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Access to Cyclobutene-Fused Azepines through Au-Catalyzed Cycloisomerization of Stable Alkyne Tethered Ketene *N,N*-Acetals

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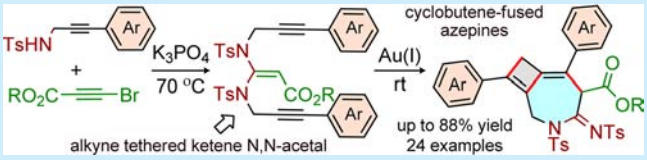
Supporting Information

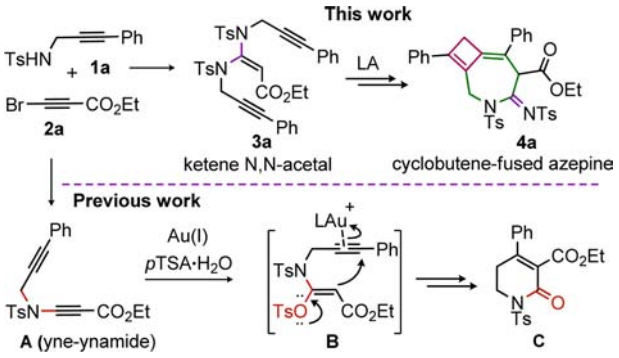
ABSTRACT: A base promoted reaction between N-protected propargyl amines and 3-bromopropiolate readily provides an array of novel stable alkyne-tethered ketene *N,N*-acetals in good yields. A wide range of structurally complex cyclobutene-fused azepine heterocycles are synthesized through the gold-catalyzed intramolecular cycloisomerization of ketene *N,N*-acetals for the first time. A plausible reaction pathway is deduced on the basis of the ^{1}H NMR studies.



Gold-catalyzed cycloisomerization has emerged as a powerful tool for the fabrication of complex cyclic architectural entities with remarkably high efficiency.[1,2] The cyclization and isomerization sequence contributes significantly toward building complexity, introducing numerous functionalities and substituents, and constructing novel cyclic molecular entities from readily accessible precursors.[1] For instance, the gold-catalyzed cycloisomerization of 1,*n*-diynes and 1,*n*-enyne enables the synthesis of various novel carbo- and heterocycles.[1,2]

Recently, we have demonstrated the Au-catalyzed, *p*-TSA·H_2O triggered hydrative cyclization of alkyne tethered ynamide **A** for the synthesis of dihydropyridinone **C** (Scheme 1).[3a] The

Scheme 1. Current Work



transient alkyne-tethered ketene N,O-acetal **B**, obtained via the attack of *p*-TSA on an activated ynamide, presumably participates in the cyclization to form **C** (Scheme 1).[3a] Since the isolation of ketene N,O-acetal **B** was not successful in our hands, we envisioned the synthesis of an analogous alkyne-tethered ketene *N,N*-acetal **3** and examined its reactivity to Au-catalysts.

The ketene *N,N*-acetals are also known as ketene aminals or 1,1-enediamines; these compounds are useful for a wide range of applications in organic synthesis.[4,5] The two enamine moieties in the ketene aminal assist in increasing the nucleophilicity at C-2 due to the inherent delocalization of the nitrogen lone pair over the double bond. Disappointingly, the exceptional reactivity of the ketene aminal made its synthesis and storage difficult,[4,5] thereby limiting its synthetic potential. Interestingly, the introduction of N-protecting groups and electron-withdrawing groups at C-2 contributes to the stability of the ketene aminals.[5a−e] A detailed literature survey revealed that there are no reports on the synthesis of stable alkyne tethered ketene *N,N*-acetals so far.

