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Accessing Enantiopure Endocyclic Sulfoximines Through Catalytic Cycloisomerization of Oxygenated Propargyl-Sulfinamides

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Abstract. In this study, a novel strategy to access endocyclic sulfoximines in an enantiopure form is reported. The approach is based on a silver nitrate-catalyzed cyclo-isomerization reaction of oxygenated propargylic sulfinamides and provides efficiently 5-membered endocyclic sulfoximines (isothiazole 1-oxide). These new heterocyclic scaffolds can be isolated or directly converted into cyclic sulfinamides via Lewis acid-mediated sulphur dealkylation reactions.

Keywords: Cyclization, Homogenous catalysis, Silver, Sulfoximine, Sulfinamide, Acetylenic ethers

The preparation and functionalization of sulfoximine derivatives have found an increasing interest over the past decades.[1] These mono-aza analogs of sulfones, presenting a sulfur-centered chirality, have found successful applications in organic synthesis as directing-groups,[2] chiral auxiliaries[3] or chiral ligands in metal catalysis.[4] They have also entered the realm of agrochemical sciences with the insecticide sulfoxalor, the so far sole marketed sulfoximine derivative, as well as in the field of medicinal chemistry as bio-isosteres of sulfones, carboxylic acids or amidines (Figure 1).[5]

In many cases, and especially for the use of sulfoximine in catalysis, the control of the absolute configuration of the sulfur center proved of major importance. Despite this growing interest, only a few methods are currently available for the synthesis of enantiopure sulfoximines, relying mainly on resolution of racemic mixtures,[6] the stereospecific imidation of enantioenriched sulfoxides[7] and oxidation of enantioenriched sulfimides,[8] or imidative kinetic resolution of racemic sulfoxides.[9] Owing to the interest of heterocyclic compounds in medicinal chemistry, different strategies to access cyclic sulfoximines have also been developed, especially for the synthesis of 6-membered and benzo-fused derivatives.[10] The preparation of 5-membered cyclic sulfoximines remains less explored[11] and their synthesis in enantiopure form is limited to rather rare examples.[11c,e,f,h]

Following our studies on the synthesis of enantiopure oxygenated propargyl-sulfinamides,[12] we envisioned that these unique substrates could provide an easy access to unprecedented enantiopure 5-membered endocyclic sulfoximines, through a simple cycloisomerization reaction, capitalizing on the activation of the electron-rich oxygenated triple bond by π-acidic transition metal catalysts.[13]

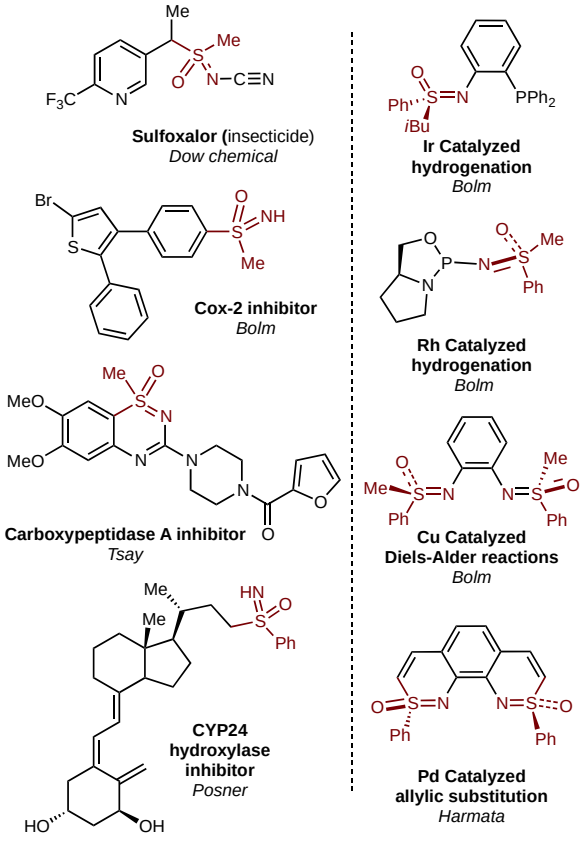

Figure 1. Examples of bioactive sulfoximines and sulfoximine-based chiral ligands for asymetric catalysis

