Cascade Reaction

Gold(I)-Catalyzed Allene–Diene–Alkyne Coupling Reaction to Polycycles

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Abstract: In general, the design of complex polycycles from simple building blocks is challenging and requires many reaction steps. Herein, we present that complex polycycles can be synthesized starting from two alkyne building blocks in a one-pot reaction using gold(I) as catalyst, in yields up to 77%. Mechanistically, the process can be described as cascade reaction in two steps: first, the allene is formed by gold(I)-catalyzed dearamatization, second, the desired product is then obtained by allene–diene–alkyne coupling. Quantum chemical investigations confirm the assumed mechanism. In sum, five new C–C bonds are built in one sweep, which is extraordinary since non-identical building blocks are combined in this reaction. The introduced new allene–diene–alkyne coupling reaction paves the way for several new syntheses of cycles and polycycles considering potential intermolecular reactions.

In organic chemistry the development of efficient and new C–C coupling reactions is highly important for the synthesis of complex molecules. Especially, catalysis by transition metals has become an important tool to design such molecules.[1] One of these transition metal-catalyzed C–C coupling reactions is the catalytic asymmetric dearamatization (CADA).[2–6] By using cheap, functionalizable and ubiquitous aromatic systems for this C–C coupling reaction it is possible to synthesize more complex polycycles.[2–6] In search of efficient transition metal catalysts to build up new C–C bonds, homogeneous gold catalysis has come to the fore.[7–11] Currently, it is possible to form up to four new C–C bonds[12] during a reaction cascade by means of homogeneous gold catalysis if the combination of identical building blocks (e.g. oligomerization) is not taken into account.[13] However, gold has been rarely used in CADA reactions compared to other transition metals.[14–17] An example of gold-catalyzed dearamatization involving one alkyne unit was shown by Bandini et al.[18] They converted napthyl propargyl ethers 1 to naphthalene-2-one derivatives 2 (Scheme 1a). This reaction can be considered as a Claisen rearrangement with subsequent intramolecular hydroxy group addition to the newly formed allene.

Our previous work in the field of gold catalysis was focused on the conversion of haloacetylenes (Scheme 1b). The advantage of these compounds is their easy accessibility[19] and their thermal stability at standard conditions.[20–22] During the last few years we and other research groups presented haloalkynylation reactions of different alkynes[23–25] and alkenes.[26–29] Mechanistic investigations proved that the formation of products obtained by addition has to take place via rearrangement.[30] However, the restriction of previous systems is that only conjugated alkynes can be used. While attempting to transfer the concept of haloalkynylation to non-conjugated haloacetylenes, we discovered a gold(I)-catalyzed allene–diene–alkyne coupling reaction to polycycles. Herein, we describe the application range as well as mechanistical investigations of this novel type of cascade reaction.

In the course of studies relating to gold(I)-catalyzed reactions of non-conjugated haloacetylenes with alkynes, compound...
classes 12 and 13 got into our focus of interest (Scheme 1d). These molecules can be prepared in a few steps from readily accessible compounds. The use of two methyl groups in ortho position is necessary to avoid gold(I)-catalyzed cyclization to the corresponding 2H-chromene; this type of reaction has already been observed for terminal alkynes (Scheme 1c).[31–34]

A similar concept was used for propargylic ethers 1 (Scheme 1a).[18] The undesired cyclization could actually be prevented and 2,5-dihydrofurans 2 emerged from gold(I)-catalyzed asymmetric dearomatization. Regarding halocycloenes 12 and 13 adequate cyclization reactions are not expected as halogen atoms are monovalent.

As test reaction the conversion of chloroacetylene 12 with alkyne 5a and [JohnPhosAu(NCMe)]SbF6[35] as gold catalyst was investigated via NMR experiments in deuterated chloroform. Within only two hours at room temperature the starting material was completely consumed. Fortunately, one single main product (yield: 47 %) was obtained (see Figure S8 and Table 1). The yields of all side products amounted to less than 5 %. However, the NMR spectra showed that not the expected enyne product (yield: 47 %) was obtained (see Figure S8 and Table 1). Within only two hours at room temperature the starting material was completely consumed. Fortunately, one single main product was obtained (entry 4). If another type of phosphine ligand like trimethylphosphine was employed, no conversion was observed (entry 6). If JohnPhosAuCl was used with NaBarF2 as counterion, the main product was no longer polycycle 14a but the multiple unsaturated system 15a (entry 3). This system was identified as allene by NMR spectroscopy. The use of gold(III) complex dichloro(2-picolinato)gold(III)[36] led exclusively to allene 15a (entry 8). The use of an NHC ligand[37] ended up in a product mixture in which polycycle 14a and allene 15a were formed in a 2:1 ratio (entry 7). Thus, the initially applied catalyst [JohnPhosAu(NCMe)]SbF6 turned out to be the best choice. In the next step, the equivalents of both starting materials and catalyst as well as temperatures and solvents were varied (entries 9–17). The highest yield of polycycle 14a (52 %) was obtained, when chloroacetylene 12 was converted with 2.5 mol-% of the catalyst and two equivalents of alkyne 5a at room temperature in chloroform.

