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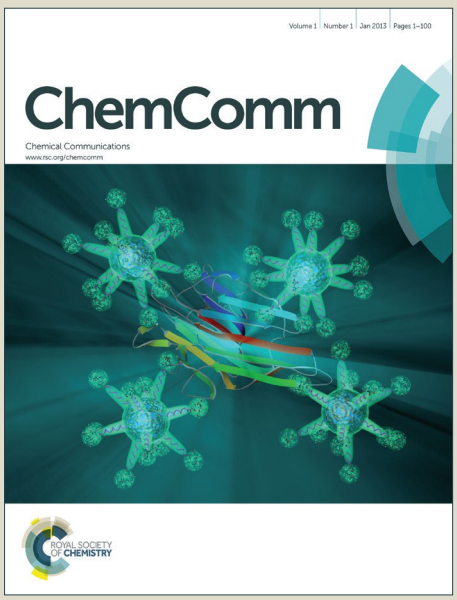

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Facile synthesis of 1-benzoazepine derivatives *via* gold-catalyzed regioselective cycloisomerization reactions of *N*-(*o*-alkynylaryl)-*N*-vinyl sulfonamides

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Gold-catalyzed, regioselective cycloisomerization of *N*-(*o*-alkynylaryl)-*N*-vinyl sulfonamides afforded high yields of 2-sulfonylmethyl-1-benzoazepine derivatives. This *7-endo-dig* selective cyclization proceeds *via* a labile 1-benzoazepine intermediate incorporating an exocyclic double bond. The cyclization substrates were assembled in two steps from readily available materials using Sonogashira coupling and a Cs_2CO_3-mediated formal vinylic substitution.

Benzo-fused, seven membered nitrogen heterocycles, commonly known as benzoazepines, are found in a variety of biologically active synthetic compounds.[1] Benzoazepines are further classified based on the extent of unsaturation as well as the position of the nitrogen atom. Among them, the 1-benzoazepine moiety forms the core units of antagonists of *N*-methyl-D-aspartate (NMDA),[2] vasopressin V_2 receptor,[3] CC chemokine receptor-5[4] as well as anti-parasitic agents[5] potentially useful for the treatment of leishmaniasis. Despite their importance, the 1-benzoazepine class of compounds has received scant synthetic attention when compared to 2- and 3-benzoazepines. Only a few methods based on approaches such as intramolecular Heck coupling,[6] iridium-catalyzed asymmetric allylic amination,[7] cyclization reactions of suitably substituted Morita-Baylis-Hillman adducts[8] and insertion of diazocarbonyl compounds to quinolinium salts (Scheme 1a)[9] have been described for the construction of 1-benzoazepines. Evidently, there is a demand for general and convenient protocols to access substituted 1-benzoazepine derivatives from readily available precursors.

Homogeneous gold catalysis constitutes a versatile method for the synthesis of carbocycles and heterocycles of varying ring sizes and oxidation levels.[10] Gold-catalyzed construction of nitrogen heterocycles follows one of the following two routes; intramolecular addition of nitrogen nucleophiles to gold-activated π-systems (carbon-nitrogen bond formation) or cyclization of nitrogen tethered enynes (carbon-carbon bond formation).[11] Formation of seven-membered nitrogen heterocycles in gold-catalyzed cyclization of nitrogen bearing π-systems, however, are relatively rare.[12] In general, nitrogen tethered 1,6- and 1,7-enynes are known to cycloisomerize in the presence of gold catalysts to afford five or six-membered nitrogen heterocycles.[13]

Recently, we reported gold-catalyzed propargyl-Claisen rearrangement of *N*-propargyl-*N*-vinyl sulfonamides leading to the divergent synthesis of 2-sulfonylmethylpyrroles and dihydropyridines.[14] The aza-enyne precursors were, in turn, conveniently prepared from 2-bromoallyl sulfones and sulfonamides *via* a base-mediated formal vinylic displacement reaction that was developed in our group.[15] This metal-free union of a vinyl bromide with sulfonamides affords *N*-vinyl sulfonamides that incorporate an allyl sulfone moiety. The conter-intuitive higher thermodynamic stability of allyl sulfones *vis-à-vis* vinyl sulfones presumably prevents the isomerization of this double bond to form the more substituted and conjugated vinyl sulfone.[16] We surmised that the nucleophilicity of these *N*-vinyl sulfonamides could be exploited in gold-catalyzed synthesis of higher nitrogen heterocycles. Our efforts along this direction culminated in the development of a gold-catalyzed, regioselective cycloisomerization of *N*-(*o*-alkynylaryl)-*N*-vinyl sulfonamides **1** to afford 1-benzoazepine derivatives **2** (Scheme 1b). Intriguingly, the more commonly observed and entropy-favored *6-exo-dig* mode of cyclization did not occur. The preliminary results of this study constitute the subject matter of this communication.