This study began with sulfinamide **3a**, obtained in a single step from the corresponding enantiopure *tert*-

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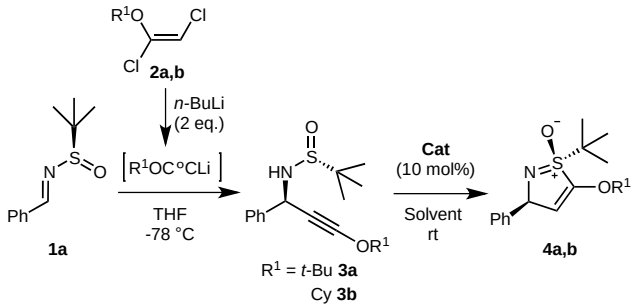
butanesulfinylimine **1a** by diastereoselective addition of the *in situ* generated lithio acetylenic ether, obtained by reaction of dichloroenol ether **2a** with *n*-butyllithium. A variety of π-acid metals were tested in dichloromethane for their ability to promote a cyclisation. Disappointingly, a very fast decomposition of the somewhat sensitive starting sulfinamide acetylenic ether **3a** was observed with $PtCl_2$, $PdCl_2$, $AuNTf_2$ or $AgNO_3$ (Table 1, entries 1-4); the presence of cinnamic derivatives in the crude mixture seemed to point out a cleavage of the C-N bond under the reaction conditions. Indeed, performing the reaction in MeOH provided almost quantitatively methyl cinnamate (Table 1, entry 5), the result of the cleavage of the carbon-nitrogen bond along with the loss of the asymmetric sulfur center (Scheme 1, chart A). We then hypothesized that introducing a less labile group on the oxygen atom could prevent this side reaction pathway, and a similar screening was conducted with sulfinamide **3b**, bearing a cyclohexyl ether instead of a *tert*-butyl ether. This substrate proved more robust, as it could be fully recovered in the presence of platinum (II) dichloride (Table 1, entry 6). However, the use of palladium (II) chloride or gold(I) triflimide did not yield the expected heterocycle: a fast disappearance of the sulfinamide was observed, along with the generation of several unidentified byproducts (Table 1, entries 7 and 8). To our delight, when a catalytic amount of silver(I) nitrate was employed, the sulfoximine **4b** could be obtained after 30 minutes of reaction. However, we could not solve a problem of poor reproducibility in this solvent with yields varying from 40 to 83 % (Table 1, entry 9). Changing the solvent from dichloromethane to anhydrous THF was highly rewarding, with a very clean reproducible reaction, yielding **4b** in 92 % yield after chromatography, as the sole product of the reaction (Table 1, entry 10).

Table 1. Formation of sulfinamide **3**, and optimisation of the cycloisomerization reaction.



Entry	Substrate	**Cat.**	Solvent	Time	Yield [%]
1	**3a**	$PtCl_2$	DCM	60	0
2	**3a**	$PdCl_2$	DCM	60	0
3	**3a**	$AuNTf_2$	DCM	60	0
4	**3a**	$AgNO_3$	DCM	30	0
5	**3a**	$AgNO_3$	MeOH	30	0[a]
6	**3b**	$PtCl_2$	DCM	60	0[b]
7	**3b**	$PdCl_2$	DCM	90	0
8	**3b**	$AuNTf_2$	DCM	60	0
9	**3b**	$AgNO_3$	DCM	30	40-83[c]
10	**3b**	$AgNO_3$	THF	30	92

[a] Full conversion to methyl cinnamate was observed. [b] Recovery of the starting sulfinamide. [c] Low reproducibility was observed.

