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## Gold(I)-Catalyzed Divergent and Diastereoselective Synthesis of Azepines by Ammoniation/Ring-Expansion Reactions

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### SUMMARY

Gold(I) catalysts enable the chemoselective addition of tailor-made N-sulfonylated azetidine derivatives onto alkynes affording bicyclic vinyl-ammonium gold intermediates. Intramolecularly intercepted by a nucleophilic carbonate or ester function adequately positioned, these ammoniums efficiently lead to ring-expanded azepine products which are important pharmacophore fragments. Depending on the substitution pattern of the starting material, divergent deauration pathways occur, stereoselectively producing monomeric or original dimeric nitrogenated seven-membered rings in good to excellent yields, such as cis-tetrahydroazepin-4,5-diol carbonate, (E)-alkylidene tetrahydroazepin-4-yl ester, and cis-bis(azepinyl)cyclobutane derivatives. One of the synthetic methods were extended to the formation of dihydrobenzazepines of high pharmaceutical value. A mechanistic study, including kinetics and labeled experiments allows to fully understand the origin of the high chemo- and diastereoselectivity of these rearrangements. Overall, this work demonstrates the underlying synthetic potential of the ammoniation catalyzed by gold for the future developments of reaction cascades and the preparation of bioactive compounds.

Keywords: Catalysis, Gold(I), Ammoniation, Ring Expansion, Azepines, and Azetidines.

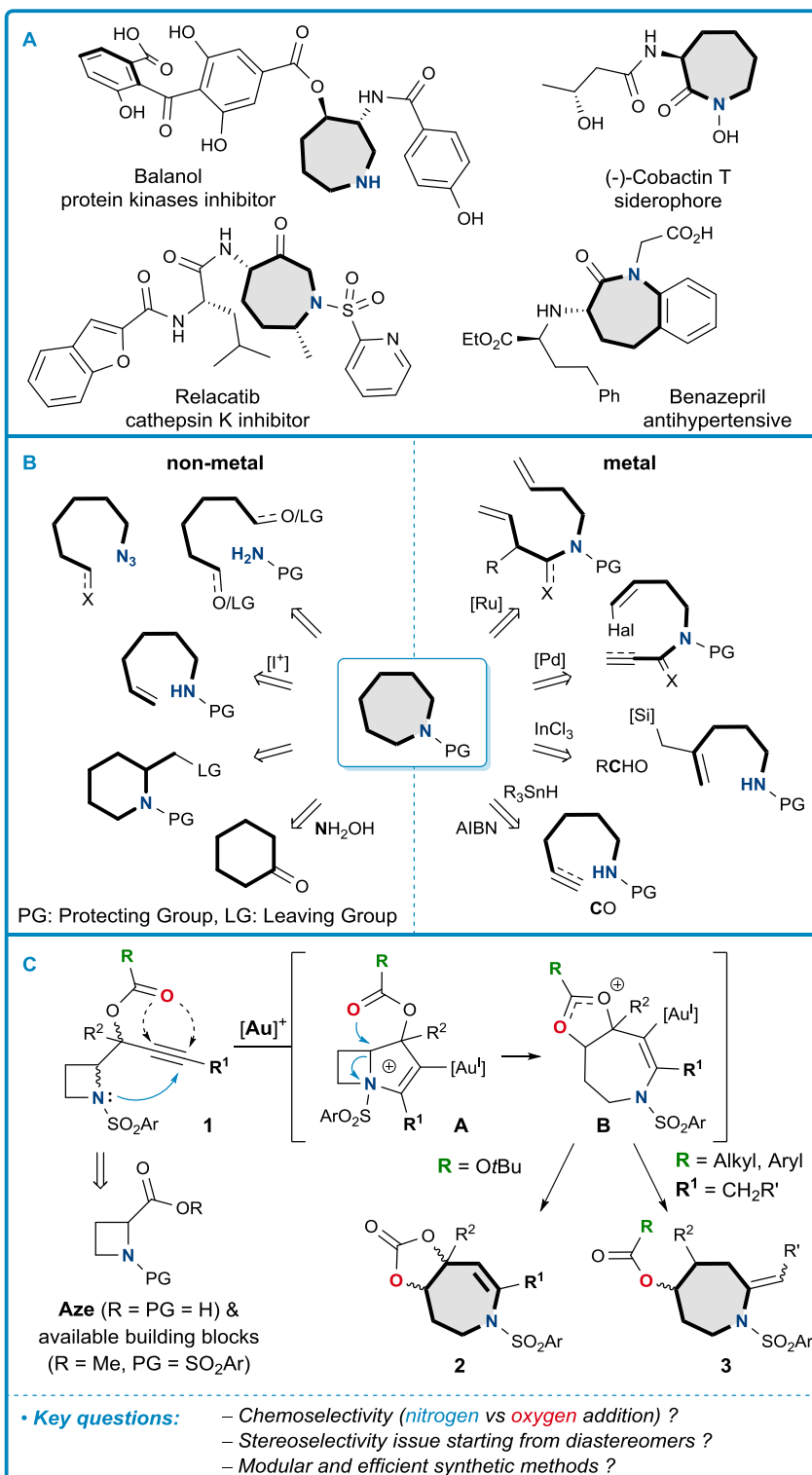
### INTRODUCTION

Azepine and its saturated derivatives are important pharmacophore fragments<sup>1</sup> present in various natural products and in a wide range of bioactive compounds (Figure 1A).<sup>2</sup> For example, seven-membered aza-ring systems can be found in the structure of balanol,<sup>3</sup> a potent inhibitor of protein kinases, or in (–)-cobactin T,<sup>4</sup> a siderophore growth promoter isolated from mycobacteria. N-Sulfonyl hydroazepine motif can also be found in the synthetic relacatib,<sup>5</sup> a potent inhibitor of human cathepsin K. The (hydro)benzazepine core is also quite common in drug structures, as exemplified by the commercial benazepril<sup>6</sup> drug, which is an angiotensin-converting-enzyme inhibitor used to treat renal insufficiency or hypertension. Considering the high pharmaceutical value of the (hydro)azepine derivatives, various routes to produce them have been developed (Figure 1B).<sup>7</sup> Nevertheless, the required conditions usually do not allow for structural variations and functionalizations. Therefore, the development of flexible methodologies for their synthesis stands as an important and timely needed task.<sup>8</sup>

In the course of our studies on complexity-generating rearrangements of aza-rings, we recently outlined a versatile ammoniation strategy based on the ability of gold(I) to promote the addition of N-sulfonylated cyclic amines on alkynes leading to vinyl-ammonium gold species (See blue arrow on 1 and intermediate A, Figure 1C).<sup>9</sup> Selective interception of these intermediates by external and

protic nucleophiles open new routes to important N-heterocycles such as pyrroles, pyrrolinones, benzosultams, and various 1-azabicyclo[m.n.0]alkane derivatives. Therefore, we wondered whether a complementary strategy could be designed for the synthesis of valuable azepine derivatives.<sup>10</sup>

With this aim, N-sulfonyl 1-(azetidin-2-yl)propargyl carbonates or esters **1** were devised as potential precursors for a gold-catalyzed cyclization/transannular ring opening<sup>11</sup> process (Figure 1C). We indeed reasoned that a carbonate or an ester group, appropriately positioned at the propargylic position, may be prone to act as an internal aprotic nucleophile able to open intermediate A, thus providing the azepine intermediate B. The evolution of the latter, and especially its ability to release gold(I) to render the whole process catalytic, would be critical for the reaction outcome.



