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The Role of Acetylides in Dual Gold Catalysis: A Mechanistic Investigation of the Selectivity Difference in the Naphthalene Synthesis from Diynes

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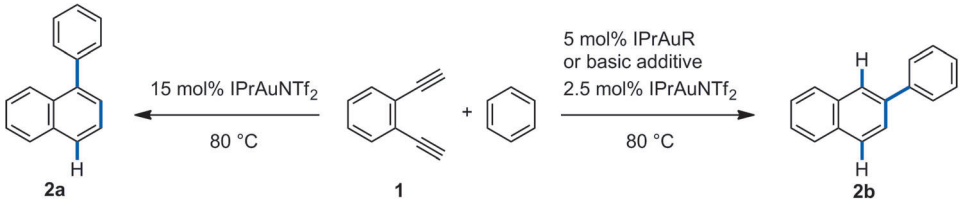
Under the conditions of dual activation catalysis with oxygen nucleophiles, β-substituted naphthalenes were obtained from 1,2-diethinyl arenes. Mechanistic studies, which include isotope labeling experiments, support that dual activation leads to β-substituted naphthalenes, whereas α-naphthalenes are formed by π activation only, and no gold acetylide or dual activation is involved in the formation of the α-substituted products. Additional experiments on substrates that led to dibenzopentalenes support these mechanistic insights.

Introduction

Recently Zhang's group[1] and our group[2–6] reported on a new reactivity pattern for gold-catalyzed reactions in which two gold fragments are used for substrate activation. One cationic gold fragment activates one π-bond of a diyne system, and the other gold molecule activates a second terminal alkyne by σ-coordination. This cooperation induces a cyclization that, dependent on the connecting tether of the diyne system, delivers carbene/vinylidene intermediates. These highly reactive intermediates have already been used for a series of fruitful transformations.[1–6]

In our first contribution on this topic, our group reported on a gold-catalyzed hydroarylating aromatization reaction.[2] Depending on the reaction conditions, either α- or β-naphthalene derivatives were formed from simple diyne **1** by the incorporation of a benzene molecule, which was used as the reaction solvent (Scheme 1).



Scheme 1. Selectivity control of the hydroarylating cyclization.

Based on these findings, we were curious to see if we could adapt this reaction to other nucleophiles.[7] We envisioned that if stronger nucleophiles were used, it might be possible to perform the reaction in an inert solvent with only a slight excess of the nucleophile.

Results and Discussion

To induce high β-selectivity, we applied σ,π-dinuclear propyne gold acetylides (dual activation catalysts; DACs) for our test reactions as these catalysts are ideal for dual activation catalysis cycles.[8] As the test system, diyne **1** was used in combination with varying equivalents of methanol as the nucleophile (Table 1). Indeed it was possible to obtain a high β-selectivity for all of the applied ratios of nucleophile to substrate. If the amount of the protic nucleophile was higher than three equivalents, the competing formation of minor amounts of the α-substituted product was observed (entries 3–5). Next, we varied the counterions of the DACs (Table 2). Only a minor effect of the counterion was visible, but the tetrafluoroborate counterion was the best choice, and a perfect β-selectivity was observed for this counterion.

We chose 1,2-dichloroethane (DCE) as the solvent for this reaction because many other solvents could be ruled out before-

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[+] Crystallographic investigation

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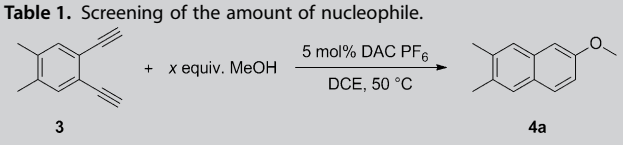
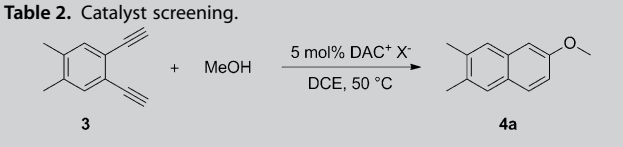
Table 1. Screening of the amount of nucleophile.



Entry	Amount of MeOH [equiv.]	Product yield [%][a] α-Substituted	β-Substituted (**4a**)
1	1	0	20
2	3	traces	44
3	5	3	39
4	10	3	40
5	50	7	29

[a] Yields determined after 3 d by GC–MS with hexamethylbenzene as internal standard.

