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Gold-Catalyzed Cyclizations of 1,6-Diynes

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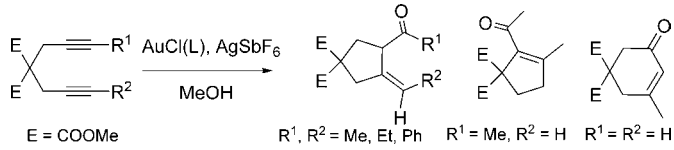
ABSTRACT



New gold-catalyzed cyclization reactions of 1,6-diynes (2,2-dipropargylmalonates) are reported. Symmetrically (Me, Et) and unsymmetrically disubstituted (Me, Et, Ph) 1,6-diynes provided stereoselectively the *Z*-cyclopentylidene derivatives in 31−60% and 49−83% yield, respectively. High regioselectivity (97:3) was obtained for the cyclization of Me/Ph-substituted 1,6-diynes. A monosubstituted terminal diyne afforded a cyclopentene derivative (2-acetyl-3-alkylcyclopent-2-ene-1,1-dicarboxylate, 43%), while the diterminal 1,6-diyne (2,2-di(prop-2-ynyl)malonate) produced a cyclohexenone derivative (3-methyl-5-oxocyclohex-3-ene-1,1-dicarboxylate, 61%). Plausible reaction mechanisms are proposed for the formation of the products.

After being neglected by organic chemists for a long time, gold catalysis of organic reactions has become a rapidly expanding field in very recent years.[1] The high oxidation potential of gold(I) to gold(III) allows most gold(I) catalyzed reactions to proceed without air exclusion.[2] Gold catalysts are exceptionally alkynophilic, but less oxophilic than other common Lewis acids. Thus, oxygen, water or alcohols are often well tolerated in contrast to reactions with most air and moisture sensitive Lewis acids or transition metal complexes. Due to the high affinity of gold complexes toward double and triple bonds, gold catalysis can afford highly selective reactions and give access to complex molecules.[3−6] Gold catalysts interact with π-systems to activate multiple bonds for nucleophilic attack.[7,8] A number of cyclization and cycloaddition reactions have been shown to take place in the presence of different gold catalysts, mainly with phosphine ligands.[2] In particular, gold-catalyzed cycloisomerisation of enynes has been extensively studied, involving selective alkyne activation by gold.[5,9,10] Such reactions often involve complex intermediates to afford a manifold of products.[1,2] The addition of alcohols to alkynes in the presence of mercury(II) salts is a well-known old reaction.[11] However, alkynes have successfully been used as substrates for gold catalysis. Hydration of alkynes to form the respective ketones by catalysis with an active cationic gold-phosphine species has been demonstrated.[12] In recent years, the gold(I)-mediated activation of alkynes toward addition of alcohols or water in the presence of acids has been investigated, mainly providing the acetal product.[13] The acetals were in a

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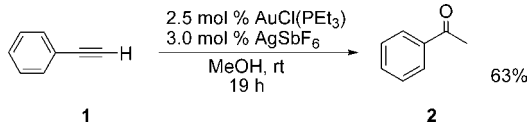
rapid equilibrium with their corresponding enol ethers and the product distribution was influenced by the substituents. In case of unsymmetrical substituted alkynes the addition took place at the less sterically hindered position. On the other hand, terminal alkynes were attacked exclusively at the higher substituted carbon.

The low yields, high temperatures and often harsh acidic conditions previously applied for the toxic mercury(II) or gold-catalyzed hydration of alkynes encouraged us to investigate less vigorous conditions for the hydration of alkynes catalyzed by gold(I) complexes. It has been shown that the catalytic activity of gold complexes is strongly dependent on the counterion.[8] In case of a strong interaction of the counterion with the gold metal center (e.g., Cl^-, CF_3COO^-), no or a low reactivity of the gold catalyst was observed. Replacing these ions by a less nucleophilic anion (e.g., SbF_6^-, BF_4^-) by adding an appropriate silver salt increases the catalytic activity.

Our introductory experiment demonstrated the hydration of the terminal phenylacetylene (**1**) in the presence of 2.5 mol % chloro(triethylphosphine)gold(I) and 3.0 mol % $AgSbF_6$ in pure methanol at room temperature. Subsequent acidic work up and flash chromatography provided acetophenone (**2**, 63%), formed by hydrolysis of the acetal intermediate (Scheme 1).

