ACS Catalysis

Viewpoint

pubs.acs.org/acscatalysis

Gold Catalysis 2.0

Ingo Braun,[†] Abdullah Mohamed Asiri,[§] and A. Stephen K. Hashmi[†,‡,*]

[†]Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

[‡]Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

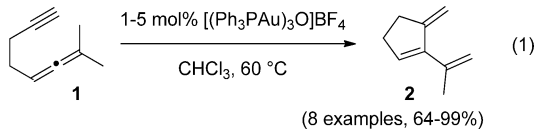
[§]Center of Excellence for Advanced Materials Research (CEAMR), King Abdulaziz University, Jeddah 21589, P.O. Box 80203, Saudi Arabia

1. INTRODUCTION

Since 2000, homogeneous gold catalysis has developed to an important sector of catalysis research.[1] Initially, the research focused mainly on methodology development, but detailed mechanistic studies quickly followed.[2] For about 7 years, applications in synthesis were increasingly reported.[3] In all these reactions, the activation of the substrate was based on the interaction with *one* gold center. After some initial publications on a potential simultaneous activation of substrates by *two* gold centers, last year, much better insights were achieved, and innovative synthetic perspectives opened up by a series of reports. Here, the basic principles and the current status of this quickly progressing new sector of dual gold catalysis will be discussed.

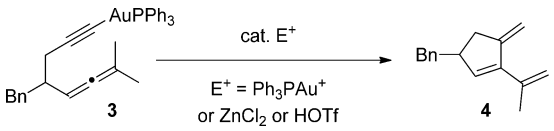
2. FIRST EVIDENCE

In 2008 Houk, Toste and co-workers published a fascinating new reaction mechanism.[4] The cycloisomerization of 1,5-allenynes **1** by the $[(Ph_3PAu)_3O]BF_4$ catalyst delivers cross-conjugated trienes **2** (eq 1).



(1)

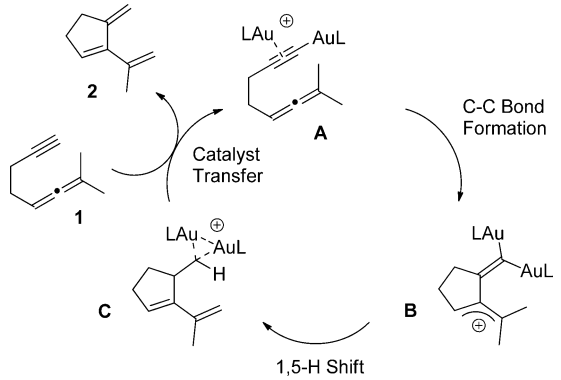
The reaction was limited to terminal alkynes, a deuterium labeling experiment showed that the hydrogen transfer during the reaction was diastereoselective, and a crossover experiment proved that the hydrogen was transferred in an intramolecular manner. Most important was the observation that the hydrogen atom of the terminal alkyne was exchanged for deuterium if the reaction was run in MeOD. The primary kinetic isotope effect of this 1,5-H-shift was 1.8−1.9, which is significantly smaller than in other 1,5-sigmatropic shifts. Several mechanistic possibilities were then investigated in detail by computational chemistry. This was accompanied by additional experiments, one of them being the preparation of the gold(I) acetylide **3**. **3** is a stable compound, but on addition of catalytic amounts of cationic gold(I) catalysts or Lewis acids, such as zinc(II), it is converted to the product **4** (interestingly, the corresponding silver acetylides did not react in this manner).



(2)

While the authors in the introduction of their publication clearly stated "... that proceeds via a unique mechanism ...", in the conclusion their statement was more hesitant; they wrote "combined experimental and computational evidence reveal that a mechanism involving nucleophilic addition of an allene double bond to a phosphinegold-complexed phosphinegold acetylide is more likely than oxidative cyclization or simple nucleophilic addition to phosphinegold-complexed substrate".[4] The overall catalytic cycle suggested is shown in Scheme 1.

Scheme 1. Mechanism Proposed by Houk and Toste



One year later, Gagosz and co-workers reported the spectacular synthesis of 10-membered, medium-sized cycloalkynes **6** from 1,10-diynes **5**.[5] Again, the ligand is a bulky phosphane ligand (the mechanistic proposal is shown in Scheme 2a), but on the basis of the proposal of Houk and Toste,[4] they also considered an alternative mechanism (Scheme 2b). Both possibilities are in accordance with deuterium isotope labeling experiments. The Houk/Toste catalyst transfer step is not considered by Gagosz. On the other hand, Gagosz already addressed the potential function of the counterion as a proton acceptor, a motive later discussed by Corma[6] and Widenhoefer[7] (see below) for the formation of species related to **A** and **I**.

