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Straightforward Synthesis of Bridged Azaoxa Skeletons: Gold-Catalyzed Aminoketalization of Garner's Aldehyde-Derived Alkynes

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In memory of Rafael Suau

Although possibly considered metabolically unstable, N,O-aminal moieties are present in a variety of products exhibiting relevant biological properties.[1] Interesting examples include the alkaloids of the zoanthamine family, which contain a bridged N,O-aminal subunit and may be used as analgesic and antiosteoporotic drugs, in addition to their potent antileukemia and antiplatelet activities.[2] The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature.[3] In particular, gold-catalyzed intramolecular addition of oxygen and nitrogen nucleophiles across a carbon–carbon triple bond is intriguing from the point of view of regioselectivity (*endo* versus *exo* cyclization) and because it is one of the most rapid and convenient methods for the preparation of heterocycles. However, it should be remarked that despite the fact that bicyclic acetals were successfully obtained with Au^{I}, Au^{III}, and Pt^{IV}-based catalysts by using two intramolecular hydroxyl groups as nucleophiles,[4] the related direct intramolecular conversion of alkynes into cyclic N,O-aminals has not been described.[5] In continuing with our interest in metal-catalyzed processes employing alkynes and allenes,[6] the direct synthesis of N,O-aminals from oxazolidine-derived alkynes emerged as an attractive transformation to develop.[7]

Taking the above aspects into consideration, we decided to study the challenging gold-catalyzed direct bis-heterocyclization of Garner's aldehyde-derived alkynes (latent and stable alkynic aminoalcohols). The structures of the alkynyloxazolidines derivatives **1** that we synthesized and used for the bis-heterocyclization reaction are shown in Figure 1.[8]

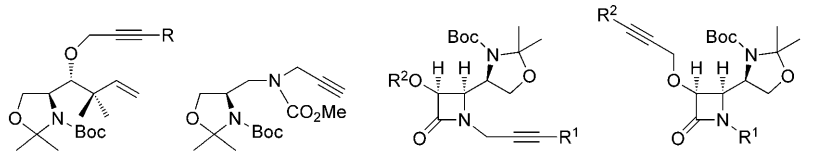

Figure 1. Structures of alkynyloxazolidines **1a–l**. Bn = benzyl, Boc = *tert*-butoxycarbonyl, PMP = 4-$MeOC_6H_4$.

To explore the reactivity of functionalized compounds **1** towards intramolecular aminoacetalization we selected alkyne **1a** as a model substrate. Attempts of the cyclization reaction of **1a** using $PdCl_2$, AgOTf, and $PtCl_2$ catalysts failed. Nicely, it was found that [$AuClPPh_3$]/AgOTf is an excellent catalytic system for this purpose. Adding a stoichiometric amount of water into the reaction system along with a catalytic amount of Brønsted acid (PTSA) did improve the yield of **2a**. Gratifyingly, after considerable experimentation, it was found that alkynic oxazolidine **1a** on exposure to the system [$AuClPPh_3$] (2.5 mol%), AgOTf (2.5 mol%), PTSA (10 mol%), and H_2O (100 mol%) in dichloromethane at 80 °C on a sealed tube, directly afforded bridged bicyclic aminal **2a** through a regio- and diastereoselective 7-*exo*/5-*exo* bis-heterocyclization (Scheme 1). AgOTf cannot be considered as a co-catalyst because its action is generally assumed to be restricted to the formation of cationic gold species by anion exchange.[9] Changing the nature of the counterion has little effect in the reaction, because replacing AgOTf by other silver salts such as $AgSbF_6$ or $AgBF_4$ did not show any appreciable difference. The comparative studies of aminal formation with addition of PTSA demonstrat-

