Gold-catalyzed cyclizations of alkyne propargylic acetates to 2,3-bis(alkylidene)cycloalkanones and their related benzene derivatives†

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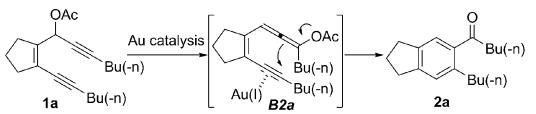
We report a new and highly-convenient Au-catalyzed cyclization of alkyne propargylic acetates leading to 2,3-bis(alkylidene)cyclohexanones and their cycloadditions with a pendant dienophile.

Due to the excellent alkynophilicity of gold,[1] particular attention has been paid to gold-based alkyne activation as an attractive strategy for developing new and efficient catalytic reactions. Terminal alkynes in the presence of a nucleophile are known to form gold–carbene complexes with gold cations.[2] Internal alkynes are weakly activated enough to react with alkenes or aldehydes as nucleophiles. Phenyl-substituted alkynes, for example, can form weak π-complexes, which undergo [2 + 2 + 2]-cycloaddition with a pendent double bond and one double bond in the phenyl ring.[3] *ortho*-Alkynylbenzaldehydes activated by gold cations were proposed to form pyrylium intermediates that reacted with alkynes, undergoing [4 + 2]-cycloaddition to afford 2-acylnaphthalenes,[4] or [3 + 2]-cycloaddition to afford 2,4,6-cycloheptatrienones upon subsequent sequential elimination followed by protolysis.[5] Propargylic acetates are very prone to isomerization under Au catalysis, to form allenyl acetates that can react with a double bond or, as nucleophiles, attack internal alkynes activated by gold catalysts. Toste *et al*. reported a novel cyclization reaction catalyzed by $AgSbF_6$ with/without Au(I) complexes as catalytic systems.[6] Immediately after Toste's report, we reported a similar result on gold-catalyzed cyclizations of alkyne propargylic acetates **A1** under much milder conditions (Scheme 1).[7] Conjugation of the intermediate allenyl acetates **B1** with the alkyne functionality, where the reacting groups are positioned *ortho* to one another on a benzene ring, would make such benzannulation to **C1** possible.

In continuing our study, we further extended our methodology to alkyne propargylic acetates, **A2** and **A3**, for facile synthesis of benzene derivatives **C2** and 2,3-bis(alkylidene)-cyclohexanones **C3**. Furthermore, some of the 2,3-bis(alkylidene)cyclohexanones could be cyclized with a pendant alkyne to give tricyclic compounds and herein we report our new results. We hypothesized that the alkynophilicity of Au(I) could activate an alkyne functionality enough to form a new-C–C bond with the allenoate intermediates **B**, so that one-pot Myers–Saito-type cyclization from linear yne-propargylic acetates could be achieved.[8] In contrast to substrates **A1** wherein a structurally rigid phenyl group serves as a tether, substrates **A2** and **A3** with/without a cyclic linker might be harder to cyclize due to their intrinsic flexibility.

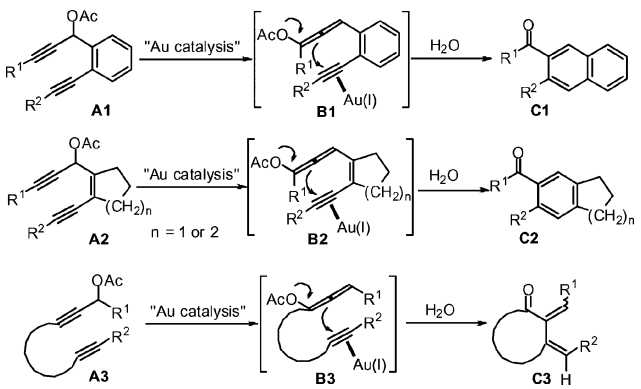
Thus, we began to study cyclization with a substrate **1a** with fixed orientations of the reacting alkyne and propargylic groups (eqn (1)).