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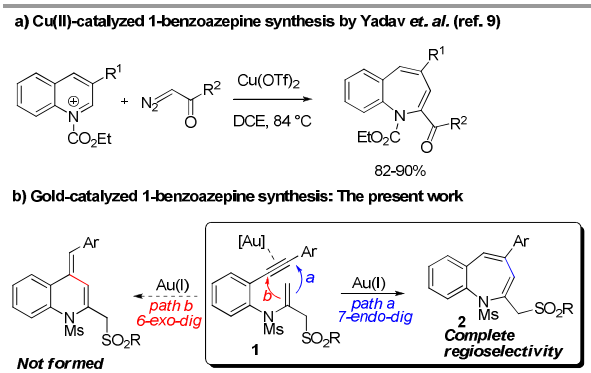
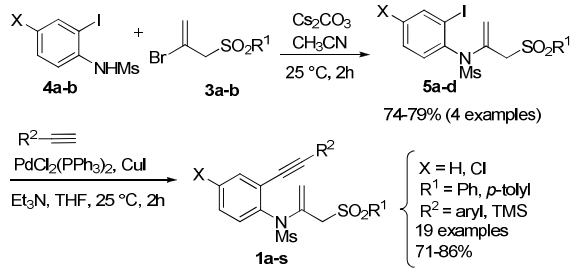


Scheme 1: (a) Yadav's method for the synthesis of fully unsaturated 1-benzoazepine derivatives. (b) The present work

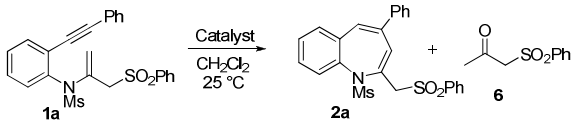
The aza-enynes **1** employed in the present study were conveniently prepared in two steps from readily available precursors. The union of bromoallyl sulfones **3a-b** and *o*-iodoaniline derivatives **4a-b** was achieved by the cesium carbonate-mediated formal vinylic displacement reaction that was recently developed in our group. Bromoallyl sulfones **3a-b** function as stable synthetic equivalents of allenyl sulfones in this reaction.[17] The *N*-vinyl sulfonamides **5a-d** were then subjected to Sonogashira coupling with various terminal alkynes to install the alkynyl functionality (Scheme 2). It is noteworthy that the potentially base-sensitive allylic sulfone unit of **5** was unaffected during the Sonogashira reaction.[16]



Scheme 2: Synthesis of cyclization substrates

With an assortment of 3-aza-1,6-enynes **1a-s** at hand, the π-activation of their alkyne subunits by gold and silver catalysts were then explored. Results of the optimization study carried out on the representative substrate **1a** are summarized in Table 1. At ambient temperature, **1a** was unchanged on treatment with $AuCl_3$, PPh_3AuCl, $AgSbF_6$ and AgOTf even after 12h (entries 1-4). The combination of $AgSbF_6$ and two gold catalysts ($AuCl_3$ and PPh_3AuCl) was also ineffective in promoting any reaction (entries 5-6). On heating, PPh_3AuCl and $AgSbF_6$ catalyzed the undesired hydrolytic cleavage of **1a** affording low yields of 2-(phenylsufonyl)acetone **6** (entries 7-8). Echavarren's gold(I) catalyst $[JohnPhosAu(CH_3CN)]SbF_6$, on the other hand, promoted the conversion of **1a** into a labile product that appeared to isomerize partially during chromatography on silica (entry 9). Further experiments revealed that the addition of 2 equivalents of triethylamine to the reaction mixture after 12h caused rapid and complete isomerization of the initially formed intermediate to afford a single, stable product (entry 10). The latter was assigned benzoazepine structure **2a** based on standard spectroscopic analysis. We observed that both acids and bases promoted the isomerization to various extents. Triethylamine was chosen for this purpose because it promoted an instantaneous and clean isomerization (< 1 min). Additionally, its use allowed a simple work-up procedure which involved the addition of silica gel to the reaction mixture, evaporation of solvent and subsequent chromatography.

