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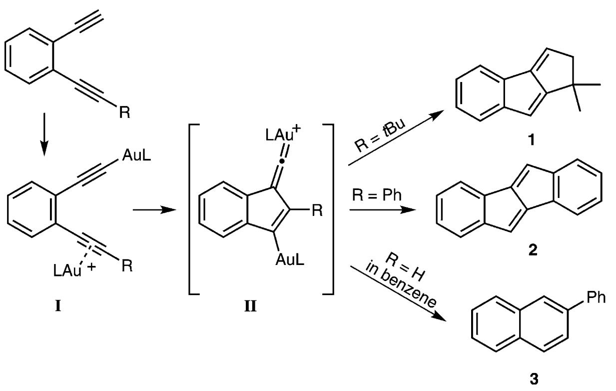
Dual Activation

Gold Vinylidene Complexes: Intermolecular C(sp^3)–H Insertions and Cyclopropanations Pathways**

A. Stephen K. Hashmi, Marcel Wieteck, Ingo Braun, Matthias Rudolph, and Frank Rominger*

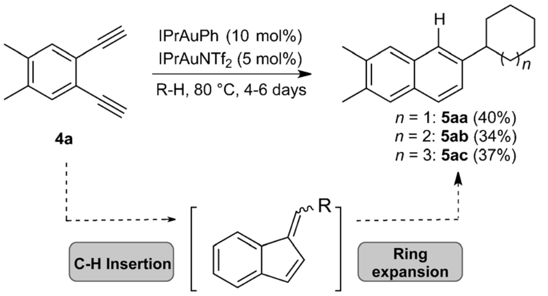
The most common reactivity pattern for gold-catalyzed transformations is the inter- or intramolecular attack of a nucleophile on a multiple bond which is activated by π-coordination to a gold catalyst. This situation opens up an immense spectrum of useful transformations for organic chemists.[1] Early this year, Zhang's group and our group independently reported on a new activation mode which comprises a dual role of the gold catalyst (Scheme 1).[2] While one molecule of gold catalyst activates an alkyne by the established π-activation mode, a second gold complex [LAu$^+$] activates a terminal triple bond by formation of a gold(I) acetylide, which changes the whole reaction pathway. Highly reactive digold intermediates **II** with a gold(I) vinylidene substructure are formed and open up entirely new reaction pathways (Scheme 1). So far, fulvene derivatives **1**[2a,d] and **2**[2c] were accessible by intramolecular sp^3 and sp^2 insertion pathways. Furthermore, the conversion of bis-terminal alkynes selectively delivered the β-substituted naphthalene product **3**.[2b] In this case even an intermolecular reaction of the vinylidene intermediate with the solvent benzene was possible. These results encouraged us to explore further possible transformations of intermediate **II** in intermolecular reactions. The results of these studies are summarized herein.



Scheme 1. First examples of rearrangements involving vinylidene gold complexes.

The ability of vinylidene intermediates to insert intramoleculary into C(sp^3)–H bonds was already exploited by Zhang's group and our group. As a consequence, first experiments were conducted to investigate the possibility of intermolecular C(sp^3)–H bond insertions. To date, for such unactivated alkanes, an intermolecular C(sp^3)–H insertion is unknown for any other gold species and its occurrence would demonstrate the immense reactivity of gold(I) vinylidene intermediates.

As a test reaction we used diyne **4a** which had already been used as substrate for the intermolecular hydroarylation reaction.[2b] To avoid regioselectivity problems, cycloalkanes were used for the possible C–H insertion. In analogy to the hydroarylating cyclization reaction, the cycloalkanes were used as the solvent and comparable reaction conditions were applied (Scheme 2), IPrAuPh was used as an additive. A fast ligand exchange of this organogold compound with the starting material initiates the dual catalysis cycle by forming an acetylide. To our delight, a conversion of the starting diyne could be monitored by thin layer chromatography, but reaction rates turned out to be much slower than for the benzene addition reaction. Nevertheless, we were able to obtain the C(sp^3)–H bond insertion products for three different cycloalkanes (Scheme 2, compounds **5aa–ac**). The relatively low yields for this type of reaction are because of a slow decomposition of the starting diyne at 80 °C in combination with the long reaction times.[3] For the product obtained with cyclohexane, crystals suitable for an X-ray crystal structure analysis were obtained.[4] It confirms the formation of the naphthalene skeleton and in perfect analogy with the hydroarylating reaction, the substituent is on the β-



Scheme 2. Intermolecular C(sp^3)–H insertion reactions.

