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Diarylprolinol as a Ligand for Enantioselective Alkynylation of Cyclic Imines

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

[a] Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain)
E-mail: carlos.vila@uv.es; jose.r.pedro@uv.es

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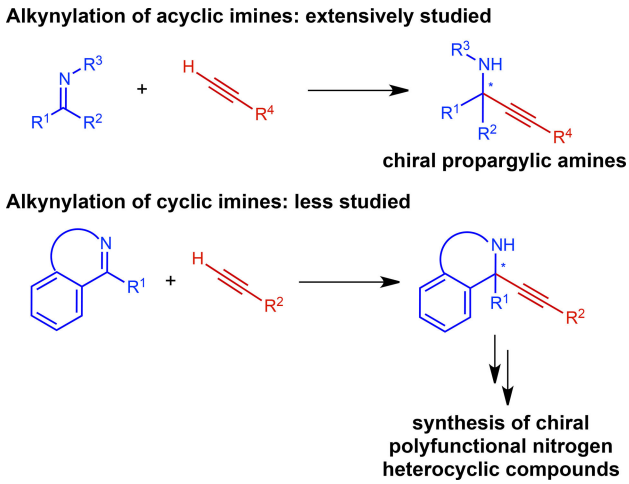
Abstract: An easily accessible prolinol derived ligand, (*S*)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol, has been efficiently applied in the catalytic enantioselective addition of terminal alkynes to cyclic imines using dimethylzinc (Me_2Zn) under mild reaction conditions. The developed catalytic system led to chiral propargylic sulfamidates with high yields (up to 97%) and excellent enantioselectivities (up to 97% ee).

Keywords: asymmetric catalysis; alkynes; zinc; amino alcohol; cyclic imines



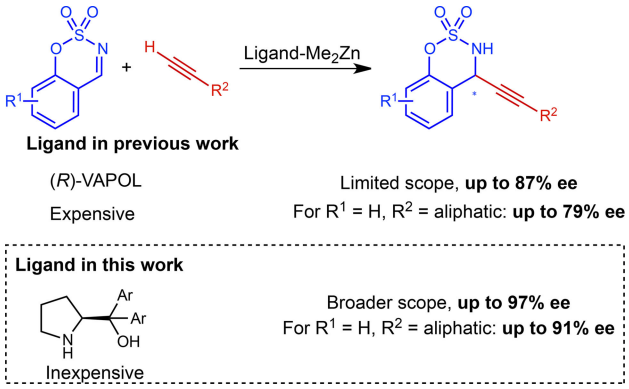
Scheme 1. Enantioselective alkynylation of imines.

The enantioselective alkynylation of imines is one of the most useful carbon-carbon bond-forming reactions for the preparation of chiral propargylic amines,[1] which are versatile building blocks for the synthesis of fine chemicals, pharmaceuticals,[2] agrochemicals[3] and natural products.[4] Recently, a large number of catalytic enantioselective methodologies have been described for the asymmetric addition of terminal alkynes to acyclic imines (Scheme 1).[5] However, the enantioselective alkynylation of cyclic imines is less studied despite their great potential for the synthesis of chiral polyfunctional nitrogen containing heterocyclic compounds.[6]

For example, different methodologies have been described for the enantioselective alkynylation of six membered cyclic *N*-acyl trifluoromethyl activated imines,[7] seven membered cyclic imines such as dibenzoxazepines,[8] and cyclic iminium ions derived from pyridines,[9] tetrahydroisoquinolines,[10] isoquinolines[9b] or quinolines.[9b,11] Another remarkable type of cyclic imines are benzoxathiazine 2,2-dioxides, which have proven to be versatile building blocks in asymmetric synthesis and in the construction of chiral benzofused cyclic sulfamidate heterocycles by the addition of organometallic nucleophiles.[12] Nevertheless, the alkynylation of benzoxathiazine 2,2-dioxides that affords chiral propargylic sulfamidates has been scarcely studied.[13]

