Catalytic Asymmetric Reactions with Seven-Membered Cyclic Imines Dibenzo[*b*,*f*][1,4]oxazepines

Lode De Munck,[a] Carlos Vila,*[a] and José R. Pedro*[a]

Abstract: The dibenzo[*b*,*f*][1,4]oxazepine scaffold is a privileged structure in medicinal chemistry that display a wide variety of biological and pharmacological activities. However, catalytic asymmetric methodologies for the synthesis of chiral dibenzo[*b*,*f*][1,4]oxazepine derivatives are scarce in the literature. This microreview presents an overview of the enantioselective reactions using these cyclic seven-membered imines as electrophile, including substrate scope, limitations and the application to the synthesis of related compounds.

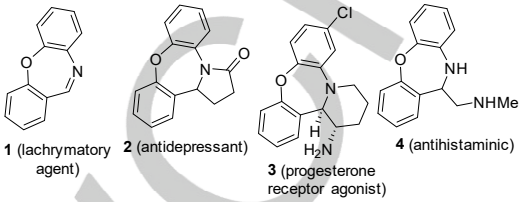
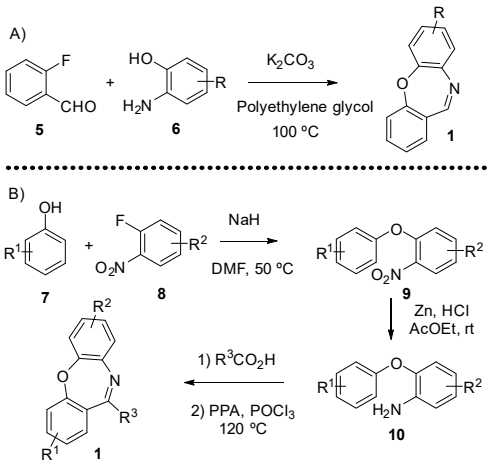


Figure 1. Examples of 11-substituted-10,11-dihydrodibenzo[b,f][1,4]oxazepine derivatives.

1. Introduction

Nitrogen-containing aromatic heterocycles are ubiquitous in agrochemicals, pharmaceuticals and natural products. In this context, dibenzo[*b,f*][1,4]oxazepine derivatives are an attractive nitrogen heterocycle compounds that recently have attracted enormous attention from the pharmaceutical industry due to the widespread biological activities presented by such compounds. [1] For example, the simple compound **1** 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. [2] Among compounds containing the dibenzoxazepine core there are antidepressants,[3] non-nucleoside HIV-1 reverse transcriptase inhibitors,[4] analgesics,[5] and anxiolytics,[6] as well as a histamine H4 receptor agonist,[7] PGE28 and calcium[8] antagonists. In this context, 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives play an important role in medicinal chemistry, For example, compound **2** have antidepressant activity, [9] compound **3** is a progesterone receptor agonist,[10] while compound **4** presents antihistaminic activity. [11] Despite the importance of this pharmacophore, catalytic asymmetric methodologies to prepare enantioenriched 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4] oxazepine derivatives are scarce in the literature. [12] This review covers the achievements in the catalytic enantioselective synthesis of such compounds paying attention on the reactions used and also in the transformations carried out on the resulting chiral dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives.

There are two general methodologies for the preparation of dibenzo[*b,f*][1,4]oxazepine derivatives **1**. For the seven-membered aldimines one of the most used methodology is the condensation-cyclization of *ortho*-fluorobenzaldehyde **5** and *ortho*-aminophenols **6** using a base (K_2CO_3) and polyethylene glycol as a solvent (Scheme 1A). The other general methodology is a various step sequence from readily available starting materials (Scheme 1B). The first step is the formation of the diaryl ethers **9** through a nucleophilic aromatic substitution between phenols **7** and *ortho*-fluoronitrobenzene derivatives **8**. After the nitro group in compounds **9** is reduced to the free amines **10**, and the last step is the formation of an amide and subsequent cyclization through a Bischler-Napieralski reaction[13] using polyphosphoric acid (PPA) and $POCl_3$ at 120 ºC obtaining imines **1**, in general with good yields. This methodology is longer than the first one, but allows the efficient synthesis for the seven-membered cyclic ketimines.