We thus envisaged that the hydroamidation of N-protected propargyl amine **1a** to the activated ynamide **A**, obtained from **1a** and **2a**, would produce **3a** (Scheme 1). We further presumed that the inherent delocalization of the nitrogen lone pair in ketene *N,N*-acetals would assist the 6-*endo*-dig attack of C-2 to the Lewis acid (LA)-activated alkyne unit with the formation of iminium species. Subsequent cleavage of the C−N bond followed by a [2 + 2]-intramolecular cycloaddition[6] with a pendant alkyne would afford an unusual cyclobutene-fused azepine skeleton **4a** (Scheme 1). The construction of cyclobutane fused heterocycles has been a particularly fascinating challenge for synthetic chemists.[2e,f] Of note, the synthetic methods for cyclobutene-fused azepine structural entities have remained elusive so far.

Herein we report a K_3PO_4 base promoted one-step method for the synthesis of stable alkyne tethered ketene *N,N*-acetals from easily accessible N-protected propargyl amines and 3-bromopropiolates. We further demonstrate the Au-catalyzed cycloisomerization of alkyne-tethered ketene *N,N*-acetals for the synthesis of cyclobutene-fused azepines.

To our delight, K_3PO_4 base assisted conjugate addition−elimination of TsN-propargyl amine (**1a**) to 3-bromopropiolate (**2a**) followed by the hydroamidation sequence successfully provided the desired alkyne-teth-ered ketene *N,N*-acetal **3a** in 78% yield (Scheme 2).[7,8] The reaction proved to be general,

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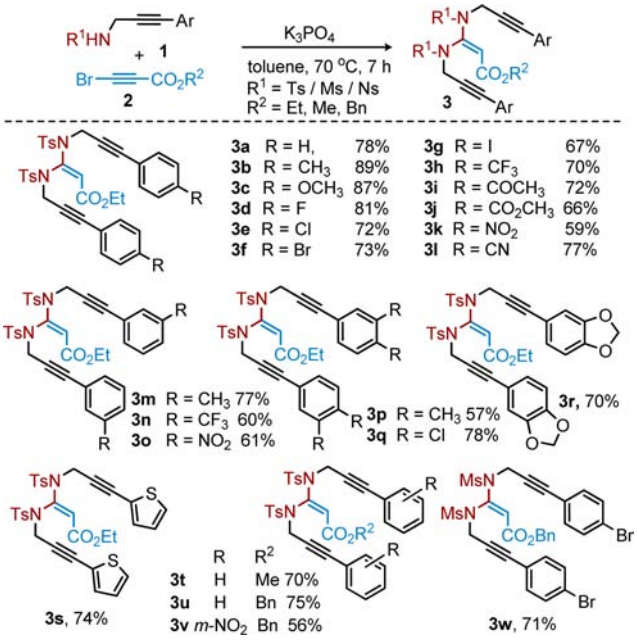
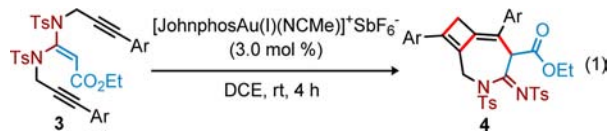
Scheme 2. Substrate Scope for the Preparation of Stable Alkyne Tethered Ketene *N,N*-Acetals 3[a,b]



[a]Reactions were carried out using **1** (1.0 mmol), **2** (0.5 mmol), K_3PO_4 (2.5 equiv) in toluene (4.0 mL) at 70 °C. [b] Isolated yields.

and a wide variety of stable alkyne tethered ketene *N,N*-acetals **3b−w** were prepared in moderate to good yields (Scheme 2). The electron-rich (Me, OMe, di-Me, and methylenedioxy) and -poor (CF_3) aryl substituted TsN-propargyl amines were reacted well with **2a**. The halo and other functional groups (F, Cl, Br, I, NO_2, ester, keto, and CN) on the aryl moiety in **1** did not affect reaction outcome. The X-ray crystallography analysis further elucidates the structure of **3l**.[8] Interestingly, the reaction was found to be compatible with the formation of thienyl-substituted aminal **3s**. The methyl or benzyl 3-bromopropiolates with **1** produced **3t−v** in moderate yields. The N−Ms protected propargyl amine was also no exception delivering **3w** in 71% yield.