In their Supporting Information, Houk and Toste discuss in detail the different mechanistic possibilities, including two pathways which were not based on dual activation, but those two pathways were not in accordance with some of the labeling studies.[4]

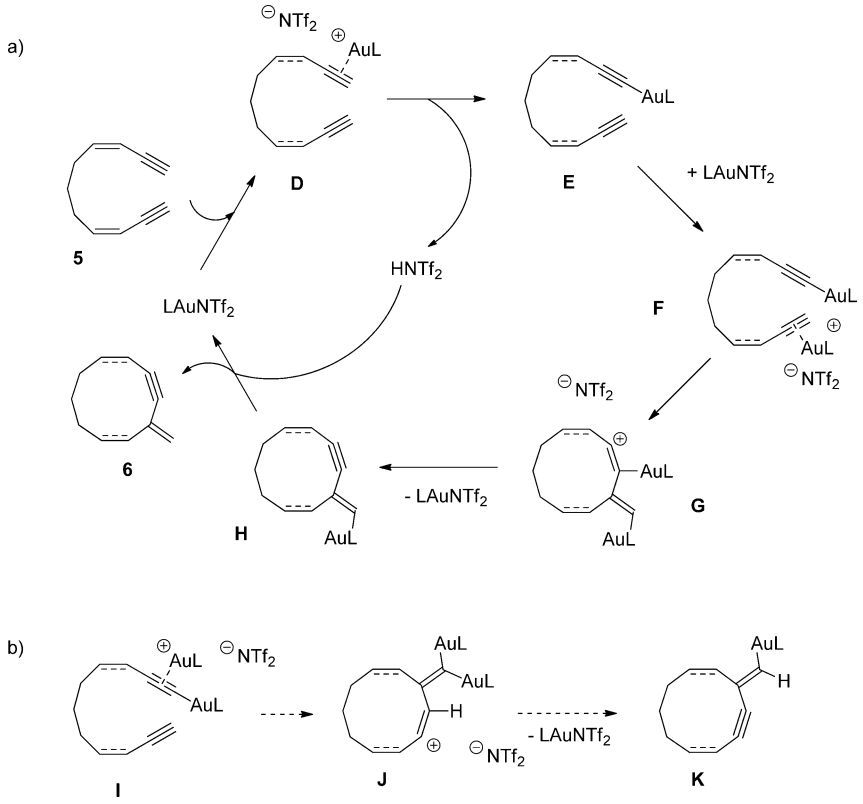
Three years later, in 2012, an intermolecular version of this alkyne-homodimerization was reported by Zhang, but no new mechanistic insights were provided in this synthetic publication.[8]

One of the open questions was the initial formation of the gold acetylide. Following an interesting investigation by Laguna and co-workers[9] on the photochemical properties of σ,π-digold acetylides with two phosphane ligands at the π-coordinated

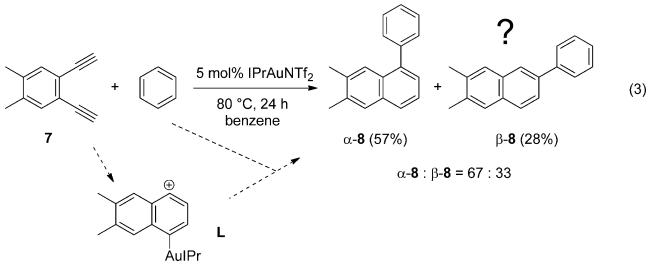
Received: June 10, 2013
Published: July 9, 2013

   dx.doi.org/10.1021/cs400437s | ACS Catal. 2013, 3, 1902−1907

Scheme 2. Mechanism Proposed by Gagosz



gold and a very unusual, unsymmetrical coordination of the alkyne with a gold−gold interaction, this was addressed only in 2011 by Corma and co-workers[6] as well as Widenhoefer and co-workers.[7] Widenhoefer in a detailed investigation proved that at low temperatures, in situ-generated $NHCAu^+$ forms a π-complex with phenylacetylene. Above −20 °C, this π-complex reacts to σ,π-digold acetylides. Corma prepared a series of such σ,π-digold acetylides with bulky phosphane ligands and demonstrated very good catalytic activity in the *intermolecular* alkene/alkyne [2 + 2] cycloaddition, a reaction based on the work of Echavarren.[10] On the other hand, a recent investigation of Fensterbank, Gimbert, and co-workers[11] indicated that although for intramolecular enyne cycloisomerizations, the dinuclear complexes can be detected by electrospray ionization mass spectrometry and the goldacetylide indeed has a high affinity for the π-coordination of a LAu^+ fragment, but these species seem not to be involved in the cycloisomerization reaction.