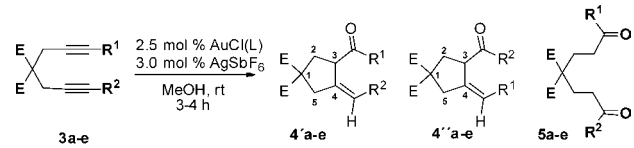
Scheme 1. Hydration of Phenylacetylene (**1**)



To the best of our knowledge, there are no reports on gold-catalyzed hydrations of diynes. When an analogous gold-catalyzed reaction was carried out with symmetrically substituted 1,6-diynes, different and new products were formed (Table 1). Dimethylpropargylmalonate **3a** underwent a cyclization reaction in the presence of 2.5 mol % [AuCl(PEt_3)] and 3.0 mol % $AgSbF_6$, providing a cyclopentylidene derivative **4a** (60%, Table 1, entry 1). The corresponding diketone **5a** formed by double hydration of the diyne **3a** was not detected. Replacing the phosphine ligand by an *N*-heterocyclic carbene (NHC) ligand (IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene) provided unchanged yield of the desired product **4a** (entry 2). A solvent consisting of a mixture of methanol and water (95/5) afforded comparable results (52% yield, entry 3).

In additional experiments we investigated the catalytic activity of the AuCl(PEt_3) and AuCl(IMes) complexes in the absence of the silver salt (entries 4 and 5). As expected, no reaction took place in the presence of 2.5 mol % of these gold catalysts. To exclude the possibility of a silver catalyzed cyclization reaction, diyne **3a** was treated with 3.0 mol % $AgSbF_6$ in methanol (entry 6). According to GC, only starting material **3a** was present in the reaction mixture after 24 h.

Table 1. Gold-Catalyzed Cyclizations of 1,6-Diynes



3a, 4a, 5a; $R^1 = R^2$ = Me
3b, 4b, 5b; $R^1 = R^2$ = Et
3c, 4´c, 4´´c, 5c; R^1 = Me, R^2 = Et
3d, 4´d, 4´´d, 5d; R^1 = Me, R^2 = Ph
3e, 4´e, 4´´e, 5e; R^1 = Et, R^2 = Ph

entry (substrate)	R^1	R^2	AuCl(L)	time [h]	ratio[a] 4′/4″	yield[b] (4′+4″)/5 [%]
1 (**3a**)	Me	Me	AuCl(PEt_3)	3	–	60/0
2 (**3a**)	Me	Me	AuCl(IMes)	3	–	60/0
3 (**3a**)	Me	Me	AuCl(PEt_3)[c]	5	–	52/0
4 (**3a**)	Me	Me	AuCl(PEt_3)[d]	24	–	0
5 (**3a**)	Me	Me	AuCl(IMes)[d]	24	–	0
6 (**3a**)	Me	Me	[e]	24	–	0
7 (**3b**)	Et	Et	AuCl(PEt_3)	3	–	[f]
8 (**3b**)	Et	Et	AuCl(IMes)[g]	21	–	[h]
9 (**3b**)	Et	Et	AuCl(PEt_3)[i]	3.5	–	31/43
10 (**3c**)	Me	Et	AuCl(PEt_3)	5	69/31	60[j]/22
11 (**3c**)	Me	Et	AuCl(IMes)	3	48/52	83[j,k]/0
12 (**3d**)	Me	Ph	AuCl(PEt_3)	3	95/5	49[j]/0
13 (**3d**)	Me	Ph	AuCl(IMes)	3	97/3	56[j,k]/0
14 (**3e**)	Et	Ph	AuCl(IMes)	3	91/9	64[j,k]/0

[a] According to GC after work up. [b] Isolated yield. [c] Reaction was performed in $MeOH/H_2O$ = 95/5. [d] Without $AgSbF_6$. [e] With 3.0 mol % $AgSbF_6$. [f] Traces according to GC. [g] With 3.0 or 5.0 mol % $AgSbF_6$. [h] Conversion (5%) according to ^1H NMR. [i] With 5 mol % AuCl(PEt_3) and 7.5 mol % $AgSbF_6$. [j] Isolated as a mixture. [k] For characterization pure samples were obtained.

These results emphasize the importance of the anion exchange to obtain catalytic activity.

Significantly lower reactivity was observed by replacing the two methylsubstituents of **3a** by two ethyl groups. In contrast to the cyclization of **3a**, the transformation of **3b** showed no or minor conversion into **4b** in the presence of 2.5 mol % [AuCl(PEt_3)] and 3.0 mol % $AgSbF_6$ (entry 7) or 2.5 mol % AuCl(IMes) and either 3.0 or 5.0 mol % $AgSbF_6$ (entry 8). Both the expected cyclopentane derivative **4b** (31%) and the dihydrated diketo-product **5b** (43%) were observed by using 5.0 mol % of the gold-phosphine catalyst and 7.5 mol % of the silver salt (entry 9).

