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Access to 1,4-Thiazepanes via Gold-Catalyzed 7-*exo*-dig Thioallylation and their Cycloisomerization to Bicyclic [4.3.1] Bridgehead-Olefinic Systems

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Abstract. A series of 1,4-thiazepanes were synthesized using gold-catalysis from 1,3-aminothioethers having two or three carbon stereocenters. The process consists in a 7-*exo*-dig cyclization with C-S bond formation and concomitant allyl S-to-C migration, which occurs intramolecularly as demonstrated by a cross-over experiment. X-ray crystal-structure analysis of one product confirmed the expected stereochemistry. Two examples of reactions, azide-alkyne cycloaddition (CuAAC) and *N*-alkylation, illustrate the potential post-functionalization of the synthesized 1,4-thiazepanes. Finally, the *N*-propargyl 1,4-thiazepanes underwent a sulfur-assisted 1,6-enyne cycloisomerization, which led through a 6-*exo*-dig cyclization to *N,S*-heterobicyclo[4.3.1] systems with a bridgehead double bond.

Keywords: Gold catalysis; Carbothiolation; Cycloisomerization; Thiazepanes; Heterocycles

Introduction

Gold-catalyzed cyclizations have become a well-recognized powerful method for the preparation of various heterocycles, which are valuable compounds in the fields of pharmaceutical, agrochemical and materials chemistry.^[1] The recent review published by Sawamura and co-workers testifies to the interest of the organic chemists' community in accessing challenging 7-membered rings and medium-sized rings (8 to 11 atoms), including heterocycles, by gold-mediated cyclization.^[2] Indeed, these molecular structures are interesting due to their presence in bioactive natural products and pharmaceuticals, however they are renowned for their limited accessibility. The intramolecular carbon-heteroatom bond formation involving the attack of a heteronucleophile on the gold-activated triple bond represents a common method to synthesize 5- and 6-membered heterocycles, but rarely used for the direct construction of larger rings.^[1-3] Only a few examples have been reported with nitrogen^[4] and oxygen^[5] nucleophiles, leading to 7-membered or medium-sized *O*- and *N*-heterocycles. In some of these cases, the 7-*exo* and 8-*endo*-dig cyclization modes have been competing. To our knowledge, there are no example of sulfur nucleophiles involved in this type of cyclization.^[6]

Recent research of our group focused on the synthesis of medium-sized *N,S*-heterocycles,^[7] which are poorly represented in the class of heterocyclic therapeutic agents,^[8] with only three 7-membered ring representatives^[9] (Figure 1).

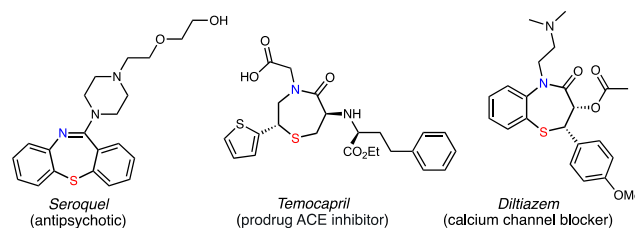
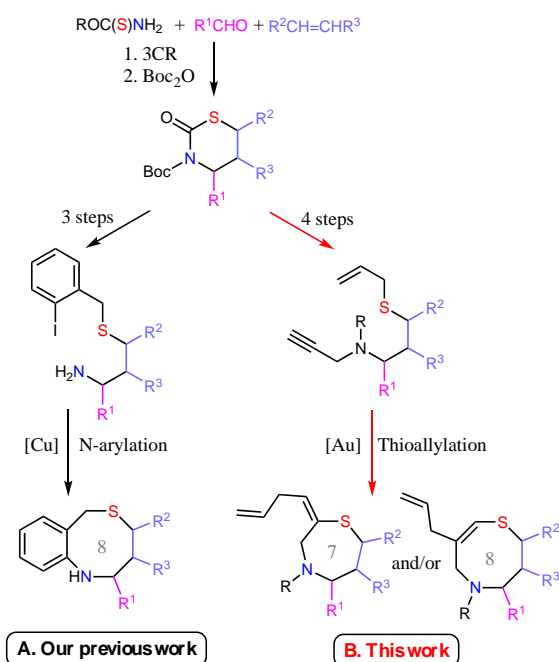


