Gold Catalysis

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Gold-Catalyzed Oxidative Ring Expansion of 2-Alkynyl-1,2-Dihydropyridines or -quinolines: Highly Efficient Synthesis of Functionalized Azepine or Benzazepine Scaffolds**

Ming Chen, Yifeng Chen, Ning Sun, Jidong Zhao, Yuanhong Liu, and Yuxue Li**

Abstract: *A gold-catalyzed highly regio- and chemoselective oxidative ring expansion of 2-alkynyl-1,2-dihydropyridines and its analogues using pyridine-N-oxide as the oxidant has been developed. Ring expansion proceeds through exclusive 1,2-migration of a vinyl or phenyl group, whereas no 1,2-H and 1,2-N migration take place. The reaction provides an efficient and attractive route to various types of medium-sized azepine derivatives in generally high to excellent yields with a broad functional group tolerance. DFT studies indicate that the reaction proceeds through the formation of a cyclopropyl gold intermediate, and no gold carbene species is involved.*

Azepine and its derivatives represent an important class of medium-sized nitrogen heterocycles, because they are key structural subunits in many bioactive alkaloids and medicinally relevant compounds.[1] For example, stemoamide is one of the typical *Stemona* alkaloids isolated from *Stemona tuberosa* Lour, a Chinese traditional medicine used for the treatment of respiratory diseases.[2] (−)-Securinine can be used for the treatment of serious diseases such as amyotrophic lateral sclerosis (ALS) and poliomyelitis.[3] The 2*H*-azepine alkaloid chalciporone is responsible for the pungent taste of the common mushroom *Chalciporus piperatus*.[4] The commercially available benazepril is an angiotensin-converting enzyme inhibitor used to treat hypertension and heart attacks[5] (Figure 1). Therefore, the development of efficient methodologies for the synthesis of azepine-containing heterocycles is highly attractive.

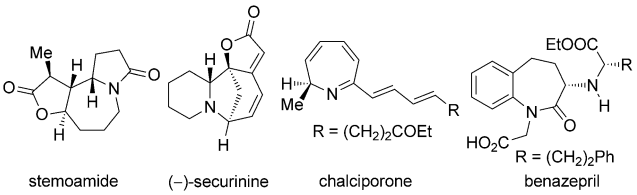
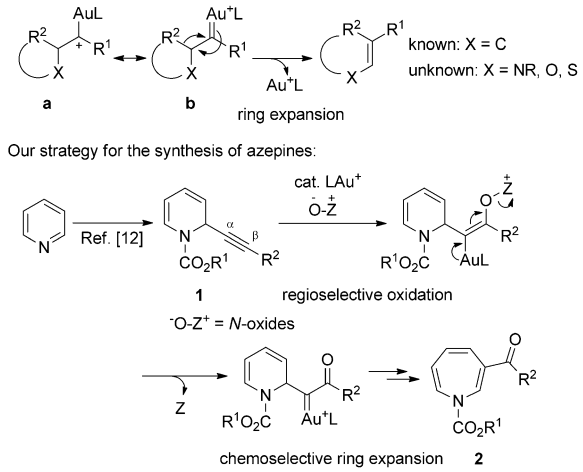


Figure 1. Representative biologically active azepines or benzazepines.



Scheme 1. Ring expansion reactions of gold carbenoid intermediates.

Recently, transformations involving electrophilic gold-stabilized carbenes or carbocations have attracted much attention, because these intermediates can undergo a diversity of valuable reactions,[6] such as C–H,[6a] N–H,[6b] O–H insertion,[6c] 1,2-migration,[6d] cyclopropanation,[6e–f] and skeletal rearrangements.[6g] Among these reactivities, the 1,2-migration of a C–C bond within a cyclized ring to the adjacent cation **a** or metal carbenoid **b** serves as an efficient protocol for the construction of new carbocycles with one-carbon ring expansion (Scheme 1, X = C).[7] We hypothesized that the related ring-expansion of a heterocycle-tethered metal carbenoid might allow the synthesis of medium-sized heterocycles (Scheme 1, X = NR, O, S) such as azepines. However, to the best of our knowledge, such reaction pattern has not been reported before.