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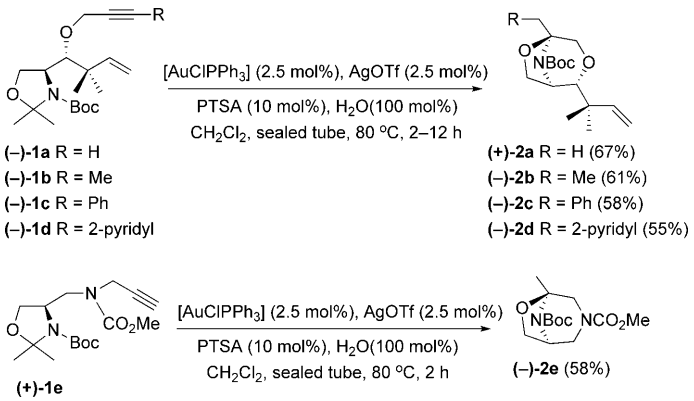
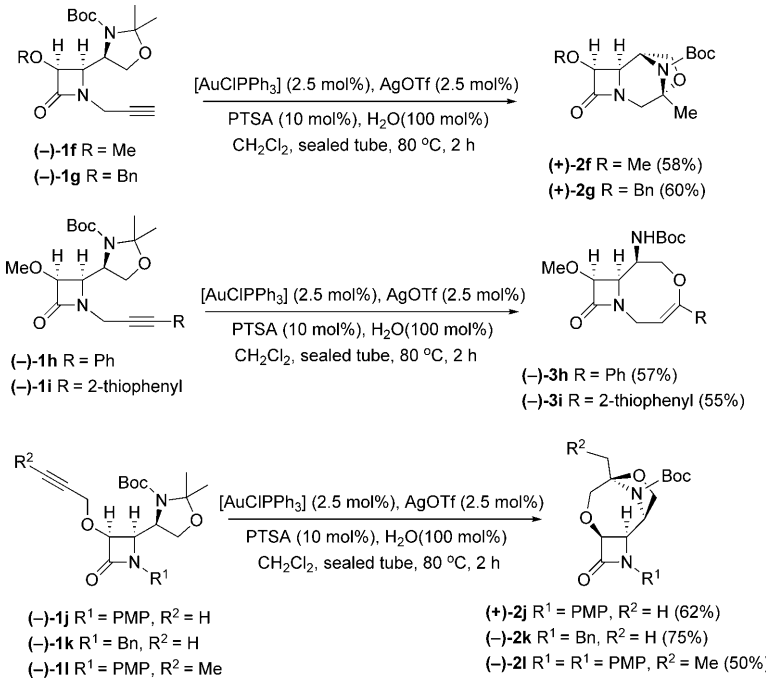


Scheme 1. Controlled N,O-cyclo-aminalization reaction of alkynyloxazolidines **1a–e** under gold-catalyzed conditions. PTSA = *p*-Toluenesulfonic acid, Tf = triflate.

ed that the presence of the Brønsted acid gives higher yields, and that the acid additive acts as a collaborator but not as a catalyst.[10] Thus, the catalytic system may consist of [Au(OTf)PPh_3] generated in situ from [AuClPPh_3] and AgOTf. Under the optimized reaction conditions, we investigated the generality of the catalytic protocol under gold catalysis for oxazolidine-tethered alkynes **1b–e**. By examining the influence of the R substituents on the alkyne side chain, we found that substrates **1a–e**, which contain hydrogen, aryl, heteroaryl, or alkyl groups were smoothly transformed into products **2** in reasonable yields (Scheme 1).