Figure 1. Therapeutic agents containing 7-membered *N,S*-heterocycles

Thus, in a previous work we developed an access to chiral (racemic and enantioenriched) 8-membered *N,S*-heterocycles via an intramolecular copper-catalyzed C-N bond formation (Scheme 1, A).^[7b] The strategy consisted in a few steps synthesis starting with a three-component cycloaddition involving an *O*-alkyl thiocarbamate, an aldehyde and an olefin, leading to 1,3-thiazin-2-ones with two or three stereogenic carbon atoms^[10] The latter were transformed into appropriately functionalized 1,3-aminothioethers, which led by intramolecular *N*-arylation to the targeted benzothiazocines. Herein we propose to access new thiazepanes and/or thiazocines starting from appropriately designed *N*-propargyl *S*-allyl 1,3-aminothioethers precursors by gold-catalyzed intramolecular carbothiolation^[11], also called thioallylation^[12] (Scheme 1, B). This approach would represent the first intramolecular C-S bond

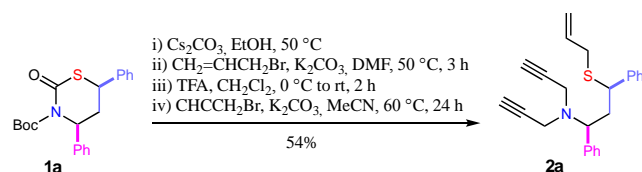
formation using gold catalysis leading to medium-sized heterocycles.



Scheme 1. Synthesis of 7- or 8-membered *N,S*-heterocycles by intramolecular metal-catalyzed carbon-heteroatom bond formation.

Results and Discussion

N,N-dipropargyl *S*-allyl aminothioether **2a** was chosen as the model substrate for the development of the proposed gold-catalyzed intramolecular thioallylation. It was prepared in four steps starting from the *N*-Boc 1,3-thiazin-2-one **1a**^[7b] and isolated in a satisfactory overall yield of 54% as a single syn-stereoisomer (Scheme 2).

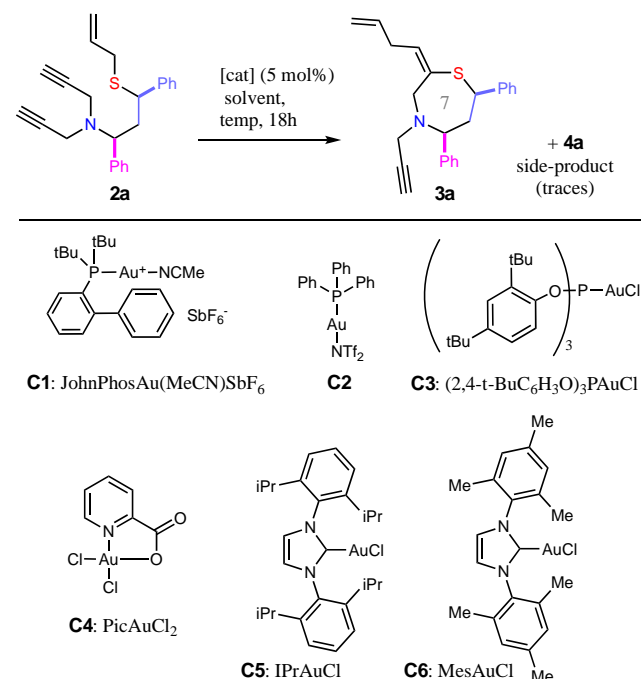


Scheme 2. Synthesis of aminothioether substrate **2a**.

To establish the optimal conditions, the progress of the reaction with substrate **2a** was monitored by thin-layer chromatography (TLC). After 18 hours the reaction was stopped and the obtained crude mixture was analyzed by ¹H NMR. At 60 °C, in dichloroethane, in the presence of 5 mol% of JohnPhosAu(MeCN)SbF₆ complex **C1** (Echavarren catalyst), after 18 hours, substrate **2a** was partially converted, and the mainly formed product was isolated in 14% yield (Table 1, entry 1). Its structure was assigned by NMR spectroscopy to the 7-membered

N,S-heterocycle **3a**. Signals of a side-product **4a** were visible in traces (< 5%) on the ¹H NMR spectra.

