi)



The enantiomeric excess (65%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 16.53 min, minor enantiomer t_r = 19.80 min.

Solid; mp 83-85 °C; $[\alpha]_D^{20}$ = -55.94 (c 1.0, $CHCl_3$, 65% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.21 (m, 3H), 7.15 – 7.11 (m, 2H), 6.89 (d, *J* = 9 Hz, 1H), 5.60 (d, *J* = 9.9 Hz, 1H), 4.57 (d, *J* = 10 Hz, 1H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.61 (dt, *J* = 6.9, 2.4 Hz, 2H), 2.32 (s, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.3 (C), 140.0 (C), 135.3 (C), 130.7 (CH), 128.5 (CH), 127.7 (CH), 126.6 (CH), 119.4 (C), 118.3 (C), 87.9 (C), 75.0 (C), 49.9 (CH), 34.4 (CH_2), 20.81 (CH_2), 20.8 (C); **HRMS** (ESI) *m/z*: 345.1262 $[M + NH_4]^+$, $C_{18\,h21}N_2O_3S$ requires 345.1273.

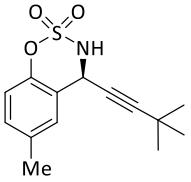
(*S*)-4-(3,3-Dimethylbut-1-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ak)



The enantiomeric excess (79%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 4.98 min, minor enantiomer t_r = 5.31 min.

Oil; $[\alpha]_D^{20}$ = -58.46 (c 1.0, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.24 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.68 (d, *J* = 10.2 Hz, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 1.28 (s, 9H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.5 (C), 130.1 (CH), 127.5 (CH), 125.5 (CH), 120.3 (C), 118.5 (CH), 97.2 (C), 72.4 (C), 49.9 (CH), 30.6 (CH_3), 27.6 (C); **HRMS** (ESI) *m/z*: 264.0693 $[M - H]^-$, $C_{13}H_{15}NO_3S$ requires 264.0694.

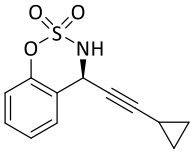
(*S*)-4-(3,3-Dimethylbut-1-yn-1-yl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bk)



The enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 4.70 min, minor enantiomer t_r = 5.33 min.

Solid; mp 103-105 °C; $[\alpha]_D^{20}$ = -93.85 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 1H), 7.14 – 7.12 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 4.81 (d, *J* = 10.2 Hz, 1H), 2.36 (s, 3H), 1.28 (s, 9H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.4 (C), 135.3 (C), 130.7 (CH), 127.9 (CH), 119.8 (C), 118.2 (CH), 97.0 (C), 72.6 (C), 49.8 (CH), 30.6 (CH_3), 27.6 (C), 20.9 (CH_3); **HRMS** (ESI) *m/z*: 278.0842 $[M - H]^-$, $C_{14}H_{16}NO_3S$ requires 278.0851.

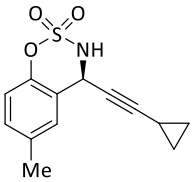
(*S*)-4-(Cyclopropylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3al)



The enantiomeric excess (74%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 9.49 min, minor enantiomer t_r = 11.12min.

Solid; mp 84-86 °C; $[\alpha]_D^{20}$ = -57.19 (c 1.0, $CHCl_3$, 74% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 4.70 (d, *J* = 9.9 Hz, 1H), 1.36 – 1.28 (m, 1H), 0.90 – 0.83 (m, 2H), 0.79 – 0.74 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 150.5 (C), 130.1 (CH), 127.6 (CH), 125.4 (CH), 120.1 (C), 118.5 (CH), 92.1 (C), 68.9 (C), 50.0 (CH), 8.5 (CH_2), 8.4 (CH_2), 0.7 (CH); **HRMS** (ESI) *m/z*: 248.0374 $[M - H]^-$, $C_{12}H_{10}NO_3S$ requires 248.0381.

(*S*)-4-(Cyclopropylethynyl)-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3bl)



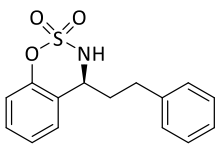
The enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 10.76 min, minor enantiomer t_r = 9.49 min.

Oil; $[\alpha]_D^{20}$ = -83.56 (c 1.0, $CHCl_3$, 78% *ee*). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 7.15 – 7.12 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 4.65 (d, *J* = 9.0 Hz, 1H), 2.36 (s, 3H), 1.36 – 1.31 (m, 1H), 0.90-0.8 (m, 2H), 0.80 - 0.74 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 148.4 (C), 135.3 (C), 130.7 (CH), 127.7 (CH), 119.6 (C), 118.3 (CH), 91.9 (C), 69.1 (C), 50.0 (CH), 20.81 (CH_3), 8.5 (CH_2), 8.4 (CH_2), 0.6 (CH); **HRMS** (ESI) *m/z*: 262.0523 $[M - H]^-$, $C_{13}H_{12}NO_3S$ requires 262.0538.

2.5.4. Synthetic procedures and characterization data for compounds 6 and 7

(*S*)-4-Phenethyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (6)

A solution of **3aa** (23.1 mg, 0.081 mmol) in absolute EtOH (7.5 mL) was stirred under H_2 in the presence of $Pd/CaCO_3$ (5%) (10.5 mg) during 1 h. Afterwards, the mixture was filtered over silica gel using EtOAc as eluent, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel afforded compound **6** (23 mg, 98%).



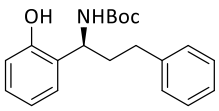
The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 10.55 min, minor enantiomer t_r = 9.01 min.

Oil; $[\alpha]_D^{20}$ = –33.7 (c 1.0, $CHCl_3$, 80% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (m, 3H), 7.26-7.23 (m, 3H), 7.18-7.16 (m, 2H), 7.02-6.99 (m, 1H), 4.73-4.64 (m, 2H), 2.97 (ddd, *J* = 13.5, 7.6, 5.7

Hz, 1H), 2.81 (dt, *J* = 13.9, 8.3 Hz, 1H), 2.42-2.34 (m, 2H); **^{13}C NMR** (75,5 MHz, $CDCl_3$) δ 151.18 (C), 140.3 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 126.5 (CH), 126.3 (CH), 125.3 (CH), 122.5 (C), 118.9 (CH), 56.6 (CH), 35.6 (CH), 31.3 (CH); **HRMS** (ESI) *m/z*: 307.1113 $[M + NH_4]^+$, $C_{15}H_{19}N_2O_3S$ requires 307.1116.

***tert*-Butyl (*S*)-(1-(2-hydroxyphenyl)-3-phenylpropyl)carbamate (7)**

To a solution of the cyclic sulfamidate **6** (0.08 mmol, 23 mg) in THF (1 mL), $LiAlH_4$ (1.0 M in THF, 3.3 equivalents, 0.264 mmol, 0.26 mL) was added dropwise at rt over 4 min.[42] The mixture was heated to 60 °C for 2.5 hours, allowed to cool down to rt, and then cooled with an ice bath. The reaction was quenched with EtOAc (1 mL), followed by the addition of EtOH (1 mL) and H_2O (1 mL). To the resulting turbid mixture Boc_2O (3 equivalents, 52 mg, 0.24 mmol) was added in one portion and the resulting mixture was stirred at rt for 1 hour. The mixture was diluted with EtOAc (15 mL) and acidified with aqueous 2 M HCl until the aqueous layer became clear. The aqueous layer was then separated and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded compound **7**.



The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 8.11 min, minor enantiomer t_r = 10.23 min.

Solid; mp 111-113 °C $[\alpha]_D^{20}$ = –31.7 (c 1.0, $CHCl_3$, 80% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 8.38 (s, 1H), 7.31 – 7.25 (m, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.20 – 7.13 (m, 4H), 6.95 – 6.91 (m, 1H), 6.88 (td, J = 7.5, 1.3 Hz, 1H), 5.02 (s, 1H), 4.81 (s, 1H), 2.77 – 2.60 (m, 2H), 2.26 – 2.16 (m, 2H), 1.44 (s, 9H); **^{13}C NMR** (75,5 MHz, $CDCl_3$) δ 157.4 8 (C), 156.1 (C), 141.1 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 126.1 (C), 120.3 (CH), 80.9 (C), 35.6 (CH_2), 33.0 (CH_2), 28.3 (CH_3); **HRMS** (ESI) *m/z*: 211.1120 $[M -H]^-$, $C_{15}H_{15}O$ requires 211.1123.

2.6. REFERENCES

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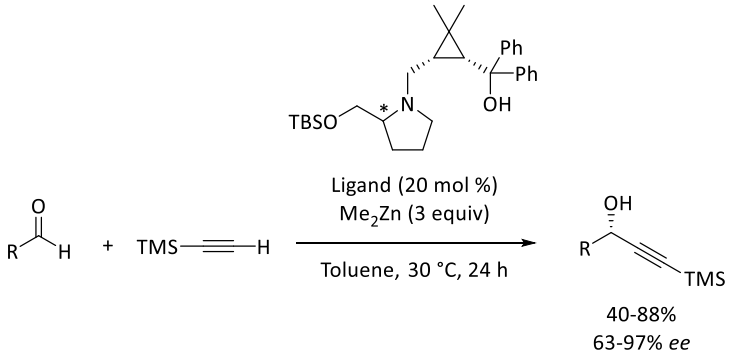
CHAPTER 3

ENANTIOSELECTIVE ALKYNYLATION OF BENZO[*e*][1,2,3]OXATHIAZINE 2,2-DIOXIDES CATALYZED BY COMPLEXES OF (*S*)-DIARYLPROLINOL-Zn

3.1. INTRODUCTION

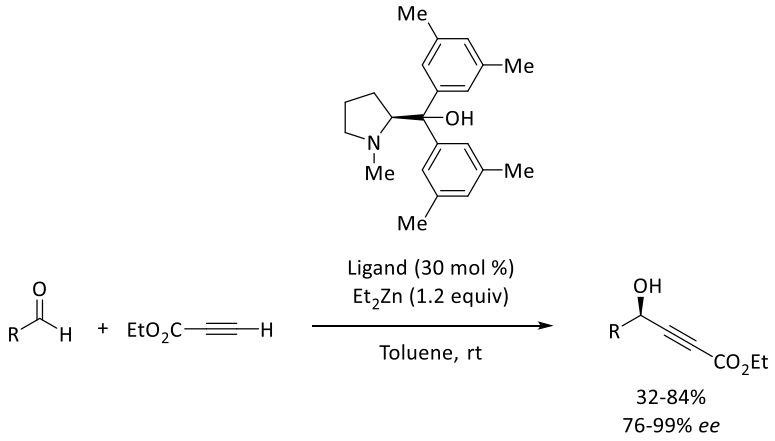
In the previoius chapter we described the enantioselctive addition of terminal alkynes to cyclic imines derived from benzoxathiazine 2,2-dioxide using (*R*)-VAPOL as ligand and Me_2Zn. Good results were obtained in terms of enantiomeric excesses. However, VAPOL is a very expensive ligand and the enantiomeric excesses show still room for improvement. With this in mind, we decided to focus our attention on the development of a superior methodology for the synthesis of chiral propargylic sulfamidates, using aminoalcohols as ligands in the addition reaction of terminal alkynes to these cyclic imines.

Chiral aminolalcohols have aready been used as ligands in various enantioselective alkynylation reactions of aldehydes. For example, in 2011 Guo and collaborators described the enantioselective addition of trimethylsilylacetylene to aldehydes catalyzed by zinc and a prolinol derivative.[1] The researchers synthesized a series of ligands, obtained by the introduction of (*S*)- or (*R*)-prolinol in the side chain of a chiral cyclopropane backbone. To induce more steric effect, the hydroxyl group in prolinol was protected with a voluminous group (*tert*-butyldimethylsilyl). Excellent results were obtained, both in yield (40-88%) and in enantiomeric excess (63-97%), in the enantioselective addition of trimethylsilylacetylene to various aromatic and alkyl aldehydes (only 10 mol % of ligand was needed in the reaction with aromatic aldehydes) (Scheme 3.1).



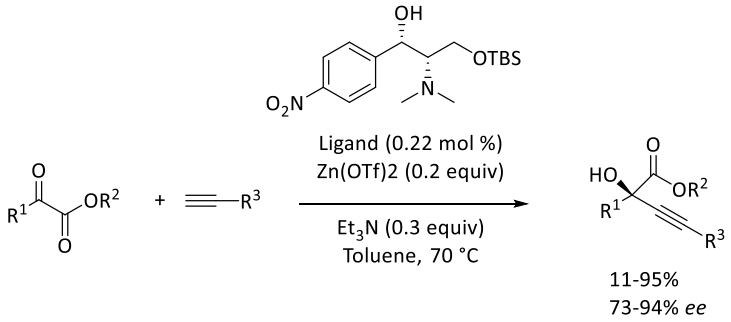
Scheme 3.1. Enantioselective addition of trimethylsilylacetylene to aldehydes catalyzed by zinc and a prolinol derivative.

Another example of the use of chiral aminoalcohols as ligands in the enantioselective alkynylation of aldehydes was described in 2011 by Kojima and collaborators as they performed an enantioselective addition of ethyl propiolate to different aromatic and alkyl aldehydes (Scheme 3.2).[2] The researchers used a diarylprolinol (30 mol %), derivated from L-prolinol, and Et_2Zn to form the catalytic system. The corresponding products were obtained with low to good yields (32-84%) and excellent enantioselectivities (76-99% *ee*).



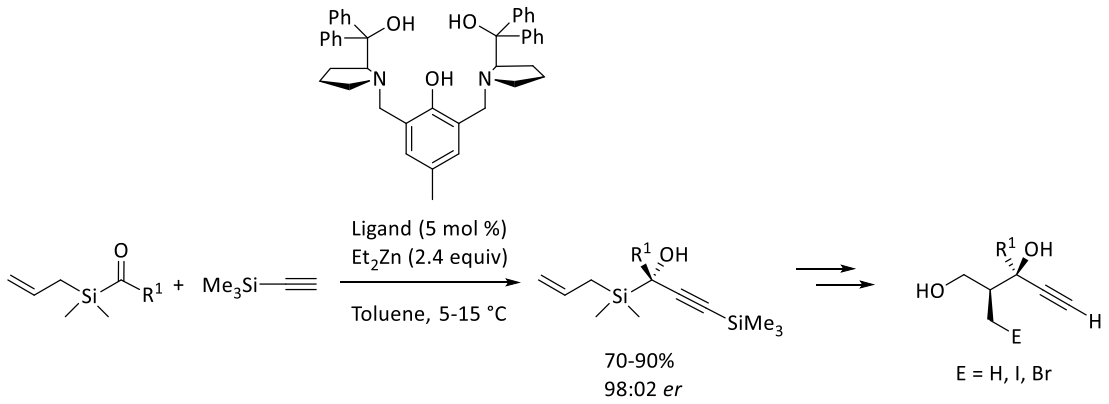
Scheme 3.2. Enantioselective addition of ethyl propiolate to different aromatic and alkyl aldehydes.

Chiral aminoalchols have been used as well in the enantioselective alkynylation of ketones, as for example in the work of Jiang and collaborators.[3] The researchers report the use of a chiral aminoalcohol in the enantioselective addition of zinc alkynylide to α-ketoesters for the synthesis of α-hydroxy-β-ynyl esters (Scheme 3.3). The reaction is catalyzed by a chiral aminoalcohol (0.22 mol %) and $Zn(OTf)_2$ (0.2 equiv). The corresponding α-hydroxy-β-ynyl esters (derived from both aromatic and alkyl ketones) were obtained with low to good yields (11-95%) and good to excellent enantioselectivities (73-94% *ee*).



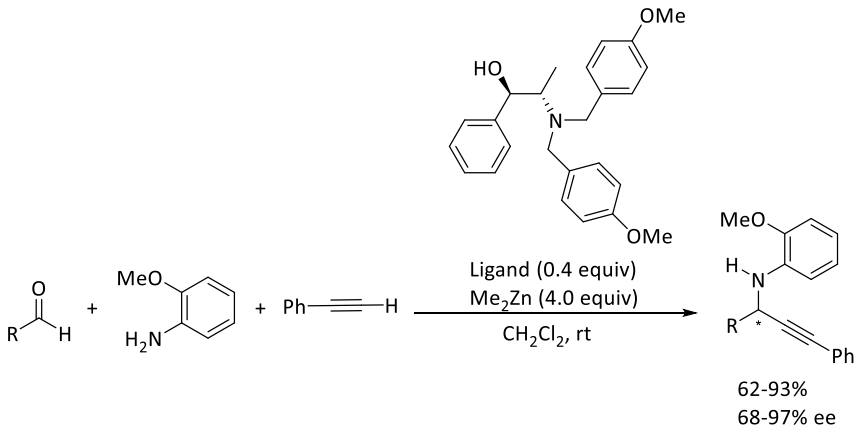
Scheme 3.3. Enantioselective addition of zinc alkynylide to α-ketoesters.

In 2013, Malek and collaborators described another exemple of the use of chiral aminoalcohols in the alkynylation of ketones. They described an enantioselective alkynylation of acyl silanes, promoted by a ProPhenol type ligand and Et_2Zn.[4] The corresponding products were obtained with good yields (70-90%) and enantiomeric ratios (98:02 *er*) (Scheme 3.4). The obtained products undergo in a one-pot process a later Brook type rearrangement and an ene-allene cyclization, leading to the, formation of three new bonds and two stereocenters in an acyclic system in a highly selective manner.



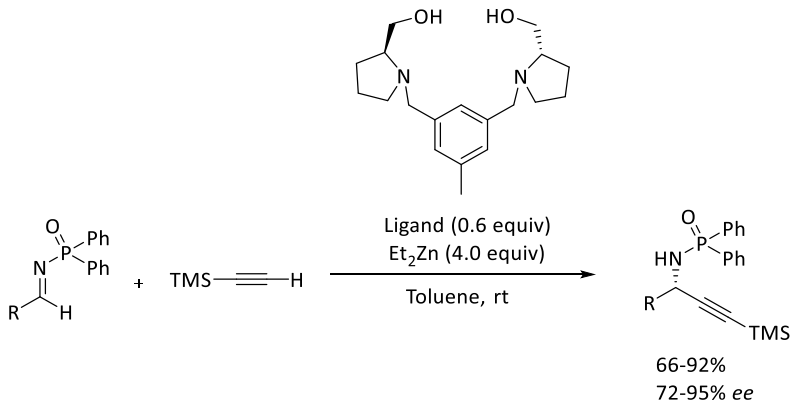
Scheme 3.4. Enantioselective alkynylation of acyl silanes, promoted by a ProPhenol type ligand and Et_2Zn.

Finally, there are also examples of the use of chiral aminoalcohols in the enantioselective alkynylation of imines. In 2007, Bolm and and collaborators described a three component synthesis of propargylic amines using Me_2Zn with various aldehydes and *o*-methoxyaniline.[5] The researchers develop the enantioselective version of the reaction, using a (1*R*, 2*S*)-norepinephrine derivative as chiral inducer (Scheme 3.5). Aromatic, heteroaromatic and α-substituted aliphatic aldehydes, *o*-methoxyaniline and phenylacetylene were used to obtain the corresponding propargylic amines in moderate to good yields and with enantioselectivities between 68 and 97%.



Scheme 3.5. One-pot enantioselective synthesis of propargylic amines using a (1*R*, 2*S*)-norepinephrine derivative as chiral inducer.

A last example of the use of chiral aminoalcohols in the enantioselective alkynylation of imines is given by Wang and collaborators.[6] They described the enantioselective nucleophilic addition of trimethylsilylacetylene to *N*-phosphinoylimines promoted by a proline derived β-amino alcohol. Different aryl, heteroaryl and alkyl imines were tested and moderate to good yields (66-92%) and enantioselectivities (72-95% *ee*) were obtained.

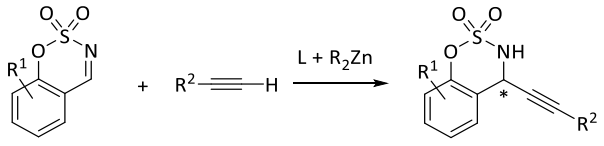


Scheme 3.6. Enantioselective addition of trimethylsilylacetylene to *N*-(diphenylphosphinoyl)imines promoted by a proline derived β-amino alcohol ligand.

As demonstrated, chiral aminoalcohols have proven to be good chiral inducers in alkynylation reactions. However, to our knowledge, they have never been used in the enantioselective alkynylation of benzoxathiazine 2,2-dioxides. In this chapter we opted for the use of diarylprolinols in the enantioselective alkynylation reaction we have developed in the previous chapter, because this kind of ligands are easy to prepare from prolinol and have already been used in different catalytic enantioselective reactions.

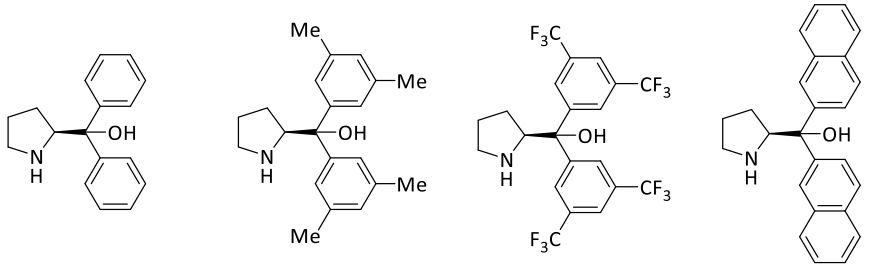
3.2. OBJETIVOS

El objetivo general de este capítulo es el desarrollo de una metodología superior para la adición de alquinos terminales a aldiminas cíclicas derivadas de salicilaldehidos (2,2-dióxido benzoxatiazinas) que transcurra con mejores excesos enantiomericos.



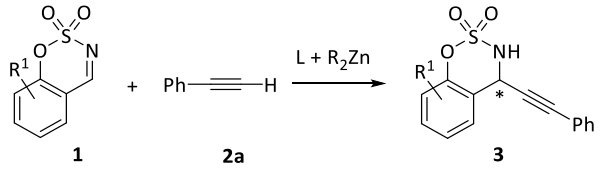
En el estudio de este segundo proyecto se considerarán los siguientes aspectos:

1. Influencia de la estructura de diversos ligandos de tipo diarilprolinol (**L9**–**L12**) sobre el rendimiento y la enantioselectividad de la reacción.

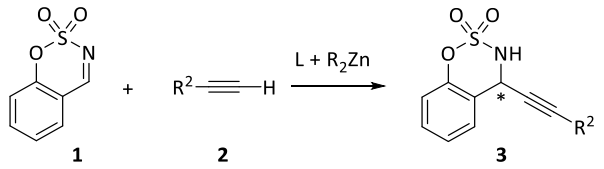


2. Influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn), número de equivalentes de dialquilzinc, disolvente y temperatura de reacción.

3. Evaluación de diversas aldiminas cíclicas del tipo 2,2-dióxido benzoxatiazina con diferente naturaleza electrónica y estérica en la reacción de alquinilación con fenilacetileno.



4. Evaluación de la aldimina cíclica base del tipo 2,2-dióxido benzoxatiazina en la reacción con diferentes alquinos terminales que presentan sustituyentes con distinta naturaleza electrónica y estérica.

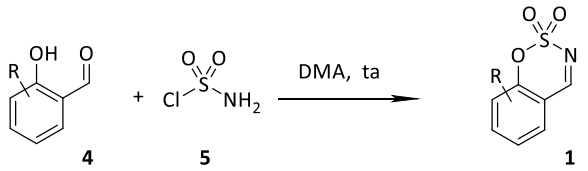


3.3. RESULTADOS Y DISCUSIÓN

3.3.1. Síntesis de 2,2-dióxido benzoxatiazinas

Con la idea de ampliar el estudio sobre el alcance y limitaciones de la reacción con relación al trabajo anterior, se sintetizaron algunas iminas más (Tabla 3.1). Estas iminas se sintetizaron utilizando el mismo procedimiento descrito anteriormente (apartado 2.3.1).

Tabla 3.1. Síntesis de 2,2-dióxido benzoxatiazinas.

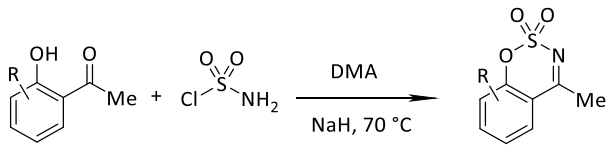


4 **5** **1**

Entrada	4	R	t (h)	1	R (%)[a]
1	**4d**	6-OMe	18	**1d**	67
2	**4h**	5-OMe	18	**1h**	59
3	**4i**	6,8-^{t}Bu	18	**1i**	71
4	**4j**	2-naftil	18	**1j**	57
5	**4k**	6-NO_2	18	**1k**	9

[a] Rendimiento después de purificación por cromatografía de columna.

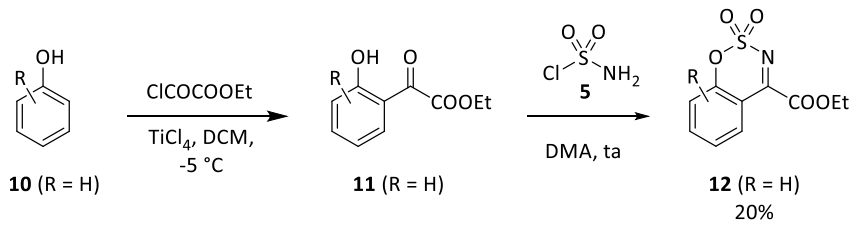
Además, se sintetizaron tres tipos de cetiminas con el esqueleto de 2,2-dióxido benzoxatiazina. La primera cetimina de tipo 2,2-dióxido benzoxatiazina que se sintetizó fue una cetimina con un grupo metilo **9** (R = H) (Esquema 3.7). La imina se sintetizó a partir de 2-hidroxiacetofenona **8** (R = H) y clorosulfonilamina **5**, preparada *in situ* a partir de isocianato de clorosulfonilo, a temperatura elevada (70 °C) en presencia de hidruro sódico utilizando como disolvente DMA.



8, R = H **5** **9**, R = H
30%

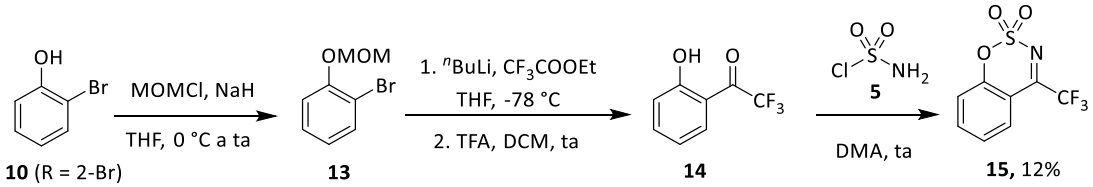
Esquema 3.7. Síntesis de una cetimina de tipo 2,2-dióxido benzoxatiazina con un grupo metilo.

Tambien se sintetizaron dos cetiminas activadas con grupos electrón-atrayentes. El primer producto que se sintetizó de este tipo fue una cetimina activada con un grupo éster etílico (**12**, R = H) (Esquema 3.8). El primer paso de la síntesis consiste en la reacción entre fenol y clorooxoacetato de etilo en la presencia de tetracloruro de titanio a -5 °C, obteniendo el correspondiente producto de acilación en *orto* (**11**, R = H). Este producto se hizo reaccionar con clorosulfonilamina **5** (preparada *in situ* a partir de isocianato de clorosulfonilo) dando como resultado el producto **12** (R = H) con un rendimiento global de 20%.



Esquema 3.8. Síntesis de una cetimina de tipo 2,2-dióxido benzoxatiazina con un grupo éster etílico.

Además se sintetizó una cetimina con un grupo trifluorometil la cual se obtuvo a partir de 2-bromofenol (**10**, R = 2-Br), siguiendo las etapas descritas en el esquema 3.9. Primero se protegió el bromofenol con MOMCl, obteniendo el compuesto **13**. Mediante un tratamiento con butil-litio, por intercambio halógeno-litio, se generó el correspondiente compuesto organolítico que se hizo reaccionar con trifluoroacetato de etilo. Por tratamiento ácido del producto resultante se obtuvo el compuesto **14**. Por último, se hizo reaccionar el compuesto **14** con clorosulfonilamina, preparada *in situ* a partir de isocianato de clorosulfonilo, a temperatura ambiente en DMA, obteniéndose el producto **15** con un rendimiento global de 12%.

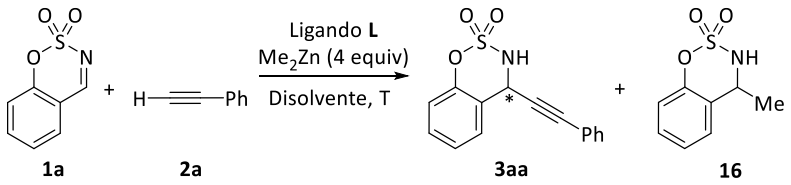


Esquema 3.9. Síntesis de una cetimina de tipo 2,2-dióxido benzoxatiazina con un grupo trifluorometilo.

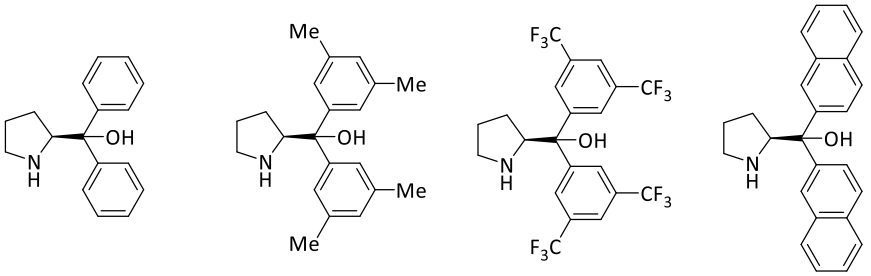
3.3.2. Optimización de las condiciones de la reacción

Como referencia para empezar el proceso de optimización de la reacción se elegieron las condiciones descritas anteriormente para la alquinilación de las 2,2-dióxido benzoxatiazinas con (*R*)-VAPOL. Este procedimiento consiste en la adición de cuatro equivalentes de Me_2Zn sobre una disolución de ligando (20 mol %), y siete equivalentes de fenilacetileno **2a** en tolueno a temperatura ambiente. Tras agitar media hora, se añade una disolución de la imina cíclica **1a** (1 equiv) en tolueno. El producto de alquinilación **3aa** se obtuvo con un buen rendimiento (80%) y una enantioselectividad moderada de 53% *ee* cuando se utilizó el ligando **L9** [(*S*)-difenil(pirrolidin-2-il)metanol)]. Con este resultado empezamos el proceso de optimización ensayando un conjunto de ligandos de tipo (*S*)-diaril(pirolidin-2-il)metanol (**L9**-**L12**) (Tabla 3.2).

Tabla 3.2. Adición enantioselectiva de fenilacetileno (**2a**) a 2,2-dióxido benzoxatiazina (**1a**). Evaluación de ligandos, reactivos de dialquilzinc, número de equivalentes de dialquilzinc, disolvente, temperatura de reacción y número de equivalentes de alquino.[a]



1a **2a** **3aa** **16**



L9 **L10** **L11** **L12**

Entrada	Ligando (x mol %)	Disolvente	T (°C)	R (%)[b]	3aa:16[c]	*ee* (%)[d]
1	**L9** (20)	Tolueno	ta	80	1:0	53
2	**L10** (20)	Tolueno	ta	85	1:0	57
3	**L11** (20)	Tolueno	ta	90	1:0.05	93
4	**L12** (20)	Tolueno	ta	86	1:0	59
5	**L11** (20)	CH_2Cl_2	ta	84	1:0	87
6	**L11** (20)	DCE	ta	90	1:0.03	83
7	**L11** (20)	Et_2O	ta	57	1:0.01	93
8	**L11** (20)	MTBE	ta	70	1:0.08	91
9[e]	**L11** (20)	Tolueno	ta	72	1:0.3[f]	87
10[g]	**L11** (20)	Tolueno	ta	96	1:0.02	93
11[g]	**L11** (20)	Tolueno	0	98	1:0.03	96
12[h]	**L11** (20)	Tolueno	0	96	1:0.01	97
13[h,i]	**L11** (20)	Tolueno	0	97	1:0.03	95
14[h]	**L11** (10)	Tolueno	0	87	1:0.05	86

[a] **1a** (0,100 mmol), **2a** (0,700 mmol) Ligando **L** (x mmol) y 1,2 M Me_2Zn en tolueno (0,400 mmol). [b] Rendimiento tras la cromatografía de columna. [c] Determinado mediante ^{1}H RMN. [d] Determinado mediante HPLC usando fases estacionarias quirales. [e] Se usó 1 M Et_2Zn en hexanos (0,4 mmol).[f] Se observó el producto de etilación. [g] Complejo de Zn quiral formado a 70 °C durante 0,5 h. [h] Complejo de Zn quiral formado a 70 °C durante 1 h. [i] 0,3 mmol de Me_2Zn.

Usando los ligandos **L10** o **L12** se obtuvo el producto de alquinilación con buen rendimiento, pero con un exceso enantiomérico moderado (53-59% *ee*) similar al obtenido con el ligando **L9** (Tabla 3.2, entradas 2 y 4). Mientras que cuando se utilizó el ligando **L11**, el producto de alquinilación **3aa** se obtuvo con una enantioselectividad elevada (93% *ee*) y un buen rendimiento de 90%. Sin embargo, la reacción con el ligando **L11** condujo también al producto de alquilación **16**, producto de reacción entre el Me_2Zn y la imina (se pudo observar un 5% de alquilación por ^{1}H RMN) (Tabla 3.2, entrada 3). Aunque la cantidad de producto de alquilación no era significativa, decidimos evaluar diferentes disolventes con el objetivo de evitar la adición de Me_2Zn a la benzoxatiazina **1a**.

El uso de disolventes clorados, como diclorometano o dicloroetano (Tabla 3.2, entradas 5 y 6) dio como resultado una disminución de la cantidad del producto de alquilación **16** pero también a una disminución de la enantioselectividad. Por su parte, el uso de disolventes tipo éter como Et_2O o MTBE (Tabla 3.2, entradas 7 y 8) proporcionó el producto del alquinilación **3aa** con una enantioselectividad más elevada, pero con un efecto negativo sobre el rendimiento y no evitó la formación del producto de alquilación. Por tanto decidimos seguir utilizando el tolueno como disolvente.

El uso de Et_2Zn como reactivo de dialquilzinc (Tabla 3.2, entrada 9) dio como resultado en un aumento considerable del producto no deseado de alquilación (1:0.3), debido a la adición directa de Et_2Zn a la imina **1a**.

Para evitar formación del producto de alquilación **16**, decidimos generar el complejo de zinc quiral a una temperatura más elevada, obteniendo el producto **3aa** con enantioselectividad y rendimiento más elevados (Tabla 3.2, entrada 10), pero todavía se pudo observar el producto de alquilación no deseado **16** (1:0.02). Al disminuir la temperatura a 0 °C, después de formar el complejo de zinc a 70 °C y antes de añadir la imina dio como resultado un incremento de la enantioselectividad hasta 96% *ee* (Tabla 3.2, entrada 11). Cuando la formación del complejo de zinc se realizó calentando a 70 °C durante 1 hora y la reacción se llevó a cabo a 0 °C el producto de alquinilación se obtuvo con una enantioselectividad elevada (97% *ee*) y sin disminución de rendimiento (Tabla 3.2, entrada 12). La formación del producto de alquilación **16** fue insignificante (menos de 5%).

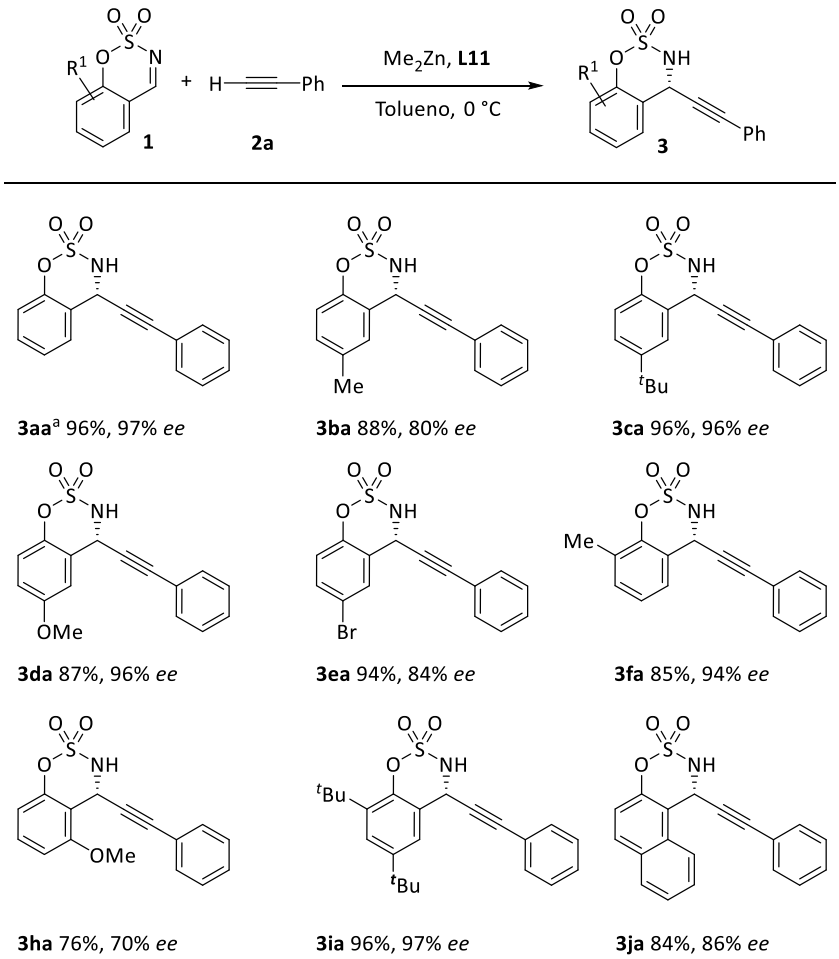
Finalmente, la disminución de la cantidad de Me_2Zn (Tabla 3.2, entrada 13) o de la cantidad de ligando hasta 10 mol % (Tabla 3.2, entrada 14) produjo un descenso en la enantioselectividad de la reacción. Por tanto consideramos como óptimas las condiciones mostradas en la entrada 12 de la tabla 3.2 en la que el producto **3aa** se obtuvo con un rendimiento de 96% y una enantioselectividad de 97% *ee*.

3.3.3. Alcance y limitaciones de la reacción

Una vez optimizadas las condiciones de reacción, se procedió a evaluar el alcance y limitaciones de la misma.

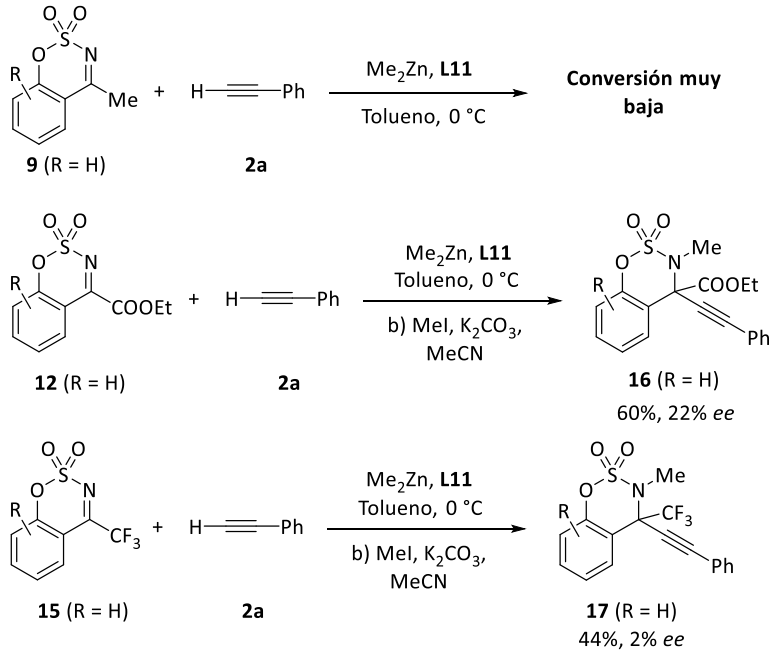
3.3.3.1. Evaluación de distintas 2,2-dióxido benzoxatiazinas

En primer lugar se evaluó la reacción entre fenilacetileno (**2a**) y varias 2,2-dióxido benzoxatiazinas con diferentes sustituyentes (Esquema 3.10). Se puede observar que la reacción tolera bien tanto grupos electrón-donantes (**3ba**-**3da**) como electrón-aceptores (**3ea**) en la posición 6 del anillo aromático obteniéndose los productos correspondientes con rendimientos altos (87-96%) y enantioselectividades elevadas (80-96% *ee*). Un sustituyente electrón-donante (Me) en la posición 8 del anillo dio un resultado en el producto **3fa** con un rendimiento de 85% y una enantioselectividad de 94% *ee*. Sin embargo, la imina cíclica con un grupo metoxi en la posición 5 dio como resultado el producto **3ha** con rendimiento y enantioseletividad inferiores (76%, 70% *ee*), seguramente debido a un aumento en el impedimiento estérico en la proximidad del átomo de carbono electrofílico. Notablemente, la presencia de dos grupos voluminosos (^{t}Bu) en posiciones 6 y 8 del anillo aromático, dio lugar al producto de adición **3ia** con una enantioselectividad excelente del 97% *ee*. Las condiciones de la reacción permitían también el uso de una imina incorporada a un grupo naftilo conduciendo al producto **3ja** con una enantioselectividad del 86% *ee*.



Esquema 3.10. Adición enantioselectiva de fenilacetileno (**2a**) a 2,2-dióxido benzoxatiazinas con **L11**/Me_2Zn: **1** (0,100 mmol), **2a** (0,700 mmol), 1,2 M Me_2Zn en tolueno (0,400 mmol) y **L11** (0,020 mmol) en tolueno a 0 °C. Rendimiento tras la cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

Con objeto de ampliar el alcance de la reacción decidimos evaluar diferentes tipos de cetiminas cíclicas (Esquema 3.11), para obtener sulfamidatos quirales con un centro estereogénico tetrasustituido. Con el sustrato **9** (R = H), una cetimina sustituida con un grupo metilo, no tuvo lugar la reacción bajo las condiciones optimizadas. Después se evaluaron dos cetiminas activadas con un grupo éster etílico y con un grupo trifluorometilo. La reacción con la cetimina activada con un éster (**12**, R = H), dio lugar al producto resultante **17** (R = H) (después de una posterior *N*-metilación necesaria para llevar a cabo la separación por HPLC) con un rendimiento de 60% y un exceso enantiomérico de 22%. La reacción con el sustrato activado por el grupo trifluorometilo (**15**, R = H), condujo al producto **18** (R = H) con un rendimiento de 44% y prácticamente racémico. En este caso también fue necesario llevar a cabo la *N*-metilación del producto, dado que la amina libre no permite la separación y análisis por cromatografía liquida (HPLC).

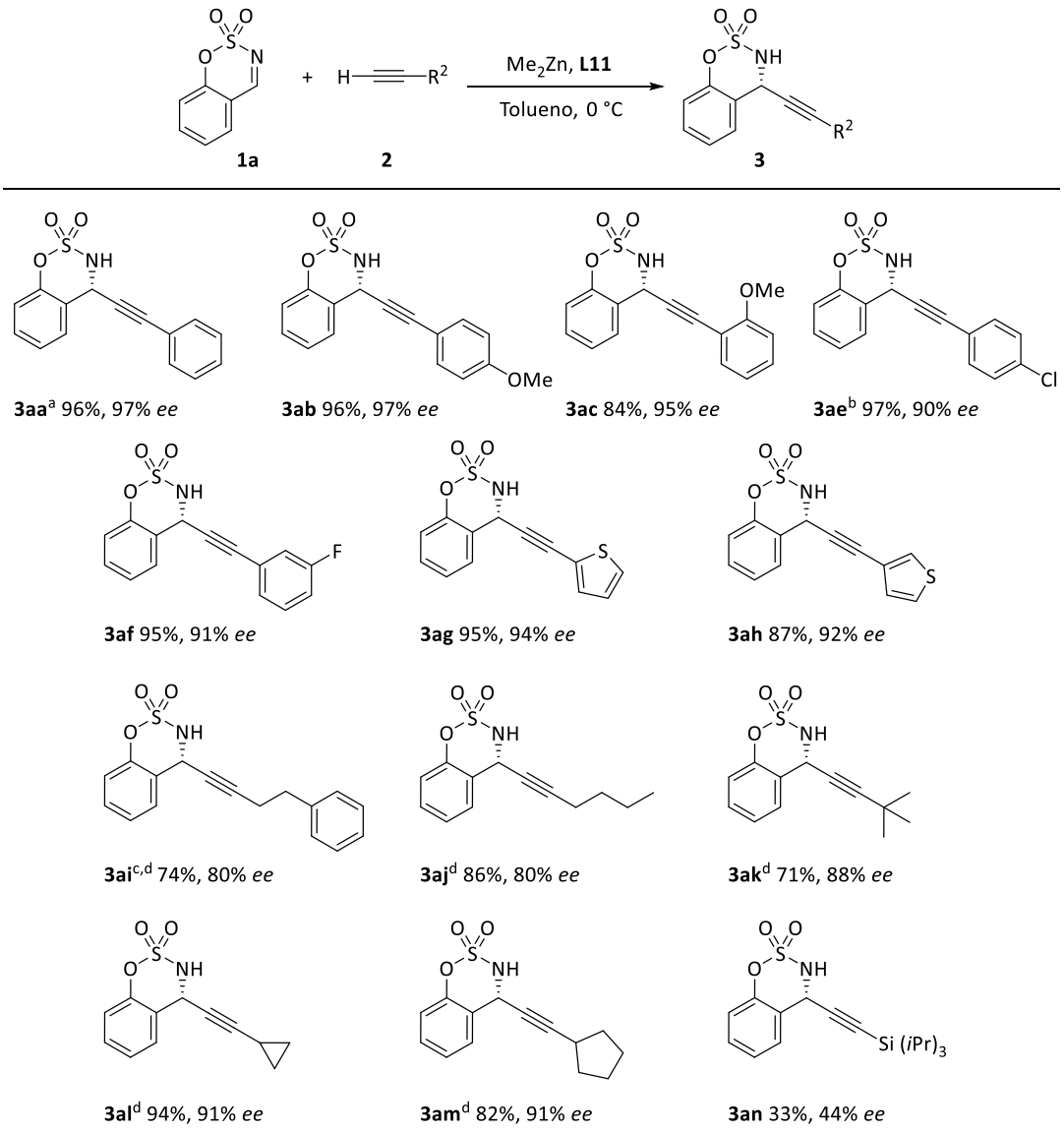


Esquema 3.11. Adición de fenilacetileno (**2a**) a cetiminas cíclicas **9**, **12**, y **15**: cetimina (0,100 mmol), **2a** (0,700 mmol), 1,2 M Me_2Zn en tolueno (0,400 mmol) y **L11** (0,020 mmol) en tolueno a 0 °C. Rendimiento tras la cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

3.3.3.2. Evaluación de distintos alquinos terminales

Una vez evaluadas diferentes 2,2-dióxido benzoxatiazinas en la reacción de adición del fenilacetileno, decidimos estudiar la influencia del alquino terminal en esta reacción. De esta manera evaluamos la reacción entre diferentes alquinos terminales **2** con diferente demanda electrónica y estérica y la 2,2-dióxido benzoxatiazina **1a** (Esquema 3.12). Se puede observar que las características electrónicas del anillo aromático del alquino terminal afecta ligeramente la enantioselectividad de la reacción. La presencia de un grupo electrón-donante en la posición *para* del anillo aromático dio lugar a la formación del producto **3ab** con rendimiento y enantioselectividad excelentes (96% y 97% *ee* respectivamente), de la misma manera que el producto **3ac**, formado a partir del alquino **2c** sustituido con un grupo metoxi en la posición *orto* del anillo aromático, que también se obtuvo con una enantioselectividad excelente (95% *ee*). La presencia de un grupo electrón-aceptor (Cl) en la posición *para,* dio lugar al producto **3ae** con un exceso enantiomérico un poco inferior (90% *ee*) pero con excelente rendimiento (97%). Un alquino con un átomo de flúor en *meta* dio como resultado el producto **3af** con buen rendimiento y un exceso enantiomérico del 91%. También se pudo demostrar que alquinos heteroaromáticos dan buenos resultados en esta reacción. Por ejemplo, los productos resultantes de la reacción con los alquinos **2g** y **2h**, alquinos con un grupo tiofeno, se obtuvieron con enantioselectividades elevadas de 92-94% *ee*. Una vez estudiados los efectos de los sustituyentes de diferentes alquinos terminales aromáticos decidimos estudiar el comportamiento de los alquinos alifáticos (**2i**-**2m**). Con los alquinos alifáticos se llevaron a cabo la reacciones a temperatura ambiente permitiendo así una mayor conversión. Cuando se utilizaron los alquinos **2i** y **2j** se obtuvieron los correspondientes sulfamidatos propargílicos **3ai** y **3aj** con excesos enantioméricos inferiores (80%), mientras que la reacción con un alquino con un grupo *terc*-butilo dio lugar al producto de alquinilación **3ak** con mejor enantioselectividad (88% *ee*). Se utilizaron también alquinos terminales unidos a un sistema cíclico los quales dieron lugar a los correspondientes sulfamidatos quirales **3al** y **3am** con elevados rendimientos y excesos enantioméricos (91% *ee*). Finalmente, se ensayó un alquino terminal

sustituido con un grupo triisopropilsililo (TIPS) **3n**, pero no se consiguió un buen resultado; tanto el rendimiento (33%) como la enantioselectividad (44% *ee*) fueron bajos.