On the other hand, the gold-catalyzed oxidation of alkynes using quinoline or pyridine *N*-oxides,[8] or sulfoxides[9] as oxygen donors has in recent years emerged as a powerful method for the rapid access to a wide variety of complex molecules. Although still under debate,[8g,h,9c,e] an α-oxo gold carbenoid was proposed as the key intermediate in these processes, generated by the addition of an oxygen donor to the gold-activated alkyne followed by fragmentation. During our ongoing program on gold-catalyzed oxidative reactions of alkynes,[10] we envisioned that an oxidation of 2-alkynyl-1,2-dihydropyridines **1** by *N*-oxides may lead to a regioselective generation of a gold carbenoid adjacent to the dihydropyr-

[*] M. Chen, Dr. Y.-F. Chen, N. Sun, J.-D. Zhao, Prof. Y.-H. Liu, Prof. Y.-X. Li
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (P. R. China)
E-mail: yhliu@sioc.ac.cn

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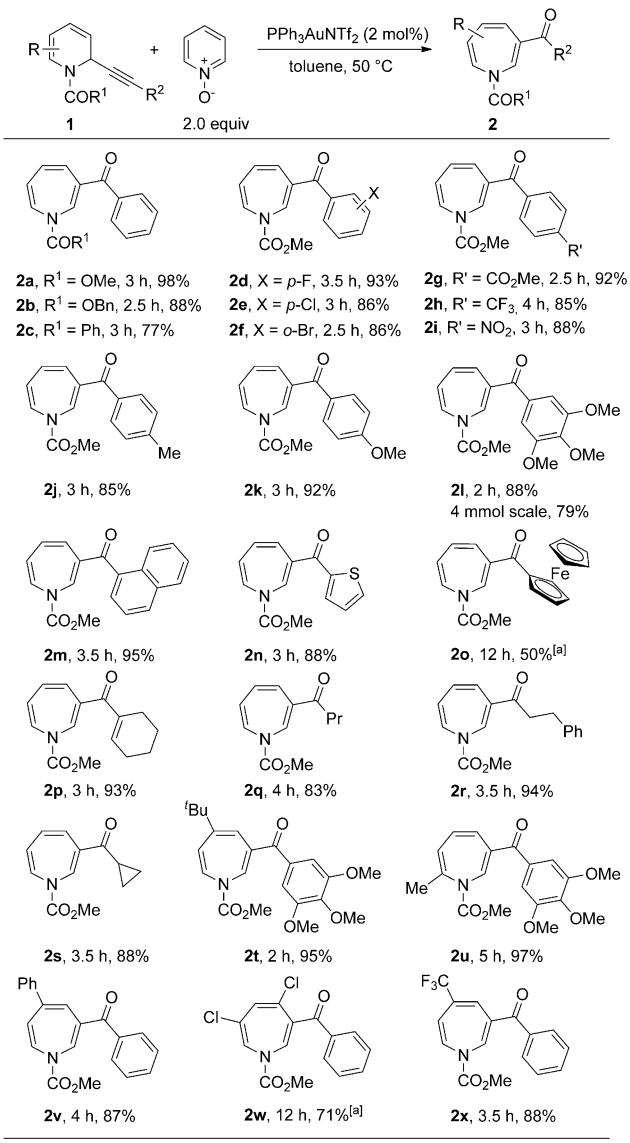
idine core due to the inductive effect of the N-CO_2R^1 group, which makes the β-carbon of the alkyne moiety more electrophilic. The subsequent ring expansion reaction may afford azepines (Scheme 1).[11] It is also noted that substrates **1** can be easily prepared from pyridines.[12] Herein, we report our success in developing a new synthetic route to azepines and benzazepines under mild reaction conditions using gold as the catalyst. Remarkably, the ring expansion proceeds through exclusive 1,2-migration of a vinylic group (C–C bond) without contamination by 1,2-H and 1,2-N migration.[13]