(A) Examples of important azepine derivatives.

(B) Main synthetic routes to azepines.

(C) The proposed gold-catalyzed ammoniation/ring expansion strategy towards azepine derivatives from azetidines.

In view of the rich gold-catalyzed chemistry<sup>12</sup> of propargylic carbonates and esters, competing pathways could also be expected (red dotted arrows on 1 in Figure 1C), since the latter are known to rearrange into 4-alkylidene-1,3-dioxolan-2-ones<sup>13</sup> or undergo 1,2- and 1,3-carbonate<sup>14</sup> or -ester<sup>15</sup> migrations with variable outcomes depending on substitution patterns and conditions.

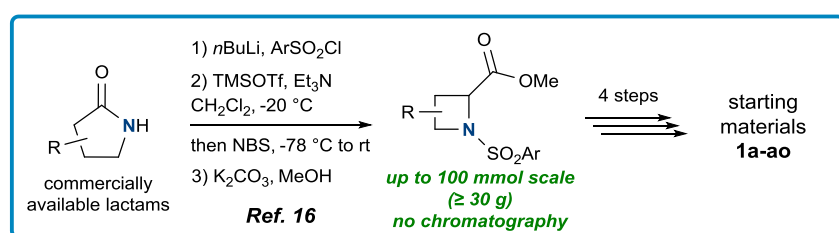
We report herein the feasibility of such rearrangements as well as their extension to cascade reactions. These studies highlight the facile sulfonyl azetidinium generation even in a complex setup, but also unveil a new deauration pathway. Overall, complex azepines 2 or 3 embedding rich substitution patterns (Figure 1C), hardly accessible via conventional methods,<sup>7,8</sup> can readily be produced through the present process.

## RESULTS AND DISCUSSION

### Gold(I)-Catalyzed Ammoniumation/Ring-Expansion Reactions

We first selected the azetidine carbonate 1a, i.e. tert-butyl (1-(1-tosylazetid-2-yl)non-2-yn-1-yl) carbonate (Table 1) as model substrate for the envisioned ring expansion. The choice of tert-butyl carbonate ester (R=OCOtBu) was guided by the possible elimination of isobutene from the tert-butoxydioxolanium moiety in intermediate B (Figure 1C) and the expected protodemetalation induced by the so-released proton.<sup>13</sup> Such a sequence would directly lead to the azepinyl carbonate 2.

This carbonate 1a and its analogs were conveniently obtained from N-sulfonyl 2-azetidincarboxylate methyl esters, the protected form of the naturally occurring aminoacid Aze. Although commercially available, the latter and more importantly its substituted analogs are readily available on multigram scale in a few steps (Scheme 1).<sup>16</sup> These building blocks provide a flexible access to various N-sulfonyl-1-(azetid-2-yl) propargyl alcohol derivatives (see Supplemental Information).

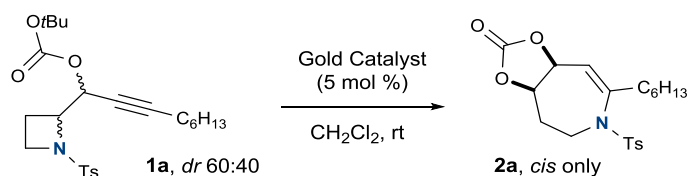


Scheme 1. Convenient route to the required azetidine precursors.

The transformation of 1a was first examined in the presence of 5 mol % of Gagosz catalyst (Ph<sub>3</sub>PAuNTf<sub>2</sub>) in dichloromethane at room temperature (Table 1, entry 1). After 24 h, only 50% conversion was obtained, but the formation of the expected N-tosyl tetrahydroazepin-4,5-diol carbonate 2a, as the single *cis* diastereomer<sup>17</sup> was observed in the <sup>1</sup>H crude NMR spectrum. Switching from bistriflimide to hexafluoroantimonate counterion strongly improved the activity of the gold catalyst as full conversion was reached after only 4 h of reaction (Entry 2). However, compound 2a was formed along with degradation products. The use of electron-withdrawing ligands improved the efficiency of the reaction up to 64% yield but again with the formation of a significant

number of unstable side-products (Entries 3 and 4). Therefore, electron-donating ligands were surveyed. Carbenic gold(I) complex only led to low reactivity and conversion (Entry 5). Biarylphosphine gold(I) complexes induced cleaner conversion and consistently led to better yields (Entries 6-8). The CyJohnPhos variant showed a slightly superior activity compared to the standard JohnPhos ligand (Entry 6 vs 7), which can be attributed to the more confining character of the latter.<sup>18</sup> The silver salt (AgSbF<sub>6</sub>) used to prepare the catalytically active gold(I) complexes proved to be unsuitable for this transformation as shown by control experiment (Entry 9). From this optimization, the CyJohnPhosAuSbF<sub>6</sub>.MeCN complex (5 mol %) was selected as the best catalyst and used for the evaluation of the reaction scope. It is noteworthy that despite the presence of two diastereomers in the starting carbonate 1a, both were consumed, leading to the exclusive formation of cis-tetrahydroazepin-4,5-diol carbonate 2a.

Table 1. Screening of reaction conditions for the formation of the N-tosyl cis-tetrahydroazepin-4,5-diol carbonate 2a from azetidine carbonate 1a.



Entry	Catalyst (5 mol %)	Time (h)	Yielda 2a (%)
1	Ph <sub>3</sub> PAuNTf <sub>2</sub>	24	50 <sup>b</sup>
2	Ph <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	4	47
3	LAuSbF <sub>6</sub> .MeCN <sub>c</sub>	4	64
4	( <i>p</i> -CF <sub>3</sub> Ph) <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	4	62
5	IPrAuPF <sub>6</sub> .MeCN	24	29 <sup>b</sup>
6	JohnPhosAuSbF <sub>6</sub> .MeCN	6	72
7	CyJohnPhosAuSbF <sub>6</sub> .MeCN	4	74
8	CyJohnPhosAuNTf <sub>2</sub>	6	70
9	AgSbF <sub>6</sub>	24	- <sup>d</sup>

Ts = *para*-toluenesulfonyl; IPr = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene; JohnPhos = (2-biphenyl)di-*tert*-butylphosphine ; CyJohnPhos = 2-(biphenyl)dicyclohexylphosphine.