Scheme 1. General methodologies for the synthesis of dibenzoxazepine derivatives **1**.

[a] Lode De Munck, Dr. C. Vila and Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 59, 46100 Burjassot, València (Spain)
Fax: (+34) 963544328
E-mail: carlos.vila@uv.es, jose.r.pedro@uv.es

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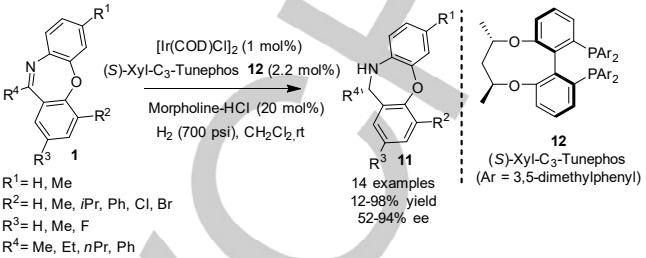
Lode De Munck graduated in pharmaceutical sciences (2011) and received his Master's in drug development (2013) from the Katholieke Universiteit Leuven (Belgium). In 2014 he received his Master's degree in organic chemistry from Valencia University (Spain). In 2017, he obtained his PhD from the same university under the supervision of Dr. Carlos Vila and Prof. José R. Pedro.

Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from Valencia University. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling reactions with organolithium reagents and asymmetric catalysis. In 2014, he was appointed as a 'Juan de la Cierva' researcher at the Organic Chemistry Department, Valencia University.

José R. Pedro graduated in chemistry from Valencia University, Spain, in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at Valencia University. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at Valencia University (AsymCat, GIUV13)

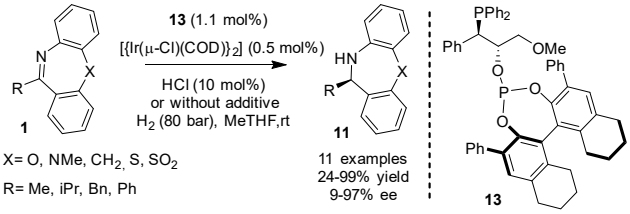
2. Catalytic Enantioselective Reductions.

The asymmetric reduction of cyclic imines is a straightforward methodology for the synthesis of chiral nitrogen heterocycles.[14] One way to obtain enantioenriched 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives is performing the asymmetric hydrogenation of the corresponding seven-membered ketimines. In 2011, the first catalytic enantioselective hydrogenation of dibenzoxazepines was described by Zhang and collaborators.[15] The hydrogenation (Scheme 2) was performed with an $[Ir(COD)Cl]_2$/(*S*)-Xyl-C3-TunePhos complex, 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 as a 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 **11** 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.



Scheme 2. Asymmetric hydrogenation of seven-membered ketimines described by Zhang.

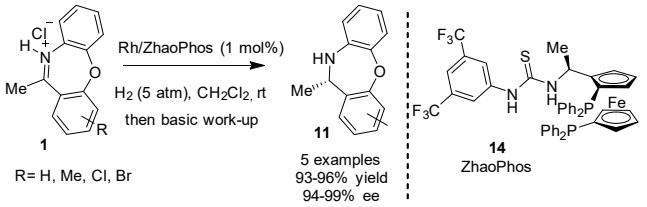
Vidal-Ferran and collaborators described in 2015, the asymmetric hydrogenation of seven-membered imines using also a chiral iridium complex.[16] In this report, the authors not only describe the hydrogenation of dibenzoxazepines, but they also apply the same reaction conditions to the sulphur, carbon, nitrogen and sulphur dioxide analogues.[17] Optimized conditions consisted in an in situ prepared $[\{Ir(\mu\text{-}Cl)(COD)\}_2]$/phosphine-phosphite complex (0.5 mol % metal, 1.1 mol % ligand) in the presence of HCl (10 mol %) using MeTHF as a solvent (Scheme 3). 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 seem to be 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.