The structure of ***ent*-4b** was unambiguously ascertained by X-Ray diffraction showing an opposite absolute configuration at the sulfur atom, due to priority changes, as a result of the nucleophilic attack on the acetylenic ether, sign of the direct interaction of the sulfur lone pair with the activated triple bond (Scheme 1). This X-ray was crucial to rule out a putative formation of a six-membered ring, arising from the nucleophilic attack of the oxygen atom of the sulfinamide on the activated triple bond. A mechanistic proposal to explain the results of metal activation is depicted on Scheme 1. The silver ion coordinates the electron-rich triple bond,[14] enhancing its electrophilicity toward a nucleophilic attack by the sulfur atom. A 5-endo dig cyclisation occurs, thus generating intermediates of type **I**. In the case of **Ia**, the *tert*-butyl group is labile enough to promote a Meyer-Schuster type rearrangement providing a cinnamyl derivative of type **II**, that subsequently degrades in DCM or generate methyl cinnamate in MeOH, via nucleophilic displacement of the sulfur-containing moiety (Scheme 1, case A). In the case of **Ib**, its higher stability allows for a protonation of the Csp^2-silver bond (either by H-shift or intermolecularly), along with the formation of the N-S double bond of sulfoximine **4b** (Scheme 1, case B).

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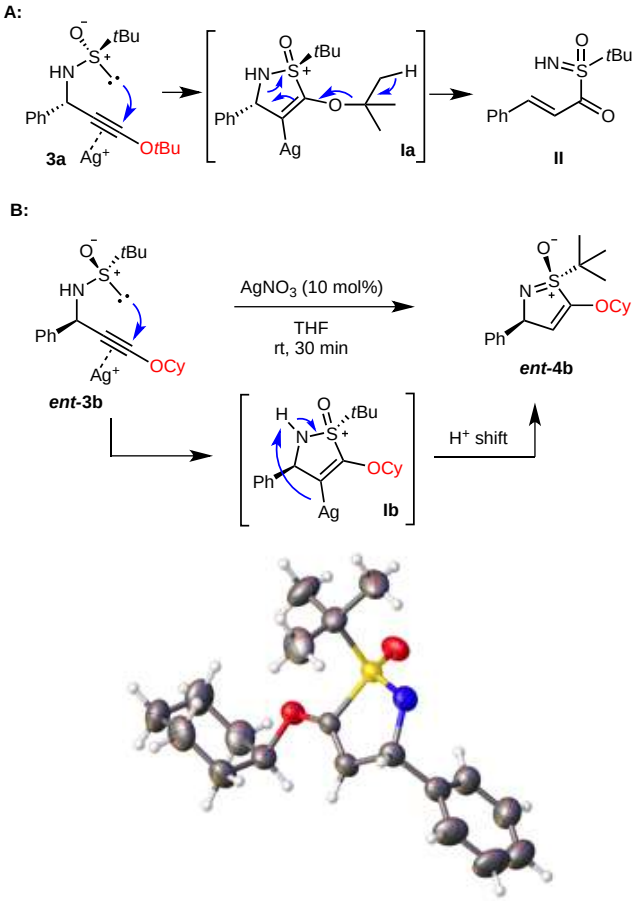
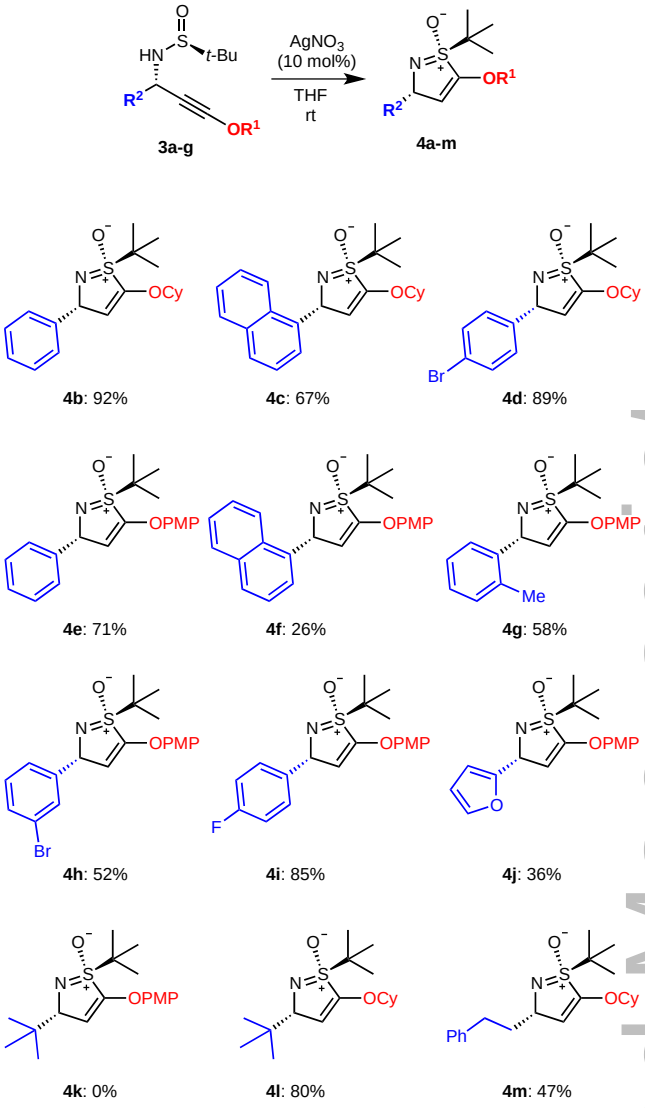