Cyclisation of unsymmetrically disubstituted 1,6-diynes would give rise to two possible regioisomers. The methyl−ethyl disubstituted diyne **3c** afforded the regioisomers **4′c** and **4″c** in 60% total yield in addition to the dihydrated diketo-product **5c** (22%) by gold(I)-phosphine catalysis (entry 10). Despite the small difference between the methyl and ethyl substituent, the formation of the acetyl substituted product **4′c** was favored (69/31). Gold(I)-NHC catalysis afforded enhanced yield (83%), but an approximately 1:1 mixture of the two regioisomers **4′c** and **4″c** was observed (entry 11). The dihydrated diketoproduct **5c** was not obtained.

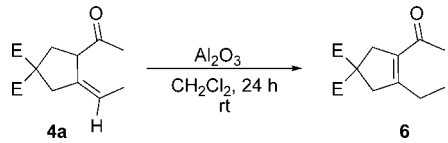
In general, the introduction of a phenyl group afforded high regioselectivities (entries 12−14). Independent of neither applying gold(I)-phosphine/-NHC complexes nor the nature of the other alkyne substituent (R^1 = Me, Et), the benzylidenecyclopentane products **4′d,e** were preferentially

formed (49−69%), consisting of 91−97% of the regioisomer mixture. The diketo products **5d,e** were not detected in any of the reactions.

Only one stereoisomer of products **4a**−**e** was observed. NOESY-NMR experiments of compounds **4a** and **4′e** indicated a *Z*-configuration of the exocyclic cyclopentylidene double bond. In both cases, a strong NOE correlation between the exocyclic alkene proton and the H-5 proton as well as between the H-3 proton and, respectively the vinylic methylprotons (**4a**) or the *ortho*-phenylprotons (**4′e**), were observed (Table 1). The absence of corresponding NOE interactions between the H-5 proton and the vinylic methyl- (**4a**) or phenyl group (**4′e**) as well as between the H-3 proton and the vinylic proton supported the same conclusion.

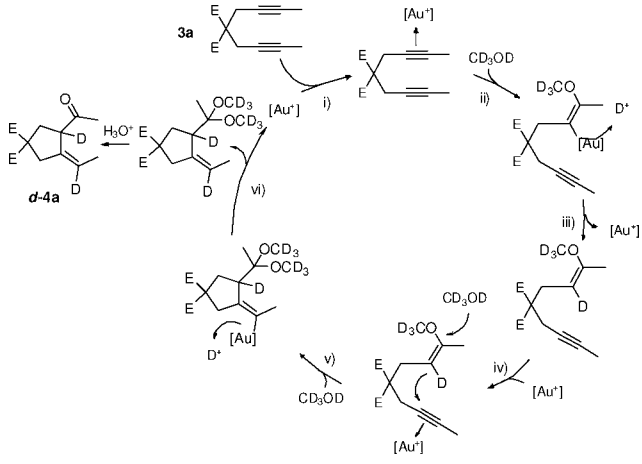
In contrast to the formation of the stable cyclopentylidene **4a**, a reaction of diyne **3a** in the presence of a ruthenium catalyst has previously been reported to provide an α,*β*-unsaturated cyclopentene product **6**.[14,15] In the present work we have obtained the cyclopentene derivative **6** by isomerization of **4a** by treatment with neutral Al_2O_3 (Scheme 2).[16]

Scheme 2. Isomerisation of **4a**



On the basis of general mechanistic knowledge on the addition of alcohols to alkynes[13] and a cyclization reaction of **3a** performed in d_4-methanol (Scheme 3), a general

Scheme 3. Proposed Mechanism for Gold Catalyzed Cyclizations



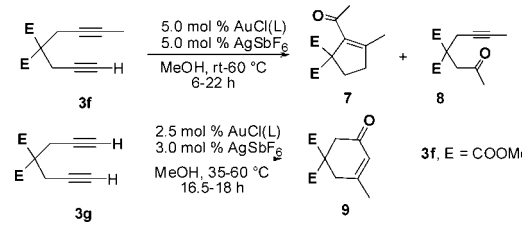
reaction mechanism is proposed for the formation of the cyclopentylidenes **4a**−**e** from 1,6-diynes **3a**−**e**. The active cationic gold complex initially coordinates to one of the triple bonds (i) followed by a nucleophilic addition of deuterated methanol (ii). An intermediate alkylenol ether is formed by replacing the gold by a deuterium and the active gold complex is regenerated (iii). Activation of the second triple bond by coordination to the gold complex (iv) and subsequent cyclization, caused by acetal formation by addition of a second deuterated methanol molecule (v), leads to the steroselective formation of a *Z*-cyclopentylidene gold intermediate. Gold-deuterium exchange (vi) regenerates the active cationic gold complex and releases a dimethoxyacetal. Acidic workup provided finally **4a**−**e**.

The deuteration experiment supported this mechanism, since, according to ^{1}H NMR spectroscopy, complete deuteration of both the 3- and 5-positions of ***d*-4a** was observed. Additionally, approximately 50% deuterium incorporation of the acetylmethyl moiety was observed, rationalized by acetal-enol ether equilibrium of the intermediates.