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[*] Prof. Dr. A. S. K. Hashmi, M. Sc. M. Wieteck, Dr. I. Braun, Dr. M. Rudolph, Dr. F. Rominger[+]
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de
Homepage: http://www.hashmi.de

[+] Crystallographic investigation.

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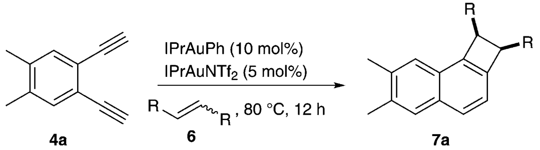
position. It is noteworthy that unlike in the case of the intramolecular C–H insertion reactions, no benzofulvene structures are obtained. Instead ring expansion and formation of the naphthalene skeleton takes place. The lack of a ring expansion in the case of fulvenes **1** and **2** (intramolecular reaction) can be explained by the strained cyclobutane derivatives that would be the final products.

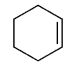
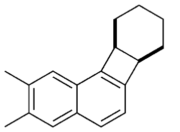
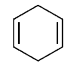
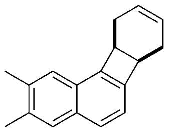
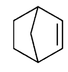
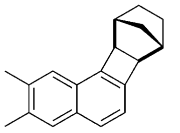
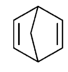
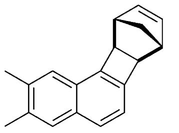
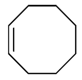
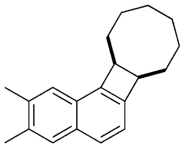
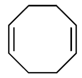
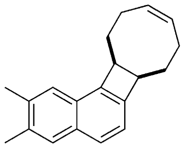
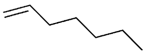
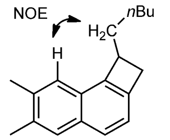
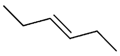
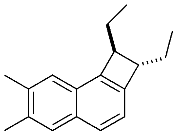
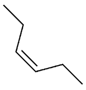
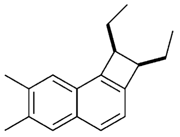
Next, we investigated alkenes as more-reactive partners. As cyclopropanation by gold carbenes is a frequently observed reactivity pattern,[5] we considered that goldvinylidene **II** might show comparable reactivity, and thus be a synthon for an alkylidene carbene.[6]

An initial experiment with diyne substrate **4a** and a mixture of 5 mol% IPrAuNTf$_2$ and 10 mol% IPrAuPh or IPrAuMe (as an additive for acetylide formation)[2b] delivered quantitative conversion of the starting material in cyclohexene as solvent (ca. 100 μmol mL^{-1}). The preparative scale of the reaction delivered the product in 64% yield (Table 1, entry 1). Fortunately, we were able to obtain crystals of **7aa** suitable for an X-ray crystal structure analysis.[4] Product **7aa** shows a naphthyl scaffold anellated to a cyclobutene ring at the α,β-position of the naphthalene core. There are only a few synthetic routes to such structures, which need drastic reaction conditions.[7] The *cis*-diastereomer was obtained exclusively. Encouraged by this initial experiment, we explored the reaction of diyne **4a** with different alkenes as solvent (ca. 100 μmol mL^{-1}). 1,4-Cyclohexadiene delivered benzocyclobutene-type products, too (entry 2). Owing to the excess of alkene, not even traces of the product of a two-fold addition could be detected. Norbornene also turned out to be a suitable alkene. In addition, the yield of the reaction was very good (entry 3). In this case, the corresponding diene norbornadiene did not deliver similar results, rather unexpectedly the yield dropped significantly (entry 4). Larger cycloalkenes were also tolerated, which was demonstrated by *cis*-cyclooctene (entry 5) and 1,5-cyclooctadiene (entry 6). Both reactions smoothly delivered the interesting bicyclo[6.2.0]decane scaffolds in high yields.