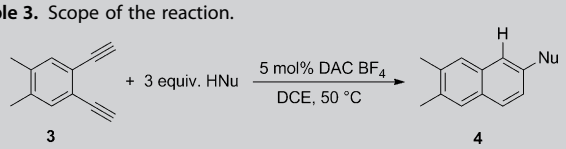
Table 2. Catalyst screening.

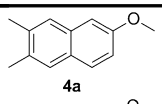
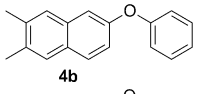
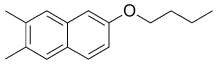
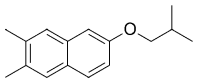
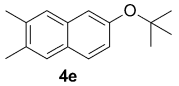
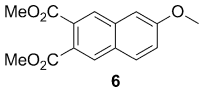


Entry	Counterion X^-	Product yield [%][a] α-Substituted	β-Substituted (**4a**)
1	SbF_6^-	4	43
2	BF_4^-	0	47
3	OTs^-	0	29
4	NNf_2^-	4	50
5	PF_6^-	3	38
6	NTf_2^-	2	43

[a] Yields determined after 18 h by GC–MS with hexamethylbenzene as internal standard.

Table 3. Scope of the reaction.



Entry	Product	Yield of β-substituted product **4** [%][a]	*t*
1	 **4a**	55	7 h
2	 **4b**	24	3 d
3	 **4c**	44	1 d
4	 **4d**	43	24 h
5	 **4e**	41	56 h
6[b]	 **6**	23	4 d

[a] Isolated yields. [b] The diester was used instead of the dimethyl substrate.

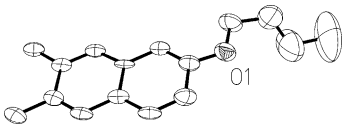


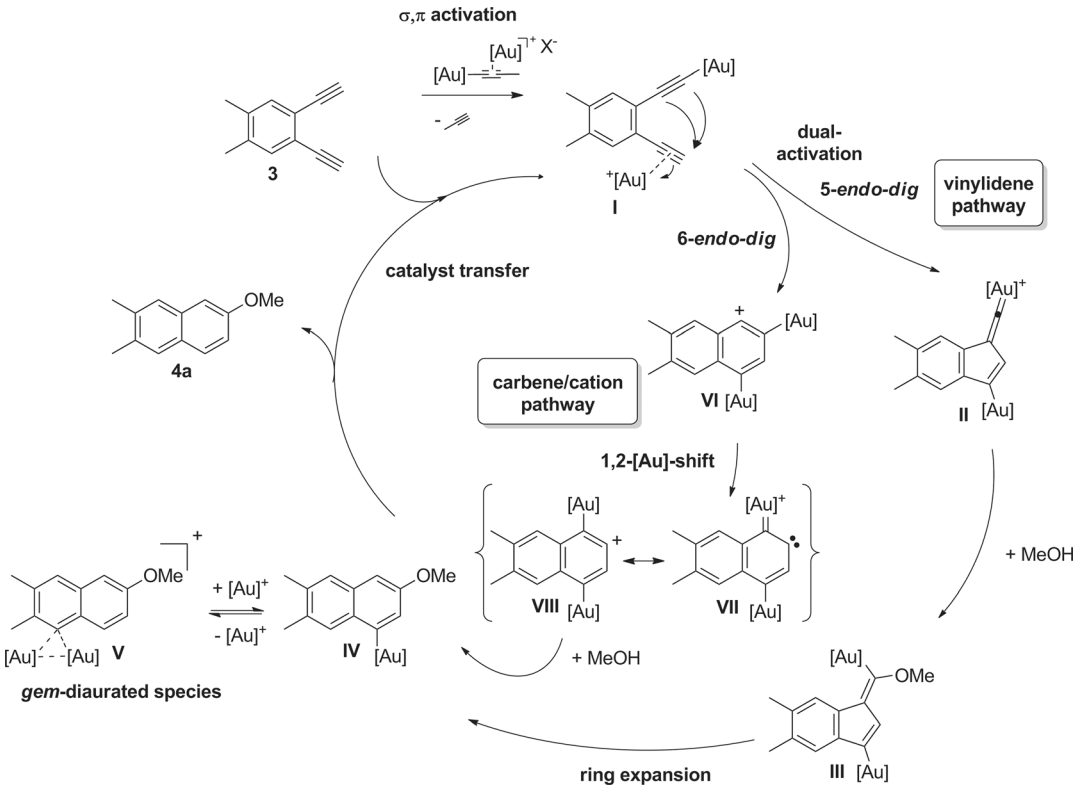
Figure 1. Solid-state structure of **4c**.