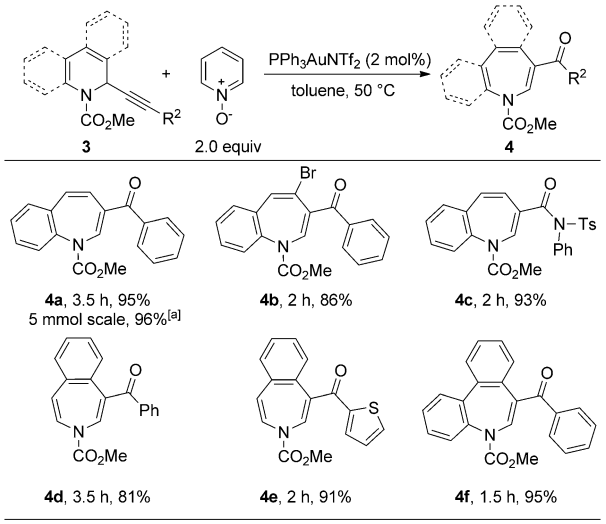
To investigate the feasibility of our hypothesis, we initially investigated the reaction of **1a** (R^2 = Ph) under the gold-catalyzed oxidation conditions. Gratifyingly, it turned out that the anticipated reaction occurred quite efficiently, and the ring-expanded 3-benzoyl-1H-azepine-1-carboxylate (**2a**) was obtained in good to high yields under various gold-catalyzed conditions.[14] For example, the use of PPh_3AuNTf_2 (2 mol%) as the catalyst and the most simple pyridine N-oxide as the oxidant resulted in the formation of **2a** in 98% yield in toluene at 50°C for 3 h (Scheme 2). The frequently used gold(I) complexes such as PPh_3AuSbF_6, PPh_3AuOTf, $IPrAuNTf_2$, or Johnphos(MeCN)$AuSbF_6$ also effectively catalyzed this rearrangement reaction. The results indicated that the reaction occurred selectively through a 1,2-migration of a vinylic group, and no 1,2-H and 1,2-N migration took place. Notably, the synthetic methods for unsaturated 1H-azepines are quite rare and usually multiple steps or specially substituted substrates are required.[15]

We next examined the substrate scope of this novel oxidative rearrangement reaction. To our delight, the reaction proved to be quite general with respect to the substitution pattern on the alkyne terminus and the dihydropyridine ring; in most cases, the desired azepine products were obtained in high to excellent yields (Scheme 2). We first investigated the effect of the nitrogen protection group and found that the reactions proceeded smoothly when substrates with N-CO_2Bn (**1b**) and N-Bz (**1c**) group were employed, affording **2b** and **2c** in 88% and 77% yields, respectively. Next, we examined the effect of substituents on the alkyne terminus. In case of aryl-substituted alkynes, a wide variety of functional groups on the aryl ring is tolerated well. For example, both electron-deficient (*p*-F, *p*-Cl, *o*-Br, *p*-CO_2Me, *p*-CF_3, and *p*-NO_2) and electron-rich (*p*-Me, *p*-OMe, 3,4,5-tri(MeO)) aryl alkynes underwent the reaction smoothly, providing the corresponding products **2d**–**2l** in high yields of 79–93%. 1-Naphthyl, 2-thienyl, and even ferrocenyl groups were also well compatible for this reaction and afforded **2m**–**2o** in 50–95% yields. Reaction of the cyclohexenyl-substituted **1p** gave **2p** in high yield of 93%. The reactions of alkyl-substituted alkynes such as propyl-, phenylethyl-, or cyclopropyl-substituted ones were also satisfactory, leading to **2q**–**2s** in 83–94% yields. Next, we anticipated that the use of substrates derived from functional pyridines would enable the incorporation of substituents on the various positions of the azepine ring. The reaction was applicable to the dihydropyridine substrates bearing alkyl, aryl, Cl, or CF_3 groups, and the corresponding products **2t**–**2x** were obtained in 71–97% yields. It should be noted that monocyclic azepines in general have a relatively low stability; it is recommended to store the products at low temperature under an inert atmosphere.



Scheme 2. Gold-catalyzed synthesis of 1H-azepines. Yields are of isolated products. [a] 80°C, 5 mol% PPh_3AuNTf_2 was used.

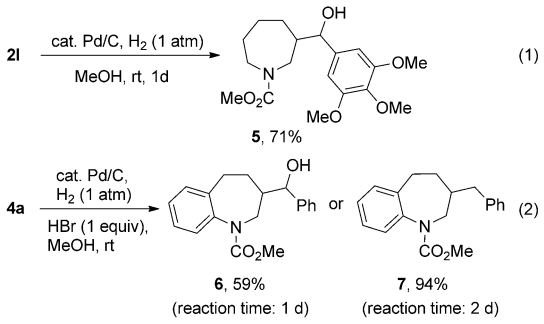
We were pleased to find that the reaction could also be extended efficiently to alkynes derived from quinolines (Scheme 3), in which 1H-benzo[b]azepines **4a** and **4b** were obtained in 95% and 86% yields, respectively. A substrate with an ynamide moiety was also suitable for this reaction, producing **4c** in 93% yield. Moreover, **3d** and **3e** derived from isoquinolines furnished 3H-benzo[d]azepines **4d** and **4e** in high yields of 81–91%. Substrate **3f** prepared from phenanthridine was efficiently transformed into dibenzo-[b,d]azepine **4f** in 95% yield. It was noted that the formation of **4d**–**4f** involved phenyl group migration. Thus an attractive advantage of this ring expansion strategy is the facile access to diverse types of azepine derivatives. The method is well adapted for gram-scale synthesis, as illustrated in the oxidation of **1l** (4 mmol scale) and **3a** (5 mmol scale), which gave



Scheme 3. Gold-catalyzed synthesis of benzazepines. Yields are of isolated products. [a] 1 mol% PPh_3AuNTf_2 was used.