Table 1. Optimization of the Au-catalyzed intramolecular thioallylation to obtain **3**.



entry	catalyst	solvent	T (°C)	Conv % (ratio 2a/3a) ^[a]
1	C1	DCE	60	23 (1/0.3) ^{[b],[c]}
2	C1	DCE	90	23 (1/0.3) ^[b]
3	C1	DMF	90	0 (1/0)
4	C2	DCE	60	28 (1/0.4)
5	C3/AgSbF₆	DCE	60	23 (1/0.3)
6	C4	DCE	60	44 (1/0.8)
7	C4	Dioxane	60	28 (1/0.4)
8	C4	Toluene	60	16 (1/0.2)
9	C4	THF	60	28 (1/0.4)
10	C4	iPrOH	60	9 (1/0.1)
11	C5/AgSbF₆	DCE	60	100 (0/1) ^{[b],[d],[e]}
12	C6/AgSbF₆	DCE	60	41 (1/0.7)
13	C5	DCE	60	0 (1/0)
14	AgSbF ₆	DCE	60	0 (1/0)

^[a] Measured by ¹H NMR in the crude mixture.

^[b] Traces of a side-product **4a** were observed in the crude mixture.

^[c] **3a** was isolated in 14% yield.

^[d] The conversion into **3a** was total after 4h.

^[e] **3a** was isolated in 87% yield.

Heating to 90 °C did not improve the conversion, however the amount of the side-product **4a** increased slightly to around 10% (entry 2). This allowed us to confirm that its signals did not correspond to thiazocine resulting from a possible 8-*endo*-dig cyclization. The thioallylation proceeds thereby selectively via a 7-*exo*-dig cyclisation leading to thiazepanes. Of note, compound **4a** was eventually isolated and its structure and formation will be discussed later. In almost all cases, only **2a** and **3a**

were observed in the crude mixture and products derived from the triple bond hydration were never detected. With the same catalyst **C1**, in DMF as the solvent, the reaction did not take place (entry 3). Additional experiments using catalyst **C2** ($\text{PPh}_3\text{AuNTf}_2$) and the phosphite-based catalyst **C3** gave results similar to that obtained with **C1** in the same conditions (entries 4 & 5 vs entry 1). The gold(III) complex PicAuCl_2 (**C4**) gave a better conversion (entry 6), but the use of other solvents than DCE was less effective (entries 7 to 10). We then turned to hindered *N*-heterocyclic carbenes (NHC) ligands, by testing two gold complexes generated respectively from IPrAuCl (**C5**) or MesAuCl (**C6**) and AgSbF_6 (entries 11 & 12). After only 4h, the first catalyst completely converted substrate **2a** to the desired product **3a**, with barely visible traces of the side-product **4a** (entry 11). Thiazepane **3a** was isolated in this case with a very good yield of 87%. The second NHC ligand was less effective leading again to an incomplete conversion (entry 12). Finally, we carried out two control experiments proving that IPrAuCl (**C5**) alone, as well as AgSbF_6 alone, did not allow access to **3a** (entries 13 & 14) and that the active catalytic species is the cationic complex IPrAuSbF_6 formed in situ. The X-ray crystallographic analysis of a single crystal obtained from **3a** allowed to unambiguously assign the stereochemistry of the compound and confirmed the *trans* thioallylation (Figure 2 and SI).^[13]

