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# Gold-Catalyzed *endo*-Cyclizations of 1,4-Diynes to Seven-Membered Ring Heterocycles

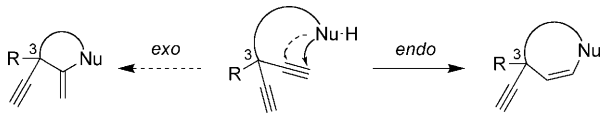
**Kristina Wilckens, Marcus Uhlemann, and Constantin Czekelius*[a]**

*Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday*

In the context of complex natural product synthesis, the preparation of saturated heterocyclic structures is of particular importance given the plethora of substances incorporating such structural motives. A significant amount of methods for the efficient preparation of five- and six-membered rings are known and widely applied. In comparison, the selective synthesis of seven-membered-ring heterocycles has evolved a smaller array of methods for their preparation, despite the fact that a number of biologically active targets incorporate such scaffolds. Polyether marine natural products like brevetoxin B[1] or maitotoxin,[2] and alkaloids like strychnine[3] may serve as examples for which total syntheses and studies towards are, without question, true landmarks in chemical science.

In recent years, gold-catalyzed processes have evolved as very efficient methods for the functionalization of alkenes, allenes, and alkynes.[4] Upon activation by the carbophilic gold complex the C–C multiple bonds can be attacked by various *O*-,[5] *N*-,[6], or *C*-nucleophiles.[7] In most cases, reaction occurs under very mild conditions and with high functional-group tolerance. Although a wide range of compound classes are accessible today by using gold catalysis, the corresponding enantioselective processes, in particular involving alkynes, remain limited in number.[8]

In this publication we would like to report our investigations in the context of gold-catalyzed intramolecular functionalization of 3,3-disubstituted 1,4-diynes (Scheme 1). This study was fueled by our interest in a synthetic method preferring *endo*- over *exo*-cyclization reactions, since the latter are predominant in gold-catalyzed processes for the synthesis of common-sized rings. In addition, such a cyclization would lead to a desymmetrization of the molecule in the case of three different substituents at the 3-position (Scheme 1). Subsequent transformations are assumed to occur in good diastereoselectivity given the small size of the alkyne functional group.




Scheme 1. Cyclization of 1,4-diynes.

We initiated our study with diynol **1** as starting material, which is readily available. It should be noted that the cyclization of related compounds has been reported by Schlosser and co-workers.[9] Here, ring closure occurred under quite harsh conditions (stoichiometric amounts of KO*t*Bu at 85 °C for 12 h). Furthermore, mixtures of *exo*- and *endo*-isomers were obtained that required separation by preparative GC methods in the majority of cases. For the cyclization of diynol **1** we investigated gold and palladium catalysts (Table 1). Palladium complexes[10] and gold chloro complexes were not successful in this respect (entries 1–3). When a cationic gold complex was prepared from [AuCl(PPh$_3$)] and AgSbF$_6$ and submitted to the cyclization reaction the desired *endo*-enol ether product could be isolated in small amounts, but the reaction was rather sluggish. Since the low yield could potentially stem from inefficient protodemetalation, protic additives were examined (entries 5–9). It is worth noting that the addition of alcohols, in particular 2-propanol, resulted in a cleaner conversion and higher isolated yield (53 %). This finding is in agreement with results reported recently by Kirsch and co-workers.[11] More acidic alcohols like $CF_3CH_2OH$ or 2,6-di-*tert*-butylphenol inhibited the reaction completely. Also addition of a base (i.e., 2,6-di-*tert*-butylpyridine, entry 10) resulted in no conversion, supporting the assumption that protodemetalation may be an essential step for efficient turnover and preventing gold

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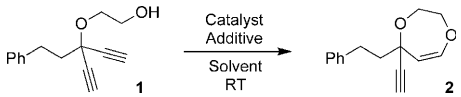
Table 1. Catalysts for the cyclization of diynols.