hand. Benzene, acetone, 1,4-dioxane, THF, and even nonpolar solvents such as cyclohexane and *n*-hexane reacted with the substrate under the reaction conditions and were, therefore, not suitable for this reaction. With the optimized conditions in hand (three equivalents of the nucleophile in combination with the tetrafluoroborate counterion), we turned our focus to the evaluation of the substrate scope (Table 3).

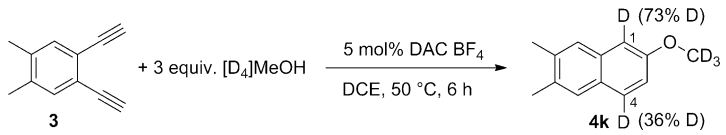
The isolated yield of β-methoxy naphthalene **4a** was only moderate (entry 1). An even lower yield was obtained by using phenol as a weaker nucleophile, which was accompanied by an increased reaction time. Thus we reverted back to other aliphatic alcohols that delivered yields in the range of 40% regardless if branched or linear alcohols were applied (entries 3–5). If we changed the aromatic backbone, lower yields for the substrate dimethyl 4,5-diethynylphthalate (**5**), which bears electron-withdrawing ester moieties, were obtained (entry 6). Unfortunately, the substrate scope was quite limited, and amine derivatives (aniline, *N*-methylaniline, morpholine, and 1-(*p*-tolylsulfonyl)pyrrole) and carbon-based nucleophiles (dimethyl malonate) were not suitable for this transformation (for details see the Supporting Information). To prove the selectivity obtained, crystals of **4c** were grown that were suitable for XRD analysis.[9] The molecular structure of the formed β-naphthol derivative **4c** is depicted in Figure 1.

Based on our previous mechanistic investigation,[2] we propose the mechanism depicted in Scheme 2. The reaction is initiated by the transfer of the two gold fragments from the DAC. The so-formed σ,π-activated starting material **I** can then undergo either a 5-*endo-dig* or a 6-*endo-dig* cyclization. Both of the pathways are reasonable and depend on the starting material. Both pathways have already been observed in the dual gold catalysis of diynes.[6,10] In the case of the 5-*endo-dig* pathway, vinylidene **II** would be formed that, after the attack of methanol, would undergo a ring expansion to form the aurated naphthyl methyl ether **IV**, which is in equilibrium with *gem*-diaurated species **V**. The same species could also be formed through the 6-*endo-dig* pathway. In this case, after the initial cyclization, a fast 1,2-shift of the gold delivers a stabilized carbene/cation **VII**/**VIII**.[11] The attack of methanol onto this species delivers the naphthyl methyl ether intermediate **IV**. The last step of the reaction cascade is catalyst transfer, which is crucial as otherwise the β-selectivity would be lost (no acetylide would be formed for the next catalytic cycle).

To support our mechanistic proposal we conducted a deuterium labeling experiment by using three equivalents of



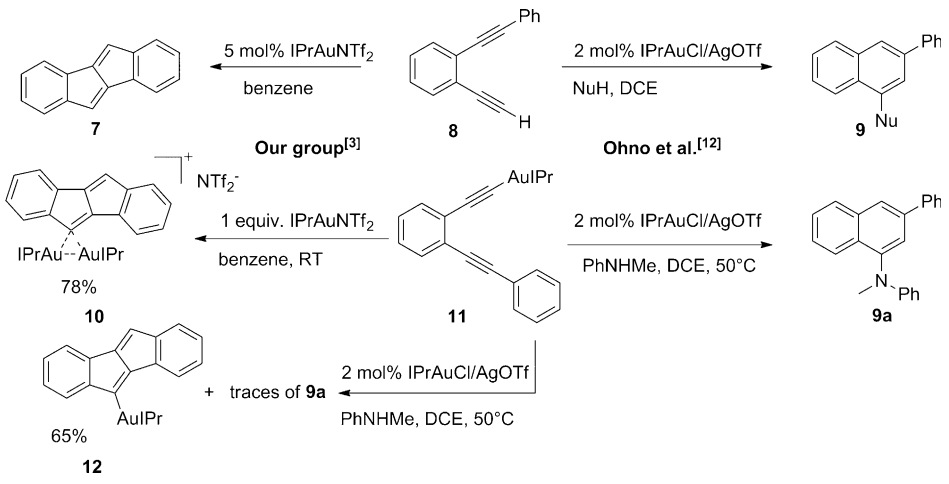
Scheme 2. Mechanistic proposal.