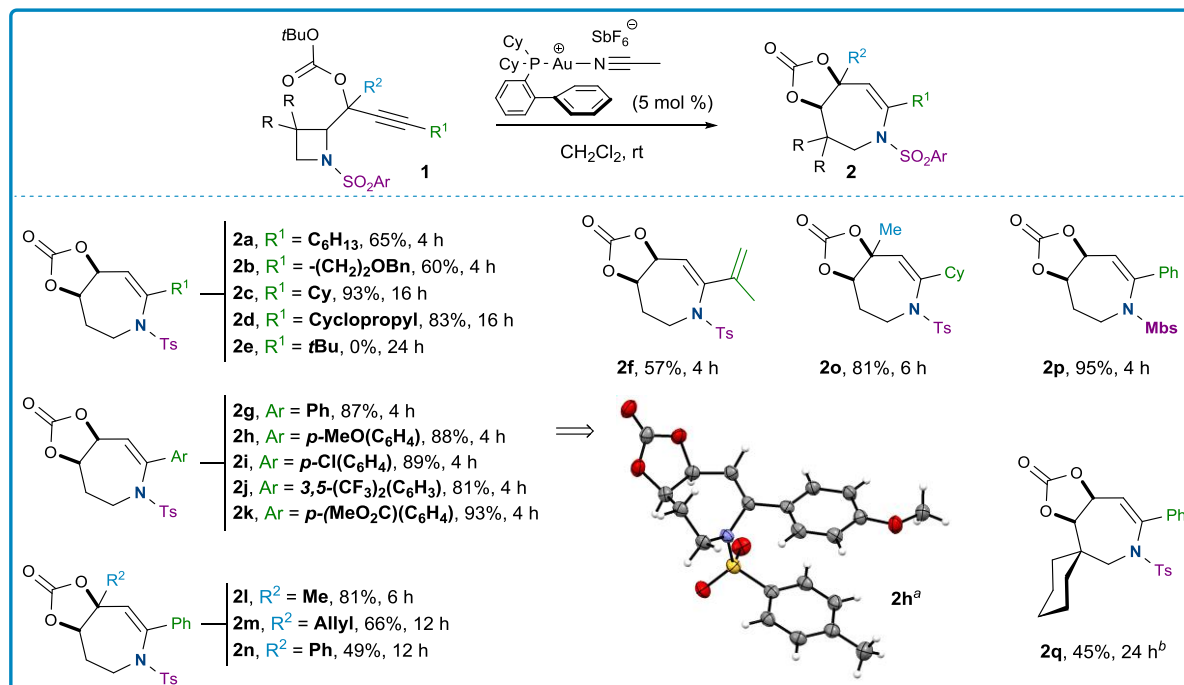
<sup>a</sup>Yield calculated by integration of the <sup>1</sup>H NMR spectrum of the crude product relative to an internal standard (dimethyl terephthalate).

<sup>b</sup>50% of conversion.

<sup>c</sup>L = tris(2,4-di-*tert*-butylphenyl)phosphite.

<sup>d</sup>No conversion.

With the optimal reaction conditions in hand (Table 1, entry 7), diversely functionalized tert-butyl N-sulfonyl 1-(azetidin-2-yl)propargyl carbonates **1** were submitted to gold catalysis, diastereoselectively affording N-sulfonyl cis-tetrahydroazepin-4,5-diol carbonates **2** (Scheme 2).



Scheme 2. Diastereoselective synthesis of various N-sulfonyl cis-tetrahydroazepin-4,5-diol carbonates **2**.

aEllipsoid representation of compound **2h** XRD structure

bReaction run with 10 mol % of gold catalyst.

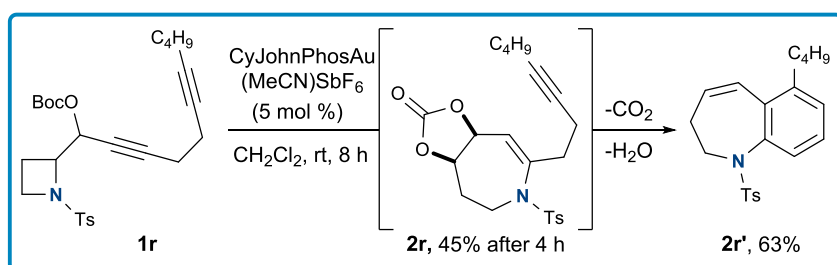
Ts = para-toluenesulfonyl; Mbs = para-methoxybenzenesulfonyl.

We first examined the effect of alkyne substitution with substrates **1a-f** ( $\text{R}^1$  on Scheme 2). The reaction proceeded in good yields with primary alkyl (**2a**) and alkoxy sidechains (**2b**). Incorporation of cyclic moieties, such as cyclohexyl or cyclopropyl  $\text{R}^1$  substituents, improved the efficiency of the reaction. A longer reaction time was however required, in line with the increase in steric hindrance. cis-Tetrahydroazepin-4,5-diol carbonates **2c** and **2d** could thus be obtained in excellent yields when compared to **2a** and **2b**. Further increase of the congestion by capping the alkyne with a tert-butyl group (**1e**) completely inhibited the reaction, even upon heating (70 °C).

Interestingly, the presence of an isopropenyl group was well tolerated, and the hydroazepine **2f** embedding a potentially useful dienyl unit was formed with reasonable efficiency. Aryl substituents at the  $\text{R}^1$  position, independently of their electron donating or withdrawing nature, were perfectly compatible, leading to compounds **2g-k** in excellent yields (81-93%). Moreover, the rearranged product **2h** furnished suitable crystals for X-ray diffraction, which confirmed the relative cis

configuration of diol carbonates **2** (See structure of **2h** on Scheme 2). Introduction of methyl, allyl or phenyl groups at the propargylic position (R<sub>2</sub>, Scheme 2) was well tolerated and the hydroazepines **2l-o** could be obtained in good to moderate yields, albeit requiring longer reaction times with sterically demanding groups. The variation of the sulfonyl moiety did not affect the rearrangement course, as attested by the formation of **2p** bearing a para-methoxybenzenesulfonyl group in excellent yield. To briefly look at the possible influence of substituent on the azetidine ring (R<sub>3</sub>, Scheme 2), we prepared and evaluated the behavior of the spiroazetidine **1q**. Under our standard conditions, the densely substituted spirohydroazepine **2q** was formed in a modest 42% yield while recovering the starting material left, and doubling the catalyst loading only slightly increased yield (45%), even after prolonged reaction time. <sup>1</sup>H NMR monitoring of this reaction revealed that only one of the diastereomers of **1q** was converted to the expected product, while the other led to degradation products.

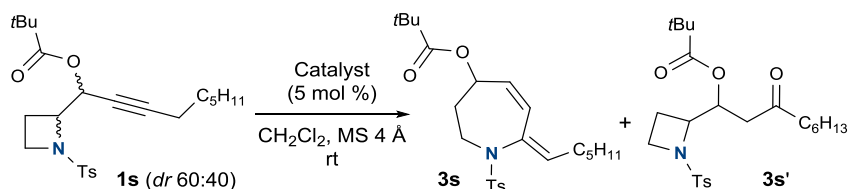
Reasoning that *cis*-tetrahydroazepin-4,5-diol carbonates **2** incorporate an enesulfonamide moiety potentially able to react further as π-nucleophiles, we envisaged a cascade involving a second cyclization step. Substrate **1r** carrying a diyne chain (Scheme 3) was therefore devised. Under standard conditions, the latter led within 4 h to the tetrahydroazepine **2r**, which could be isolated at that stage in modest yield. However, if not isolated, this compound evolved towards the formation of the dihydrobenzazepine **2r'** as expected. Indeed, **2r** could undergo another cyclization on the second alkyne moiety, which was followed by tautomerization of the so-formed iminium-vinylgold intermediate, demetallation and subsequent elimination of carbon dioxide and water (See Figure S1 in Supplemental Information). It is worth mentioning that once isolated, **2r** replaced under reaction conditions provided the benzazepine **2r'**. This sequence thus enabled a benzannulation cascade starting from **1r**, yielding the benzazepine derivative **2r'** in 63% yield after 8 h.



Scheme 3. Gold-catalyzed cascade rearrangement of azetidine carbonate derivative **1r** into benzazepine derivative **2r'**.