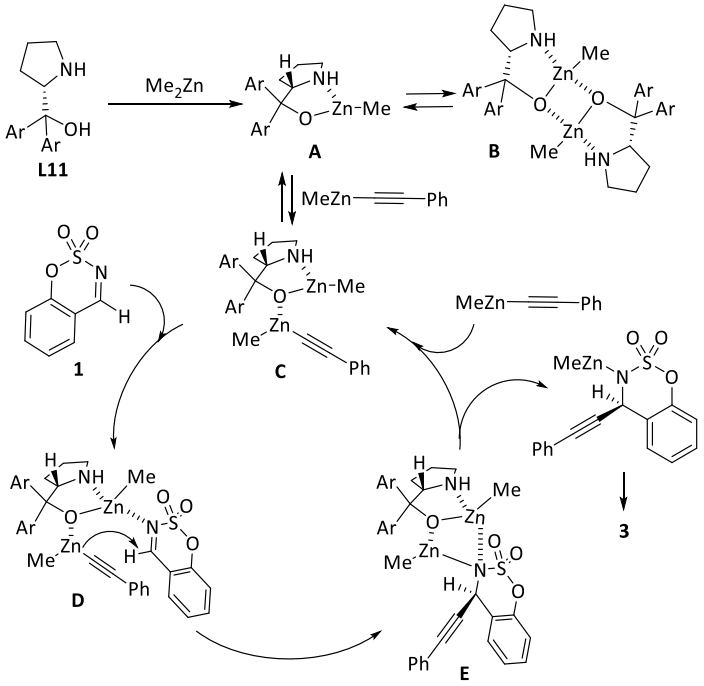
Esquema 3.12. Adición enantioselectiva de diferentes alquinos terminales **2** a la 2,2-dióxido benzoxatiazina (**1a**): **1a** (0,100 mmol), **2** (0,700 mmol), 1,2 M Me_2Zn en tolueno (0,400 mmol) y **L11** (0,020 mmol) en tolueno a 0 °C. Rendimiento tras la cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [a] 1:0.01 ratio de productos de alquinilación:metilación. [b] 1:0.03 ratio de productos de alquinilación:metilación. [c] 1:0.04 ratio de productos de alquinilación:metilación. [d] Reacción a temperatura ambiente.e

3.3.4. Determinación de la configuración absoluta

La configuración absoluta fue determinada por comparación con compuestos descritos en el capítulo anterior. Concretamente, se comparó el signo de la rotación óptica resultando que la configuración absoluta del centro estereogénico formado en la reacción es (*R*). La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

3.3.5. Propuesta mecanística para la alquinilación de 2,2-dióxido benzoxatiazinas con complejos de (*S*)-diarilprolinol-Zn

El esquema 3.13 muestra un posible mecanismo para la reqcción de alquinilación de 2,2-dióxido benzoxatiazinas con el complejo preparado a partir de Me_2Zn y un ligando de tipo diarilprolinol. Como se ha estudiado ya en alquilación con Et_2Zn y Me_2Zn catalizadas por ligandos de tipo amino alcohol, se forma en primer lugar un complejo **A** entre Me_2Zn y el ligando **L11**.[7] Este complejo de tipo alcóxido de zinc está en equilibrio con el complejo **B**, un dímero del complejo **A**. El complejo **B** es más estable, pero no puede participar en la reacción de alquinilación, debido que su tamaño impide la coordinación del alquino y el sustrato. El complejo **A** esta también en equilibrio con el complejo **C**, donde se ha incorporado el zincato-mixto (metilalquinilzinc), formado previamente en la reacción de desprotonación del alquino por parte del Me_2Zn. Este metilalquiniluro de zinc se coordina con el oxígeno del diarilprolinol del complejo **A**. La siguiente etapa es la incorporación del sustrato **1**, la 2,2-dióxido benzoxatiazina, al complejo **C**, mediante la coordinación del átomo de nitrógeno de la imina a un átomo de zinc del complejo. La coordinación se produce con el átomo de zinc quelado al amino alcohol. La coordinación a este átomo de Zn se debe a su mayor acidez de Lewis, precisamente por su quelación con el amino alcohol. La coordinación da lugar a la formación del complejo **D**. En acetiluros de alquilzinc, el grupo alquinil es más reactivo que el grupo alquil. Por este motivo tiene lugar una transferencia del acetiluro a la cara *Re* de la imina cíclica, generando el sulfamidato propargílico de zinc **E**. Después de la disociación del sulfamidato, se obtiene el producto final **3** y una nueva molécula del complejo **A**, que incorpora el metilalquinilzinc generando de nuevo el complejo **C**, completando el ciclo catalítico.



Esquema 3.13. Propuesta mecanística para la alquinilación de 2,2-dióxido benzoxatiazinas con un complejo de Me_2Zn-ligando de tipo diarilprolinol.

3.4. CONCLUSIONES

1. Se ha diseñado un método enantioselectivo de adición de alquinos terminales a aldiminas cíclicas de tipo 2,2-dióxido benzoxatiazina catalizada por un sistema formado por un ligando del tipo diaril (*S*)-prolinol y Me_2Zn en tolueno a 0 °C.

2. Se ha estudiado la reacción con diferentes ligandos de tipo diarilprolinol, obteniéndose los productos de alquinilación con enantioselectividades moderadas. La reacción con (*S*)-bis(3,5-bis(trifluorometil)fenil)(pirrolidin-2-il)metanol (**L11)** condujo a un exceso enantiomérico excelente.

3. Los sustituyentes sobre el anillo aromático de la aldimina cíclica afectan en cierta manera a la enantioselectividad y al rendimiento de la reacción de adición enantioselectiva de fenilacetileno. Un sustituyente en la posición 5 conduce a una enantioselectividad moderada, mientras que sustituyentes en posiciones 6 y 8 conducen a enantioselectividades elevadas.

4. Se han ensayado seis alquinos aromáticos con grupos electrón-donantes y electrón-aceptores en la reacción con diferentes 2,2-dióxido benzoxatiazina con rendimientos y enantioselectividades elevadas. La reacción con alquinos heteroaromáticos y alifáticos también condujo a los productos de alquinilación con enantioselectividades elevadas.

5. Se ha propuesto un posible mecanismo para la alquinilación de 2,2-dióxido benzoxatiazinas con un complejo de Me_2Zn-ligando de tipo diarilprolinol.

3.5. EXPERIMENTAL SECTION

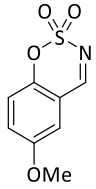
3.5.1. General experimental methods

Reactions were carried out under nitrogen in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel. Commercially available alkynes were used as received.

3.5.2. General synthetic procedure and characterization data for compounds 1

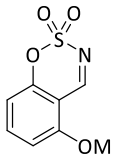
Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of salicylaldehyde **4** (10 mmol) in DMA (15 mL) at 0 °C. After addition, the reaction was placed at room temperature and stirred for 18 h. After, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash chromatography obtaining product **1**. The products previously described in literature, are only characterized with ^{1}H and ^{13}C NMR.

6-Methoxybenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1d)[8]



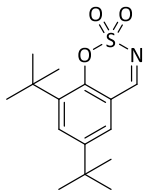
White solid; 111-113 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.36-7.26 (m, 2H), 7.14 (d, *J* = 2.8 Hz, 1H), 3.93 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (CH), 157.1 (C), 148.1 (C), 124.4 (CH), 119.8 (CH), 115.7 (C), 113.0 (CH), 56.1 (CH_3) ppm.

5-Methoxybenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1h)



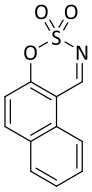
White solid; 102-104 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.01 (d, *J* = 0.4 Hz, 1H), 7.64 (t, *J* = 8.5 Hz, 1H), 6.83 – 6.79 (m, 2H), 3.99 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.0 (CH), 159.7 (C), 155.2 (C), 138.9 (CH), 110.1 (CH), 107.6 (CH), 106.2 (C), 56.6 (CH_3) ppm. **HRMS** (ESI) *m/z*: 214.0173 $[M + H]^+$, $C_8H_8NO_4S$ requires 214.0169.

6,8-Di-*tert*-butylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1i)[9]



White solid; 93-96 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 1.47 (s, 9H), 1.36 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9 (CH), 151.1 (C), 148.9 (C), 139.9 (C), 132.7 (CH), 125.43 (CH), 115.8 (C), 35.1 (C), 34.9 (C), 31.2 (CH_3), 29.7 (CH_3) ppm.

Naphtho[1,2-*e*][1,2,3]oxathiazine 3,3-dioxide (1j)[10]

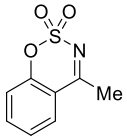


White solid; 187-189 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 8.01 – 7.94 (m, 1H), 7.82 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.5 (C), 155.7 (C), 139.6 (CH), 130.7 (CH), 130.6 (C), 129.7 (CH), 127.3 (CH), 120.6 (CH), 117.2 (CH), 109.7 (C) ppm.

3.5.3. General synthetic procedure and characterization data for compound 9

Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of 2-hydroxyacetophenone **8** (R = H) (10 mmol) in DMA (15 mL) at 0 °C. After addition, the reaction was placed at room temperature and in the next hour, NaH (60% in oil, 24 mmol) is added in portions. Afterwards, the reaction was stirred for 18 h. Afterwards, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash chromatography obtaining product **9** (R = H).

4-Methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9a)[11]



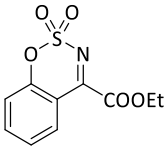
White solid; mp 114-116 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 2.73 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.2 (C), 137.1 (CH), 128.4 (CH), 125.8 (CH), 119.1 (CH), 116.4 (C), 23.7 (CH_3) ppm.

3.5.4. Synthetic procedures and characterization data for compound 12

To a solution of phenol (**10**, R = H) (10 mmol) in dichloromethane (12 mL) at -5 °C, $TiCl_4$ (11 mmol) was added. After 5 minutes, ethyl chlorooxoacetate (11 mmol) was added dropwise over 2 minutes. Th reaction was stirred at -5 °C overnight. After completion, the resulting mixture was diluted with dichloromethane (10 mL) and was poured into a previously cooled 1M HCl (50 mL) solution. The mixture was further acidified with concentrated HCl (1 mL) and extracted with dichloromethane (3x50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography obtaining product **11** (R = H).

Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of product **11** (R = H) (10 mmol) in DMA (15 mL) at 0 °C. After the addition, the reaction was placed at room temperature and stirred for 18 h. After, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue purified by flash chromatography obtaining product **12** (R = H).

Ethyl benzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (12)[12]



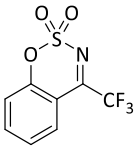
Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.79 (ddd, *J* = 8.4, 7.5, 1.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.35 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.1 (C), 160.8 (C), 154.8 (C), 138.1 (CH), 130.2 (CH), 126.3 (CH), 119.2 (CH), 113.6 (C), 64.0 (CH_2), 14.0 (CH_3).

3.5.5. Synthetic Procedures and characterization data for compound 15

To a solution of NaH (60% in oil, 30 mmol) in THF (10 mL) at 0 °C, 2-bromophenol (**10**, R = 2-Br) (20 mmol) dissolved in THF (20 mL) was added.[13] The reaction was stired at 0 °C for 1 hour. MOMCl was added after 1 hour at 0 °C. The reaction was then stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O (3x30 mL) and the organic phase was dried over Na_2SO_4. To the crude product **13** (20 mmol), dissolved in THF (50 mL) at -78 °C, ^{n}BuLi (24 mmol) was added dropwise. After 1 hour CF_3COOEt was added at -78 °C. After 1.5 hours, the reaction was quenched with saturated NH_4Cl, extracted with Et_2O (3x50 mL), washed with brine and the organic phase was dried with Na_2SO_4. The crude product was then dissolved in 50 mL CH_2Cl_2 and TFA (100 mmol) was added. This solution was stirred for 18 hours. Afterwards, the reaction was washed with 3x30 mL 1M KH_2PO_4/NaOH pH7 buffer and brine (50 mL). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography, obtaining product **14**.

Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of product **14** (10 mmol) in DMA (15 mL) at 0 °C. After addition, the reaction was placed at room temperature and stirred for 18 h. After, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography obtaining product **15**.

4-(Trifluoromethyl)benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (15)[13]



Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (dp, *J* = 8.1, 1.8 Hz, 1H), 7.86 (ddd, *J* = 8.3, 7.4, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 7.6, 1.1 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.1 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.1 (q, $J_{C\text{-}F}$ = 37.6 Hz, C), 155.1 (C), 138.8 (CH), 128.5 (q, $J_{C\text{-}F}$ = 3.2 Hz, CH), 126.7 (CH), 119.6 (CH), 118.3 (q, $J_{C\text{-}F}$ = 281.4 Hz, C), 111.7 (C).

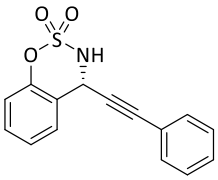
3.5.6. General synthetic procedures and characterization data for compounds 3, 17 and 18

General procedure for the enantioselective alkynylation reaction: A 1.2 M Me_2Zn solution in toluene (0.400 mmol) was added dropwise to a solution of **L11** (0.020 mmol) and alkyne **2** (0.700 mmol) in toluene (0.3 mL) and was heated to 70 °C under nitrogen atmosphere. After stirring for 1 hour, the reaction mixture was cooled to 0 °C and a solution of benzoxathiazine 2,2-dioxide **1** (0.100 mmol) in toluene (1.0 mL) was added via syringe at 0 °C. The reaction was stirred at this temperature until TLC analysis indicated full conversion of the starting material. The reaction was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, purification by flash chromatography on silica gel affording compound **3**.

General procedure for the non-enantioselective alkynylation reaction: A 1.2 M Me_2Zn solution in toluene (0.300 mmol) was added dropwise to a solution of racemic BINOL (0.020 mmol) and alkyne **2** (0.700 mmol) in toluene (0.4 mL) at room temperature under nitrogen atmosphere. After stirring for 1 hour, a solution of benzoxathiazine 2,2-dioxide **1** (0.100 mmol) in toluene (1.0 mL) was added via syringe. The reaction was stirred until TLC analysis indicated full conversion of the starting material. The reaction was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification by flash chromatography on silica gel affording racemic compound **3**.

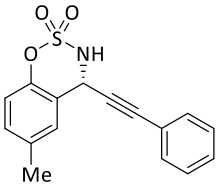
The products described in the previous chapter are not fully characterized again.

(*R*)-4-(Phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3aa)



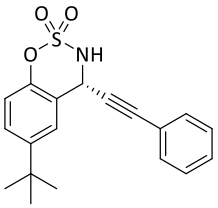
The enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 22.57 min, minor enantiomer t_r = 14.77 min. Oil; $[\alpha]_D^{20}$ = +46.1 (c 1.0, $CHCl_3$, 97% *ee*).

(*R*)-6-Methyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ba)



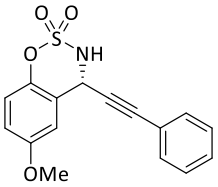
The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 27.09 min, minor enantiomer t_r = 17.62 min. Oil; $[\alpha]_D^{20}$ = +76.6 (c 1.0, $CHCl_3$, 80% *ee*).

(*R*)-6-(*tert*-Butyl)-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ca)



The enantiomeric excess (96%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 17.73 min, minor enantiomer t_r = 12.60 min. Oil; $[\alpha]_D^{20}$ = +112.9 (c 1.0, $CHCl_3$, 96% *ee*).

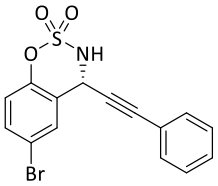
(*R*)-6-Methoxy-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3da)



The enantiomeric excess (96%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 32.60 min, minor enantiomer t_r = 21.05 min.

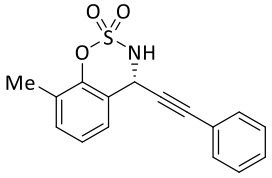
Oil; $[\alpha]_D^{20}$ = +125.5 (c 1.0, $CHCl_3$, 96% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.42 – 7.32 (m, 3H), 7.09 (dd, *J* = 2.9, 0.9 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 6.90 (ddd, *J* = 9.0, 2.9, 0.7 Hz, 1H), 5.89 (s, 1H), 4.90 (s, 1H), 3.82 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.9 (C), 144.3 (C), 132.0 (2 x CH), 129.5 (CH), 128.5 (2 x CH), 121.0 (C), 120.4 (C), 119.6 (CH), 115.8 (CH), 112.2 (CH), 87.7 (C), 82.3 (C), 55.8 (CH_3), 50.3 (CH) ppm. **HRMS (ESI)** *m/z*: 316.0651 $[M + H]^+$, $C_{16}H_{14}NO_4S$ requires 316.0638.

(*R*)-6-Bromo-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ea)



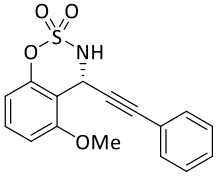
The enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 13.45 min, minor enantiomer t_r = 11.57 min. Oil; $[\alpha]_D^{20}$ = +119.4 (c 1.0, $CHCl_3$, 84% *ee*).

(*R*)-8-Methyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3fa)



The enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 22.05 min, minor enantiomer t_r = 13.09 min. Oil; $[\alpha]_D^{20}$ = +6.5 (c 1.0, $CHCl_3$, 94% *ee*).

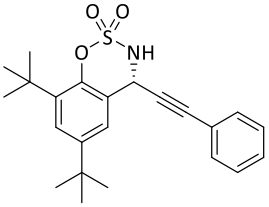
(*R*)-5-Methoxy-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ha)



The enantiomeric excess (70%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 32.77 min, minor enantiomer t_r = 18.69 min.

Oil; $[\alpha]_D^{20}$ = +94.0 (c 1.0, $CHCl_3$, 70% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.36 – 7.27 (m, 4H), 6.78 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.69 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.78 (s, 1H), 4.99 (s, 1H), 3.93 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.1 (C), 151.0 (C), 131.8 (2 x CH), 130.3 (CH), 128.8 (CH), 128.3 (2 x CH), 122.0 (C), 111.2 (CH), 108.8 (C), 107.9 (CH), 84.9 (C), 83.9 (C), 56.2 (CH_3), 47.1 (CH) ppm. **HRMS** (ESI) m/z: 316.0649 $[M + H]^+$, $C_{16}H_{14}NO_4S$ requires 316.0638.

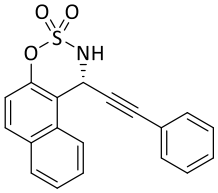
(*R*)-6,8-Di-*tert*-butyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ia)



The enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 16.61 min, minor enantiomer t_r = 9.01 min.

Oil; $[\alpha]_D^{20}$ = +61.0 (c 1.0, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 3H), 7.43 – 7.33 (m, 4H), 5.89 (d, *J* = 10.1 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 1.44 (s, 9H), 1.34 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.8 (C), 147.6 (C), 139.2 (C), 131.9 (2 x CH), 129.4 (CH), 128.5 (2 x CH), 125.0 (CH), 122.1 (CH), 121.3 (C), 120.3 (C), 87.7 (C), 82.9 (C), 50.4 (CH), 35.2 (C), 34.8 (C), 31.3 (3 x CH_3), 30.1 (3 x CH_3) ppm. **HRMS (ESI)** *m/z*: 398.1800 $[M + H]^+$, $C_{23}H_{28}NO_3S$ requires 398.1784.

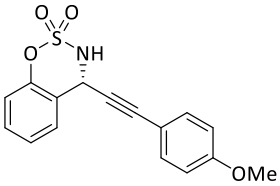
(*R*)-1-(Phenylethynyl)-1,2-dihydronaphtho[1,2-*e*][1,2,3]oxathiazine 3,3-dioxide (3ja)



The enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 32.14 min, minor enantiomer t_r = 18.95 min.

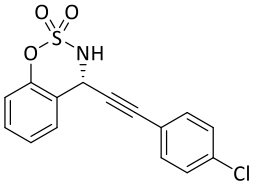
Oil; $[\alpha]_D^{20}$ = +191.8 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 – 8.20 (m, 1H), 7.89 (d, *J* = 9.1 Hz, 2H), 7.64 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.23 (m, 3H), 7.18 (d, *J* = 9.1 Hz, 1H), 6.23 (s, 1H), 5.30 (s, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.4 (C), 131.8 (2 x CH), 131.5 (CH), 131.4 (C), 129.8 (CH), 129.2 (CH), 129.0 (CH), 128.3 (2 x CH), 127.7 (CH), 126.0 (CH), 123.5 (CH), 121.4 (C), 118.6 (CH), 112.6 (C), 87.7 (C), 83.7 (C), 49.0 (CH) ppm. **HRMS** (ESI) *m/z*: 336.0704 $[M + H]^+$, $C_{19}H_{14}NO_3S$ requires 336.0689.

(*R*)-4-((4-Methoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ab)



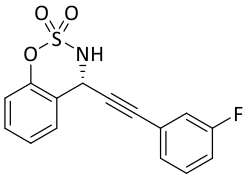
The enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 35.21 min, minor enantiomer t_r = 26.54 min. Oil; $[\alpha]_D^{20}$ = +28.0 (c 1.0, $CHCl_3$, 97% *ee*).

(*R*)-4-((4-Chloroyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ae)



The enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 19.61 min, minor enantiomer t_r = 13.48 min. Mp 93 °C; $[\alpha]_D^{20}$ = +29.0 (c 1.0, $CHCl_3$, 90% *ee*).

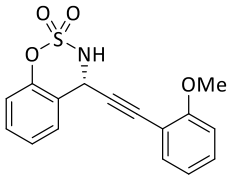
(*R*)-4-((4-Fluorophenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3af)



The enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 19.62 min, minor enantiomer t_r = 12.44 min.

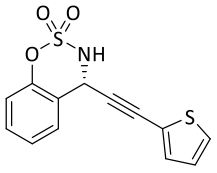
Oil; $[\alpha]_D^{20}$ = +41.6 (c 1.0, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 1H), 7.40 (dddd, *J* = 8.2, 7.4, 1.7, 0.8 Hz, 1H), 7.36 – 7.24 (m, 3H), 7.22 – 7.16 (m, 1H), 7.15 – 7.07 (m, 1H), 7.06 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.94 (d, *J* = 9.3 Hz, 1H), 4.94 (d, *J* = 9.3 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.3 (d, *J* = 247.5 Hz, C), 150.6 (C), 130.5 (CH), 130.2 (d, *J* = 8.6 Hz, CH), 127.9 (d, *J* = 3.2 Hz, CH), 127.5 (CH), 125.7 (CH), 122.8 (d, *J* = 9.5 Hz, C), 119.3 (C), 118.8 (CH, d, *J* = 23.2 Hz), 118.8 (CH), 117.0 (CH, d, *J* = 21.1 Hz), 86.4 (d, *J* = 3.5 Hz, C), 83.3 (C), 50.1 (CH) ppm. **HRMS** (ESI) *m/z*: 304.3010 $[M + H]^+$, $C_{15}H_{11}FNO_3S$ requires 304.0438.

(*R*)-4-((2-Methoxyphenyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ac)



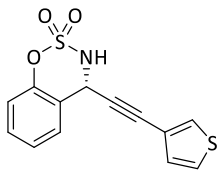
The enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 34.63 min, minor enantiomer t_r = 22.80 min. mp 103-105 °C; $[\alpha]_D^{20}$ = +31.2 (c 1.0, $CHCl_3$, 95% *ee*).

(*R*)-4-(Thiophen-2-ylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ag)



The enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 23.13 min, minor enantiomer t_r = 16.82 min. Oil; $[\alpha]_D^{20}$ = +43.6 (c 1.0, $CHCl_3$, 94% *ee*).

(*R*)-4-(Thiophen-3-ylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ah)

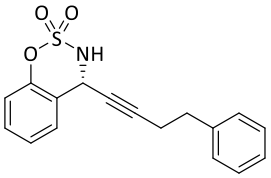


The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 24.90 min, minor enantiomer t_r = 17.25 min.

Oil; $[\alpha]_D^{20}$ = +46.1 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 2H), 7.39 (dddd, *J* = 8.2, 7.4, 1.7, 0.8 Hz, 1H), 7.32 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.26 (td, *J* = 7.6, 1.2 Hz, 1H), 7.16 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.92 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 8.0

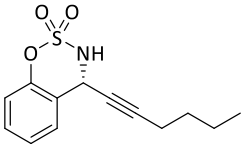
Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.5 (C), 130.7 (CH), 130.4 (CH), 129.8 (CH), 127.6 (CH), 125.9 (CH), 125.6 (CH), 120.1 (C), 119.5 (C), 118.7 (CH), 83.0 (C), 82.1 (C), 50.3 (CH) ppm. **HRMS** (ESI) *m/z*: 292.0107 $[M + H]^+$, $C_{13}H_{10}NO_3S_2$ requires 292.0097.

(*R*)-4-(4-Phenylbut-1-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ai)



The enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 24.64 min, minor enantiomer t_r = 26.71 min. Oil; $[\alpha]_D^{20}$ = +31.0 (c 1.0, $CHCl_3$, 78% *ee*).

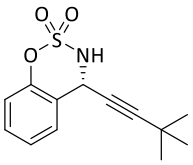
(*R*)-4-(Hex-1-yn-1-yl)-4H-benzo[*e*][1,2,3]oxathiazin-3-ide 2,2-dioxide (3aj)



The enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 20.09 min, minor enantiomer t_r = 17.12 min.

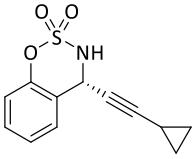
Oil; $[\alpha]_D^{20}$ = +58.2 (c 1.0, $CHCl_3$, 80% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 1H), 7.36 (dddd, *J* = 8.2, 7.4, 1.7, 0.8 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.73 – 5.64 (m, 1H), 4.71 (d, *J* = 10.0 Hz, 1H), 2.30 (td, *J* = 7.0, 2.3 Hz, 2H), 1.61 – 1.49 (m, 3H), 1.48 – 1.35 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.5 (C), 130.1 (CH), 127.6 (CH), 125.4 (CH), 120.2 (C), 118.5 (CH), 89.1 (C), 73.9 (C), 50.00 (CH), 30.3 (CH_2), 21.9 (CH_2), 18.3 (CH_2), 13.5 (CH_3) ppm. **HRMS** (ESI) *m/z*: 266.0848 $[M + H]^+$, $C_{13}H_{16}NO_3S$ requires 266.0845.

(*R*)-4-(3,3-Dimethylbut-1-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3ak)



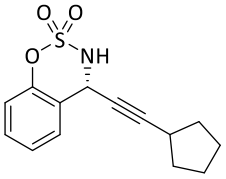
The enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 4.90 min, minor enantiomer t_r = 5.37 min. Oil; $[\alpha]_D^{20}$ = +71.9 (c 1.0, $CHCl_3$, 88% *ee*).

(*R*)-4-(Cyclopropylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3al)



The enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 9.77 min, minor enantiomer t_r = 11.17 min. mp 84-86 °C; $[\alpha]_D^{20}$ = +55.7 (c 1.0, $CHCl_3$, 91% *ee*).

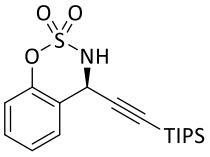
(*R*)-4-(Cyclopentylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3am)



The enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 21.96 min, minor enantiomer t_r = 17.32 min.

Oil; $[\alpha]_D^{20}$ = +62.0 (c 1.0, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 1H), 7.28 (dddd, *J* = 8.2, 7.4, 1.7, 0.8 Hz, 1H), 7.20 – 7.12 (m, 1H), 6.93 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.65 – 5.55 (m, 1H), 4.65 (d, *J* = 10.0 Hz, 1H), 2.70 – 2.58 (m, 1H), 1.97 – 1.81 (m, 2H), 1.70 – 1.48 (m, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.5 (C), 130.1 (CH), 127.6 (CH), 125.4 (CH), 120.3 (C), 118.5 (CH), 93.4 (C), 73.3 (C), 50.0 (CH), 33.6 (CH_2), 33.5 (CH_2), 29.9 (CH), 25.0 (CH_2) ppm. **HRMS** (ESI) *m/z*: 276.0705 $[M - H]^-$, $C_{14}H_{14}NO_3S$ requires 276.0700.

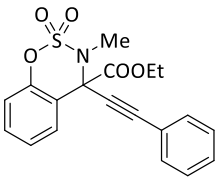
(*R*)-4-((Triisopropylsilyl)ethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (3an)



The enantiomeric excess (44%) was determined by chiral HPLC (Chiralpak ASH), hexane-iPrOH 99:01, 1 mL/min, major enantiomer t_r = 16.97 min, minor enantiomer t_r = 11.94 min.

Oil; $[\alpha]_D^{20}$ = +25.1 (c 1.0, $CHCl_3$, 44% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 - 7.51 (m, 1H), 7.37 (dddd, *J* = 8.2, 7.4, 7.1, 1.8 Hz, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 1.10 – 1.09 (21H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.6 (C), 130.3 (CH), 127.5 (CH), 125.5 (CH), 119.5 (C), 118.6 (CH), 99.9 (C), 90.5 (C), 50.33 (CH), 18.5 (CH_3), 11.0 (CH) ppm. **HRMS** (ESI) *m/z*: 366.1557 $[M + H]^+$, $C_{18\ h28}NO_3Si$ requires 366,1553.

Ethyl 3-methyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (17)

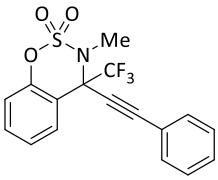


Enantioselective alkynylation of product **12** was achieved following the general procedure for the enantioselective alkynylation reaction of products **1**. Methylation of the product was performed after purification of the reaction mixture. The purified product was dissolved in MeCN (1 mL), K_2CO_3 (5 equiv) and MeI (5 equiv) were added the reaction was stirred for 1 h. Afterwards, the reaction was filtered and the final product **17** was obtained in quantitative yield.

The enantiomeric excess (22%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose-1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 8.71 min, minor enantiomer t_r = 9.24 min.

Orange oil; $[\alpha]_D^{20}$ = -3.4 (c 1.0, $CHCl_3$, 22% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.46 – 7.28 (m, 5H), 7.06 (dd, *J* = 8.2, 1.3 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.25 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8 (C), 149.2 (C), 132.0 (CH), 131.7 (CH), 130.8 (CH), 129.8 (CH), 128.5 (CH), 125.4 (CH), 120.7 (C), 118.4 (C), 118.3 (CH), 90.0 (C), 82.2 (C), 69.0 (C), 63.7 (CH_2), 35.4 (CH_3), 13.8 (CH_3) ppm; **HRMS** (ESI) *m/z*: 372.3889 $[M + H]^+$, $C_{19}H_{17}NO_5S$ requires 372.3900.

4-(Phenylethynyl)-4-(trifluoromethyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (18)



Enantioselective alkynylation of product **14** was achieved following the general procedure for the enantioselective alkynylation reaction of products **1**. Methylation of the product was performed after purification of the reaction mixture. The purified product was dissolved in MeCN (1 mL), K_2CO_3 (5 equiv) and MeI (5 equiv) were added the reaction was stirred for 1 h. Afterwards, the reaction was filtered and the final product 1**8** was obtained in quantitative yield.

The enantiomeric excess (2%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 6.46 min, minor enantiomer t_r = 6.01 min.

Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85 (dp, *J* = 8.0, 1.3 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.49 – 7.35 (m, 4H), 7.22 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.38 (d, *J* = 0.7 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.2 (C), 132.2 (CH), 132.1 (CH), 130.5 (q, $J_{c\text{-}f}$ = 1.3 Hz, CH), 130.2 (CH), 128.6 (CH), 126.7 (CH), 123.3 (q, $J_{c\text{-}f}$ = 288 Hz, C), 120.0 (C), 119.6 (C), 119.4 (CH), 91.7 (C), 78.1 (C), 67.5 (q, $J_{c\text{-}f}$ = 32.5, C), 33.6 (q, $J_{c\text{-}f}$ = 2.2 Hz, CH_3) ppm. **HRMS** (ESI) *m/z*: 368.0559 $[M + H]^+$, $C_{17}H_{13}F_3NO_3S$ requires 368.0563.

3.6. REFERENCES

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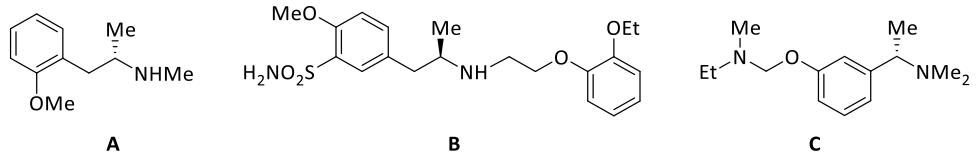
CHAPTER 4

ENANTIOSELECTIVE ALKYLATION OF DIBENZO[*b,f*][1,4]OXAZEPINES CATALYZED BY COMPLEXES OF (*R*)-VAPOL-Zn

4.1. INTRODUCTION

Additions of organometallic reagents to imines and imine derived compounds such as hydrazones and oximes, is an old an well-known reaction.[1] However, there are two important problems in the addition reactions to imines: the poor electrophilicity of the azomethine carbon and the tendency of the imines to undergo deprotonation rather than addition. As already discussed in the previous chapter, a method to increase the reactivity of the double C=N bond, is the introduction of electron-withdrawing groups on the nitrogen of the imine, which can be made by *N*-alkylation, *N*-oxidation, *N*-acylation or *N*-sulfonylation among others. On the other hand, in order to avoid deprotonation, less strong basic reagents are used to obtain the alkyl addition products to the azomethine carbon. Examples of these reagents are allylboranes, allylboronates, alkylcoppers, alkyl cuprates and alkylzincs.

So, the catalytic asymmetric addition of organometallic reagents to C=N double bonds of imines is an excellent route to obtain optically active amines bearing a stereogenic center at the α-position (the importance of the synthesis of optically active compounds has already been discussed).[2] The optically active α-branched amines are important building blocks and this type of structure can be found in numerous biologically and pharmacologically active compounds, such as Methoxyphenamine (a β_2-adrenergic antagonist for treatment of asthma) (Figure 4.1, **A**),[3] Rivastigmine (an acetylcholine esterase inhibitor for treatment of Alzheimer's disease) (Figure 4.1, **B**)[4] and Tamsulosin (a selective α_1- adrenergic antagonist in the treatment of prostatic hyperplasia) (Figure 4.1, **C**).[5]



A **B** **C**

Figure 4.1. (**A**) Methoxyphenamine (**B**) Rivastigmine (**C**) Tamsulosin.

As mentioned before, a possible way to prepare chiral amines is the addition of dialkylzinc reagents to imines. However, dialkylzinc reagents are nucleophilic organometallic compounds with low reactivity and generally react slowly or not react at all with imines due to the rather nonpolar character of the C-Zn bond. There are a few methods to overcome this problem. One method is based in the use of transition metal salts inducing transmetalation or complexation, forming functionalized dialkylzinc reagents, improving the reactivity of the dialkylzinc towards the imine. Examples of transition metals that are often used are copper,[2, 6-8] rhodium,[9] zirconium[10-12] and titanium.[13] Another method of activation of dialkylzinc reagents is the use of Lewis basic ligands, making the Zn more Lewis acidic. This methodology is highly desirable in order to avoid the use of other transition metal salts. Next, the most important examples of alkylation of imines with dialkylzinc reagents in the absence of other transition metals is described.

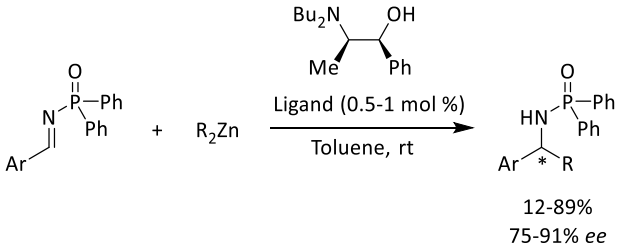
4.1.1. Catalytic enantioselective alkylation of imines with dialkylzinc reagents

A striking observation in the catalytic enantioselective alkylation of imines using a dialkylzinc reagents is that most of the examples described in absence of other transition metals are performed with *N*-diphenylphosphinoylimines, which can be explained by the stronger electrophilicity of the carbon atom of the imine group and the easy removing of the phosphinoyl group to give free amines.

In this part, we will limit our discussion to those examples that use substoichiometric amounts of ligand. Methods using stoichiometric amounts of ligand are very abundant in the literature.[14-17]

4.1.1.1. Catalytic enantioselective alkylation of *N*-diphenylphosphinoylimines with dialkylzinc reagents

The first example of a highly enantioselective addition of dialkylzinc reagents to the C=N double bonds of imines (*N*-diphenylphosphinoylimines) using from stoichiometric to catalytic amounts of ligand was described by Soai in 1992.[18] This group used 0.5-1 equivalents of a chiral β-amino alcohol **I** (Scheme 4.1) to obtain various ethylated, methylated and *n*- butylated aromatic phosphinoylamines in good yields and good to excellent enantioselectivities. The enantioselectivities varied from 84-91% *ee* when a stoichiometric amount of ligand is used to 85-87% *ee* when 0.5 equivalents of ligand were used. Even when the authors used 0.1 equivalents of ligand, the enantioselectivity was still high (75% *ee*), but the yield decreased to only 12%. This article was also the first one that described an alkylation reaction of a carbon-nitrogen double bond with an enantiomeric excess higher than 90%.



Scheme 4.1. Catalytic enantioselective alkylation of *N*-diphenylphosphinoylimines promoted by (1*S*,2*R*)-2-(Dibutylamino)-1-phenylpropan-1-ol.

In 2002, the same group described an addition of dialkylzinc reagents to *N*-diphenylphosphinoylimines using catalytic amounts of chiral carbosilane dendritic ligands bearing aminol alcohol moieties.[19] Although these ligands have a flexible backbone and are known to be difficult to coordinate with organometallic reagents, this research group achieved interesting results. When ligand **I** (4 chiral sites, 0.25 equivalents) and ligand **II** (12 chiral sites, 0.083-0.13 equivalents) (Figure 4.2) were used in the Et_2Zn and $^{i}Pr_2Zn$ addition reaction to various aromatic *N*-diphenylphosphinoylimines, the corresponding products were obtained in good yields (70-79 %) and good to excellent enantiomeric excesses (82-92% *ee*). Ligand **III** was also used in the same reaction, though the reaction needed 0.5 equivalents of the ligand to obtain good results (71-81%, 86-94% *ee*).

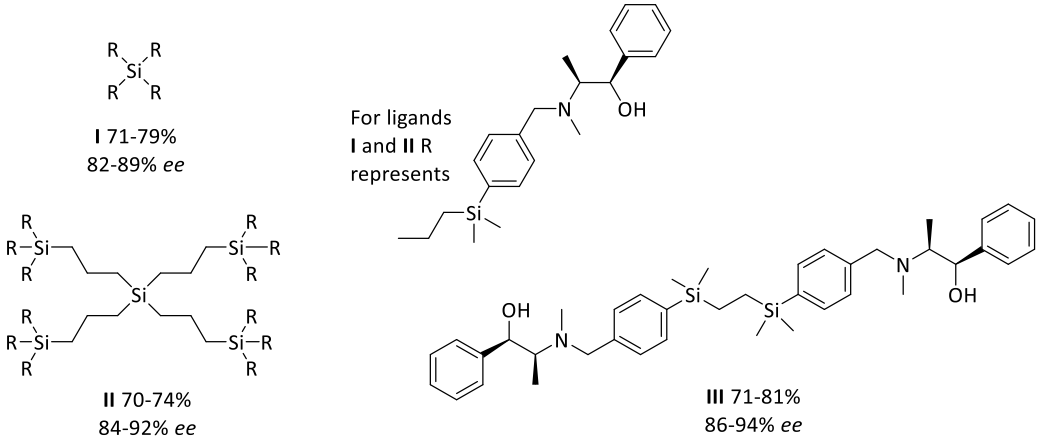
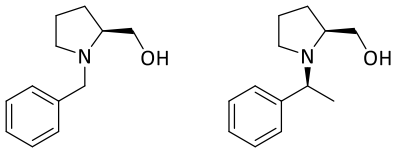


Figure 4.2. Chiral carbosilane dendritic ligands bearing aminol alcohol moieties.

In 2007, Yus group described the addition of dialkylzinc reagents to *N*-diphenylphosphinoylimines catalyzed by β-amino alcohols derived from L-prolinol.[20, 21] The commercially available *N*-benzyl-*L*-prolinol **IV** (0.5 equivalents) (Figure 4.3) was tested in the Et_2Zn addition reaction with various substituted imines obtaining the corresponding chiral diphenylphosphinoylamines in moderate to good yields (36-86%) and moderate to excellent enantiomeric excesses (58-92% *ee*). The reaction, under the same reaction conditions, was also performed with Me_2Zn (51%, 90% *ee*), $^{i}Pr_2Zn$ (80%, 90% *ee*) and $^{n}Bu_2Zn$ (64%, 90% *ee*). In the same article, the authors performed a further screening of ligands of various β-amino alcohols derived from *L*-prolinol, in which ligand **V** led to a good yield (80%) and an excellent enantioselectivity (94% *ee*) for the reaction between Et_2Zn and *N*-(diphenylphosphinoyl)benzaldimine.

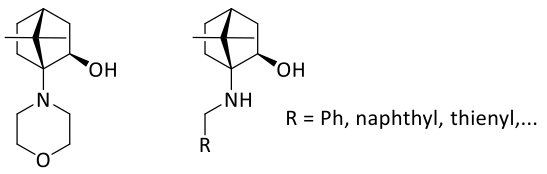


IV 36-86%
58-92% *ee*

V 80%
94% *ee*

Figure 4.3. β-Aminoalcohols derived from L-prolinol.

Recently, in 2015, Uang and collaborators published their efforts on the enantioselective addition of dialkylzinc to aromatic aldimines mediated by β-amino alcohols derived from camphor (Figure 4.4).[22] The reaction conditions (0.6 equivalents of ligand **VI**, 3 equivalents of Et_2Zn at 28 °C in toluene/hexane) were used with various aromatic *N*-diphenylphosphinoylimines, obtaining excellent results both in yield (85-97%) as in enantioselectivity (85-98% *ee*). For the reaction with Me_2Zn, 1 equivalent of ligand was needed to obtain excellent yields (85-86%) and enantioselectivities (97-98% *ee*). The researchers also used different *N*-monosubstituted amino alcohols **VII** (0.6 equivalents) and all of them gave excellent results (91-99% yield, 91-95% *ee*). To decrease the number of equivalents of chiral ligand in the reaction, they tested various additives in the Et_2Zn addition to *N*-(diphenylphosphinoyl)benzaldimine. The use of MeOH (1.8 equivalents) and only 0.1 equivalents of ligand lead to the reaction product with similar results than when used 0.6 equivalents of ligand. Again, they applied the optimized reaction conditions to various imines, using 0.1 equivalents of the phenyl substituted ligand **VII**, for the addition of Et_2Zn leading to good results (52-92% yield, 79-92% *ee*). The addition of Me_2Zn could also be made with 0.1 equivalents of ligand **VII**, obtaining the resulting product in a yield of 78% and an enantiomeric excess of 93% *ee*.



VI 85-97%
85-98% *ee*

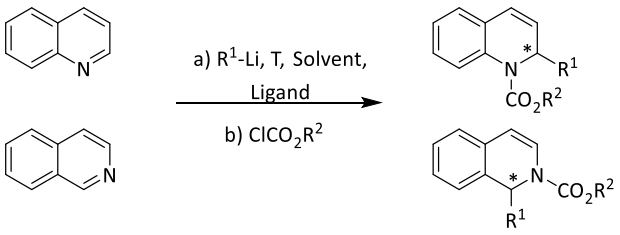
VII 52-92%
79-92% *ee*

Figure 4.4. β-Amino alcohols derived from camphor.

4.1.1.2. Catalytic enantioselective alkylation of cyclic imines

There are only few reports of catalytic enantioselective alkylation of cyclic imines in the literature. In 2001, Chrzanowska described an enantioselective addition of organolithium reagents to 3,4-dihydroisoquinoline.[23] On the other hand, Alexakis described the enantioselective addition of organolithium reagents to isoquinoline[24] in 2002 and to quinoline in 2004[25] and 2005.[26] However, all

of the authors use stoichiometric amounts of chiral ligands (Scheme 4.2). However, the catalytic enantioselective alkylation of cyclic imines with dialkylzinc reagents is, to the best of our knowledge, not described in the literature.



Scheme 4.2. Enantioselective alkylation of cyclic imines.

4.1.2. Catalytic enantioselective reactions of dibenzo[*b,f*][1,4]oxazepines

As we have mentioned, the enantioselective addition of dialkylzinc reagents to cyclic imines has not been described in the literature except in the case of quinoline and isoquinoline. Consequently, we thought in the use of seven membered cyclic imines (dibenzo[*b,f*][1,4]oxazepines) as electrophiles.

The dibenzo[*b,f*][1,4]oxazepine structure **A** (Figure 4.5) is a privileged scaffold in medicinal chemistry. This motif is present in many physiologically and biologically active compounds (Figure 4.5) such as non-nucleoside HIV-1 reverse transcriptase inhibitors **B**,[27] histamine H_4 receptor agonist **C**[28] and PGE_2 antagonist **D**.[29-31] Furthermore the compound **A** is commonly known as CR gas and is used as an incapacitating agent and a lachrymatory agent (it is 6 to 10 times more powerful than CS gas, 2-chlorobenzalmalononitrile, the active compound of tear gas) as it works as an extremely potent activator of the human transient receptor potential Ankyrin 1 (TRPA1) channel.[32]

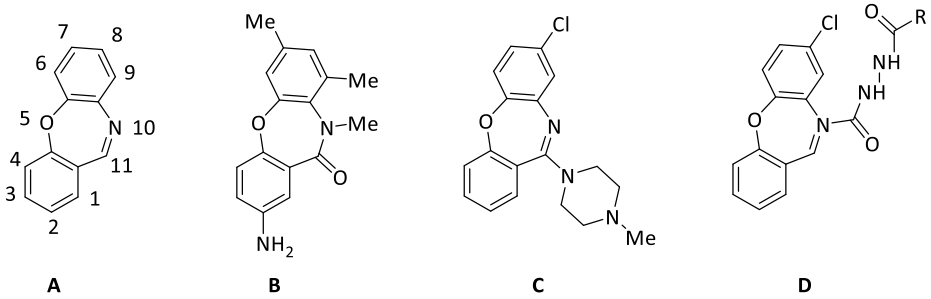
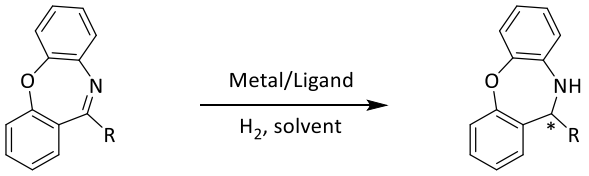


Figure 4.5. (**A**) Structure of dibenzo[*b,f*][1,4]oxazepane (**B**) HIV-1 reverse transcriptase inhibitor (**C**) Histamine H_4 receptor agonist (**D**) PGE_2 antagonist.

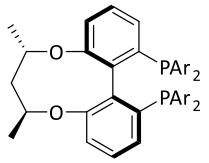
Despite that the cyclic seven membered dibenzoxazepines are very interesting scaffolds, very few examples of catalytic enantioselective reactions with this kind of imines have been described in literature. These examples include hydrogenations, Mannich reactions, an alkynylation reaction and a propargylation reaction.