Scheme 3. Deuterium labeling experiment.

$[D_4]$MeOH as a the nucleophile (Scheme 3). Deuterium incorporation in the naphthalene backbone was exclusively found in the 1- (73% D) and 4-positions (36% D). This result strongly suggests that each or both pathways discussed in Scheme 2 can be involved. Deuterium incorporation in the 1-postion can be explained by the nucleophilic attack/protodeauration step from carbene/cation **VII**/**VIII** to the aurated naphthyl methyl ether **IV** if the reaction proceeds by the 6-*endo-dig* pathway. If the vinylidene pathway is favored, the deuterium is incorporated by the $[D_4]$MeOH-induced ring-expansion step from vinylidene **II** to the aurated naphthyl methyl ether **IV**. The deuterium incorporation in the 4-position results from a $[D_4]$MeOH-mediated protodeauration of the aurated naphthyl methyl ether **IV** to product **4a**. The lower deuterium incorporation in the 4-position with respect to the 1-position can be interpreted as a result of the competing catalyst transfer step that causes a protodeauration by the H atom of the diyne starting material.

During the preparation of this manuscript, the group of Ohno reported on a cascade reaction of diynes that bear one phenyl-substituted alkyne in combination with a terminal alkyne. In their case, the exclusive formation of the α-substituted product was observed by using an external nucleophile (Scheme 4, top right).[12] This is completely in line with our findings for the related hydroarylating aromatization,



Scheme 4. Results of Ohno et al. and Hashmi et al. for the catalytic conversion of **8** and **11**.

which was α-selective if no additive (a base or an organogold species) was present.[2] However, there was a contradiction between the mechanistic proposal that was discussed for the formation of the α-substituted product and other preceding mechanistic insights. The authors speculate that for the formation of the α-substituted product an acetylide complex can be the key intermediate. This assumption is based on an experiment with gold acetylide **11** that was reported to deliver quantitative amounts of the α-substituted product **9a** if catalytic amounts of a cationic gold source were present (Scheme 4, bottom right).[13] In addition, if Ohno et al. used a deuterated alkyne and 10 equivalents of EtOH as the nucleophile, almost a complete loss of deuterium was observed after the transformation, which was explained by an exchange process in which the intermediate gold acetylide was reprotonated. The involvement of an acetylide in the formation of the α-isomers is contradictory to our observation as exclusively β-substituted products are formed if additives for acetylide formation are present or if stoichiometric reactions that start from the preformed acetylides are performed. Furthermore, with exactly the same starting material in the absence of a nucleophile, our group was able to obtain benzopentalenes **7** (Scheme 4, top left). In addition, we could show that in this reaction *gem*-diaurated benzopentalenes were formed if an acetylide was used as the starting material in a stoichiometric experiment. For us it was not understandable that the same acetylide could give the α-substituted product in high yield. It seems clear that upon dual activation, intramolecular trapping should be favored, and, furthermore, in the case of an acetylide as the starting material, we would expect a β-substituted product to be formed if an external nucleophile could trap the intermediate.

With this in mind, we performed the reaction with acetylide **11** and *N*-methylaniline under exactly the same conditions as those used by the Ohno group. In our experiment, we were able to detect 65% of monoaurated benzopentalene **12** accompanied by only traces of the α-substituted product **9a** (< 7%; even <3% if the reaction was performed in CH_2Cl_2 that was saturated with water; Scheme 4). The fact that only traces of the α-substituted product can be seen in the ^{1}H NMR spectrum of the crude material is clear evidence that gold acetylides are not involved in the formation of the α-substituted product. Instead, if a gold acetylide is formed, direct trapping of the intermediate vinylidene occurs and the outcome is the expected benzopentalene product.