Having a wide array of stable alkyne tethered ketene *N,N*-acetals **3** in hand, we then investigated the Au-catalyzed cycloisomerization of **3**.[8] A careful screening of various Au-catalysts and solvents revealed that the compound **3a** transformed to **4a** (80%) under the optimized conditions shown in eq 1; the X-ray crystallography analysis established the structure of **4a** (Figure 1).[8]



The essence of the optimized cycloisomerization conditions is examined assessing the reactivity as well as the scope of this transformation (Scheme 3). The compounds **3b** and **3c** having electron donating *p*-Me and *p*-OMe groups on the aryl ring underwent cycloisomerization efficiently, furnishing **4b** and **4c** (X-ray structure) in 74%, 75% yields, respectively.[8] The desired products **4d−g** were isolated in excellent yields from the corresponding halo group (F, Cl, Br, and I) bearing precursors **3d−g**. The CF_3-bearing product **4h** was obtained in 75% yield.

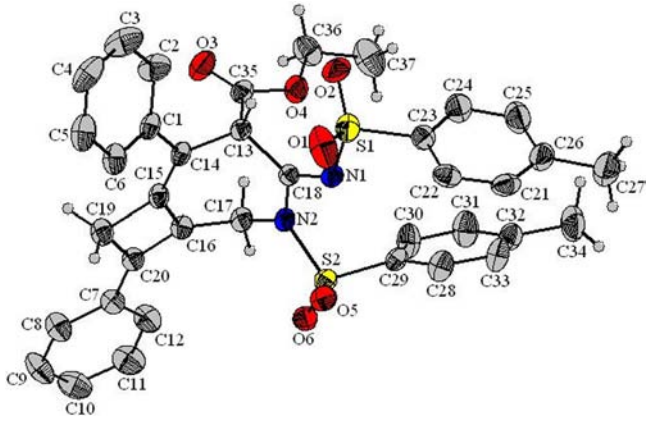
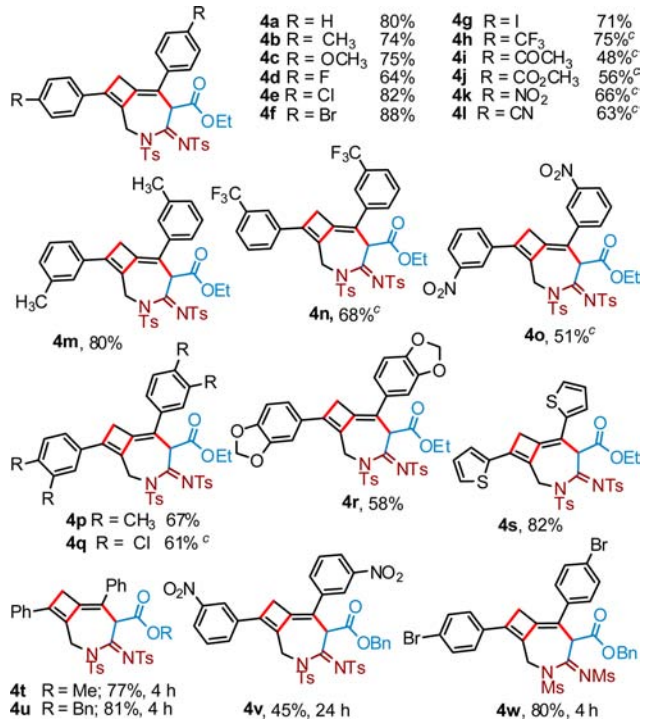


Figure 1. ORTEP plots for X-ray crystal structure of **4a**.

Scheme 3. Synthesis of Cyclobutene-Fused Azepines 4, Substrate Scope I[a,b]



[a]Reactions were carried out using **3** (0.2 mmol), catalyst **A** (3.0 mol %) in DCE (3.0 mL) at room temperature for 4 h. [b] Isolated yields. [c] Reaction continued for 20 h.