4.1.2.1. Catalytic enantioselective hydrogenations of dibenzo[b,f][1,4]oxazepines



Scheme 4.3. Hydrogenation of dibenzoxazepines.

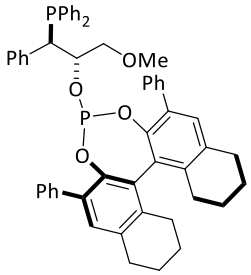
In 2011, the first catalytic enantioselective hydrogenation (Scheme 4.3) of benzoxazepines was described by Zhang and collaborators.[33] The hydrogenation was performed with an $[Ir(COD)Cl]_2$/(*S*)-Xyl-C_3*-TunePhos (**VIII**) complex (Figure 4.6), which was chosen after an intensive optimization of the reaction conditions. The reaction conditions include the presence of 20 mol % of an additive (morpholine-HCl, Brønsted acid), while only a 2.2 mol % of ligand is needed. Various differently substituted alkyl and aryl ketimines were hydrogenated under the reaction conditions, obtaining the corresponding chiral amines in poor to good yields (12-98%) and moderate to excellent enantioselectivities (52-94% *ee*). The worst results were obtained in the case of aryl ketimines.



VIII (Ar = 3,5-dimethylphenyl)
12-98%
52-94% *ee*

Figure 4.6. (*S*)-Xyl-C_3*-TunePhos ligand.

Vidal-Ferran and collaborators described in 2015, the asymmetric hydrogenation of seven membered imines using also a chiral iridium complex.[34] In this report, the authors not only describe the hydrogenation of dibenzoxazepines, but they also apply the same reaction conditions to the sulphur, carbon, nitrogen and sulphur dioxide analogues. Optimized conditions for the hydrogenation reactions were: *in situ* prepared $[\{Ir(\mu\text{-}Cl)(COD)\}_2]$/phosphine-phosphite complex (0.5 mol % metal, 1.1 mol % ligand **IX**) (Figure 4.7) and MeTHF as solvent in the presence of HCl (10 mol %). In general, good results were obtained, both in yields (24-99%) as in enantioselectivities (9-97% *ee*). However, some remarks have to be made. In first place, aryl ketimines were less reactive than the alkyl ketimines, leading to the final products with low yields and enantioselectivities. Another remark is the low enantioselectivity of the reaction with the carbon-analogue, which is lower when compared with the other analogues.

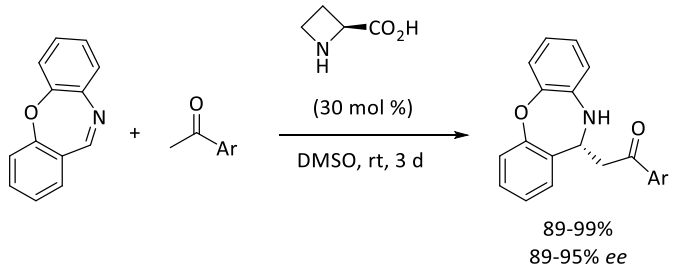


IX 24-99%
9-97% *ee*

Figure 4.7. Phosphine-phosphite ligand.

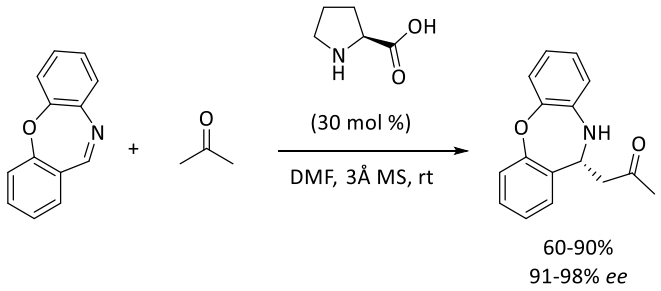
4.1.2.2. Catalytic enantioselective Mannich reactions of dibenzo[*b,f*][1,4]oxazepines

The first catalytic enantioselective direct Mannich reaction using benzoxazepines as electrophiles was published in 2014 (Scheme 4.4).[35] Wang and collaborators described the Mannich reaction between dibenzo[*b,f*][1,4]oxazepines and acetophenone under the following optimized conditions: 30 mol % of (*S*)-azetidine-2-carboxylic acid, which functions as a organocatalyst, in DMSO at room temperature. The corresponding Mannich product was obtained in good yield (94%) and excellent enantiomeric excess (93% *ee*). Various substituted acetophenones were tested under the reaction conditions, obtaining in general similar yields and enantioselectivities. However, a methoxy group in *ortho* position of the aromatic ring did not allow the reaction to take place, which can be explained by steric effects. The scope of the reaction was extended by using various substituted dibenzoxazepines, leading to similar yields (89-99%) and enantioselectivities (89-95% *ee*). No enantioselectivity was obtained when an α-substituted acetophenone was used (64% yield, 0% *ee*)



Scheme 4.4. Mannich reaction between dibenzo[*b,f*][1,4]oxazepines and acetophenone.

More recently, the same group described the enantioselective Mannich reaction using acetone as nucleophile (Scheme 4.5).[36] Interestingly, in the reaction with acetone, compared with the reaction with acetophenone, the best organocatalyst was (*S*)-proline (30 mol %). The presence of 3Å molecular sieves in the solution with DMF, increases the enantioselectivity. This beneficial effect of the molecular sieves can be attributed to the minimization of the moisture or to the reduction of the basicity of the nitrogen atom. These reaction conditions were applied to several differently substituted cyclic seven membered imines, obtaining good to excellent yields (60-90%) and high to excellent enantiomeric excess (91-98%). The reaction conditions could also be applied to the reaction of 2-butanone with dibenzo[*b,f*][1,4]oxazepine, obtaining the resulting product in good yield (92%) and excellent enantiomeric excess (96%)

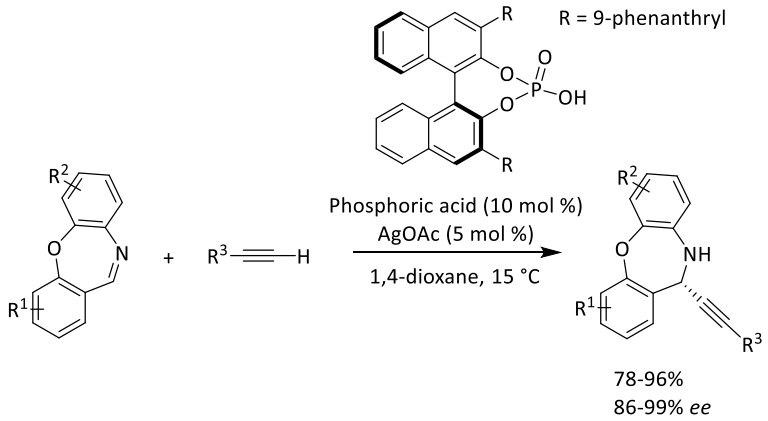


Scheme 4.5. Mannich reaction between dibenzo[*b,f*][1,4]oxazepine and acetone.

4.1.2.3. Catalytic enantioselective alkynylation of dibenzo[*b,f*][1,4]oxazepines

In 2014, Wang and collaborators described the first and only alkynylation reaction with dibenzoxazepines.[37] This publication is also the first report of an catalytic enantioselective alkynylation of seven membered cyclic imines in general. The optimized conditions of the reaction consists in performing the alkynylation reaction at 15 °C in 1,4-dioxane, in the presence of an AgOAc/chiral

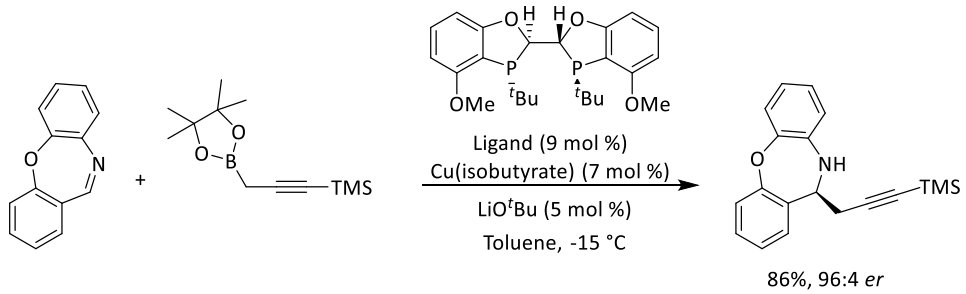
phosphoric acid complex (5 mol % AgOAc and 10 mol % chiral phosphoric acid) (Scheme 4.6). These conditions allowed the authors to test various terminal aromatic, heteroaromatic and alkyl alkynes as nucleophiles, which led to good results (38-92% yield, 78-95% *ee*). With the alkyne that gave the best result in the reaction with dibenzo[*b,f*][1,4]oxazepine (ethynylcyclohexane; 92% yield, 95% *ee*), the reaction was tested with different substituted dibenzo[*b,f*][1,4]oxazepines. Excellent results were obtained both in yield (78-96%) and enantioselectivity (86-99% *ee*). The reaction conditions were also used for the addition of a terminal 1,3-diyne, which resulted in slightly lower values for yield (53-90%) and enantioselectivity (63-96% *ee*). The authors also performed various transformations on the reaction product such as the reduction of the triple bond of the alkyne to the corresponding alkane and alkene, without any loss of enantiopurity.



Scheme 4.6. Catalytic enantioselective alkynylation reaction of dibenzo[*b,f*][1,4]oxazepines.

4.1.2.4. Catalytic enantioselective propargylation of dibenzo[*b,f*][1,4]oxazepines

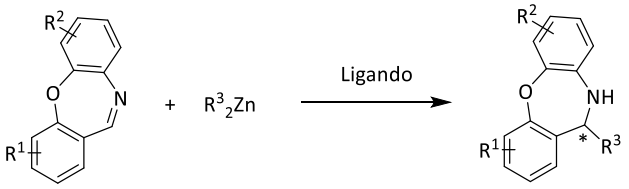
Very recently, Fandrick and coworkers presented a copper-catalyzed asymmetric propargylation of cyclic aldimines in general.[38] The authors performed the propargylation reaction for a series of cyclic imines, one of which was a dibenzo[*b,f*][1,4]oxazepine. The reaction conditions were optimized for the reaction between a propargyl borolane and a dihydroisoquinoline. The reaction gives the best results when performed in toluene at -15 °C in the presence of a Cu(isobutyrate)/MeOBIBOP complex. These conditions were also applied on the reaction with dibenzo[*b,f*][1,4]oxazepine, obtaining the chiral homopropargylic cyclic amine in good yield (86%) and good enantiomeric ratio (96:4) (Scheme 4.7).



Scheme 4.7. Catalytic enantioselective propargylation reaction of dibenzo[*b,f*][1,4]oxazepine.

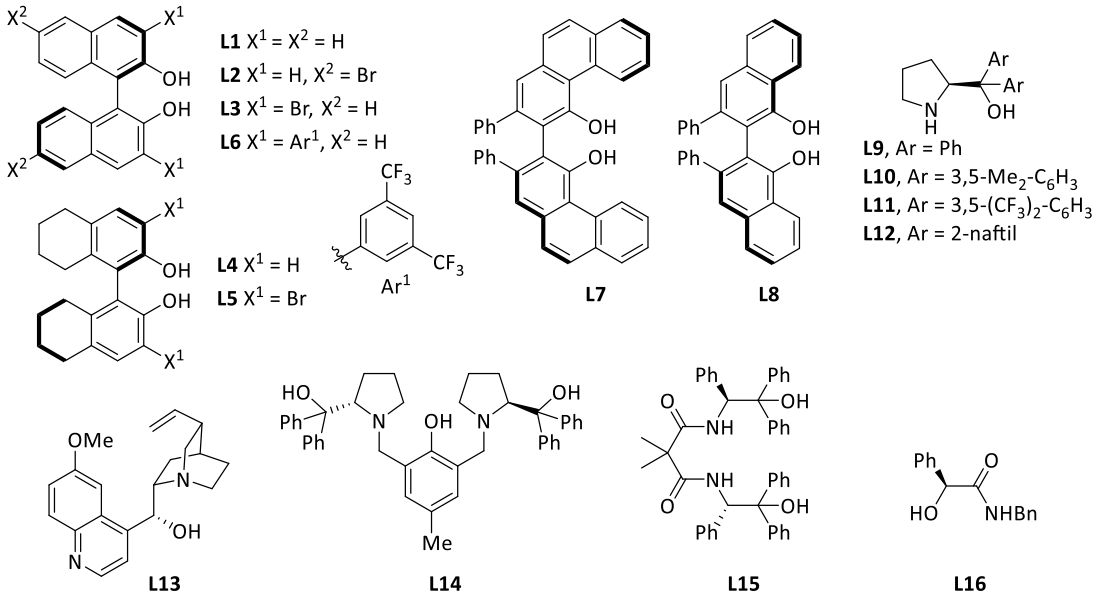
4.2. OBJETIVOS

El objetivo general de este capítulo es el desarrollo de un método catalítico y enantioselectivo de adición de reactivos de dialquilzinc a aldiminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina que transcurra con buenos rendimientos y excesos enantioméricos.



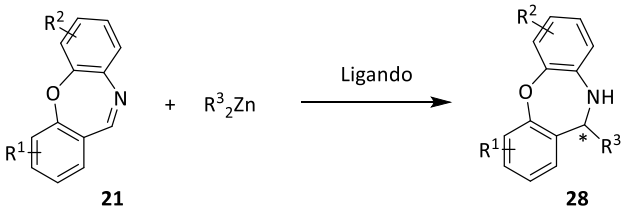
En el estudio de este proyecto se consideran los siguientes aspectos:

1. Influencia de la estructura de diversos ligandos de tipo (*R*)-BINOL (**L1**-**L6**), (*R*)-VAPOL (**L7**), (*R*)-VANOL (**L8**), ligandos derivados de (*S*)-prolinol (**L9**-**L12**), quinina (**L13**), ligando de Trost (**L14**) y dos α-hidroxiamidas (**L15** y **L16**) sobre el rendimiento y la enantioselectividad de la reacción.



2. La influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn) y disolvente de la reacción.

3. Evaluación de diversas aldiminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina con diferente naturaleza electrónica y estérica en la reacción con reactivos de dialquilzinc.



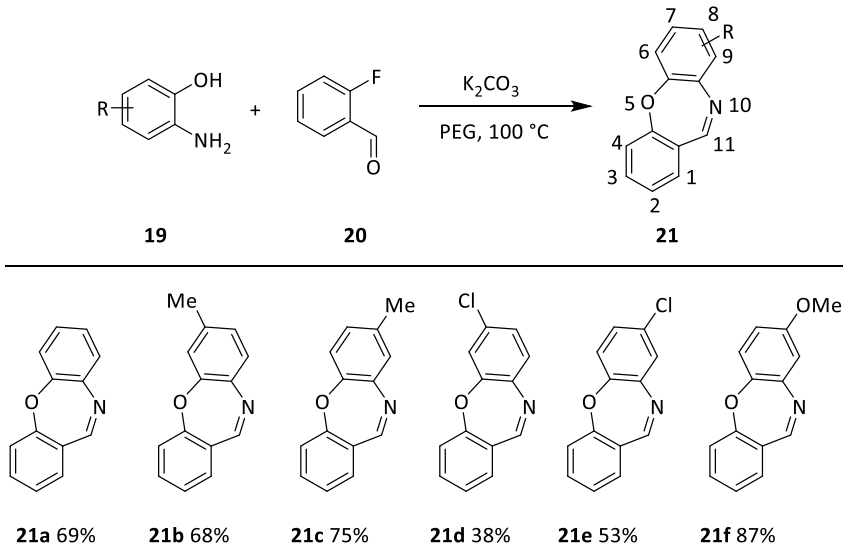
4. Determinación de la configuración absoluta del centro estereogénico presente en los productos obtenidos.

4.3. RESULTADOS Y DISCUSIÓN

4.3.1. Síntesis de dibenzo[*b,f*][1,4]oxazepinas

4.3.1.1. Síntesis de dibenzo[*b,f*][1,4]oxazepinas sustituidas en posiciones 7 y 8

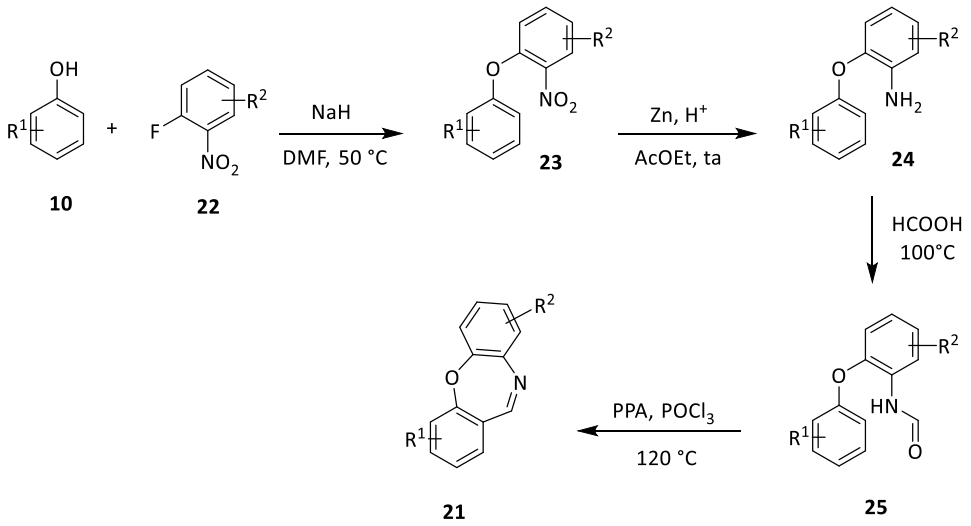
Las dibenzo[*b,f*][1,4]oxazepinas sustituidas en posiciones 7 y 8 se han preparado a partir de varios 2-aminofenoles con diferentes sustituyentes **19** y 2-fluorobenzadehido **20** en un único paso, utilizando K_2CO_3 como base y PEG (polietilenoglicol) como disolvente (Esquema 4.8). Se trata de una reacción de condensación de la amina y el aldehído seguido por una sustitución nucleofílica aromática. La síntesis transcurre con rendimientos que van de moderados a excelentes. Los mejores rendimientos se obtuvieron con 2-aminofenoles con sustituyentes de tipo electrón-donante (**21b**, **21c** y **21f**).



Esquema 4.8. Síntesis de dibenzo[*b,f*][1,4]oxazepinas sustituidos en posiciones 7 y 8. **19** (5,5 mmol), **20** (5,0 mmol), K_2CO_3 (5,0 mmol). Rendimiento después de purificación por cromatografía de columna.

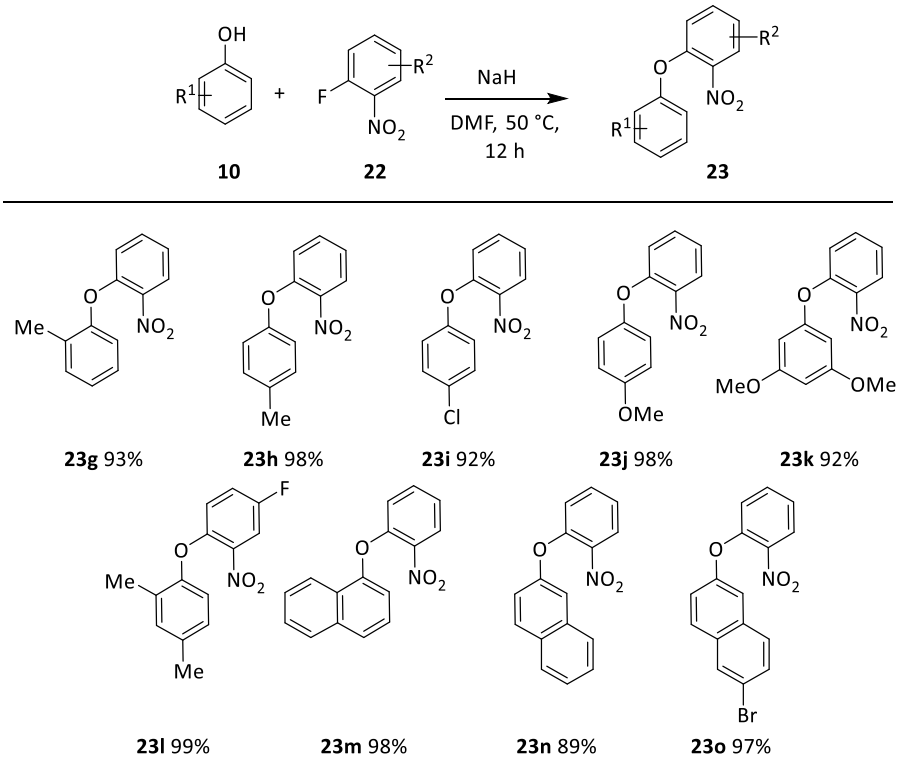
4.3.1.2. Dibenzo[*b,f*][1,4]oxazepinas sustituidas en posiciones 1-4

La síntesis de este tipo de dibenzo[*b,f*][1,4]oxazepinas también se puede llevar a cabo por el método anterior, a partir de 2-fluorobenzaldehidos convenientemente sustituidos. Pero estos son caros y por este motivo se ha optado por una síntesis que, aunque más larga, resulta más asequible y barata. La secuencia utilizada está descrita en la literatura (Esquema 4.9).[33]



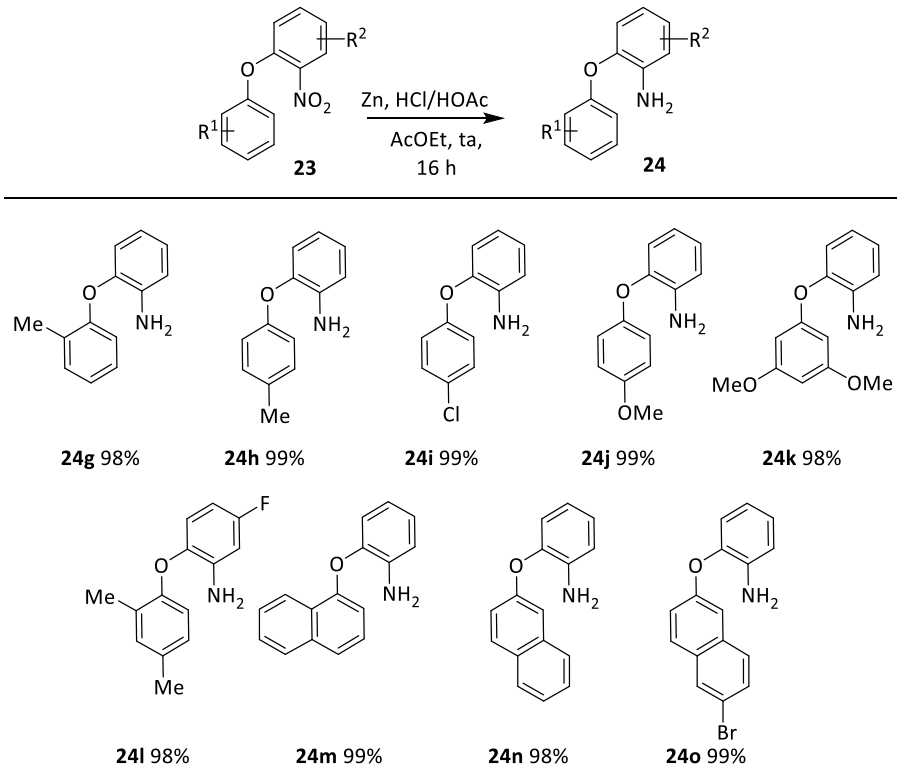
Esquema 4.9. Síntesis de dibenzo[*b,f*][1,4]oxazepinas sustituidas en posiciones 1-4.

La primera etapa de la secuencia sintética consiste en la reacción entre derivados de fenol (**10**) y derivados de 1-fluoro-2-nitrobenceno (**22**). En primer lugar se desprotona el fenol con NaH y el fenóxido resultante actúa como nucleófilo en la sustitución nucleofílica aromática con el 1-fluoro-2-nitrobenceno **22**. Las reacciones muestran una alta conversión y selectividad siendo los rendimientos obtenidos elevados (89-99%) (Esquema 4.10).



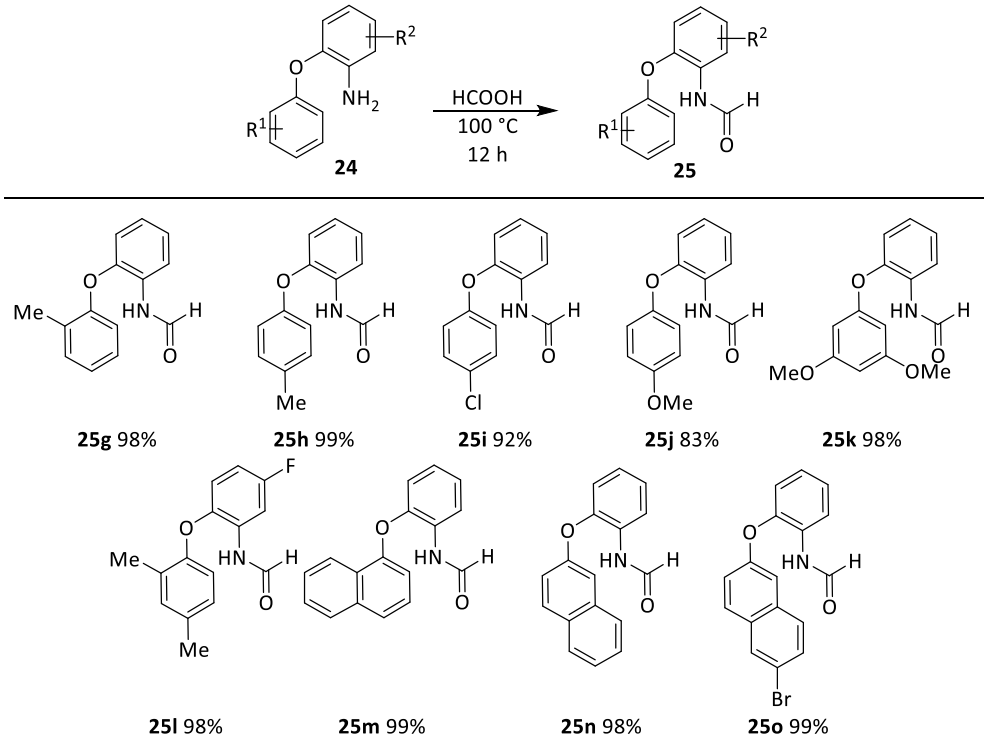
Esquema 4.10. Primera etapa de la síntesis de dibenzo[*b,f*][1,4]oxazepinas en posiciones 1-4. **10** (15 mmol), **22** (10 mmol), NaH (16 mmol). Rendimiento después de purificación por cromatografía de columna.

La segunda etapa consiste en la reducción del grupo nitro con Zn metálico en una disolución ácida para la obtención de las aminas **24**. La reacción funciona muy bien y los rendimientos son practicamente cuantitativos (Esquema 4.11). Los productos se obtienen suficientemente puros después de la extracción y se utilizaron directamente en la siguiente etapa.



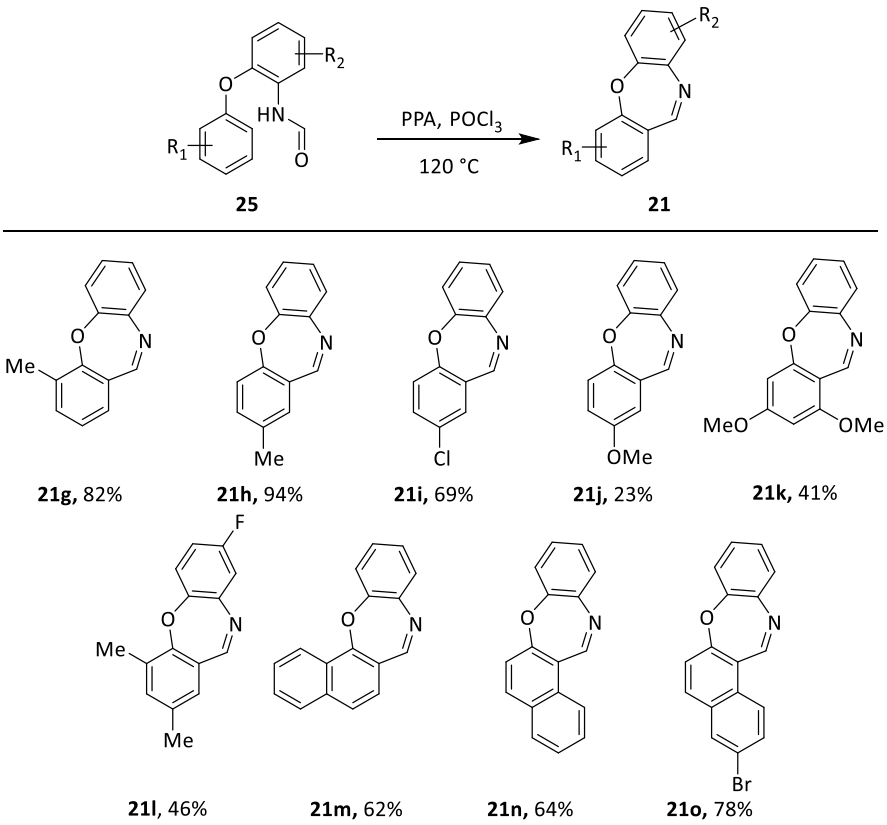
Esquema 4.11. Segunda etapa de la síntesis de dibenzo[*b,f*][1,4]oxazepinas en posiciones 1-4. **23** (8 mmol), **Zn** (240 mmol). Rendimiento después de purificación por cromatografía de columna.

La amina formada en la etapa anterior se disuelve en ácido fórmico y se calienta hasta 100 °C durante 12 horas, lo cual da lugar a la formación de la amida **25**. Estas amidas no requieren purificación y se utilizaron directamente en la siguiente etapa de la síntesis (Esquema 4.12).



Esquema 4.12. Tercera etapa de la síntesis de dibenzo[*b,f*][1,4]oxazepinas en posiciones 1-4. **24** (7,5 mmol), HCOOH (5 mL).

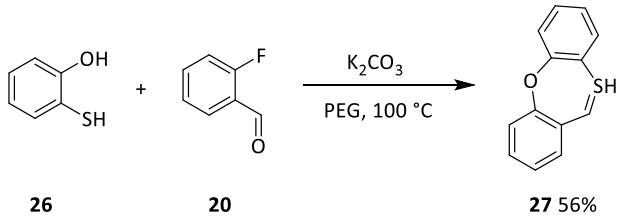
La última etapa es la ciclación del producto **25** mediante la reacción de Bischler-Napieralski (Esquema 4.13). El tricloruro de fosforilo se coordina al oxígeno de la amida, aumentando la electrofilia del átomo de carbono del grupo carbonilo, facilitando la reacción de Friedel-Crafts. Tras la eliminación del grupo fosforilo se obtiene la imina **21**. Los rendimientos obtenidos son muy variable, desde bajos (23%) a excelentes (94%), dependiendo de los sustituyentes del anillo aromático.



Esquema 4.13. Última etapa de la síntesis de dibenzo[*b,f*][1,4]oxazepinas en posiciones 1-4. **25** (4 mmol), $POCl_3$ (20 mmol). Rendimiento después de purificación por cromatografía de columna.

4.3.1.3. Síntesis de dibenzo[*b,f*][1,4]tiazepina

La dibenzo[*b,f*][1,4]tiazepina **27** se preparó mediante la reacción entre 2-aminotiofenol **26** y el 2-fluorobenzadehido **20** en una única etapa, utilizando K_2CO_3 como base en PEG (polietilenoglicol) (Esquema 4.14). Esta reacción es del mismo tipo que la utilizada anteriormente para la síntesis de las dibenzoxazepinas (**21a**-**21f**). El rendimiento de la reación de formación de la dibenzotiazepina **27** es moderado (56%).



Esquema 4.14. Síntesis de dibenzo[*b,f*][1,4]tiazepina.

4.3.2. Optimización de las condiciones de la reacción

El proceso de optimización de las condiciones de la reacción se inició estudiando la reacción entre Et_2Zn y la dibenzo[*b,f*][1,4]oxazepina (**21a**), en presencia de un ligando quiral utilizando diclorometano como disolvente. Se han ensayado varios tipos de ligandos [de tipo (*R*)-BINOL (**L1**-**L6**), (*R*)-VAPOL (**L7**), (*R*)-VANOL (**L8**), ligandos derivados de (*S*)-prolinol (**L9**-**L12**), quinina (**L13**), el ligando de Trost (**L14**) y dos α-hidroxiamidas (**L15** y **L16**)] (Tabla 4.1).

En la evaluación de los ligandos se ensayaron, en primer lugar, varios derivados de tipo (*R*)-BINOL. Se puede observar que en general, los rendimientos (16-36%) y las enantioselectividades (8-50% *ee*) son bajos (Tabla 4.1, Entradas 1-6), aunque la presencia de un átomo de bromo en las posiciones 6 y 6' (Tabla 4.1, entrada 2) da lugar al producto correspondiente **28a** con una enantioselectividad moderada (50% *ee*), pero con un rendimiento bajo (34%).

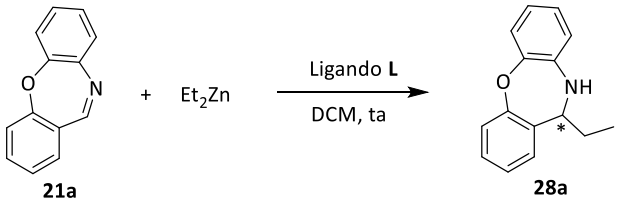
Cuando se utilizó (*R*)-VAPOL (**L7**) como ligando, se observó un aumento en la enantioselectividad de la reacción hasta un 61% *ee*, sin embargo, el rendimiento obtenido resultó bajo (36%) (Tabla 4.1, entrada 7). (*R*)-VANOL (**L8**), un ligando menos voluminoso comparado con (*R*)-VAPOL (**L7**), condujo al producto **28a** en forma prácticamente racémica (5% *ee*) (Tabla 4.1, entrada 8).

Aunque el resultado con (*R*)-VAPOL (**L7**) era prometedor, decidimos evaluar otros ligandos quirales. En primer lugar se ensayaron ligandos derivados de (*S*)-prolinol (**L9**-**L12**) (Tabla 4.1, entradas 9-12). Los rendimientos obtenidos con estos ligandos fueron más elevados (40-53%). Sin embargo, la enantioselectividad de la reacción fue prácticamente nula (0-5%). El uso de quinina (**L13**) tampoco dio lugar a mejores resultados (30% rendimiento, 5% *ee*) (Tabla 4.1, entrada 13). El ligando de Trost (**L14**), un ligando descrito anteriormente en reacciones de alquilación,[39] dio como resultado un rendimiento de 48%, pero un exceso enantiomérico de 20%, lo cual no mejora el resultado obtenido con **L7** (Tabla 4.1, entrada 14).

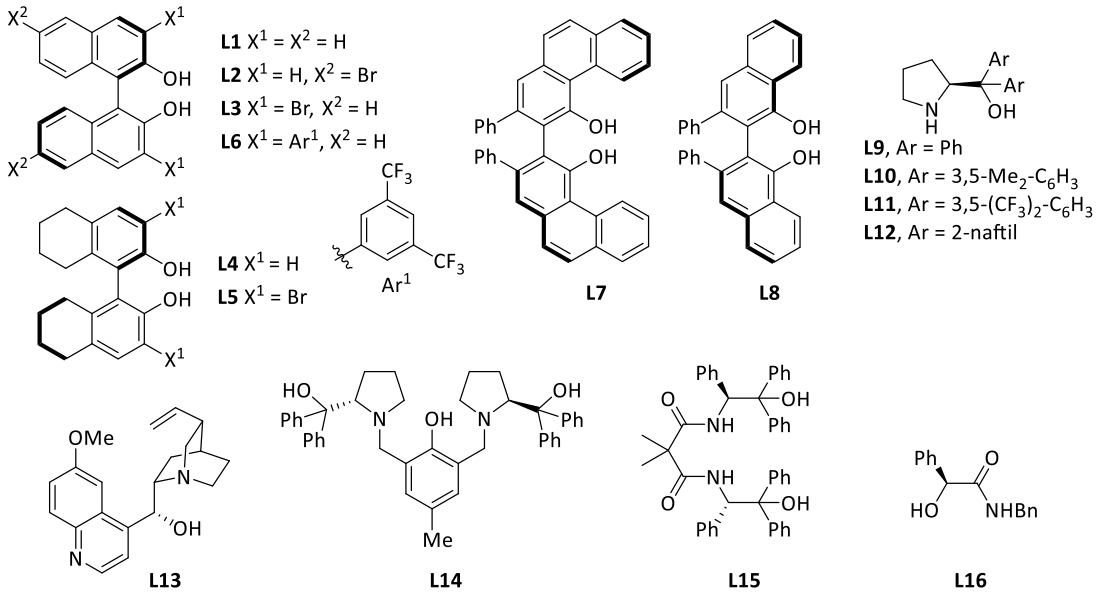
Por último, también se utilizaron como ligandos la bis-α-hidroxiamida **L15** y la α-hidroxiamida **L16**, obteniéndose resultados decepcionantes (Tabla 4.1, entradas 15 y 16).

Una vez identificado el ligando **L7** como el que proporcionaba los mejores resultados entre los ligandos examinados, continuamos el proceso de optimización ensayando la reacción con diferentes reactivos de dialquilzinc y disolventes (Tabla 4.2).

Tabla 4.1. Adición enantioselectiva de Et_2Zn a dibenzo[*b,f*][1,4]oxazepina **21a**. Screening de ligandos.[a]



21a **28a**

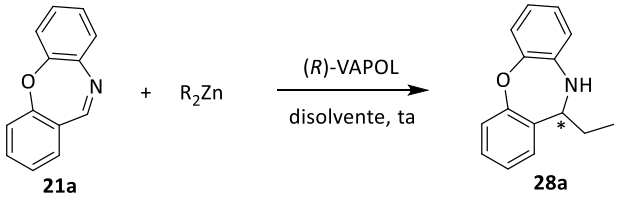


L13 **L14** **L15** **L16**

Entrada	Ligando	t (h)	R (%)[b]	*ee* (%)[c]
1	**L1**	22	36	37
2	**L2**	22	34	50
3	**L3**	23	20	14
4	**L4**	21	16	8
5	**L5**	21	22	18
6	**L6**	22	18	19
7	**L7**	22	36	61
8	**L8**	24	40	5
9	**L9**	22	47	0
10	**L10**	22	53	0
11	**L11**	22	48	1
12	**L12**	22	55	5
13	**L13**	22	30	5
14	**L14**	22	48	20
15	**L15**	22	19	-11
16	**L16**	22	33	8

[a] **21a** (0,100 mmol), Ligando **L** (0,020 mmol) y 1M Et_2Zn en hexanos (0,500 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enatiomérico determinado mediante HPLC usando fases estacionarias quirales.

Tabla 4.2. Reacción de adición enantioselectiva de Et_2Zn a dibenzo[*b,f*][1,4]oxazepina **21a**. Screening de reactivos de dialquilzinc y disolvente.[a]



21a **28a**

Entrada	Disolvente	R_2Zn (R)	t (h)	R (%)[b]	*ee* (%)[c]
1	DCM	Et	22	53	61
2	DCM	Me	96	/	/
3	DCE	Et	22	68	38
4	Tolueno	Et	22	49	45
5	AcOEt	Et	22	58	44
6	THF	Et	22	70	27
7	Et_2O	Et	22	53	69
8	$^{i}Pr_2O$	Et	22	49	42
9	MTBE	Et	22	52	54

[a] **21a** (0,100 mmol), Ligando **L7** (0,020 mmol) y 1M Et_2Zn en hexanos (0,500 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

En primer lugar se ensayó la adición de Me_2Zn a la dibenzo[*b,f*][1,4]oxazepina **21a**, sin embargo no se observó la formación del producto de adición de Me_2Zn a la imina (Tabla 4.2, Entrada 2)

Como se puede observar en la tabla 4.2, el uso de dicloroetano (entrada 3) aumenta el rendimiento de la reacción con Et_2Zn (68%), pero la enantioselectividad disminuye hasta un 38% *ee*. Cuando se utiliza tolueno como disolvente (Tabla 4.2, Entrada 4), se observa una disminución de la enantioselectividad, aunque el rendimiento se mantiene. Cuando se utiliza acetato de etilo (Tabla 4.2, entrada 5) como disolvente el producto de adición se obtuvo con un rendimiento de 58% y una enantioselectividad de 44% *ee*.

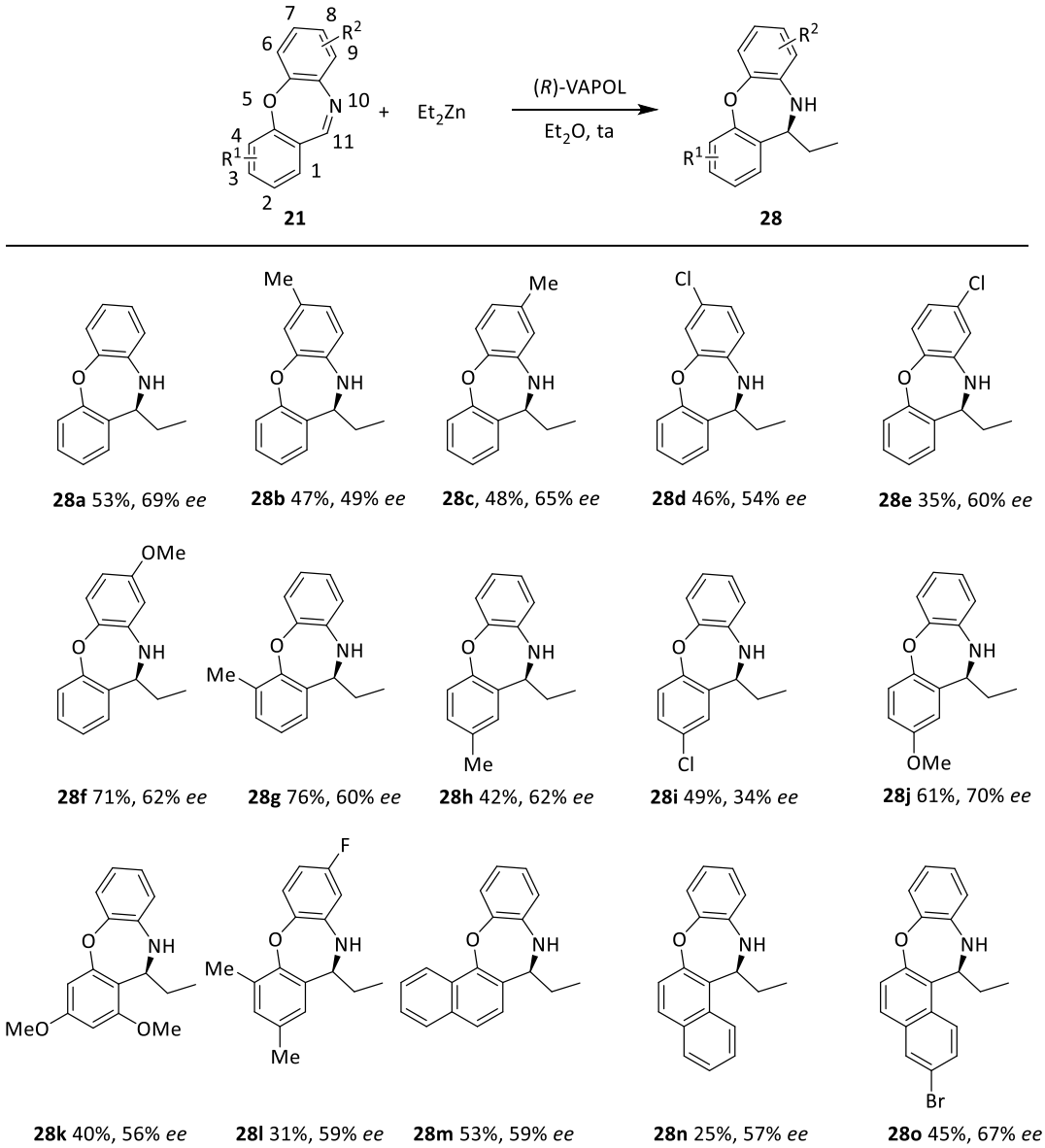
Se ensayaron también diferentes disolventes de tipo éter. El mejor rendimiento (70%) de la reacción se observa cuando se utilizó THF (Tabla 4.2, Entrada 5) como disolvente, pero la enantioselectividad disminuyó hasta un 27% *ee*. El éter etílico resultó ser el mejor disolvente para la reacción de adición de Et_2Zn a la dibenzo[*b,f*][1,4]oxazepina (Tabla 4.2, entrada 7). El uso de éter isopropílico o metil *terc*-butil éter no condujo a ninguna mejora en el rendimiento y tampoco en la enantioselectividad de la reacción (Tabla 4.2, entradas 8 y 9).

En resumen, se obtuvieron los mejores resultados cuando la reacción entre la dibenzo[*b,f*][1,4]oxazepina y dietilzinc se llevó a cabo a temperatura ambiente utilizando éter etílico como disolvente.

4.3.3. Alcance y limitaciones de la reacción

4.3.3.1. Reacción entre dietilzinc y diferentes dibenzo[*b,f*][1,4]oxazepinas

Para estudiar el alcance y las limitaciones de la reacción, se decidió ensayar las condiciones de reacción optimizadas con varias iminas de tipo dibenzo[*b,f*][1,4]oxazepina con diferentes sustituyentes en ambos anillos aromáticos (**21**) (Esquema 4.15).



Esquema 4.15. Reacción de adición enantioselectiva de Et_2Zn a dibenzo[*b,f*][1,4]oxazepinas **21**. **21** (0,100 mmol), Ligando **L7** (0,020 mmol) y 1M Et_2Zn en hexanos (0,500 mmol). Rendimiento después de purificación por cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

Primero se estudió la reacción con las iminas sustituidas en posiciones 7 y 8. La presencia de un grupo electrón-donante (metilo) en la posición 7 conduce al producto de reacción **28b** con una enantioselectividad (49% ee) inferior a la obtenida para el compuesto que lleva el mismo grupo en la posición 8 (**28c**, 65% *ee*). El mismo efecto se puede observar si el sustituyente es un grupo electrón-atrayente (**28d**, 54% *ee* y **28e**, 60% *ee*). Los rendimientos de las reacciones con iminas cíclicas

sustituidas en posiciones 7 y 8 son generalmente bajos (35-48%). Sin embargo, la presencia de grupo metoxi en la posición 8 (**28f**) conduce a un rendimiento mucho mayor de 71% con una enantioselectividad de un 62% *ee*, la cual es parecida a la enantioselectividad observado en la formación del compuesto **28c** (con un grupo metilo en posición 8). Se puede concluir que la presencia de un sustituyente (electrón-donante o electrón-atrayente) en posición 8 da lugar a mejores resultados que la presencia de un sustituyente en la posición 7.

A continuación, se ensayaron iminas cíclicas con diferentes sustituyentes en las posiciones 1-4. La reacción de adición de Et_2Zn a dibenzo[*b,f*][1,4]oxazepina **21g** (con un grupo metilo en la posición 4) dio lugar al producto **28g** con un buen rendimiento de 76% y una enantioselectividad de 60% *ee*. La presencia del mismo grupo, pero en posición 2 condujo al producto **28h** con una enantioselectividad parecida (62% *ee*) pero con un rendimiento inferior (42%). Un grupo electrón-atrayente (cloro) en la posición 2 conduce al producto de reacción (**28i**) con una enantioselectividad baja de 34% *ee* y con un rendimiento de 49%. Sin embargo la presencia de un grupo metoxi en la posición 2 conduce a los mejores resultados, con un rendimiento de 61% y una enantioselectividad de 70% *ee* (**28j**). Como se puede observar, la presencia de un grupo electrón-donante en la posición 4 aumenta el rendimiento de la reacción, mientras la presencia de un grupo electrón-atrayente en la posición 2 disminuye la enantioselectividad de la reacción.

