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Enantioselective alkynylation of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides catalysed by (*R*)-VAPOL-Zn complexes: Synthesis of chiral propargylic cyclic sulfamidates.

Lode De Munck,[a] Alicia Monleón,[a] Carlos Vila,[a] M. Carmen Muñoz[b] and José R. Pedro*[a]

(*R*)-VAPOL-Zn(II) complexes catalysed the enantioselective addition of terminal alkynes to cyclic benzoxathiazine 2,2-dioxides, providing the corresponding chiral propargylic sulfamidates with high yields (up to 93%) and good enantiomeric excesses (up to 87%).

Introduction

Chiral amines are omnipresent in nature and represent a key structural motif in numerous pharmaceutical drugs and biologically active compounds.[1] Therefore, the development of efficient methodologies for the enantioselective synthesis of chiral amines represents a pivotal topic in organic synthesis.[2] In this context, sulfamidates represent an interesting class of amine derivatives, which are present in some pharmaceutical and biological active compounds (Figure 1).[3] Moreover, sulfamidates can serve as versatile building blocks for organic synthesis.[4]
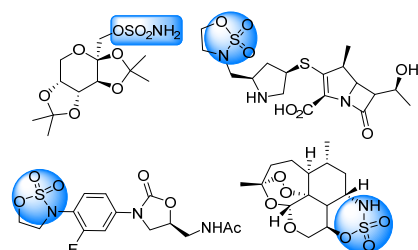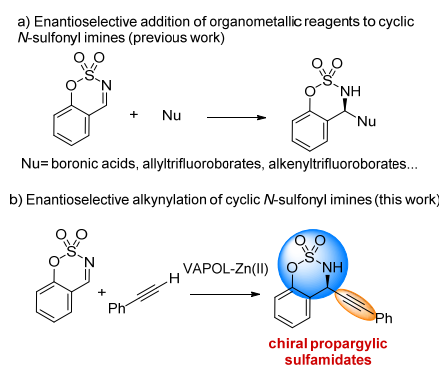

Figure 1 Different sulfamidate bioactive coumpounds.

Very recently, cyclic benzoxathiazine 2,2-dioxides have received remarkably attention and have proven to be a versatile building block for the synthesis of optically pure benzo-fused cyclic sulfamidate heterocycles. These cyclic imines, derived from salicylic aldehydes, have a rigid structure that reduces the conformational mobility and avoid the E/Z isomerization, facilitating the stereodiferentiation and making them optimum partners for enantioselective transformations. Therefore, these cyclic aldimines have been used as electrophilic substrates in various enantioselective reactions such as the addition of boronic acids,[5] allyltrifluoroborates,[6] alkenyltrifluoroborates,[7] asymmetric hydrogenations,[8] Mannich reactions,[9] or different enantioselective cycloadditions.[10] However, to the best of our knowledge, the asymmetric addition of terminal alkynes to benzoxathiazine 2,2-dioxides remains unexplored (Scheme 1), despite the synthetic potential of the alkyne moiety. Therefore, the development of new methodologies for the synthesis of chiral propargylic sulfamidates is a highly desired goal. In this context, the asymmetric alkynylation of imines is the most efficient method for obtaining chiral propargyl amines.[11] Generally, the asymmetric alkynylation is focused on acyclic imines[12] whereas the corresponding alkynylation of cyclic imines[13] have been less studied, despite the synthetic potential for the preparation of optically active nitrogen heterocycles. Herein we report our results on the enantioselective addition of terminal alkynes to benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides catalyzed by (*R*)-VAPOL-Zn(II) complexes for the synthesis of chiral propargylic sulfamidates.

a) Enantioselective addition of organometallic reagents to cyclic *N*-sulfonyl imines (previous work)

Nu= boronic acids, allyltrifluoroborates, alkenyltrifluoroborates...

b) Enantioselective alkynylation of cyclic *N*-sulfonyl imines (this work)

chiral propargylic sulfamidates

Scheme 1 Enantioselective addition of organometallic reagents to benzoxathiazine 2,2-dioxides.

