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Reversal of Selectivity in Gold-Catalyzed Cyclizations of 3,3-Disubstituted 1,4-Diynes

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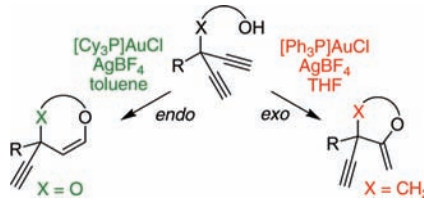
ABSTRACT



A general synthetic access to 3,3-disubstituted 1,4-diynes bearing a quaternary carbon center from acetylacetone was developed. The compounds were cyclized to the corresponding enol ethers by cationic gold complexes. The reactions occur in complete *exo*-selectivity in contrast to compounds incorporating an alkoxy substituent in the 3-position. A mechanistic rationale for this reversal of selectivity is provided.

Alkyne functionalization has become an extremely wide field in organic chemistry and provides access to a plethora of new functional groups and compound classes.[1] Of particular importance are methods involving catalytic amounts of transition metal complexes for C−C-bond formation or heteroatom functionalization.[2] In recent years, gold catalysts[3] evolved to be particularly useful in this respect because they allow attack of various *O*-,[4] *N*-,[5] or *C*-nucleophiles[6] to the C−C triple bond under very mild conditions and in high efficiency.

Recently, we reported the first desymmetrization of 1,4-diynes which is among the first reports of enantioselective

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diyne functionalizations involving chiral gold complexes (Scheme 1).[7] Therein, we found that 3-alkoxy-1,4-diynes

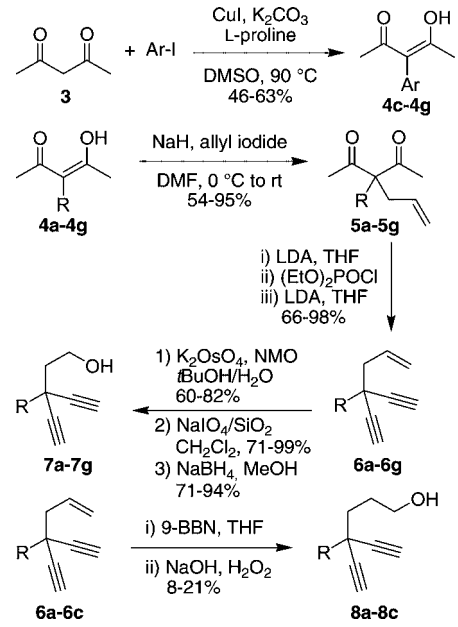
Scheme 1. *Endo*-Cyclization of 1,4-Diynes Derived from 3-Alkoxy-1,4-diynes Using a Gold Catalyst

showed a surprising tendency to undergo *endo*-cyclization to form seven-membered heterocycles selectively. In order to allow access to structures bearing quaternary carbon centers we investigated transformations involving diynes with a quaternary carbon atom in the 3-position. We thought that such studies could contribute to a deeper understanding of the factors leading to preferential *endo*- or *exo*-cyclization of 1,4-diynes as well as related gold-catalyzed transformations involving propargylic carboxylates.[8] In this publication we report a general synthetic access to 3,3-disubstituted 1,4-diynes and their successful cyclization to the corresponding enol ethers using gold catalysts. The products of this process, *exo*-enol ethers, are versatile and useful building blocks for the preparation of functionalized saturated heterocycles.

In contrast to the starting materials as depicted in Scheme 1 which are easily obtained by addition of metal acetylides to the corresponding esters followed by *O*-alkylation, 1,4-diynes bearing only aryl- or alkyl-substituents are significantly more difficult to prepare. In fact, at the outset of this study a general synthetic pathway toward this compound class was still pending.

Initial attempts to prepare 3,3-disubstituted 1,4-diynes by arylation/alkylation of malonic acid derivatives revealed that decarboxylation and decarbonylation processes severely hampered the formation of the diyne functional group. In order to circumvent this issue acetylacetone derivatives were investigated. In particular, 3-aryl-acetylacetones **4** were synthesized by copper-mediated reaction of aryl iodides with 2,4-pentanedione (Scheme 2).[9] While benzylation[10] of acetylacetone was straightforward the introduction of a cyclohexyl

Scheme 2. Preparation of 3-Hydroxyethyl-diynes and 3-Hydroxypropyl-diynes from Acetylacetone



substituent gave the best results with 3-bromo-cyclohexene followed by catalytic hydrogenation.[11] Subsequent alkylation to the 3,3-disubstituted compounds proved difficult with various haloalkanes incorporating protected hydroxy functionalities and gave product mixtures due to concomitant *O*-alkylation. It was found that solely allyl iodide gave satisfying results by preferential *C*-alkylation. Transformation of the diketones **5** to the 1,4-diynes **6** was achieved *via* the enol phosphates following a procedure by Negishi.[12] At this point the stage was set to transform the allyl substituent into the corresponding alcohol functionality serving as the nucleophile in the gold-catalyzed cyclization. We were pleased to find that dihydroxylations showed a high degree of chemoselectivity. In this respect, catalytic use of potassium osmate gave superior results compared to perruthenate reagents with respect to yield and product purity. In order to generate a hydroxyethyl substituent in the 3-position the diols were cleaved by sodium periodate and the intermediate aldehyde was reduced using $NaBH_4$.