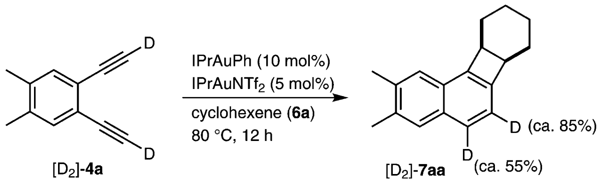
Next we applied non-cyclic alkenes as starting materials. To our surprise, unsymmetrical 1-heptene only delivered one single product albeit in only moderate yield (entry 7). The NOE-NMR spectrum of compound **7ag**, showing cross-peaks of the protons of the methylene group directly bound to the cyclobutene ring and an aromatic singlet. Based on the proximity of these groups, only the structure shown for **7ag** is possible. To further investigate the stereochemical course of the reaction, both *trans* and *cis*-3-hexene were used as reactants (entries 8 and 9). The reaction turned out to be highly stereoselective and each of the products obtained was diastereomerically pure (even in the ^{1}H NMR spectra of the crude products no traces of the other diastereoisomer were detectable). The double bond configurations of the starting alkenes were cleanly translated into the final product. The configuration was assigned by the ^3J-coupling constants in proton NMR spectrum (*cis*: 10.5 Hz vs. *trans*: 1.4 Hz). Further proof was provided by the X-ray crystal structure analysis of compound **7ai**.[4] These results exclude a step-wise process with cationic intermediates for the intermolecular attack at the olefin.

Table 1: Gold-catalyzed synthesis of cyclobutene derivatives **7a**.



Entry	Olefin		Product	(yield)
1		**6a**		**7aa** (64%)
2		**6b**		**7ab** (65%)
3		**6c**		**7ac** (81%)
4		**6d**		**7ad** (41%)
5		**6e**		**7ae** (84%)
6		**6f**		**7af** (71%)
7		**6g**		**7ag** (64%)
8		**6h**		**7ah** (49%)
9		**6i**		**7ai** (28%)

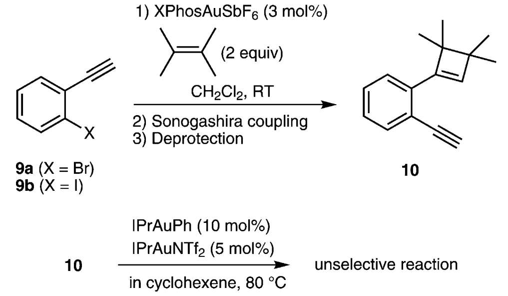
Our next aim was to gain further insight into the reaction mechanism. A first experiment was performed with substrate [D$_2$]-**4a** bearing deuterium labels at both of the terminal positions of the alkyne (Scheme 3). In the product, a high degree of isotopic labeling was observed for the aromatic hydrogen atom next to the ring fusion point. In addition more than 50% deuterium labeling could be detected at the second aromatic proton that is generated after cyclization. The deuterium labeling of the product shows a close relationship



Scheme 3. Isotopic labeling experiment.

to our previously reported hydroarylating aromatization product and thus is evidence for a related reaction pathway.[2b] Slightly lower isotopic labeling might be influenced from traces of acid in the absence of basic additives (these were used for the labeling experiments of the hydroarylating reaction).

Recently, Echavarren and co-workers reported on a gold-catalyzed intermolecular [2+2] cycloaddition of alkynes with alkenes.[8] To explore if a related mechanism (i.e. an initial [2+2] cycloaddition followed by enyne cyclization with the second alkyne moiety) is relevant for our reaction, a control experiment using the original conditions of Echavarren et al. was conducted (CH_2Cl_2, cyclohexene/alkyne 2:1, 3 mol% *tert*-butyl XPhosAuSbF_6, room temperature), but no conversion of diyne substrate **4a** was observed (not even the formation of a [2+2] cycloaddition product took place). In addition, we tested the reaction of phenylacetylene in cyclohexene using our catalyst system. Even after 3 days at 80 °C no reaction was observed. To evaluate if a cyclobutene **10** might be a possible intermediate, we synthesized this species, starting from *ortho*-alkynylhaloarenes **9** (Scheme 4). It is noteworthy that for alkynes **9** Echavarren's cyclobutene synthesis did not work for cyclohexene (which readily reacts with our diyne substrates). Instead we used tetramethyethylene (an alkene which turned out to be unreactive with our diyne systems). We then converted this possible intermediate under our conditions. As result, only an unselective reaction was detected. Together with the mentioned orthogonal reactivity of the alkenes, this clearly excludes a [2+2] mechanism in the first reaction step.



Scheme 4. Control experiment with cyclobutene **10**.