Table 1. Optimization of reaction conditions for cycloisomerization of *N*-vinyl sulfonamide **1a**.[a]



Entry	Catalyst (loading, mol%)	Time (h)	Product (Yield)[b]
1[c]	$AuCl_3$ (2)	12	**1a**
2[c]	PPh_3AuCl (2)	12	**1a**
3[c]	$AgSbF_6$ (5)	12	**1a**
4[c]	AgOTf (5)	12	**1a**
5[c]	$AuCl_3$ (2) & $AgSbF_6$ (5)	12	**1a**
6[c]	PPh_3AuCl (2) & $AgSbF_6$ (5)	12	**1a**
7[d]	PPh_3AuCl (2)	2	**6** (44%)
8[d]	AgOTf (5)	2	**6** (53%)
9[e]	$(JohnPhos)Au(CH_3CN)SbF_6$ (2)	12	-
10	**$(JohnPhos)Au(CH_3CN)SbF_6$ (2), then 2 equiv Et_3N**	**12**	**2a (89%)**

[a]Reaction conditions: **1a**, catalyst, CH_2Cl_2, 25 °C; [b]isolated yields; [c]**1a** was isolated unchanged; [d]reaction at 40 °C; [e]**1a** was consumed and the product isomerized during chromatography to afford a mixture of products.

The results depicted in Table 1 clearly demonstrate the superior catalytic ability of Echavarren's catalyst $[JohnPhosAu(CH_3CN)]SbF_6$ when compared to $AuCl_3$ and PPh_3AuCl.[18] Interestingly, the *7-endo* mode of cylization is preferred here over the kinetically favored *6-exo* pathway leading to quinoline-class of products. The efficiency and exclusive regioselectivity of the pilot reaction prompted us to explore the method's scope and generality for the construction of benzoazepine system. Thus, all the available 3-aza-1,6-enynes **1a-s** were subjected to the optimized conditions for cycloisomerization. Pleasingly, these substrates emulated their congener **1a** in gold-catalysed cycloisomerization reactions to afford excellent yields of corresponding benzoazepines **2a-r** (Table 2). Single crystal X-ray analysis of the representative benzoazepine **2r** confirmed the assigned structure.[19] Disappointingly, the trimethylsilyl-substituted

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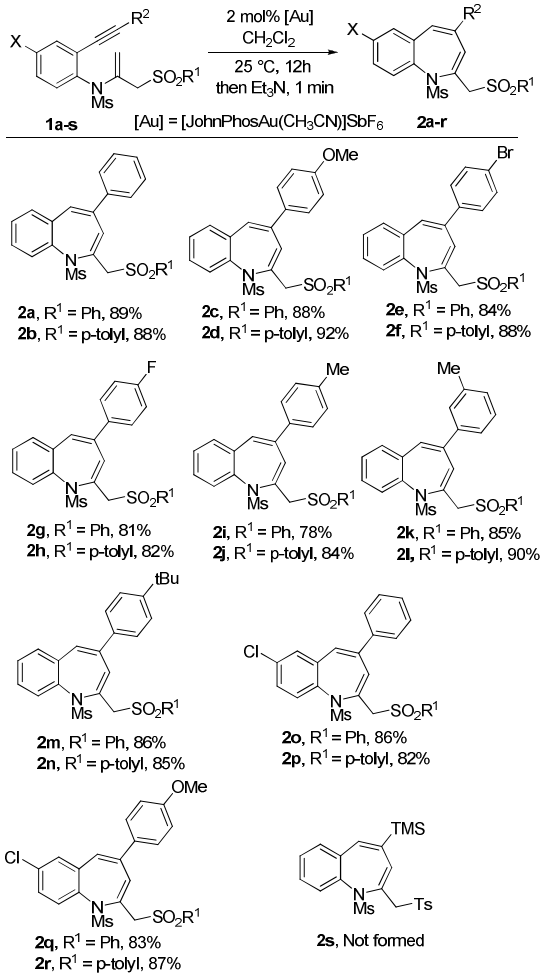
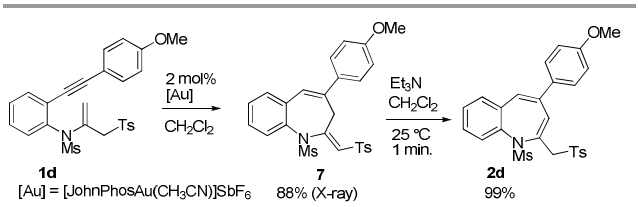
alkyne **1s** afforded an intractable mixture of products on exposure to the gold catalyst. Attempts to generate the corresponding terminal alkyne by desilylation of **1s** also furnished a mixture of products presumably formed via the base-mediated isomerization of the allyl sulfone moiety.

Table 2. Scope of gold-catalyzed cycloisomerization of 3-aza-1,6-enynes 1a-s.[a,b]



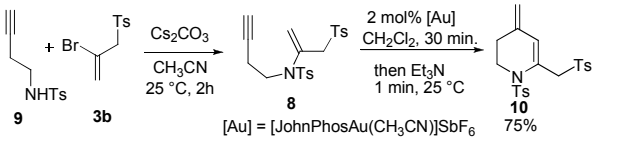
[a]Reaction conditions: **1a-s** (0.20 mmol), Au-catalyst (3 mg, 2 mol %), CH_2Cl_2 (2 mL), 25 °C, 12h, then Et_3N (0.06 mL, 0.40 mmol), 1 min. [b]Yields of products isolated after column chromatography.