Sulfamidates are an interesting class of amine derivatives present in some pharmaceuticals and biological active compounds[14] and they also play an important role as building blocks for organic synthesis.[15] For this reason, we focused our efforts in the preparation of chiral propargylic sulfamidates by the direct addition of terminal alkynes to cyclic benzoxathiazine 2,2-dioxides. We have recently reported this reaction by using dimethylzinc and (*R*)-VAPOL as catalyst.[13] However, the reaction did not proceeded with high enantioselectivities (56 to 87% ee) and only a limited number of cyclic imines and aliphatic alkynes were tolerated. In addition, we were not satisfied with the use of the commercially available but expensive (*R*)-VAPOL.[16] We believe that the success of an enantioselective catalytic process also implies the utilization of easily accessible and inexpensive ligands. Therefore, we decided to continue studying the

alkynylation of benzoxathiazine 2,2-dioxides in order to develop an enhanced methodology by using a more simple and economical ligand that could afford better enantioselectivities (Scheme 2). For this purpose, we thought in the use of chiral amino alcohols as chiral ligands.



Scheme 2. Enantioselective alkynylation of cyclic benzoxathiazine 2,2-dioxides.

Chiral amino alcohols have been used in several zinc mediated alkynylation reactions of aldehydes,[17] ketones[18] and imines,[19] because amino alcohol-Zn catalytic systems are particularly noteworthy in terms of its operational simplicity and mild reaction conditions. However, chiral amino alcohols have been rarely used in catalytic enantioselective alkynylation of cyclic imines. Among the chiral amino alcohols described in the literature, chiral diarylprolinols are a very convenient class of ligands for asymmetric catalysis as they can be easily prepared from proline and, in some cases, are commercially available. Therefore, we decided to apply this kind of ligands in enantioselective alkynylation reactions. Herein, we report a highly efficient catalytic system for the alkynylation of cyclic benzoxathiazine 2,2-dioxides using a diarylprolinol-Zn(II) complex as catalyst, affording the corresponding chiral propargylic sulfamidates with higher enantiomeric excesses than with the previously described catalytic system.[13]

We initiated our studies by evaluating the addition of phenyl-acetylene (**2a**) to cyclic benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (**1a**) in the presence of a series of diarylprolinol-Zn(II) complexes. A 1.2 M Me_2Zn solution in toluene (4 eq.) was added dropwise to a solution of ligand **L** (0.2 eq.) and phenylacetylene (7 eq.) in toluene at room temperature. After stirring for 0.5 h the reaction mixture, a solution of the cyclic imine **1a** in toluene was added. Under these reaction conditions, several diarylprolinol-type ligands **L1**–**L4** were tested (Table 1, entries 1–4). When ligands **L1**, **L2** and **L4** were used, the corresponding chiral propargylic sulfamidates **3aa** were obtained with good yields (80–86%) but moderate enantioselectivities (53–59% ee). Gratefully, when (*S*)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol (**L3**) was utilized as a ligand, product **3aa** was gained with 90% yield and high enantioselectivity (93% ee) (entry 3, Table 1). However, we observed the formation of product **4**, obtained by the addition of Me_2Zn to the cyclic imine **1a.** Although the ratio between product **3aa:4** was not significant (1:0.05, determined by ^1H NMR), we wanted to avoid the formation of product **4.** Therefore, different solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, Et_2O and MTBE were tested (entries 5–8, Table 1). Utilization of chlorinated solvents resulted in a decreased enantioselectivity of the reaction, whereas the use of ethereal solvents led to high enantiomeric excess, but had a negative influence on the yield. Et_2Zn was also tested as a zinc reagent (entry 9, Table 1); however, higher amount of the addition of Et_2Zn to the imine **1a** was observed. In order to avoid the formation of this undesired product, we generated the chiral zinc complex at higher temperature, obtaining product **3aa** with higher yield and selectivity (entry 10, Table 1). When we performed the reaction at 0 °C (entry 12, Table 1), we could increase the enantiomeric excess to 97%, without compromising the yield (96%). Finally, lowering the amount of Me_2Zn to 3 equivalents or the ligand amount to 10 mol% had a detrimental effect on the enantioselectivity (entries 13 and 14, respectively).