También se aplicaron las condiciones optimizadas en la reacción con iminas cíclicas di- y tri-sustituidas en las posiciones 1-4. El sustrato **21k** (1,3-dimetoxi) experimentó la reacción de adición enantioselectiva de Et_2Zn dando lugar al compuesto **28k** con un rendimiento de 40% y una enantioselectividad de 56% *ee*. En la reacción con el sustrato **21l** (8-fluoro-2,4-dimetildibenzo[*b,f*][1,4]oxazepina) se pudo observar un rendimiento algo inferior (31%), aunque la enantioselectividad observada fue ligeramente superior (59% *ee*). Así pues, la reacción con las iminas di- y trisustituidas condujo a los productos resultantes con rendimientos y enantioselectividades ligeramente inferiores a los obtenidos en las reacciones con las iminas monosustituidas.

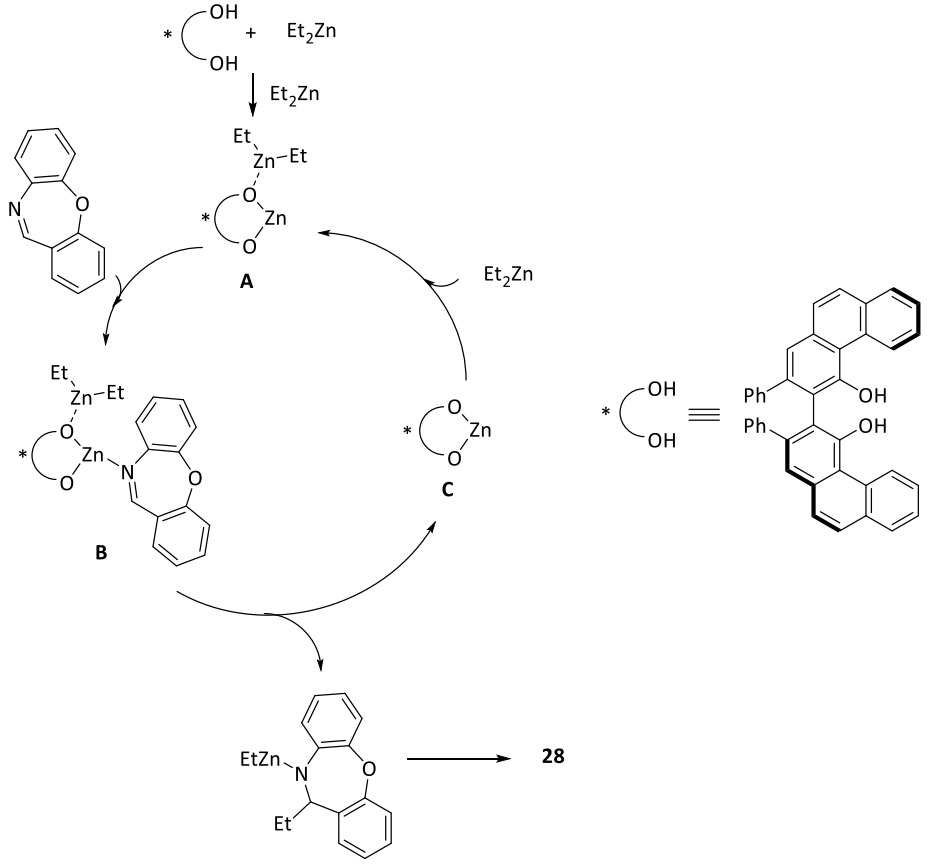
Finalmente, se llevaron a cabo las reacciones de adición enantioselectiva de Et_2Zn a las iminas derivadas de 1- y 2-naftol. La reacción con la imina derivada del 1-naftol **21m** conduce al producto de reacción con un rendimiento de 53% y una enantioselectividad de 59% *ee*, mientras que la reacción con la imina derivada del 2-naftol da lugar al producto **28n** con un rendimiento muy inferior (25%), pero una enantioselectividad de 57% *ee*. Curiosamente, la presencia de un grupo bromo en la posición 3 del sustrato **21o**, derivado del 2-naftol, conduce a un aumento en el rendimiento (45%) y la enantioselectividad (67% *ee*). Así pues, la reacción con la imina derivada del 1-naftol da mejores resultados que con la imina derivada de 2-naftol, aunque la presencia de un grupo bromo en la posición 3 del 2-naftol mejora el rendimiento y la enantioselectividad. También se evaluó la reacción con la dibenzotiazepina **27**, pero desafortunadamente la reacción no tuvo lugar.

4.3.4. Determinación de la configuración absoluta

La configuración absoluta fue determinada por comparación con compuestos descritos anteriormente en la literatura. Concretamente, se comparó el signo de la rotación especifica del compuesto **28a** con la del mismo compuesto descrito por Zhou, resultando que la configuración absoluta del centro estereogénico formado en la reacción es (*S*).[33] La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

4.3.5. Propuesta mecanística para la alquilación de benzoxazepinas catalizada por complejos de (*R*)-VAPOL-Zn

El esquema 4.16 muestra un posible mecanismo para la reacción de alquilación de benzoxazepinas catalizada por complejos de (*R*)-VAPOL-Zn, el cual está basado en el mecanismo de la alquinilación de 2,2-dioxido benzoxatiazinas catalizada por complejos de (*R*)-VAPOL-Zn que hemos propuesto en el capítulo 2. En primer lugar se produce la desprotonación del ligando VAPOL por parte del dietilzinc, lo cual da lugar al complejo **A** (VAPOL zincato-dietilzinc). Este complejo **A** se coordina con la imina cíclica (benzoxazepina) formando el complejo **B**. En este complejo se produce la transferencia del grupo etilo desde el etilzinc al carbono azometínico de la imina, lo cual libera el producto de reacción y el VAPOL-zincato **C**. Se completa el ciclo catalítico tras la coordinación de una nueva molecula de dietilzinc al complejo **C**, generando de nuevo el complejo **A**.



Esquema 4.16. Propuesta mecanística para la alquilación de benzoxazepinas catalizada por complejos de (*R*)-VAPOL-Zn.

4.4. CONCLUSIONES

1. Se ha diseñado un método enantioselectivo de adición de Et_2Zn a aldiminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina catalizada por un complejo (*R*)-VAPOL-Zn(II) a temperatura ambiente y utilizando éter etílico como disolvente.

2. La reacción con iminas con un sustituyente (electrón-donante o atrayente) en posición 8 dio lugar a mejores resultados que la reacción con iminas con un sustituyente en la posición 7.

3. La presencia de un grupo electrón-donante en la posición 4 aumenta el rendimiento de la reacción, mientras la presencia de un grupo electrón-atrayente en la posición 2 disminuye la enantioselectividad de la reacción.

4. La reacción con iminas di- y trisustituidas conduce a los productos resultantes con rendimientos y enantioselectividades ligeramente inferiores a los obtenidos en las reacciones con iminas monosustituidas.

5. La reacción con la imina derivada del 1-naftol da mejores resultados que con la imina derivada de 2-naftol, aunque la presencia de un grupo bromo en la posición 3 del 2-naftol mejora el rendimiento y la enantioselectividad.

6. La configuración absoluta fue determinada por comparación de los datos del compuesto **28a** con los descritos en la bibliografía para este mismo compuesto, resultando ser (*S*). Al resto de productos se les asignó la misma configuración absoluta asumiendo que la reacción sigue el mismo curso estereoquímico.

7. Se ha propuesto un posible mecanismo para la alquilación de dibenzoxazepinas con un complejo de Me_2Zn-VAPOL.

4.5. EXPERIMENTAL SECTION

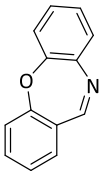
4.5.1. General experimental methods

Reactions were carried out under nitrogen in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel.

4.5.2. General synthetic procedure and characterization data for compounds 21 substituted in positions 7 and 8

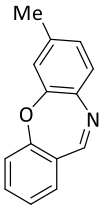
2-Aminophenol **19** (5.5 mmol, 1.1 eq.) was dissolved in 10 mL PEG. 2-Fluorobenzaldehyde **20** (5.0 mmol, 1 eq) and K_2CO_3 (5.0 mmol, 1 eq.) were added. The reaction mixture was heated to 100 °C for 2 h. The reaction process was followed by TLC. Once the reaction was finished, the reaction mixture was cooled to rt and 20 mL water was added to quench the reaction. The reaction mixture was extracted with EtOAc (3x20 mL), washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography, obtaining product **21**.[35]

Dibenzo[*b,f*][1,4]oxazepine (21a)[35]



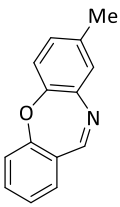
Orange solid; mp 69-71 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.56 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.37 – 7.33 (m, 1H), 7.32 – 7.28 (m, 2H), 7.27 – 7.21 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.6 (CH), 160.4 (C), 152.7 (C), 140.5 (C), 133.3 (CH), 130.1 (CH), 129.2 (CH), 128.8 (CH), 127.3 (C), 125.7 (CH), 125.1 (CH), 121.4 (CH), 120.7 (CH).

8-Methyldibenzo[*b,f*][1,4]oxazepine (21b)[35]



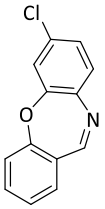
Brown solid; mp 46-47 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.42 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.32 (dd, J = 7.6, 1.7 Hz, 1H), 7.19 (dd, J = 7.5, 1.1 Hz, 1H), 7.15 (dt, J = 2.5, 1.0 Hz, 1H), 7.11 (dt, J = 8.1, 0.7 Hz, 1H), 7.01 – 6.98 (m, 2H), 2.30 (d, J = 0.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.6 (CH), 150.5 (C), 140.0 (C), 135.4 (C), 133.2 (CH), 130.1 (CH), 129.5 (CH), 129.3 (CH), 127.4 (C), 124.9 (CH), 120.9 (CH), 120.6 (CH), 20.6 (CH_3).

7-Methyldibenzo[*b,f*][1,4]oxazepine (21c)[35]



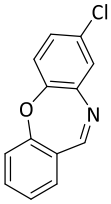
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.42 (ddd, J = 8.1, 7.3, 1.8 Hz, 1H), 7.31 (dd, J = 7.6, 1.7 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.16 (dd, J = 7.5, 1.1 Hz, 1H), 7.11 (ddd, J = 8.1, 1.0, 0.5 Hz, 1H), 7.00 – 6.90 (m, 2H), 2.31 (d, J = 0.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.3 (C), 159.8 (CH), 152.3 (C), 139.4 (C), 138.0 (C), 133.2 (CH), 130.1 (CH), 129.0 (CH), 127.4 (C), 126.4 (CH), 125.0 (CH), 121.8 (CH), 120.7 (CH), 20.8 (CH_3).

8-Chlorodibenzo[*b,f*][1,4]oxazepine (21d)[35]



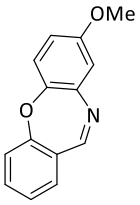
Brown solid; mp 93-94 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.45 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.25 – 7.18 (m, 1H), 7.16 (dd, J = 8.6, 2.6 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.03 (d, J = 8.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.7 (CH), 160.3 (C), 151.3 (C), 141.4 (C), 133.6 (CH), 130.6 (C), 130.3 (CH), 128.9 (CH), 128.4 (CH), 127.1 (C), 125.3 (CH), 122.4 (CH), 120.7 (CH).

7-Chlorodibenzo[*b,f*][1,4]oxazepine (21e)[35]



Brown solid; mp 76-77 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.45 (ddd, J = 8.1, 7.3, 1.8 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.25 – 7.17 (m, 1H), 7.17 – 7.09 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.8 (CH), 159.9 (C), 152.8 (C), 139.2 (C), 133.9 (C), 133.6 (CH), 130.2 (CH), 130.0 (CH), 127.2 (C), 125.9 (CH), 125.4 (CH), 121.8 (CH), 120.7 (CH).

8-Methoxydibenzo[*b,f*][1,4]oxazepine (21f)



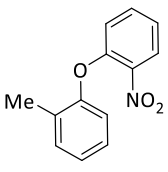
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.43 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H), 7.32 (dd, J = 7.6, 1.7 Hz, 1H), 7.18 (td, J = 7.5, 1.1 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 3.1 Hz, 1H), 6.75 (dd, J = 8.8, 3.1 Hz, 1H), 3.76 (s, 3Ht), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.1 (CH), 160.7 (C), 157.1 (C), 146.5 (C), 141.0 (C), 133.4 (CH), 130.1 (CH), 127.3 (C), 124.9 (CH), 121.7 (CH), 120.5 (CH), 114.6 (CH), 113.0 (CH), 55.7 (CH_3). **HRMS** (ESI) *m/z*: 226.0859 $[M + H]^+$, $C_{14}H_{12}NO_2$ requires 226.0863.

4.5.3. General synthetic procedures and characterization data for compounds 21 substituted in positions 1-4

Synthetic procedure and characterization data for compounds 23

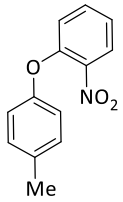
NaH (16 mmol, 1.6 eq.) was added to 10 mL of DMF. Next, a solution of phenol (**10**) (15 mmol, 1.5 eq.) in DMF (10 mL) was added dropwise to the reaction mixture. The mixture was stirred for 30 minutes, and a solution of 1-fluoro-2-nitrobenzene (**22**) (10 mmol, 1 eq.) in 4 mL DMF was added dropwise. After stirring for 12 h at 50 °C, the mixture was cooled to room temperature and 25mL of saturated aqueous NH_4Cl solution was added, the mixture was extracted with 50 mL EtOAc, washed with H_2O (4x 20 mL) and dried over $MgSO_4$. The solvent was removed and the crude product was purified by flash chromatography, obtaining product **23**.

1-Methyl-2-(2-nitrophenoxy)benzene (23g)[40]



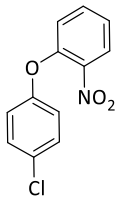
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.2, 1.7 Hz, 1H), 7.42 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.23 – 7.16 (m, 1H), 7.16 – 7.08 (m, 2H), 6.92 (dd, J = 7.8, 1.5 Hz, 1H), 6.79 (dd, J = 8.4, 1.2 Hz, 1H), 2.22 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.0 (C), 151.2 (C), 140.4 (C), 134.0 (CH), 131.8 (CH), 130.1 (C), 127.4 (CH), 125.8 (CH), 125.3 (CH), 122.1 (CH), 119.9 (CH), 118.3 (CH), 16.0 (CH_3).

1-Nitro-2-(*p*-tolyloxy)benzene (23h)[41]



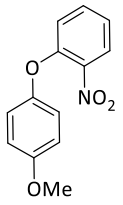
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.2, 1.7 Hz, 1H), 7.44 (ddd, J = 8.5, 7.4, 1.7 Hz, 1H), 7.20 – 7.09 (m, 3H), 6.99 – 6.89 (m, 3H), 2.33 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.3 (C), 151.3 (C), 141.1 (C), 134.4 (C), 134.0 (CH), 130.5 (CH), 125.6 (CH), 122.6 (CH), 119.8 (CH), 119.4 (CH), 20.7 (CH_3).

1-(4-Chlorophenoxy)-2-nitrobenzene (23i)[42]



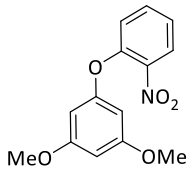
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.1, 1.7 Hz, 1H), 7.51 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.01 (dd, J = 8.3, 1.3 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.6 (C), 150.1 (C), 142.7 (C), 134.2 (CH), 130.1 (CH), 129.7 (C), 125.8 (CH), 123.7 (CH), 120.8 (CH), 120.2 (CH).

1-(4-Methoxyphenoxy)-2-nitrobenzene (23j)[41]



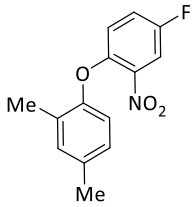
Yellow oil; ^{1}H **NMR** (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.1, 1.7 Hz, 1H), 7.42 (ddd, J = 8.4, 7.4, 1.7 Hz, 1H), 7.10 (ddd, J = 8.1, 7.4, 1.2 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.94 – 6.86 (m, 3H), 3.79 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.8 (C), 151.9 (C), 148.6 (C), 140.7 (C), 134.0 (CH), 125.6 (CH), 122.2 (CH), 121.1 (CH), 118.9 (CH), 115.1 (CH), 55.7 (CH_3).

1,3-Dimethoxy-5-(2-nitrophenoxy)benzene (23k)[43]



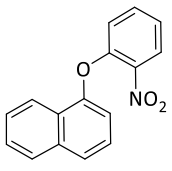
Yellow oil; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.1, 1.7 Hz, 1H), 7.49 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.18 (ddd, J = 8.3, 7.4, 1.3 Hz, 1H), 7.07 (dd, J = 8.3, 1.3 Hz, 1H), 6.26 (t, J = 2.2 Hz, 1H), 6.17 (d, J = 2.2 Hz, 2H), 3.74 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.7 (C), 157.6 (C), 150.2 (C), 141.3 (C), 134.1 (CH), 125.7 (CH), 123.4 (CH), 120.9 (CH), 97.6 (CH), 96.6 (CH), 55.5 (CH_3).

1-(2,4-Dimethylphenoxy)-4-fluoro-2-nitrobenzene (23l)



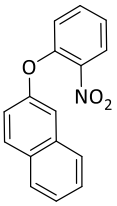
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.7, 3.1 Hz, 1H), 7.15 (ddd, J = 9.2, 7.2, 3.1 Hz, 1H), 7.06 (s, 1H), 6.98 (ddt, J = 8.0, 2.4, 0.7 Hz, 1H), 6.82 – 6.76 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (75 MHz, CDCl3) δ 156.2 (d, $J_{c\text{-}f}$ = 245.8 Hz, CF), 150.9 (C), 147.9 (d, $J_{c\text{-}f}$ = 3.0 Hz, C), 139.9 (d, $J_{c\text{-}f}$ = 7.6 Hz, C), 135.0 (C), 132.5 (CH), 129.5 (C), 128.0 (CH), 121.2 (d, $J_{c\text{-}f}$ = 23.0 Hz, CH), 119.6 (d, $J_{c\text{-}f}$ = 7.7 Hz, CH), 119.4 (CH), 112.8 (d, $J_{c\text{-}f}$ = 27.8 Hz, CH), 20.7 (CH_3), 15.9 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -119.1. **HRMS** (ESI) *m/z*: 262.0873 $[M + H]^+$, $C_{14}H_{13}FNO_3$ requires 262.0874.

1-(2-Nitrophenoxy)naphthalene (23m)[44]



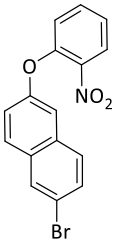
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 – 8.10 (m, 1H), 7.99 (dd, J = 8.1, 1.7 Hz, 1H), 7.88 (dd, J = 7.0, 2.4 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 – 7.37 (m, 2H), 7.20 – 7.13 (m, 1H), 7.03 (dd, J = 7.6, 1.0 Hz, 1H), 6.88 (dd, J = 8.4, 1.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$ δ 151.3 (C), 151. (C), 140.9 (C), 135.0 (C), 134.2 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 126.5 (C), 125.8 (CH), 125.6 (CH), 124.9 (CH), 122.9 (CH), 121.8 (CH), 119.6 (CH), 114.5 (CH).

2-(2-Nitrophenoxy)naphthalene (23n)[45]



Orange oil; ^{1}H **NMR** (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.2, 1.7 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.74 – 7.69 (m, 1H), 7.53 – 7.48 (m, 1H), 7.48 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.29 – 7.18 (m, 2H), 7.05 (dd, J = 8.3, 1.3 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl3) δ 153.5 (C), 150.7 (C), 141.4 (C), 134.2 (CH), 134.1 (C), 130.7 (C), 130.3 (CH), 127.8 (CH), 127.3 (CH), 126.8 (CH), 125.8 (CH), 125.4 (CH), 123.3 (CH), 120.8 (CH), 119.6 (CH), 115.0 (CH).

2-Bromo-6-(2-nitrophenoxy)naphthalene (23o)

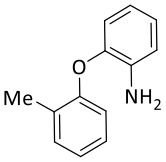


Orange solid; mp 97-100 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H), 7.76 (ddd, J = 8.2, 1.7, 0.6 Hz, 1H), 7.60 – 7.50 (m, 3H), 7.34 – 7.20 (m, 3H), 7.07 (dd, J = 8.4, 1.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.1 (C), 150.1 (C), 147.3 (C), 134.3 (CH), 132.6 (C), 131.6 (CH), 130.2 (C), 129.9 (CH), 129.4 (CH), 128.9 (CH), 125.9 (CH), 123.8 (CH), 121.2 (CH), 120.5 (CH), 119.1 (C), 114.5 (CH). **HRMS** (ESI) *m/z*: 343.9918 $[M + H]^+$, $C_{16}H_{11}BrNO_3$ requires 343.9917.

Synthetic procedure and characterization data for compounds 24

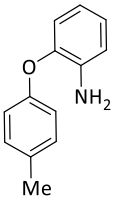
Compound **23** (8 mmol, 1 eq.) was dissolved in 50 mL of EtOAc and 62.5 mL of AcOH was added dropwise. The mixture was cooled to 0 °C and 62.5 mL of concentrated HCl was added dropwise. Afterwards, zinc powder (240 mmol, 30 eq.) was added in portions. The mixture was warmed to room temperature and stirred for 16 h. The mixture was cooled to 0 °C and 150 mL of 33% NH_3 in water solution was added dropwise. The crude mixture was extracted DCM (4x100 mL), dried over $MgSO_4$ and the solvent was removed by evaporation, obtaining the crude amine **24**.[40]

2-(*o*-Tolyloxy)aniline (24g)[40]



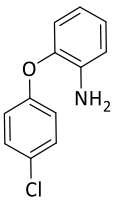
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 7.15 – 7.08 (m, 1H), 7.00 (td, J = 7.4, 1.3 Hz, 1H), 6.92 (ddd, J = 7.9, 5.3, 3.5 Hz, 1H), 6.83 – 6.76 (m, 2H), 6.70 – 6.62 (m, 2H), 3.80 (s, 2H), 2.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.9 (C), 144.1 (C), 137.8 (C), 131.3 (CH), 128.7 (C), 127.1 (CH), 123.9 (CH), 123.2 (CH), 118.7 (CH), 118.2 (CH), 117.5 (CH), 116.2 (CH), 16.1 (CH_3).

2-(*p*-Tolyloxy)aniline (24h) [40]



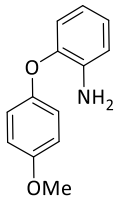
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.12 – 7.06 (m, 2H), 6.99 – 6.91 (m, 1H), 6.89 – 6.84 (m, 2H), 6.81 (td, J = 7.8, 1.5 Hz, 2H), 6.68 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 3.75 (s, 2H), 2.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.1 (C), 143.7 (C), 138.5 (C), 132.2 (C), 130.1 (CH), 124.5 (CH), 119.7 (CH), 118.7 (CH), 117.3 (CH), 116.3 (CH), 20.6 (CH_3).

2-(4-Chlorophenoxy)aniline (24i)[42]



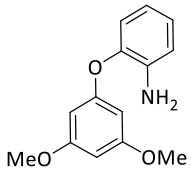
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.21 (d, J = 2.3 Hz, 1H), 6.97 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.87 – 6.77 (m, 3H), 6.69 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H), 3.74 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.2 (C), 142.7 (C), 138.7 (C), 129.6 (CH), 127.6 (C), 125.3 (CH), 120.3 (CH), 118.9 (CH), 118.3 (CH), 116.6 (CH).

2-(4-Methoxyphenoxy)aniline (24j)[46]



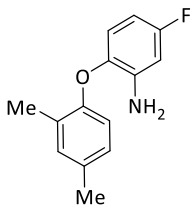
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.95 – 6.88 (m, 3H), 6.87 – 6.82 (m, 2H), 6.81 – 6.73 (m, 2H), 6.66 (ddd, J = 8.1, 7.2, 1.6 Hz, 1H), 3.77 (s, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.4 (C), 150.7 (C), 144.6 (C), 138.1 (C), 124.0 (CH), 119.0 (CH), 118.6 (CH), 118.6 (CH), 116.2 (CH), 114.8 (CH), 55.7 (CH_3).

2-(3,5-Dimethoxyphenoxy)aniline (24k)



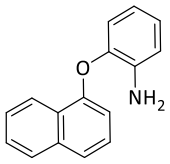
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.97 (ddd, J = 7.9, 7.2, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.5 Hz, 1H), 6.79 (dd, J = 7.9, 1.6 Hz, 1H), 6.70 (ddd, J = 8.0, 7.3, 1.6 Hz, 1H), 6.23 – 6.14 (m, 1H), 6.13 (d, J = 2.2 Hz, 2H), 3.74 (s, 2H), 3.77 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.6 (C), 159.5 (C), 142.5 (C), 138.8 (C), 125.1 (CH), 120.7 (CH), 118.8 (CH), 116.5 (CH), 95.6 (CH), 94.8 (CH), 55.4 (CH_3). **HRMS** (ESI) *m/z*: 246,1125 $[M + H]^+$, $C_{14}H_{16}NO_3$ requires 246,1125.

2-(2,4-Dimethylphenoxy)-5-fluoroaniline (24l)



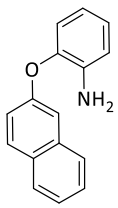
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 (d, J = 1.9 Hz, 1H), 6.91 (ddt, J = 8.2, 2.3, 0.7 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 8.8, 5.3 Hz, 1H), 6.50 (dd, J = 9.9, 2.9 Hz, 1H), 6.32 (ddd, J = 8.8, 8.2, 3.0 Hz, 1H), 3.91 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3 (d, $J_{c\text{-}f}$ = 239.2 Hz, CF), 152.8 (C), 140.2 (d, $J_{c\text{-}f}$ = 2.4 Hz, C), 139.0 (d, $J_{c\text{-}f}$ = 11.5 Hz, C), 132.7 (C), 132.0 (CH), 128.2 (C), 127.5 (CH), 118.7 (d, $J_{c\text{-}f}$ = 10.1 Hz, CH), 117.0 (CH), 104.2 (d, $J_{c\text{-}f}$ = 23.4 Hz, CH), 102.7 (d, $J_{c\text{-}f}$ = 26.8 Hz, CH), 20.6 (CH_3), 16.0 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -120.02. **HRMS** (ESI) *m/z*: 232.1130 $[M + H]^+$, $C_{14}H_{15}FNO$ requires 232.1132.

2-(Naphthalen-1-yloxy)aniline (24m)[44]



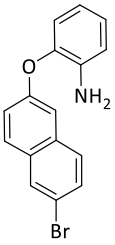
Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 – 8.29 (m, 1H), 7.91 – 7.81 (m, 1H), 7.58 – 7.47 (m, 3H), 7.32 (dd, J = 8.2, 7.6 Hz, 1H), 7.01 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H), 6.87 (ddd, J = 7.9, 4.5, 1.5 Hz, 2H), 6.80 (dd, J = 7.6, 1.0 Hz, 1H), 6.72 (ddd, J = 7.9, 7.2, 1.5 Hz, 1H), 3.84 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.1 (C), 143.4 (C), 138.5 (C), 134.9 (C), 127.7 (CH), 126.6 (CH), 126.0 (C), 125.8 (CH), 124.9 (CH), 122.5 (CH), 121.9 (CH), 120.2 (CH), 118.9 (CH), 116.5 (CH), 110.3 (CH).

2-(Naphthalen-2-yloxy)aniline (24n)[45]



Orange solid; mp 75-80 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.27 (dd, J = 8.9, 2.5 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.02 (ddd, J = 7.9, 7.3, 1.4 Hz, 1H), 6.93 (dd, J = 8.0, 1.5 Hz, 1H), 6.85 (dd, J = 7.9, 1.6 Hz, 1H), 6.74 (ddd, J = 7.9, 7.2, 1.6 Hz, 1H), 3.77 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.3 (C), 143.0 (C), 138.8 (C), 134.3 (C), 129.9 (C), 129.9 (CH), 127.7 (CH), 127.0 (CH), 126.5 (CH), 125.1 (CH), 124.4 (CH), 120.6 (CH), 118.9 (CH), 116.6 (CH), 111.6 (CH).

2-((6-Bromonaphthalen-2-yl)oxy)aniline (24o)



White solid; mp 92-94 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) 7.94 (d, J = 1.7 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.47 (dd, J = 8.8, 1.8 Hz, 1H), 7.28 (dd, J = 8.9, 2.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.93 (dd, J = 8.1, 1.5 Hz, 1H), 6.86 (dd, J = 7.9, 1.6 Hz, 1H), 6.75 (ddd, J = 7.9, 7.3, 1.6 Hz, 1H), 3.79 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.1 (C), 142.9 (C), 139.3 (C), 133.2 (C), 131.3 (C), 130.3 (CH), 130.1 (CH), 129.4 (CH), 129.1 (CH), 125.9 (CH), 121.2 (CH), 120.2 (CH), 119.3 (CH), 118.4 (C), 117.1 (CH), 111.7 (CH). **HRMS** (ESI) *m/z*: 314.0184 $[M + H]^+$, $C_{16}H_{13}BrNO$ requires 314.0175.

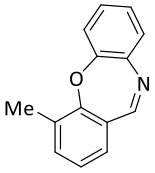
Synthetic procedure for compound 25

The amine **24** (7.5 mmol, 1 eq.) was dissolved in 5 mL of formic acid. The mixture was heated under reflux (100 °C) for 12 h. Afterwards, the reaction mixture was cooled to room temperature and quenched with 20 mL of $NaHCO_3$ (sat.) solution. Followed by an extraction with dichloromethane (3x20 mL), washed with brine (20mL) and dried over $MgSO_4$. The solvent was removed and the crude product **25** was used for the next step without purification.[35]

Synthetic procedure and characterization data for compounds 21 substituted in positions 1-4

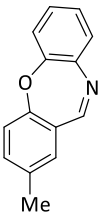
Compound **25** (4.0 mmol, 1 eq.), polyphosphoric acid (PPA) (106 mmol, 10.4 g) and phosphoryl chloride ($POCl_3$)(20 mmol, 5 eq.) were mixed. The reaction mixture was stirred 3 h at 120 °C. Afterwards the mixture was cooled to room temperature, it was poured on 200 mL iced water and treated with 33% NH_3 in water solution. The mixture was extracted with 3x100 mL of DCM, washed with 100 mL of brine and dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography, obtaining product **21**.[33]

4-Methyldibenzo[*b,f*][1,4]oxazepine (21g)[35]



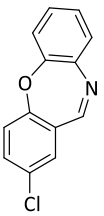
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.38 – 7.34 (m, 1H), 7.31 (ddd, J = 7.4, 1.8, 0.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.18 – 7.13 (m, 3H), 7.07 (t, J = 7.5 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.0 (CH), 158.3 (C), 152.6 (C), 140.8 (C), 134.6 (CH), 130.2 (C), 129.1 (CH), 128.5 (CH), 127.7 (CH), 127.3 (C), 125.6 (CH), 124.6 (CH), 121.6 (CH), 16.1 (CH_3).

2-Methyldibenzo[*b,f*][1,4]oxazepine (21h)[35]



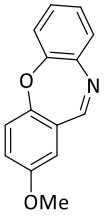
Orange solid; mp 59-60 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.36 – 7.31 (m, 1H), 7.24 – 7.17 (m, 2H), 7.17 – 7.12 (m, 1H), 7.12 – 7.07 (m, 2H), 7.01 (d, J = 8.3 Hz, 1H), 2.30 (d, J = 0.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.7 (CH), 158.3 (C), 152.8 (C), 140.5 (C), 134.7 (C), 133.9 (CH), 130.3 (CH), 129.2 (CH), 128.7 (CH), 127.0 (C), 125.5 (CH), 121.3 (CH), 120.4 (CH), 20.5 (CH_3).

2-Chlorodibenzo[*b,f*][1,4]oxazepine (21i)



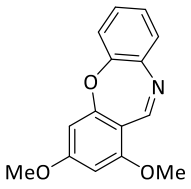
Yellow solid; mp 98-100 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.43 – 7.30 (m, 2H), 7.29 (d, J = 2.6 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.11 – 7.05 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9 (CH), 154.4 (C), 152.4 (C), 140.2 (C), 133.0 (CH), 130.5 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 128.4 (C), 126.0 (CH), 122.2 (CH), 121.3 (CH). **HRMS** (ESI) *m/z*: 230.0365 $[M + H]^+$, $C_{13}H_9ClNO$ requires 230.0367.

2-Methoxydibenzo[*b,f*][1,4]oxazepine (21j)[35]



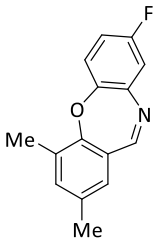
Orange solid; mp 75-76 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.34 (dd, J = 7.2, 2.3 Hz, 1H), 7.24 – 7.12 (m, 2H), 7.11 – 7.08 (m, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.95 (dd, J = 8.8, 3.0 Hz, 1H), 6.80 (d, J = 3.0 Hz, 1H), 3.77 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.2 (CH), 156.7 (C), 154.1 (C), 152.9 (C), 140.4 (C), 129.1 (CH), 128.8 (CH), 127.7 (C), 125.6 (CH), 121.5 (CH), 121.2 (CH), 118.9 (CH), 113.9 (CH), 55.8 (CH_3).

1,3-Dimethoxydibenzo[*b,f*][1,4]oxazepine (21k)



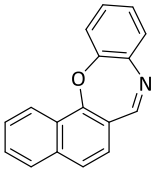
Yellow solid; mp 102-105 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.31 – 7.26 (m, 1H), 7.18 – 7.11 (m, 2H), 7.08 – 7.01 (m, 1H), 6.27 (dd, J = 2.3, 0.6 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.8 (C), 164.0 (C), 160.2 (C), 157.2 (CH), 152.6 (C), 141.6 (C), 128.5 (CH), 127.8 (CH), 125.7 (CH), 121.2 (CH), 109.8 (C), 97.3 (CH), 95.1 (CH), 55.9 (CH_3), 55.7 (CH_3). **HRMS** (ESI) *m/z*: 256.0972 $[M + H]^+$, $C_{15}H_{14}NO_3$ requires 256.0968.

8-Fluoro-2,4-dimethyldibenzo[*b,f*][1,4]oxazepine (21l)



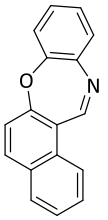
Yellow solid; mp 73-76 °C; yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.13 (dt, J = 2.3, 0.7 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.96 (d, J = 2.1 Hz, 1H), 6.88 (ddd, J = 8.9, 7.6, 3.1 Hz, 1H), 2.39 (s, 3H), 2.27 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.2 (C), 159.7 (d, $J_{c\text{-}f}$ = 243.2 Hz, CF), 156.2 (C), 148.9 (d, $J_{c\text{-}f}$ = 2.7 Hz, C), 141.8 (d, $J_{c\text{-}f}$ = 10.8 Hz, C), 135.6 (CH), 134.4 (C), 129.6 (C), 128.0 (CH), 126.8 (C), 122.0 (d, $J_{c\text{-}f}$ = 9.4 Hz, CH), 115.2 (d, $J_{c\text{-}f}$ = 24.1 Hz, CH), 114.6 (d, $J_{c\text{-}f}$ = 23.3 Hz, CH) 20.5 (CH_3), 16.0 (CH_3). **^{19}F NMR**(282 MHz, $CDCl_3$) δ -118.31. **HRMS** (ESI) *m/z*: 242.0971 $[M + H]^+$, $C_{15}H_{13}FNO$ requires 242.0976.

Benzo[*b*]naphtho[2,1-*f*][1,4]oxazepine (21m)



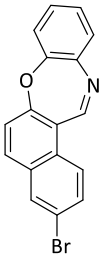
Yellow solid; mp 90-92 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.59 – 8.54 (m, 1H), 7.85 (dd, J = 7.1, 2.4 Hz, 1H), 7.70 – 7.57 (m, 3H), 7.46 – 7.37 (m, 2H), 7.33 – 7.27 (m, 2H), 7.27 – 7.18 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.3 (CH), 156.5 (C), 152.7 (C), 141.1 (C), 136.2 (C), 129.1 (CH), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.1 (CH), 126.5 (C), 125.8 (CH), 125.1 (CH), 124.8 (CH), 123.1 (CH), 122.0 (C), 121.4 (CH). **HRMS** (ESI) *m/z*: 246.0921 $[M + H]^+$, $C_{17}H_{12}NO$ requires 246.0913.

Benzo[*b*]naphtho[1,2-*f*][1,4]oxazepine (21n)



Orange solid; mp 124-127 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.10 (dd, J = 8.5, 0.9 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.58 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.47 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.30 (d, J = 8.9 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.17 – 7.13 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.0 (C), 159.1 (CH), 153.2 (C), 141.5 (C), 134.2 (CH), 131.6 (C), 131.0 (C), 128.7 (CH), 128.4 (CH), 128.1 (CH), 125.8 (CH), 125.7 (CH), 122.7 (CH), 121.1 (CH), 120.3 (CH), 120.0 (C). **HRMS** (ESI) *m/z*: 246.0912 $[M + H]^+$, $C_{17}H_{12}NO$ requires 246.0913.

3-Bromobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepine (21o)

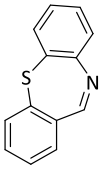


Yellow solid; mp 170-173 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.01 – 7.93 (m, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.9, 2.1 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.23 – 7.10 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.1 (C), 158.3 (CH), 153.0 (C), 141.3 (C), 133.1 (CH), 132.1 (C), 131.3 (CH), 130.6 (CH), 130.1 (C), 128.6 (CH), 128.2 (CH), 126.0 (CH), 124.4 (CH), 121.6 (CH), 121.1 (CH), 120.2 (C), 119.7 (C). **HRMS** (ESI) *m/z*: 324.0023 [M + H]$^+$, $C_{17}H_{11}BrNO$ requires 324.0019.

4.5.4. Synthetic procedure and characterization data for compound 27

2-Aminobenzenethiol **26** (1.1 mmol, 1.1 eq.) was dissolved in 10 mL of PEG. 2-Fluorobenzaldehyde **20** (1 mmol, 1 eq.) and K_2CO_3 (1 mmol, 1 eq.) were added. The reaction mixture was heated to 100 °C for 3 h. The mixture was cooled to room temperature and 20 mL of water was added to quench the reaction. The mixture was extracted with EtOAc (3x20 mL), washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography, obtaining product **27**.[33]

Dibenzo[*b,f*][1,4]thiazepine (27)[47]



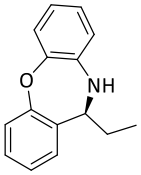
Yellow solid; mp 123-125 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.44 – 7.26 (m, 7H), 7.15 (ddd, J = 7.7, 5.6, 3.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.2 (CH), 148.5 (C), 139.4 (C), 137.2 (C), 132.7 (CH), 131.6 (CH), 131.4 (CH), 129.4 (CH), 129.2 (CH), 128.8 (C), 128.2 (CH), 127.2 (CH), 126.9 (CH).

4.5.5. General synthetic procedures and characterization data for compounds 28

General procedure for the enantioselective alkylation reaction: A 1M Et_2Zn solution in hexanes (0.50 mmol) was added dropwise on a solution of **L7** (0.020 mmol) in diethyl ether (0.3 mL) at room temperature under nitrogen atmosphere. After stirring 30 min., a solution of dibenzo[*b,f*][1,4]oxazepine **21** (0.10 mmol) in diethyl ether (1.0 mL) was added via syringe. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded compound **28**.

General procedure for the non-enantioselective alkylation reaction: A 1M Et_2Zn solution in hexanes (0.50 mmol) was added dropwise in diethyl ether (0.3 mL) at room temperature under nitrogen atmosphere. After stirring 30 minutes, a solution of dibenzo[*b,f*][1,4]oxazepine **21** (0.10 mmol) in diethyl ether (1.0 mL) was added via syringe. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), washed with brine (10 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded compound **28**.

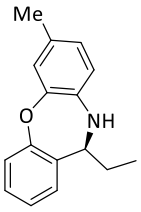
(*S*)-11-Ethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28a)[33]



The enantiomeric excess (69%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 95:05, 0.5 mL/min, major enantiomer t_r = 12.88 min, minor enantiomer t_r = 14.07 min.

Oil; $[\alpha]_D^{20}$ = +13.8 (c 1.0, $CHCl_3$, 69% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 (ddd, *J* = 8.0, 7.0, 1.9 Hz, 1H), 7.18-7.13 (m, 2H), 7.11 – 7.02 (m, 2H), 6.85 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.66 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.33 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.96 (s, 1H), 2.21 – 1.95 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.2 (C), 144.0 (C), 137.6 (C), 134.0 (C), 128.7 (C), 127.1 (C), 124.4 (C), 124.1 (C), 121.7 (C), 121.0 (C), 118.8 (C), 118.5 (C), 58.8 (CH), 27.8 (CH_2), 11.4 (CH_3).

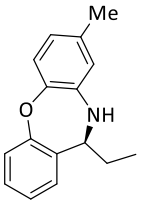
(*S*)-11-Ethyl-7-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28b)



The enantiomeric excess (49%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 9.34 min, minor enantiomer t_r = 10.19 min.

Oil; $[\alpha]_D^{20}$ = +2.7 (c 1.0, $CHCl_3$, 49% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 1H), 7.14 (ddd, *J* = 7.5, 3.4, 1.6 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.93 – 6.90 (m, 1H), 6.70 – 6.65 (m, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 4.29 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.87 (s, 1H), 2.23 (s, 3H), 2.17 – 1.79 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.0 (C), 144.0 (C), 134.8 (C), 134.0 (C), 128.8 (C), 128.6 (CH), 127.2 (CH), 124.8 (CH), 123.9 (CH), 122.0 (CH), 121.0 (CH), 118.8 (CH), 59.0 (CH), 27.7 (CH_2), 20.2 (CH_3), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 240.1383 $[M + H]^+$, $C_{16}H_{18}NO$ requires 240.1383.

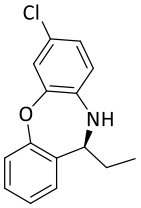
(*S*)-11-Ethyl-8-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28c)



The enantiomeric excess (65%) was determined by chiral HPLC (Chiralpak IC) hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 7.26 min, minor enantiomer t_r = 6.63 min.

Oil; $[\alpha]_D^{20}$ = +13.6 (c 1.0, $CHCl_3$, 65% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 1H), 7.14 (ddd, *J* = 7.5, 3.3, 1.6 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.50 – 6.43 (m, 1H), 6.38 (dd, *J* = 1.9, 0.5 Hz, 1H), 4.32 (dd, *J* = 7.9, 6.9 Hz, 1H), 3.93 (s, 1H), 2.18 (s, 3H), 2.16 – 1.98 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.3 (C), 142.0 (C), 137.2 (C), 134.0 (C), 133.9 (C), 128.7 (CH), 127.1 (CH), 124.0 (CH), 121.4 (CH), 120.9 (CH), 119.4 (CH), 118.9 (CH), 58.7 (CH), 27.8 (CH_2), 20.6 (CH_3), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 240.1383 $[M + H]^+$, $C_{16}H_{18}NO$ requires 240.1383.

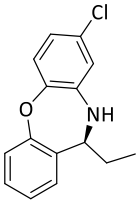
(*S*)-7-Chloro-11-ethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28d)



The enantiomeric excess (54%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 9.51 min, minor enantiomer t_r = 7.78 min.

Oil; $[\alpha]_D^{20}$ = +2.2 (c 1.0, $CHCl_3$, 54% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 1H), 7.17 – 7.12 (m, 2H), 7.12 – 7.05 (m, 2H), 6.81 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 4.30 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.95 (s, 1H), 2.19 – 1.97 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.7 (C), 144.0 (C), 136.4 (C), 133.8 (C), 128.9 (CH), 127.2 (CH), 124.5 (CH), 124.2 (CH), 122.5 (C), 121.8 (CH), 121.0 (CH), 119.1 (CH), 58.7 (CH), 27.7 (CH_2), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 260.0832 $[M + H]^+$, $C_{15}H_{15}ClNO$ requires 260.0837.

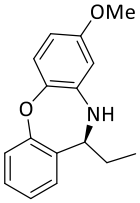
(*S*)-8-Chloro-11-ethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28e)



The enantiomeric excess (60%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 11.19 min, minor enantiomer t_r = 8.89 min.

Oil; $[\alpha]_D^{20}$ = +14.3 (c 1.0, $CHCl_3$, 60% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 1H), 7.18 – 7.05 (m, 3H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.58 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 4.06 (s, 1H), 2.20 – 1.97 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.0 (C), 142.4 (C), 138.8 (C), 133.8 (C), 129.2 (C), 129.0 (CH), 127.2 (CH), 124.4 (CH), 122.8 (CH), 120.9 (CH), 118.1 (CH), 117.5 (CH), 58.6 (CH), 27.8 (CH_2), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 260.0835 $[M + H]^+$, $C_{15}H_{15}ClNO$ requires 260.0837.

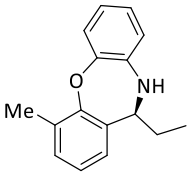
(*S*)-11-Ethyl-8-methoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28f)



The enantiomeric excess (62%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 16.89 min, minor enantiomer t_r = 15.65 min.

Oil; $[\alpha]_D^{20}$ = +19.5 (c 1.0, $CHCl_3$, 62% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 1H), 7.17 – 7.11 (m, 2H), 7.10 – 7.04 (m, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.21 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.10 (d, *J* = 2.9 Hz, 1H), 4.41 – 4.28 (m, 1H), 4.00 (s, 1H), 3.70 (s, 3H), 2.15 – 1.98 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.1 (C), 157.6 (C), 156.5 (C), 138.4 (C), 134.0 (C), 128.8 (CH), 127.0 (CH), 124.1 (CH), 122.2 (CH), 120.8 (CH), 103.6 (CH), 103.3 (CH), 58.4 (CH), 55.4 (CH_3), 27.8 (CH_3), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 256.1328 $[M + H]^+$, $C_{16}H_{18}NO_2$ requires 256.1332.

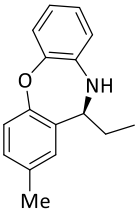
(*S*)-11-Ethyl-4-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28g)



The enantiomeric excess (60%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 6.55 min, minor enantiomer t_r = 5.71 min.

Oil; $[\alpha]_D^{20}$ = +26 (c 1.0, $CHCl_3$, 60% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 7.01 – 6.96 (m, 2H), 6.85 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.64 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.37 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.97 (s, 1H), 2.42 (s, 3H), 2.25 – 1.93 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.4 (C), 143.2 (C), 138.2 (C), 134.2 (C), 130.3 (C), 130.2 (CH), 124.4 (CH), 123.9 (CH), 122.0 (CH), 118.3 (CH), 118.2 (CH), 58.2 (CH), 27.5 (CH_2), 16.3 (CH_3), 11.5 (CH_3). **HRMS (ESI)** *m/z*: 240.1381 $[M + H]^+$, $C_{16}H_{18}NO$ requires 240.1383.

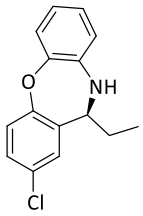
(*S*)-11-Ethyl-2-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28h)



The enantiomeric excess (62%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 8.69 min, minor enantiomer t_r = 7.96 min.

Oil; $[\alpha]_D^{20}$ = +17.5 (c 1.0, $CHCl_3$, 62% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 3H), 6.94 (d, *J* = 1.2 Hz, 1H), 6.84 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.65 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.28 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.31 (s, 3H), 2.23 – 1.71 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.0 (C), 144.1 (C), 137.7 (C), 133.6 (C), 129.0 (CH), 127.6 (CH), 124.3 (C), 124.2 (CH), 121.6 (CH), 120.7 (CH), 118.7 (CH), 118.5 (CH), 58.8 (CH), 27.8 (CH_2), 20.8 (CH_3), 11.5 (CH_3). **HRMS (ESI)** *m/z*: 240.1385 $[M + H]^+$, $C_{16}H_{18}NO$ requires 240.1383.

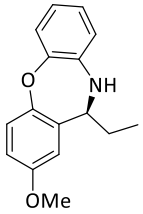
(*S*)-2-Chloro-11-ethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28i)



The enantiomeric excess (34%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 95:05, 1 mL/min, major enantiomer t_r = 11.79 min, minor enantiomer t_r = 12.69 min.

Oil; $[\alpha]_D^{20}$ = +11.2 (c 1.0, $CHCl_3$, 34% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.13-7.07 (m, 2H), 7.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.87 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.68 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 1H), 2.28 – 1.79 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.6 (C), 143.7 (C), 137.3 (C), 135.7 (C), 129.0 (CH), 128.5 (CH), 127.0 (CH), 124.6 (CH), 122.5 (CH), 121.6 (CH), 119.1 (CH), 118.6 (CH), 58.3 (CH), 27.5 (CH_2), 11.3 (CH_3). **HRMS (ESI)** *m/z*: 260.0837 [M + H]$^+$, $C_{15}H_{15}ClNO$ requires 260.0837.