[a] Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain).
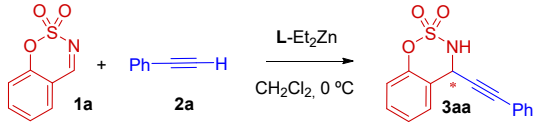[b] Departament de Física Aplicada, Universitat Politècnica de València, Camino de Vera s/n, 46022 València (Spain).
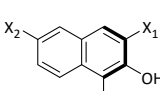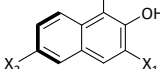
Results and discussion

Our initial studies were focused on the addition of phenylacetylene (**2a**) to cyclic benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (**1a**) in the presence of BINOL-zinc type complexes. A 1 M Et$_2$Zn solution in hexanes (3 eq.) was added dropwise to a mixture of ligand **L** (0.2 eq.) and alkyne (7.2 eq.) in CH$_2$Cl$_2$ at room temperature. After stirring for 1 h the reaction mixture was cooled to 0 °C and then a solution of the cyclic *N*-sulfonyl imine **1a** (1 eq.) in CH$_2$Cl$_2$ was added. Under these reaction conditions several BINOL-type ligands **L1**-**L6** were tested (Table 1, entries 1-6), and although the corresponding product **3aa** was obtained with good yields, the enantiomeric excesses were poor. After, we decided to examine vaulted ligands like (*R*)-VAPOL (**L7**) and (*R*)-VANOL (**L8**). The use of **L7** as a ligand, gained the product **3aa** with good enantioselectivity (78%), although the yield was moderate (38%). Finally, when (*R*)-VANOL (**L8**) was used as a ligand, **3aa** was afforded in 65% yield, but the enantiomeric excess was lower (entry 8, Table 1).

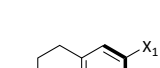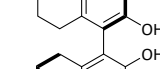**Table 1** Optimization of the reaction conditions. Ligand screening.[a]
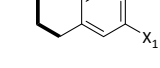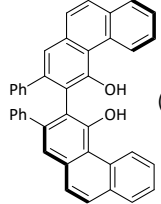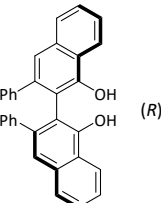
Entry	Ligand (**L**)	t(h)	Yield of **3aa** (%)[b]	ee (%)[c]
1	**L1**	3	41	30
2	**L2**	2	57	3
3	**L3**	2	60	6
4	**L4**	4	32	4
5	**L5**	2	61	3
6	**L6**	2	68	15
7	**L7**	3	38	-78[d]
8	**L8**	2	65	-54

[a] **1a** (0.090 mmol), **2a** (0.650 mmol), 1 M Et$_2$Zn in hexanes (0.270 mmol), **L1-L8** (0.018 mmol) in CH$_2$Cl$_2$ at 0 ºC. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Opposite enantiomer was obtained.

The optimization of the reaction conditions was continued using (*R*)-VAPOL as a ligand testing different dialkyl zinc reagents, solvents and temperatures (Table 2). The use of Me$_2$Zn instead of Et$_2$Zn (Entry 2 versus entry 1, Table 2), afforded the corresponding chiral amine **3aa** with similar enantioselectivity but with higher yield. Different solvents were screened, obtaining the best enantiomeric excess when dichloroethane was used. Lowering the temperature to -20 °C had a detrimental effect (entry 7). However, when the temperature was increased to room temperature similar results were achieved.
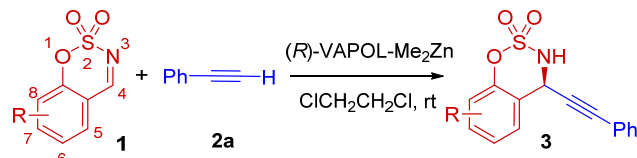
Table 2 Optimization of the reaction conditions.[a]