Scheme 3. Asymmetric hydrogenation of seven-membered ketimines described by Vidal-Ferran.

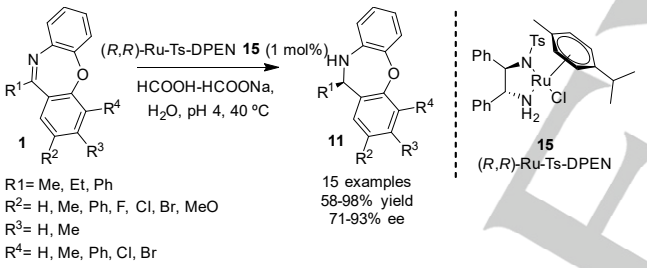
Zhang, Dong, Hu and collaborators described in 2017, the asymmetric hydrogenation of seven-membered imines using Rh/bisphosphine-thiourea ligand ZhaoPhos (Scheme 4).[18] In order to have high enantioselectivities, the authors use oxazepine-type seven-membered cyclic imine hydrochlorides, obtaining the corresponding seven-membered amines, after basic work-up, with high yields and excellent enantioselectivities (up to 99% ee). The authors consider that the success of this

methodology is the anion-bonding interaction between the chloride and the thiourea moiety of the catalyst.



Scheme 4. Asymmetric hydrogenation of seven-membered ketimines described by Zhang, Dong and Hu.

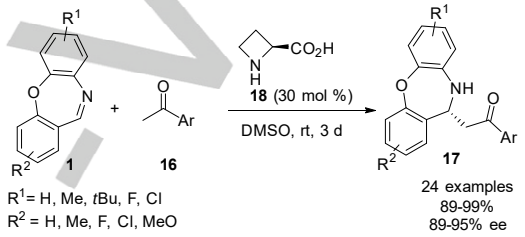
Bhanage and More, described in 2017,[19] the asymmetric reduction of dibenzoxazepines in the presence of a (*R*,*R*)-Ru-Ts-DPEN complex **15** using water as a solvent, and HCOOH-HCOONa as a green hydrogen source (Scheme 5). The corresponding cyclic amines **11** were obtained with good yields (85-98%) and high enantioselectivities (71-93% ee). 11-Phenyldibenzo[*b*,*f*][1,4]oxazepine was also used as a substrate, obtaining the corresponding product with moderate yield (58%) but good ee (80%).



Scheme 5. Asymmetric transfer hydrogenation of seven-membered ketimines described by Bhanage.

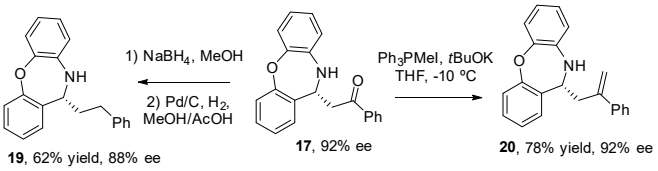
3. Catalytic Enantioselective Mannich Reactions

Another methodology that has been used for prepare chiral amines, is the asymmetric Mannich reaction.[20] The first organocatalytic enantioselective Mannich reaction using dibenzoxazepines as electrophiles was published in 2014 (Scheme 3). [21] Wang and collaborators described the Mannich reaction between dibenzo[*b,f*][1,4]oxazepines **1** and acetophenone **16** under the following optimized conditions: 30 mol % of (*S*)-azetidine-2-carboxylic acid **18**, which functions as a organocatalyst, in DMSO at room temperature. The DMSO gave the best conversion and enantioselectivity, while cyclic aminoacids gave the best enantioselectivities. This fact is remarkable, because direct asymmetric Mannich reaction of acetophenone using cyclic amino acids by enamine catalysis is challenging.[22] The ring size of amino acids was found to play a key role, and the four-membered (*S*)-azetidine-2-carboxylic acid **18** gave the corresponding chiral Mannich product **17** in good yield (94%) and excellent enantiomeric excess (93% ee). Whereas, five-membered (*S*)-proline gave high enantioselectivity but moderate yield, and no reaction occurred with the six-membered (*S*)-pipecolic acid. Various substituted acetophenones were also tested under the reaction conditions, obtaining in general similar yields and enantioselectivities (Scheme 6). However, a methyl 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 6. Enantioselective Mannich addition of acetophenone to dibenzo[*b,f*][1,4]oxazepine derivatives.