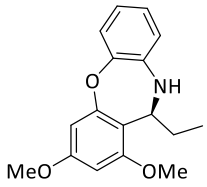
(*S*)-11-Ethyl-2-methoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28j)



The enantiomeric excess (70%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 15.15 min, minor enantiomer t_r = 12.7 min.

Oil; $[\alpha]_D^{20}$ = +14.2 (c 1.0, $CHCl_3$, 70% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.6 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.84 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.74 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 6.65 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.31 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.78 (s, 3H), 2.21 – 1.94 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.9 (C), 151.1 (C), 144.2 (C), 137.7 (C), 135.0 (C) 124.3 (CH), 121.6 (CH), 121.6 (CH), 118.6 (CH), 118.4 (CH), 112.8 (CH), 112.7 (CH), 58.5 (CH), 55.6 (CH_3), 27.5 (CH_2), 11.4 (CH_3). **HRMS (ESI)** *m/z*: 256.1341 [M + H]$^+$, $C_{16}H_{18}NO_2$ requires 256.1332.

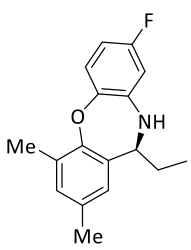
(*S*)-11-Ethyl-1,3-dimethoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28k)



The enantiomeric excess (56%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 30.15 min, minor enantiomer t_r = 39.63 min.

Oil; $[\alpha]_D^{20}$ = -6.8 (c 1.0, $CHCl_3$, 56% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.85 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.64 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 4.51 (dd, *J* = 8.4, 6.9 Hz, 1H), 4.14 (s, 1H), 2.16 – 1.87 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9 (C), 158.2 (C), 157.0 (C), 143.4 (C), 137.7 (C), 124.4 (CH), 121.6 (CH), 118.5 (CH), 118.3 (CH), 115.3 (C), 98.0 (CH), 94.7 (CH), 55.8 (CH_3), 55.4 (CH_3), 51.5 (CH), 29.0 (CH_2), 11.3 (CH_3). **HRMS (ESI)** *m/z*: 286.1435 [M + H]$^+$, $C_{17}H_{20}NO_3$ requires 286.1438.

(*S*)-11-Ethyl-8-fluoro-2,4-dimethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (28l)

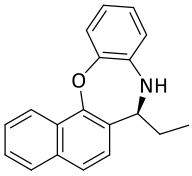


The enantiomeric excess (59%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 7.31 min, minor enantiomer t_r = 4.83 min.

Oil; $[\alpha]_D^{20}$ = +23.6 (c 1.0, $CHCl_3$, 59% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 8.7, 5.7 Hz, 1H), 6.92 (dd, *J* = 1.4, 0.7 Hz, 1H), 6.77 (d, *J* = 1.7 Hz, 1H), 6.27 (ddd, *J* = 8.7, 7.8, 3.0 Hz, 1H), 6.21 (dd, *J* = 10.3, 2.9 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 4.03 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H), 2.18 – 1.97 (m, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ

159.6 (d, *J* = 239.3 Hz, C), 153.3 (C), 139.5 (d, *J* = 11.1 Hz, C), 133.6 (C), 130.9 (CH), 129.9 (C), 125.0 (CH), 122.68 (d, *J* = 10.2 Hz, CH), 112.1 (C), 104.1 (d, *J* = 1.4 Hz, CH), 103.8 (d, *J* = 4.8 Hz, CH), 58.0 (CH), 27.6 (CH_2), 20.8 (CH_3), 16.1 (CH_3), 11.5 (CH_3). **HRMS (ESI)** *m/z*: 272.1444 $[M + H]^+$, $C_{17}H_{19}FNO$ requires 272.1445.

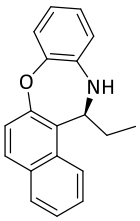
(*S*)-7-Ethyl-7,8-dihydrobenzo[*b*]naphtho[2,1-*f*][1,4]oxazepine (28m)



The enantiomeric excess (59%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 95:05, 0.5 mL/min, major enantiomer t_r = 15.43 min, minor enantiomer t_r = 14.21 min.

Oil; $[\alpha]_D^{20}$ = +6.6 (c 1.0, $CHCl_3$, 59% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (ddd, *J* = 3.0, 1.3, 0.8 Hz, 1H), 7.82-7.79 (m, 1H), 7.60 – 7.51 (m, 2H), 7.48 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 7.32 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 6.87 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.71 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.49 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.39 – 2.02 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.1 (C), 144.0 (C), 138.1 (C), 134.1 (C), 129.0 (C), 127.6 (CH), 127.5 (C), 126.2 (CH), 126.1 (CH), 125.2 (CH), 124.5 (CH), 123.6 (CH), 122.0 (CH), 121.8 (CH), 118.8 (CH), 118.8 (CH), 59.1 (CH), 28.2 (CH_2), 11.5 (CH_3). **HRMS (ESI)** *m/z*: 276.1378 $[M + H]^+$, $C_{19}H_{18}NO$ requires 276.1383.

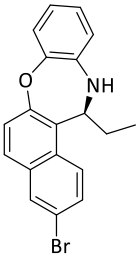
(*S*)-13-Ethyl-12,13-dihydrobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepine (28n)



The enantiomeric excess (57%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 95:05, 0.5 mL/min, major enantiomer t_r = 59.66 min, minor enantiomer t_r = 29.82 min.

Oil; $[\alpha]_D^{20}$ = -126.7 (c 1.0, $CHCl_3$, 57% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.53 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.41 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.88 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 6.71 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.88 (dd, *J* = 8.6, 6.4 Hz, 1H), 2.40 – 2.09 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.3 (C), 143.9 (C), 137.4 (C), 131.2 (C), 130.8 (C), 129.1 (CH), 128.8 (CH), 127.0 (CH), 126.6 (C), 124.4 (CH), 124.3 (CH), 122.2 (CH), 121.9 (CH), 121.4 (CH), 119.0 (CH), 118.6 (CH), 54.7 (CH), 29.0 (CH_2), 11.6 (CH_3). **HRMS (ESI)** *m/z*: 276.1382 $[M + H]^+$, $C_{19}H_{18}NO$ requires 276.1383.

(*S*)-3-Bromo-13-ethyl-12,13-dihydrobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepine (28o)



The enantiomeric excess (67%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 37.28 min, minor enantiomer t_r = 16.95 min.

Oil; $[\alpha]_D^{20}$ = -80.2 (c 1.0, $CHCl_3$, 67% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.1 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.89 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 6.72 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 1H), 6.64 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.80 (dd, *J* = 8.5, 6.4 Hz, 1H), 2.33 – 2.09 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.4 (C), 143.8 (C), 137.1 (C), 132.0 (C), 130.7 (CH), 129.9 (CH), 128.2 (CH), 127.2 (C), 124.4 (CH), 124.1 (CH), 123.7 (CH), 123.2 (C), 121.3 (CH), 119.3 (CH), 118.8 (CH), 118.3 (C), 54.8 (CH), 29.0 (CH_2), 11.5 (CH_3). **HRMS (ESI)** *m/z*: 354.0485 $[M + H]^+$, $C_{19}H_{17}BrNO$ requires 354.0488.

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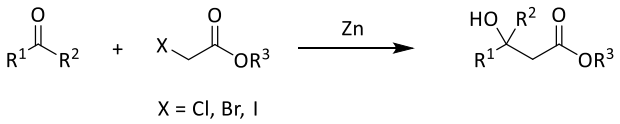
CATALYTIC ENANTIOSELECTIVE AZA-REFORMATSKY REACTIONS OF BENZO[*e*][1,2,3]OXATHIAZINE 2,2-DIOXIDES

CHAPTER 5

5.1. INTRODUCTION

The classical Reformatsky reaction, discovered in 1887,[1] provides a convenient synthesis of β-hydroxy esters through a zinc mediated reaction between α-haloesters and aldehydes or ketones (Scheme 5.1).[2-4] Nowadays the Reformatsky reaction includes all those reactions resulting from the metal insertion into the carbon-halogen bond activated by carbonyl or carbonyl related groups in vicinal or vinylogous positions, with a variety of different electrophiles. There are many examples with different metals such as samarium, tin, cobalt and indium (all metals that are used in low oxidation state). The reaction is a powerful methodology for C-C bond formation and an important alternative for the base induced aldol reaction, with a wide application in organic synthesis, due to the remarkable functional group tolerance and mild reaction conditions.



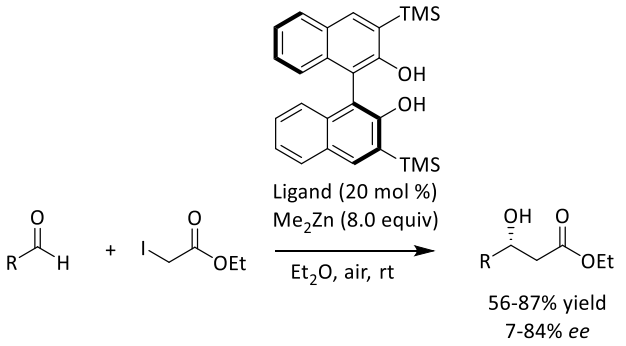
Scheme 5.1. Classical Reformatsky reaction

The classical problem of the Reformatsky reaction due to the difference in the activation degree of different zinc sources could be tackled with the introduction of special forms of activated zinc. This fact made that more efficient and mild conditions could be used and opened the possibility for the development of stereoselective variants of the Reformatsky reaction.[5] However, although these methodologies had various limitations due to its intrinsic heterogeneous character, of which the most important are low yields and stereoselectivities, with narrow substrate scope compared with the classical aldol reaction.

These limitations were a major drawback until 2000, when Honda introduced the homogeneous Reformatsky reaction based on the use of Me_2Zn or Et_2Zn as a zinc source.[6, 7] Although the introduction of the homogeneous Reformatsky reaction opened doors for the development of catalytic enantioselective methodologies, until today, its applications are rather scarce.

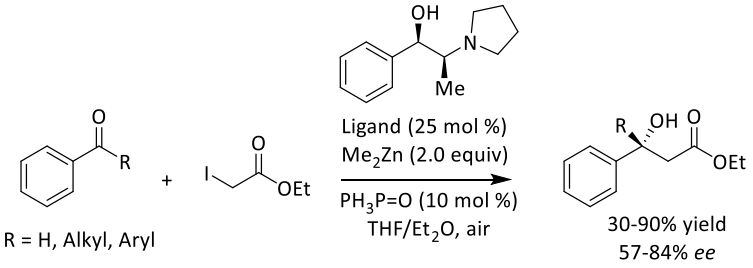
5.1.1. Catalytic enantioselective Reformatsky reactions of aldehydes

The first catalytic enantioselective Reformatsky reaction with aldehydes was described in 2008 by Feringa and coworkers (Scheme 5.2).[8] A possible explanation for the late appearance of this first example, is the high reactivity of aldehydes and therefore the low control of the enantioselectivity. The procedure described by Feringa consists in the slow addition (10 minutes) of the aldehyde to the reaction mixture using 20 mol % of ligand, ethyl iodoacetate and Me_2Zn in Et_2O under air atmosphere. The chiral ligand used was a readily available BINOL type ligand. The slow addition was required to avoid the non catalyzed reaction (background reaction). Several aromatic, heteroaromatic and aliphatic aldehydes were applied in the reaction, leading to the corresponding chiral β-hydroxyesters in good yields and low to good enantioselectivities (7-84% *ee*).



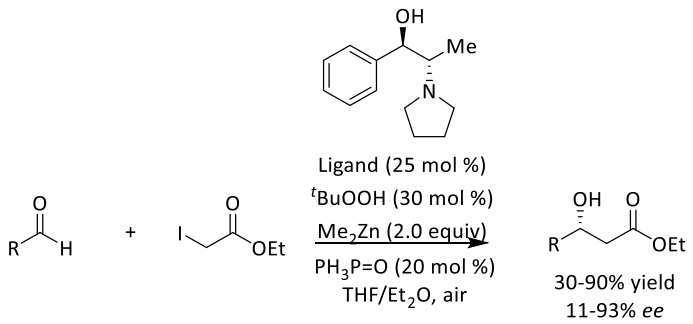
Scheme 5.2. First catalytic enantioselective Reformatsky reaction with aldehydes.

In the same year, Cozzi described a dimethylzinc mediated, oxidatively promoted Reformatsky reaction of ethyl iodoacetate using aldehydes and ketones as electrophiles.[9] This group describes two protocols for the non-enantioselective Reformatsky reaction of aldehydes and ketones. Method A is more suited for non enolizable aldehydes and consists in the addition of the latter to a solution of Me_2Zn and ethyl iodoacetate in Et_2O, connecting the reaction flask to air. Method B, on the other hand, consists in the addition of all the reagents consecutively in the reaction flask. This method was more appropriate for aliphatic enolizable ketones and aldehydes. Triphenylphosphine oxide was added to the reaction as an additive to speed up the reaction allowing also the reaction with rather unreactive and challenging ketones. In the same work, they evaluated also an enantioselective version of the reaction, with the addition of a chiral aminoalcohol ligand [(1*R*, 2*S*)-*N*-pyrrolidinylephedrine] (Scheme 5.3). The products were obtained in good yields and enantioselectivities.



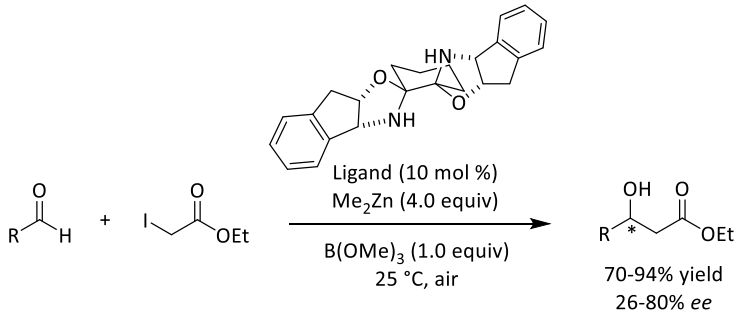
Scheme 5.3. Catalytic enantioselective Reformatsky reaction with ketones and aldehydes.

Few months later, the same research group described a Me_2Zn mediated, *tert*-butylhydroperoxide promoted, catalytic enantioselective Reformatsky reaction with aldehydes (Scheme 5.4).[10] In this report, the authors tried to decrease the big amounts of Me_2Zn used in the previous report described by Feringa.[8] They observed that in the reaction between benzaldehyde and ethyl iodoacetate promoted by Me_2Zn and a norephedrine derived chiral ligand [(1*R*, 2*S*)-*N*-pyrrolidinylephedrine] under air atmosphere and at low temperature there were problems in the initiation step of the radical cycle with oxygen. They reasoned that the addition of *t*BuOOH as promotor could favor the establishment of a radical cycle at low temperature, while $Ph_3P=O$ functions as a reaction accelerator. They were able to decrease the number of equivalents needed of Me_2Zn to 2, obtaining the corresponding products in good yields and low to good enantioselectivities (11-93% *ee*).



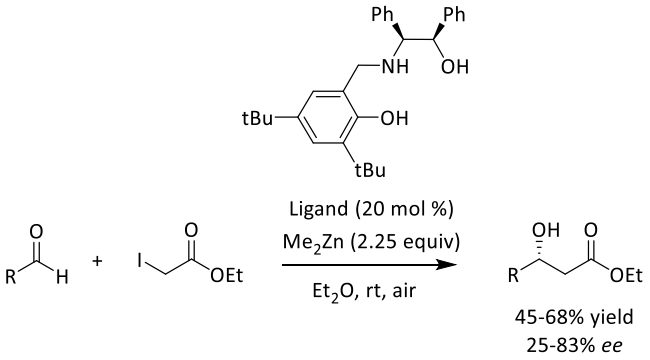
Scheme 5.4. Catalytic enantioselective Reformatsky reaction with aldehydes in the presence of ^{t}BuOOH.

In 2011, Wolf described a bisoxazolidine catalyzed enantioselective Reformatsky reaction with aldehydes (Scheme 5.5).[11] They used 4-bromobenzaldehyde, which is significantly less prone to descomposition than benzaldehyde, for optimization of the reaction conditions. They noticed that the Reformatsky reaction is sensitive to various, unusual, parameters such as flask size, the timing of the exposure to air and the addition sequence of the Me_2Zn. After optimization, various aldehydes were tested, with slow addition, in the reaction with ethyl iodoacetate, in the presence of Me_2Zn and a chiral bisoxazolidine ligand. The corresponding products were obtained in good yields and moderate to good enantioselectivities (26-80% *ee*). Noteworthy is the use of stoichiometric amounts of trimethoxyborane, which induces transmetalation and so facilitates the catalyst turnover.



Scheme 5.5. Bisoxazolidine catalyzed enantioselective Reformatsky reaction with aldehydes.

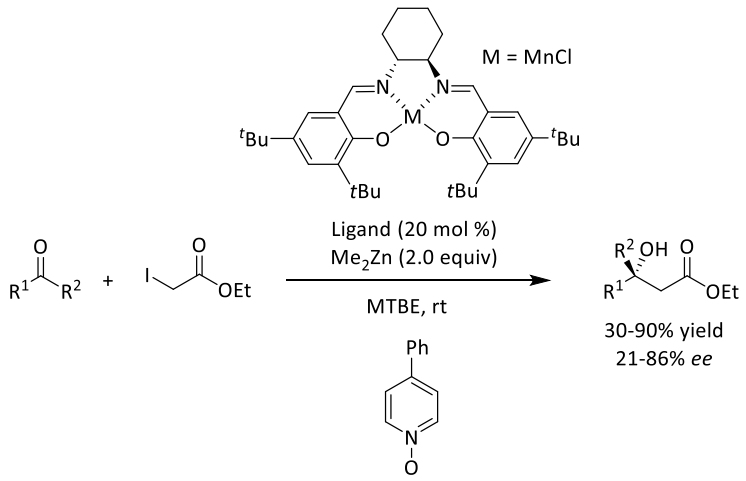
In 2014, Li and He described an asymmetric Reformatsky reaction of aldehydes catalyzed by novel β-amino alcohols and zinc complexes (Scheme 5.6).[12] The researchers performed the addition of ethyl iodoacetate to various aldehydes under air conditions in the presence of 2.25 equivalents of Me_2Zn and 20 mol % of 2,4-di-*tert*-butyl-6-(((2-hydroxy-1,2-diphenylethyl)amino)methyl)phenol as a ligand. The corresponding products were obtained in moderate yields and moderate to good enantioselectivities (25-83% *ee*).



Scheme 5.6. Asymmetric Reformatsky reaction with aldehydes catalyzed by novel β-amino alcohols and zinc complexes.

5.1.2. Catalytic enantioselective Reformatsky reactions of ketones

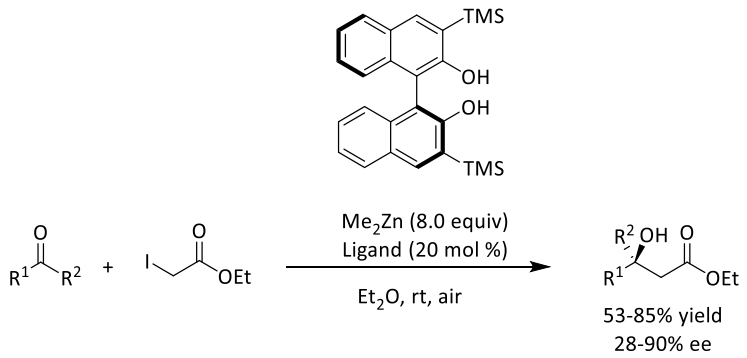
In 2006, Cozzi described the first catalytic enantioselective Reformatsky reaction with ketones (Scheme 5.7).[13] The researcher tested various esters in the reaction with acetophenone in the presence of Me_2Zn and a manganese salen complex, noticing that an increase in the steric hindrance led to a decrease in the enantioselectivity of the reaction, giving the best enantioselectivity when ethyl iodoacetate was used (63% *ee*). The reaction was performed in MTBE at reflux temperature in the presence of 4-phenylpyridine *N*-oxide. Other ketones were also tested, but although the conversions were good, the enantioselectivities were low. Lowering the temperature brought better results; at room temperature, the use of various ketones led to the corresponding products in good yields (30-90%) and moderate enantioselectivities (21-86% *ee*).



Scheme 5.7. The first catalytic enantioselective Reformatsky reaction with ketones.

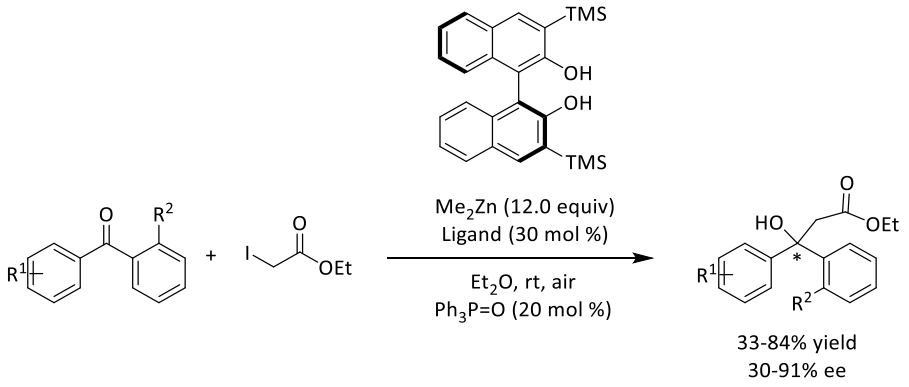
Two years later, in 2008, Feringa and coworkers reported a catalytic enantioselective Reformatsky reaction with ketones using chiral BINOL type ligands (Scheme 5.8).[14] With the optimized conditions in hand, consisting in the slow addition (30 minutes) of the ketone to a solution of Me_2Zn, ethyl iodoacetate and a BINOL type ligand in diethyl ether in the presence of air, they were able to obtain the β-hydroxyesters from aromatic, heteroaromatic and aliphatic ketones in good yields (53-85%) and moderate to good enantioselectivities (28-90% *ee*). In the same report, the researchers also

mention the enantioselective Reformatsky reaction of phenyl(*o*-tolyl)-methanone, resulting in moderate yield (40%), but good enantioselectivity (82% *ee*).



Scheme 5.8. Catalytic enantioselective Reformatsky reaction with ketones using (*S*)-3,3'-bis(trimethylsilyl)-[1,1'-binaphthalene]-2,2'-diol.

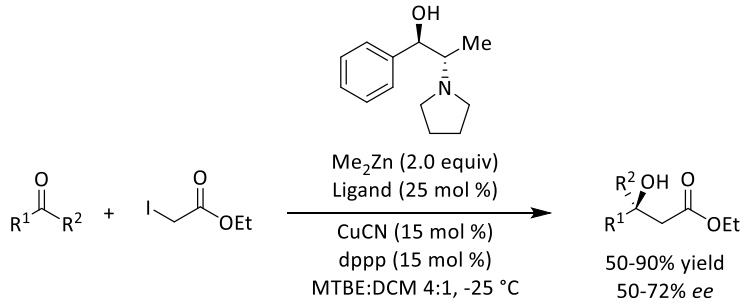
The same researchers reported in the same year a catalytic enantioselective Reformatsky reaction with *ortho*-substituted diarylketones, which they already introduced earlier (Scheme 5.9).[14, 15] In the optimization of the reaction conditions it became clear that only *ortho* substituted diaryketones are suitable substrates; *meta* and *para* substituted substrates resulted in racemic carbinols. The reaction conditions include the presence of triphenylphosphine oxide, which enhances the yield of the reaction, but especially the enantioselectivity. The reaction is performed in the presence of 12 equivalents of Me_2Zn and 6 equivalents of ethyl iodoacetate and 30 mol % of a readily available BINOL type ligand. The corresponding β-hydroxyesters were obtained in low to good yields (33-84%) and moderate to good enantioselectivities (30-91% *ee*).



Scheme 5.9. Catalytic enantioselective Reformatsky reaction with *ortho*-substituted diarylketones.

In 2010, Cozzi and Benfatti described a copper promoted enantioselective Reformatsky type reaction with ketones (Scheme 5.10).[16] Cozzi and collaborators observed in previous works that the reproducibility of the Reformatsky reactions may present some problems and they suggest that such problems must lie in the formation of radicals. Therefore they investigated new methods of generating radicals in an easier and controlled way. For this purpose, they used copper(I) or copper(II) salts. The reaction took place at lower temperature (-25 °C), using a catalytic amount of *N*-pyrrolidinyl norephedrine (25 mol %), CuCN (15 mol %), a phosphine additive [1,3-bis(diphenylphosphanyl)propane, dppp] (15 mol %), Me_2Zn and ethyl iodoacetate. The reactions, with rather long reaction times (14-48 h) led to moderate to high yields (50-90%), but low to moderate enantioselectivities (50-72% *ee*), with aromatic and aliphatic ketones. Altough the objective was to

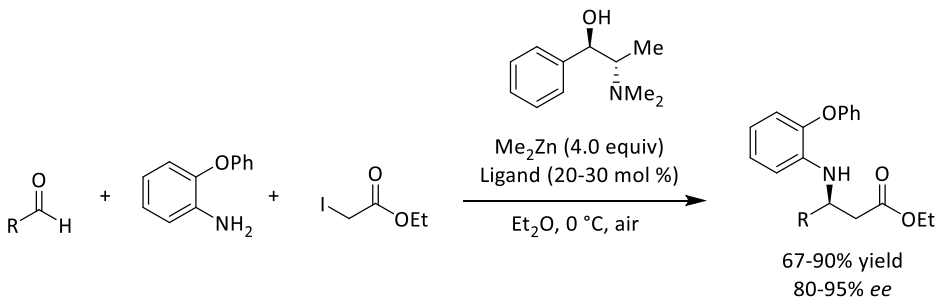
improve the previously described results, Cozzi´s reaction conditions did not improve the results described in the literature.



Scheme 5.10. Copper promoted enantioselective Reformatsky reaction of ketones.

5.1.3. Catalytic enantioselective Reformatsky reactions of imines

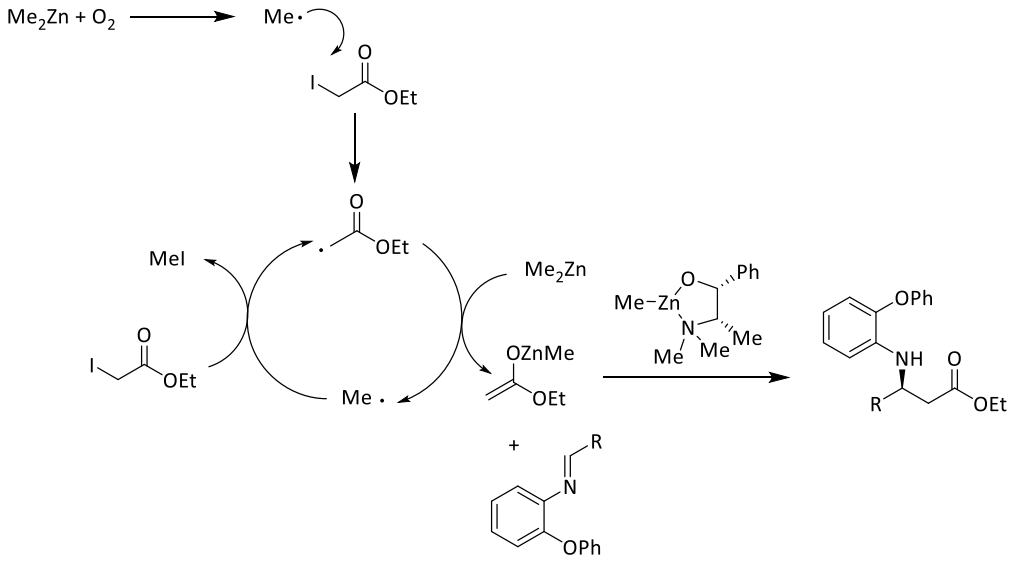
Imines can be used as electrophiles in Reformatsky reactions, instead of the typical aldehydes and ketones. However, due to the low reactivity of imines, the catalytic enantioselective aza-Reformatsky reaction is scarcely explored, despite the possibility of easy synthesis of chiral β-amino acids, an important building block in synthetic organic chemistry.[17, 18] On the other hand, this transformation can be problematic, since it can lead to an undesired mixture of β-amino esters and β-lactams. These problems can be avoided by the use of chelating imines derived from 2-methoxyaniline, as described by Snapper and collaborators in a non-enantioselective nickel catalyzed aza-Reformatsky reaction.[19] Hoveyda and collaborators described in the same year, the three-component enantioselective synthesis of propargylamines catalyzed by Zr, using imines derived from the more bulky *o*-phenoxyaniline instead of 2-methoxyaniline, getting an improvement in the enantioselectivity of the reaction.[20] This is exactly what Cozzi and coworker did when they described the first enantioselective aza-Reformatsky reaction in 2005, using 1.6 equivalents of ligand (*N*-methylephedrine).[21] One year later, Cozzi described the catalytic version of this reaction, using 20-30 mol % of the same ligand (Scheme 5.11).[22] In the catalytic version of the reaction, 1 equivalent of differently substituted benzaldehydes and *o*-phenoxyaniline are mixed with 4 equivalents of Me_2Zn to form the imine under nitrogen atmosphere. After more than 3 hours, the nitrogen atmosphere was carefully changed to an air atmosphere, followed by an addition of solvent and *N*-methylephedrine. After placing the reaction at 0 °C, ethyl iodoacetate was added to give the formation of the β-amino esters in high yields (67-90%) and enantioselectivities (80-95% *ee*). A drawback of the reaction is the necessity of a bulky directing group in *ortho* position of the aromatic ring.



Scheme 5.11. Catalytic enantioselective one-pot three-component aza-Reformatsky reaction.

An important discovery made by Cozzi was the necessity for air in the reaction, what led him thinking in a radical mechanism with Me_2Zn. Another aspect he reasoned is that the reaction is

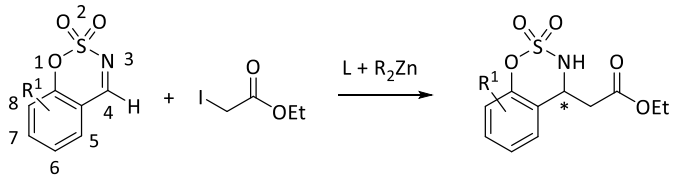
dependent on several, uncommon, parameters such as the size of the flask, the surface area and the quantity of the solvent. In the same article he proposed a possible mechanism (Scheme 5.12), suggesting a radical mechanism.



Scheme 5.12. Possible mechanism for the catalytic enantioselective one-pot three-component aza-Reformatsky reaction.

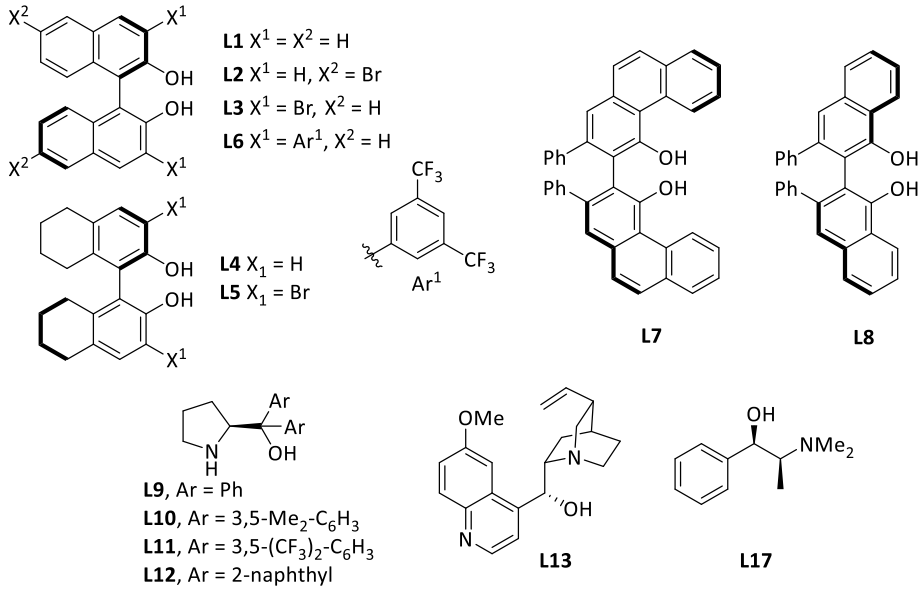
5.2. OBJETIVOS

El objetivo general de este capítulo es el desarrollo de un método catalítico y enantioselectivo que permita llevar a cabo la reacción de aza-Reformatsky de iminas cíclicas de tipo 2,2-dióxido benzoxatiazina (**1**) con iodoacetato de etilo (**29**) que transcurra con buenos rendimientos y excesos enantioméricos.



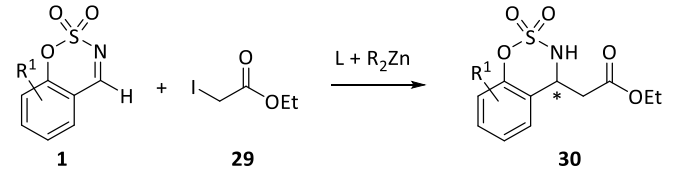
En el estudio de este proyecto se considerarán los siguientes aspectos:

1. La influencia de diferentes ligandos de tipo BINOL (**L1**-**L6**), (*R*)-VAPOL (**L7**), (*R*)-VANOL (**L8**), derivados de (*S*)-prolinol (**L9**-**L12**), quinina (**L13**) y *N*-metilefedrina (**L17**) sobre el rendimiento y la enantioselectividad de la reacción.

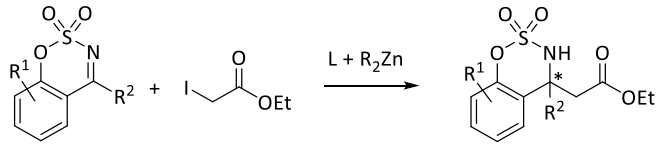


2. La influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn), número de equivalentes de dialquilzinc, disolvente y temperatura de reacción.

3. Evaluación de diversas aldiminas cíclicas de tipo 2,2-dióxido benzoxatiazina (**1**) con diferente naturaleza electrónica y estérica en la reacción con iodoacetato de etilo (**45**).



4. Evaluación de diversas cetiminas cíclicas de tipo 2,2-dióxido benzoxatiazina (**9**) con diferente naturaleza electrónica y estérica en la reacción con iodoacetato de etilo (**45**).



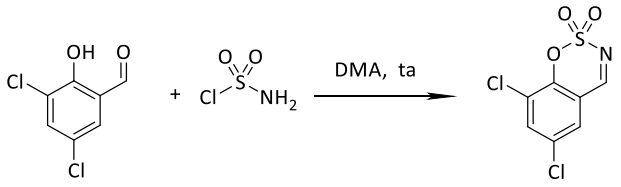
5. Evaluación de distintas transformaciones sintéticas de los productos obtenidos basadas en en la reactividad de los grupos éster y sulfamidato sin pérdida de pureza óptica.

6. Determinación de la configuración absoluta del centro estereogénico.

5.3. RESULTADOS Y DISCUSIÓN

5.3.1. Síntesis de 2,2-dióxido benzoxatiazinas

Con el objeto de llevar a cabo un estudio amplio del alcance y limitaciones de la reacción de aza-Reformatsky a aldiminas de tipo 2,2-dióxido benzoxatiazinas que incluyera iminas doblemente sustituidas se sintetizó la aldimina disustituida en las posiciones 6 y 8 del anillo aromático con átomos de cloro (Esquema 5.13). Se siguió la misma metodología usada anteriormente, obteniendo la aldimina cíclica **1l** con un rendimiento moderado (40%)

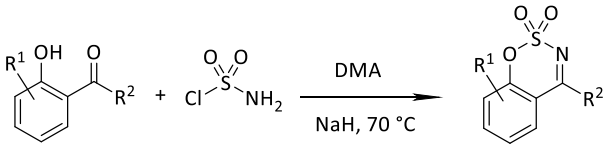


4l **5** **1l** 40%

Esquema 5.13. Síntesis de una aldimina de tipo 2,2-dióxido benzoxatiazina disustituida.

Con el mismo propósito también se sintetizaron varias cetiminas de tipo 2,2-dióxido benzoxatiazinas (**9**). Estas iminas fueron sintetizadas a partir de diferentes 2-hidroxiacetofenonas **8** en una reacción con clorosulfonilamina, preparada *in situ* a partir de isocianato de clorosulfonilo, en DMA en presencia de hidruro sódico a 70 °C (Tabla 5.1). Los rendimientos de estas reacciones fueron más bajos que el de las reacciones llevadas a cabo con los correspondientes salicilaldehidos debido a la menor electrofilia del grupo carbonilo de las hidroxiacetofenonas.

Tabla 5.1. Sintesis de cetiminas de tipo 2,2-dióxido benzoxatiazina.



8 **5** **9**

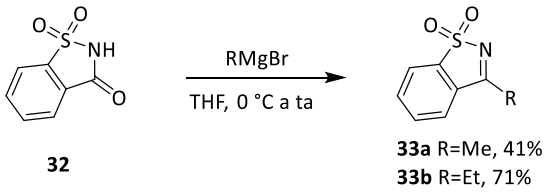
Entrada	8	R^1	R^2	t (h)	9	R (%)[a]
1	**8a**	H	Me	18	**9a**	30
2	**8b**	6-Me	Me	18	**9b**	35
3	**8c**	6-Cl	Me	18	**9c**	32
4	**8d**	7-Me	Me	18	**9d**	40
5	**8e**	7-OMe	Me	18	**9e**	37
6	**8f**	6-Cl, 7-Me	Me	18	**9f**	29
7[b]	**8g**	H	Me	18	**9g**	30
8	**8h**	H	Et	18	**9h**	32
9	**8i**	H	CH_2CH_2Ph	18	**9i**	28

[a] Rendimiento después de purificación por cromatografía de columna. [b] La imina fue sintetizada a partir de 2-acetil-1-naftol

5.3.2. Síntesis de *N*-sulfonil cetiminas cíclicas de 5 miembros

También se sintetizaron dos *N*-sulfonil cetiminas de cinco miembros (**33**) mediante la adición de reactivos de Grignard a sacarina (**32**) (Esquema 5.14).[23] En la reacción de adición se genera el

correspondiente aminal el cual experimenta una deshidratación espontánea generando las *N*-sulfonil cetiminas **33**. El rendimiento fue moderado (41%) para la reacción de la sacarina con MeMgBr, mientras que cuando se utilizó EtMgBr se obtuvo mejor rendimiento (71%)



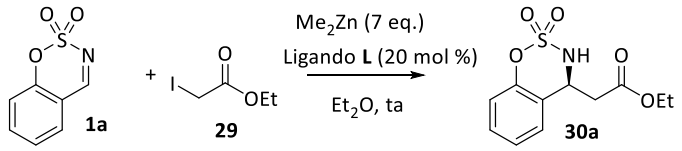
Esquema 5.14. Síntesis de *N*-sulfonil cetiminas cíclicas de 5 miembros.

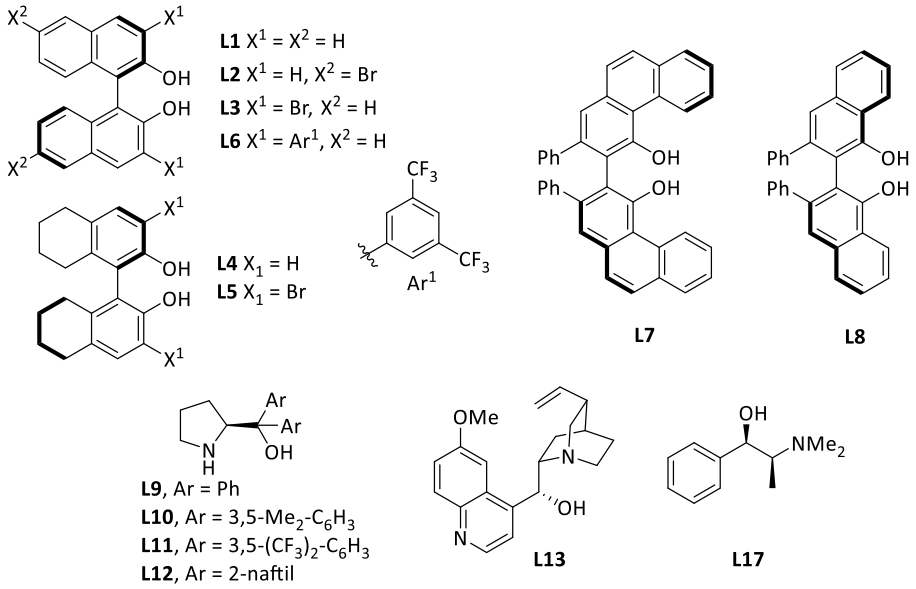
5.3.3. Optimización de las condiciones de reacción

Como se ha visto en los antecedentes bibliográficos solo hay descrito un ejemplo de una reacción catalítica enantioselectiva de tipo aza-Reformatsky descrito en la bibliografía. Por tanto decidimos estudiar este tipo de reacción utilizando iminas cíclicas, como son las benzoxatiazinas. El estudio de la reacción de aza-Reformatsky entre iodoacetato de etilo (**45**) y las iminas cíclicas de tipo 2,2-dióxido benzoxatiazina se inició con la optimización de las condiciones de la reacción. El proceso de optimización se llevó a cabo ensayando un conjunto de ligandos en presencia de 7 equivalentes de Me_2Zn (1,2 M en tolueno) empleando Et_2O como disolvente a temperatura ambiente (Tabla 5.2). Como ligandos se utilizaron diferentes ligandos quirales de tipo BINOL (**L1**-**L6**), (*R*)-VAPOL (**L7**), (*R*)-VANOL (**L8**), derivados de (*S*)-prolinol (**L9**-**L12**), quinina (**L13**) y *N*-metilefedrina (**L17**) (Tabla 5.2).

Como se puede observar en la tabla 5.2, la utilización de ligandos de tipo BINOL (**L1**-**L6**), conduce a los productos de adición con rendimientos altos entre 79 y 94%, aunque los excesos enantioméricos de los productos obtenidos fueron bajos (2-26% *ee*) (Tabla 5.2, entradas 1-6). El uso de (*R*)-VAPOL (**L7**) o de (*R*)-VANOL (**L8**), tampoco dio buenos resultados, obteniéndose rendimientos buenos, pero enantioselectividades bajas (16-20% *ee*) (Tabla 5.2, entradas 7 y 8). Con el objetivo de mejorar la enantioselectividad de la reacción, se ensayó un derivado del aminoácido (*S*)-prolina, un diarilprolinol (*S*)-difenil(pirrolidin-2-il)metanol] (**L9**). El uso de este ligando dio lugar a un resultado prometedor, obteniéndose el producto de adición con un rendimiento elevado (74%) y una enantioselectividad de 75% (Tabla 5.2, entrada 9). Para completar la evaluación de los ligandos de tipo aminoalcohol, también se ensayaron la quinina (**L13**) y la *N*-metilefedrina (**L17**), pero los excesos enantioméricos de los productos obtenidos fueron muy bajos (0-10% *ee*) (Tabla 5.2, entradas 10 y 11). Una vez identificado **L7** como el mejor ligando para la reacción de aza-Reformatsky objeto del estudio, continuamos el proceso de optimización ensayando la reacción con diferentes reactivos de dialquilzinc y disolventes a varias temperaturas (Tabla 5.3).

Tabla 5.2. Reacción de aza-Reformatsky enantioselectiva de 2,2-dióxido benzoxatiazina (**1a**) con iodoacetato de etilo (**29**). Evaluación de ligandos.[a]





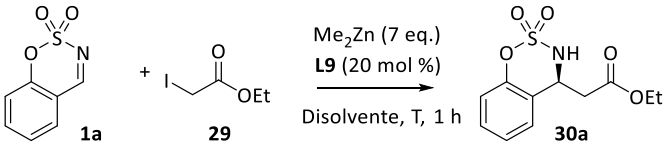
Entrada	Ligando	t (h)	R (%)[b]	*ee* (%)[c]
1	**L1**	1	86	15
2	**L2**	1	81	26
3	**L3**	1	87	2
4	**L4**	1	94	15
5	**L5**	1	79	5
6	**L6**	1	92	-16
7	**L7**	1	54	-20
8	**L8**	1	78	4
9	**L9**	1	74	75
10	**L13**	1	84	0
11	**L17**	1	79	-10

[a] **1a** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L** (0,020 mmol). [b] Rendimiento después la purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

Como se puede observar en la tabla 5.3, una disminución en la cantidad de Me_2Zn usado en la reacción, dio lugar a una disminución en el rendimiento y la enantioselectividad de la reacción (Tabla 5.3, entrada 2). Cuando se ensayó la reacción en presencia de Et_2Zn en lugar de Me_2Zn dio lugar al β-amino éster **30a** con mayor rendimiento (88%), pero se observó también un descenso notable de la enantioselectividad hasta 60% *ee* (Tabla 5.3, entrada 3).

El uso de diferentes disolventes clorados y no clorados, como MTBE, *i*Pr_2O, THF, tolueno y CH_2Cl_2, no mejoró la enantioselectividad de la reacción (Tabla 5.3, entradas 4-8). No obstante se pudo observar un mejora en el rendimiento (hasta 91%) sin disminución de la enantioselectividad utilizando MTBE como disolvente (Tabla 5.3, entrada 4).

Tabla 5.3. Reacción de aza-Reformatsky enantioselectiva de 2,2-dióxido benzoxatiazina (**1a**) con iodoacetato de etilo (**29**). Evaluación de los reactivos de dialquilzinc, número de equivalentes de dialquilzinc, disolventes y temperatura de reacción.[a]



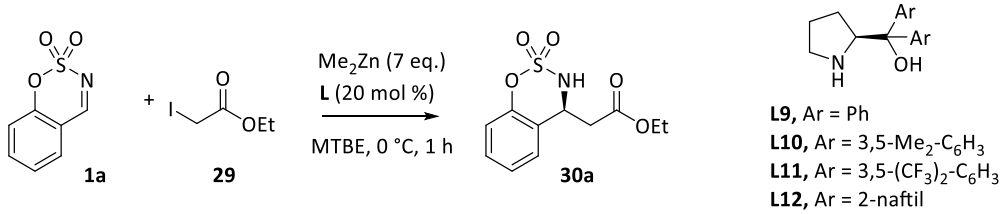
Entrada	Disolvente	T (°C)	R (%)[b]	*ee* (%)[c]
1	Et_2O	ta	74	75
2[d]	Et_2O	ta	70	73
3[e]	Et_2O	ta	88	60
4	MTBE	ta	91	75
5	$^{i}Pr_2O$	ta	87	69
6	THF	ta	42	28
7	Tolueno	ta	95	70
8	CH_2Cl_2	ta	95	55
9	MTBE	0	74	80
10	MTBE	-10	96	77

[a] **1a** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L9** (0,020 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [d] Se usaron 3 equivalentes de Me_2Zn (0,3 mmol) [e] Se usó 1M Et_2Zn en hexanos (0,7 mmol).

Por último, se llevó a cabo la reacción a temperaturas más bajas (Tabla 5.3, entradas 9 y 10). Cuando la temperatura de la reacción fue 0 °C, el producto **30a** se obtuvo con un 80% *ee*, aunque el rendimiento de la reacción fue menor (74%). Mientras que cuando se llevó a cabo la reacción a -10 °C, el β-amino éster **30a** se obtuvo con mejor rendimiento pero con menor exceso enantiomérico.

No estando totalmente satisfechos con los resultados obtenidos, decidimos evaluar otros ligandos del tipo diarilprolinol en las condiciones optimizadas para **L9** (Tabla 5.4).

Tabla 5.4. Reacción de aza-Reformatsky enantioselectiva de 2,2-dióxido benzoxatiazina (**1a**) con iodoacetato de etilo (**29**) utilizando Me_2Zn en MTBE a 0°C. Evaluación de ligandos de tipo diarilprolinol.[a]



Entrada	Ligando	t (h)	R (%)[b]	*ee* (%)[c]
1	**L9**	1	74	80
2	**L10**	1	88	79
3	**L11**	1	86	92
4	**L12**	1	96	80
5[c]	**L11**	1	89	87

[a] **1a** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L9-L12** (0,020 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [c] Se usó 10 mol % del ligando.