3. THE PUZZLE OF AN UNEXPECTED REGIOSELECTIVITY

Then, in 2012, a crucial new perspective was opened by the investigation of diynes of type **7**.[12] Unexpectedly, not only α-**8** but also β-**8** were obtained. Control experiments proved that

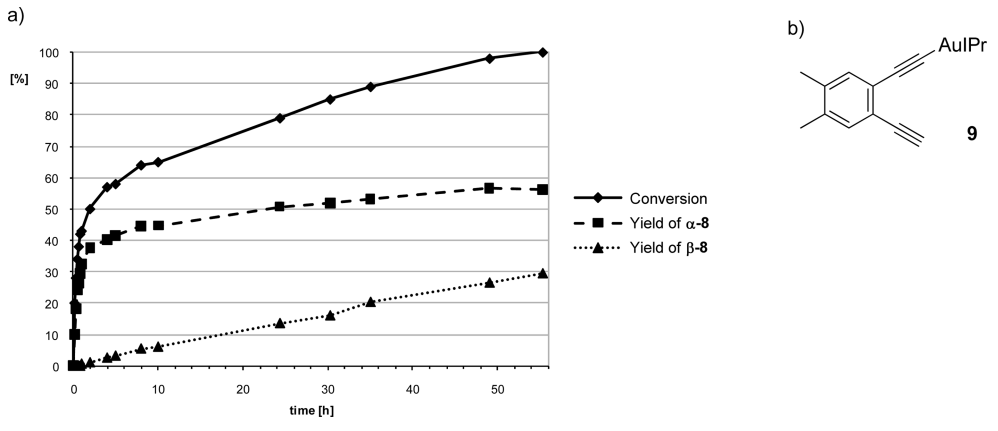


Figure 1. A switch of mechanism and the role of gold acetylide **9**.

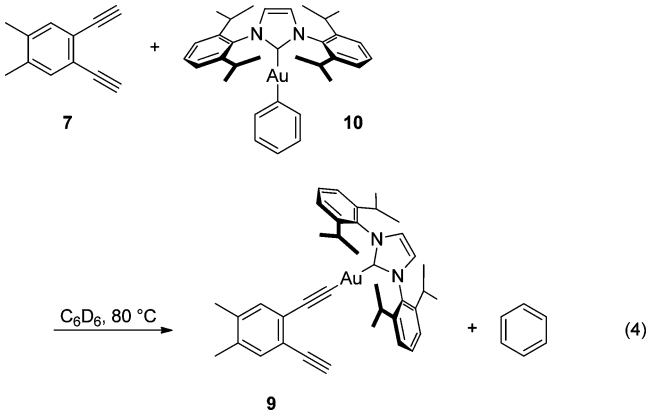
dx.doi.org/10.1021/cs400437s | *ACS Catal.* 2013, 3, 1902−1907

β-**8** was not generated by a rearrangement of α-**8** or by an initial hydroarylation of one of the alkynes followed by an enyne cycloisomerization. Thus, the mechanism for the formation of β-**8** was new and of significant interest.

The first crucial evidence for the mechanism of the formation of β-**8** was the kinetic analysis, which revealed that in the initial phase of the reaction, the formation of α-**8** is fast, but then the formation of α-**8** became very slow, and at the same time, the product β-**8** begins to appear (Figure 1a). This clearly indicated a switch of mechanism. The terminal alkyne suggested a possible slow formation of the gold(I)-acetylide complex **9** (Figure 1b). Thus, **9** was prepared, but it turned out to be a perfectly stable compound, even at 80 °C. The second crucial evidence was an experiment with a catalytic amount of a gold(I) catalyst and a stoichiometric amount of **9**, which *exclusively* gave β-**8**.

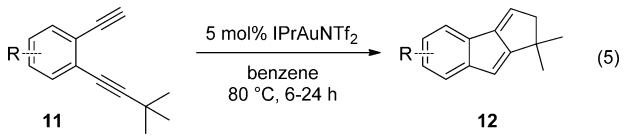
Combined, these two results show that two different catalytic cycles compete. Initially, a classical electrophilic activation of **7** by only one gold complex forms α-**8** in high selectivity. Slowly (seemingly much more slowly that in Fensterbank's[11] experiments with phenylacetylene) some of the gold(I) complex then "leaches" to the gold acetylide, which then is able to form β-**8** with high selectivity. Indeed, in the presence of simple bases such as triethylamine or even Al_2O_3, which speed up the initial formation of **9**, mainly β-**8** (98:2) was observed.