Entry	R$_2$Zn (eq.)	Solvent	t (h)	T(ºC)	**3aa** (%)[b]	ee (%)[c]
1	Et$_2$Zn (3 eq.)	CH$_2$Cl$_2$	4	0	38	78
2	Me$_2$Zn (3 eq.)	CH$_2$Cl$_2$	2	0	84	75
3	Me$_2$Zn (3 eq.)	Toluene	3	0	73	80
4	Me$_2$Zn (3 eq.)	ClCH$_2$CH$_2$Cl	2	0	88	82
5	Me$_2$Zn (1.5 eq.)	ClCH$_2$CH$_2$Cl	2	0	95	59
6	Me$_2$Zn (4 eq.)	ClCH$_2$CH$_2$Cl	2	0	84	83
7	Me$_2$Zn (4 eq.)	ClCH$_2$CH$_2$Cl	3	-20	62	77
8	Me$_2$Zn (4 eq.)	ClCH$_2$CH$_2$Cl	2	10	86	83
9	Me$_2$Zn (4 eq.)	ClCH$_2$CH$_2$Cl	2	rt	89	83
10[d]	Me$_2$Zn (4 eq.)	ClCH$_2$CH$_2$Cl	2	rt	89	82

[a] **1a** (0.090 mmol), **2a** (0.650 mmol) and (*R*)-VAPOL (0.018 mmol). [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.[d] 0.360 mmol of **2a** was used

Once the reaction conditions were optimized (entry 10, Table 1), the scope of the reaction was evaluated in Table 3. Using phenylacetylene as the nucleophile, several cyclic imines **1** were investigated. Various substituents in the phenyl ring of the cyclic *N*-sulfonyl imine **1**, such as methyl, *tert*-butyl and bromide were tolerated under the reaction conditions and the corresponding propargylic sulfamidates were gained with good yields and enantioselectivities. However, the presence of a *tert*-butyl group in the 6 position led to a decreased enantioselectivity of the reaction (entry 4).

Table 3 Enantioselective addition of phenylacetylene (**2a**) to different benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (**1**).[a]
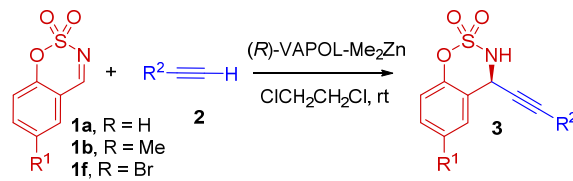
Entry	**1**	R	t (h)	**3**	Yield (%)[b]	ee (%)[c]
1	**1a**	H	3	**3aa**	89	82
2	**1b**	6-Me	3	**3ba**	81	87
3	**1c**	8-Me	3	**3ca**	70	73
4	**1d**	6-*t*Bu	3	**3da**	69	56
5	**1e**	8-*t*Bu	2	**3ea**	64	81
6	**1f**	6-Br	2	**3fa**	59	80

[a] **1** (0.090 mmol), **2a** (0.360 mmol), 2 M Me$_2$Zn in toluene (0.360 mmol), (*R*)-VAPOL (0.018 mmol). [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.

To further investigate the scope of this methodology, we explored the reaction with several terminal alkynes, with different electronic and steric demands (Table 4). The electronic properties of the aromatic ring of the terminal alkynes did not appear to affect the reactivity and enantioselectivity of the reaction. The corresponding

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products were obtained with high yields (72-93%) and good enantioselectivities (80-87 %ee). However, when the alkynylation was performed with an aromatic alkyne with a methoxy group in *ortho* position (**2c**, entries 3 and 4), the chiral sulfamidate was afforded with lower enantioselectivity presumably due to steric effects. Heteroaromatic alkynes (**2f**), were also suitable nucleophiles for this reaction (entries 10-11). Finally, aliphatic alkynes (**2g-2i**) were evaluated, and the corresponding products **3** were gained in moderate to good enantioselectivities (entries 12-17).