Thus the mechanism based on the dual-activation scenario seems to operate. For this reaction mode, the initial step would involve a gold acetylide as the reactive species. To check the reactivity of a gold acetylide, we prepared gold acetylide **8a** from diyne **4a** and IPrAuCl (Et_3N/CH_2Cl_2, room temperature, 92%) and subjected it to stoichiometric amounts of activated catalyst in cyclohexene (Scheme 5). The starting material **8a** was consumed within seconds and a crystalline solid could be isolated. To assign the product structure definitely, an X-ray crystal structure analysis was conducted (Figure 1). In complete accordance to our recently published results on dual gold catalysis,[2b–d] a *gem*-diaurated species **11aa** was formed (Scheme 5). The structural core of the final product was already present, in addition two gold atoms are connected to the δ-position of the naphthalene unit. As these atoms originate from electrophilic attack at the mono-aurated derivatives,[9] from our preceding work[2b–d] it is clear that in the last stage of the reaction the mono-gold derivative of compound **11aa** should be an intermediate. In perfect analogy to our previously reported related *gem*-diaurated species, this compound was catalytically active for the transformation (3 mol% **11aa** for the conversion of **4a** into **7aa**; isolated in 62% yield).

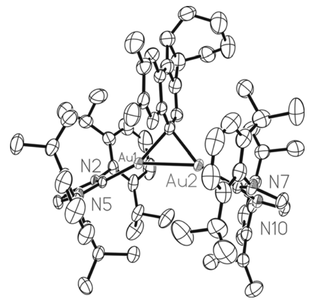
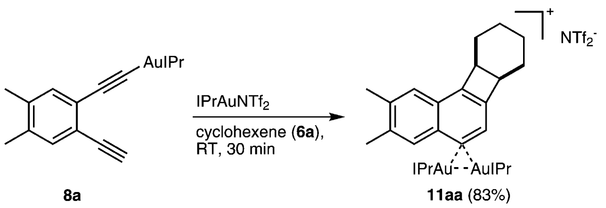
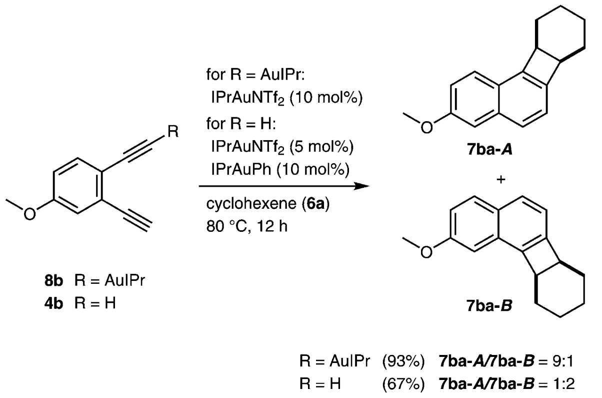


Figure 1. Crystal structure of **11aa** (H atom omitted, thermal ellipsoids set at 50% probability).



Scheme 5. Isolation of the diaurated benzocyclobutene **11aa**.

Our next experiments addressed the positional selectivity of the alkene incorporation. We prepared the unsymmetrically substituted diyne **4b** and subjected it to a catalytic amount of our catalyst combination in cyclohexene (Scheme 6). After work-up, a mixture of two regioisomeric products was obtained, favoring **7ba-*B*** (2:1). We assume that the difference in pK_a values triggers the selectivity. The methoxy group *para* to the alkyne should disfavor its acetylide formation, thus it is likely that the cyclohexene unit is incorporated at the other acetylide moiety. Additional proof for this assumption was obtained with the unsymmetrically substituted mono-acetylide **8b** (for the synthesis of **8b** see Supporting Information). The results of the reaction under catalytic conditions revealed a high 9:1 positional selectivity and furthermore regioisomer **7ba-*A*** was favored in this case. The positional selectivity of the cyclohexene towards the gold