(1)

(1) 5 mol% $NaAuCl_4/PPh_3$, EDC, 80°C, 15h — trace
(2) 5 mol% $(PPh_3)AuCl/AgSbF_6$, MC/acetonitrile (1:1), rt, 10 h — 10%
(3) 5 mol% $(PEt_3)AuCl/AgSbF_6$, MC/acetonitrile (1:1), rt, 10 h — 25%
(4) 5 mol% $(PEt_3)AuCl/AgSbF_6$, MC/acetonitrile (1:1), 50 °C, 10 h — 68%

Substrate **1a** was easily isomerized to the corresponding yne-allenoate **B2a**, but difficult to make undergo further cyclization to **2a**. Our reported conditions, a mixture of $NaAuCl_4$ and PPh_3 (5 mol%) in 1,2-dichloroethane (EDC) solvent, did not promote cyclization even after prolonged heating at 80 °C for 15 h. Upon hydrolysis during extractive work-up, the yne-enone, the hydrolyzed product from **B2a**, was isolated in 76% yield as the major product, with a trace of **2a**. Changing the catalyst to Au(I) compounds was successful. Although chlorotriphenylphosphine gold(I) in methylene chloride (MC) did not catalyze the present cyclization, these conditions with added silver hexafluoroantimonate did cyclize **1a** to **2a** in 10% yield. Further tuning the reaction conditions, using chlorotriethylphosphine gold(I) with $AgSbF_6$ as a co-catalyst in 1 : 1 cosolvent of MC and CH_3CN, catalyzed this cyclization at rt and 50 °C in 25% and 68% yields, respectively. With these conditions, we tested other structurally similar substrates (eqn (2 and 3)).[9] Three substrates **1b–d** were



Scheme 1

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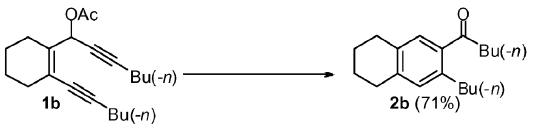
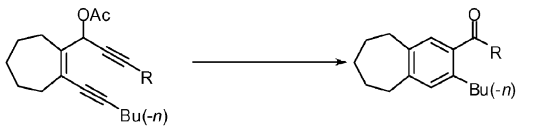
† Electronic supplementary information (ESI) available: Experimental details and spectral data of new compounds **2a–d**, **4a–f**, and **5h–i**. See DOI: 10.1039/b705320g.

smoothly cyclized to the benzene derivatives **2b–d** in moderate to good yields. Cyclohexene-tethered substrate **1b** was better than cyclopentene-tethered substrate **1a**.



(2)

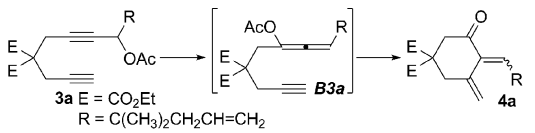


(3)

conditions: $AuCl(PPh_3)$, 10 mol% AgOTf, EDC/CH_3CN (1:1), 60 °C

Cycloheptene-tethered substrates **1c** and **1d**, however, were transformed to the **2c** and **2d** in 45% and 30% yields, respectively.

We then attempted to extend this cyclization to yne-propargylates with an acyclic alkyl tether. In contrast to type **A1** and **A2** substrates, type **A3** substrates, with an acyclic alkyl tether, were expected to be much harder to cyclize. Thus, we began to study the present cyclization with a substrate **3a**, having a *gem*-diester group between two triple bonds, since such *gem*-diester groups would promote cyclization *via* the Thorpe–Ingold effect (eqn (4)).