While the initial formation of the gold acetylide had then been understood, the other end of the catalytic cycle, the catalyst transfer was still a critical question. Assuming an aryl gold(I) intermediate similar to **10**, at the end of the catalytic cycle, a direct proton transfer from the next alkyne substrate molecule **7** to **10** going along with the formation of the gold actylide **9** should be essential to maintaining a good β-selectivity. If **9** would not be regenerated directly but another proton source would generate free LAu^+, the α-selectivity of the latter species would not allow a good overall β-selectivity. It could be proved that a direct and highly selective protonation with **7** was possible (eq 4). Although the pK_a of the free alkyne



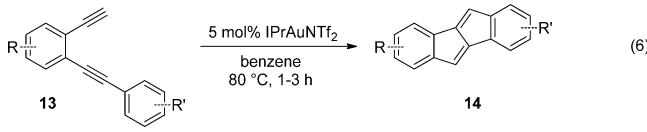
is only about +25, the formation of the thermodynamically favored gold acetylide **9** assists this process.

At that stage, it was still unclear why **9** with LAu^+ leads to β-**8**. Here, we needed the third crucial evidence: the reaction of the substrate **11** with a *tert*-butyl group led not to a naphthalene, but to a benzofulvene **12** (eq 5).[13] This indicated two things: the formation of a five-membered ring by the first cyclization and the formation of a second five-membered ring by a C,H activation of a primary, nonactivated C−H bond at a *tert*-butyl group. In parallel work, the group of Zhang[14] not only



found similar conversions, but also by a detailed computational analysis addressed the possible mechanism, which revealed a highly interesting bifurcation situation and included both conceivable pathways: the formation of a vinylidene species and the formation of aurated aryl cations as reactive species. In these two investigations, different ligand systems were used; we focused on NHC ligands, whereas the Zhang group had very good success with the BrettPhos ligand in the presence of *N*-oxides.

This assumption of an initial formation of a five-membered ring rather than a six-membered ring was further supported by the conversion of the corresponding substrates **13** with an aryl group instead of the *tert*-butyl group. Now, dibenzopentalenes **14** were formed as products (eq 6), and again, there were two five-membered rings in the product.[15]



4. PUTTING TOGETHER A MECHANISTIC HYPOTHESIS

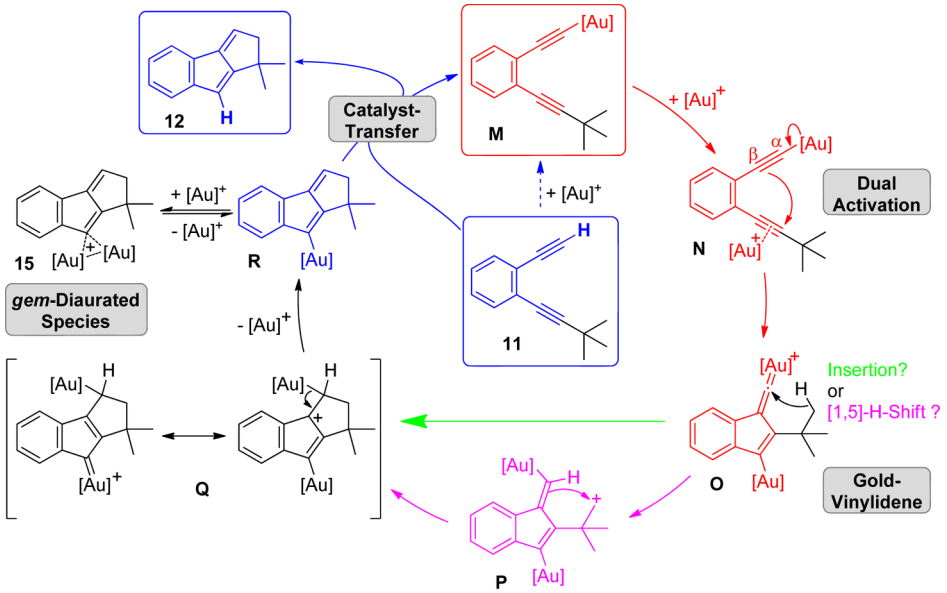
These results in combination with a series of deuterium isotope labeling experiments and the important additional computational results of the Zhang group led to the following new mechanistic cycle (Scheme 3).