At this stage, the influence of the internal nucleophile moiety was surveyed by switching the carbonate group for a pivalate ester. In the previous tert-butyl carbonate series (substrates **1a-r**), catalytic turnover was enabled by the release of a tert-butyl cation, precursor of isobutene and a proton which allowed the pivotal demetallation step.<sup>13</sup> However, with an ester function as internal nucleophile, such deauration<sup>19</sup> step would require an alternative elimination pathway to afford the desired azepine derivative while maintaining a viable catalytic cycle. We thus investigated the capability of azetidynyl propargyl pivaloyl ester **1s** to rearrange upon gold activation (Table 2).

Table 2. Screening of reaction conditions for the formation of *N*-tosyl (*E*)-2-hexylidene tetrahydroazepine **3s** from azetidine **1s**.



Entry	Catalyst (5 mol %)	Time (h)	Yield <sup>a</sup> (%)	
			3s	3s'
1	CyJohnPhosAuSbF6.MeCN	2	32b	18
2	Ph <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	2	5b	19
3	CyJohnPhosAuSbF6.MeCN	4	54	-
4	Ph <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	4	66	-
5	Cy <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	4	52	-
6	(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	4	80	-
7	LAuSbF <sub>6</sub> .MeCN <sup>c</sup>	4	59	-
8	AgSbF <sub>6</sub> 24	- <sup>d</sup>	-	-

Ts = para-toluenesulfonyl; CyJohnPhos = 2-(biphenyl)dicyclohexylphosphine.

<sup>a</sup>Yield calculated by integration of the <sup>1</sup>H NMR spectrum of the crude product relative to an internal standard (dimethyl terephthalate).

<sup>b</sup>Reaction carried out without molecular sieves (MS).

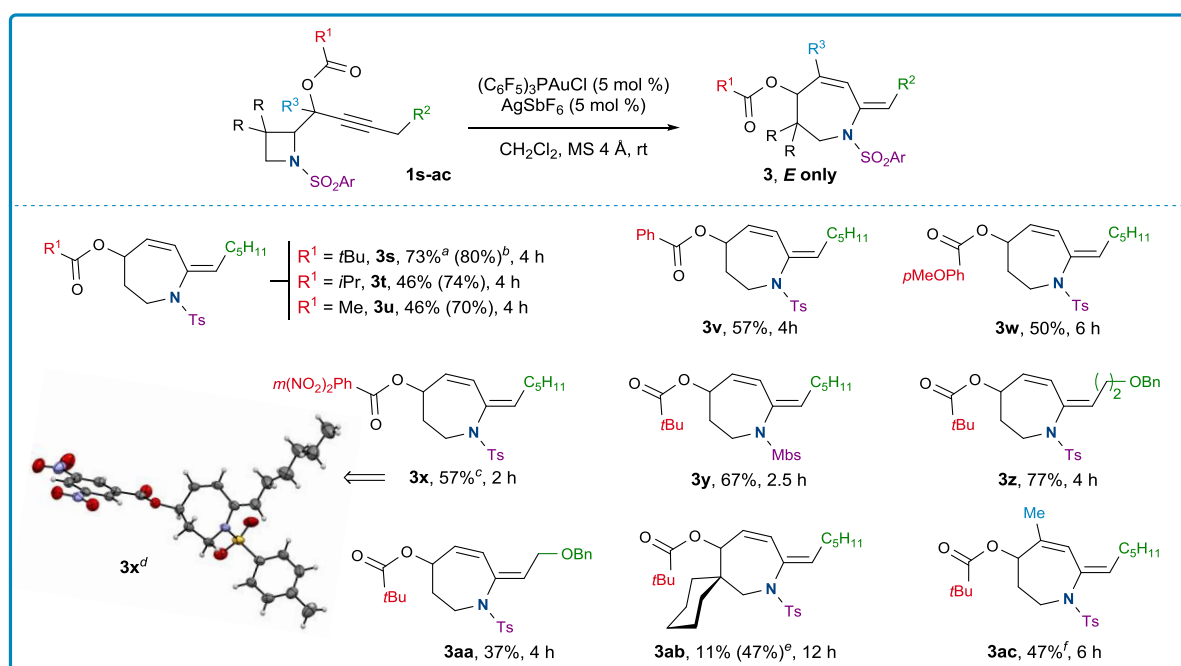
<sup>c</sup>L = tris(2,4-di-tert-butylphenyl)phosphite.

<sup>d</sup>No conversion.

Unfortunately, conditions determined for the carbonate series only led to disappointing results. Azepine derivative **3s** was rapidly obtained at room temperature in dichloromethane, but in low yield along with several side-products (Table 2, entry 1). Applying another classical gold catalyst also provided similar results (entry 2). Among side-products, the alkyne hydration derivative **3s'** was clearly identified by <sup>1</sup>H NMR as the major compound. To avoid its formation, molecular sieves (4 Å) were added in the reaction mixture. This modification drastically changed the reaction efficiency. **3s** was interestingly obtained as a single diastereomer in 66% yield in 4 h with triphenylphosphine as ligand, but when CyJohnPhos was used instead, a modest yield of 54% was still observed (entries 3 and 4). Electronic effects of various gold(I) ligands were then evaluated, in view of their strong influence on catalyst activity.<sup>20</sup> With an electron-rich tricyclohexylphosphine ligand, **3s** was obtained with a slightly lower yield, whereas a marked improvement was observed with the electron-poor tris-pentafluorophenylphosphine ligand (entries 5-6 vs 4). Switching to a phosphite derivative did not

improve this outcome further (entry 7). Counterions<sup>21</sup> and solvents<sup>22</sup> are also known to influence gold catalyst selectivity and efficiency; however, additional screening of both parameters did not lead to a sensible improvement, the best combination remaining hexafluoroantimonate anion in dichloromethane (See Table S1 in Supplemental Information). As for carbonate-tagged substrates, a control experiment showed that AgSbF<sub>6</sub> alone was inefficient in this transformation (entry 8).

Notably, the obtained azepine derivative **3s** possesses an exocyclic double bond, in contrast to the regular outcomes starting from carbonates. The (E)-stereochemistry of this unusual alkylidene tetrahydroazepine structure was unambiguously established by NOESY NMR experiment. With the best conditions in hand (Table 2, entry 6), we then explored the scope of this second unprecedented transformation (Scheme 4).<sup>23</sup>



Scheme 4. Diastereoselective Synthesis of various N-sulfonyl E-alkylidene tetrahydroazepines **3**.

isolated yield.

<sup>b</sup>Calculated yield relative to an internal standard (dimethyl terephthalate).

<sup>c</sup>Reaction run at 70 °C in dichloroethane (DCE) for 2 h.

<sup>d</sup>Ellipsoid representation of compound **3x** XRD structure.

<sup>e</sup>Reaction run with 10 mol % of catalyst.

<sup>f</sup>Reaction run at 0 °C.

Ts = para-toluenesulfonyl; Mbs = para-methoxybenzenesulfonyl.