The keto, ester, nitro, and cyano functional groups on arenes in the ketene *N,N*-acetals **3i−l** did not affect the cycloisomerization; however, the reaction proceeded sluggishly, justifying the poor activation by the Au-complex to the electron-deficient alkynes, and the products **4i−l** were obtained in moderate to good yields. The cycloisomerization of *m*-Me, *m*-CF_3, and *m*-NO_2 on aryl-ring containing ketene aminals **3m−o** led to the desired products **4m−o**. The products **4p** and **4q** having two methyl or chloro groups on arenes in *m*-/*p*-positions were isolated in 67% and 61% yields, respectively. Similarly, **4r** (58%) was produced from **3r**. Gratifyingly, the 2-thienyl substituted ketene aminal **3s** underwent cycloisomerization delivering **4s** in 82% yield. The methyl and benzyl ester groups did not show pronounced effect to the efficiency and reactivity;

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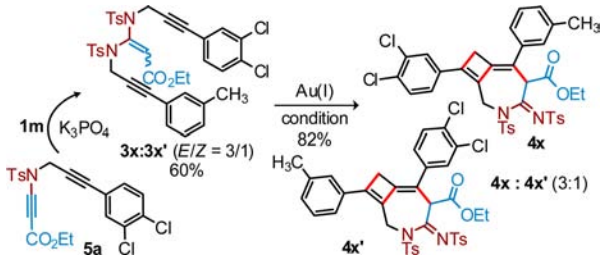
the products **4t** and **4u** were produced in 77% and 81% yields, respectively. A moderate yield of **4v** is the consequence of the electron-deficient *m*-NO_2-phenyl substituted alkyne moiety on **3v**; recovering 26% of **3v** after performing the reaction for 24 h. Gratifyingly, the *N*-mesyl protected compound **3w** efficiently cycloisomerized to result in **4w** in good yield.

We next looked into the cycloisomerization of the unsymmetrical alkyne-tethered ketene *N,N*-acetal. Interestingly, the reaction of ynamide **5a**,[3a] with **1m** in the presence of K_3PO_4, delivered a nonseparable *E*/*Z* (3/1) mixture of **3x** and **3x′** in 60% yield. Gratifyingly, the cycloisomerization of **3x** and **3x′** under the optimized conditions led to a nonseparable mixture of cyclobutene-fused azepines **4x** and **4x′** (3:1, 82%) (Scheme 4). The regioselective attack of the C-2 enediamine to the

Scheme 4. Cycloisomerization of Unsymmetrical 3



electron-rich substituted alkyne possibly allows the formation of major product **4x**.[8] This preliminary observation needs detailed investigations.

To probe the occurrence of the intramolecular attack of an enamine nucleophile to the Au-activated alkyne moiety for the conversion of **3** to **4**, a reaction between an electron-rich and -deficient aryl moiety bearing ketene aminals **3b** and **3h** was performed under the optimized conditions for 4 h.[8] The compounds **4b** (72%) and **4h** (51%) were exclusively isolated.[8] We did not even observe a trace of the crossover products. It is thus clear that the intramolecular cyclization of **3** led exclusively to **4**.

To understand the probable path of the reaction, we performed a series of ^{1}H NMR measurements. The compound **3f** (spectrum I) was thus subjected to the optimized catalytic conditions in $CDCl_3$ in the NMR tube (Figure 2). The ^{1}H NMR spectrum of the crude mixture was recorded in regular time intervals. Surprisingly, we observed an instant shift of vinyl-H_a (5.76 ppm, s) in **3f** to (6.32 ppm, t) in 5 min (spectrum II). The two propargyl $-CH_2$ protons in **3f** [4.50 (s) and 4.63 (s) ppm] are shifted to [4.91 (dd) and 5.29 (bt) ppm] with finer splitting, reflecting the chemically nonequivalent nature of one of the $-CH_2$ groups; the two Me-groups of N-Ts are also moved from 2.40 and 2.37 ppm to 2.44 and 2.52 ppm along with minor relevant changes found in the aryl-ring and CO_2Et protons (spectrum II). These observations support the rapid formation of a transient six-membered N-heterocycle. As the time proceeds, the intensity of relevant peaks of the transient species (spectrum II) slowly reduced with the appearance of the corresponding peaks related to **4f** (spectrum III); this transition was noticed from 15 min. As observed from the crude ^{1}H NMR spectrum, the reaction was complete in 105 min (spectrum IV) with the disappearence of the peaks in spectrum II. These studies truly witness the cycloisomerization of **3** to **4**.