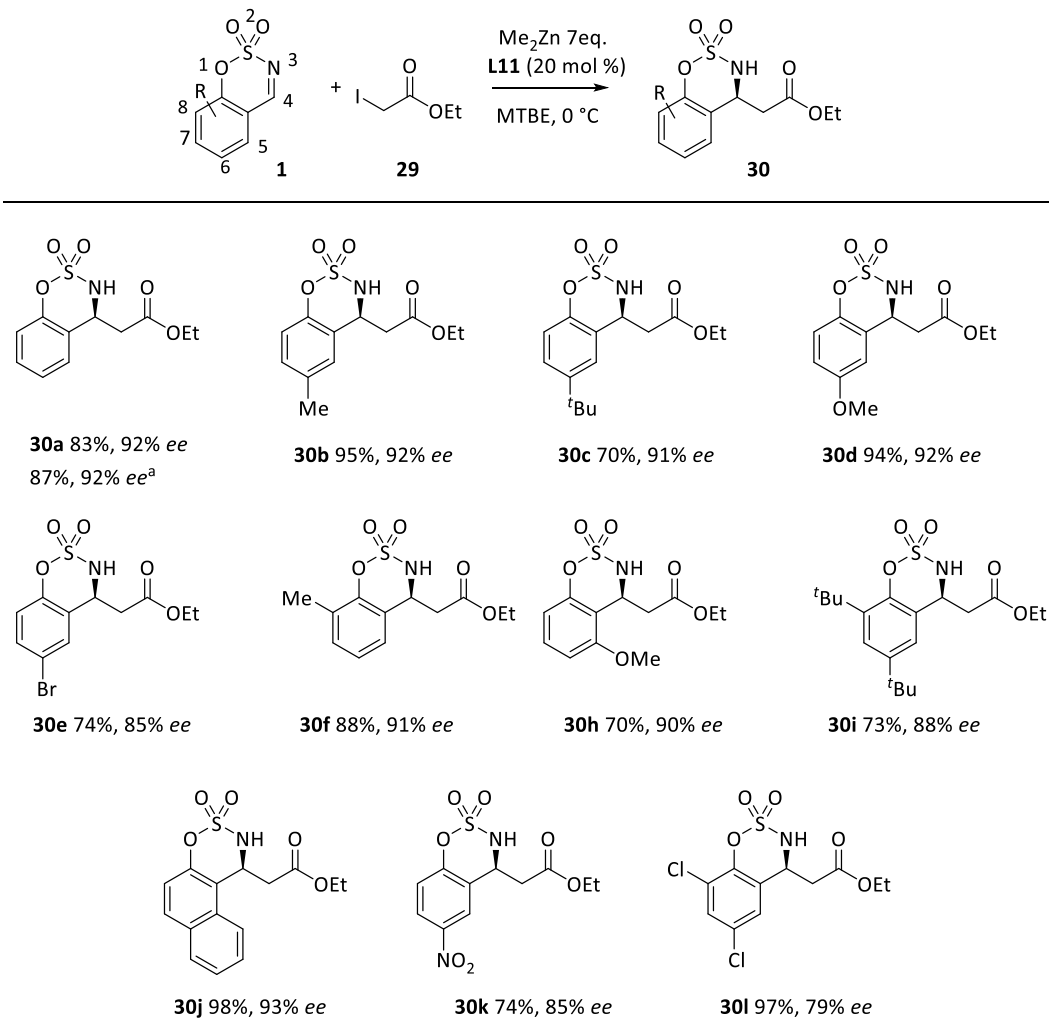
El uso de los ligandos **L10** y **L12** dio resultados similares tanto de rendimiento como de enantioselectividad al obtenido con el ligando **L9** (Tabla 5.4, entradas 2 y 4) . Sin embargo, el uso del ligando **L11** [(*S*)-bis(3,5-bis(trifluorometil)fenil)(pirrolidin-2-il)metanol], dio lugar al producto final con un rendimiento elevado (86%) y un exceso enantiomérico excelente de 92% (Tabla 5.4, entrada 3). Finalmente, una disminución de la cantidad de ligando utilizando 10 mol % dio lugar a un descenso ligero en la enantioselectividad (87% *ee*) (Tabla 5.4, entrada 5). Por tanto, se consideran como condiciones óptimas las indicadas en la entrada 3 (Tabla 5.4).

5.3.4. Alcance y limitaciones de la reacción

En el estudio del alcance y limitaciones de la reacción, se utilizaron las condiciones optimizadas llevando a cabo la reacción de aza-Reformatsky de distintas aldiminas y cetiminas de tipo 2,2-dióxido benzoxatiazina (**1** y **9**) con iodoacetato de etilo (**29**).

5.3.4.1. Evaluación de distintas aldiminas de tipo 2,2-dióxido benzoxatiazina

En primer lugar se evaluó la reacción de aza-Reformatsky enantioselectiva de varias aldiminas de tipo 2,2-dióxido benzoxatiazina (**1**) con iodoacetato de etilo (**29**). Los resultados se puede observar en el esquema 5.15.



Esquema 5.15. Reacción de aza-Reformatsky enantioselectiva de varias aldiminas **1** con iodoacetato de etilo (**29**): **1** (0,10 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L11** (0,020 mmol). Rendimiento

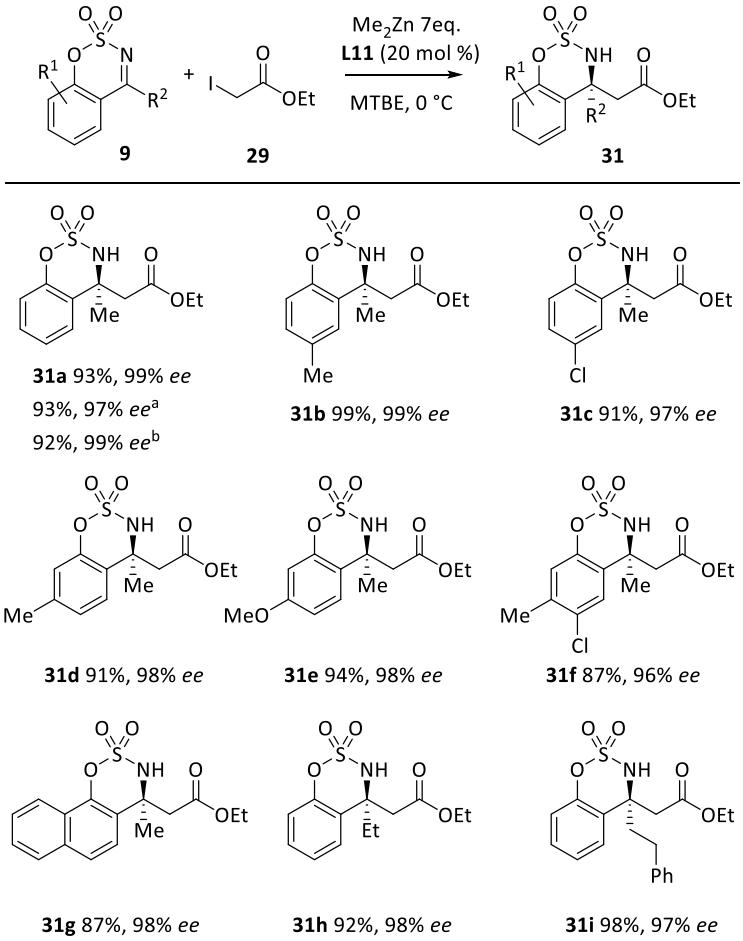
después de purificación por cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [a] Reacción a mayor escala (0,4 mmol).

Se ensayó la reacción bajo las condiciones optimizadas con varias aldiminas sustituidas en la posición 6. Se puede observar en el esquema 5.15 que la presencia de un grupo electrón-donante no influye en la enantioselectividad de la reacción de manera que aldiminas sustituidas con un grupo metilo (**1b**), *terc*-butil (**1c**) o metoxi (**1d**) proporcionan los correspondientes productos de adición con buenos rendimientos (70-95%) y excesos enatioméricos de 91-92%. La presencia de un grupo electrón-atrayente (bromo) en la posición 6 da lugar al producto de la reacción de aza-Reformatsky **30e** con buen rendimiento (74%) y una enantioselectividad un poco inferior (85% *ee*). La reacción incluso se pudo llevar a cabo con una aldimina sustituida en la posición 6 con un grupo nitro (**1k**) con buena enantioselectividad (85% *ee*) y con buen rendimiento (74%). También fueron evaluados aldiminas cíclicas sustituidas en las posiciones 8 y 5 con grupos electrón-donantes obteniéndose buenos resultados. Así la presencia de un grupo metilo en la posición 8 dio lugar al producto **30f** con buen rendimiento (88%) y una enantioselectividad del 91% *ee*, mientras que la presencia de un grupo metoxi en la posición 5 condujo al producto **30h** con buen rendimiento (70%) y una enantioselectividad elevada del 90% *ee*. La reacción con la imina **1j**, una imina cíclica con un anillo de naftilo, dio lugar al producto correspondiente **30j** con excelente rendimiento (98%) y un exceso enantiomérico elevado (93% *ee*). Por último, iminas cíclicas disustituidas en las posiciones 6 y 8 (**1i** y **1l**), con un impedimento estérico considerable, demostraron ser buenos sustratos para la reacción de aza-Reformatsky, dando lugar a los correspondientes productos de reacción con buenos rendimientos (73-97%) y enantioselectividades elevadas (79-88% *ee*).

5.3.4.2. Evaluación de distintas cetiminas de tipo 2,2-dióxido benzoxatiazina

También se evaluó la reacción de aza-Reformatsky de varias cetiminas de tipo 2,2-dióxido benzoxatiazina (**9**) con iodoacetato de etilo (**29**). Los resultados se pueden observar en el esquema 5.16.

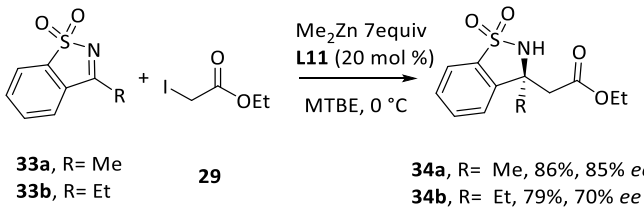
Una importante observación que se deriva de los resultados recogidos en el esquema anterior, es que la utilización de cetiminas, generalmente menos reactivas que las aldiminas, conduce a los correspondientes productos de reacción con rendimientos y enantioselectividades excelentes y siempre superiores a las enantioselectividades de las correpondientes aldiminas. La reacción con la cetimina **9a** conduce al β-amino éster **31a** con un centro estereogénico cuaternario con un rendimiento del 93% y una enantioselectividad excelente del 99% *ee*. Incluso la utilización de un 10 mol % de ligando permitió la obtención de **31a** con un rendimiento similar y un ligero descenso del exceso enantiomérico (97%). La presencia de grupos electrón-donantes (**9b**) o electrón-atrayentes (**9c**) prácticamente no tiene ninguna influencia en los resultados obtenidos; se pudieron obtener los productos correspondientes con rendimientos altos (91-99%) y enantioselectividades excelentes (97-99% *ee*). Cuando los grupos electrón-donantes están en la posición 7 (**9d** y **9e**) también se obtienen rendimientos altos (91-94%) y enantioselectividades excelentes (98% *ee*). Las condiciones también permiten llevar a cabo la reacción con un sustrato disustituido (**9f**) obteniéndose el β-amino éster **31f** con un rendimiento alto (87%) y una enantioselectividad excelente (96% *ee*). Un resultado similar se obtuvo en la reacción con el sustrato **9g**, una cetimina con un grupo naftilo, dando lugar al producto **31g** con un exceso enantiomérico del 98%. También se utilizaron cetiminas con diferentes grupos alquilo en la posición 4. Cuando en esta posición hay un grupo etilo o un grupo 2-feniletilo, los productos resultantes (**31h** y **31i**) se obtuvieron con rendimientos altos (92-98%) y enantioselectividades excelentes (97-98% *ee*).



Esquema 5.16. Reacción de aza-Reformatsky enantioselectiva de varias cetiminas con iodoacetato de etilo (**29**): **9** (0,10 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L11** (0,020 mmol). Rendimiento después de purificación por cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [a] Se usó 10 mol % **L11** [b] Reacción a mayor escala (0,4 mmol).

5.3.4.3. Evaluación de distintas *N*-sulfonil cetiminas cíclicas de 5 miembros

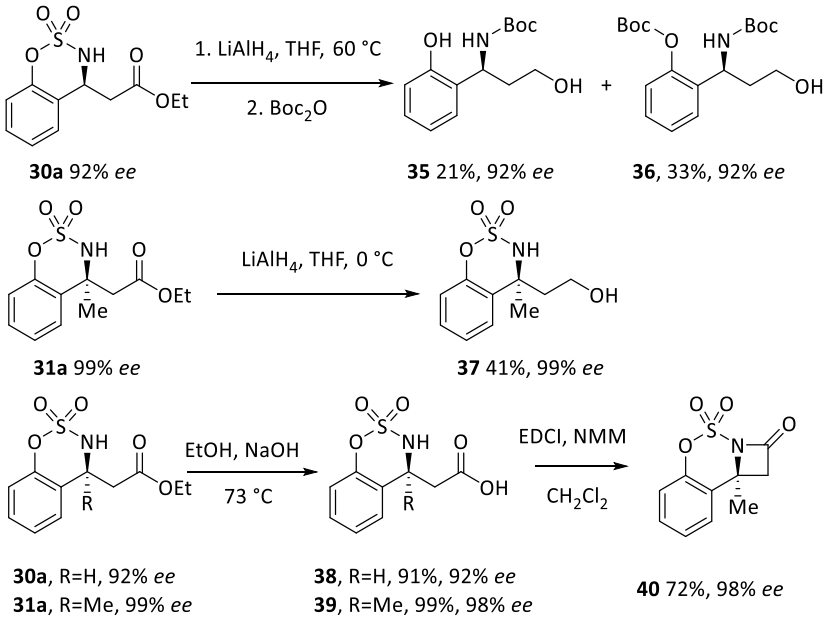
Una vez estudiado el comportamiento de diferentes cetiminas de 6 miembros decidimos ampliar el estudio del alcance y limitaciones de la reacción, ensayando la reacción con dos cetiminas cíclicas de 5 miembros de tipo *N*-sulfonil **33** bajo las condiciones optimizadas. Las benzosultamas resultantes **34a** y **34b** se obtuvieron con buenos rendimientos (79-86%) y enantioselectividades (70-85% *ee*) (Esquema 5.17).



Esquema 5.17. Reacción de aza-Reformatsky enantioselectiva de cetiminas cíclicas de 5 miembros con iodoacetato de etilo (**29**): **33** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L11** (0,020 mmol). Rendimiento después de purificación por cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

5.3.5. Transformaciones sintéticas

Para demostrar la utilidad de los productos obtenidos, se realizaron varias transformaciones sintéticas con los β-amino esteres quirales (Esquema 5.18). La primera transformación que se realizó fue la reducción del éster **30a** a alcohol primario con apertura del anillo del benzosulfamidato con $LiAlH_4$ a 60 °C seguido por una protección de la amina resultante con carbonato di-*terc*-butilo (Boc_2O). Se obtuvieron dos productos de reacción **35** y **36** con rendimientos bajos pero conservando la pureza óptica.



Esquema 5.18. Transformaciones sintéticas

Otra transformación que se llevó a cabo fue la reducción del éster **31a** con hidruro de aluminio y litio a 0 °C, para evitar la apertura del anillo del benzosulfamidato, dando lugar al γ-amino alcohol **37** con un rendimiento moderado, pero conservando el exceso enantiomérico.

Finalmente se abordó la saponificación del grupo éster, con la idea de obtener los correspondientes β-aminoácidos. Este tipo de compuestos son muy importantes en química orgánica y medicinal por ser precursores de péptidos y peptidomiméticos,[24, 25] además de β-lactamas, que son uno de los antibióticos más importantes en química farmacéutica.[26-28] La saponificación de **30a** y **31a** se llevó a cabo con NaOH/EtOH obteniéndose los correspondientes β-aminoácidos **38** y **39** con buenos rendimientos y sin pérdida de pureza óptica. La β-lactama quiral **40**, que contiene tres anillos fusionados y un estereocentro cuaternario, se preparó a partir del β-aminoácido **39** utilizando EDCI [1-etil-3-(3-dimetilaminopropil)carbodiimida] y *N*-metilmorfolina (NMM) como reactivos y se obtuvo un rendimiento del 72% manteniendo la pureza optica (98% *ee*).

5.3.6. Determinación de la configuración absoluta

La determinación de la estereoquímica para los compuestos **30** se hizo mediante correlación química del compuesto **35**, el cual está descrito en la literatura,[29] comparando el signo de la rotación especifica del compuesto. Así se pudo establecer que la configuración absoluta es (*S*). Por su parte la determinación de la configuración absoluta de los compuestos **31** se hizo mediante el estudio de difracción de Rayos X de monocristal del compuesto **31f**. El carbono esterogénico también presenta la configuración (*S*) (parámetro de Flack: 0.01(2)) (Figura 5.1). La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

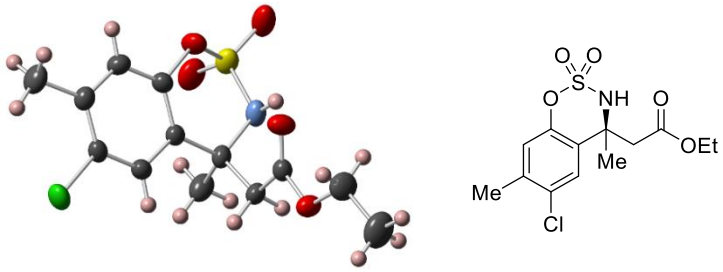
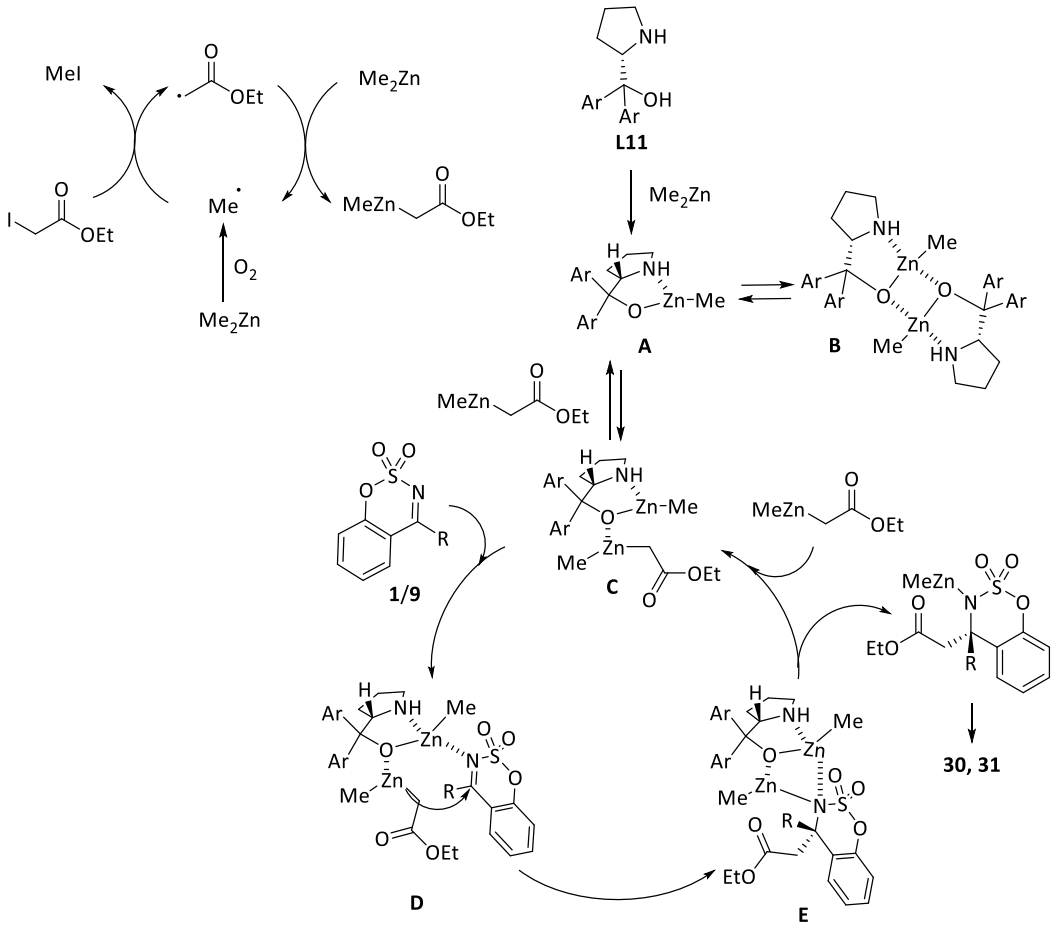


Figura 5.1. Estructura del compuesto **31f** determinada por Rayos X.

5.3.7. Propuesta mecanística para la reacción de aza-Reformatsky de 2,2-dióxido benzoxatiazinas

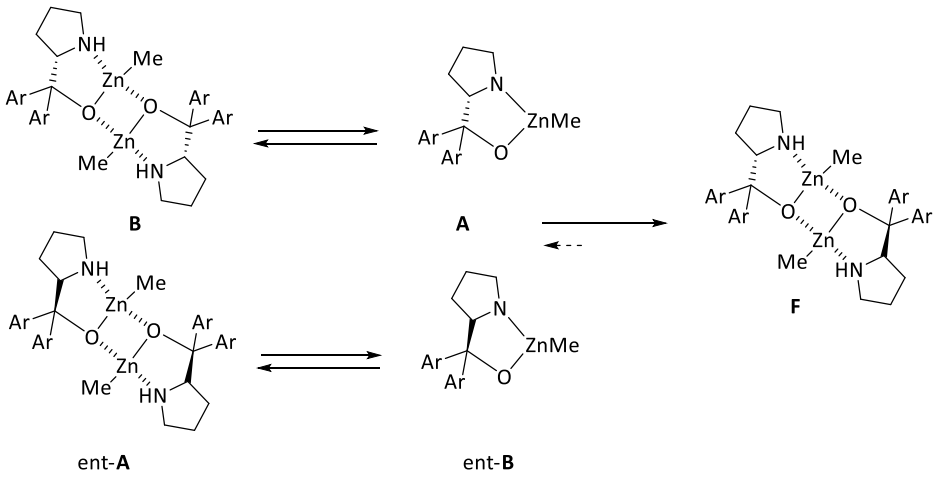
El esquema 5.19 muestra un posible mecanismo para la reacción de aza-Reformatsky de 2,2-dióxido benzoxatiazinas con un complejo formado a partir de Me_2Zn y un ligando de tipo diarilprolinol (**L11**). Como ya se ha estudiado en las reacciones de alquilación con Et_2Zn y Me_2Zn catalizadas por ligandos de tipo amino alcohol, se forma en primer lugar un complejo **A** entre Me_2Zn y el ligando **L11**. Este complejo de tipo alcóxido de zinc está en equilibrio con el complejo **B**, un dímero del complejo **A** formado por coordinación de átomos de oxígeno y de zinc.[30] El complejo **B** es más estable, pero no puede participar en la reacción de Reformatsky, debido a que su tamaño impide la coordinación del reactivo y la imina. Al complejo **A** se adiciona el zincato-metilacetato de etilo formando el complejo **C**. Este zincato se forma a partir del iodoacetato de etilo y Me_2Zn en presencia de oxígeno, mediante un ciclo donde el Me_2Zn actúa como un precursor de radicales de metilo.[31] La presencia de radicales se pudo demonstrar llevando a cabo la reacción en presencia de TEMPO en la que se obtuvo el producto **27a** con un rendimiento muy bajo (7%), lo cual se puede atribuir a la inhibición en la formación de radicales provocada por el TEMPO. Tras la coordinación de la imina **1**/**9** al complejo **C**, se obtiene el complejo **D**, sobre el cual tiene lugar la transferencia del nucleófilo a la cara *Si* de la imina cíclica generando el sulfamidato de zinc **E**. Después de la disociación del sulfamidato, se obtiene el β-amino éster **30**/**31**, regenerando el monómero **A**, completando el ciclo catalítico.

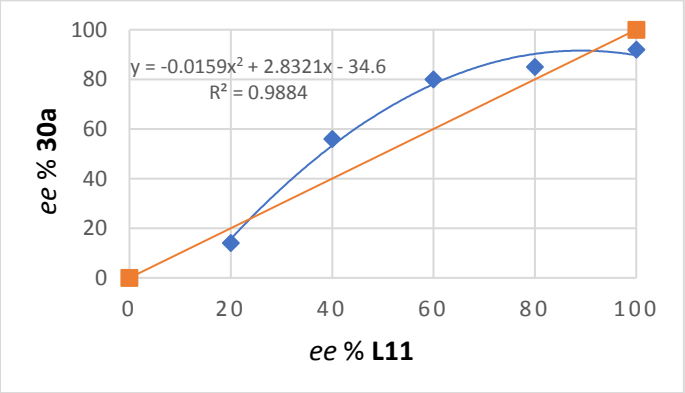


Esquema 5.19. Propuesta mecanística para la reacción de aza-Reformatsky de 2,2-dióxido benzoxatiazinas con un complejo de Me_2Zn-ligando de tipo diarilprolinol.

Con objeto de obtener información sobre la estructura de la especie catalítica que participa en el ciclo catalítico propuesto, examinamos la posibilidad de efectos no lineales en la reacción de Reformatsky de la 2,2-dióxido benzoxazina **1a** y el iodoacetato de etilo. Para ello se llevó a cabo la reacción, a partir de dimetilzinc y el diarilprolinol **L11**, con diferentes excesos enantioméricos. La gráfica (Figura 5.2) muestra una correlación no lineal positiva entre el ee del producto **30a** y el exceso enantiomérico del ligando **L11**. Este resultado sugiere que en disolución deben existir tres complejos dímeros: dos de ellos, homoquirales (*S*,*S*) y su enantiomero (*R*,*R*) formados mediante equilibrios de "auto reconocimiento" a partir de los correspondientes complejos monoméricos idénticos, y el tercero hetereroquiral (*S,R*) formado mediante un equilibrio de "no-auto reconocimiento" a partir de los dos complejos monoméricos enantiómeros. Prácticamente todo el complejo monomérico minoritario se transforma en el complejo dímero heteroquiral, termodinámicamente más estable, mientras que el exceso del complejo monomérico mayoritario forma el complejo dímero homoquiral, menos estable. Este último muestra mayor tendencia a disociarse en el monómero activo, por lo que es el responsable de la actividad catalítica, mientras que el enantiómero monomérico minoritario no participa en la reacción, puesto que está formando parte del dímero heteroquiral.

Así pues, el efecto no lineal positivo puede explicarse mediante la participación de especies catalíticas diméricas inactivas, que se encuentran en equilibrio con la forma monomérica que es la especie catalítica activa.[30]





ee % L11	*ee* % 30a
100	92
80	85
60	80
40	56
20	14

Figura 5.2. Efecto no-linear en la reacción de Reformatsky de 2,2-dióxido benzoxatiazinas

5.4. CONCLUSIONES

1. Se ha diseñado un método enantioselectivo para llevar a cabo la reacción de aza-Reformatsky de aldiminas (**1**) y cetiminas (**9**) cíclicas de tipo 2,2 dióxido benzoxatiazina con iodoacetato de etilo (**29**) catalizada por un sistema formado por un ligando de tipo (*S*)-prolinol [(*S*)-bis(3,5-bis(trifluorometil)fenil)(pirrolidin-2-il)metanol] y Me_2Zn a 0 °C en MTBE.

2. La reacción de aza-Reformatsky bajo las condiciones optimizadas se puede llevar a cabo con aldiminas cíclicas del tipo 2,2-dióxido benzoxatiazinas (**1**) con sustituyentes en diferentes posiciones del anillo aromático obteniéndose los correpondientes productos con buenas enantioselectividades (79-93%*ee*) y rendimientos elevados (70-98%).

3. La reacción de aza-Reformatsky bajo las condiciones optimizadas se puede llevar a cabo con cetiminas cíclicas de tipo 2,2-dióxido benzoxatiazinas (**9**) con sustituyentes en diferentes posiciones del anillo aromático obteniéndose los correspondientes productos con excelentes enantioselectividades (96-99% *ee*) y rendimientos (87-98%).

4. Las condiciones optimizadas también se pueden aplicar en la reacción con cetiminas cíclicas de 5 miembros de tipo *N*-sulfonil (**33**), obteniéndose los productos resultantes con elevados rendimientos (79-86%) y excesos enantiomericos (70-85%).

5. Se han podido sintetizar γ-amino alcoholes (**35**-**37)**, β-aminoácidos (**38** y **39**) y una β-lactama (**40**) mediante transformaciones sintéticas a partir de los compuestos **30a** y **31a**.

6. La determinación de la configuración absoluta para los compuestos **30** se hizo mediante correlación química del compuesto **35**. Para los compuestos **31** se determinó la configuración absoluta mediante difracción de Rayos X de monocristal del producto **31f**. En ambos casos la configuración absoluta resultante es (*S*). La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

7. Se ha propuesto un posible mecanismo para la reacción de Reformatsky de 2,2-dióxido benzoxatiazinas con iodoacetato de etilo (**29**) catalizada por un complejo de Me_2Zn-ligando de tipo diarilprolinol.

5.5. EXPERIMENTAL SECTION

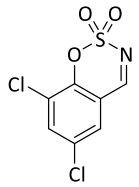
5.5.1. General experimental methods

Reactions were carried out under nitrogen round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel.

5.5.2. Synthetic procedure and characterization data for compound 1l

Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of salicylaldehyde **4l** (10 mmol) in DMA (15 mL) at 0 °C. After the addition, the reaction was placed at room temperature and stirred for 18 h. Aftewards, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography obtaining product **1l**.

6,8-Dichlorobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1l)[32]

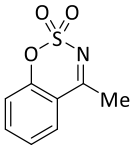


Yellow oil; **^{1}H NMR** (300 MHz, CDCl3) δ 8.62 (s, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.9 (CH), 148.9 (C), 137.2 (CH), 131.6 (C), 128.3 (CH), 125.2 (C), 116.79 (C) ppm.

5.5.3. General synthetic procedure and characterization data for compounds 9

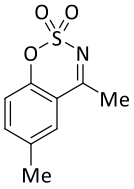
Formic acid (20 mmol) was carefully added (dropwise) to chlorosulfonylisocyanate (20 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature to form **5**. After 2 hours, the reaction was placed at 0 °C and diluted with DMA (15 mL). This solution was then added dropwise to a solution of 2-hidroxiacetofenona **8** (10 mmol) in DMA (15 mL) at 0 °C. After addition, the reaction was placed at room temperature and in the next hour, NaH (60% in oil, 24 mmol) was added in portions. Afterwards, the reaction was stirred for 18 h. After, the reaction was quenched with 100 mL ice cold water. The solution was then extracted with 3 x 50 mL dichloromethane, washed with 3 x 50 mL water and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography obtaining product **9**.

4-Methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9a)[33]



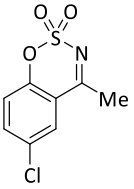
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 2.73 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ177.2 (C), 151.3 (C), 137.1 (CH), 128.4 (CH), 125.8 (CH), 119.1 (CH), 116.4 (C), 23.7 (CH_3) ppm.

4,6-Dimethylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9b)[33]



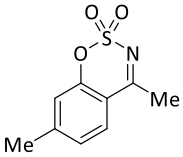
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 1H), 7.54 – 7.48 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 2.71 (s, 3H), 2.44 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.3 (C), 151.5 (C), 137.8 (CH), 135.9 (C), 128.3 (CH), 118.8 (CH), 116.2 (C), 23.7 (CH_3), 20.9 (CH_3) ppm.

6-Chloro-4-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9c)[33]



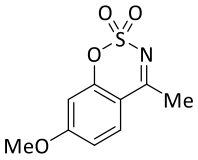
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 2.72 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C), 151.8 (C), 136.8 (CH), 131.3 (C), 128.0 (CH), 120.6 (CH), 117.3 (C), 23.7 (CH_3) ppm.

4,7-Dimethylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9d)[33]



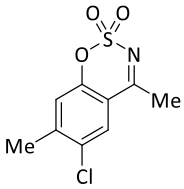
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 8.1, 1.6, 0.7 Hz, 1H), 7.08 (d, *J* = 0.6 Hz, 1H), 2.68 (s, 3H), 2.48 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.2 (C), 153.5 (C), 149.5 (C), 128.3 (CH), 126.8 (CH), 119.1 (CH), 114.1 (C), 23.6 (CH_3), 22.1 (CH_3) ppm.

7-Methoxy-4-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9e)



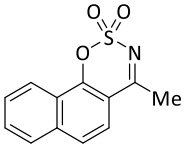
Clear oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.9 Hz, 1H), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 3.92 (s, 3H), 2.65 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.5 (C), 166.5 (C), 155.9 (C), 130.1 (CH), 113.3 (CH), 109.9 (C), 102.9 (CH), 56.3 (CH_3), 23.6 (CH_3) ppm. **HRMS** (ESI) *m/z*: 228.0328 $[M + H]^+$, $C_9H_{10}NO_4S$ requires 228.0325.

6-Chloro-4,7-dimethylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9f)



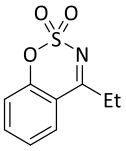
Clear oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.18 (d, *J* = 0.6 Hz, 1H), 2.69 (s, 3H), 2.50 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C), 151.6 (C), 147.1 (C), 131.5 (C), 128.25 (CH), 121.0 (CH), 115.3 (C), 23.6 (CH_3), 21.1 (CH_3) ppm. **HRMS** (ESI) *m/z*: 245.9988 $[M + H]^+$, $C_9H_9ClNO_3S$ requires 245.9986.

4-Methylnaphtho[2,1-*e*][1,2,3]oxathiazine 2,2-dioxide (9g)[34]



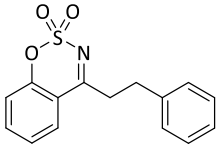
Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (ddt, *J* = 8.0, 1.5, 0.7 Hz, 1H), 7.92 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.83 – 7.66 (m, 4H), 2.81 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.0 (C), 137.4 (C), 137.0 (C), 131.2 (CH), 128.2 (CH), 127.9 (CH), 125.3 (CH), 123.5 (C), 123.0 (CH), 121.7 (CH), 111.6 (C), 24.4 (CH_3) ppm.

4-Ethylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9h)[33]



Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.70 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 7.39 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 3.10 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.7 (C), 153.5 (C), 136.8 (CH), 127.7 (CH), 125.8 (CH), 119.2 (CH), 116.1 (C), 29.3 (CH_2), 9.6 (CH_3) ppm.

4-Phenethylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (9i)

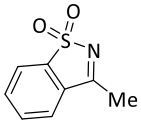


Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 7.39 – 7.20 (m, 7H), 3.39 – 3.31 (m, 2H), 3.20 – 3.11 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.1 (C), 153.6 (C), 139.7 (C), 136.9 (CH), 128.8 (CH), 128.4 (CH), 127.8 (CH), 126.7 (CH), 125.8 (CH), 119.2 (CH), 116.2 (C), 37.6 (CH_2), 31.5 (CH_2) ppm. **HRMS** (ESI) *m/z*: 288.0696 [M + H] +, $C_{15}H_{14}NO_3S$ requires 288.0689.

5.5.4. General synthetic procedure and characterization data for compounds 33

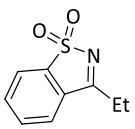
To saccharin **32** (10.0 mmol), dissolved in THF (20 mL) at 0 °C under N_2 atmosphere, alkylmagnesium bromide (23 mmol) was added slowly. The reaction was stirred at room temperature during 18 h. Afterwards, the reaction was poured carefully onto ice and the solution was acidified (2M HCl). The aqueous layer was then extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was then purified by flash chromatography, obtaining product **33**.[23]

3-Methylbenzo[*d*]isothiazole 1,1-dioxide (33a)[35]



Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.80 – 7.72 (m, 1H), 7.71 – 7.66 (m, 1H), 2.67 (s, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.1 (C), 139.6 (C), 133.9 (CH), 133.6 (CH), 131.6 (C), 124.1 (CH), 122.4 (CH), 17.6 (CH_3) ppm.

3-Ethylbenzo[*d*]isothiazole 1,1-dioxide (33b)[36]



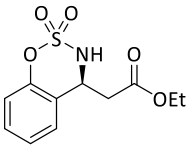
Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 1H), 7.79 – 7.71 (m, 2H), 7.71 – 7.66 (m, 1H), 3.02 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.1 (C), 139.8 (C), 133.9 (CH), 133.5 (CH), 131.2 (C), 123.7 (CH), 122.4 (CH), 24.8 (CH_2), 9.3 (CH_3) ppm.

5.5.5. General synthetic procedures and characterization data for compounds 30, 31 and 34

General procedure for the enantioselective Reformatsky reaction: In a two-neck 50 mL round bottom flask (one neck covered with a septum, the other neck with a drying finger, filled with $CaCl_2$), purged with N_2, the ligand **L11** was added in solid by opening the septum. The ligand was dissolved with 3 mL of MTBE, followed by the addition of ethyl iodoacetate **29** (2 eq, 0.200 mmol). This dissolution was placed in an ice bath (0 °C) and stirred during 5 minutes at 0 °C. Me_2Zn was added (7 eq, 0.700 mmol), immediately followed by the addition of the substrate by opening the septum. The reaction was stirred at 0 °C until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded compound **30, 31** or **34**.

General procedure for the non-enantioselective Reformatsky reaction: In a two-neck 50 mL round bottom flask (one neck covered with a septum, the other neck with a drying finger, filled with $CaCl_2$), purged with N_2 3 mL of MTBE was added, followed by the addition of ethyl iodoacetate **2** (2 eq, 0.200 mmol). This dissolution was stirred during 5 minutes at rt. Me_2Zn was added (7 eq, 0.700 mmol), immediately followed by the addition of the substrate **1, 4** or **6** in solid by opening the septum. The reaction was stirred at rt until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3x15 mL), dried over $MgSO_4$ and dried under reduced pressure. Purification by flash chromatography on silica gel afforded compound **30, 31** or **34**.

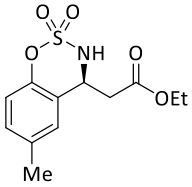
Ethyl (*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30a)



The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 11.88 min, minor enantiomer t_r = 15.15 min.

Oil; $[\alpha]_D^{20}$ = -20.1 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 1H), 7.26 – 7.15 (m, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 7.09 – 6.98 (m, 1H), 5.92 (d, *J* = 9.1 Hz, 1H), 5.13 (dddd, *J* = 9.2, 6.8, 3.8, 1.0 Hz, 1H), 4.13 (qd, *J* = 7.2, 0.6 Hz, 2H), 3.31 (dd, *J* = 16.9, 6.7 Hz, 1H), 2.98 (dd, *J* = 16.9, 3.8 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (C), 151.4 (C), 129.9 (CH), 125.6 (CH), 125.4 (CH), 120.7 (C), 119.1 (CH), 61.5 (CH_2), 53.9 (CH), 37.1 (CH_2), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 272.0587 $[M + H]^+$, $C_{11}H_{14}NO_5S$ requires 272.0593.

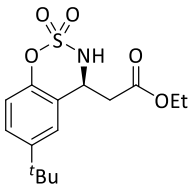
Ethyl (*S*)-2-(6-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30b)



The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 13.66 min, minor enantiomer t_r = 16.89 min.

Oil; $[\alpha]_D^{20}$ = -23.4 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 1H), 6.95 (dt, *J* = 1.7, 0.8 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.75 (s, 1H), 5.09 (dd, *J* = 7.0, 3.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.29 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.96 (dd, *J* = 16.8, 3.7 Hz, 1H), 2.32 (d, *J* = 0.7 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (C), 149.3 (C), 135.2 (C), 130.4 (CH), 125.9 (CH), 120.3 (C), 118.8 (CH), 61.5 (CH_2), 53.9 (CH), 37.3 (CH_2), 20.8 (CH_3), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 286.0744 $[M + H]^+$, $C_{12}H_{16}NO_5S$ requires 286.0749.

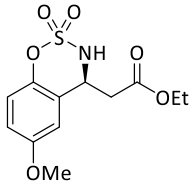
Ethyl (*S*)-2-(6-(*tert*-butyl)-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30c)



The enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 9.67 min, minor enantiomer t_r = 11.08 min.

Oil; $[\alpha]_D^{20}$ = -19.9 (c 1.0, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 8.7, 2.4, 0.8 Hz, 1H), 7.14 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.85 (d, *J* = 9.0 Hz, 1H), 5.13 (dddt, *J* = 8.8, 6.9, 3.9, 0.9 Hz, 1H), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.34 (dd, *J* = 16.7, 6.9 Hz, 1H), 2.97 (dd, *J* = 16.7, 3.7 Hz, 1H), 1.29 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.9 (C), 149.2 (C), 148.5 (C), 126.9 (CH), 122.4 (CH), 119.8 (C), 118.5 (CH), 61.5 (CH_2), 54.2 (CH), 37.4 (CH_2), 34.5 (C), 31.3 (CH_3), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 328.1213 $[M + H]^+$, $C_{15}H_{22}NO_5S$ requires 328.1219.

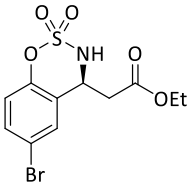
Ethyl (*S*)-2-(6-methoxy-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30d)



The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 14.90 min, minor enantiomer t_r = 18.84 min.

Oil; $[\alpha]_D^{20}$ = -42.5 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 9.0 Hz, 1H), 6.85 (ddd, *J* = 9.0, 2.9, 0.7 Hz, 1H), 6.66 (dd, *J* = 2.8, 0.9 Hz, 1H), 5.83 (d, *J* = 8.3 Hz, 1H), 5.08 (td, *J* = 7.7, 3.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 1H), 3.78 (s, 2H), 3.28 (dd, *J* = 16.9, 6.9 Hz, 1H), 2.96 (dd, *J* = 16.9, 3.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (C), 156.7 (C), 145.1 (C), 121.6 (C), 119.9 (CH), 114.9 (CH), 110.9 (CH), 61.5 (CH_2), 55.7 (CH_3), 54.0 (CH), 37.3 (CH_2), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 302.0693 $[M + H]^+$, $C_{12}H_{16}NO_6S$ requires 302.0698.

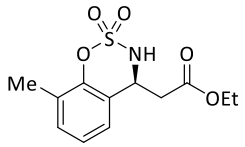
Ethyl (*S*)-2-(6-bromo-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30e)



The enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 9.10 min, minor enantiomer t_r = 11.27 min.

Oil; $[\alpha]_D^{20}$ = -44.6 (c 1.0, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (ddd, *J* = 8.8, 2.4, 0.8 Hz, 1H), 7.31 (dd, *J* = 2.3, 1.0 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 5.93 (s, 1H), 5.10 (dd, *J* = 6.5, 3.8 Hz, 1H), 4.16 (qd, *J* = 7.2, 1.8 Hz, 2H), 3.29 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.98 (dd, *J* = 17.0, 3.8 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm.**^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 (C), 150.5 (C), 132.9 (CH), 128.6 (CH), 122.7 (C), 120.8 (CH), 118.0 (C), 61.8 (CH_2), 53.6 (CH), 36.8 (CH_2), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 349.9692 $[M + H]^+$, $C_{11}H_{13}BrNO_5S$ requires 349.9698.

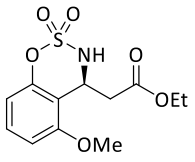
Ethyl (*S*)-2-(8-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30f)



The enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 10.29 min, minor enantiomer t_r = 14.16 min.

Oil; $[\alpha]_D^{20}$ = -9.4 (c 1.0, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 (ddt, *J* = 7.4, 1.7, 0.8 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (ddt, *J* = 7.7, 1.5, 0.7 Hz, 1H), 5.89 (d, *J* = 9.0 Hz, 1H), 5.11 (ddd, *J* = 9.5, 6.7, 3.8 Hz, 1H), 4.14 (qd, *J* = 7.2, 0.7 Hz, 2H), 3.30 (dd, *J* = 16.9, 6.7 Hz, 1H), 2.97 (dd, *J* = 16.9, 3.8 Hz, 1H), 2.28 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.9 (C), 149.9 (C), 131.3 (CH), 128.5 (C), 124.7 (CH), 123.0 (CH), 120.5 (C), 61.5 (CH_2), 53.9 (CH), 37.2 (CH_2), 15.6 (CH_3), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 286.0744 $[M + H]^+$, $C_{12}H_{16}NO_5S$ requires 286.0749.

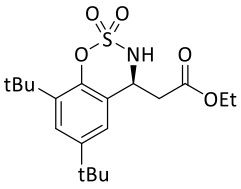
Ethyl (*S*)-2-(5-methoxy-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30h)



The enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 12.80 min, minor enantiomer t_r = 16.47 min.

Oil; $[\alpha]_D^{20}$ = -60.7 (c 1.0, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (td, *J* = 8.4, 0.7 Hz, 1H), 6.71 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.65 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.59 (d, *J* = 6.4 Hz, 1H), 5.20 (ddd, *J* = 9.6, 6.5, 2.9 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.37 (dd, *J* = 16.9, 9.9 Hz, 1H), 2.99 (dd, *J* = 16.9, 3.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.6 (C), 156.3 (C), 151.8 (C), 129.9 (CH), 111.12 (CH), 109.6 (C), 107.0 (CH), 61.01 (CH_2), 55.9 (CH_3), 52.0 (CH), 36.8 (CH_2), 14.1 (CH_3) ppm. **HRMS** (ESI) *m/z*: 302.0693 $[M + H]^+$, $C_{12}H_{16}NO_6S$ requires 302.0698.

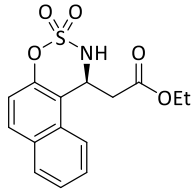
Ethyl (*S*)-2-(6,8-di-*tert*-butyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30i)



The enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 6.99 min, minor enantiomer t_r = 8.23 min.

Oil; $[\alpha]_D^{20}$ = -22.9 (c 1.0, $CHCl_3$, 88% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 2.3, 0.7 Hz, 1H), 6.99 (dd, *J* = 2.4, 0.9 Hz, 1H), 5.74 (d, *J* = 8.7 Hz, 1H), 5.09 (dddt, *J* = 8.9, 7.3, 3.8, 0.8 Hz, 1H), 4.15 (qd, *J* = 7.1, 0.6 Hz, 2H), 3.31 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.95 (dd, *J* = 16.7, 3.9 Hz, 1H), 1.41 (s, 9H), 1.29 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0 (C), 148.3 (C), 147.5 (C), 139.4 (C), 124.5 (CH), 121.2 (C), 120.4 (C), 61.4 (CH_2), 54.1 (CH), 38.0 (CH_2), 35.1 (C), 34.7 (C), 31.3 (CH_3), 30.0 (CH_3), 14.1 (CH_3) ppm. **HRMS** (ESI) *m/z*: 384.1839 $[M + H]^+$, $C_{19}H_{30}NO_5S$ requires 384.18**45**.

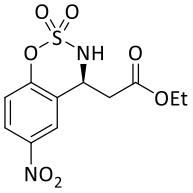
Ethyl (*S*)-2-(3,3-dioxido-1,2-dihydronaphtho[1,2-*e*][1,2,3]oxathiazin-1-yl)acetate (30j)



The enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 9.70 min, minor enantiomer t_r = 12.79 min.

Oil; $[\alpha]_D^{20}$ = -37.3 (c 1.0, $CHCl_3$, 93% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.80 (m, 2H), 7.71 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 5.77 (ddd, *J* = 10.9, 6.3, 2.4 Hz, 1H), 5.43 (d, *J* = 6.2 Hz, 1H), 4.28 (qd, *J* = 7.2, 1.7 Hz, 2H), 3.66 (dd, *J* = 17.5, 10.9 Hz, 1H), 2.97 (dd, *J* = 17.5, 2.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.1 (C), 149.1 (C), 131.2 (C), 131.1 (CH), 129.4 (CH), 129.3 (C), 128.2 (CH), 125.9 (CH), 122.0 (CH), 118.4 (CH), 113.6 (C), 61.4 (CH_2), 53.3 (CH), 38.0 (CH_2), 14.2 (CH_3) ppm. **HRMS** (ESI) *m/z*: 322.0744 $[M + H]^+$, $C_{15}H_{16}NO_5S$ requires 322.0749.

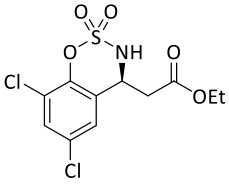
Ethyl (*S*)-2-(6-nitro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30k)



The enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 16.93 min, minor enantiomer t_r = 30.37 min.