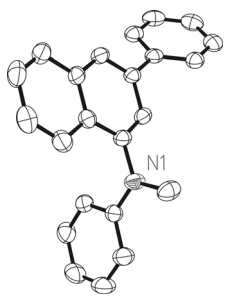
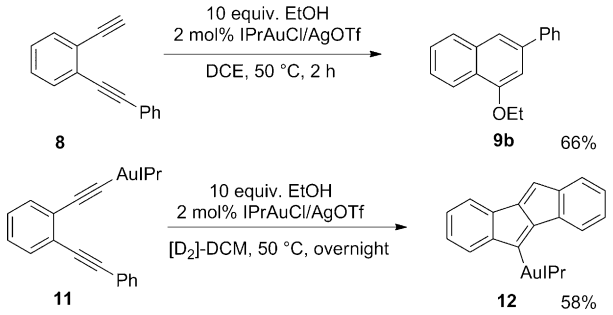


Figure 2. Solid-state structure of **9a**.

Indeed, only the α-substituted product **9a** can be obtained if the reaction is performed in the absence of an acetylide and by using *N*-methylaniline as the nucleophile. When we reproduced the reaction, we were able to obtain crystals suitable for XRD analysis, and the results deliver the final proof for the α-substitution (Figure 2).[9] We assume that in this case, the reaction pathway is related to the α-pathway of the hydroarylating aromatization and the products are not derived from acetylides as starting materials. Both the cyclization by the free acetylene followed by a nucleophilic attack onto the so-formed aryl cation or the formation of an enamine/enol ether intermediate and a subsequent attack of the nucleophilic double bond onto the second alkyne are reasonable. Nevertheless, still no precise mechanistic picture exists for the formation of the α-substituted products.

As Ohno et al. used ethanol as the nucleophile for both their screening reaction and most of their mechanistic investigations, we performed test reactions with this nucleophile too.

All their reported transformations were performed under an Ar atmosphere, therefore, we assumed that dry conditions (inert gas atmosphere, dry solvents, molecular sieves) were crucial. At first we encountered problems in trying to reproduce this reaction, but by variation of several parameters we found that trace amounts of water in the reaction mixture are essential for this reaction mode. The next reactions were, therefore, performed under air and without molecular sieves. First we reacted acetylide **11** with 2 mol% of IPrAuCl/AgOTf in the presence of 10 equivalents of ethanol. This gave monoaurated benzopentalene species **12**, the product also obtained with *N*-methylaniline as the nucleophile (Scheme 4). The isolation of **12** in 58% yield was possible despite the fact that the product was fairly unstable during column chromatography (Scheme 5).



Scheme 5. Gold(I)-catalyzed conversion of **8** and **11**.

With the purified product in hand, single crystals suitable for XRD analysis were obtained, which gave unambiguous proof of the formation of the monoaurated benzopentalene system.[9] Interestingly, two different modifications were obtained in the solid state.[9] Both solid-state molecular structures are depicted in Figure 3. In addition to the expected conformer with an orthogonal alignment of the two ligands, a conformer with all of the residues in one plane can be found in the other modification. The superimposed structures document this phenomenon well.

Next, both groups together re-investigated the assumption of the Ohno group that the D/H exchange of the starting material (which can be monitored during the course of the reaction) and the accompanying loss of deuterium labeling in the product allows us to conclude that a gold acetylide is involved in the catalytic cycle. To evaluate if the acetylide can be protodemetalated, which would be crucial for H/D exchange, we