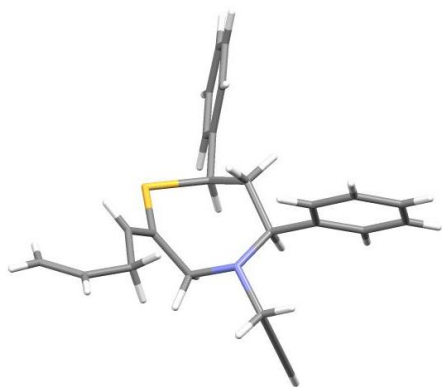
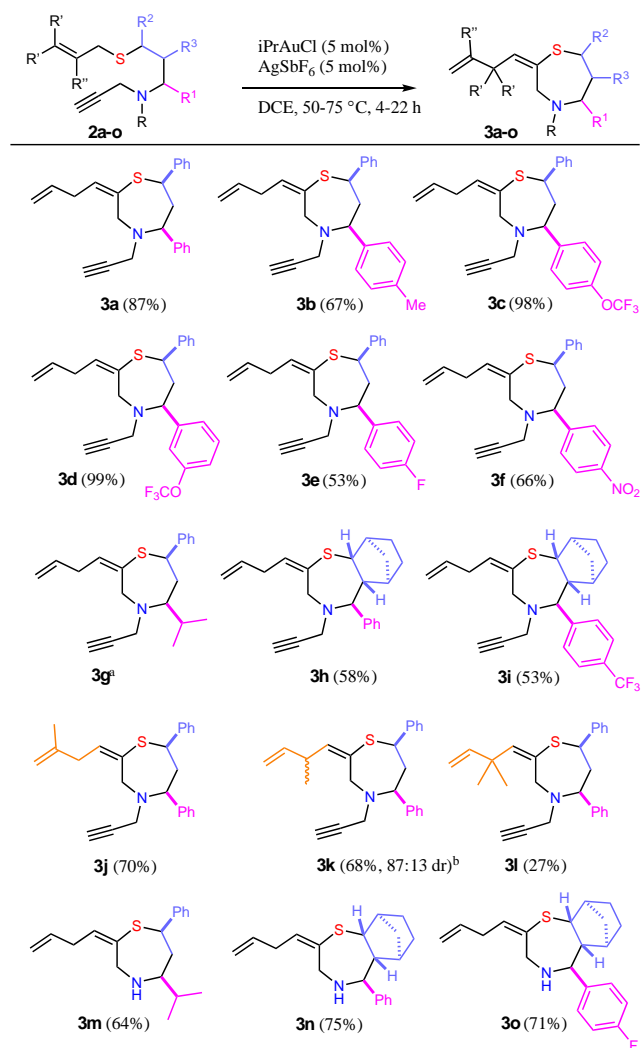


Figure 2. X-ray structure of **3a** (50% probability ellipsoids).

To explore the substrate scope and limitations of this new gold-catalyzed reaction, a range of 1,3-aminothioethers **2b-o** was synthesized similarly to **2a** from the corresponding *N*-Boc 1,3-thiazin-2-ones **1** derived from styrene or norbornene and various aldehydes (experimental details are given in SI). These substrates were placed under the optimized reaction conditions (Table 1, entry 11) and the obtained results are summarized in Table 2.

Table 2. Scope of the Au-catalyzed intramolecular thioallylation accessing thiazepanes

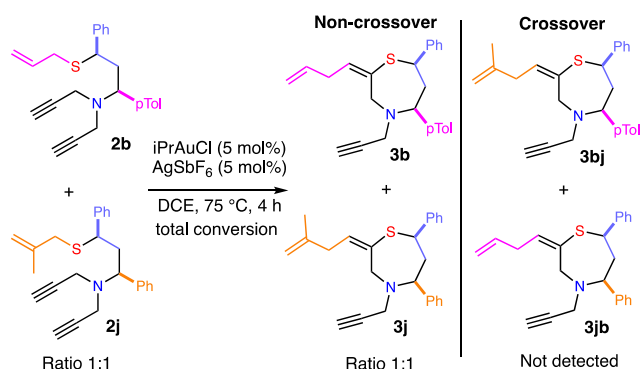


^[a] Thiazepane **3g** was obtained along with a side-product **4g**, as an inseparable mixture, in 86:14 ratio, with a combined yield of 88%. ^[b] Ratio measured by ¹H NMR.