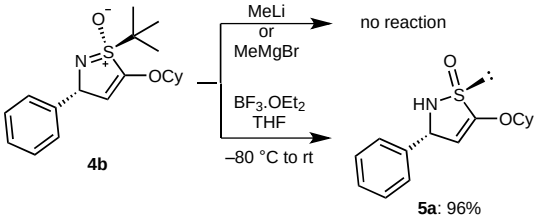
Scheme 1: Mechanistic proposal for the degradation of **3a** (A) and for the formation of **4b** (B) in the presence of silver nitrate; X-ray structure of sulfoximine ***ent*-4b** (obtained from the enantiomer of **3b**)

With optimal cyclisation conditions in hand, a variety of oxygenated propargyl sulfinamides were prepared[12] from both aromatic and aliphatic sulfinylimines bearing cyclohexyl and *p*-methoxyphenyl acetylenic ethers, in order to study the scope of the reaction. The results of the silver-catalyzed cycloisomerization to 5-membered cyclic sulfoximines are summarized in Scheme 2. Modifications on the aromatic part were well tolerated, as the naphthyl (**4c**) and a *p*-bromophenyl-substituted (**4d**) derivatives were obtained with similar efficiencies compared to the phenyl one. The use of *p*-methoxyphenyl (PMP) acetylenic ether proved successful with different aromatic or heteroaromatic substituents: phenyl, *o*-tolyl, *m*-bromophenyl and *p*-fluorophenyl were all effective for the formation of the cyclic sulfoximines (**4e,g,h,i**), whereas the naphthyl and furyl proved less compatible, with lower yields of the products (**4f**, 26 % and **4j**, 36 %). Starting with alkyl substituents at the propargylic position proved somewhat puzzling: the PMP derivative (**4k**) could not be obtained whereas the cyclohexyl cyclic sulfoximine **4l** could be secured in very high yield (80 %). With the dihydrocinnamyl derivative **3m**, the cyclized product **4m** could still be obtained, albeit in a much lower yield (47%).



Scheme 2. Scope of the silver catalyzed cycloisomerization of oxygenated propargyl-sulfinamides **3**.

We next turned our attention on exploring the reactivity of these novel heterocyclic scaffolds. Attempts to react compound **4b** with organometallic species such as MeLi or MeMgBr did not lead to any nucleophilic addition, but treatment by Lewis acids such as boron trifluoride triggered the loss of the *tert*-butyl group attached to the sulfur atom, yielding the cyclic sulfinamide **5b** in high yield (Scheme 3).[15] We could ascertain the relative configuration of the product as *cis* with X-ray structures of two products (**5d** and **5f**).