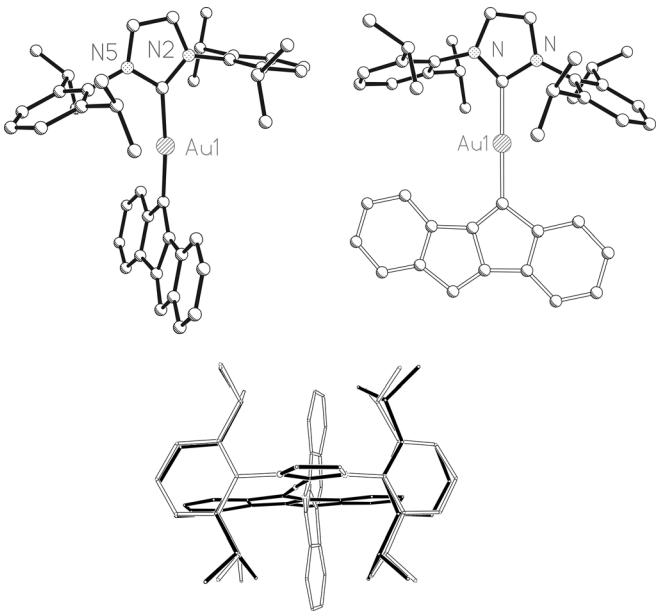
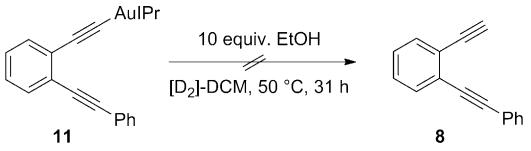


Figure 3. Solid-state structure of **12**.

heated acetylide **11** for 31 h at 50 °C but no traces of protodeauration were visible (Scheme 6). To exclude the involvement of a terminal alkyne in the exchange process, the same reaction was conducted in the presence of equimolar amounts of phenylacetylene but again no exchange was observed.

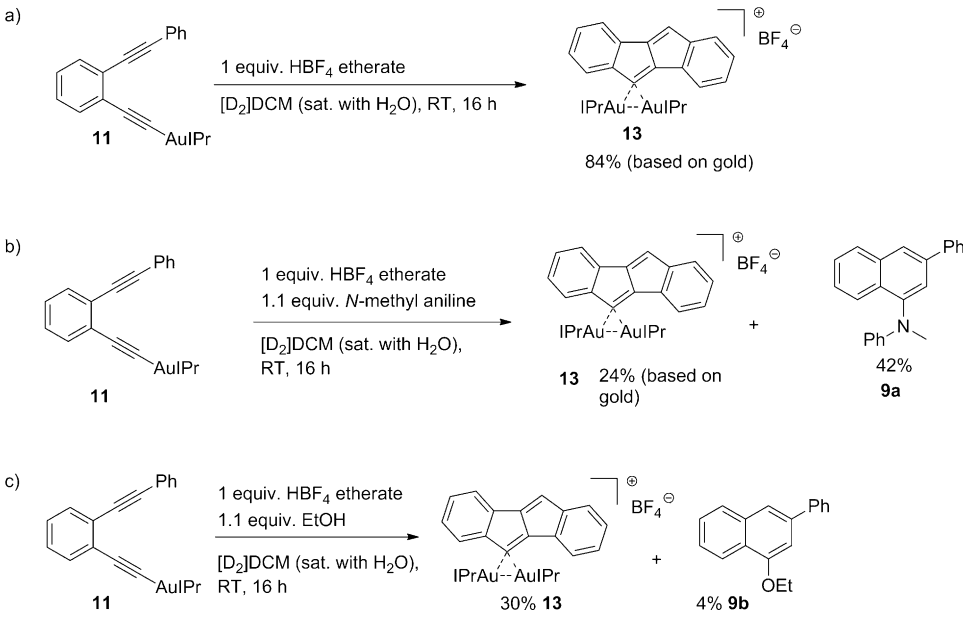
As one might speculate that a second Au atom or a strong acid (which is indeed released during acetylide formation if no base is present) might be necessary for an exchange process, we subjected **11** to stoichiometric amounts of acid (both in normal CD_2Cl_2 and in CD_2Cl_2 that was saturated with water; Scheme 7).

Indeed in all three cases the formation of the digold species **13** was observed in yields up to 84% (referring to gold; yield determined by ^{1}H NMR spectroscopy), whereas free diyne **8** was not seen in the ^{1}H NMR spectra. This indicated that the protodemetalation of **11** is possible and then in a subsequent reaction **13** is formed by the dual activation pathway. If the same reaction was conducted in the presence of *N*-methylaniline as a potential nucleophile, the formation of significant amounts of the α-substituted product **9a** was observed (Scheme 7b). This can be explained by the generation of free alkyne (in combination with free active catalyst) in the presence of a strong nucleophile that can deliver the α-substituted product through the non-acetylide pathway. In the presence of EtOH as a weaker nucleophile, hardly any α-substituted **9b** was obtained (Scheme 7c), although 30% of **13** was formed. Furthermore, we subjected σ,π-*gem*-diaurated phenylacetylene **14** (**11** can cyclize through activation of the second alkyne) to stoichiometric amounts of acid at 50 °C (Scheme 8). It is not unexpected that no protodeauration takes place in this case as there are reports by Brown and Widenhofer who used exactly the reverse reaction for the preparation of σ,π-gold complexes.[14]