First, we examined 1,3-aminothioethers **2b-f** bearing two aryl groups next to the sulfur and the nitrogen atoms. All of them underwent 7-*exo*-dig thioallylation successfully, leading to the desired thiazepanes **3b-f** with good to excellent yields (almost quantitative for **3c** and **3d**). When substrate **2g** with an isopropyl next to the nitrogen was used, an inseparable mixture of the expected product **3g** and the minor side-product **4g** (in a ratio of 86/14) was obtained with a combined yield of 88%. Norbornane derivatives **2h** and **2i** were subjected to the same reaction conditions and also led to the desired products **3h** and **3i**, respectively. We then examined the reaction on substrates carrying on sulfur other allylic groups. *S*-methallyl aminothioether **2j** afforded thiazepane **3j** in 70% yield. Starting from the *S*-crotyl derivative **2k**, product **3k** was obtained in 68% yield as an inseparable mixture of two diastereomers (in 87:13 ratio) resulting from the 1,3-migration with inversion of the crotyl group. ¹H NMR NOESY experiments did not allow us to assign the stereochemistry of each component. The *S*-prenyl

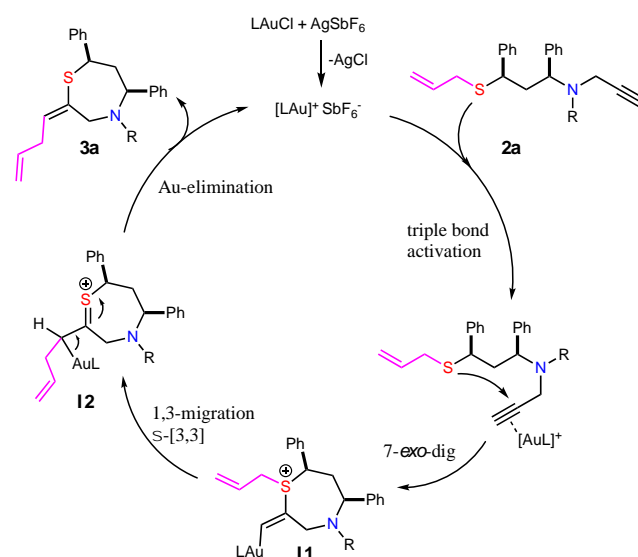
aminothioether **2l** could also be transformed in the expected product **3l**, however with a lower yield of 27%. It is to notice that precursors bearing an internal triple bond (with ethyl or phenyl on the propargyl triple bond) were unreactive under the standard reaction conditions.

Finally, monopropargylated precursors **2m-o** were also tested in order to establish the feasibility of our reaction on secondary *N*-propargyl amines. To our satisfaction, the transformation also worked, leading to the desired NH-thiazepanes **3m-o** in good yields. Moreover, the presence of the secondary amine in the obtained heterocycle opens the possibility of structural variation, for example by its transformation into a tertiary amine (by *N*-alkylation or metal-catalyzed *N*-arylation) or an amide (by *N*-acylation). We then examined the mode of the thioallylation, intramolecular versus intermolecular. For this purpose, we undertook a crossover experiment by placing under the gold-catalyzed conditions an equimolecular mixture of substrates **2b** and **2m** (Scheme 3). At the end of the reaction, the analysis of the resulting crude mixture (by ¹H NMR and LC/MS) clearly showed only the presence of products **3b** and **3j** (in a 1:1 ratio) and no crossover of allyl/methallyl groups yielding **3bj** or **3jb** occurred. This result confirmed that the S-to-C allyl migration occurs intramolecularly.