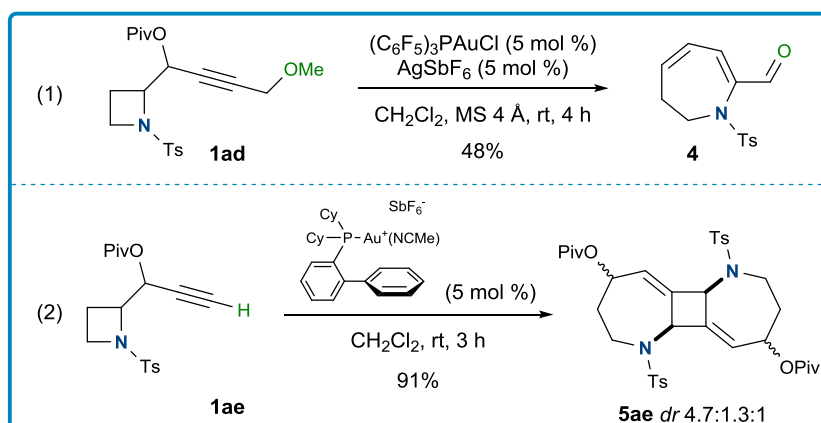
We first surveyed the effect of the internal nucleophile, i.e. the ester moiety, on the reaction efficiency. Changing the nature of the ester influenced the yield, an unsurprising trend given its

expected role within the rearrangement (see Figure 1C). The less bulky iso-butyryl and acetyl groups provided compounds 3t and 3u in lower yields compared to the pivaloyl (Piv) derivative 3s. Such difference could be attributed to the steric hindrance of the tert-butyl group, pushing the nucleophilic oxygen closer to the transient C–ammonium bond. Benzoyl groups also led to azepines 3v-x in lower yields, in line with their lower nucleophilicity, but also due to stability problems under these conditions. Such reduced propensity to undergo the cascade rearrangement was even more apparent in the case of an appended 3,5-dinitrobenzoyl group: here, heating to 70 °C was required to generate 3x in a modest yield of 57%. Nevertheless, 3x provided crystals suitable for X-ray diffraction. The resulting structure matched our previous assumptions from NMR data and confirmed the (E)-geometry of the exocyclic alkene. Variation of the N-sulfonyl protecting group (SO<sub>2</sub>Ar) proved fully compatible with the rearrangement conditions. Indeed, using N-para-methoxybenzenesulfonyl (Mbs) group instead of N-tosyl group allowed the formation of 3y in a similar yield. Alkyne substituents R<sub>2</sub> were also tunable as demonstrated by the formation of azepines 3s, 3z and 3aa bearing alkyl or protected hydroxyl groups. The marked sensitivity of compound 3aa, due to the presence of a benzyloxy functional group at the allylic position, could explain the lower yield obtained in that case. Substitutions of the azetidine moiety (1ab) as well as of the propargylic position (1ac) were also compatible with the reaction conditions, although the expected azepines 3ab and 3ac were obtained in lower yields.<sup>23</sup>

Interestingly, the analog 1ad carrying a CH<sub>2</sub>OMe group did lead to the expected product 3ad as shown by NMR, but the latter cannot be isolated. Instead, the dihydroazepine 2-carbaldehyde 4 was obtained, although with a modest 47% yield (Scheme 5, Eq 1). Such compound could originate from the expected azepine 3ad after pivaloyl elimination and proton loss driven by the conjugation of the final product 4 during the purification step (See Figure S2 in Supplemental Information).

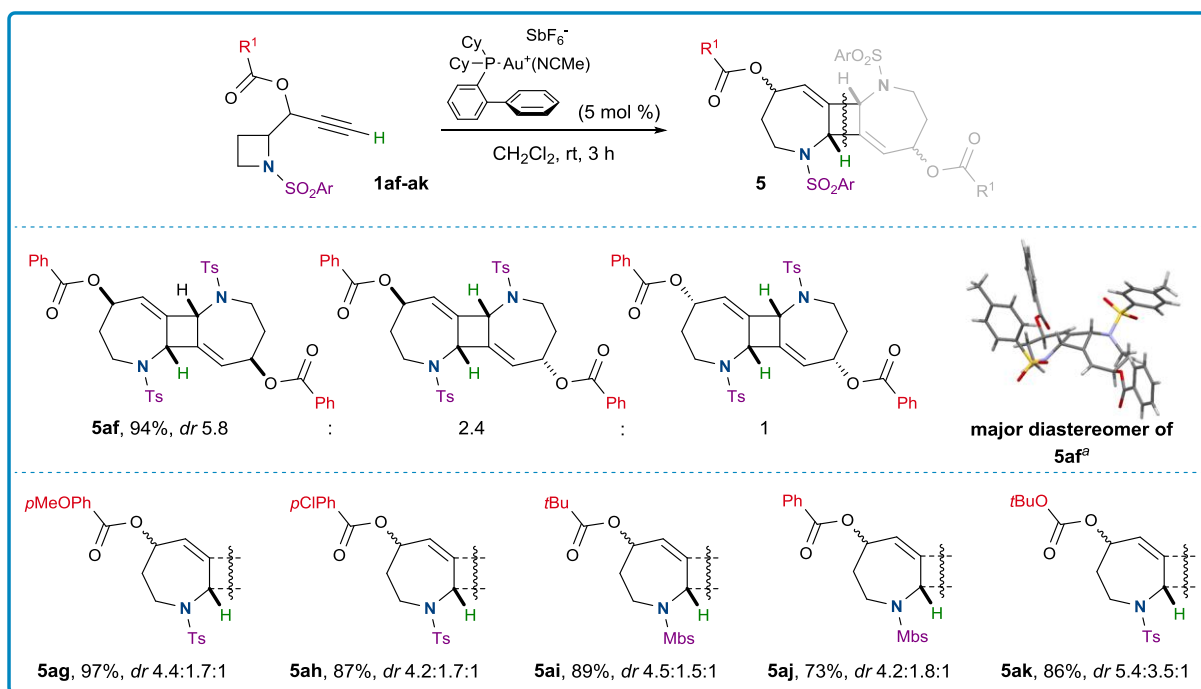
The outcome of this new gold-catalyzed rearrangement depends on the final deauration step. This requirement was ensured by the presence of a methylene link between the alkyne and its R<sub>2</sub> substituent (See Scheme 4), from which a proton shift would selectively form an exocyclic E-double bond. Such requirement was highlighted by the lack of azepine formation with substrates bearing a tert-butyl or a phenyl group directly linked to the alkyne moiety. In these cases, degradation mostly occurred (See Figure S3 in Supplemental Information).

In sharp contrast, compound 1ae bearing a terminal alkyne evolved through an alternative and unprecedented deauration pathway, affording the unexpected compound 5ae as a mixture of three diastereomers. A high yield was achieved using the CyJohnPhosAuSbF<sub>6</sub>.MeCN complex (Scheme 5, Eq 2). The compound structure, established from extensive NMR investigations, proved to be a dimeric bis(azepinyl)cyclobutane<sup>24</sup> with a cis stereochemistry of the cyclobutane moiety (see below).



Scheme 5. Gold-catalyzed rearrangement of azetidine derivatives **1ad** and **1ae**.

Considering its original nature, we briefly evaluated the scope of this dimerization reaction (Scheme 6). As for the formation of hydroazepines **3**, modulation of the ester function as well as the sulfonyl group was perfectly tolerated in this transformation, leading to compounds **5af-ak** in high yields (73–97%). All dimers **5** were obtained as a mixture of only 3 diastereomers in similar ratios (~4.5:1.7:1) which could be separated by flash column chromatography. Two of them were symmetrical compounds as hinted by their relatively simple  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. For all of them,  $n\text{Oe}$  experiments revealed the proximity of the two cyclobutane protons, and thus suggested the *cis* stereochemistry of the central cyclobutane. To determine their relative stereochemistry, crystals of major diastereomers **5af** and **5ah** were grown, and X-ray diffraction confirmed the *cis* stereochemistry of the cyclobutane hydrogens and established the *syn* relationship for the two ester substituents. These data allowed assigning the relative stereochemistry of each diastereomer (Scheme 6). Of note, the same result was obtained with the azetidine carbonate **1ak** bearing a terminal alkyne, affording the dimeric *cis*-bis(azepinyl)cyclobutane dicarbonate **5ak** in high yield as a mixture of 3 diastereomers as well. Such unexpected *cis*-cyclobutyl structure clearly arose from a diastereoselective homodimerization process.