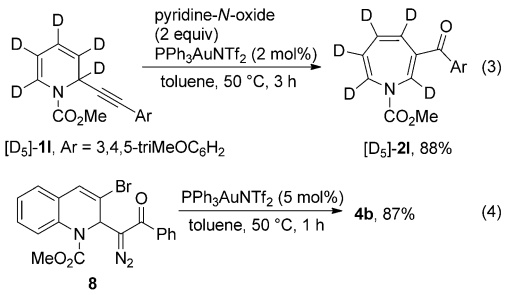
the corresponding **2l** and **4a** in 79% and 96% yield, respectively (see Schemes 2 and 3). The structure of azepines was further confirmed by X-ray crystallographic analyses of **2l**, **4b**, and **4e**.[16]

Many natural products contain a saturated azepane ring. Therefore, hydrogenation reactions were performed on azepine **2l** and benzazepine **4a**. To our delight, azepane **5** could be efficiently formed from **2l** in 71% yield [Eq. (1)].



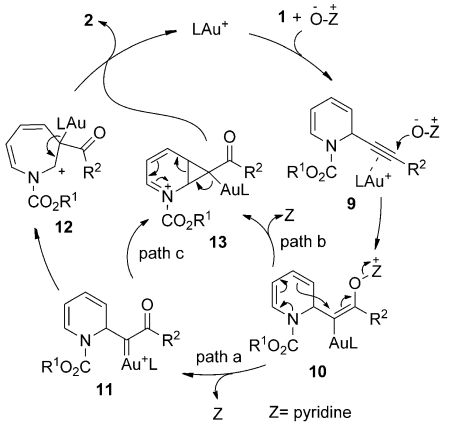
The structure of **5** was confirmed by X-ray crystallographic analysis of its ketone derivative.[16] The tetrahydrobenzo[*b*]-azepine **6** was found to be produced in 59% yield under acidic conditions.[17] Interestingly, extending the reaction time to two days led to the formation of dehydroxylated product **7** in 94% yield, possibly due to the dehydration of the initially formed **6** to give an alkene intermediate, which underwent further hydrogenation to furnish **7** [Eq. (2)].

To understand the mechanism, a deuterium-labeling experiment was performed. Treatment of [D_5]-**1l** under the standard reaction conditions provided [D_5]-**2l** in 88% yield without significant loss of deuterium, indicating that no cleavage of the propargylic C–H bond was involved [Eq. (3)]. We also examined the rearrangement reaction of diazocarbonyl compound **8**[18] in the presence of gold catalyst. The



reaction occurred smoothly at 50 °C with 5 mol% PPh_3AuNTf_2 to give the azepine **4b** in 87% yield [Eq. (4)]. In the absence of the gold catalyst, no desired product was observed. These results suggested that a gold carbenoid might be involved in the reaction process.