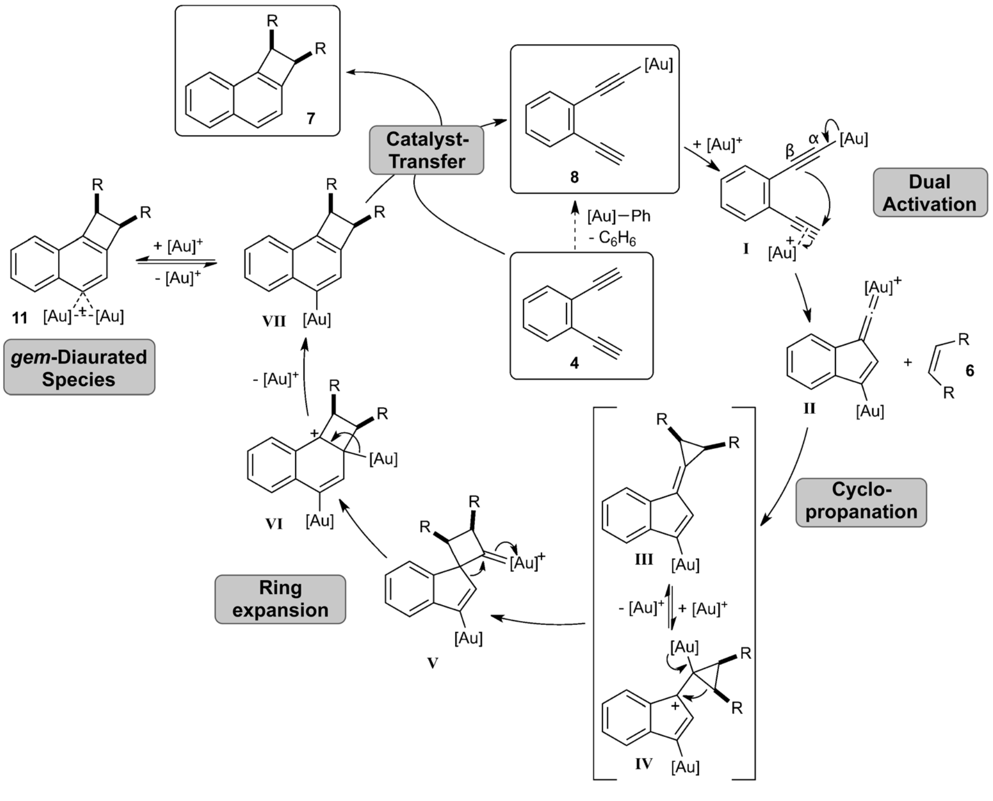


Scheme 6. Positional selectivity of the alkene incorporation.

acetylide also excludes the alkyne/alkene [2+2] cycloaddition pathway. Previous mechanistic investigations by Corma[10] have revealed that gold acetylides are unreactive for the cycloaddition which is confirmed by the non-reactivity of IPr-substituted phenylacetylide under our reaction conditions.

The mechanistic investigation clearly indicates a reaction pathway which shows a close relationship to previously reported dual gold-catalyzed reactions. Our mechanistic rationale is depicted in Scheme 7. The catalytic cycle is initiated by ligand exchange with the phenyl gold complex that is added. After the formation of the gold acetylide, the attack of the β-carbon at the π-activated alkyne leads to the formation of highly active vinylidene intermediate (**I**→**II**). These first steps are identical to the hydroarylating aromatization reaction.[2b] In the next step, a stereospecific cyclopropanation takes place, which indicates an alkylidene carbenoid reactivity of the vinylidene (if an electrophilic attack at the olefin would occur, involving an open-chained carbenium ion, the reaction should not be stereospecific for acyclic *cis*- and *trans*-alkenes). The methylenecyclopropane **IV** then undergoes a gold-catalyzed ring-expansion cascade. The rearrangement of methylenecyclopropanes to cyclobutenes catalyzed by platinum[11] or palladium[12] were recently published. Upon coordination of the gold to the highly activated double bond of **III**, a cyclobutane carbene intermediate **V** is formed, which after a shift of the vinyl group delivers the molecular skeleton of the product. Simple elimination of the cationic gold catalyst [Au]$^+$ from **VI** then regenerates the aromatic ring. Finally, the catalytic cycle is closed by a catalyst transfer of mono-aurated compound **VII** (which is in equilibrium with *gem*-diaurated species **11**) onto the starting diyne **4** under regeneration of the σ-activated starting material **8**.

In conclusion, based on highly reactive gold vinylidene species two new intermolecular reaction pathways were developed. Even normally inactive species, such as cycloalkanes react with these high-energy intermediates. Furthermore, these species might be regarded as alkylidene carbene synthons, species that are usually generated under harsh reaction conditions and by using toxic reagents. The alkene incorporation reaction presented herein once more demonstrates the advantages of dual gold catalysis. Complex polycyclic aromatic systems are available in only one reaction step from simple diyne precursors. By using the powerful reactivity of gold vinylidenes, completely new reactions will become available.



Scheme 7. Mechanism.

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[4] CCDC 883063 (**5aa**), CCDC 883060 (**7aa**), CCDC 883061 (**7ai**), and CCDC 883062 (**9aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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