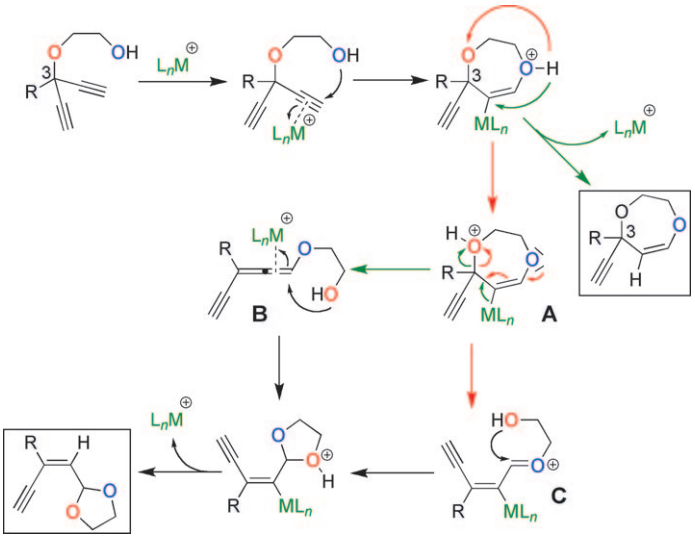

| | Catalyst | Cat. loading [mol %] | Additive | Solvent | Yield [%] |
|---|---|---|---|---|---|
| 1 | $AuCl_3$ | 20 | – | MeOH | 0 |
| 2 | [AuCl($Me_2S$)] | 20 | – | toluene | 0 |
| 3 | [AuCl($PPh_3$)] | 20 | – | toluene | 0 |
| 4 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | – | toluene | 12 |
| 5 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | $H_2O$ (5 equiv) | toluene | 16 |
| 6 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | *i*PrOH (5 equiv) | toluene | 53 |
| 7 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | *t*BuOH (5 equiv) | toluene | 20 |
| 8 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | $CF_3CH_2OH$ (5 equiv) | toluene | 0 |
| 9 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | 2,6-di-*t*Bu-phenol (1 equiv) | toluene | 0 |
| 10 | [AuCl($PPh_3$)]/$AgSbF_6$ | 5 | 2,6-di-*t*Bu-pyridine (0.5 equiv) | toluene | 0 |
| 11 | [AuCl($PCy_3$)]/$AgBF_4$ | 5 | – | toluene | 53 |

vinyl species from undergoing deleterious side reactions. Along these lines we also investigated gold complexes that incorporate more electron-rich phosphine ligands and found [AuCl($PCy_3$)]/$AgBF_4$ to be equally effective even in the absence of alcohols (entry 11).

Optimization studies revealed that reactions in toluene proceeded best among the solvents tested (MeOH, $CH_3CN$, THF, $CH_2Cl_2$, $PhCH_3$). Furthermore, screening of different silver salts (AgOTf, $AgBF_4$, $AgSbF_6$, $AgO_2CPh$) showed $AgBF_4$ to be superior. At this point it should be noted that appropriate control experiments were done to ensure that neither [AuCl($PCy_3$)], $AgBF_4$, nor simple Brønsted-acids like *p*-TsOH alone would catalyze the reaction. It is worth noting that $AgBF_4$ did not catalyze the cyclization itself, but had a detrimental effect on the enol ether product when present for an extended period of time. Therefore, the gold chloro complex was used in a small excess in the reaction.

At this point the substrate scope of the reaction was investigated (Table 2). By employing a catalyst prepared in situ from [AuCl($PCy_3$)] (5 mol %) and $AgBF_4$ (3 mol %), substituted diynols were cyclized effectively.[12] For all substrates investigated the exclusive formation of the corresponding *endo*-enol ether was observed. This selectivity is not limited to diynols, since also an alkynol related to **5** bearing an alkyne and an ethyl group instead of two alkyne groups undergoes *endo*-cyclization selectively in limited yield (10%, see Supporting Information).[13] Diynol substrates with terminal alkyne groups and branched as well as unbranched alkyl substituents are converted to the corresponding *endo*-enol ethers (entries 1–5). In the case of an unsubstituted phenyl group (**11**, entry 6) the desired product **12** was isolated in only 17% yield, together with acetal **13** (41% yield) formed by rearrangement. A mechanistic proposal for this rearrangement is provided in Scheme 2.