After optimization of the reaction conditions, we evaluated the substrate scope of this reaction on a preparative scale. Therefore, we used different arylacetylenes (3–7; see Scheme 2) in which both triple bond substituents were varied. At first, we had a closer look at alkyl arylacetylenes 5. The length of the alkyl chain plays no important role, if the second substituent is a phenyl group (14a-c). In all cases the yields amount to ca.

We wanted to examine if the yield obtained in the cascade reaction can be increased. Therefore, we tested different gold catalysts in the first step (entries 1–8 in Table 1). Nevertheless, we were not able to improve the yield (47 %) that was obtained by using [JohnPhosAu(NCMe)]SbF6. The usage of sterically demanding ligands like XPhos led to distinctly lower yields for polycycle 14a (30 %; entry 4). If another type of phosphine ligand like trimethylphosphine was employed, no conversion was observed (entry 6). If JohnPhosAuCl was used with NaBarF2 as counterion, the main product was no longer polycycle 14a but the multiple unsaturated system 15a (entry 3). This system was identified as allene by NMR spectroscopy. The use of gold(III) complex dichloro(2-picolinato)gold(III)[36] led exclusively to allene 15a (entry 8). The use of an NHC ligand[37] ended up in a product mixture in which polycycle 14a and allene 15a were formed in a 2:1 ratio (entry 7). Thus, the initially applied catalyst [JohnPhosAu(NCMe)]SbF6 turned out to be the best choice. In the next step, the equivalents of both starting materials and catalyst as well as temperatures and solvents were varied (entries 9–17). The highest yield of polycycle 14a (52 %) was obtained, when chloroacetylene 12 was converted with 2.5 mol-% of the catalyst and two equivalents of alkyne 5a at room temperature in chloroform.

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Table 1. Optimization of the reaction conditions for the gold(I)-catalyzed coupling of 12 with alkyne 5a.[a]

| Entry | Catalyst | Conditions | Yield [%] | Conversion [%] |
|-------|----------|------------|----------|---------------|
| 1     | [JohnPhosAu(NCMe)]SbF6 (5 mol-%)[35] | RT, 2 h, CDCl3 | 47 | 100 |
| 2     | JohnPhosAuCl (5 mol-%)/AgNTf2 (10 mol-%)[37] | RT, 2 h, CDCl3 | 37 | 97 |
| 3     | JohnPhosAuCl (5 mol-%)/NaBarF2 (10 mol-%) | RT, 2 h, CDCl3 | 9 | 42 |
| 4     | tBuXPhosAuNTf2 (5 mol-%)[37] | RT, 2 h, CDCl3 | 38 | 100 |
| 5     | CyJohnPhosAuCl (5 mol-%)/AgSbF6 (10 mol-%) | RT, 2 h, CDCl3 | 24 | 97 |
| 6     | MeP,NuAuCl (5 mol-%)/AgSbF6 (10 mol-%) | RT, 2 h, CDCl3 | – | 98 |
| 7     | IPrAuCl (5 mol-%)/AgNTf2 (10 mol-%)[37] | RT, 2 h, CDCl3 | 52 | 100 |
| 8     | Dichloro(2-picolinato)gold(III) (5 mol-%)[36] | RT, 2 h, CDCl3 | – | 19 |
| 9     | [JohnPhosAu(NCMe)]SbF6 (2.5 mol-%) | RT, 2 h, CDCl3 | 43 | 100 |
| 10    | [JohnPhosAu(NCMe)]SbF6 (1 mol-%) | RT, 2 h, CDCl3 | 40 | 100 |
| 11    | [JohnPhosAu(NCMe)]SbF6 (2.5 mol-%) | RT, 2 h, C6D6 | 26 | 100 |
| 12    | [JohnPhosAu(NCMe)]SbF6 (2.5 mol-%) | RT, 2 h, CDCl3 | 37 | 100 |
| 13    | [JohnPhosAu(NCMe)]SbF6 (2.5 mol-%) | RT, 2 h, DCE | 10 | 0 |
40%. The yield was increased by a methoxy group in para position (57%, 14d), if a propyl group is attached to the triple bond as second substituent. A lower yield was found if the second substituent is a methyl group (26%, 14e).