The lower reactivity of the diethylsubstituted diyne **3b** to undergo cyclization (Table 1, entries 4−6) may be explained by the sterical hindrance appearing by approaching the two ethyl groups in order to undergo cyclization in step v). The regioselectivity in the cyclization of diynes **3c**−**e** would be dependent on stereochemical as well as electronic effects. The observed favored formation of products **4′c**−**e** may be controlled by the preference of the active cationic gold complex, acting as a Lewis acid, initially to activate the alkyne with the higher electron density. Alternatively, different electrophilic character of the two possible gold-alkyne complexes would favor nucleophilic addition at the more electrophilic alkyne.[17] The results revealed that the phenylsubstituted alkyne moiety of the Me/Ph or Et/Ph substituted 1,6-diynes (**3d**,**e**) is less favored for nucleophilic attack, as shown by the nearly entire formation of **4′d**,**e**.

Terminal 1,6-diynes did not follow the same reaction pathway, since two different cyclic products, respectively **7** and **9**, were formed when mono- and diterminal diynes **3f** and **3g** underwent gold-catalyzed cyclizations (Table 2).

Table 2. Reaction of Terminal Alkynes



entry	substrate	AuCl(L)	*t* [°C]	time [h]	prod.	yield[a] [%]
1	**3f**	$AuCl(PEt_3)$	rt	28	**8**	53
2	**3f**	$AuCl(PEt_3)$[b]	60	24	**7**	43
3	**3f**	AuCl(IMes)	60	18	**7**	30
4	**3g**	$AuCl(PEt_3)$	35	16.5	**9**	61
5	**3g**	AuCl(IMes)	60	18	**9**	19

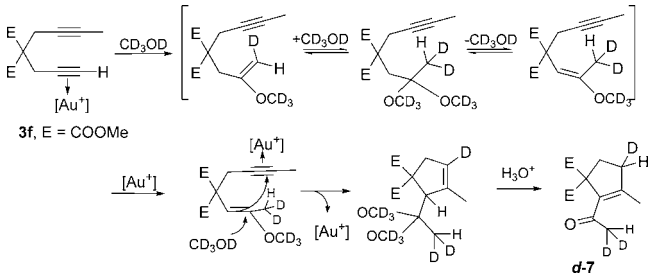
[a] Isolated yield. [b] With 3.0 mol % $AuCl(PEt_3)$ and 3.5 mol % $AgSbF_6$.

At lower concentration and temperature a selective hydration of the terminal acetylene moiety of **3f** took place and

only ketone **8** (53%) was isolated (Table 2, entry 1). Higher temperature was required for the cyclization of diyne **3f** into a cyclopentene product **7** by gold-phosphine (43%) or gold-NHC (30%) catalysis (entries 2−3).

The formation of product **7** may be rationalized by a nucleophilic attack of methanol to the gold activated terminal alkyne to form an enol ether that may undergo isomerization into the higher substituted enol ether via an acetal (Scheme 4). A second methanol attack enables cyclization by acetal

Scheme 4. Proposed Mechanisms for Cyclization of Diyne **3f**



formation and attack at the gold activated alkyl-alkyne. Final acidic hydrolysis and isomerization provides product **7**. A deuteration experiment supported this mechanism, since full incorporation of deuteration had taken place in the 4-position and, respectively, 50−60% in the acetylmethyl-position, according to ^{1}H NMR spectroscopy.

Cyclisation of the diterminal diyne **3g** afforded the cyclohexenone product **9** (61%) by gold-phosphine catalyzed cyclization and acidic workup (Table 2, entry 4). Application of the gold-NHC system at elevated temperature gave lower yield (19%, entry 5). A mechanism similar to the formation of **7** may be proposed (Scheme 3), initiated by enol ether/acetal formation. A comparable mechanism for the formation of cyclohexene **9** has recently been reported.[18] However, the previous $MeAuPPh_3$ catalyzed reaction only took place under acidic conditions in the presence of water at 70 °C.

In conclusion, a new gold-catalyzed cyclization reaction of disubstituted 1,6-diynes has been developed, providing *Z*-cyclopentylidene derivatives. Mono- and diterminal 1,6-diynes afforded α,*β*-unsaturated cyclopentene and cyclohexenone products. Plausible reaction mechanisms are proposed for the formation of the products. Further investigations on gold-catalyzed cyclization reactions of diynes including modified substrates, new gold complexes and further mechanistical studies are in progress.

Supporting Information Available: Full experimental details, characterization for all compounds **3e**, **4a**, **4b**, **5b**, **4′c**, **4″c**, **5c**, **4′d**, **4″d**, **4′e**, **4″e**, **6**, **7**, **8**, **9** and copies of ^{1}H, ^{13}C and NOESY NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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