If C(3)-*O*-bond cleavage is facilitated by the phenyl group, the five-membered ring acetal is obtained through either alkoxy allene **B** or oxonium intermediate **C**.[14] When product **12** was isolated and resubmitted to the reaction conditions no isomerization to **13** was detected. The proposed mechanism is supported by the fact that electron-withdrawing substituents as well as substituents in *ortho*-position (entries 7–11) give only small quantities of the rearranged product. In the latter case, coplanarity of the aromatic ring with the benzylic $sp^2$-center would lead to significant $A^{1,3}$-strain. Phenyl-substituted alkyne **24** (entry 12) gives predominantly the corresponding rearranged 1,3-enyne product **25**, forming an extended conjugated system. Since gold acetylide species may play a role in



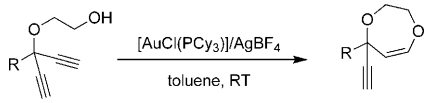

Scheme 2. Mechanistic proposal for the rearrangement of oxodiynols.

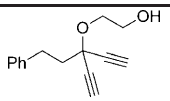
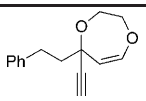
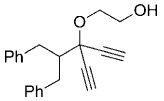
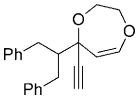
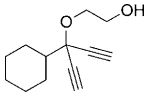
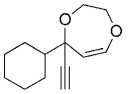
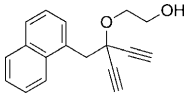
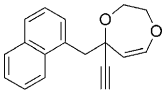
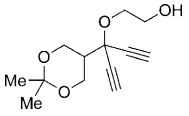
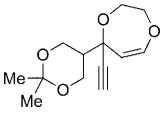
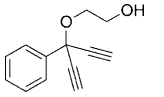
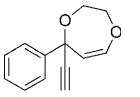
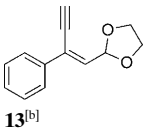
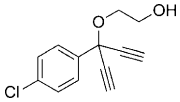
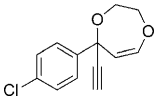
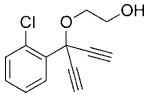
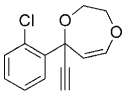
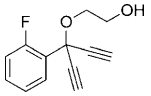
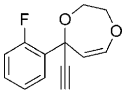
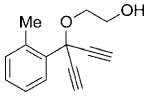
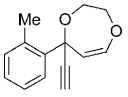
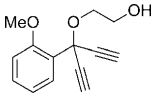
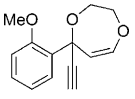
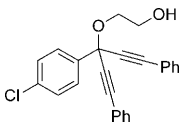
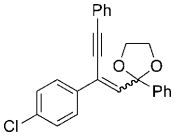
an alternative pathway, compound **18** deuterated only at both alkyne moieties (C≡C–D) was cyclized. Deuterium was found exclusively at the 1-position of enol ether **19**. In contrast, cyclization of **18** deuterated only at the hydroxy group (OD) provided the enol ether with D incorporation solely at the 2-position. These results suggest that gold acetylides are presumably not involved in the main pathway of the reaction.

To expand the scope of the reaction further, gold-catalyzed cyclizations of diynamides to the corresponding tetrahydrooxazepines were investigated (Table 3).[15] It was found that cyclization of diyne sulfonamides occurred readily, while carboxamides (i.e. benzamides and trifluoroacetamides) and unprotected primary amines were not suitable substrates under these conditions. Using [AuCl($PCy_3$)]/$AgBF_4$ as the catalyst, the cyclization of the diyne sulfonamides did not go to completion, presumably due to catalyst degradation. It was found, however, that the gold complex

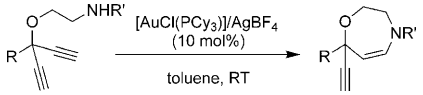
Table 2. Cyclization of diynols to dioxepine derivatives.[a]

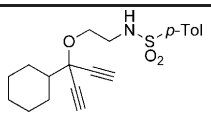
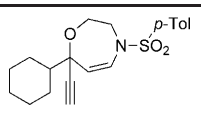
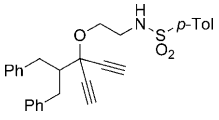
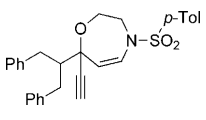
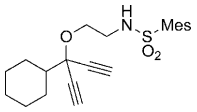
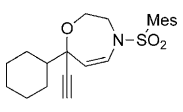
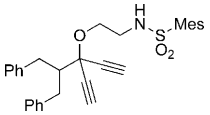
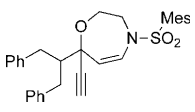