It was of interest to identify the unstable intermediate that presumably isomerized on exposure to triethylamine to afford the benzoazepines **2a-r**. Our efforts along this direction met with fortuitous success in the case of the *p*-methoxyphenyl group-bearing aza-enyne **1d**. Flash chromatography of the reaction mixture after gold-catalyzed reaction (without triethylamine treatment) of the latter afforded a single compound. The latter was stable enough to permit complete spectroscopic analysis and it was assigned the benzoazepine structure **7** in which the double bond occupied an exocyclic position (Scheme 3). Unambiguous evidence for the assigned structure and geometry of the exocyclic double bond was obtained by single crystal X-ray analysis.[19] It was observed that **7** was stable in crystalline state but isomerized slowly in solution (see ESI for details). Treatment of **7** with triethylamine caused rapid isomerization to afford quantitative yield of the benzoazepine **2d**. By analogy, it may be deduced that the gold-catalyzed cycloisomerizations of aza-enynes **1a-s** generate vinylic sulfone products (such as **7**) that are then transformed into the more stable allylic sulfone **2a-s** *via* base (or acid) mediated isomerization.[16]

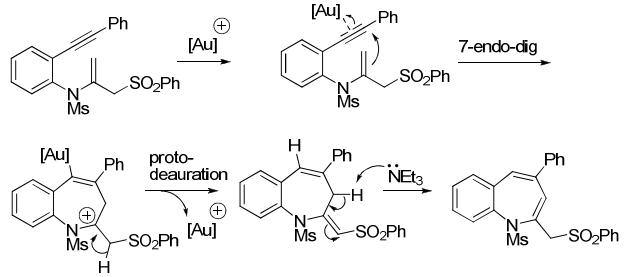


Scheme 3. Isolation of intermediate **7** and its Et_3N-mediated isomerization

The above-described regioselective gold-catalysed cycloisomerization of benzenoid 3-aza-1,6-enynes **1a-s** inspired us to examine the reaction of an aliphatic analogue under similar conditions. A representative aliphatic 3-aza-1,6-enyne **8** was prepared via the cesium carbonate-mediated vinylic displacement reaction of bromoallyl sulfone **3b** with yne-sulfonamide **9** (Scheme 4). On subjecting **8** to the conditions of gold-catalyzed cycloisomerization, the 4-methylene tetrahydropyridine derivative **10** was obtained in 75% yield. Evidently, **10** is formed *via* a 6-exo-dig mode of cyclization. Presumably, this is the result of bonding of the gold catalyst to the less hindered terminal carbon of the alkyne unit. The flexible bis-methylene tether in **8** could also impose a higher entropic demand on the 7-endo mode of cyclization.



Scheme 4. Gold-catalyzed cycloisomerization of aliphatic 3-aza-1,6-enyne **8** to afford a 4-methylene tetrahydropyrdine derivative **10**.



Scheme 5. A mechanistic hypothesis for the Au-catalyzed cycloisomerization

A simplified mechanistic rationalization for the gold-catalyzed cycloisomerization can be advanced as depicted in Scheme 5. The alkyne unit activated by co-ordination to the Au(I) catalyst suffers a nucleophilic attack via the electron rich end of the enamine-like olefin of **1a**. Loss of the acidic α-sulfonyl proton from **11** generates the exocyclic olefin **12**. Exposure to triethylamine promotes the isomerization of the double bond into the endocyclic position to

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afford the final product **2a**. The *7-endo-dig* ring closure is uncommon in gold-catalyzed cycloisomerizations of enynes, however, a preference for this pathway has been reported in isolated cases of formation of 7-membered lactams from aryl ring-bearing alkynes.[20]

In conclusion, an exclusively *7-endo-dig*-selective, gold-catalyzed cycloisomerization of *N*-(*o*-alkynylaryl)-*N*-vinyl sulfonamides to afford 2-sulfonylmethyl-4-arylbenzoazepines in excellent yields is developed. This unique class of nitrogen heterocycles can be conveniently synthesized from readily available precursors that are, in turn, assembled via a base-mediated vinylic substitution reaction of 2-bromoallyl sulfones and aniline-sulfonamides. The present protocol allows the generation of a library of hitherto inaccessible benzoazepines for biological evaluation. The well-known pharmacological importance of closely related benzodiazepines makes such an endeavor worthwhile and efforts along this direction are currently underway.

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