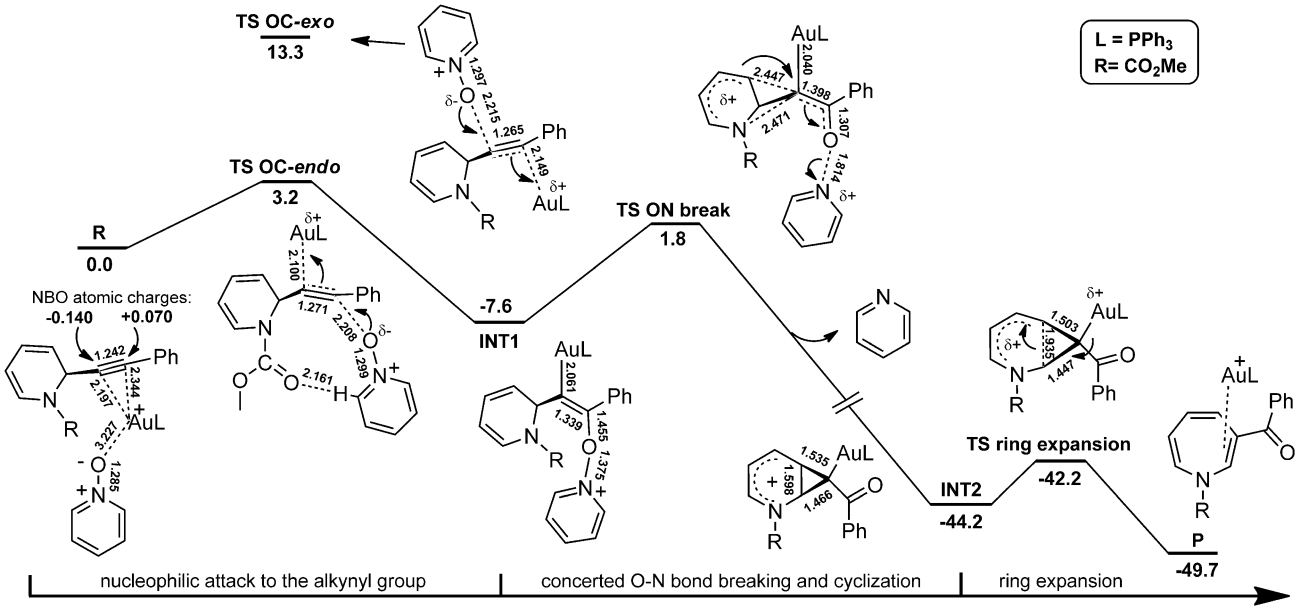
Based on the above results, we propose the following mechanism for this reaction (Scheme 4). Attack of pyridine



Scheme 4. Possible reaction mechanism.

N-oxide onto the gold-coordinated alkyne enables the formation of vinyl gold intermediate **10** with high regioselectivity. Fragmentation of **10** would afford the α-oxo gold carbenoid **11**, which undergoes ring expansion through 1,2-migration of the C–C bond to generate a cation **12**. Deauration of **12** delivers the azepine products **2** (path a). Alternatively, a cyclopropyl gold intermediate **13** might be generated through attack of the double bond on the vinyl gold moiety[8f] in **10**. This could be followed by ring opening to furnish the azepine **2** (path b).[11,19] **13** may also be formed from **11** (path c).

To disclose the reaction mechanism, density functional theory (DFT) studies were performed.[14] As shown in Scheme 5, the gold catalyst and substrate **1a** form the reactant complex **R** (0.0 kcal mol^{-1}). Under the activation of the catalyst, the O atom of the pyridine *N*-oxide attacks the C≡C bond in *exo* or *endo* manner (**TS OC-*exo***, 13.3 kcal mol^{-1}; **TS OC-*endo***, 3.2 kcal mol^{-1}). The *endo* attack is much more favorable and leads to intermediate **INT1** (−7.6 kcal mol^{-1}). The positive natural bond orbital (NBO) atomic charges (+0.070) on the alkynyl carbon[20] connected with the phenyl



Scheme 5. The calculated pathways of gold-catalyzed oxidative ring expansion of 2-alkynyl-1,2-dihydropyridines. The relative free energies (ΔG) are in kcal mol^{-1}. The selected bond lengths are in Å. Selected NBO charges are given. Calculated at the PBE1PBE/6-31 + G**/SDD level.

group, and the hydrogen bonding between the ester group and the *N*-oxide may account for this regioselectivity. Subsequently, the concerted N–O bond breaking and cyclization (**TS ON-break**, 1.8 kcal mol^{-1}) afford the cyclopropyl gold intermediate INT2. In this concerted process, the forming gold carbene is attacked by the electron-rich C=C double bond on the dihydropyridine ring, similar to that in the formal 3,3-rearrangement of alkynyl aryl sulfoxides.[9e] Intrinsic reaction coordinate (IRC) calculations confirmed that no gold carbene species formed along the reaction pathway.[14] In the last step, the ring expansion of **INT2** leads to the final product. Therefore, the calculated results indicate that the 1,2-migration of the vinylic group proceeds stepwise, and path b (Scheme 4) is the most favorable pathway.

In summary, we have succeeded in developing a gold-catalyzed highly regioselective oxidative ring expansion of 2-alkynyl-1,2-dihydropyridine and its analogues using pyridine-*N*-oxide as the oxidant. The reaction provides an efficient and attractive route to various types of azepine derivatives in generally high to excellent yields with broad functional group tolerance. These results demonstrate the great synthetic utility of this methodology.

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