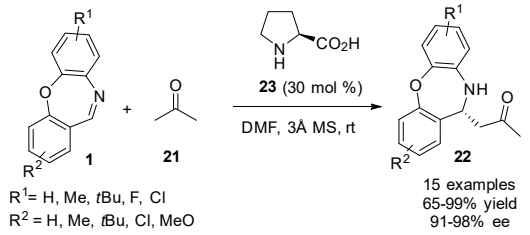
They also performed a gram scale reaction, obtaining similar results in terms of yield and enantioselectivity. To further demonstrate the practical use of their methodology, they accomplished several transformations with the carbonyl group in the chiral Mannich products (Scheme 7). They described the decarbonylative reduction and the Wittig reaction, with good results.



Scheme 7. Synthetic transformations of the enantioenriched Mannich products.

More recently, in 2015, the same group described the enantioselective Mannich reaction using acetone **21** as nucleophile (Scheme 8).[23] In the reaction with acetone, compared with the reaction with acetophenone, the best organocatalyst was (*S*)-proline **23** (30 mol %), while (*S*)-azetidine-2-carboxylic acid **18** gave high enantioselectivity but lower yield. The presence of 3Å molecular sieves in the reaction mixture with DMF as a solvent, increased 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 (65-99%) 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 8. Enantioselective Mannich addition of acetone to dibenzo[*b,f*][1,4]oxazepine derivatives.

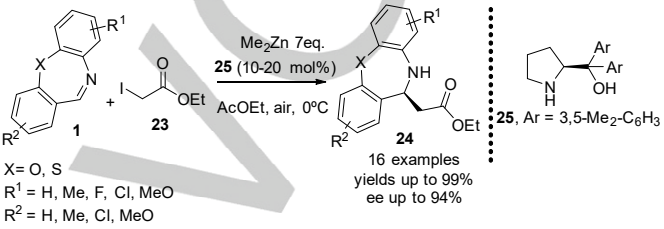
The same authors described very recently, the same Mannich reaction but using dibenzo[*b,f*][1,4]thiazepines as seven-membered cyclic imines and various alkyl methyl ketones using **23** as catalyst and DMF as a solvent, obtaining the corresponding 11-substituted 10,11-dihydrodibenzo[*b,f*][1,4]thiazepines with excellent enantioselectivities (91-99% ee).[24]

4. Catalytic Enantioselective Addition of Organometallic Reagents

The catalytic asymmetric addition reactions of organometallic reagents to imines[25] are central processes in synthetic chemistry to prepare chiral amines. The enantioselective addition of organometallic reagents to acyclic imines have been extensively studied in the literature. However, the corresponding addition of organometallic reagents to cyclic imines is less studied, despite their great potential for the synthesis of chiral nitrogen containing heterocyclic compounds. In this context, very few examples have been described using dibenzo[*b,f*][1,4]oxazepines as electrophiles.