Scheme 2. Evaluation of the substrate scope of the gold(I)-catalyzed coupling of haloacetylenes 12 and 13 with alkynes 3–7.

A methyl group in ortho position lowers the yield to 23% (14f). If the alkyl group in 5 is substituted by chlorine (3a), no significant change was observed (40%, 14h). The corresponding bromo derivative 14g was isolated in 13% yield. Terminal alkynes (6) are also tolerated; the corresponding products were obtained in yields of ca. 25% (14i, 14j and 14l) and 10% (14k), respectively. Diarylacetylenes (7) form as well polycycles with 12. The resulting products were isolated in yields up to 77%. In these products the more electron-rich aromatic ring is bound to the position which is closer to the carbonyl group. If bromo derivative 13 was used instead of chloroacetylene 12, the conversion to polycycle 14q was not complete. Even after one week at room temperature or after a few days at 40 °C, the allene and only small amounts of polycycle 14q (11%) were found.

Next, we wanted to elucidate the mechanism of this remarkable coupling reaction. In the first step, the role of the allene was investigated; we wanted to find out whether this allene embodies an intermediate or a side product. Therefore, we converted chloroacetylene 12 without alkyne 5a using gold(III) as catalyst. The allene 15a was isolated in 57% yield (Scheme 3a). Afterwards, we converted 15a under the optimized reaction conditions with [JohnPhosAu(NCMe)]SbF₆ as catalyst and 5a by NMR experiments. Polycycle 14a was obtained in 55% yield. Thus, the formation of 15a via gold-catalyzed Claisen rearrangement can be described as the first sequence of the cascade reaction.

Scheme 3. Gold(I)-catalyzed reaction of chloroacetylenes 12 and 16 in presence and absence of alkyne 5a.

Interestingly, the NMR yield of 14a after conversion of 15a with alkyne 5a (55%) was not much higher than the NMR yield of 14a obtained in the reaction of 12 and 5a (52%, Scheme 3a). This means that the one-pot cascade reaction is almost as efficient as the stepwise process. Please note, the reaction of 12 with [JohnPhosAu(NCMe)]SbF₆ as catalyst without alkyne 5a led to a complete conversion (Scheme 3a), but only a variety of oligomeric compounds was formed, which could not be separated by column chromatography. Therefore, we assume that – utilizing JohnPhosAu⁺ as catalytic species – allene 15a (which is formed in the first step) reacts with the diene unit of the cycle. This leads to the formation of oligomeric structures due to the absence of intercepting alkynes. Another preparative mechanistic indication was achieved via conversion of 16 under the optimized reaction conditions. Bicycle 17 was obtained in 67% yield whether alkyne 5a was present or not. The formation of the product underlines the assumption that the allene unit is cyclized with the diene unit building a five-membered ring. The formed cation can be stabilized by deprotonation. Thus, the second sequence of the cascade reaction probably starts with the formation of a five-membered ring.
The above-mentioned experimental indications were used to calculate the cascade reaction mechanism via quantum chemical methods. Arylacetylene 12 and alkyne 6a were utilized as model substances. In order to optimize the geometrical parameters of all stationary points, the density functional B3LYP\(^{[38–40]}\) together with the dispersion correction via Becke–Johnson damping\(^{[41]}\) (D3BJ) was employed. As basis sets 6-31G(d) was applied for the elements C, H, O, P, and Cl, whereas def2-TZVP was used for Au. Furthermore, single-point calculations on the optimized structures were performed using B3LYP-D3BJ with basis sets 6-311++G(d,p) (for C, H, O, P, and Cl) and def2-TZVP (for Au). To take solvent effects into account, chloroform was considered as reaction solvent by using the SMD\(^{[42]}\) model.