With the optimized reaction conditions in our hands (entry 12, Table 1), we turned our attention to stablishing the scope with respect to both the cyclic imines **1** and alkynes **2** (Scheme 3 and 4). First, we explored the reaction with several terminal alkynes bearing different electronic and steric demands (Scheme 3). The electronic properties of the aromatic ring of the terminal alkynes affected slightly the enantioselectivity of the reaction. The presence of a methoxy group in the *para* position resulted in the formation of **3ab** with excellent yield (96%) and excellent enantioselectivity (97% ee). The use of *para*-chloro-ethynylbenzene (**2c**) gave the corresponding product **3ac** with 97% yield and high enantiomeric excess (90% ee). An alkyne bearing a substituent in *meta* gave **3ad** in excellent yield and 91% ee. Remarkably, when the alkynylation was performed with an aromatic alkyne having a methoxy group in the *ortho* position (**2e**), the chiral sulfamidate **3ae** was afforded with excellent enantioselectivity (95% ee). Heteroaromatic alkynes (**2f** and **2g**) were also suitable nucleophiles for this reaction, and the corresponding chiral products **3af** and **3ag** were obtained with enantioselectivities up to 94% ee. Finally, in order to fully study the scope of the reaction, aliphatic alkynes (**2h**–**2l**) were evaluated. The reactions were performed at room temperature since this allowed to

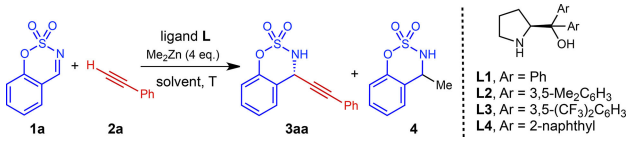
obtain high conversions and good enantioselectivities. When but-3-yn-1-ylbenzene (**2h**) or hex-1-yne (**2i**) were used, the corresponding products were obtained with a lower enantiomeric excess (80% ee). The more hindered 3,3-dimethylbut-1-yne **2j** gave better enantioselectivity (88% ee). Alternatively, employment of cyclic terminal alkynes such as ethynylcyclopropane (**2k**) and ethynylcyclopentane (**2i**) led to the corresponding sulfamidates **3ak** and **3al** in high yields and enantiomeric excesses over 90%.

After studying the reaction with different alkynes, we focused our attention in the use of various benzoxathiazine 2,2-dioxides **1** (Scheme 4).[20] Both electron-donating and electron-withdrawing groups with different steric demand in the 6 position (**3ba**–**3ea**) were well tolerated, obtaining high yields and good to high enantiomeric excesses (80% to 96% ee). A cyclic imine bearing a substituent in the 8 position gave product **3fa** in 85% yield and 94% ee. However, the presence of a methoxy group in the 5 position led to a decrease in the enantioselectivity of the reaction (**3ga**, 76% yield, 70% ee). Remarkably, the sterically hindered cyclic imine **1h** with two *t*Bu substituents was a suitable substrate for the alkynylation reaction, affording the desired product **3ha** with excellent enantiomeric excess (97% ee). An imine containing a naphthyl group could also be applied in the reaction giving **3ia** in good yield (84%) and enantioselectivity (86% ee).

Furthermore, we performed several synthetic transformations with the chiral propargylic sulfamidate **3aa** (Scheme 5). By hydrogenation of the triple bond, compound **4** could be prepared (81% yield), which by treatment with $LiAlH_4$, followed by a Boc protection, gave the corresponding product **5** (78% yield) with a slightly decrease in the optical purity of **3aa**.

A plausible mechanism for the enantioselective alkynylation reaction using a prolinol-derived ligand is shown in Scheme 6. Similarly to the alkylation with Me_2Zn or Et_2Zn catalyzed by amino alcohols, complex **A** is generated by the reaction of ligand **L3** and Me_2Zn, which is in equilibrium with the more stable dimer complex **B.**[21,22] Complex **A** is also in equilibrium with complex **C**, where a methyl alkynyl organozinc species has coordinated to the oxygen atom of complex **A**. This is followed by the coordination of benzoxathiazine 2,2-dioxide to the Zn atom chelated by the amino alcohol, because to its higher Lewis acidity among both Zn atoms, generating complex **D.** It is known that, in alkylzinc acetylides,[23] the alkynyl moiety is more reactive than the alkyl one and, therefore, the acetylide is transferred to the *Re* face of the cyclic imine generating the chiral propargylic zinc sulfamidate complex **E**. Once the sulfamidate is released to further afford the final product **3**, another methyl alkynyl organozinc specie is coordinated to the zinc alkoxide monomer regenerating complex **C**.