Scheme 6. Diastereoselective Synthesis of cis-bis(azepinyl)cyclobutane derivatives **5**.

aStick representation of major diastereomer **5af** XRD structure.

Ts = para-toluenesulfonyl; Mbs = para-methoxybenzenesulfonyl.

### Mechanistic Studies and Hypothesis

The large set of results obtained from these gold-catalyzed rearrangements tends to support the proposed mechanism<sup>25</sup> through the opening of an ammonium bicyclic intermediate (A on Figure 1C). Nevertheless, they also raised several questions.

- How is such an intermediate formed? Does it arise either from direct nucleophilic addition of the aminosulfonyl group or from a cascade initiated through an ester or carbonate addition?
- In the former case, why is the aminosulfonyl group more nucleophilic than an ester or carbonate carbonyl?
- Why a single stereoisomer is produced starting from a mixture of diastereomers?

As mentioned above, propargylic esters or carbonates, such as derivatives **1**, are well-known to undergo 1,2- or 1,3-oxo-migrations as a starting point for many cascade transformations.<sup>14,15</sup> To get clues on these alternatives and decipher the actual mechanistic pathway, substrates labeled at specific positions were prepared and submitted to our standard reaction conditions (Figure 2A). Both tert-butyloxycarbonyl and pivaloyl derivatives **1al** and **1am** D-labeled at the propargylic position afforded the hydroazepines **2al** and **3am** still mono-deuterated at the same position (Eq. 1 & 2 on Figure 2A). Moreover, compound **1an**, 17O-enriched at the carbonyl oxygen, provided a single isotopomer **3an**, in which this oxygen atom became the alkoxy group of the ester moiety, as revealed

by 17O NMR analysis (Figure 2A, Eq. 3). Therefore, these results excluded any cascade initiated by propargylic 1,2- or 1,3-oxo-shift,<sup>15</sup> and confirmed that the carbonyl oxygen is acting as nucleophile as expected.

These results also imply that the aminosulfonyl group would be more nucleophilic than the carbonyl oxygen from an ester or a carbonate. The nitrogen lone pair in sulfonamides could be π-conjugated with vacant sulfur orbitals, in a planar arrangement, and thus be less nucleophilic than in amines. However, pyramidalization often occurred and especially in N-sulfonyl azetidines,<sup>26</sup> rendering the amino part of sulfonamide more nucleophilic. As N-sulfonyl pyrrolidines are less pyramidalized,<sup>26</sup> competition between N- and O-cyclization should occur. To confirm such effect, we prepared the five-membered ring analogs 6a-b from proline and submitted them to the corresponding standard conditions (Figure 2B). This pyrrolidiny propargylic carbonate 6a did not provide the possible azocine derivative, but only the product 7 resulting from Meyer-Schuster rearrangement through 1,3-oxo addition,<sup>27</sup> in modest yield (Eq. 5). Similarly, the pyrrolidiny propargylic ester 6b only gave a complex mixture, in which any azocine derivative could be detected (Eq. 6).

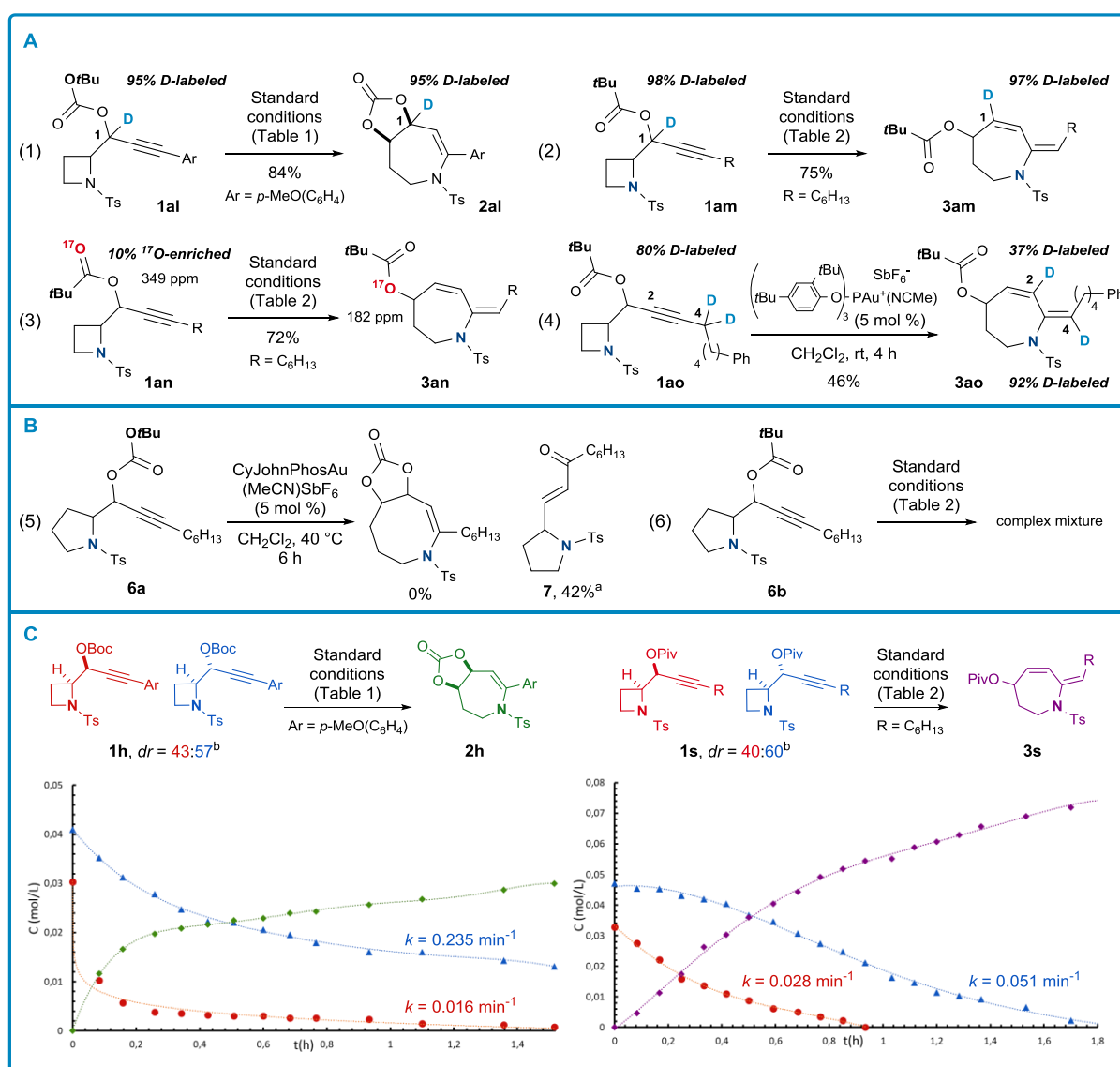


Figure 2. Mechanistic Study.

aCalculated yield relative to an internal standard (dimethylterephthalate).

bThe relative configuration of each diastereomer was established from the X-ray structure of the corresponding propargylic alcohol of the major diastereoisomer of 2g (See compound IIg in Supplemental Information).