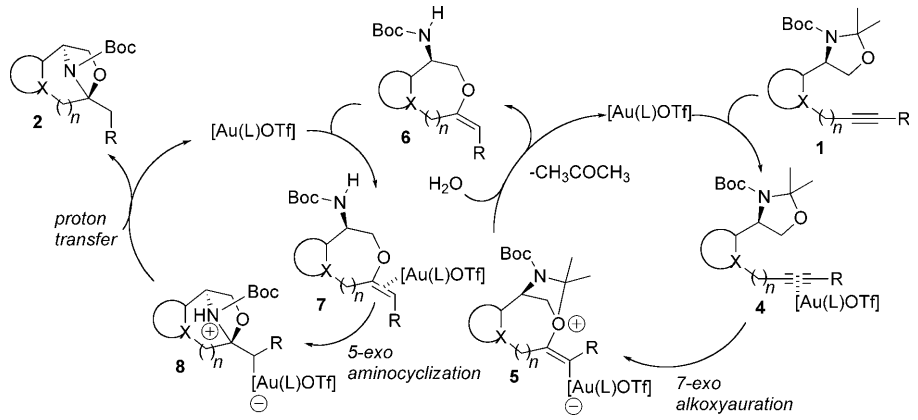
To assess the scope of this reaction, the even more challenging enantiopure alkynyloxazolidine-tethered 2-azetidinones **1f–l** were tested as cyclization precursors. Using the terminal alkynes **1f,g**, the system [Au(OTf)PPh_3] gave the desired tricyclic bridged N,O-aminals **2f,g** as the sole isomers in reasonable yields (Scheme 2). Next, we investigated the reactivity of nonterminal alkynes **1h,i**. Notably, substituted and unsubstituted 2-azetidinone-tethered alkynes at the terminal position followed different reactivity patterns. Alkynyloxazolidines **1h,i** exclusively afforded the bicyclic adducts **3h,i**, but the bis-cyclization products could not be obtained (Scheme 2). These results show that the oxygen atom participates in the first cyclization reaction to form a fused eight-membered ring, which is not followed by the second cyclization of the NBoc group. Significantly, in contrast to the gold-catalyzed reaction of terminal alkynyloxazolidines **1f,g**, which lead to the 6-oxa-3,8-diazabicyclo[3.2.1]octane derivatives **2f,g** through a 7-*exo*/5-*exo* bis-heterocyclization of the oxazolidine group towards the internal alkyne carbon (proximal adducts), the reaction of alkynyloxazolidines **1h,i** substituted at the terminal end under identical conditions gave the 1,5-oxazocine derivatives **3h,i** (distal adducts) as the sole products (Scheme 2), through an exclusive 8-*endo* oxycyclization by attack of the oxygen atom to the external alkyne carbon. To our delight, when the alkyne substituent was moved from position N1 to C3, as in 3,4-tethered alkynyloxazolidines **1j–l**, it furnished the corresponding bridged adducts **2j–l** in fair yields and as only one isomer in its reaction with the gold catalytic system (Scheme 2). The precious metal-catalyzed 8-*exo*/5-*exo* bis-heterocyclization of alkynyloxazolidines **1j–l** gave tricyclic bridged N,O-aminals **2j–l** containing a seven-membered ring (Scheme 2). Remarkably, Scheme 2 shows how the mild conditions of gold catalysis allow the chemoselective formation of anellated β-lactams without harming the sensitive four-membered ring. Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, upon purification of sensitive bridged azaoxacycles **2** by flash chromatography, some decomposition was observed, which may be responsible for the moderate isolated yields.

A possible pathway for the gold-catalyzed alkynyloxazolidine cyclization may initially involve the formation of a π-complex **4** through coordination of the gold salt to the triple bond of alkynyloxazolidines **1**.[11] Next, 7-*exo* oxymetalation forms zwitterionic enol vinylmetal species **5**. Intermediates **5** did evolve through demetalation and oxazolidine hydrolysis forming methylenic oxacycles **6** and releasing the metal cat-



Scheme 2. Direct gold-catalyzed heterocyclization of alkynyloxazolidines **1f–l**. PMP = 4-MeOC_6H_4.

alyst into the first catalytic cycle. Methylenic oxacycles **6** enter the second catalytic cycle generating species **7** by coordination of the alkene group with the metal and thus enhancing the electrophilicity of the resulting enol ether. Subsequent intramolecular nucleophilic attack of the nitrogen to the more substituted alkene position would form the ate complex **8**. Demetalation linked to proton transfer liberates adduct **2** with concomitant regeneration of the gold catalyst, thus closing the second catalytic cycle (Scheme 3).



Scheme 3. Mechanistic explanation for the gold-catalyzed bis-heterocyclization of alkynyloxazolidines **1**. L = ligand.

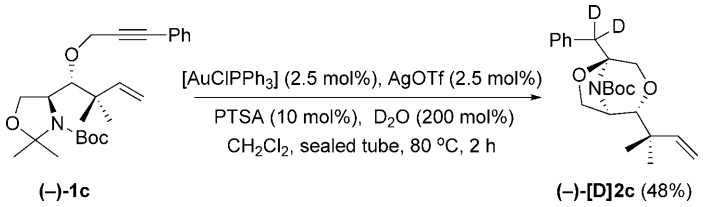
In the conversion of alkynyloxazolidines **1** into azaoxacycles **2**, a possible first step is water addition onto the triple bond that results in the corresponding ketone intermediate, which might suffer a further transacetalization. However, this mechanistic scenario seems less likely because the addition of a stoichiometric amount of water into the reaction system did slightly improve the yield of bridged N,O-acetals **2**, but it is not essential. Thus, the reaction of alkynyloxazolidine **1a** could be carried out with the exclusion of water to afford bridged azaoxacycle **2a** in a reasonable 52% yield.