Table 4 Enantioselective addition of different terminal alkynes **2** to benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (**1**) .[a]


| Entry	1	2 (R²)	t (h)	3	yield (%)[b]	ee (%)[c]
1	**1a**	**2b** (R²= 4-MeOC$_6$H$_4$)	2	**3ab**	92	81
2	**1b**	**2b** (R²= 4-MeOC$_6$H$_4$)	2	**3bb**	79	87
3	**1a**	**2c** (R²= 2-MeOC$_6$H$_4$)	3	**3ac**	91	65
4	**1b**	**2c** (R²= 2-MeOC$_6$H$_4$)	3	**3bc**	78	68
5	**1a**	**2d** (R²= 3,5-diMeOC$_6$H$_4$)	2	**3ad**	88	80
6	**1b**	**2d** (R²= 3,5-diMeOC$_6$H$_4$)	3	**3bd**	93	82
7[d]	**1f**	**2d** (R²= 3,5-diMeOC$_6$H$_4$)	3	**3fd**	63 (40)[d]	81 (96)[d]
8	**1a**	**2e** (R²= 4-ClC$_6$H$_4$)	3	**3ae**	72	82
9	**1b**	**2e** (R²= 4-ClC$_6$H$_4$)	3	**3be**	75	86
10	**1a**	**2f** (R²= 2-thienyl)	2	**3af**	64	79
11	**1b**	**2f** (R²= 2-thienyl)	3	**3bf**	91	86
12	**1a**	**2g** (R²= PhCH$_2$CH$_2$)	18	**3ag**	63	60
13	**1b**	**2g** (R²= PhCH$_2$CH$_2$)	4	**3bg**	77	66
14	**1a**	**2h** (R²= cyclopropyl)	18	**3ah**	83	74
15	**1b**	**2h** (R²= cyclopropyl)	18	**3bh**	91	78
16	**1a**	**2i** (R²= *t*Bu)	18	**3ai**	71	79
17	**1b**	**2i** (R²= *t*Bu)	18	**3bi**	54	86

[a] **1** (0.090 mmol), **2** (0.360 mmol), 2 M Me$_2$Zn in toluene (0.360 mmol), (*R*)-VAPOL (0.018 mmol). [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Yield and enantiomeric excess after crystallization are given in parentheses

The absolute configuration of the propargylic stereogenic center in compound **3fd** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Figure 2); the configuration of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.[14]
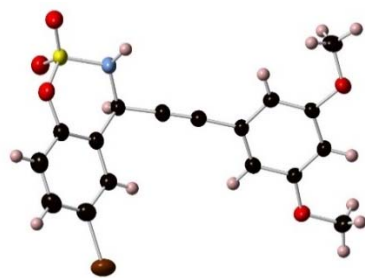
Figure 2 X-ray structure of compound **3fd**.

After the further study of the scope of the reaction, we focused our attention on the synthetic transformations of the product **3aa.** Hydrogenation of the triple bond of **3aa** could be easily carried out with Pd/CaCO$_3$ in a 93% yield, giving product **4** without loss of enantioselectivity (Scheme 3). Moreover, treatment of product **4** with LiAlH$_4$ and subsequent Boc protection, gave the corresponding product **5** without loss of the enantiomeric purity (Scheme 2).
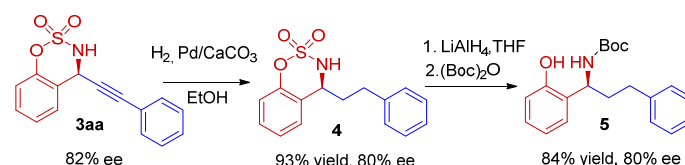
Scheme 2. Synthetic transformations of **3aa**.

Conclusions

In summary, we have described the enantioselective alkynylation of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides catalysed by (*R*)-VAPOL-Zn(II) complexes. This approach has provided a new methodology to synthesize optically active propargylic sulfamidates with high yields and good enantioselectivities. The reaction shows a wide substrate scope for different cyclic *N*-sulfonyl imines and terminal alkynes, both aromatic and aliphatic. Furthermore, synthetic transformations of the chiral propargylic sulfamidate were carried out. The present study extends the scope of the catalytic asymmetric addition of organometallic reagents to benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide.

Acknowledgements

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14   CCDC-1401764 (for **3fd**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre viawww.ccdc.cam.ac.uk/data_request/cif.