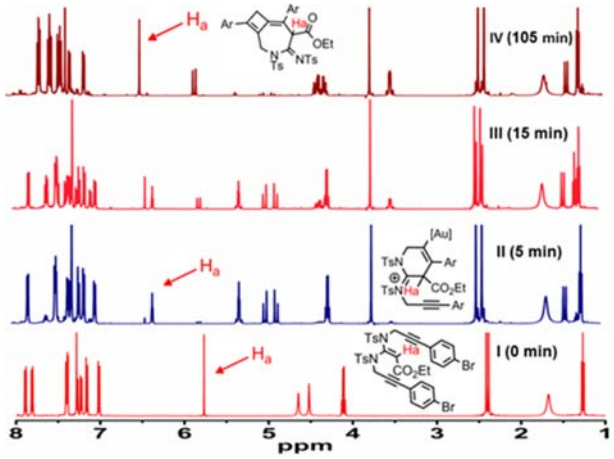
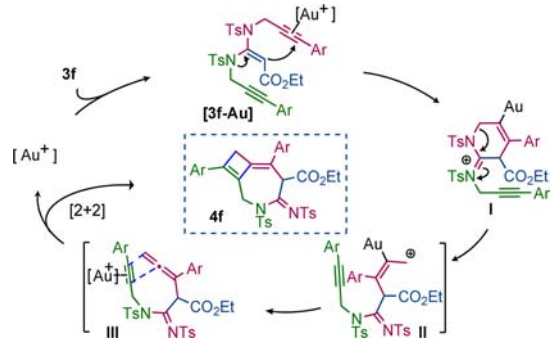


Figure 2. ^{1}H NMR Experiment.

Scheme 5. Plausible Mechanistic Cycle



Although the mechanism details are yet to be established, the plausible mechanistic cycle is sketched in Scheme 5.[1f] The reaction begins with the activation of the triple bond of ketene *N,N*-acetal by the Au-catalyst, triggering the regioselective 6-*endo*-dig attack of the olefin C-2 of enediamine. The inherent participation of the nitrogen lone pair assists this cyclization[3a] and allows the rapid formation of a six-membered iminium-gold-vinyl species **I**; the ^{1}H NMR experiment study supports this fact (Figure 2). The cleavage of the C−N bond in **I** would then generate the vinyl-gold-allyl-cation species **II** *in situ*. The removal of the Au-species from **II** readily forms the transient allene-species **III**. Finally, [2 + 2]-cycloaddition between the reactive allene and Au-activated alkyne produces the azabicyclo-[5.2.0]nona-1(9),5-diene-5-carboxylate heterocycles with the release of the Au-complex.[6] Although we could not detect the allene intermediate in the ^{1}H NMR experiment, the participation of an allene intermediate suitably explains the formation of an unusually strained cyclobutene-fused azabicyclic moiety.

In conclusion, we have demonstrated a synthetically viable strategy for the preparation of a wide array of bench-stable alkyne-tethered ketene-*N,N*-acetals for the first time, from easily accessible N-Ts/Ms protected propargyl amines and 3-bromopropiolates under the influence of the K_3PO_4 base. The gold-catalyzed cycloisomerization of alkyne-tethered ketene aminals delivered the rather unusual cyclobutene-fused azepine skeletons; the reaction exhibits a good substrate scope and tolerates various functional groups. The ^{1}H NMR studies allowed deducing a plausible reaction pathway. These

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preliminary results would boost the development of novel transformations on ketene aminals.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) See the Supporting Information for details.