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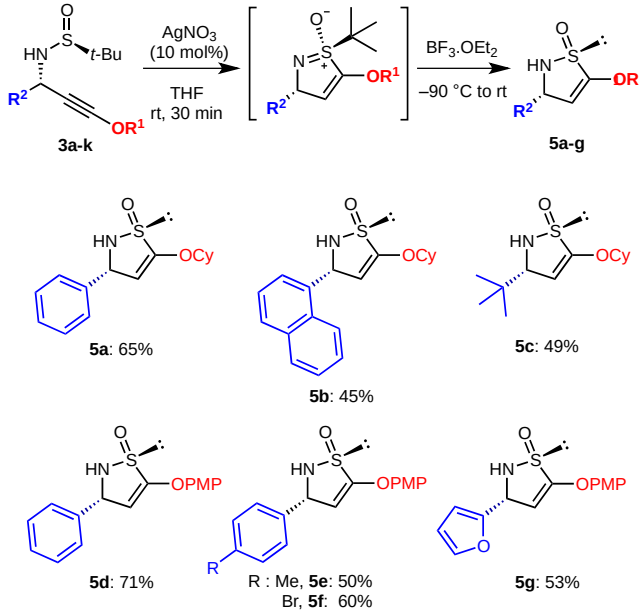
Scheme 3. Reactivity of the cyclic sulfoximine **4b**

Interestingly, this derivative could also be obtained in a one-pot procedure, by directly treating the cycloisomerization reaction mixture at –80 °C by the Lewis acid. In this way, different cyclic sulfinamides were rapidly prepared from the corresponding propargylic sulfinamides (Scheme 4), using aromatic and aliphatic substituents at both the propargylic center and the acetylenic ether part. The phenyl, naphthyl and *tert*-butyl cyclohexyloxy-tethered cyclic sulfinamides **5b-d** were all obtained in fair yields over the two steps one pot process. With a PMP-ether, the cyclic sulfinamides **5e-h** bearing aromatic substituents at the initial propargylic position were obtained in good yields over the two steps.



Scheme 4. Scope of the one pot preparation of cyclic sulfinamides

To conclude, a range of new 5-membered heterocycles incorporating an enantiopure sulfoximine motif were prepared via a silver-catalyzed 5-endo-dig cyclisation of oxygenated propargyl-sulfinamides. The products could be converted into the corresponding cyclic sulfinamides upon de-*tert*-butylation reaction triggered by boron trifluoride. The reactivity of these new heterocyclic scaffolds is still underway as well as the study of potential bio-activities of this unprecedented family of heterocycles.

Experimental Section

Typical procedure for the silver catalyzed cyclisation:

To a solution of **3b-l** (0.1 mmol) in dry THF (0.06 M) at room temperature was added silver nitrate (10 mol%, 0.01 mmol). The reaction was monitored by TLC (eluent AcOEt/Pentane 40:60) until disappearance of the starting material (30 minutes). The reaction mixture was then filtered over celite, washed with dichloromethane and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel to afford pure **4b-l**.

Typical procedure for the one-pot synthesis of cyclic sulfinamides 5b-h:

To a solution of **3b-l** (0.1 mmol) in dry THF (0.06 M) at room temperature was added silver nitrate (10 mol%, 0.01 mmol). After disappearance of the starting material (30 to 60 min), the reaction was cooled to 78 °C and $BF_3.Et_2O$ (1.1 eq) was added dropwise. The reaction mixture was then allowed to warm to room temperature over one hour. The reaction was quenched with diluted $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduce pressure. The purification of the crude material by flash chromatography on silica gel yielded the pure cyclic sulfinamides **5b-h**.

CCDC-1579950, 1579951, and 1579952 contains the supplementary crystallographic data for compounds *ent*-**4b**, **5d**, and **5f** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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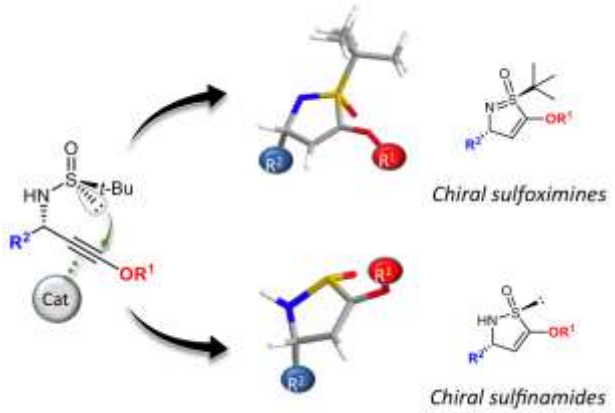

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