Table 1. Optimization of the reaction conditions.[a]

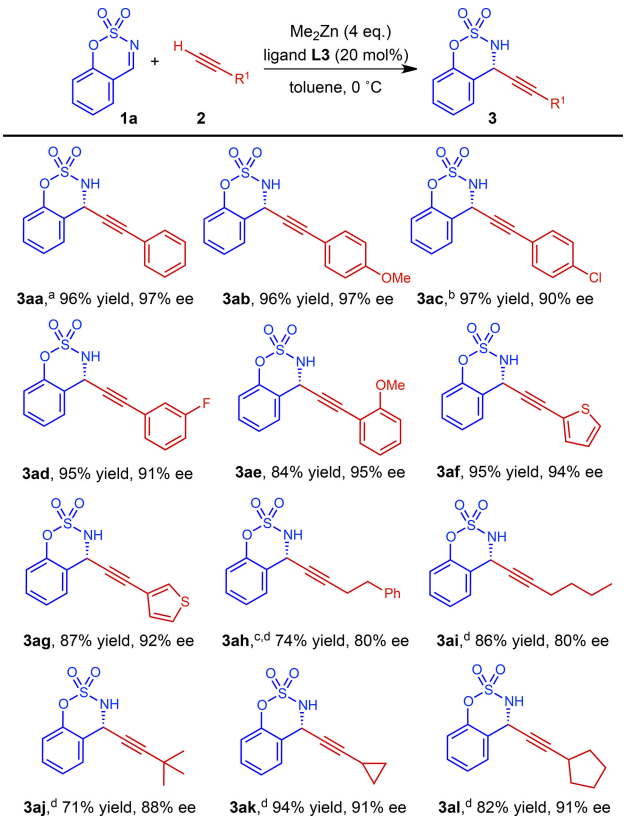


1a 2a 3aa 4

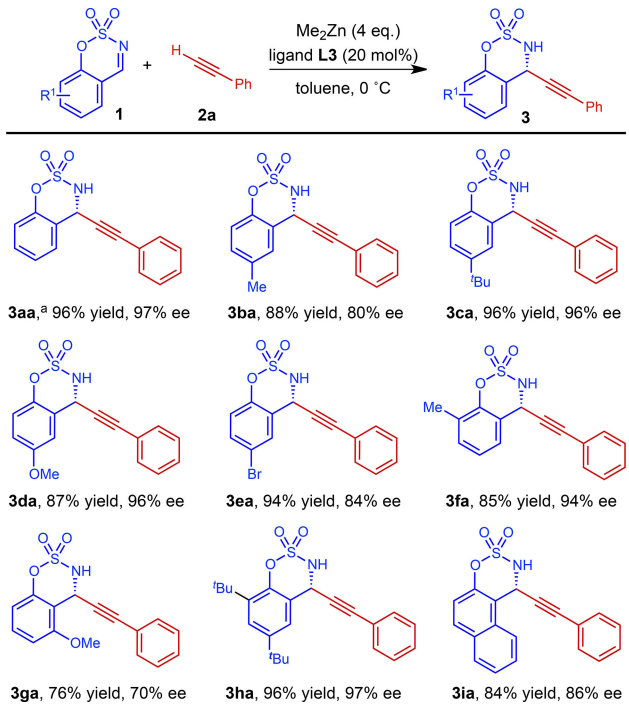
Entry	L (x mol%)	Solvent	T (°C)	Yield (%)[b]	3aa:4[c]	ee (%)[d]
1	**L1** (20)	toluene	rt	80	1:0	53
2	**L2** (20)	toluene	rt	85	1:0	57
3	**L3** (20)	toluene	rt	90	1:0.05	93
4	**L4** (20)	toluene	rt	86	1:0	59
5	**L3** (20)	CH_2Cl_2	rt	84	1:0	87
6	**L3** (20)	DCE	rt	90	1:0.03	83
7	**L3** (20)	Et_2O	rt	57	1:0.01	93
8	**L3** (20)	MTBE	rt	70	1:0.08	91
9[e]	**L3** (20)	toluene	rt	72	1:0.3[f]	87
10[g]	**L3** (20)	toluene	rt	96	1:0.02	93
11[g]	**L3** (20)	toluene	0	98	1:0.03	96
12[h]	**L3** (20)	toluene	0	96	1:0.01	97
13[h,i]	**L3** (20)	toluene	0	97	1:0.03	95
14[h]	**L3** (10)	toluene	0	87	1:0.05	86