The gold(I) acetylide **M** is crucial for the reaction. π-Coordination of a second (dual activation) $[Au]^+$ unit to the other triple bond activates the system for an electrophilic attack in the β-position of the gold acetylide (species **N**). This leads to a gold(I) vinylidene-like species, **O**. In the organometallic chemistry of gold, the vinylidenegold(I) complexes are unknown, but recently, the corresponding allenylidenes have been prepared and investigated; there is barely any Au=C double bond character (see section 5).[16] Thus, these reagents are highly electrophilic carbenoids, and the next step is an insertion into the C−H bond of the *tert*-butyl group. Looking at other results (for example, the concerted reaction with olefins discussed below), this should proceed in a concerted way. A stepwise sequence involving a hydride abstraction and a subsequent electrophilic attack[17] of the carbenium ion at the vinylgold unit should show competing Wagner−Meerwein rearrangements at the stage of the primary carbocationic intermediate, **P**. Then elimination of $[Au]^+$ from **Q** should deliver the vinylgold(I) species **R**. Readdition of $[Au]^+$ at the ipso position of gold forms a side-equilibrium with the gem-diaurated species **15**. In this and all other related reactions, these digold species could be isolated and characterized by crystal structure analyses. The reversibility of the side equilibrium was proven by adding some of the digold species to the substrate, and the catalysis started again. The final step is the catalyst transfer, the protodeauration by the alkyne (as investigated in eq 4).

In these reactions leading to two new five-membered rings, no ring expansion to a six-membered ring, that is, a naphthalene core, is possible. By such a ring expansion, the second five-membered ring would suffer a ring contraction to deliver

dx.doi.org/10.1021/cs400437s | ACS Catal. 2013, 3, 1902−1907

Scheme 3. Mechanistic Cycle for the Formation of Benzofulvenes by Gold-Catalyzed Dual Activation



a four-membered ring, which is thermodynamically not feasible (eq 7).

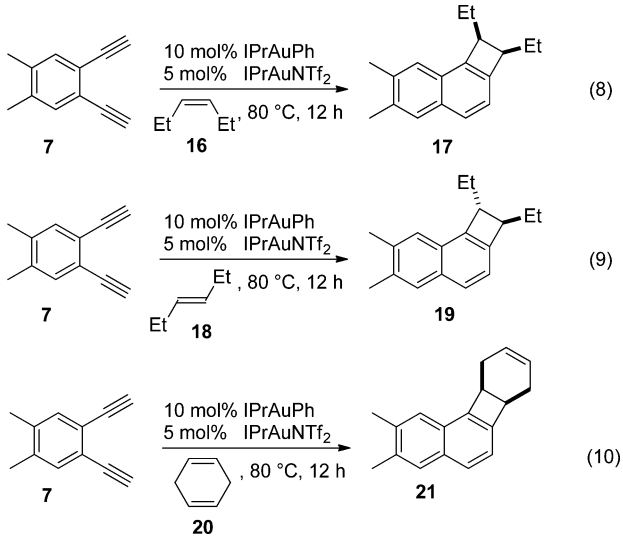
(7)

It was also possible to conduct the reactions involving C,H activation in an intermolecular manner, but the symmetrical hydrocarbons had to be used as solvents, and the yields were low.[18] Nevertheless, these were the first examples of intermolecular gold-catalyzed C,H activations.

Since in the intermolecular case by the C,H activation and in the case of the synthesis of the *β*-substituted naphthalene **8**, no second five-membered ring is generated, now napthalenes are accessible by the ring expansion of the five-membered ring that was formed in the initial cyclization step. A mechanistic scheme for the naphthalene synthesis is shown in Scheme 4. The intramolecular H shift in the step from **S** to **T** was proven by labeling studies. The carbenoid species, **T**, then would allow the ring expansion.

Another intermolecular reaction was the formation of benzocyclobutenes by reaction of diynes **7** with alkenes. This new reaction added two important new facts to the overall picture: First of all, the reaction proceeded diastereoselectively. A (*Z*)-olefin such as **16** would lead to the cis product **17** (eq 8). The corresponding (*E*)-olefin **18** delivers the trans product **19** (eq 9). This indicates a concerted reaction, which is the reason for assuming a concerted C,H-insertion rather than a stepwise process initiated by a [1,5]-H shift in Scheme 3 (species **O** directly to **Q** and not **O** via **P** to **Q**).

Second, one might suspect the participation of Bergman-like cyclization pathways of these ene-diynes, involving radical intermediates, but the typical interceptor for such radicals, the hydrogen atom donor 1,4-cyclohexadiene (**20**) still gave the benzocyclobutene **21**, and no products of a hydrogen addition were detected (eq 10).