Oil; $[\alpha]_D^{20}$ = -44.7 (c 1.0, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.24 (ddd, *J* = 9.1, 2.6, 0.8 Hz, 1H), 8.13 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 6.14 (d, *J* = 7.1 Hz, 1H), 5.19 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.41 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.10 (dd, *J* = 17.4, 3.9 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5 (C), 155.8 (C), 144.5 (C), 125.5 (CH), 122.0 (C), 121.7 (CH), 120.2 (CH), 62.0 (CH_2), 53.6 (CH), 36.3 (CH_2), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 334.0706 $[M + NH_4]^+$, $C_{11}H_{16}N_3O_7S$ requires 334.0735.

Ethyl (*S*)-2-(6,8-dichloro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (30l)

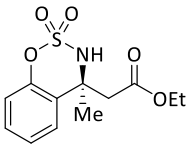


The enantiomeric excess (79%) was determined by chiral HPLC (Lux Amylose-1), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 5.57 min, minor enantiomer t_r = 6.05 min.

Oil; $[\alpha]_D^{20}$ = -42.6 (c 1.0, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.08 (dd, *J* = 2.4, 1.0 Hz, 1H), 5.89 (s, 0H), 5.10 (ddt, *J* = 6.0, 3.8, 0.9 Hz, 1H), 4.23 – 3.99 (m, 2H), 3.29 (dd, *J* = 17.2, 6.3 Hz, 1H), 3.00 (dd, *J* = 17.2, 3.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5 (C), 146.3 (C), 130.5 (CH), 130.3 (C), 125.1 (C),

124.0 (CH), 123.7 (C), 61.9 (CH_2), 53.8 (CH), 36.7 (CH_2), 14.0 (CH_3) ppm. **HRMS** (ESI) *m/z*: 339.9808 [M + H]$^+$, $C_{11}H_{12}Cl_2NO_5S$ requires 339.9813.

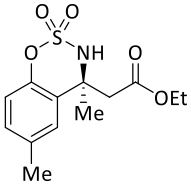
Ethyl (*S*)-2-(4-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31a)



The enantiomeric excess (99%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 12.93 min, minor enantiomer t_r = 16.03 min.

Oil; $[\alpha]_D^{20}$ = -22.0 (c 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.20 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.02 (dt, *J* = 8.2, 0.8 Hz, 1H), 6.53 (s, 1H), 4.03 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.10 (d, *J* = 15.7 Hz, 1H), 2.80 (d, *J* = 15.7 Hz, 1H), 1.81 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5 (C), 150.1 (C), 129.8 (CH), 126.2 (CH), 125.5 (CH), 124.9 (C), 119.4 (CH), 61.4 (CH_2), 61.2 (C), 45.3 (CH_2), 29.3 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 286.0740 [M + H]$^+$, $C_{12}H_{16}NO_5S$ requires 286.0744.

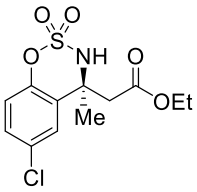
Ethyl (*S*)-2-(4,6-dimethyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31b)



The enantiomeric excess (99%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 14.25 min, minor enantiomer t_r = 18.31 min.

Oil; $[\alpha]_D^{20}$ = -44.8 (c 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.13 – 7.04 (m, 1H), 6.97 (d, *J* = 1.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 4.14 – 3.94 (m, 2H), 3.09 (d, *J* = 15.7 Hz, 1H), 2.78 (d, *J* = 15.7 Hz, 1H), 2.33 (s, 3H), 1.79 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5 (C), 147.9 (C), 135.2 (C), 130.4 (CH), 126.3 (CH), 124.5 (C), 119.0 (CH), 61.3 (CH_2), 61.1 (C), 45.3 (CH_2), 29.3 (CH_3), 20.9 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 300.0904 [M + H]$^+$, $C_{13}H_{18}NO_5S$ requires 300.0900.

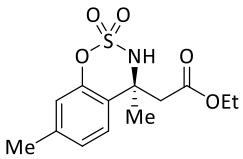
Ethyl (*S*)-2-(6-chloro-4-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31c)



The enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 8.98 min, minor enantiomer t_r = 11.23 min.

Oil; $[\alpha]_D^{20}$ = -59.8 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H), 4.18 – 3.94 (m, 2H), 3.07 (d, *J* = 15.9 Hz, 1H), 2.81 (d, *J* = 15.9 Hz, 1H), 1.80 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.4 (C), 148.6 (C), 130.7 (C), 129.9 (CH), 126.6 (C), 126.1 (CH), 120.8 (CH), 61.6 (CH_2), 61.0 (C), 45.1 (CH_2), 29.2 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 320.0358 [M + H]$^+$, $C_{12}H_{15}ClNO_5S$ requires 320.0354

Ethyl (*S*)-2-(4,7-dimethyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31d)

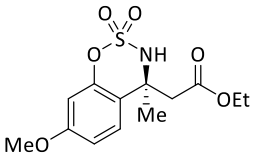


The enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 13.61 min, minor enantiomer t_r = 17.71 min.

Oil; $[\alpha]_D^{20}$ = -29.5 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (ddd, *J* = 8.0, 1.6, 0.6 Hz, 1H), 6.83 (d, *J* = 0.7 Hz, 1H), 6.49 (s, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.07 (d, *J* = 15.7 Hz, 1H), 2.78 (d, *J* = 15.7 Hz, 1H), 2.32 (s, 3H), 1.78 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 (C), 149.8 (C), 140.3 (C), 126.4 (CH), 125.8 (CH), 121.8 (C), 119.5

(CH), 61.4 (CH_2), 61.0 (C), 45.3 (CH_2, 29.4 (CH_3), 20.9 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 300.0910 $[M + H]^+$, $C_{13}H_{18}NO_5S$ requires 300,0900.

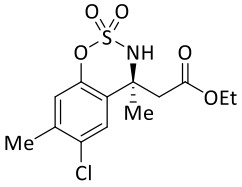
Ethyl (*S*)-2-(7-methoxy-4-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31e)



The enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 14.81 min, minor enantiomer t_r = 19.27 min.

Oil; $[\alpha]_D^{20}$ = -34.5 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 6.51 (s, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.04 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H), 1.77 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0 (C), 160.7 (C), 151.2 (C), 127.2 (CH), 117.0 (C), 113.0 (CH), 104.2 (CH), 61.8 (CH_2), 61.3 (C), 56.0 (CH_3), 45.8 (CH_2), 29.9 (CH_3), 14.5 (CH_3) ppm. **HRMS** (ESI) *m/z*: 316.0855 $[M + H]^+$, $C_{13}H_{18}NO_6S$ requires 316.0849.

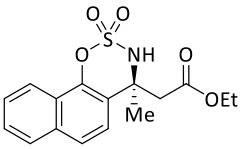
Ethyl (*S*)-2-(6-chloro-4,7-dimethyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31f)



The enantiomeric excess (96%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 10.41 min, minor enantiomer t_r = 12.87 min.

Oil; $[\alpha]_D^{20}$ = -58.2 (c 1.0, $CHCl_3$, 96% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.91 (s, 1H), 6.50 (s, 1H), 4.26 – 3.90 (m, 2H), 3.05 (d, *J* = 15.9 Hz, 1H), 2.79 (d, *J* = 15.9 Hz, 1H), 2.34 (s, 3H), 1.78 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5 (C), 148.2 (C), 138.3 (C), 130.9 (C), 126.2 (CH), 123.8 (C), 121.3 (CH), 61.6 (CH_2), 60.8 (C), 45.1 (CH_2), 29.3 (CH_3), 19.8 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 334.0521 $[M + H]^+$, $C_{13}H_{17}ClNO_5S$ requires 334.0511.

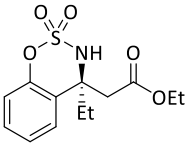
Ethyl (*S*)-2-(4-methyl-2,2-dioxido-3,4-dihydronaphtho[2,1-*e*][1,2,3]oxathiazin-4-yl)acetate (31g)



The enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 10.42 min, minor enantiomer t_r = 14.49 min.

Oil; $[\alpha]_D^{20}$ = -20.1 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 – 8.17 (m, 1H), 7.84 – 7.79 (m, 1H), 7.70 – 7.66 (m, 1H), 7.61 – 7.55 (m, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.70 (s, 1H), 3.99 (qd, *J* = 7.1, 1.4 Hz, 1H), 3.19 (d, *J* = 15.7 Hz, 2H), 2.87 (d, *J* = 15.7 Hz, 1H), 1.88 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 (C), 1**45**.3 (C), 133.8 (C), 127.6 (CH), 127.4 (CH), 127.3 (CH), 125.2 (CH), 124.7 (C), 122.0 (CH), 121.4 (CH), 119.3 (C), 61.5 (C), 61.4 (CH_2), 45.0 (CH_2), 28.9 (CH_3), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 336.0893 $[M + H]^+$, $C_{16}H_{18}NO_5S$ requires 336.0900.

Ethyl (*S*)-2-(4-ethyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31h)

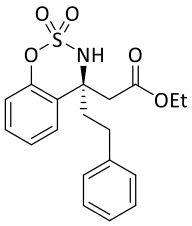


The enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 11.40 min, minor enantiomer t_r = 13.99 min.

Oil; $[\alpha]_D^{20}$ = -7.9 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (ddd, *J* = 8.2, 6.4, 2.6 Hz, 1H), 7.24 – 7.12 (m, 2H), 7.05 – 7.00 (m, 1H), 6.40 (s, 1H), 4.03 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.00 (d, *J* = 15.7 Hz, 1H), 2.85 (d, *J* = 15.7 Hz, 1H), 2.40 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.84 (dq, *J* = 14.5, 7.2 Hz,

1H), 1.06 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.7 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C), 150.4 (C), 129.7 (CH), 126.1 (CH), 125.4 (CH), 125.0 (C), 119.3 (CH), 64.2 (C), 61.4 (CH_2), 42.1 (CH_2), 33.6 (CH_2), 13.8 (CH_3), 7.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 300.0899 $[M + H]^+$, $C_{13}H_{18}NO_5S$ requires 300.0900.

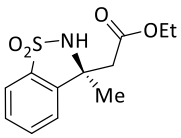
Ethyl (*S*)-2-(2,2-dioxido-4-phenethyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetate (31i)



The enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 13.57 min, minor enantiomer t_r = 22.65 min.

Oil; $[\alpha]_D^{20}$ = -36.3 (c 1.0, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 3H), 7.22 – 7.14 (m, 5H), 7.04 (dt, *J* = 8.1, 0.8 Hz, 1H), 6.58 (s, 1H), 4.11 – 3.94 (m, 2H), 3.10 (d, *J* = 15.7 Hz, 1H), 3.03 – 2.85 (m, 2H), 2.72 – 2.60 (m, 2H), 2.14 – 2.00 (m, 1H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.1 (C), 150.2 (C), 140.7 (C), 129.8 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 126.0 (CH), 125.5 (CH), 124.7 (C), 119.4 (CH), 63.7 (C), 61.5 (CH_2), 42.9 (CH_2), 42.5 (CH_2), 29.8 (CH_2), 13.8 (CH_3) ppm. **HRMS** (ESI) *m/z*: 376.1214 $[M + H]^+$, $C_{19}H_{22}NO_5S$ requires 376.1213.

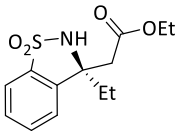
Ethyl (*S*)-2-(3-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)acetate (34a)



The enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 70:30, 1 mL/min, major enantiomer t_r = 27.13 min, minor enantiomer t_r = 50.07 min.

Oil; $[\alpha]_D^{20}$ = -34.2 (c 1.0, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (ddd, *J* = 7.6, 1.2, 0.7 Hz, 1H), 7.64 (td, *J* = 7.5, 1.2 Hz, 1H), 7.54 (td, *J* = 7.5, 1.1 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.26 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.87 (s, 2H), 1.70 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.22 (C), 143.08 (C), 135.06 (C), 133.31 (CH), 129.61 (CH), 122.80 (CH), 121.49 (CH), 61.36 (CH_2), 60.71 (C), 44.58 (CH_2), 27.47 (CH_3), 14.00 (CH_3) ppm. **HRMS** (ESI) *m/z*: 270.0808 $[M + H]^+$, $C_{12}H_{16}NO_4$ requires 270.0795.

Ethyl (*S*)-2-(3-ethyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)acetate (34b)



The enantiomeric excess (70%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 70:30, 1 mL/min, major enantiomer t_r = 30.28 min, minor enantiomer t_r = 57.56 min.

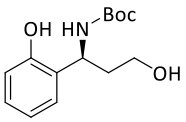
Oil; $[\alpha]_D^{20}$ = -16.9 (c 1.0, $CHCl_3$, 70% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (ddd, *J* = 7.7, 1.2, 0.7 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.55 (td, *J* = 7.6, 1.1 Hz, 1H), 7.37 – 7.31 (m, 1H), 5.86 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.94 – 2.79 (m, 2H), 2.13 – 1.83 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.3 (C), 141.3 (C), 135.8 (C), 133.2 (CH), 129.7 (CH), 123.0 (CH), 121.6 (CH), 64.5 (C), 61.4 (CH_2), 44.0 (CH_2), 32.5 (CH_2), 14.0 (CH_3), 8.1 (CH_3) ppm. **HRMS** (ESI) *m/z*: 284.0964 $[M + H]^+$, $C_{13}H_{18}NO_4S$ requires 284.0951.

5.5.6. Synthetic Procedures and characterization data for compounds 35-40

***tert*-Butyl (*S*)-(3-hydroxy-1-(2-hydroxyphenyl)propyl)carbamate (35)[29] and *tert*-butyl (*S*)-(1-(2-((*tert*-butoxycarbonyl)oxy)phenyl)-3-hydroxypropyl)carbamate (36)**

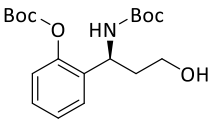
To a solution of **30a** (0.100 mmol) in THF (1 mL), $LiAlH_4$ (1.0 M in THF, 3.3 equivalents, 0.33 mmol) was added dropwise at rt over 4 min. The mixture was heated to 60 °C for 2.5 hours, allowed to cool down to rt, and then cooled with an ice bath. The reaction was quenched with EtOAc (1 mL),

followed by the addition of EtOH (1 mL) and H_2O (1 mL). To the resulting turbid mixture Boc_2O (1.2 equivalents, 0.12 mmol) was added in one portion and the resulting mixture was stirred at rt overnight. The mixture was diluted with EtOAc (15 mL) and acidified with aq 2 M HCl until the aqueous layer became clear. The aqueous layer was then separated and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded compound **35** and **36**.



The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 14.11 min, minor enantiomer t_r = 19.13 min.

Oil; $[\alpha]_D^{20}$ = -41.6 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.18 – 7.07 (m, 2H), 6.85 (dd, *J* = 17.2, 7.8 Hz, 2H), 5.57 (s, 1H), 5.01 (dd, *J* = 14.5, 8.3 Hz, 1H), 3.79 – 3.60 (m, 2H), 2.87 (s, 1H), 2.19 – 1.88 (m, 2H), 1.70 (s, 1H), 1.44 (s, 9H) ppm. **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 157.1 (C), 154.3 (C), 128.6 (CH), 127.9 (CH), 127.35 (C), 120.5 (CH), 116.8 (CH), 80.5 (C), 59.5 (CH_2), 47.9 (CH), 37.6 (CH_2), 28.4 (CH_3) ppm. **HRMS** (ESI) *m/z*: 268.1552 $[M + H]^+$, $C_{14}H_{22}NO_4$ requires 268.1543.

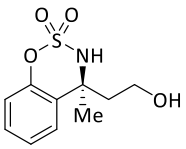


The enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak ADH), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 9.45 min, minor enantiomer t_r = 15.42 min.

Oil; $[\alpha]_D^{20}$ = -52.8 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.16 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.17 (d, *J* = 8.5 Hz, 1H), 5.03 (d, *J* = 2.9 Hz, 1H), 3.76 – 3.59 (m, 2H), 3.21 – 2.96 (m, 1H), 2.05 – 1.79 (m, 2H), 1.55 (s, 9H), 1.42 (s, 9H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 156.3 (C), 151.8 (C), 148.6 (C), 133.6 (C), 128.6 (CH), 128.1 (CH), 126.4 (CH), 123.0 (CH), 84.0 (C), 79.9 (C), 59.0 (CH_2), 47.9 (CH), 38.6 (CH_2), 28.3 (CH_3), 27.7 (CH_3) ppm. **HRMS** (ESI) *m/z*: 368.2081 $[M + H]^+$, $C_{19}H_{30}NO_6$ requires 368.2068.

(*S*)-4-(2-Hydroxyethyl)-4-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (37)

To a solution of **31a** (0.100 mmol, 28.5 mg) in THF (1 mL), $LiAlH_4$ (1.0 M in THF, 1.1 equivalents, 0.11 mmol) was added dropwise at 0 °C over 4 min. The reaction was stirred at 0 °C until completion (TLC). The mixture was diluted with EtOAc (10 mL) and acidified with aq 2 M HCl until the aqueous layer became clear. A saturated solution of Rochelle salt was added (5 mL) and the mixture was stirred for 2 hours. The aqueous layer was then separated and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded compound **37** (41% yield, 9.9 mg).

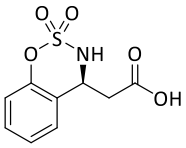


The enantiomeric excess (99%) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 11.81 min, minor enantiomer t_r = 9.56 min.

Oil; $[\alpha]_D^{20}$ = -16.6 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 7.20 (td, *J* = 7.6, 1.4 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.99 (s, 1H), 3.93 – 3.79 (m, 1H), 3.66 – 3.47 (m, 1H), 2.28 (ddd, *J* = 15.4, 10.9, 3.3 Hz, 1H), 2.11 (ddd, *J* = 15.4, 4.0, 2.1 Hz, 1H), 1.56 (s, 3H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 151.0 (C), 129.3 (CH), 126.5 (CH), 125.6 (CH), 125.5 (C), 119.5 (CH), 63.8 (C), 59.9 (CH_2), 42.9 (CH_2), 30.2 (CH_3) ppm **HRMS** (ESI) *m/z*: 244.0631 $[M + H]^+$, $C_{10}H_{14}NO_4S$ requires 244.0638.

(*S*)-2-(2,2-Dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetic acid (38)

To a solution of **30a** (0.15 mmol, 40.65 mg) in EtOH (1 mL) NaOH 1M (1 mL) wasw added. The dissolution was stirred at reflux temperature (73 °C) for 2 hours. The reaction was quenched with HCl 2M (5 mL) and extracted with dichloromethane (3x15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Product **38** was obtained (91% yield, 33.2 mg).

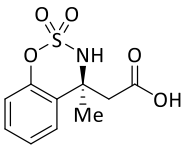


The enantiomeric excess (92%) was determined by chiral HPLC (Cellulose-3), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 65.60 min, minor enantiomer t_r = 70.15 min.

Oil; $[\alpha]_D^{20}$ = -22.1 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, CD_3OD) δ 7.34 (t, *J* = 7.0 Hz, 2H), 7.22 (td, *J* = 7.2, 1.2 Hz, 1H), 7.05 – 6.97 (m, 1H), 5.13 (dd, *J* = 9.1, 4.8 Hz, 1H), 4.90 (s, 2H), 3.08 (qd, *J* = 16.4, 7.0 Hz, 2H) ppm. **^{13}C NMR** (75.5 MHz, CD_3OD) δ 173.8 (C), 152.6 (C), 130.5 (CH), 128.0 (CH), 126.3 (CH), 123.3 (C), 119.6 (C), 55.0 (CH), 40.3 (CH_2) ppm. **HRMS** (ESI) *m/z*: 242.0075 $[M - H]^-$, $C_9H_8NO_5S$ requires 242.0123.

(*S*)-2-(4-Methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)acetic acid (39)

To a solution of **31a** (0.15 mmol, 42.8 mg)) in EtOH (1 mL) NaOH 1M (1 mL) was added. The dissolution was stirred at reflux temperature (73 °C) for 2 hours. The reaction was quenched with HCl 2M (5 mL) and extracted with dichloromethane (3x15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Product **39** was obtained (99% yield, 38.2 mg).

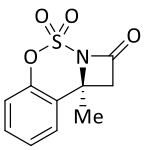


The enantiomeric excess (99%) was determined by chiral HPLC (Amylose-1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 6.55 min, minor enantiomer t_r = 9.10 min.

Oil; $[\alpha]_D^{20}$ = -13.9 (c 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 8.2, 6.6, 2.4 Hz, 1H), 7.22 (tt, *J* = 7.5, 3.6 Hz, 2H), 7.06 – 7.00 (m, 1H), 3.22 (d, *J* = 16.3 Hz, 1H), 2.87 (d, *J* = 16.3 Hz, 1H), 1.82 (s, 3H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 174.6 (C), 149.8 (C), 130.0 (CH), 125.9 (CH), 125.9 (CH), 125.1 (C), 119.5 (CH), 60.7 (C), 44.6 (CH_2), 29.2 (CH_3) ppm. **HRMS** (ESI) *m/z*: 258.0443 [M + H], $C_{10}H_{12}NO_5S$ requires 258.0431.

(*S*)-9*b*-Methyl-1,9b-dihydro-2*H*-azeto[1,2-*c*]benzo[*e*][1,2,3]oxathiazin-2-one 4,4-dioxide (40)

To a solution of **39** (0.10 mmol, 25.7 mg)) in dichloromethane *N*-methylmorpholine (1.1 eq, 0.11 mmol) was added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.1 eq, 0.11 mmol). The reaction was stirred at rt for 2 hours. The mixture was quenched with HCl 1M (5 mL) and extracted with dichloromethane (3x15 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting mixture was then purified by flash chromatography, obtaining compound **40** (72% yield, 17.2 mg).



The enantiomeric excess (98%) was determined by chiral HPLC (Amylose-1), hexane-iPrOH 90:10, 1 mL/min, major enantiomer t_r = 15.65 min, minor enantiomer t_r = 12.28 min.

Oil; $[\alpha]_D^{20}$ = -75.6 (c 1.0, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (ddd, *J* = 8.2, 5.5, 3.6 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.16 – 7.10 (m, 1H), 3.59 (d, *J* = 16.4 Hz, 1H), 3.42 (d, *J* = 16.4 Hz, 1H), 2.03 (s, 3H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.2 (C), 149.4 (C), 130.6 (CH), 127.0 (CH), 126.6 (CH), 125.3 (C), 120.0 (CH), 63.4 (C), 54.7 (CH_2), 26.2 (CH_3) ppm. **HRMS** (ESI) *m/z*: 257.0578 $[M + NH_4]^+$, $C_{10}H_{13}N_2O_4S$ requires 257.0591.

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CHAPTER 6

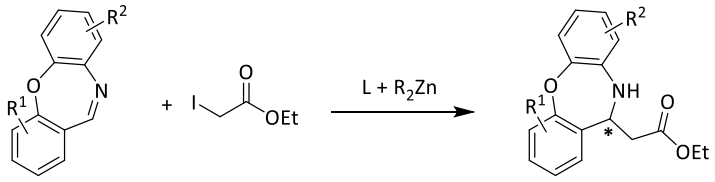
CATALYTIC ENANTIOSELECTIVE AZA-REFORMATSKY REACTIONS OF DIBENZO[*b,f*][1,4]OXAZEPINES

6.1. INTRODUCTION

With the results of the previous chapter in mind, in which we were able to perform the first example of an aza-Refromatsky reaction of cyclic imines (Chapter 5), we wanted to test the reaction conditions on different cyclic imines. For this reason we chose to study the aza-Reformatsky reaction of dibenzo[*b,f*][1,4]oxazepines, imines used before in this thesis (Chapter 4).

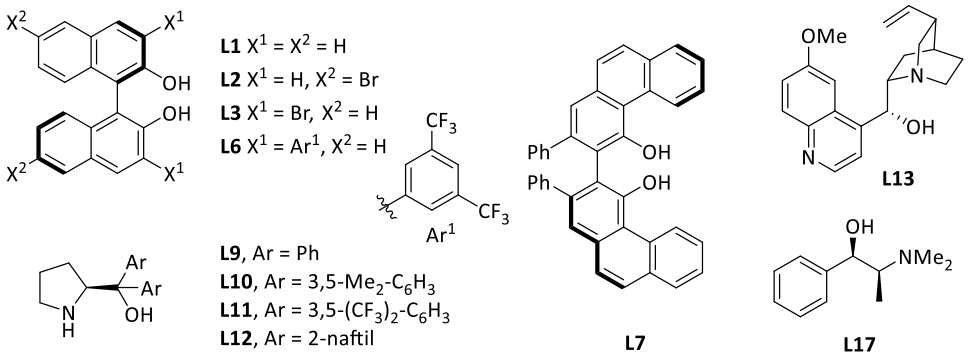
6.2. OBJETIVOS

El objetivo general de este capítulo es el desarrollo de un método catalítico y enantioselectivo que permita llevar a cabo la reacción de aza-Reformatsky de aldiminas cíclicas de tipo dibenzoxazepina con iodoacetato de etilo que transcurra con buenos rendimientos y excesos enantioméricos.



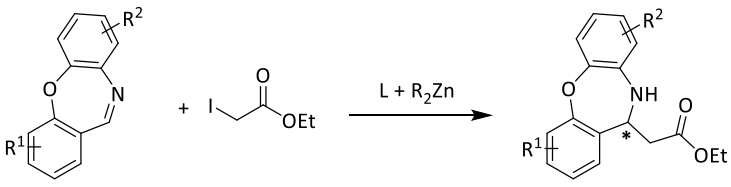
En el estudio de este proyecto se considerarán los siguientes aspectos:

1. La influencia de la estructura de diversos ligandos quirales de tipo BINOL (**L1**-**L3** y **L6**), (*R*)-VAPOL (**L7**), derivados de (*S*)-prolinol (**L9**-**L12**) quinina (**L13**) y *N*-metilefedrina (**L17**) sobre el rendimiento y la enantioselectividad de la reacción.



2. La influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn), el número de equivalentes de reactivo de dialquilzinc, disolvente, concentración y temperatura de reacción.

3. Evaluación de diversas aldiminas cíclicas de tipo dibenzoxazepina **21** con diferente naturaleza electrónica y estérica.



4. Evaluación de distintas transformaciones sintéticas de los productos obtenidos basadas en la reactividad del grupo éster sin pérdida de pureza óptica.

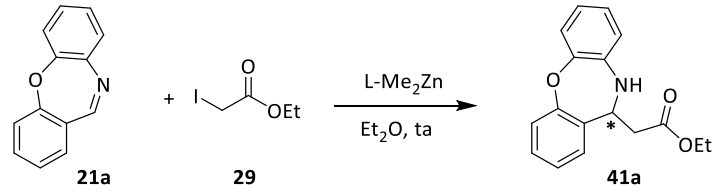
5. Determinación de la configuración absoluta del centro estereogénico presente en las aminas quirales.

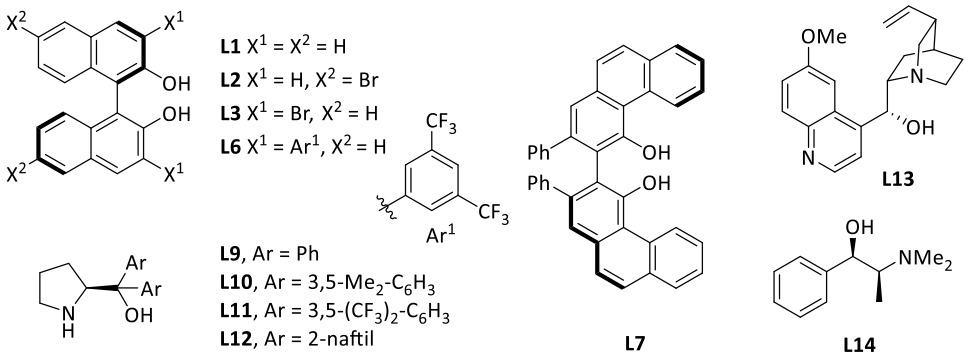
6.3. RESULTADOS Y DISCUSIÓN

6.3.1. Optimización de las condiciones de la reacción

El estudio de la reacción de aza-Reformatsky entre iodoacetato de etilo (**29**) con iminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina **21** se inició con el proceso de optimización de las condiciones de la reacción. En primer lugar se inició el proceso de optimización ensayando un conjunto de ligandos [de tipo (*R*)-BINOL (**L1**, **L2**, **L3** y **L6**), (*R*)-VAPOL (**L7**), derivados de (*S*)-prolinol (**L9**-**L12**), quinina (**L13**) y *N*-metilefedrina (**L14**)], en presencia de 7 equivalentes de Me_2Zn empleando Et_2O como disolvente a temperatura ambiente (Tabla 6.1), condiciones que se usaron también en la optimización de las condiciones de reacción del apartado anterior.

Tabla 6.1. Reacción de aza-Reformatsky de la dibenzoxazepina **21a** con iodoacetato de etilo (**29**). Evaluación de ligandos.[a]





Entrada	Ligando	t (min)	R (%)[b]	*ee* (%)[c]
1	**L1**	30	62	0
2	**L2**	30	68	0
3	**L3**	30	70	5
4	**L6**	30	44	3
5	**L7**	30	52	10
6	**L9**	30	57	34
7	**L10**	30	42	46
8	**L11**	30	71	39
9	**L12**	30	36	43
10	**L13**	30	45	-14
11	**L14**	30	45	-31

[a] **21a** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L** (0,020 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

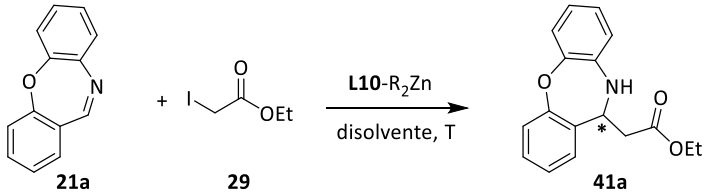
Los resultados de estas reacciones se puede encontrar en la tabla 6.1. Como se puede observar, en las reacciones con ligandos de tipo BINOL se obtiene el producto **41a** con rendimientos moderados (44-70%) pero prácticamente como mezcla racémica (0-5% *ee*) (entradas 1-4). Un

resultado similar se pudo observar cuando se usó (*R*)-VAPOL como ligando (Tabla 6.1, entrada 5), obteniéndose el producto **41a** con un rendimiento de un 52% y un exceso enantiomérico de 10%. Sin embargo cuando se utilizaron ligandos derivados de (*S*)-prolinol (**L9**-**L12**) se observó un aumento considerable en la enantioselectividad de la reacción. El uso del ligando **L9** [(*S*)-difenil(pirrolidin-2-il)metanol] dio lugar al producto final con un rendimiento del 57% y una enantioselectividad del 34% *ee*. Resultados similares se pudieron observar con el uso de ligandos sustituidos en los anillos aromáticos, derivados de **L9** (**L10**-**L12**), con rendimientos entre 36% y 71% y enantioselectividades entre 39% y 46% *ee*. El mejor resultado se observó con el ligando **L10** (Tabla 6.1, entrada 7) (42% de rendimiento y 46% *ee*). Con el objetivo de mejorar la enantioselectividad de la reacción, se ensayaron también la quinina (**L13**) y la *N*-metilefedrina (**L14**), pero el exceso enantiomérico obtenido era inferior al obtenido con los ligandos de tipo prolinol (Tabla 6.1, entradas 10 y 11).

Una vez identificado el ligando **L10** como el que proporcionaba el mejor resultado entre los ligandos examinados, continuamos el proceso de optimización ensayando la reacción con diferentes disolventes, número de equivalentes de iodoacetato de etilo (**45**), temperaturas, concentraciones y reactivos de dialquilzinc (Tabla 6.2).

En primer lugar se estudió el efecto del disolvente en la reacción de aza-Reformatsky (Tabla 6.2, entradas 2-10). Utilizando tolueno como disolvente se obtuvo el producto de reacción con un rendimiento (33%) y un exceso enantiomérico (37% *ee*) inferiores a los obtenidos con éter etílico (Tabla 6.2, entrada 2). Sin embargo la utilización de disolventes como diclorometano, metil *terc*-butil éter o isopropil éter (Tabla 6.2, entradas 3-5) dio lugar al producto de reaccion con rendimientos (44-54%) y excesos enantiomericos (53-55% *ee*) superiores. La reacción en THF (Tabla 6.2, entrada 6) condujo a una mejora en el rendimiento (63%) de la reacción, pero no tanto en el exceso enantiomérico (49%). La reacción en dicloroetano (Tabla 6.2, entrada 7) dio lugar al producto de adición con un rendimiento (51%) y una enantioselectividad (56% *ee*) algo mejores. Cuando se hizo la reacción en acetonitrilo (Tabla 6.2, entrada 8), se observó un pequeño incremento en el rendimiento (53%), mientras que la reacción en cloroformo (Tabla 6.2, entrada 9) condujo al producto de adición con un rendimiento bajo (29%). En ambos casos, la enantioselectividad no mejoró (46 y 48% *ee* respectivamente). Finalmente, cuando se utilizó acetato de etilo como disolvente (Tabla 6.2, entrada 10) se obtuvo el mejor resultado, tanto en rendimiento (63%) como en enantioselectividad (59% *ee*).

Tabla 6.2. Reaccion de aza-Reformatsky enantioselectiva de la dibenzoxazepina **21a** con iodoacetato de etilo (**29**). Evaluación de reactivos de dialquilzinc, número de equivalentes de reactivos de dialquilzinc, disolvente, número de equivalentes de iodoacetato de etilo (**29**), concentración y temperatura de reacción.[a]



21a **29** **41a**

	Disolvente	T (°C)	t (min)	R (%)[b]	*ee* (%)[c]
1	Et_2O	ta	30	42	46
2	Tolueno	ta	30	33	37
3	CH_2Cl_2	ta	30	44	53
4	MTBE	ta	30	47	55
5	$^{i}Pr_2O$	ta	30	54	53
6	THF	ta	30	63	49
7	$ClCH_2CH_2Cl$	ta	30	51	56
8	CH_3CN	ta	30	53	48
9	$CHCl_3$	ta	30	29	46
10	AcOEt	ta	30	63	59
11	AcOEt	0	30	22	90
12[d]	AcOEt	0	30	78	82
13[d]	AcOEt	-10	180	46	90
14[d]	AcOEt	-20	180	22	90
15[d, e]	AcOEt	0	30	75	68
16[d, f]	AcOEt	0	30	71	74
17[d, g]	AcOEt	0	30	97	86
18[d, h]	AcOEt	0	40	73	74
19[d, i]	AcOEt	0	60	92	83

[a] **21a** (0,100 mmol), **29** (0,200 mmol), 1,2 M Me_2Zn en tolueno (0,700 mmol), **L10** (0,020 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [d] Se utilizaron 3 equivalentes de iodoacetato de etilo (**29**) (0,3 mmol) [e] Se utilizó 1M Et_2Zn en hexano (0,70 mmol) [f] Se llevó a cabo la reacción en 1,5 mL de AcOEt [g] Se llevó a cabo la reacción en 6 mL de AcOEt [h] Se utilizaron 10 equivalentes de Me_2Zn [i] Se utilizaron 5 equivalentes de Me_2Zn.

Cuando se disminuyó la temperatura de la reacción a 0 °C (Tabla 6.2, entrada 11), se observó un incremento espectacular de la enantioselectividad hasta un 90% *ee*, pero desafortunadamente un rendimiento muy bajo de tan solo 22%. Al aumentar la cantidad de iodoacetato de etilo (**29**) hasta 3 equivalentes (Tabla 6.2, entrada 12), mejoró el rendimiento de la reacción (78%), pero disminuyó la enantioselectividad (82% *ee*). Al disminuir la temperatura, a -10 °C y -20 °C (Tabla 6.2, entradas 13 y 14), se mejoró la enantioselectividad (90% *ee*), pero afectó negativamente el rendimiento de la reacción (22-46%).

El uso de Et_2Zn en lugar de Me_2Zn disminuyó la enantioselectividad de la reacción (68% *ee*) (Tabla 6.2, entrada 15).

También se evaluó la concentración de reactivos en el medio de reacción. Un aumento en la concentración (o un descenso en el volumen) de reactivos condujo a un descenso en la enantioselectividad (74% *ee*), manteniéndose el rendimiento (71%) (Tabla 6.2, entrada 16). Sin embargo, cuando se llevó a cabo la reacción a una concentración más baja (mayor volumen de

disolvente), se pudo observar un aumento en el rendimiento de la reacción hasta un 97% y en la enantioselectividad (86% *ee*) (Tabla 6.2, entrada 17).

También se evaluó el efecto producido por la variación en el número de equivalentes de Me_2Zn utilizados. Tanto un aumento como un diminución en el número de equivalentes produjo una disminución en el rendimiento (79-92%) y en la enantioselectividad (74-83% *ee*) (Tabla 6.2, entradas 18 y 19).

En resumen, se obtiene el mejor resultado cuando la reacción entre la dibenzoxazepina **21a** y el iodoacetato de etilo (**29**) se lleva a cabo en acetato de etilo como disolvente (6 mL) a 0 °C en presencia de 7 equivalentes de Me_2Zn y 20 mol % del ligando **L10**.

6.3.2. Alcance y limitaciones de la reacción

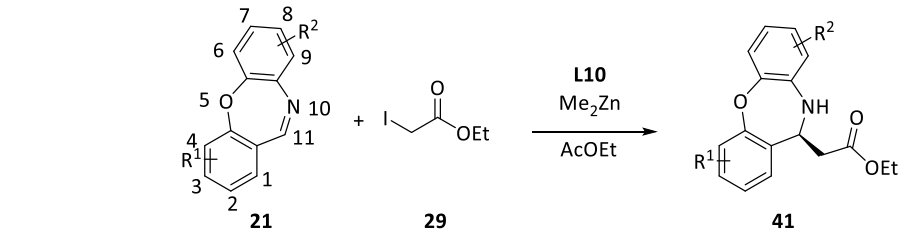
6.3.2.1. Reacción entre iodoacetato de etilo y diferentes dibenzo[*b,f*][1,4]oxazepinas

Una vez optimizadas las condiciones de reacción, se procedió a estudiar el alcance y las limitaciones de la reacción. Para ello se evaluaron varias iminas de tipo dibenzo[*b,f*][1,4]oxazepina diferentemente sustituidas **21** (Esquema 6.1).

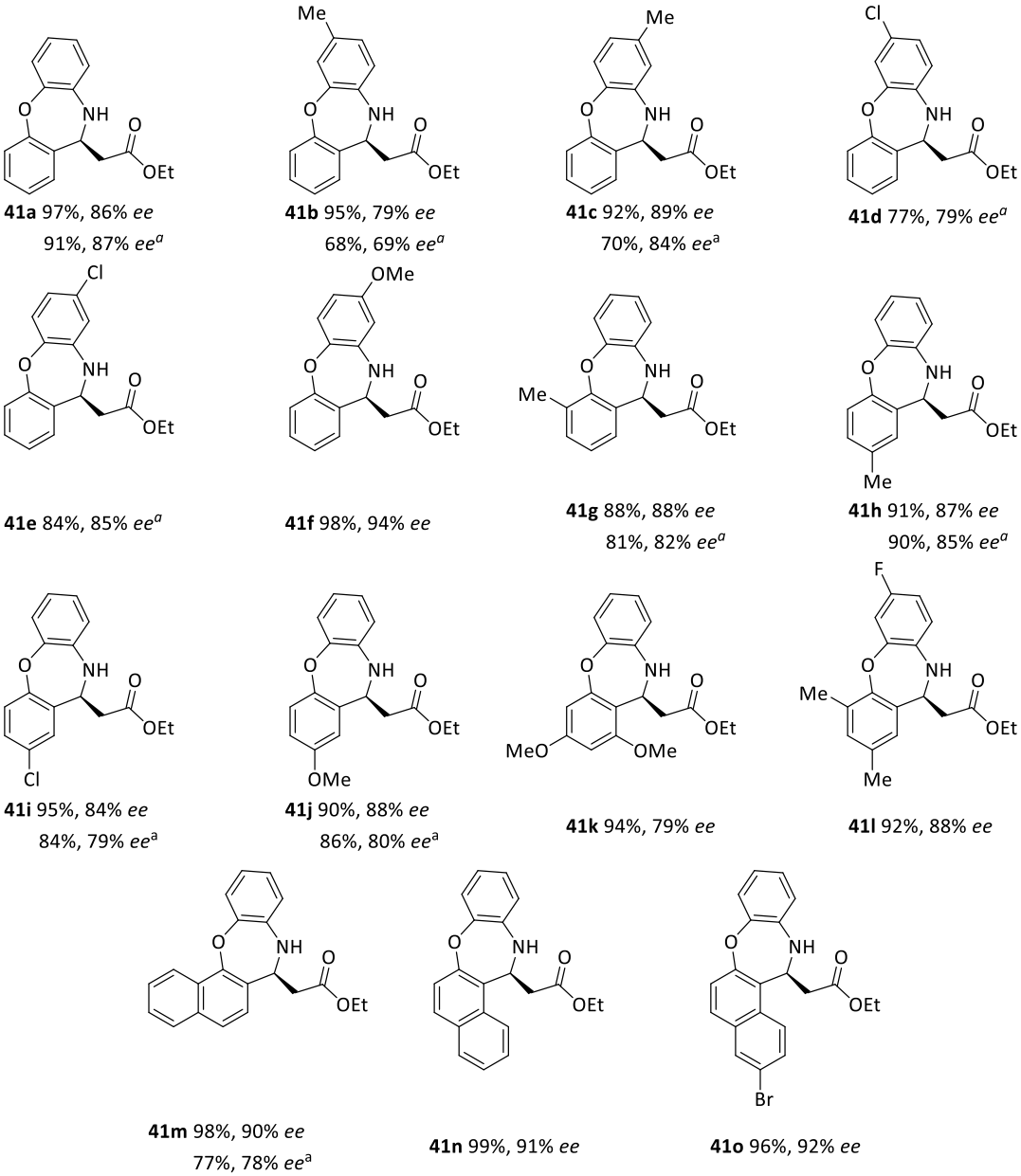
En primer lugar, se evaluaron iminas de tipo dibenzo[*b,f*][1,4]oxazepinas sustituidas en posiciones 7 y 8 (**21b-21f**). La presencia de un grupo electrón-donante (metilo), en la posición 7, condujo al producto **41b** con un rendimiento de 95% y un exceso enantiomérico de 79%. Sin embargo, la presencia del mismo grupo electrón-donante en la posición 8 dio lugar al β-amino ester **41c** con un rendimiento de 92% y exceso enantiomérico más elevado de 89%. Se pudo observar el mismo efecto cuando los sustituyentes son grupos electrón-atrayentes. Es decir la enantioselectividad es mayor cuando el sustituyente está situado en la posición 8. El producto **41d**, con un átomo de cloro en la posición 7, se obtuvo con un rendimiento del 77% y un exceso enantiomérico de 79%, mientras que el producto **41e**, con un átomo de cloro en la posición 8, se obtuvo con un rendimiento de 84% y un exceso enantiomérico más elevado (85%). Finalmente, cuando la reacción se llevó a cabo con el sustrato **24f**, sustituido con un grupo metoxi en la posición 8, se obtuvo el correspondiente β-amino ester **41f** con un rendimiento excelente (98%) y un exceso enantiomérico muy elevado (94%).

Posteriormente se ensayaron iminas mono-sustituidas en las posiciones 2 y 4. Un grupo metilo en la posición 4 condujo al producto **41g** con un rendimiento del 88% y un exceso enantiomérico de 88%. La presencia del mismo grupo en la posición 2 dio lugar al producto **41h** con un rendimiento del 91% y un exceso enantiomérico similar (87%). La reacción con la imina sustituida con un grupo cloro en la posición 6 dio como resultado el producto **41i** con un rendimiento elevado (95%) y un exceso enantiomérico de 84%. La presencia de un grupo metoxi en la misma posición dio lugar al producto **41j** con un rendimiento del 90% y un exceso enantiomérico de 88%. Se puede observar que la presencia de grupos electrón-donantes o electrón-atrayentes en sustratos monosustituidos no tiene demasiada influencia a la enantioselectividad de la reacción.

También se evaluaron sustratos con varios sustituyentes bajo las condiciones optimizadas. La reacción con el sustrato **21k**, sustituido con dos grupos metoxi en las posiciones 1 y 3, proporcionó el producto **41k** con un rendimiento del 94% y un exceso enantiomérico del 79%. Se observa un descenso en la enantioselectividad, seguramente debido a un aumento en el impedimento estérico. Cuando se utilizó el sustrato trisustituido **21l**, con dos grupos metilo en las posiciones 2 y 4 y un átomo de fluor en la posición 7, se obtuvo el β-amino ester **41l** con un rendimiento del 92% y un exceso enantiomérico del 88%.



21 **29** **41**

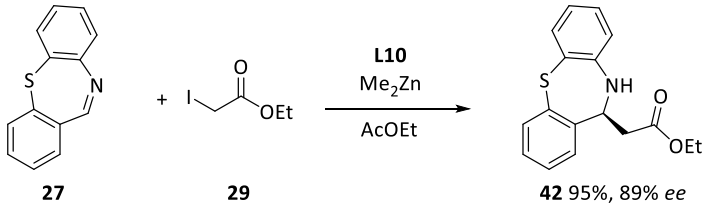


Esquema 6.1. Reacción de aza-Reformatsky enantioselectiva de iminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina **21** con iodoacetato de etilo (**29**). **21** (0,100 mmol), **29** (0,300 mmol), Ligando **L10** (0,020 mmol) y 1,2M Me_2Zn en tolueno (0,700 mmol). Rendimiento después de purificación por cromatografía de columna. Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales. [a] Se utilizaron 10 mol % del ligando **L10**.

También han sido evaluados diferentes sustratos derivados del naftol. El sustrato **21m**, derivado del 1-naftol, dio lugar al producto **41m** con un rendimiento de 98% y un exceso enantiomérico elevado de (90%). El producto **41n**, derivado del 2-naftol, se obtuvo con un

rendimiento (99%) y un exceso enantiomérico (91% *ee*) similares. Finalmente, el producto **41o**, derivado del 2-naftol sustituido con un grupo bromo en la posición 6, se obtuvo con un rendimiento excelente (96%) y un exceso enantiomérico elevado (92%). Por tanto, los sustratos derivados del naftol dan resultados excelentes en la reacción de aza-Reformatsky.

Finalmente se ensayó la dibenzo[*b,f*][1,4]tiazepina bajo las condiciones optimizadas, obteniéndose el producto **42** con elevado rendimiento (95%) y un exceso enantiomérico de 89%, mostrando que también las dibenzotiazepinas son sustratos excelentes para la reacción de aza-Reformatsky (Esquema 6.2).



27 **29** **42** 95%, 89% *ee*

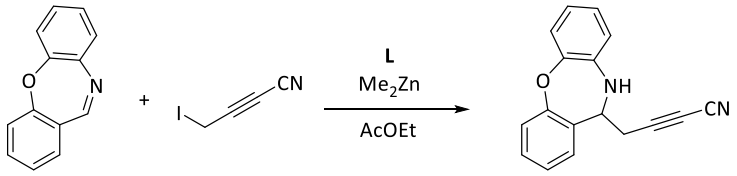
Esquema 6.2. Reacción de aza-Reformatsky enantioselectiva de la dibenzo[*b,f*][1,4]tiazepina **27** con iodoacetato de etilo (**29**). **27** (0,100 mmol), **29** (0,300 mmol), Ligando **L10** (0,020 mmol) y 1,2 M Me_2Zn en tolueno (0,700 mmol). Rendimiento de después de purificación por cromatografía de columna. Excesos enantioméricos determinados mediante HPLC usando fases estacionarias quirales.

6.3.2.2. Reacción de la dibenzo[*b,f*][1,4]oxazepina con diferentes reactivos de Reformatsky

Se decidió aplicar las condiciones optimizadas a la reacción de la dibenzo[*b,f*][1,4]oxazepina **21a** con los reactivos de Reformatsky generados a partir de 2-iodoacetonitrilo (**43**) y 2-iodo-1-feniletan-1-ona (**45**).