(A) Labeling experiments.

(B) Rearrangement of pyrrolidine derivatives 6a and 6b.

(C) Kinetics experiments.

As mentioned above, the starting material was used as a mixture of diastereomers, but both were converted into a single product isomer, in the carbonate as well as in the ester series. This is particularly prevailing in the carbonate rearrangement, and the production of a single cis carbonate starting from two diastereomers suggests epimerization and equilibration along the reaction pathway.

Furthermore, discrepancies in terms of reactivity were notable when comparing the evolution of each starting diastereomers in some cases (see i.a. the formation of 2q, Scheme 2). To address and understand the stereochemical course of both reactions, kinetic experiments were performed on substrate 1h and 1s (Figure 2C). For the -OBoc derivative 1h, the minor diastereomer (red dots) was consumed significantly faster than the major one (blue triangles) (Figure 2C, left). Both diastereomers reacted according to an exponential decay fitting first-order kinetics. A similar behavior could be observed in the case of the ester derivative 1s. At the beginning of the reaction, the concentration of the major diastereomer (blue triangles) only slowly decreased, whereas the concentration of the minor diastereomer (red dots) rapidly decreased following an exponential regime (Figure 2C, right). After 25 min, the major diastereomer adopted a similar exponential regime. Again, these profiles agreed with first-order kinetics. In both carbonate and ester series, the minor diastereomer (cis) was the more reactive, the carbonate being more reactive than the ester. Such reactivity difference probably reflects different pathways involving stereochemical constraints. This could arise at the opening of the bicyclic ammonium intermediate A, which must exist as a mixture of cis and trans diastereomers (Acis and Atrans), depending on the stereochemistry of the starting material 1. In the case of Acis the carbonyl function is appropriately placed to interact with the bridging C–N orbital, as shown by preliminary calculations (see Figure 3A and Figure S4 in Supplemental Information). Thus, ring expansion could rapidly occur via intramolecular nucleophilic substitution affording the dioxolanium intermediate Bcis. For the intermediate Atrans, the carbonyl group of the ester or carbonate moiety cannot be properly aligned to allow the opening of the azetidinium ring (see Figure 3A and Figure S4 in Supplemental Information). Moreover, the ring expansion should lead to dioxolanium Btrans with conformational constraints. The latter could drive a ring-opening/ring-closing equilibrium via the ene-iminium intermediate C, a process that would lead to epimerization to Bcis. These various factors probably account for the slower conversion of the major diastereomer. Overall, these data suggest that the azetidinium opening is the driving force due to the four-membered ring strain release.

Considering such features as well as the results of the labeling experiments, the following mechanisms can be postulated (Figure 3A). Nucleophilic addition of the strongly pyramidalized sulfonylated nitrogen to the gold(I)-activated alkyne should furnish cis and trans vinyl-ammonium-gold bicyclic intermediates (Acis and Atrans), which could evolve to an equilibrated mixture of cis and trans azepinyl carbonates and azepinium ester (Bcis, Btrans, and C respectively). The final step is the crucial deauration.

In the Boc series (1a-q, R = OtBu), the Bcis intermediate affords the cis-tetrahydroazepin-4,5-diol carbonate 2 by elimination of isobutene and a proton, which allowed deauration.<sup>13</sup> This elimination-deauration process seems to be faster for the Bcis intermediate than for the Btrans intermediate, as only the cis hydroazepinyldiol carbonate 2 is produced. It seems also faster than any other deauration pathway (see below).

In the ester series (1s-ac, R = Alkyl, Aryl), the demetallation step depends on the R1 substituent. With at least a methylene group (R1 = CH<sub>2</sub>R<sub>2</sub> on Figure 4A) adjacent to the vinyl or iminium group in B or C respectively, protodeauration would occur via a diastereoselective proton elimination from this methylene unit (B1 or C1, Figure 4A), followed by an electrophilic cleavage of the C-Au bond, leading to compounds 3. Molecular modeling of simplified C1 intermediate, (see Figure S5 in Supplemental Information) highlighted that only the exocyclic E double bond can be formed considering the steric clash between the side chain (R<sub>2</sub>) and the sulfonyl moiety (SO<sub>2</sub>R). The formation of degradation products with ester substrates bearing a tert-butyl or a phenyl group directly linked to the alkyne moiety supported the latter protodeauration pathway (See Figure S3 in Supplemental Information). To further corroborate this mechanism, substrate 1ao deuterated at the C-4 position (80%) was prepared and submitted to a pre-activated catalyst to limit adventitious presence of water brought by silver salt (Figure 2B, Eq. 4). Deuterium incorporation was observed at C-2 (37%) and C-4 (92%; starting material numbering) in the resulting product 3ao. The C-2 deuteration strongly supports protodeauration at that position through the proposed mechanism.

With terminal alkynes 1af-ak (C<sub>2</sub>, R<sub>1</sub> = H on Figure 3B), a totally different process occurred leading to diastereomeric cis-bis(azepinyl)cyclobutane derivatives 5 (See Scheme 6). Such compounds could only arise from homodimerization. The latter could be due to the addition of the vinyl gold moiety of the azepinium C<sub>2</sub> to the iminium moiety of another C<sub>2</sub> monomer (D1 on Figure 3B).<sup>28</sup> The resulting adduct still containing a vinyl gold and an iminium able to react intramolecularly to provide dimer 5 (D2 on Figure 3B). The always cis stereochemical outcome revealed that this dimerization is a stepwise process; a concerted reaction would indeed give the trans cyclobutane analog. The observed diastereomers resulted from the syn or anti relationship of the carbonate or ester substituents and this could be explained by addition on one face or the other of the azepinium C.

Deauration was thus achieved in this series by an unprecedented process. Interestingly, this also confirmed the above proposed mechanism (Figure 3A) through the azepinium intermediate C.