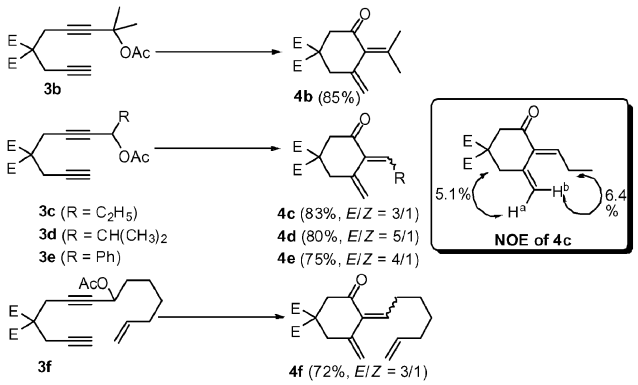


(4)

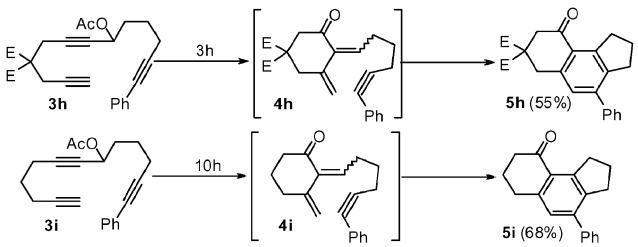
(1) 5 mol% $(PEt_3)AuCl/AgSbF_6$, MC/acetonitrile (1:1), 80 °C, 10 h 45%
(2) 5 mol% $(PPh_3)AuCl/AgSbF_6$, MC/acetonitrile (1:1), 80 °C, 6 h 70%

Acyclic yne-propargylic acetate **3a** was easily isomerized to the corresponding yne-allenoate **B3** under various conditions, but difficult to make undergo further cyclization to **4a**. Our reported conditions, chlorotriethylphosphine gold(I) with silver hexafluoroantimonate in MC–acetonitrile, did catalyze cyclization of **3a** to **4a** in 45% yield. Further tuning the reaction conditions, using chlorotriphenylphosphine gold(I) with $AgSbF_6$ as a cocatalyst in 1 : 1 cosolvent of CH_2Cl_2 and CH_3CN catalyzed this cyclization at 80 °C in 70% yield. We tested additional structurally diverse substrates (Scheme 2).[10]

All substrates **3b–f** (E = CO_2Et) were successfully cyclized to the corresponding diene derivatives **4b–f** in 72% to 85% yields. Due to the Lewis acidity of the gold catalyst, the initially formed dienes were isomerized upon prolonged heating, to the more stable dienes in the cases of **4c** and **4d**. Use of 10 mol% of catalysts dramatically decreased the reaction temperature to room temperature, where no thermal isomerization occurred. Stereoselectivities for the double bond formed during this cyclization were not good, giving an *E*/*Z* mixture of products from 3 : 1 to 5 : 1 ratios, which was confirmed on the basis of NOE experiments with **4c**. We have attempted to further manipulate the initially formed dienes with a pendant dienophile in an appropriate position, so that the corresponding tricyclic carbocycles could be isolated for



Scheme 2



cond: 10 mol% $AuCl(PPh_3)$, 10 mol% $AgSbF_6$, EDC, rt. E = COOEt.

Scheme 3

synthetic building blocks. The newly formed diene in **4f**, however, did not undergo intermolecular Diels–Alder reaction.

We prepared two new substrates **3h** and **3i**, each having a pendant triple bond. These were smoothly cyclized under our conditions and further underwent intramolecular [4 + 2]-cycloaddition and oxidation even at room temperature, to afford the corresponding benzene derivatives **5h** and **5i** in 55% and 68% yields, respectively (Scheme 3). Yet the oxidants are unknown.

In conclusion, we have discovered a highly-convenient Au-catalyzed cyclization of alkyne propargylic acetates leading to 2-acyl-1,3-butadiene skeletons. Depending on the substrates, the present study could provide easy access to valuable building blocks for polycyclic compounds.

Acknowledgements

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