4.1. Catalytic Reformatsky Reactions

Catalytic enantioselective Reformatsky[26,27] reaction using imines as electrophiles provides a suitable methodology for the synthesis of chiral β-amino esters, which are a significant class of building blocks in synthetic chemistry, due to they have been used for the synthesis of optically pure γ-amino alcohols or β-amino acids. [28] Despite the great potential of the catalytic asymmetric aza-Reformatsky reaction in organic synthesis, this reaction is scarcely studied in the literature.[29] Very recently Pedro and Vila[30] described the catalytic enantioselective aza-Reformatsky reaction using dibenzo[*b,f*][1,4]oxazepines as electrophiles. In this report, the authors described the use of a readily available diaryl prolinol as a chiral ligand, $ZnMe_2$ as a zinc source and ethyl iodoacetate as nucleophile in the presence of air atmosphere, leading to the synthesis of chiral ethyl 2-(10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)acetate derivatives with excellent yields (up to 98%) and high enantioselectivities (up to 94% ee) (Scheme 9). The presence of air is essential due to the radical mechanism proposed by Cozzi for the aza-Reformatsky reactions.[29a] The addition of ethyl iodoacetate is accelerated in the presence of Me_2Zn and oxygen. In the presence of oxygen, Me_2Zn forms alkyl peroxides (ZnOOMe) that are able to initiate radical reactions, such as the formation of methyl radicals which react with ethyl iodoacetate giving ethyl acetate radicals.



Scheme 9. Catalytic enantioselective aza-Reformatsky reaction with dibenzo[*b,f*][1,4]oxazepine derivatives.

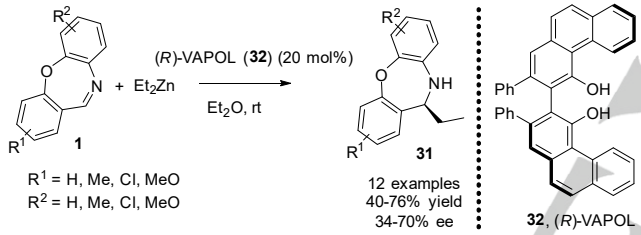
Scheme 10. Synthetic transformations of the Reformatsky products.

To highlight the synthetic utility of this methodology, the authors carried out several chemical transformations for the synthesis of interesting chiral compounds bearing a dibenzo[*b,f*][1,4]oxazepine scaffold (Scheme 10). For example, a chiral β-amino acid **26** was prepared in 90% yield by simple saponification of the ester moiety. The chiral amino alcohol **27**, was synthesized by reduction of the β-amino ester with $LiAlH_4$.

Moreover, a 11-vinyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine **28** was easily synthesized by a three step reaction sequence with an overall yield of 54% yield and maintaining the optical purity. Finally, a Suzuki cross-coupling reaction was performed, affording the 10,11-dihydrodibenzo[*b,f*][1,4]oxazepine derivative **30**, in 83% yield and 90% ee.

4.2. Catalytic Addition of Et_2Zn.

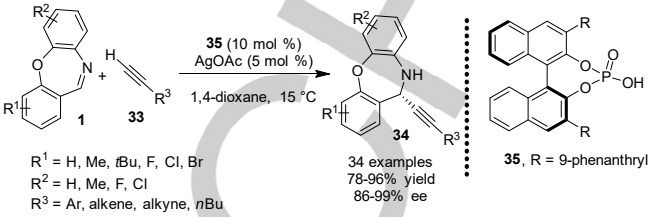
The asymmetric addition of dialkylzinc reagents to imines is also a convenient methodology to prepare chiral amines. Several examples of the enantioselective addition of organozinc reagents to acyclic imines have been described in the literature.[25c] However, the corresponding addition of dialkylzinc reagents to cyclic imines has been hardly studied, and only one example have been reported in 2017, where an enantioselective addition of Et_2Zn to dibenzo[*b,f*][1,4]oxazepine derivatives catalyzed by (*R*)-VAPOL-Zn(II) complexes (Scheme 8) is described.[31] This methodology has provided an approach to the synthesis of optically active 11-ethyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives with good yields (up to 76%) and moderate enantioselectivities (up to 70% ee).



Scheme 11. Enantioselective alkylation of seven-membered imines.