5. EXTENSION OF THE BASIC PRINCIPLE

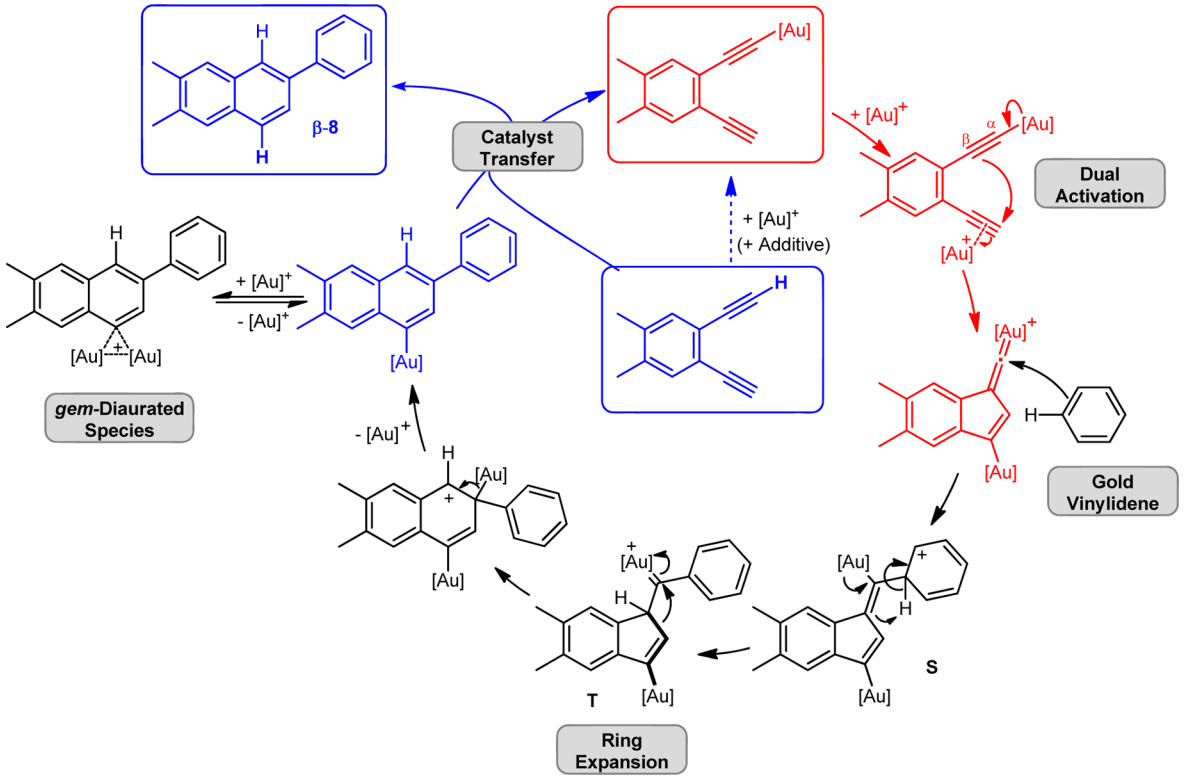
There was also an alternative pathway for the synthesis of the six-membered ring. It had already been puzzling that the calculation of Zhang and co-workers[14] showed that the cyclization mode leading to a six-membered ring should be preferred, but the five-membered ring was observed in the reaction forming benzofulvenes. When changing to a thiophene instead of the benzene ring in the backbone (**22**), the six-membered ring in **23** was formed (Scheme 5).[19] Experimentally, C,H activation was again possible, but even more interesting, the calculations showed that in a bifurcation pathway, the six-membered ring formation (**U**, not the vinylidene **V**) is preferred, and the intermediate **W**/**X** possesses carbene character on the position for the C,H activation. In the case of the thiophene, the anellation of two five-membered rings is energetically less feasible. With substrates bearing the alkyl group on the alkyne at the 2-position of the thiophene, the yields were significantly higher, which might indicate an additional interaction with the thiophene sulfur atom.

Another interesting aspect is the 1,2-[Au]-shift converting species **U** to **W**/**X**; for the transition state of this shift, a gold(I) aryne species could be located.[19] These findings are now confirmed by D. H. Aue, Liming Zhang, and co-workers for en-diyne substrates.[20]