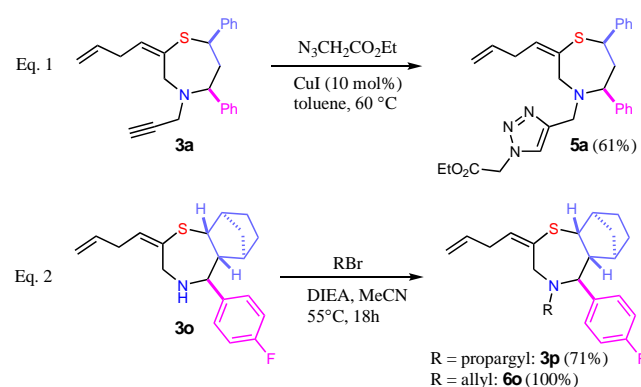
Scheme 3. Crossover experiment

A plausible reaction mechanism based on the relevant literature^[11] is given in Scheme 4. Gold(I) activates the triple bond of substrate **2a** which is attacked by the sulfur nucleophile via a 7-*exo*-dig cyclization mode leading to the cyclic *trans* sulfonium vinyl-gold species **11**. The 1,3-migration of the allyl group from the sulfur to the carbon atom bonded to the gold affords intermediate **12**. This occurs intramolecularly (as showed by the crossover experiment) via a Claisen-type rearrangement (as indicated by the inversion of the crotyl and prenyl moieties in products **3k** and **3l**, Table 2). Finally, elimination of the cationic gold species closes the catalytic cycle releasing the 7-membered *N,S*-heterocycle **3a** with the catalyst regeneration.



Scheme 4. Proposed thioallylation mechanism

Taking advantage of the substituents on the nitrogen of thiazepines **3** (hydrogen or propargyl), we illustrated the possibilities of their post-transformations with two examples (Scheme 5). Compound **3a** was engaged in a copper-catalyzed alkyne-azide cycloaddition (CuAAC) with ethyl azidoacetate, which led to the triazole derivative **5a** in 61% yield (Scheme 5, eq. 1). Then, compound **3o** was reacted with propargyl or allyl bromide leading to the *N*-propargyl or *N*-allyl thiazepines **3p**^[14] and **6o** in 71% and 100% yield, respectively (Scheme 5, eq. 2).

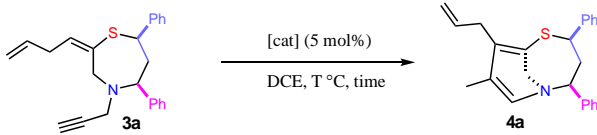


Scheme 5. Post-functionalization of **3**.

At this stage of the study, we focused on the formation and identification of product **4a** obtained in some experiments along with the desired compound **3a** (see Table 1, entries 1, 2 and 11). We first checked whether **4a** arises from **3a** (Table 3). Indeed, by performing the reaction on **3a** at 90 °C, in dichloroethane, in the presence of 5 mol% of gold

complex **C1**, the substrate was half converted after 18 hours into the expected product **4a**, confirming our assumption (Table 3, entry 1). In this case we succeeded in the isolation of a pure sample of **4a** which was fully characterized by NMR spectroscopy and allowed us to determine an unprecedented heterobicyclo[4.3.1] system with a bridgehead double bond.^[15] The two-dimensional nuclear Overhauser spectroscopy experiment (2D-NOESY) showed that the methylene bridge was situated on the same side with the protons next to the nitrogen and sulfur atoms (see in the Supporting Information). From a structural point of view the obtained *N*-propargyl thiazepane **3a** correspond to a 1,6-enyne and is therefore prone to cycloisomerization under gold-catalysis leading to **4a**. Gold-catalyzed enyne cycloisomerizations represents a powerful method to access a wide structural diversity of cyclic systems^[16] and the transformation of **3** to **4** represents to our knowledge an unprecedented case. We then attempted to optimize the cycloisomerization of **3a** to **4a**. Experiments using IPrAuCl (**C5**), which was efficient in the thioallylation, did not give satisfactory results for the cycloisomerization (Table 3, entries 2 to 4). We then returned to test other phosphine-based gold complexes. By using **C7** with a very hindered phosphine, in the presence of AgSbF₆, **3a** was completely converted into **4a**, which was isolated in 64% yield (entry 5). Finally, complex **C8** led to a similar result, allowing to obtain product **4a** in 60% isolated yield (entry 6). Again, products derived from the triple bond hydration were never detected. Obviously, we have then attempted the tandem transformation directly from *N,N*-dipropargyl *S*-allyl aminothioether **2a** to the bicyclic product **4a**. Unfortunately, this was not successful and a mixture of **2a**, **3a** and **4a** was obtained whatever the catalyst (or mixture of catalysts) used. The best result, however disappointing, was obtained with **C7**/AgSbF₆ at 90°C in DCE, by extending the reaction time to 48 h, leading to a ratio of **2a**/**3a**/**4a** of 1:0.2:1.