| | Substrate | Product | t [h] | Yield [%] |
|---|---|---|---|---|
| 1 |  **1** |  **2** | 1 | 53 |
| 2 |  **3** |  **4** | 5 | 75 |
| 3 |  **5** |  **6** | 2.5 | 55 |
| 4 |  **7** |  **8** | 0.5 | 46 |
| 5 |  **9** |  **10** | 3 | 31 |
| 6 |  **11** |  **12**  **13**[b] | 1 | 17 (**12**) 41 (**13**) |
| 7 |  **14** |  **15** | 2.5 | 37 |
| 8 |  **16** |  **17** | 1 | 68 |
| 9 |  **18** |  **19** | 2 | 65 |
| 10 |  **20** |  **21** | 3 | 50 |
| 11 |  **22** |  **23** | 6 | 30 |
| 12 |  **24** |  **25** | 1 | 88 |

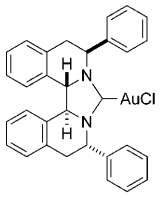
[a] Reactions were performed in toluene (0.1 M) employing 5 mol% $[AuCl(PCy_3)]$ and 3 mol% $AgBF_4$. [b] The corresponding *Z* isomer was formed in small quantities (<10%), but could not be isolated in pure form.

Table 3. Cyclization of diynamides to tetrahydrooxazepine derivatives.[a]

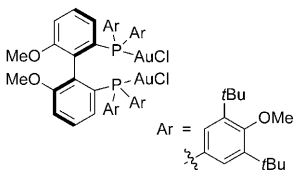



| | Substrate | Product | t [h] | Yield [%] (rsm)[c] |
|---|---|---|---|---|
| 1 |  **26** |  **27** | 1.25 | 35 (55) |
| 2 |  **28** |  **29** | 1.25 | 36 (29) |
| 3[b] |  **30** |  **31** | 1.25 | 9 (81) |
| 4[b] |  **32** |  **33** | 1.25 | 20 (60) |

[a] Reactions were performed in toluene (0.1 M) employing 10 mol% $[AuCl(PCy_3)]$ and 10 mol% $AgBF_4$. [b] Mes = 2,4,6-trimethylphenyl. [c] rsm = Yield of recovered starting material.



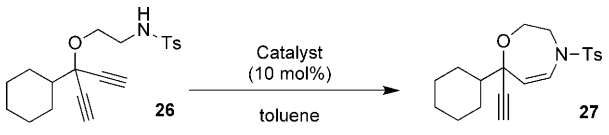
$[AuCl(NHC^H)]/AgBF_4$



$[(AuCl)_2MeOBIPHEP]/AgBF_4$

$[AuCl(NHC^H)]$ incorporating a carbene ligand reported by Herrmann and co-workers[16] performed well in the cyclization reaction leading to full conversion of diyne-sulfonamide **26** (Scheme 3).

Studies towards the enantioselective desymmetrization of diynamides[6f,g,8] employing chiral gold complexes showed that the use of optically pure $NHC^H$ ligand resulted in low enantioselectivity (17% *ee*, Scheme 3).[17] It was demonstrat-




**26** → **27**

$[AuCl(NHC^H)]/AgBF_4$ : 66%, 17% *ee*

$[(AuCl)_2MeOBIPHEP]/AgBF_4$ : 23%, 60% *ee*

Scheme 3. Synthesis of enantiomerically enriched oxazepine derivatives.

ed however that a gold catalyst prepared from [$(AuCl)_2$MeOBIPHEP] and $AgBF_4$[6d,f,18] provided the corresponding product with 60% *ee*, albeit in lower yield due to limited catalyst lifetime. Studies addressing the synthesis of sterically more encumbered, chiral NHC ligands and their application in enantioselective gold-catalyzed reactions are currently under investigation.

In summary, a gold-catalyzed cyclization of 1,4-diynes has been developed by employing cationic gold complexes. The cyclization occurs exclusively in an *endo*-fashion under mild conditions and provides access to dihydrodioxepines and tetrahydrooxazepines. Cyclizations of diynamides with sulfonamide protecting groups and optically active gold complexes allowed the preparation of enantiomerically enriched N-protected tetrahydrooxazepines.

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**Keywords:** alkynes · asymmetric catalysis · gold · nitrogen heterocycles · oxygen heterocycles

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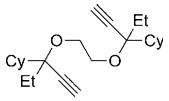


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[18] The catalyst was prepared using 10 mol% [$(AuCl)_2$MeOBIPHEP] and 10 mol% $AgBF_4$.

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