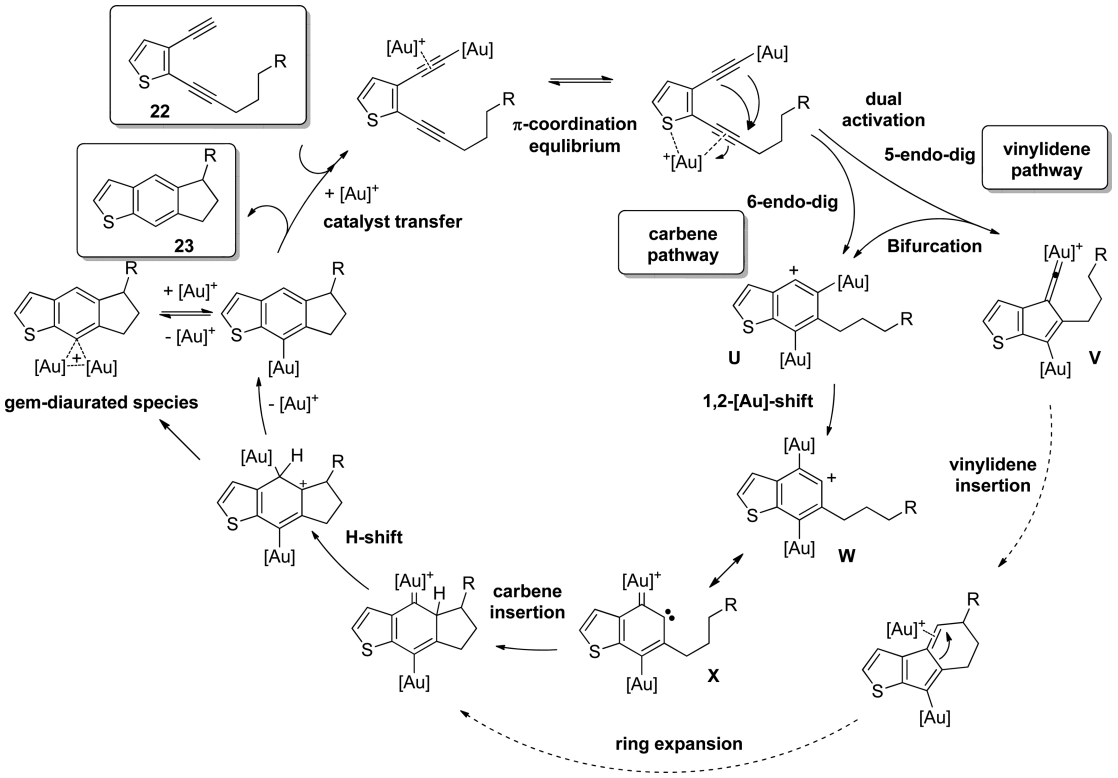
As a consequence, the possibility of a species, **W**/**X**, not being formed via the vinylidenegold(I) complex immediately made clear

dx.doi.org/10.1021/cs400437s | *ACS Catal.* 2013, 3, 1902−1907

Scheme 4. Mechanistic Cycle for the Formation of B-Substituted Naphthalenes by Gold-Catalyzed Dual Activation



Scheme 5. Mechanistic Cycle for the Formation Anellated Benzothiophenes by Gold-Catalyzed Dual Activation



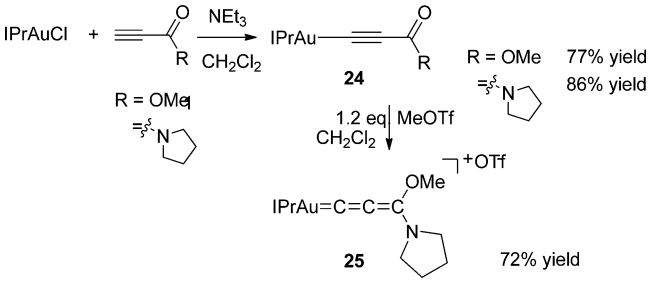
that for the formation of six-membered rings in other reactions (such as *β*-**8**, the intermolecular reactions, **17**, **19**, or **21**) a similar pathway has to be considered as an alternative to the initially assumed ring expansion (e.g., Scheme 4, species **T**). This is currently being investigated in our group.

6. GOLD ALLENYLIDENES

The electronic structure of the vinylidene intermediates also raised interest whether allenylidene complexes of gold(I) are accessible. The corresponding experiments started with the formation of **24** and its subsequent alkylation to **25** (Scheme 6)

dx.doi.org/10.1021/cs400437s | *ACS Catal.* 2013, 3, 1902−1907

Scheme 6. Generation of "Gold(I) Allenylidenes"

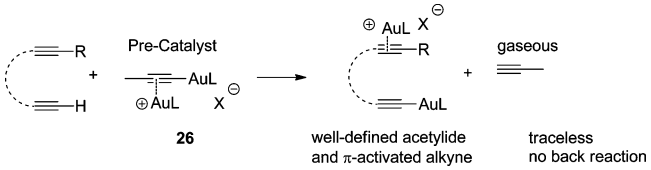


and included detailed structure investigations, both experimentally and by computational methods.[16] Because of the strong donors, the main stabilization of the carbenium ion came from the lone pair of the heteroatom (O or N) and not from gold; there is no significant Au−C double bond character.