Table 3. Optimization of the Au-catalyzed cycloisomerization of 1,6-enyne **3a**.

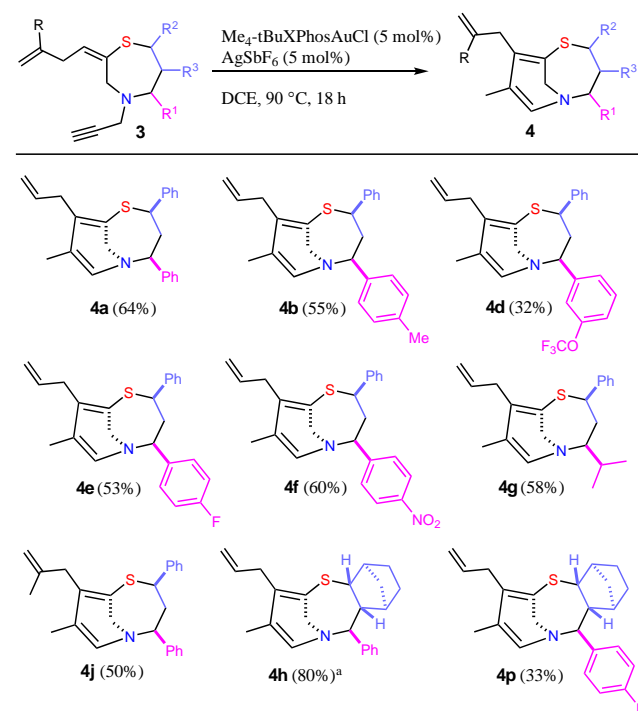
				
C1: JohnPhosAu(MeCN)SbF ₆ C5: IPrAuCl C7: Me ₄ tBuXPhosAuCl C8: XPhosAuNTf ₂				
entry	catalyst	T (°C)	Conv % (ratio 3a / 4a) ^[a]	Isolated yield %
1	C1	90	50 (1/1)	nd ^[b]
2	C5 /AgSbF ₆	90	50 (1/1)	nd ^[b]

3	C5 /AgSbF ₆	120	100 (0/1)	12 ^[c]
4	C5 /AgNTf ₂	90	75 (1/3) ^[d]	nd ^[b]
5	C7 /AgSbF ₆	90	100 (0/1)	64
6	C8	90	100 (0/1)	60

^[a] Measured by ¹H NMR in the crude mixture; ^[b] Not determined; ^[c] Due to degradation. ^[d] The reaction time was 96h.

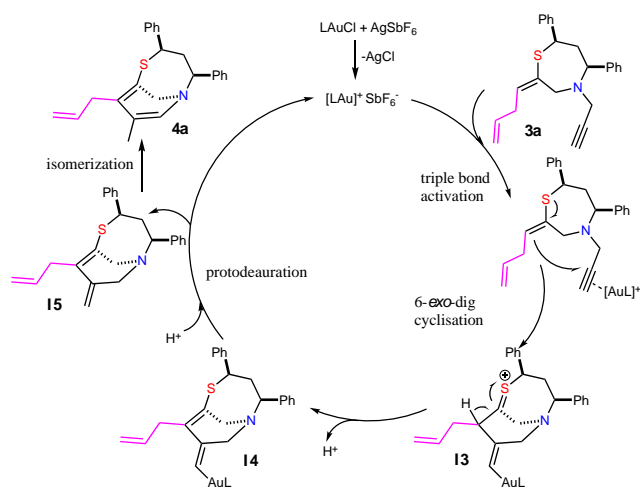
Finally, the optimal reaction conditions used in Table 3, entry 5, were used to extend the cycloisomerization of other substrates **3** to their bicyclic derivatives **4** (Table 4). Six selected substrates **3** bearing two aryl substituents on the ring (**3a**, **b**, **d**, **e**, **f**, **j**) led to the expected corresponding bicyclic products **4** with satisfactory yields ranging from 32% for the **4d** to 64% for **4a**. *N*-propargyl thiazepane **3g** with phenyl and isopropyl substituents could not be obtained pure from **2g** (see Table 2), however it was prepared by *N*-propargylation of **3m** and isolated in 55% yield (see SI). Submitted to cycloisomerization conditions, **3g** led to the expected bicyclic product **4g**, which was isolated in 58% yield.^[17] Norbornane-fused thiazepane **3h** was also transformed in its tricyclic derivative **4h**, for which, because its instability, the ¹H and ¹³C NMR experiments have been performed on the crude product. On the other hand, starting from norbornane-derived substrate **3p** with 4-fluorobenzene substituent, we were able to obtain product **4p** with an isolated yield of 33%. In this case, the 2D-NOESY NMR experiment showed that the newly formed methylene bridge was placed on the same side with the proton next to the nitrogen atom (see spectra in the Supporting Information).