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.7 mmol), 1.2 M Me_2Zn in toluene (0.4 mmol) and ligand **L** (x mol%) in 1.5 mL of solvent.
[b] Isolated yield after column chromatography.
[c] Determined by ^1H NMR.
[d] Determined by HPLC using chiral stationary phase.
[e] Et_2Zn (0.4 mmol) was used.
[f] The ethylation product was observed.
[g] The chiral zinc complex was formed at 70 °C for 0.5 h.
[h] The chiral zinc complex was formed at 70 °C for 1 h.
[i] 3 eq. of Me_2Zn were used.

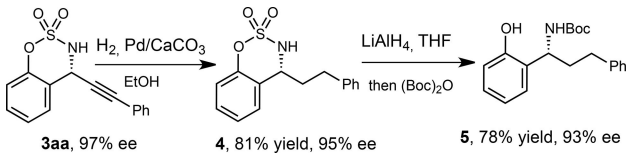
In conclusion, we have successfully developed a highly enantioselective alkynylation of benzo[*e*][1,2,3]-oxathiazine 2,2-dioxides catalyzed by chiral diaryl-prolinol-Zn(II) complexes. The corresponding chiral propargylic sulfamidates are obtained with good yields (up to 97%) and good to excellent enantioselectivities (up to 97% ee). This methodology features the use of economical and commercially available (*S*)-bis(3,5-bis (trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol **L3** as a chiral ligand for the enantioselective alkynylation of benzoxathiazine 2,2-dioxides under mild reaction conditions and provides access to highly optically pure chiral propargylic sulfamidates, important chiral building blocks in organic synthesis.



Scheme 3. Scope of the alkynylation of cyclic imines: **1a** (0.1 mmol), **2** (0.7 mmol), 1.2 M Me_2Zn in toluene (0.4 mmol) and **L3** (20 mol%) in toluene at 0 °C. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.



Scheme 4. Scope of the alkynylation of cyclic imines: **1** (0.1 mmol), **2a** (0.7 mmol), 1.2 M Me_2Zn in toluene (0.4 mmol) and **L3** (20 mol%) in toluene at 0 °C. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase. [a] 1:0.01 ratio of alkynylation:methylation product.



Scheme 5. Synthetic transformations of product **3aa**.

Experimental Section

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 **L3** (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 solution 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 (3×15 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 afforded compound **3**.

Acknowledgements

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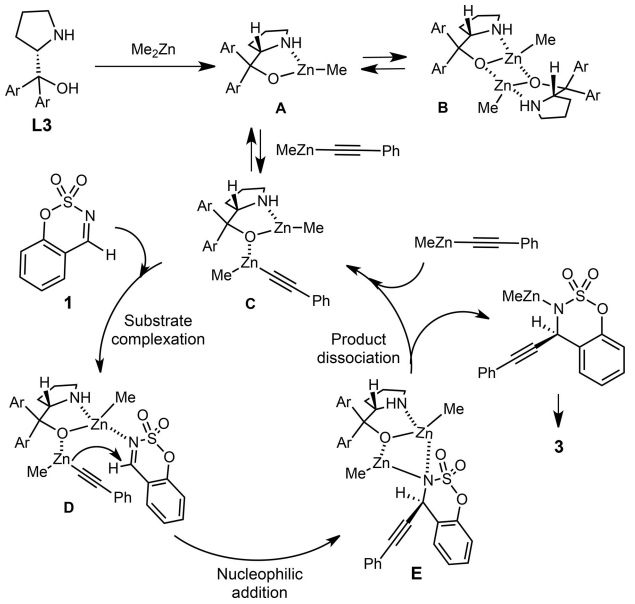

Scheme 6. Plausible mechanism of the enantioselective alkynylation using a prolinol-type ligand.

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Diarylprolinol as a Ligand for Enantioselective Alkynylation of Cyclic Imines

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L. De Munck, A. Monleón, C. Vila*, J. R. Pedro*