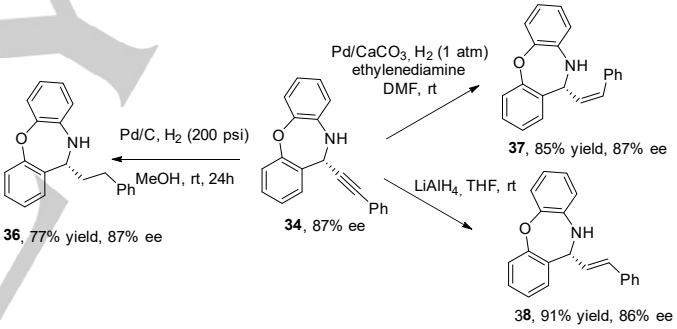
4.3. Catalytic Addition of Terminal Alkynes

The enantioselective alkynylation of imines is one of the most useful carbon-carbon bond-forming reactions for the preparation of chiral propargylic amines,[32] which are versatile building blocks for the synthesis of fine chemicals, pharmaceuticals, agrochemicals and natural products. In 2014, Wang and collaborators described the first and single alkynylation reaction of dibenzoxazepines.[33] This publication is also the first report of a 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 **35**) (Scheme 12). These conditions allowed the authors to test various terminal aromatic, heteroaromatic and aliphatic 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 the unsubstituted 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).



Scheme 12. Enantioselective alkynylation of seven-membered imines.

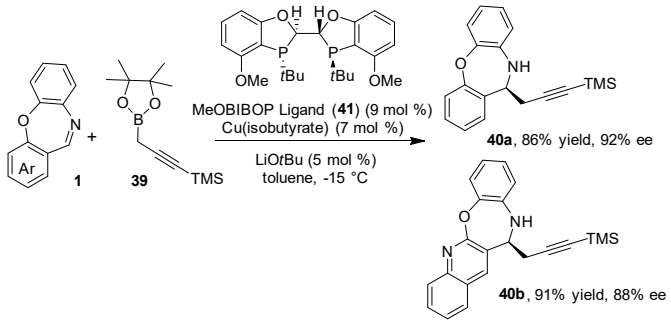
The authors also performed various reduction reactions on the propargylic cyclic amines obtained, such as the reduction of the triple bond of the alkyne to the corresponding alkane (**36**) and alkene (**37** and **38**). This last reduction was carried out selectively to the *E* isomer (**38**) or the *Z* isomer (**37**) relying on the reaction conditions, without any loss of enantiopurity of the starting material (Scheme 13).



Scheme 13. Transformations of the cyclic propargylic amines **34**.

4.4. Catalytic Propargylation

Very recently, Fandrick and coworkers presented a copper-catalyzed asymmetric propargylation of aldimines[34] using propargyl borolane as a propargylic agent.[35] The authors performed the propargylation reaction for a series of cyclic imines, two of which were seven-membered cyclic imines **1**. The reaction conditions were optimized in 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 propargylic cyclic amine derivative **40a** in good yield (86%) and good enantiomeric excess (92 % ee) (Scheme 14).The benzo[2,3][1,4]oxazepino[7,6-*b*]quinoline was also used as an electrophile obtaining the chiral propargylic amine **40b** bearing 2 heterocycles with 91% yield and 88% ee.



Scheme 14. Enantioselective propargylation of dibenzo[*b,f*][1,4]oxazepine.

5. Conclusions

As summarized in this review, the dibenzo[b,f][1,4]oxazepines are highly interesting electrophiles. Several successful catalytic asymmetric methodologies have been described in the literature for the synthesis of enantioenriched 11-substituted-10,11dihydrodibenzo[*b,f*][1,4]oxazepine derivatives, over the last 6 years. However, these electrophiles have not been exploited to its full potential and there are still plenty of room to develop new enantioselective reactions with these seven-membered cyclic imines.

Acknowledgements

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Keywords: Asymmetric catalysis • cyclic imines • dibenzoxazepines • nitrogen heterocycles • chiral amines

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MICROREVIEW

Asymmetric catalysis

Lode De Munck,[a] Carlos Vila,[a] and José R. Pedro*[a]*

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