Cuando se aplicaron las condiciones optimizadas a la reacción entre 2-iodoacetonitrilo (**43**) y dibenzo[*b,f*][1,4]oxazepina **21a**, se obtuvo el producto **44** con buen rendimiento (73%), pero con un exceso enantiomérico bajo (50%) (Tabla 6.3, entrada 1). La disminución de la temperatura de reacción a 0 °C dio como resultado una disminución tanto en el rendimiento (61%) como en el exceso enantiomérico (44%) (Tabla 6.3, entrada 2). A la vista de estos pobres resultados se decidió hacer una pequeña evaluación de ligandos (**L11** y **L12**). El uso del ligando **L11** proporcionó al producto con un buen rendimiento (72%), pero con un exceso enantiomérico bajo (9% *ee*) (Tabla 6.3, entrada 3), mientras que la utilización del ligando **L12** dio lugar al producto **44** con un rendimiento moderado (67%) y un exceso enantiomérico de 50% (Tabla 6.3, entrada 4). Así pues, bajo las condiciones optimizadas, la reacción de aza-Reformatsky de la dibenzo[*b,f*][1,4]oxazepina **21a** con 2-iodoacetonitrilo (**43**) no dio resultados satisfactorios.

Tabla 6.3. Reacción de aza-Reformatsky enantioselectiva de la dibenzoxazepina **21a** con 2-iodoacetonitrilo (**43**). Evaluación de ligandos.[a]



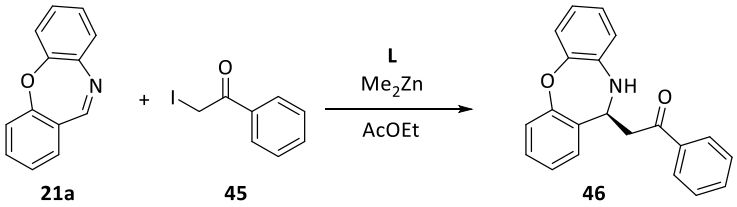
21a **43** **44**

	Ligando	T (°C)	t (min)	R (%)[b]	*ee* (%)[c]
1	**L10**	ta	45	73	50
2	**L10**	0	40	61	44
3	**L11**	ta	30	72	9
4	**L12**	ta	30	67	50

[a] **21a** (0,100 mmol), **43** (0,300 mmol), Ligando **L** (0,020 mmol) y 1,2 M Me_2Zn en tolueno (0,700 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

Las condiciones optimizadas también fueron aplicadas a la reacción entre 2-iodo-1-feniletan-1-ona (**45**) y dibenzo[*b,f*][1,4]oxazepina **21a**, dando lugar al producto **46** con un buen rendimiento (76%) pero una enantioselectividad baja (25% *ee*) (Tabla 6.4, entrada 1). También en este caso se llevó a cabo una pequeña evaluación de ligandos (**L11** y **L12**) (Tabla 6.4, entrada 2 y 3). El ligando **L11** dio lugar al producto de adición **46** con los mejores resultados (rendimiento de 65% y un exceso enantiomérico de 40%). Así pues, tampoco, la reacción de aza-Reformatsky con 2-iodo-1-feniletan-1-ona dio resultados satisfactorios. La configuración absoluta del compuesto **46** se pudo determinar mediante correlación química del compuesto.[1]

Tabla 6.4. Reacción de aza-Reformatsky enantioselectiva de la dibenzoxazepina **21a** con 2-iodo-1-feniletan-1-ona (**45**). Evaluación de ligandos.[a]



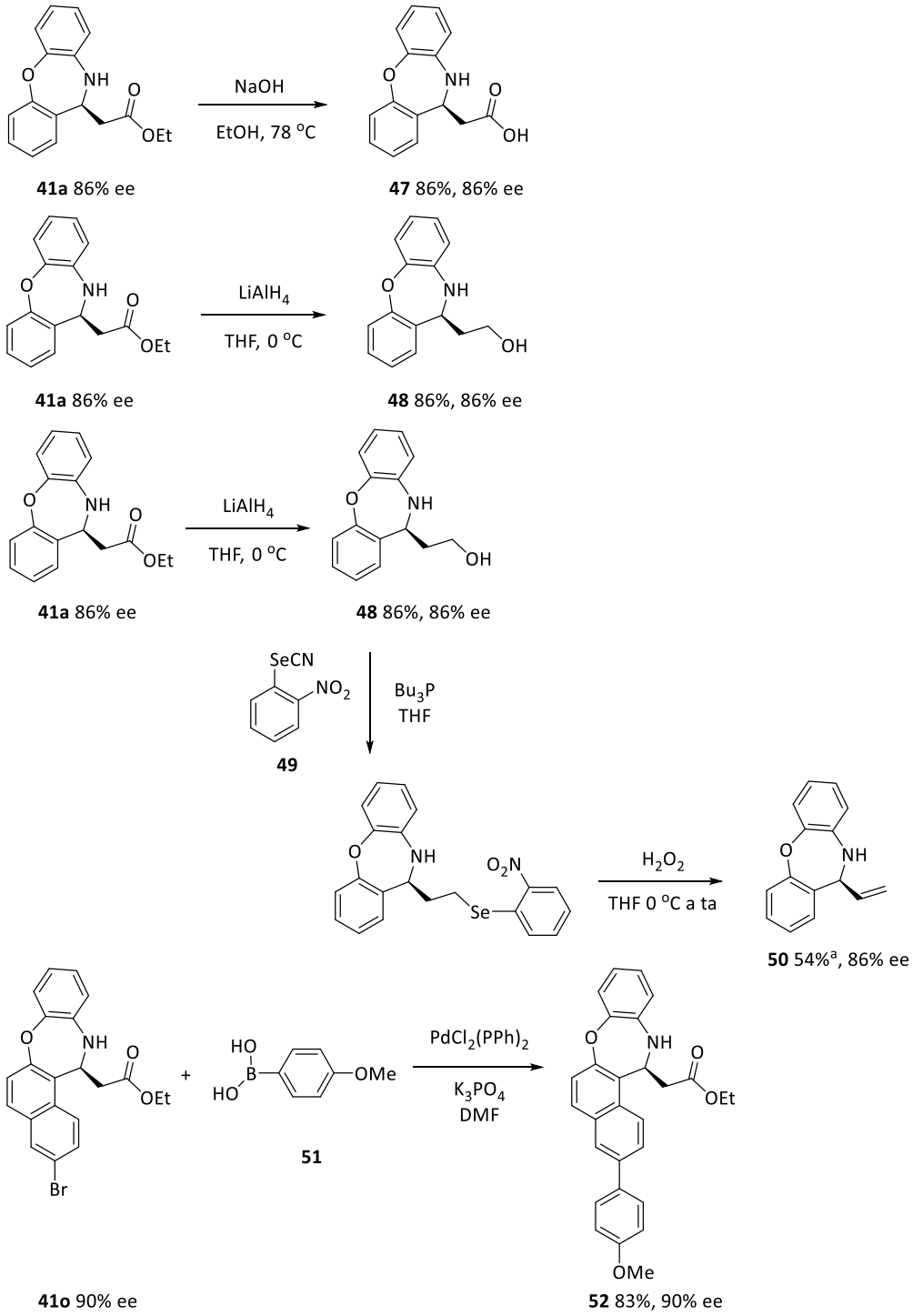
21a **45** **46**

	Ligando	T (°C)	t (min)	R (%)[b]	*ee* (%)[c]
1	**L10**	ta	120	76	25
2	**L11**	ta	9	65	40
4	**L12**	ta	105	**45**	28

[a] **21a** (0,100 mmol), **45** (0,300 mmol), Ligando **L** (0,020 mmol) y 1,2 M Me_2Zn en tolueno (0,700+0,300 mmol). [b] Rendimiento después de purificación por cromatografía de columna. [c] Exceso enantiomérico determinado mediante HPLC usando fases estacionarias quirales.

6.3.3. Transformaciones sintéticas

Para demostrar la utilidad de los productos obtenidos, se realizaron varias transformaciones sintéticas de los productos obtenidos (Esquema 6.3).



Esquema 6.3. Transformaciones sintéticas. [a] Rendimiento global de la reacción.

La primera transformación que se realizó fue la saponificación del éster **41a** con hidróxido sódico en etanol a 78 °C, obteniendo el β-aminoácido **47** con buen rendimiento (86%) y manteniendo el exceso enantiomérico. Esta transformación permite la síntesis de β-aminoácidos a partir de β-amino ésteres obtenidos anteriormente.

Una segunda transformación que se realizó fue la reducción del éster **41a** con $LiAlH_4$ a 0 °C, dando lugar al correspondiente 1,2-amino alcohol **48** con un buen rendimiento (86%) y conservando la pureza óptica.

Una tercera transformación, consistió en una secuencia sintética de tres etapas, equivalente formalmente a una reacción de vinilación de la imina. En primer lugar, se llevó a cabo la reducción del éster **41a** al correspondiente 1,2-amino alcohol **48**. Una reacción posterior del alcohol obtenido con *o*-nitrofenilselenocianato (**49**) y tributilfosfina seguida por una oxidación con peróxido de hidrógeno, dio lugar al producto **50**.[2] El rendimiento global de la secuencia fue del 54% y se mantuvo el exceso enantiomérico (86% *ee*).

Finalmente, a partir del producto **41o** se pudo sintetizar el producto **52** sin pérdida de pureza óptica, mediante una reacción de acoplamiento cruzado con el ácido borónico **51** catalizada por paladio, con un rendimiento de 83%.[3] Este resultado es interesante, ya que permite una gran variedad de funcionalizaciones debido al gran número de ácidos borónicos existentes en el mercado.

6.3.4. Determinación de la configuración absoluta

El compuesto **41o** nos permitió obtener una muestra adecuada para el estudio por difracción de Rayos X de monocristal. La configuración absoluta del carbono esterogénico se estableció como *(S)* (parámetro de Flack: 0.004(4)) (Figura 6.1). La configuración de los productos restantes se ha asignado admitiendo el mismo mecanismo de reacción para todos los sustratos.

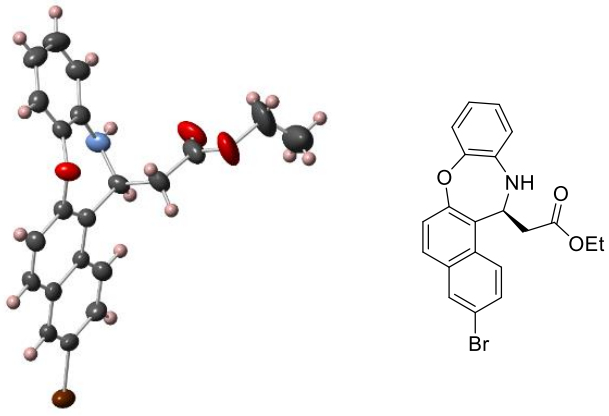
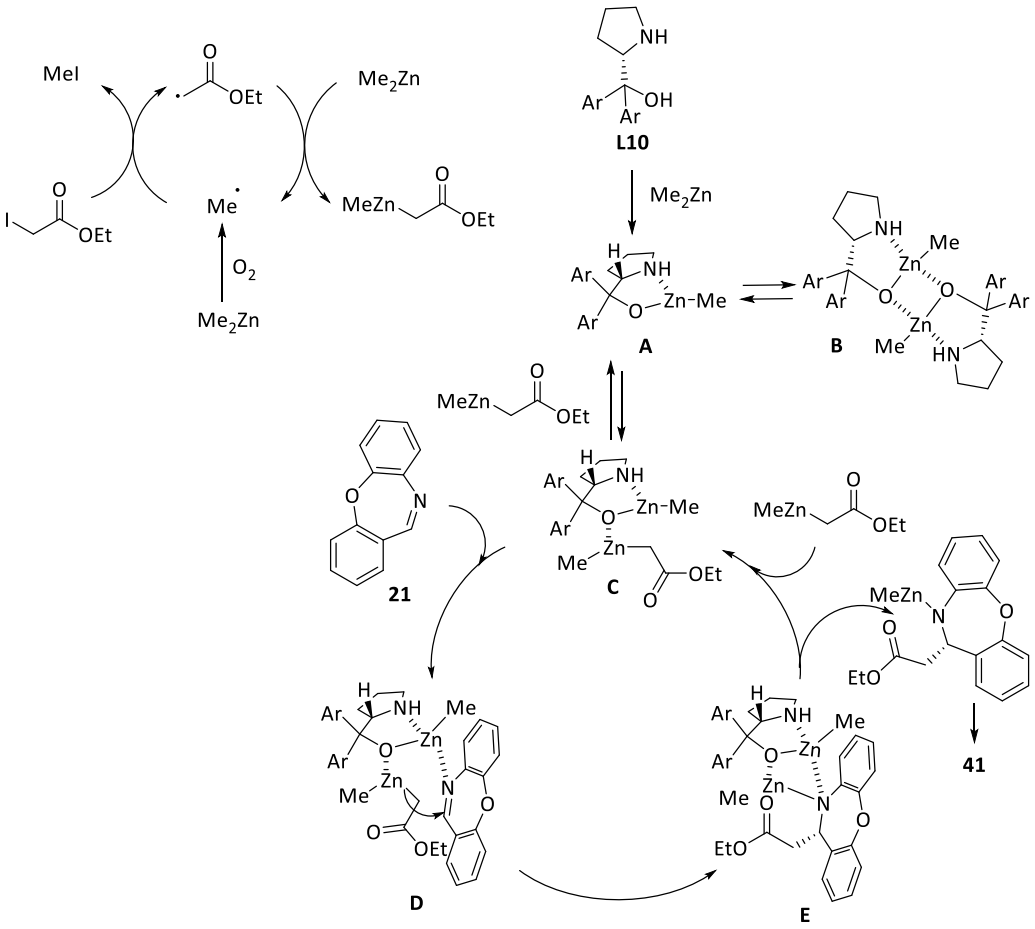


Figura 6.1. Estructura del compuesto **41o** determinada por Rayos-X .

6.3.5. Propuesta mecanística para la reacción de aza-Reformatsky de dibenzoxazepinas

El mecanismo (esquema 6.4) que se propone se basa en el mecanismo presentado en el capítulo anterior (reacción de aza-Reformatsky de 2,2-dióxido benzoxatiazinas). En primer lugar se forma un complejo **A** entre el ligando y Me_2Zn (en este caso con el ligando **L10**). Este complejo **A** está en equilibrio con un complejo **B** (dímero del complejo **A**) que no participa en la reacción. El complejo **A** se coordina con un zincato-metilacetato de etilo (formado en un paso previo, en la reacción del iodoacetato de etilo con Me_2Zn y oxígeno), formando el complejo **C**. A este complejo **C** se coordina la imina **21**, dando lugar a la formación del complejo **D**. En este complejo tiene lugar la reacción de aza-Reformatsky mediante la transferencia del nucleófilo a la cara *Si* de la imina cíclica generando el producto **E**, a partir del cual se obtiene el β-amino éster **41**, regenerando el monómero **A** y completando el ciclo catalítico.



Esquema 6.4. Propuesta mecanística para la reacción de aza-Reformatsky de dibenzoxazepinas con iodoacetato de etilo y un complejo de Me_2Zn-ligando de tipo diarilprolinol.

6.4. CONCLUSIONES

1. Se ha diseñado un método enantioselectivo que permite la reacción de aza-Reformatsky de aldiminas cíclicas de tipo dibenzo[*b,f*][1,4]oxazepina (**21**) con iodoacetato de etilo (**29**) catalizada por un sistema formado por el ligando (*S*)-bis(3,5-dimetilfenil)(pirrolidin-2-il)metanol y Me_2Zn a 0 °C utilizando AcOEt como disolvente.

2. La reacción de aza-Reformatsky bajo las condiciones optimizadas con aldiminas cíclicas admite sustituyentes en diferentes posiciones del anillo aromático obteniéndose buenos resultados, tanto de rendimiento (77-99%) como de enantioselectividad (79-94%).

3. Se han podido sintetizar varios productos derivados de los β-aminoésteres resultantes de la reacción de aza-Reformatsky: un β-aminoácido (**47**), un 1,2-aminoalcohol (**48**), una vinilamina (**50**) y un producto de acoplamiento cruzado (**52**) mediante transformaciones sintéticas sencillas a partir de los compuestos **41a** y **41o**

4. La determinación de la configuración absoluta para los compuestos **41** se ha podido llevar a cabo por difracción de Rayos X de monocristal del producto **41o**. Se puede concluir que la configuración absoluta es (*S*).

5. Se ha propuesto un mecanismo posible para la reacción de Reformatsky de dibenzo[*b,f*][1,4]oxazepinas con iodoacetato de etilo y un complejo de Me_2Zn-ligando de tipo diarilprolinol.

6.5. EXPERIMENTAL SECTION

6.5.1. General experimental methods

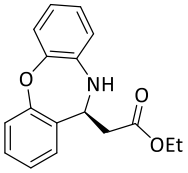
Reactions were carried out under air in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel.

6.5.2. General synthetic procedures and characterization data for compounds 41, 42, 44 and 46

General procedure for the enantioselective Reformatsky reaction: A two-neck 50 mL round bottom flask (one neck covered with a septum, the other neck with a drying finger, filled with $CaCl_2$), was flushed with nitrogen for 5 min. The ligand (*S*)-bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (0.02/0.01 mmol) was added to the flask and dissolved in 5 mL of EtOAc. Ethyl iodoacetate (**29**) or 2-iodoacetonitrilo (**43**) or 2-iodo-1-feniletan-1-ona (**45**) (0.3 mmol, 3 eq.) was added and the mixture was stirred at 0 °C. After 10 min dimethyl zinc solution (1.2 M in toluene) (7 mmol, 7 eq.) was added and immediately afterwards a dibenzo[*b,f*][1,4]oxazepine **21** or **27** (0.1 mmol, 1 eq.) dissolved in 1 mL EtOAc was added. The mixture was stirred for 60 min at 0 °C and quenched with 10 mL saturated aqueous NH_4Cl solution. The mixture was extracted with DCM (3x20 mL), washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed; the crude product was put on silica gel and purified by flash chromatography, obtaining the corresponding product.

General procedure for the non-enantioselective Reformatsky reaction: A two-neck 50 mL round bottom flask (one neck covered with a septum, the other neck with a drying finger, filled with $CaCl_2$), was flushed with nitrogen for 5 min. EtOAc was added to the flask (5 mL). Ethyl iodoacetate (**29**) or 2-iodoacetonitrilo (**43**) or 2-iodo-1-feniletan-1-ona (**45**) (0.2 mmol, 2 eq.) was added. After 5 min of stirring the dimethyl zinc solution (1.2 M in toluene) (7 mmol, 7eq.) was added and immediately afterwards dibenzo[*b,f*][1,4]oxazepine **21** or **27** (0.1 mmol, 1 eq.) dissolved in 1 mL EtOAc. The mixture was stirred for 60 min at rt. After the reaction was stopped with 10 mL saturated aqueous NH_4Cl, the mixture was extracted DCM (3x20 mL), washed with brine (20 mL) and dried over $MgSO_4$.

Ethyl (S)-2-(10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41a)

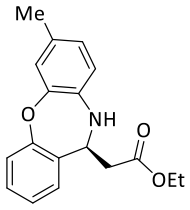


Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 16.7 min, minor enantiomer t_r = 20.3 min.

Yellow oil; $[\alpha]_D^{20}$ -59.2 (c 0.5, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.18 – 7.12 (m, 2H), 7.11 – 7.00 (m, 2H), 6.85 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.67 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.76 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.47 (s, 1H), 4.13 (q, *J* = 7.1

Hz, 2H), 3.32 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.86 (dd, *J* = 16.6, 4.3 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.08 (C), 157.11 (C), 143.92 (C), 137.04 (C), 132.18 (C), 129.32 (CH), 127.81 (CH), 124.63 (CH), 124.33 (CH), 121.75 (CH), 121.23 (CH), 119.22 (CH), 118.92 (CH), 60.68 (CH_2), 54.71 (CH), 40.11 (CH_2), 14.14 (CH_3). **HRMS** (ESI) *m/z*: 284,1281 $[M + H]^+$, $C_{17}H_{18}NO_3$ requires 284,1281.

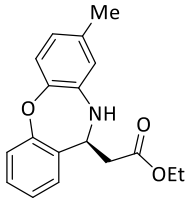
Ethyl (S)-2-(7-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41b)



Enantiomeric excess (79%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 18.9 min, minor enantiomer t_r = 21.8 min.

Yellow oil; $[\alpha]_D^{20}$ = -10.2 (c 1.0, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 1H), 7.16 – 7.10 (m, 2H), 7.07 – 7.00 (m, 1H), 6.91 (dd, *J* = 2.1, 0.8 Hz, 1H), 6.70 – 6.64 (m, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.74 (dd, *J* = 10.0, 4.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.27 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.83 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.21 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3) δ 172.1 (C), 157.0 (C), 144.1 (C), 134.2 (C), 132.0 (C), 129.3 (C), 129.2 (CH), 127.9 (CH), 125.1 (CH), 124.1 (CH), 122.1 (CH), 121.2 (CH), 119.2 (CH), 60.7 (CH_2), 54.9 (CH), 39.9 (CH_2), 20.2 (CH_3), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 298.1437 $[M + H]^+$, $C_{18}H_{20}NO_3$ requires 298.1438.

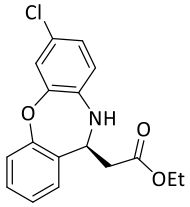
Ethyl (S)-2-(8-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41c)



Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 15.4 min, minor enantiomer t_r = 17.0 min.

Yellow oil; $[\alpha]_D^{20}$ = -38.3 (c 1.0, $CHCl_3$, 89% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 7.13 (dt, *J* = 7.5, 1.4 Hz, 2H), 7.03 (td, *J* = 7.4, 1.4 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.50 – 6.44 (m, 1H), 6.37 (dd, *J* = 2.0, 0.9 Hz, 1H), 4.74 (d, *J* = 9.6 Hz, 1H), 4.41 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.32 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.16 (d, *J* = 0.7 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1 (C), 157.3 (C), 142.0 (C), 136.6 (C), 134.2 (C), 132.2 (C), 129.3 (CH), 127.8 (CH), 124.2 (CH), 121.5 (CH), 121.2 (CH), 119.9 (CH), 119.3 (CH), 60.7 (CH_2), 54.7 (CH), 40.1 (CH_2), 20.6 (CH_3), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 298.1436 $[M + H]^+$, $C_{18}H_{20}NO_3$ requires 298.1438.

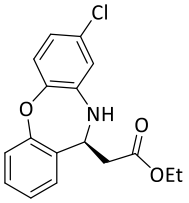
Ethyl (S)-2-(7-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41d)



Enantimeric excess (79%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 16.4 min, minor enantiomer t_r = 23.0 min.

Yellow oil; $[\alpha]_D^{20}$ = -7.6 (c 0.33, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.13 – 7.05 (m, 1H), 7.11 – 7.03 (m, 1H), 6.81 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 4.74 (dd, *J* = 10.1, 4.1 Hz, 1H), 4.49 (s, 1H), 4.13 (q, *J* = 7.3 Hz, 2H), 3.30 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.83 (dd, *J* = 16.6, 4.1 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.0 (C), 156.7 (C), 143.9 (C), 135.8 (C), 131.9 (C), 129.5 (CH), 127.8 (CH), 124.7 (CH), 124.5 (CH), 123.0 (C), 121.8 (CH), 121.2 (CH), 119.5 (CH), 60.8 (CH_2), 54.5 (CH), 39.9 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 218.0891 $[M + H]^+$, $C_{17}H_{17}ClNO_3$ requires 218.0891.

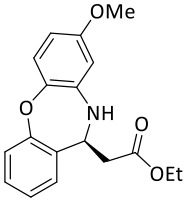
Ethyl (S)-2-(8-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41e)



Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 16.6 min, minor enantiomer t_r = 19.4 min.

Yellow oil; $[\alpha]_D^{20}$ = -44.1 (c 0.5, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 1H), 7.15 (t, *J* = 1.9 Hz, 1H), 7.13 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.59 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 4.74 (ddd, *J* = 9.8, 5.3, 4.1 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.33 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.2 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.9 (C), 156.9 (C), 142.3 (C), 138.2 (C), 132.0 (C), 129.6 (CH), 129.5 (C), 127.8 (CH), 124.7 (CH), 122.9 (CH), 121.2 (CH), 118.6 (CH), 117.9 (CH), 60.8 (CH_2), 54.4 (CH), 40.1 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 218.0885 $[M + H]^+$, $C_{17}H_{17}ClNO_3$ requires 218.0891.

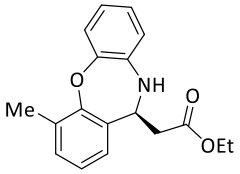
Ethyl (S)-2-(8-methoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41f)



Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 28.5 min, minor enantiomer t_r = 34.2 min.

Yellow oil; $[\alpha]_D^{20}$ = -41.6 (c 1.0, $CHCl_3$, 94% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 1H), 7.13 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.21 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.09 (d, *J* = 2.9 Hz, 1H), 4.76 (dd, *J* = 10.0, 4.2 Hz, 1H), 4.49 (s, 1H), 4.22 – 4.07 (m, 2H), 3.68 (s, 2H), 3.35 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.91 – 2.79 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1 (C), 157.5 (C), 156.6 (C), 138.3 (C), 137.8 (C), 132.2 (C), 129.4 (CH), 127.8 (CH), 124.4 (CH), 122.3 (CH), 121.1 (CH), 104.3 (CH), 103.6 (CH), 60.7 (CH_2), 55.4 (CH_3), 54.5 (CH), 40.2 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 314.1379 $[M + H]^+$, $C_{18}H_{20}NO_4$ requires 314.1387.

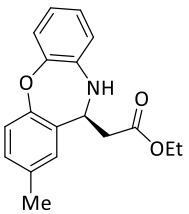
Ethyl (*S*)-2-(4-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41g)



Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 9.9 min, minor enantiomer t_r = 8.2 min.

Yellow oil; $[\alpha]_D^{20}$= -78.2 (c 1.0, $CHCl_3$, 88% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 2.6, 1.1 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.00 – 6.96 (m, 1H), 6.97 – 6.91 (m, 1H), 6.84 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 6.65 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.54 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.76 (dd, *J* = 9.9, 4.3 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.39 (dd, *J* = 16.5, 9.9 Hz, 1H), 2.88 (dd, *J* = 16.5, 4.3 Hz, 1H), 2.40 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C), 155.4 (C), 143.1 (C), 137.5 (C), 132.5 (C), 130.8 (CH), 130.6 (C), 125.2 (CH), 124.6 (CH), 124.2 (CH), 122.1 (CH), 118.7 (CH), 118.6 (CH), 60.6 (CH_2), 54.4 (CH), 40.0 (CH_2), 16.3 (CH_3), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 298.1432 $[M + H]^+$, $C_{18}H_{20}NO_3$ requires 298.1438.

Ethyl (*S*)-2-(2-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41h)

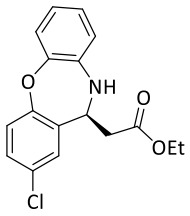


Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 12.6 min.

Yellow oil; $[\alpha]_D^{20}$ = -50.7 (c 1.0, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08 – 7.01 (m, 3H), 6.94 (s, 1H), 6.83 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.66 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.70 (dd, *J* = 10.1, 4.1 Hz, 1H), 4.**45** (s, 1H), 4.13 (q, *J* = 6.9 Hz,

2H), 3.33 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.27 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C), 155.0 (C), 144.1 (C), 137.1 (C), 133.9 (C), 131.8 (C), 129.7 (CH), 128.3 (CH), 124.5 (CH), 121.7 (CH), 120.9 (CH), 119.1 (CH), 118.9 (CH), 60.7 (CH_2), 54.7 (CH), 40.1 (CH_2), 20.7 (CH_3), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 298.1433 $[M + H]^+$, $C_{18}H_{20}NO_3$ requires 298.1438.

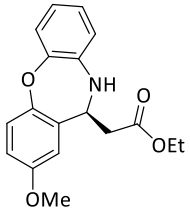
Ethyl (*S*)-2-(2-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41i)



Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 14.3 min, minor enantiomer t_r = 24.7 min.

Yellow oil; $[\alpha]_D^{20}$ = -32.2 (c 1.0, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.86 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1H), 6.69 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.72 (dd, *J* = 9.8, 4.3 Hz, 1H), 4.45 (s, 1H), 4.14 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.27 (dd, *J* = 16.6, 9.8 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.3 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.7 (C), 155.6 (C), 143.7 (C), 136.7 (C), 133.7 (C), 129.1 (CH), 127.7 (CH), 124.9 (CH), 122.7 (CH), 121.7 (CH), 119.6 (CH), 119.1 (CH), 60.8 (CH_2), 54.3 (CH), 39.8 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 318.0885 $[M + H]^+$, $C_{17}H_{17}ClNO_3$ requires 318.0892.

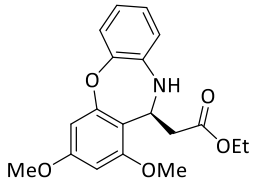
Ethyl (*S*)-2-(2-methoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41j)



Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 20.7 min, minor enantiomer t_r = 26.6 min.

Beige oil, $[\alpha]_D^{20}$ = -34.7 (c 1.0, $CHCl_3$, 88% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.10 – 7.03 (m, 2H), 6.83 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.74 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.70 – 6.61 (m, 2H), 6.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.71 (dd, *J* = 10.0, 4.1 Hz, 1H), 4.45 (s, 1H), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.74 (s, 3H), 3.35 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.86 (dd, *J* = 16.6, 4.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1 (C), 156.0 (C), 151.0 (C), 144.1 (C), 137.1 (C), 133.1 (C), 124.6 (CH), 122.0 (CH), 121.6 (CH), 119.0 (CH), 118.8 (CH), 113.8 (CH), 113.1 (CH), 60.7 (CH_2), 55.7 (CH_3), 54.6 (CH), 40.0 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 314.1386 $[M + H]^+$, $C_{18}H_{20}NO_4$ requires 314.1387.

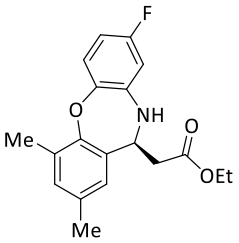
Ethyl (*S*)-2-(1,3-dimethoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41k)



Enantiomeric excess (79%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose-1), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 42.7 min, minor enantiomer t_r = 37.8 min.

Beige oil; $[\alpha]_D^{20}$ = -26.2 (c 1.0, $CHCl_3$, 79% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.85 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.68 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.14 (dd, *J* = 10.6, 3.4 Hz, 1H), 4.53 (s, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 3.23 (dd, *J* = 16.9, 10.7 Hz, 1H), 2.66 (dd, *J* = 16.9, 3.4 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.6 (C), 160.3 (C), 158.3 (C), 156.7 (C), 144.3 (C), 137.5 (C), 124.7 (CH), 121.6 (CH), 119.3 (CH), 119.2 (CH), 113.0 (C), 97.8 (CH), 94.7 (CH), 60.4 (CH_2), 55.8 (CH_3), 55.4 (CH_3), 46.8 (CH), 39.8 (CH_2), 14.2 (CH_3). **HRMS** (ESI) *m/z*: 344.1500 $[M + H]^+$, $C_{19}H_{22}NO_5$ requires 344.1493.

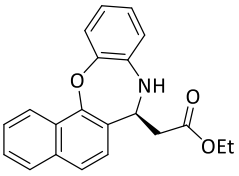
Ethyl (*S*)-2-(8-fluoro-2,4-dimethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate (41l)



Enantiomeric excess (88 was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose-1), hexane-*i*PrOH 80:20, 1.0 mL/min, major enantiomer t_r = 5.1 min, minor enantiomer t_r = 8.0 min.

Yellow oil; $[\alpha]_D^{20}$ = -90.8 (c 1.0, $CHCl_3$, 88% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 7.01 (dd, *J* = 8.7, 5.6 Hz, 1H), 6.93 (dt, *J* = 2.3, 0.8 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.28 (ddd, *J* = 8.8, 7.8, 3.0 Hz, 1H), 6.21 (dd, *J* = 10.3, 2.9 Hz, 1H), 4.69 (dt, *J* = 9.4, 4.3 Hz, 1H), 4.53 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.39 (dd, *J* = 16.6, 10.0 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.34 (s, 3H), 2.23 (d, *J* = 0.7 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1 (C), 159.7 (d, $J_{c\text{-}f}$ = 240.1 Hz, CF), 153.3 (C), 139.3 (d, $J_{c\text{-}f}$ = 2.6 Hz, C), 138.9 (d, $J_{c\text{-}f}$ = 11.0 Hz, C), 133.9 (C), 131.9 (C), 131.5 (CH), 130.1 (C), 125.7 (CH), 122.8 (d, $J_{c\text{-}f}$ = 10.3 Hz, CH), 104.5 (d, $J_{c\text{-}f}$ = 5.6 Hz, CH), 104.2 (d, $J_{c\text{-}f}$ = 9.2 Hz, CH), 60.7 (CH2), 54.1 (CH), 40.2 (CH2), 20.7 (CH3), 16.1 (CH3), 14.2 (CH3). **^{19}F NMR** (282 MHz, CDCl3) δ -119.73. **HRMS** (ESI) *m/z*: 330.1499 $[M + H]^+$, $C_{19}H_{20}FNO_3$ requires 330.1500.

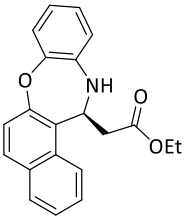
Ethyl (*S*)-2-(7,8-dihydrobenzo[*b*]naphtho[2,1-*f*][1,4]oxazepin-7-yl)acetate (41m)



Enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 30.5 min, minor enantiomer t_r = 36.5 min.

Orange oil; $[\alpha]_D^{20}$ = -136.1 (c 1.0, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 8.50 – 8.42 (m, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.55 – 7.52 (m, 1H), 7.48 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.87 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.72 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 4.89 (dd, *J* = 9.9, 4.2 Hz, 1H), 4.56 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.41 (dd, *J* = 16.7, 10.0 Hz, 1H), 2.96 (dd, *J* = 16.7, 4.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C), 152.2 (C), 144.1 (C), 137.5 (C), 134.3 (C), 127.6 (CH), 127.4 (C), 126.9 (C), 126.5 (CH), 126.4 (CH), 125.7 (CH), 124.8 (CH), 123.9 (CH), 122.1 (CH), 121.8 (CH), 119.4 (CH), 119.3 (CH), 60.7 (CH_2), 55.0 (CH), 40.3 (CH_2), 14.2 (CH_3). **HRMS** (ESI) *m/z*: 334.1447 $[M + H]^+$, $C_{21}H_{20}NO_3$ requires 334.1438.

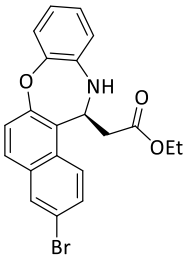
Ethyl (*S*)-2-(12,13-dihydrobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepin-13-yl)acetate (41n)



Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 18.3 min, minor enantiomer t_r = 44.2 min.

Beige oil; $[\alpha]_D^{20}$= +125.9 (c 1.0, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.53 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.41 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.88 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 6.72 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.6 Hz, H), 5.57 (dd, *J* = 10.1, 3.8 Hz, 1H), 4.64 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.49 (dd, *J* = 17.0, 10.1 Hz, 1H), 2.89 (dd, *J* = 17.1, 3.9 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 154.8 (C), 144.2 (C), 137.2 (C), 130.9 (C), 130.6 (C), 129.8 (CH), 128.8 (CH), 127.0 (CH), 124.8 (C), 124.7 (CH), 124.6 (CH), 122.2 (CH), 121.7 (CH), 121.5 (CH), 119.5 (CH), 119.0 (CH), 60.7 (CH_2), 49.2 (CH), 40.2 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 334.1439 $[M + H]^+$, $C_{21}H_{20}NO_3$ requires 334.1438.

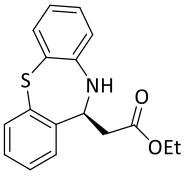
Ethyl (*S*)-2-(3-bromo-12,13-dihydrobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepin-13-yl)acetate (41o)



Enantiomeric excess (92%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose-1), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 22.2 min, minor enantiomer t_r = 43.1 min.

White solid; Mp 80-82C; $[\alpha]_D^{20}$= +93.5 (c 1.0, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.1 Hz, 1H), 7.88 (d, *J* = 9.5 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.89 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.73 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 6.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.49 (dd, *J* = 10.0, 4.1 Hz, 1H), 4.61 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.43 (dd, *J* = 17.1, 9.9 Hz, 1H), 2.88 (dd, *J* = 17.1, 4.0 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C), 154.9 (C), 144.0 (C), 137.0 (C), 132.0 (C), 130.7 (CH), 130.2 (CH), 129.2 (C), 128.8 (CH), 125.2 (C), 124.8 (CH), 124.1 (CH), 123.0 (CH), 121.5 (CH), 119.8 (CH), 119.1 (CH), 118.6 (C), 60.8 (CH_2), 49.4 (CH), 40.1 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 412.0547 $[M + H]^+$, $C_{21}H_{19}BrNO_3$ requires 412.0543.

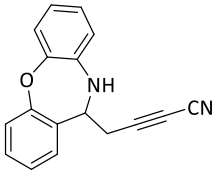
Ethyl (*S*)-2- (10,11-dihydrodibenzo[*b,f*][1,4]thiazepin-11-yl)acetate (42)



Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 20.6 min, minor enantiomer t_r = 19.3 min.

Clear oil; $[\alpha]_D^{20}$ = -34.8 (c=1, $CHCl_3$, 89% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.27 – 7.16 (m, 3H), 7.13 (dd, *J* = 7.0, 2.2 Hz, 1H), 6.92 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 6.61 (ddd, *J* = 7.7, 7.3, 1.4 Hz, 1H), 6.**45** (dd, *J* = 8.1, 1.3 Hz, 1H), 5.77 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.33 (s, 1H), 4.17 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.21 (dd, *J* = 15.6, 9.9 Hz, 1H), 2.92 (dd, *J* = 15.6, 4.7 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.7 (C), 146.3 (C), 142.8 (C), 135.5 (C), 131.9 (CH), 131.8 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.2 (CH), 119.2 (CH), 118.9 (CH), 117.9 (C), 60.9 (CH_2), 54.2 (CH), 39.9 (CH_2), 14.2 (CH_3). **HRMS** (ESI) *m/z*: 300.1054 $[M + H]^+$, $C_{17}H_{18}NO_2S$ requires 300.1053.

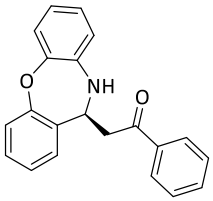
4-(10,11-Dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)but-2-ynenitrile (44)



Enantiomeric excess (50%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 22.7 min, minor enantiomer t_r = 25.7 min.

Yellow oil; $[\alpha]_D^{20}$ -48.9 (c 0.5, $CHCl_3$) (50% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (ddd, *J* = 8.1, 7.1, 1.9 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.11 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.08 (td, *J* = 3.6, 1.3 Hz, 1H), 6.90 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.72 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.57 – 4.41 (m, 2H), 3.38 (dd, *J* = 16.7, 9.1 Hz, 1H), 3.00 (dd, *J* = 16.8, 5.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.0 (C), 143.6 (C), 135.9 (C), 130.4 (C), 130.3 (CH), 128.2 (CH), 125.2 (CH), 124.9 (CH), 121.9 (CH), 121.6 (CH), 119.9 (CH), 118.9 (CH), 118.0 (C), 55.7 (CH), 25.8 (CH_2). **HRMS** (ESI) *m/z*: 237.1014 $[M + H]^+$, $C_{15}H_{13}N_2O$ requires 237.1022

(S)-2-(10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)-1-phenylethan-1-one (46)[1]



Enantiomeric excess (40%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1.0 mL/min, major enantiomer t_r = 29.1 min, minor enantiomer t_r = 30.7 min.

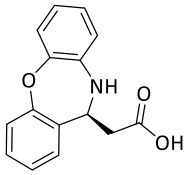
Yellow oil; $[\alpha]_D^{20}$ -29.5 (c 1.0, $CHCl_3$) (40% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (t, *J* = 1.4 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.45 – 7.36 (m, 2H),

7.29 – 7.16 (m, 3H), 7.12 – 7.02 (m, 2H), 6.81 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.65 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.53 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.94 (dd, *J* = 9.7, 3.4 Hz, 1H), 4.61 (s, 1H), 4.13 (dd, *J* = 18.1, 9.7 Hz, 1H), 3.51 – 3.38 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.1 (C), 157.1 (C), 143.7 (C), 137.1 (C), 136.6 (C), 133.4 (CH), 132.6 (C), 129.3 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 124.7 (CH), 124.4 (CH), 121.7 (CH), 121.3 (CH), 119.0 (CH), 119.0 (CH), 54.5 (CH), 44.2 (CH_2).

6.5.3. Synthetic procedures and characterization data for compounds 47, 48, 50 and 52

(*S*)-2-(10,11-Dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetic acid (47)

To a solution of **41a** (0.10 mmol) in EtOH (1 mL) aq. 1 M NaOH (1 mL) was added. The reaction mixture was stirred at reflux temperature (73 °C) for 2 hours. The reaction was quenched with HCl 2M (5 mL) and extracted with dichloromethane (3x15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo, obtaining product **47**.

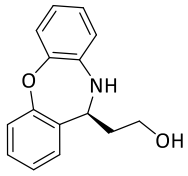


Enantiomeric excess (86%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose-1), hexane-*i*PrOH 90:10, 1mL/min, major enantiomer tr = 13.6 min, minor enantiomer tr = 20.9 min.

Brown oil; $[\alpha]_D^{20}$ = -34.1 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 7.20 – 7.03 (m, 4H), 6.90 (td, *J* = 7.6, 1.4 Hz, 1H), 6.81 – 6.74 (m, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 4.82 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.42 (dd, *J* = 17.0, 9.7 Hz, 1H), 2.96 (dd, *J* = 17.0, 3.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.6 (C), 157.0 (C), 144.3 (C), 136.3 (C), 131.7 (C), 129.5 (CH), 127.9 (CH), 124.8 (CH), 124.5 (CH), 121.8 (CH), 121.3 (CH), 119.9 (CH), 119.4 (CH), 54.5 (CH), 39.7 (CH2). HRMS (ESI) *m/z*: 256.0972 [M + H]+, $C_{15}H_{14}NO_3$ requires 256.0968.

(*S*)-2-(10,11-Dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)ethan-1-ol (48)

To a solution of **41a** (0.10 mmol) in THF (1 mL), $LiAlH_4$ (1.0 M in THF, 1.1 equivalents, 0.11 mmol) was added dropwise at 0 °C over 4 min. The reaction was stirred at 0 °C until completion (TLC). The mixture was diluted with EtOAc (10 mL) and acidified with aq. 2 M HCl until the aqueous layer became clear. A saturated dissolution of Rochelle salt was added (5 mL) and the mixture was stirred for 2 hours. The aqueous layer was then separated and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum. The residue was purified by flash chromatography, obtaining product **48**.[43]



Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 90:10, 1mL/min, major enantiomer t_r = 8.2 min, minor enantiomer t_r = 19.7 min.

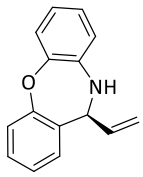
Orange oil; $[\alpha]_D^{20}$ = -6.0 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.17 (dt, *J* = 7.9, 1.6 Hz, 2H), 7.08 (ddd, *J* = 7.2, 4.0, 1.3 Hz, 2H), 6.86 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.68 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.59 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.68 (dd, *J* = 9.2, 5.4 Hz, 1H), 3.90 (ddd, *J* = 11.2, 6.8, 4.5 Hz, 1H), 3.78 (ddd, *J* = 11.1, 6.8, 4.6 Hz, 1H), 2.41 (dddd, *J* = 13.8, 9.2, 7.1, 4.5 Hz, 1H), 2.24 (dddd, *J* = 13.7, 9.3, 7.0, 4.5 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.3 (C), 144.1 (C), 137.4 (C), 134,0 (C), 128.9 (CH), 127.0 (CH), 124.5 (CH), 124.4 (CH), 121.8 (CH), 121.1 (CH), 119.2 (CH), 119.0 (CH), 60.7 (CH_2), 54.8 (CH), 36.9 (CH_2). **HRMS** (ESI) *m/z*: 242.1174 $[M + H]^+$, $C_{15}H_{16}NO_2$ requires 242.1176.

(*S*)-11-Vinyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine (50)

To a solution of **41a** (0.10 mmol) in THF (1 mL), $LiAlH_4$ (1.0 M in THF, 1.1 equivalents, 0.11 mmol) was added dropwise at 0 °C over 4 min. The reaction was stirred at 0 °C until completion (TLC). The mixture was diluted with EtOAc (10 mL) and acidified with aq. 2 M HCl until the aqueous layer became clear. A saturated dissolution of Rochelle salt was added (5 mL) and the mixture was stirred for 2 hours. The aqueous layer was then separated and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum. The residue was purified by flash chromatography, obtaining product **48**.

To a solution of **48** in THF (1 mL), *o*-nitrophenylselenocyanate (**48**) (2.4 equivalents) and *n*-Bu_3P (2.5 equivalents) were added. The solution was stirred 4 hours at room temperature. The solvent was removed and the crude product was used for the next step.

The crude product was dissolved in THF (1 mL) and was treated at 0 °C with 50% aqueous hydrogen peroxide (5 equivalents). The solution was, after addition of hydrogen peroxide, placed at room temperature for 2 hours. The solution was quenched with water and extracted with dichloromethane (3x15 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography, obtaining product **50**.

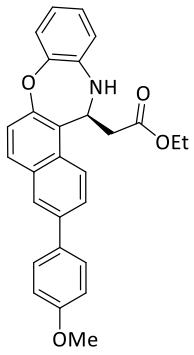


The enantiomeric excess (86%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 90:10, 1mL/min, major enantiomer t_r = 8.64 min, minor enantiomer t_r = 11.22 min.

Orange oil; $[\alpha]_D^{20}$ = -5.9 (c 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.18 (ddd, *J* = 7.9, 3.2, 1.6 Hz, 2H), 7.12 – 7.05 (m, 2H), 6.88 (ddd, *J* = 7.8, 7.4, 1.5 Hz, 1H), 6.70 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.32 (ddd, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.37 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.30 (dt, *J* = 10.3, 1.2 Hz, 1H), 5.14 (d, *J* = 6.8 Hz, 1H), 4.00 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.2 (C), 144.7 (C), 138.1 (CH), 137.6 (C), 132.8 (C), 129.1 (CH_2), 127.5 (CH), 124.5 (CH), 124.3 (CH), 121.8 (CH), 121.1 (CH), 119.5 (CH), 118.9 (CH), 116.6 (CH), 59.4 (CH). **HRMS** (ESI) *m/z*: 224.1063 $[M + H]^+$, $C_{15}H_{14}NO$ requires 224.1070.

Ethyl (*S*)-2-(3-(4-methoxyphenyl)-12,13-dihydrobenzo[*b*]naphtho[1,2-*f*][1,4]oxazepin-13-yl)acetate (52)

To a solution of **41o** (0.100 mmol) in DMF (2 mL), potassium phosphate *n*-hydrate (8 equivalents) and *p*-methoxy-phenylboronic acid **51** (2 equivalents) were added. This solution was bubbled with N_2 for 30 minutes and afterwards $PdCl_2(PPh)_2$ (10 mol %) was added and the reaction was placed at 100 °C for 4 hours. Afterwards, the reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the solution was extraced with dichloromethane (3x15 mL). The organic phase was then washed with water (2x15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography, obtaining product **52**.



The enantiomeric excess (90%) was determined by chiral HPLC (Phenomenex Lux® 5µm Amylose 1), hexane-iPrOH 80:20, 1 mL/min, major enantiomer t_r = 26.27 min, minor enantiomer t_r = 40.11 min.

Brown oil; $[\alpha]_D^{20}$ = +57.0 (c 1.0, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.70 – 7.62 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.17 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.91 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 6.76 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.60 (dd, *J* = 10.0, 3.7 Hz, 1H), 4.68 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.51 (dd, *J* = 17.1, 10.1 Hz, 1H), 2.94 (dd, *J* = 17.1, 3.9 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 159.3 (C), 154.6 (C), 144.2 (C), 137.2 (C), 136.9 (C), 133.0 (C), 131.3 (C), 129.8 (CH), 129.4 (C), 128.2 (CH), 126.3 (CH), 125.8 (CH), 124.8 (C), 124.7 (CH), 122.8 (CH), 122.1 (CH), 121.5 (CH), 119.5 (CH), 119.0 (CH), 114.4 (CH), 60.7 (CH_2), 55.4 (CH), 49.4 (CH_3), 40.2 (CH_2), 14.1 (CH_3). **HRMS** (ESI) *m/z*: 440.18**45** $[M + H]^+$, $C_{28}H_{26}NO_4$ requires 440.1856.

6.6. REFERENCES

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