It may be contemplated that under these reaction conditions the oxazolidine might be hydrolyzed first. Thus, we prepared the Boc-protected amino alcohol derived from **1f** using $BiCl_3$ (for details see the Supporting Information) to compare the catalytic efficiency with the parent alkynyloxazolidine **1f**. Under the standard bis-cyclization conditions ([$AuClPPh_3$] (2.5 mol%), AgOTf (2.5 mol%), PTSA (10 mol%), and H_2O (100 mol%), dichloromethane, 80°C, sealed tube), comparable yields of adduct **2f** were obtained starting from both alkynyloxazolidine **1** or its free amino alcohol.

Alternatively, we carried out an experiment to check whether oxazolidines derivatives that do not have the tethered alkyne hydrolyze under gold-catalyzed conditions. Thus, after treating (*R*)-*tert*-butyl-4-[(2*R*,3*S*)-3-acetoxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]-2,2-dimethyloxazolidine-3-carboxylate under the standard bis-cyclization conditions for 16 hours, the above oxazolidine lacking alkyne groups gave the corresponding amino alcohol, which could be isolated in moderate yield. It should be noted the prolonged reaction time for hydrolysis in comparison with the short time (2 h) for completion of the reaction of bis-heterocyclization in related alkynyl oxazolidines. Besides, the fact that the reaction of oxazolidine **1a** catalyzed by the π-philic gold complexes [Au(counteranion)PPh_3] alone in the absence of acid additive proceeded to afford the corresponding bridged N,O-acetal **2a**, may also support this order of steps: the N,O-acetal in species **1** attacks the alkyne and the resulting oxonium is then hydrolyzed. However, taking all the experiments into account, a mechanistic scenario that involves the initial formation of the 1,2-amino alcohol followed by bis-heterocyclization cannot be completely ruled out.

Gold is a possible source of protons owing to the equilibrium between gold(I) and H_2O. Taking into account that alkylgold compounds are difficult to protonate,[12] it is also likely that the catalytic cycle on the left side of Scheme 3 may be proton-catalyzed.

Although the isolation of bicycles **3h**,**i** from the reactions of **1h**,**i** outlined in Scheme 2 was fortuitous, the result argues in favor of the mechanism shown in Scheme 3, because an observable intermediate of type **6** was formed. This argument was further corroborated by the observation that when alkynyloxazolidine **1c** was treated under heterocyclization conditions employing D_2O (200 mol%) instead of H_2O, adduct **2c** with incorporation of two deuterium atoms at the methylenic group was achieved (Scheme 4).



Scheme 4. Gold-catalyzed bis-heterocyclization of alkynyloxazolidine **1c** in presence of D_2O.

In conclusion, an efficient gold-catalyzed synthetic route to bridged azaoxa skeletons from easily accessible alkynyloxazolidine substrates under mild conditions has been reported. The reactions were found to proceed with complete control of product regio- and stereoselectivity in the presence of the combined gold/silver and acid catalyst system. Further exploration of the mechanism, scope, and synthetic applications of the present reaction are currently under way.

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Keywords: alkynes · gold · heterocycles · selectivity · synthetic methods

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[7] In the current work, popular protected N,O-building blocks are used. Thus, starting from one N,O-acetal unit and getting another bicyclic N,O-acetal and releasing the protecting group is a new and very useful reaction; maybe one could find a term for that, for example "N,O-transacetalization" (cleavage of one N,O-acetal and formation of another one) as related to transamination.

[8] The terminal alkynyloxazolidines **1a** and **1e** required for our study were prepared from Garner's aldehyde, through a metal-mediated carbonyl-allylation followed by O-propargylation or through a reductive amination followed by a N-carboxylation, respectively (for details see the Supporting Information). The terminal alkynyloxazolidines **1f**,**g** and **1j**,**k** were prepared from imines of Garner's aldehyde through a Staudinger reaction (for details see the Supporting Information). The methyl-substituted alkynyloxazolidine **1b** was prepared through base-promoted O-propargylation (for details see the Supporting Information). The aryl-substituted alkynyloxazolidines **1c**,**d**,**h**,**i**, and **l** were prepared from **1a**,**f**, and **j** through a Sonogashira coupling (for details see the Supporting Information).

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