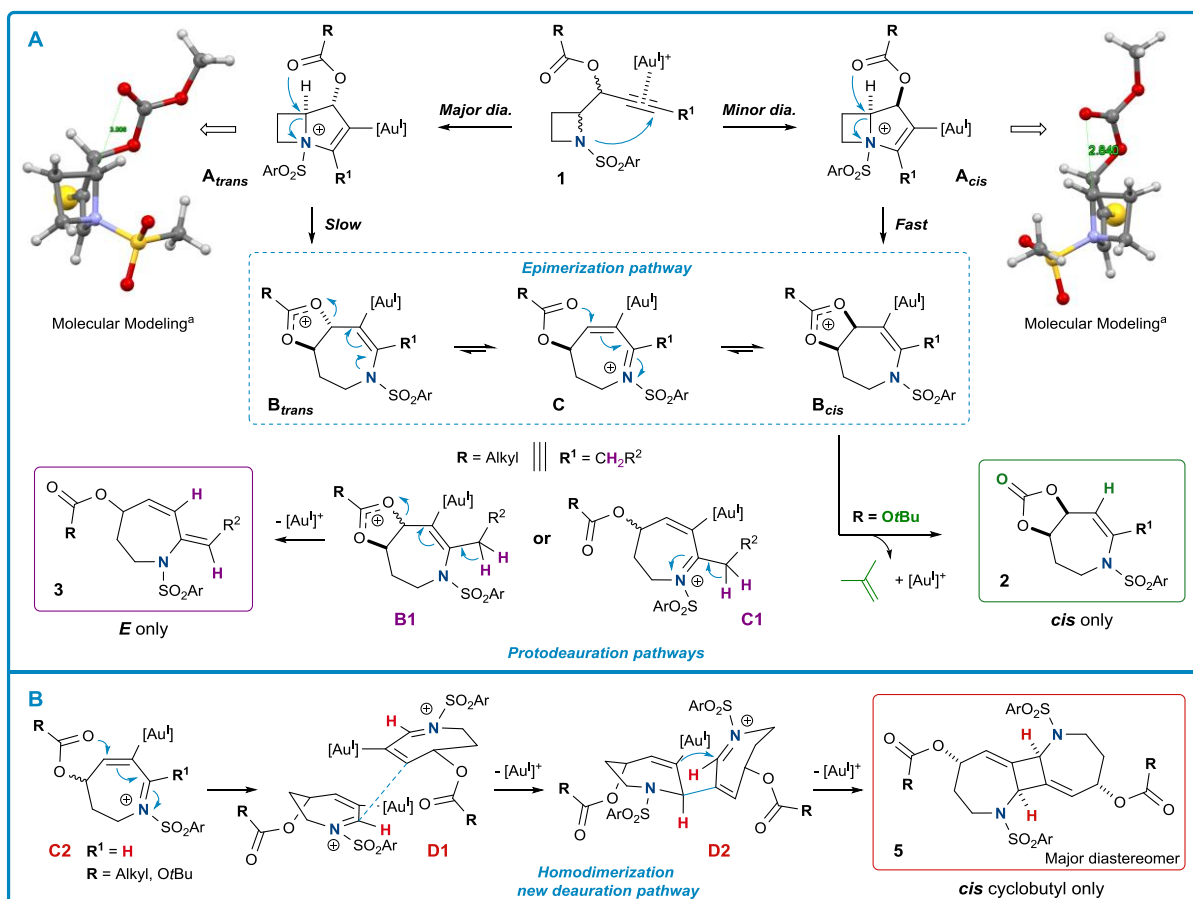


Figure 3. Proposed Mechanism.

aSimplified Molecular Modeling (MMFF) of the Postulated Vinyl-ammonium-gold(I) Intermediates Acis and Atrans.

(A) Proposed formation of the azetidyl carbonates 2 and esters 3.

(B) Proposed mechanism for the dimerization leading to 5.

## Conclusion

In conclusion, we developed a modular and efficient ring-expansion of readily available N-sulfonyl-1-(azetidin-2-yl)propargyl alcohol derivatives 1 catalyzed by gold(I). *cis*-Tetrahydroazepin-4,5-diol carbonates 2 (17 examples, 45-95%) were obtained from tert-butyl N-sulfonyl 1-(azetidin-2-yl)propargyl carbonates catalyzed by gold (I), while N-sulfonyl 1-(azetidin-2-yl)propargyl esters afforded *E*-2-alkylidene tetrahydroazepin-5-ol esters 3 (12 examples, 11-77%). These synthetic methods were extended to the formation of dihydrobenzoazepine 2' and *cis*-bis(azepinyl)cyclobutane derivatives 5 (7 examples, 73-97%) by varying the functionalization pattern of the starting materials. Finally, a rigorous mechanistic study allowed us to fully understand the origin of the high chemo- and stereoselectivity of these gold-catalyzed rearrangements. Further investigations to extend such strategy to other cyclic or acyclic secondary sulfonamides are ongoing in our laboratory.

## EXPERIMENTAL PROCEDURES

### Resource Availability

### Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Aurélien Blanc (ablanc@unistra.fr).

### Materials Availability

This study did not generate new unique reagents.

### Data and Code Availability

Crystallographic data for 2g, 2h, 3x, 5af, 5ah, and 1lg have been deposited in the Cambridge Crystallographic Data Center (CCDC) under accession numbers CCDC: 1936619, 1936620, 1848775, 1862796, 1862856 and 1936597. These data can be obtained free of charge from the CCDC at [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

### Representative Experimental Procedures for Gold(I)-Catalyzed Reactions

Synthesis of cis-tetrahydroazepin-4,5-diol carbonates 2: To the appropriate 1-(1-sulfonylazetid-2-yl)yn-1-yl carbonate 1 (1 eq.) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (c = 0.1 M) was added [CyJohnPhosAu(MeCN)]SbF<sub>6</sub> (5 mol %). The reaction mixture was stirred at room temperature until completion (typically 4 h). The solvent was then removed under reduced pressure and the crude residue was purified by chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O/heptane) leading to the desired cis-tetrahydroazepin-4,5-diol carbonate derivative 2.

Synthesis of E-2-alkylidene tetrahydroazepin-5-ol esters 3: The appropriate 1-(1-sulfonylazetid-2-yl)yn-1-yl ester 1 (1 eq.) and 4 Å molecular sieves were dried under reduced pressure and placed under argon atmosphere, then anhydrous CH<sub>2</sub>Cl<sub>2</sub> (c = 0.2 M) was added. Chloro[tris(2,3,4,5,6-pentafluorophenyl)phosphine]gold(I) (5 mol %) and AgSbF<sub>6</sub> (5 mol %) were dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (c = 0.2 M). The reaction mixture was stirred at room temperature for 15 min shielded from light. This solution was added to the solution of 1-(1-sulfonylazetid-2-yl)yn-1-yl esters 1. The reaction mixture was stirred at room temperature shielded from light until completion (typically 4 h). The solvent was then removed under reduced pressure and the crude residue was purified by chromatography using Et<sub>3</sub>N deactivated silica (SiO<sub>2</sub>, Et<sub>2</sub>O/heptane) leading to the desired E-2-alkylidene tetrahydroazepin-5-ol derivative 3.

Synthesis of cis-bis(azepinyl)cyclobutane Derivatives 5: To a solution of the appropriate 1-(1-sulfonylazetid-2-yl)prop-2-yn-1-yl ester 1 (1 eq.) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (c = 0.1 M) at room temperature was added the gold catalyst [CyJohnPhosAu(MeCN)]SbF<sub>6</sub> (5 mol %). The reaction mixture was stirred at room temperature until completion (typically 3 h). The solvent was then removed under reduced pressure and the crude residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc/heptane) leading to the desired cis-bis(azepinyl)cyclobutane derivative 5.

## SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at ...

Document S1. Supplemental Experimental Procedures, Table S1, and Figures S1–S5.

Table S1. Full Optimization of the Formation of Compound 2s.

Figure S1. Proposed Mechanism for Compound 2r'.

Figure S2. Proposed Mechanism for the Formation of 4.

Figure S3. 1-(1-Sulfonylazetid-2-yl)yn-1-yl Esters 1ap and 1aq Submitted to Standard Conditions

Figure S4. Molecular Modeling of the Postulated Vinyl-ammonium-gold(I) Intermediates Acis and Atrans

Figure S5. Molecular Modeling of the Postulated Dipolar Azepinium-Gold(I) Intermediate C Towards Formation of Intermediate D.

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## AUTHOR CONTRIBUTIONS

R.P., S.M., and N.K. performed all the synthetic experimental work. R.P. performed kinetics, labelling experiments, and molecular modeling calculations. A.B. directed the project. A.B. wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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23. It is worth mentioning that N-sulfonyl alkylidene tetrahydroazepines 3 are sensitive toward elimination and column chromatography. Appropriately neutralized silica gel (see experimental procedures section) must be used to ensure efficient purifications along with good isolated yields.
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