Table 4. Au-catalyzed cycloisomerization of *N*-propargyl thiazepanes **3**.



^[a] Crude yield

Inspired by some cases of 1,6-enyne cycloisomerization from the literature^[18] we propose the mechanism shown in Scheme 6 for the cycloisomerization of *N*-propargyl thiazepane **3a** to bicyclic bridged structure **4a**. Cationic gold activates the triple bond of the 1,6-enyne system of **3a** promoting its attack by the vinylic carbon, assisted by the sulfur electron-donation. The cyclization takes place according to a 6-*exo*-dig pathway leading to the sulfenium vinyl-gold species **I3**. Proton elimination from **I3** produces intermediate **I4** which undergoes protodeauration to regenerate the catalyst affording product **I5**. The latter is transformed into the final bicyclic product **4a** via exocyclic to endocyclic double bond isomerization.



Scheme 6. Proposed cycloisomerization mechanism

Conclusion

In summary, we have developed a gold-catalyzed 7-*exo*-dig cyclization leading to 1,4-thiazepanes having two or three carbons stereocenters. The reaction proceeds via the thioallylation of a terminal alkyne and represents the first example of a gold-catalyzed intramolecular C-S bond formation leading to a seven-membered heterocycle. The possibility of post-functionalization of the synthesized 1,4-thiazepanes was illustrated by two examples of reactions, the Cu-catalyzed azide-alkyne cycloaddition and the *N*-alkylation. The *N*-propargyl 1,4-thiazepanes underwent a 1,6-enyne cycloisomerization, leading via a 6-*exo*-dig cyclization to *N,S*-containing bicyclic [4.3.1] bridgehead-olefinic systems with unique structure. The IPrAuCl/AgSbF₆ catalytic system was the best for the thioallylation, while Me₄tBuXPhosAuCl/AgSbF₆ was found to be the most efficient for the cycloisomerization. We are continuing to explore the potential of metal-catalyzed cyclizations of 1,3-aminothioethers to enlarge the molecular diversity of *N,S*-heterocyclic structures.

Experimental Section

General procedure for the synthesis of thiazepanes 3. To a solution of **2** (1 equiv) into DCE (0.05M of the substrate) was added [IPr]AuCl (5 mol%) and AgSbF₆ (5 mol%). The reaction mixture was stirred at 50-75 °C for 4 to 22 h. After completion of the reaction (TLC monitoring), the reaction mixture was filtrated on celite, and the crude product was purified by column chromatography using heptane/AcOEt/NEt₃ (90/10/1) to afford **3**.

General procedure for the synthesis of compounds 4. To a solution of **3** (1 equiv) into DCE (0.05M of the substrate) was added [Me₄tBuXPhos]AuCl (5 mol%) and AgSbF₆ (5 mol%). The reaction mixture was stirred at 90 °C for 18 h. After completion of the reaction (TLC monitoring), the reaction mixture was filtrated on celite, and the crude product was purified by column chromatography using heptane/AcOEt/NEt₃ (99/1/1) to afford **4**.

Acknowledgements

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