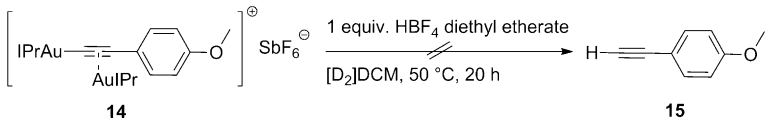


Scheme 6. Reaction of **11** with ethanol.

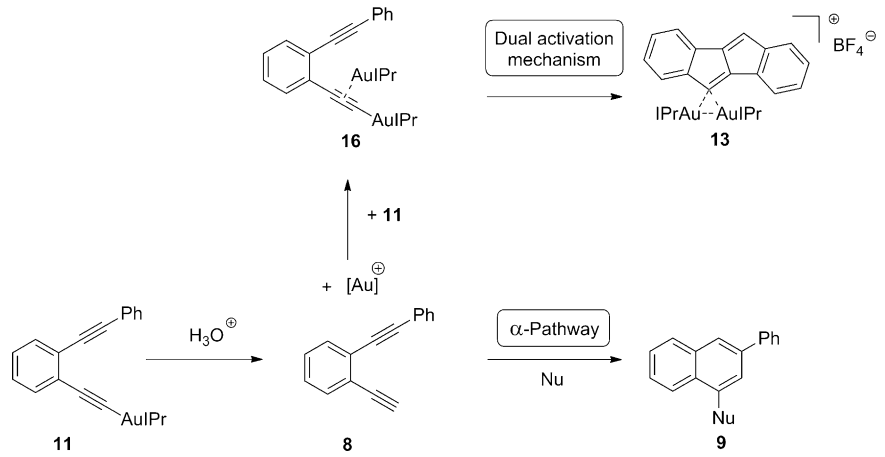
No exchange could be monitored even at elevated temperatures. This shows that in contrast to **11** no protodemetalation is possible with σ,π-*gem*-diaurated complexes. The reason for the H/D exchange process reported by the Ohno group remains unclear. Two options are reasonable. One could be the direct H/D exchange via a gold π-coordinated alkyne, which increases the acidity of the proton at the alkyne. On the other hand, it is possible that an equilibrium between the free



Scheme 7. Reaction of **11** with HBF_4 etherate.



Scheme 8. σ,π-*gem*-Diaurated phenylacetylene **14** does not react with acid.



Scheme 9. Two possible pathways.

alkyne and the gold acetylide exists. This process is induced by the acid that is generated if no additive is present. This indicates that under the reaction conditions traces of acetylides might be formed, but for the formation of the α-substituted product the reverse reaction of the equilibrium must take place, which releases the free alkyne that then undergoes cyclization. In the presence of a dual catalyst or if one starts with an acetylide and catalytic amounts of a gold catalyst no acid is released and, therefore, the α-pathway is suppressed (Scheme 9).

Conclusions

We have shown that **β**-substituted naphthalene systems can be generated by a dual catalyzed gold reaction. The scope of the reaction is limited and only oxygen nucleophiles were suitable. Although for this kind of transformation acetylides are assumed to be key intermediates, we have shown that in the gold(I)-catalyzed formation of **α**-substituted naphthalene derivatives, which was previously reported by the Ohno group, gold(I) acetylenes **11** as true intermediate structures are unlikely. If **11** is formed, it follows the reaction mechanism to form benzopentalenes as reported by the Hashmi group in previous contributions. For the formation of the α-substituted product **9**, free alkyne **8** is necessary in combination with free catalyst. Even if acetylides are present in the reaction, the equilibrium between free alkyne/cationic gold and acetylide/acid enables an α-pathway if a strong nucleophile is present.

Acknowledgements

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Keywords: alcohols · alkynes · isotopic labeling · gold · reaction mechanisms

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