The first sequence of the cascade reaction is the formation of the allene starting with chloroacetylene 12 and JohnPhosAu\(^+\) as catalytic-active species. The coordination of the gold(I) complex is accompanied by free-energy reduction amounting to 15.4 kcal/mol (Figure 1). Please note that the coordination of JohnPhosAu\(^+\) to acetylene 6a (\(\Delta G = -16.2\) kcal/mol) is energetically favored compared to the complexation of 12. However, the reactions of the thusly formed complex with acetylenes 6a and 12, respectively, require high activation energies, making the complexation of 6a a dead end (Figures S8–9). Complex 18a, which is formed by coordination of JohnPhosAu\(^+\) to acetylene 12, was used as reference for all subsequent reaction steps. The rate-determining step of the first cascade reaction sequence (allene formation) is the cyclization to oxonium ion 20a (10.0 kcal/mol). This ion converts into gold(I) allene complex 22a in the second step. Therefore, a barrier of 7.4 kcal/mol needs to be overcome.

After that, two reaction paths are possible: on the one hand, decomplexation can take place leading to the catalytic species and allene 15a (this allene formation corresponds to the end
of the first cascade reaction sequence). On the other hand, the formation of bicyclic cation 24a can occur initiating the second cascade reaction sequence (allene–diene–alkyne coupling). According to calculations, the second sequence (intramolecular cyclization) is more favored (12.5 kcal/mol) than the formation of free allenes (15.3 kcal/mol). This agrees well with the results showing a polymerization in case of converting 12 in absence of 5a with JohnPhosAu⁺ as catalytic species.

Let us now consider the second cascade reaction sequence (allene–diene–alkyne coupling): the first step is again rate-determining and corresponds to the addition of alkyne 6a to cation 24a with formation of vinyl cation 26a (Figure 2). The activation energy for this step amounts to 9.1 kcal/mol. The vinyl cation is stabilized by the phenyl ring, which also explains the regioselectivity of the attack of 6a to 24a. A possible competing reaction to the addition of alkyne 6a to cation 24a is the addition of alkyne 12 to cation 24a. However, the required activation energy for the latter reaction path is distinctly higher (15.5 kcal/mol; Figure S10). In the next step, two intramolecular C–C bonds are simultaneously formed leading to gold(I)-stabilized cation 28a. Proceeding from this σ complex, π complex 30a is formed by a 1,2-hydride shift. Decomplexation leads to the final product 14i.

In Figure 3 the most important intermediates are illustrated in a catalyst cycle. The whole cycle consists of two sequences; in both gold(I) complexed allene 22a is passed. Allene formation takes place via two-step gold-catalyzed Claisen-like rearrangement (black in Figure 3). Allene 22a functions as origin of two branches: on the one hand, the formation of allene 15a is enabled by decomplexation (green in Figure 3), on the other hand, the intramolecular 5-endo-trig-cyclization to 24a is possible (blue in Figure 3). Alkyne 6a can be added to intermediate 24a ending up in the formation of gold complexed polycycle 30a via two further steps. Decomplexation leads to final product 14i and finishes the catalyst cycle.

In sum, we were able to show that polycycles can be designed from haloacetylenes and alkynes by gold(I) catalysis. In our case, the haloacetylene was an o,o-dimethyl-substituted propargyl ether. The reaction tolerates a wide range of alkyne substrates like alkylaryl, diaryl, halo- and terminal alkynes. The achieved preparative yields amount up to 77 %. Experimental and quantum chemical investigations showed that the mechanism can be described as cascade reaction with two sequences. The first sequence is a gold(I)-catalyzed dearomatization in which the corresponding allene is built from propargyl ether by formal Claisen rearrangement (isolation of the allene is possible). The second sequence is a new reaction type: four new C–C bonds are formed by an allene–diene–alkyne coupling leading to the corresponding polycycle. Altogether, even five C–C bonds are newly formed during the whole cascade. The described allene–diene–alkyne coupling reaction has the potential to exploit new ways of polycycle formation starting from simple building blocks. Especially, the option of expanding the reaction to obtain intermolecular products is promising and deserves further exploration.

Supporting Information (see footnote on the first page of this article): Figures and Tables syntheses of the new compounds, NMR experiments, computational details, cartesian coordinates and absolute energies for all calculated compounds, ¹H NMR and ¹³C NMR spectra of the new compounds.

Conflict of Interest
There is no conflict of interest to declare.

Acknowledgments
This work was supported by the Deutsche Forschungsgemeinschaft (DFG; HA 2973/17-1). The authors would like to thank Adrian Schützmann, Petra Schneider and Katrin Steiger for synthetic support. Open access funding enabled and organized by Projekt DEAL.
Keywords: C–C bond formation · Cyclization · Dearomatization · DFT calculations · Gold catalysis

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Received: September 1, 2020