Initial trials for the gold-catalyzed cyclization of 3-hydroxyethyl-1,4-diynes **7** employing reaction conditions developed earlier for substrates as depicted in Scheme 1 ($[Cy_3P]AuCl/AgBF_4$ in toluene) showed very poor conversions. Screening experiments revealed that a catalyst obtained from $[Ph_3P]AuCl$ and $AgBF_4$ gave better results, in particular when THF was employed as solvent.[13] All hydroxyethyl-substituted 1,4-diynes **7** underwent fast cyclization under these conditions (Table 1, entries 1−7). Branched and

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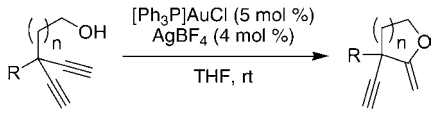
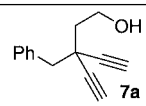
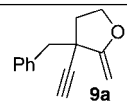
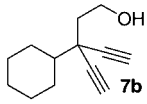
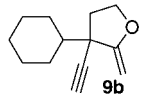
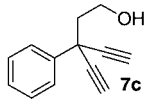
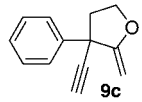
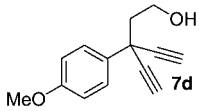
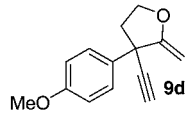
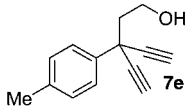
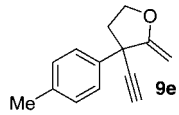
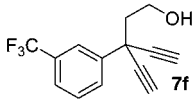
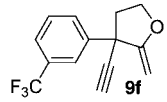
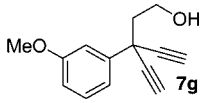
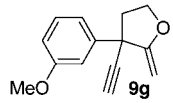
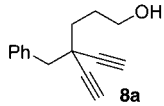
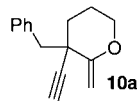
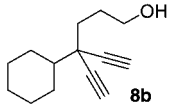
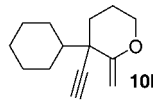
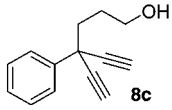
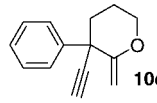
(13) Control experiments revealed that neither $[Ph_3P]AuCl$ nor $AgBF_4$ alone led to product formation.

Table 1. Gold-Catalyzed Cyclizations of 3,3-Disubstituted 1,4-Diynes[a]



entry	substrate	product	yield (%)
1			83
2			97
3			99
4			77
5			80
6			76
7			93
8			62
9			70
10			62

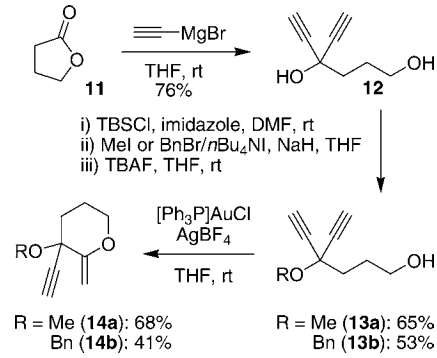
[a] Reaction conditions: $[Ph_3P]AuCl$ (5 mol %), $AgBF_4$ (4 mol %), THF, rt, 1−2 h.

unbranched aliphatic as well as electron-rich and electron-deficient aromatic substituents are well tolerated in the 3-position. The products could be obtained in yields of 76−99%. As expected the products show some sensitivity under acidic conditions. Therefore, the amount of $AgBF_4$ (4 mol %) was always kept below the loading of $[Ph_3P]AuCl$ (5 mol %). It is worth highlighting that all cyclizations occurred with complete *exo*-selectivity, in contrast to 3-alkoxy-substituted 1,4-diynes **1** investigated earlier showing complete *endo*-selectivity in the cyclizations (Scheme 1).

Hence, the question was raised whether the shorter linker length of the 3-hydroxyethyl substituent and the smaller ring size of the corresponding enol ether products was causing this reversal in selectivity. Therefore, 1,4-diynes **8** with a longer 3-hydroxypropyl substituent were prepared by hydroboration of the allyl derivatives **6**. It was found however that the gold-catalyzed cyclization under the given reaction conditions also led to complete *exo*-selectivity for the formation of the six-membered ring enol ethers in 62−70% yield (Table 1, entries 8−10).