7. DUAL ACTIVATION CATALYSTS

The next problem to be addressed was the optimal catalyst. The ideal ratio of gold acetylide to LAu^+ is 1:1, which is difficult to achieve by mixing different precatalysts or precatalyst and base. With an insufficient amount of base, free LAu^+ would remain, which, for example, in the naphthalene synthesis ruins the β-selectivity (Figure 1). On the other hand, an excess of base would place most of the gold in the form of the gold acetylide. One solution could be to use the diaurated species such as **15**, but this is not the ideal form of a stable precatalyst because the organic moiety in **15** will lead to 1 equiv (with regard to the catalyst) of a product-related impurity (unless a specific precatalyst from the substrate will be used, but then, each reaction would need a specific precatalyst). The same applies for other gold organyls, such as gold acetylides or arylgold compounds. We finally developed a family of different catalysts **26** (DACs, Scheme 7), which were easily accessible,

Scheme 7. Activation via Dual Activation Catalysts (DACs)



could be stored, and proved to be active in a number of reactions proceeding by a dual activation mechanism.[21]

8. SUMMARY AND FUTURE OUTLOOK

The concept of dual activation by gold has provided entirely new perspectives in the field. New organometallic intermediates have been characterized, new and unusual mechanisms have been investigated (both experimentally and by computational chemistry), and interesting new reactions have been developed.

In the meantime, in the current literature, the concept of dual activation by gold catalysts has attracted sufficient attention that researchers now are starting to run experiments specifically to exclude dual activation mechanisms for some of the reactions they investigate,[22,23] and in synthesis first applications, which nicely demonstrate and expand the scope of the dual activation principle in gold catalysis, are being published.[24]

AUTHOR INFORMATION

Corresponding Author

*E-mail: hashmi@hashmi.de.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936.
(2) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241.
(3) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448−2462.
(4) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517−4526.
(5) Odabachian, A.; Le Goff, X. F.; Gagosz, F. *Chem.—Eur. J.* **2009**, *15*, 8966−8970.
(6) Grirrane, A.; Garcia, H.; Corma, A.; Álvarez, E. *ACS Catal.* **2011**, *1*, 1647−1653.
(7) Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003−6009.
(8) Sun, S.; Kroll, J.; Luo, Y.; Zhang, L. *Synlett* **2012**, 54−56.
(9) This was a really close race. Although this paper was printed only in 2012, it was submitted on 2011-5-13; reference 4, on 2011-8-18; reference 3, on 2011-9-6. Blanco, M. C.; Cámara, J.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; López-de-Luzuriaga, J. M.; Olmos, M. E.; Villacampa, M. D. *Organometallics* **2012**, *31*, 2597−2605.
(10) Lopez-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292−9294.
(11) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, *2*, 2417−2422.
(12) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644−661.
(13) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem.* **2012**, *124*, 4532−4536; *Angew. Chem., Int. Ed.* **2012**, *51*, 4456−4460.
(14) This manuscript was submitted before reference 13. Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31−34.
(15) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555−562.
(16) Hansmann, M. M.; Rominger, F.; Hashmi, A. S. K. *Chem. Sci.* **2013**, *04*, 1552−1559.
(17) Hashmi, A. S. K.; Häffner, T.; Yang, W.; Pankajakshan, S.; Schäfer, S.; Schultes, L.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2012**, *18*, 10480−10486.
(18) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem.* **2012**, *124*, 10785−10789; *Angew. Chem., Int. Ed.* **2012**, *51*, 10633−10637.
(19) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem.* **2013**, *125*, 2653−2659; *Angew. Chem., Int. Ed.* **2013**, *52*, 2593−2598.
(20) Wang, Y.; Yepremyan, A.; Ghorai, S.; Todd, R.; Aue, D. H.; Zhang, L. *Angew. Chem., Int. Ed.* **2013**, DOI: 10.1002/anie.201301057.
(21) Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. *Chem.—Eur. J.* **2013**, *19*, 1058−1065.
(22) Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, P. W. H. *J. Am. Chem. Soc.* **2012**, *134*, 10811−10814.
(23) Obradors, C.; Echavarren, A. M. *Chem.—Eur. J.* **2013**, *19*, 3547−3551.
(24) Vachhani, D. D.; Galli, M.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Chem. Commun.* **2013**, DOI: 10.1039/C3CC43418D.