The puzzling experimental finding of selectivity reversal for the gold-catalyzed cyclization of structurally closely related compounds prompted us to take a closer look into these transformations. The nature of the solvent used under the optimized conditions (THF) compared to toluene cannot account for the regiochemical reversal: When diynol **7c** was treated with $[Cy_3P]AuCl/AgBF_4$ in toluene or THF the corresponding *exo*-enol ether was obtained as the sole isomer in a yield of 38% and 60%, respectively.[14] Since ring size does not appear to be the exclusive determining factor for regioselectivity the influence of the 3-alkoxy linkage compared with a 3-alkyl substitution was scrutinized. 3-Alkoxy-3-hydroxy-propyl-1,4-diynes **13** were prepared as test substrates by addition of magnesium acetylide to γ-butyrolactone and subsequent alkylation (Scheme 3). When these compounds were submitted to the cyclization reaction using $[Ph_3P]AuCl$ and $AgBF_4$ in THF, exclusive formation of the *exo*-enol ethers **14** was observed. This strongly indicates that the electron-withdrawing effect of the C(3) atom toward the C−C triple bond alone does not dictate the regioselectivity.

Scheme 3. Preparation and Gold-Catalyzed Cyclization of 3-Alkoxy-3-hydroxypropyl-1,4-diynes

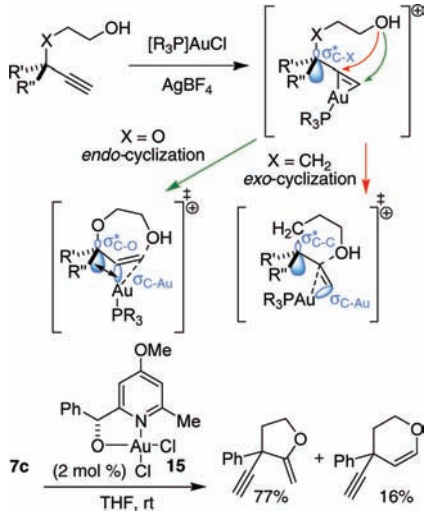


At this stage one could speculate whether an interaction of the oxygen atom in the 3-alkoxy substituent with the catalytic gold center could potentially alter the course of the cyclization reaction. Coordination of the oxygen atom and concomitant activation of the triple bond by the gold atom is unlikely for geometric reasons when an *anti*-attack of the

(14) Cyclization of diynes **1** with $[Ph_3P]AuCl$ in toluene leads to selective formation of the *endo*-isomers.

nucleophile with respect to the metal center is assumed. In order to explain the different regioselectivities in the gold-catalyzed cyclizations of compounds **1**, **7**, and **13**, one may suggest a stereoelectronic effect to operate (Scheme 4). As

Scheme 4. Mechanistic Rationale for the *Endo*-Cyclization of 3-Alkoxy-1,4-diynes and Cyclization of **7c** with Au(III) Catalysts



the first step for alkyne activation, coordination of the cationic gold center to the alkyne is assumed.[8f] The electrophilic formal metallacyclopropene formed is then attacked by the hydroxy group providing the corresponding gold-vinyl species which upon protodeauration leads to product formation. In the majority of cases reported so far this attack leads to *exo*-products.[3,8] In cases of preferential *endo*-cyclization, the reaction outcome has been attributed to unfavorable ring size, steric repulsion, or electronic stabilization of the partial positive charge at the alkyne carbon by substituents.[15] From comparison of the two potential transition state geometries for *endo*- versus *exo*-cyclization of 1,4-diynes, also a stereoelectronic interaction of the σ(C−Au) orbital with the σ^*(C−X) orbital may be proposed. In the case of diynes **1** (X = O) such an interaction would prefer the *endo*-cyclization which is observed. For diynes **7** with alkyl substitution (X = CH_2) the σ^*(C−C) orbital is higher in energy rendering an interaction with σ(C−Au) less favorable leading to the preferred *exo*-cyclization. This mechanistic rationale is also in line with the outcome in the cyclizations of diynes **13**. Here, the alkoxy substituent cannot adopt a geometry suitable for σ(C−Au)↔ σ^*(C−O) interaction. In this context it is interesting to note that the cyclization of **7c** with a Au(III) complex yields a mixture of *exo*- and *endo*-products (Scheme 4).[16] Such observations have also been reported for related Au(III)-catalyzed transformations.[6f,17] The different complex geometries and orbital energies of Au(I) and Au(III) may account for this finding, but a detailed mechanistic understanding would require additional experimental and computational studies.

Summarizing, a general synthetic route for the preparation of 3,3-disubstituted 1,4-diynes has been developed. The gold-catalyzed cyclization provided the corresponding *exo*-enol ether products in 62−99% yield with complete regioselectivity. Studies toward the development of an asymmetric version of this process and computational studies are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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