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Explanation of “Silver Effects” in Gold(I)-Catalyzed Hydroalkoxylation of Alkynes

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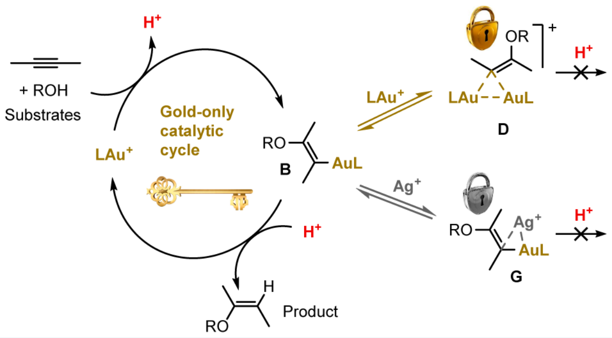
S *Supporting Information*

ABSTRACT: An extensive experimental NMR study of gold-catalyzed hydroalkoxylation was conducted to explain the influence of a silver salt additive on the gold-catalyzed process (silver effect). Addition of silver salt may have no effect or a negative or positive effect on gold-catalyzed hydroalkoxylation. However, silver was shown to be essentially innocent (plays no role) with regard to the mechanism of the catalytic process itself. The effect occurs only if silver induces variations in the fraction of in-cycle organogold intermediates and H^+. This is associated with the formation of the argento vinyl gold species **G**, which was shown to be an off-cycle intermediate. This species is formed by trapping the vinyl gold species **B** with Ag^+; in the same way, the diaurated species **D** (another possible off-cycle intermediate) is formed by trapping **B** with LAu^+. The argento vinyl gold species **G1** was extensively characterized in solution by various NMR techniques at different temperatures. Furthermore, bringing together our results and the topical research of others, we introduced classification of silver effects to eliminate the confusion around the interpretation of erratic effects. Reactions that are separately catalyzed either by silver or by gold were beyond the scope of this study (for those reactions a “true” silver effect would take place).



KEYWORDS: *gold catalysis, hydroalkoxylation, silver effect, reaction kinetics, reaction mechanism*

1. INTRODUCTION

For a long time silver salts AgX have been routinely used to activate gold chloride complexes by halogen abstraction in order to convert them to active gold catalysts or for the synthesis of various gold complexes (eq 1).[1] The precipitation

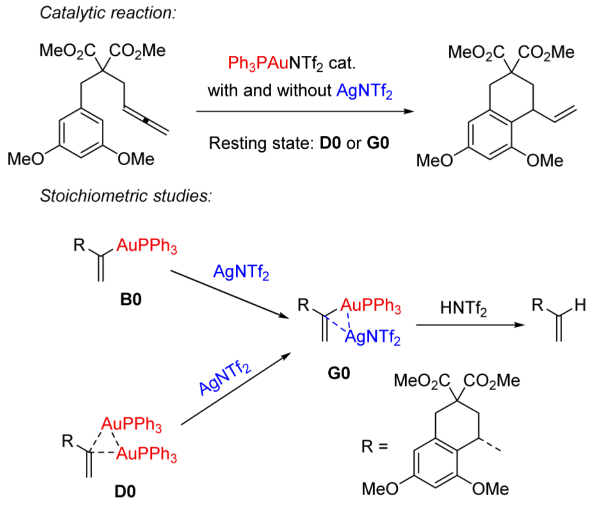
$$\mathrm{LAuCl} + \mathrm{Ag^+X^-}\ (+\ \mathrm{Nu}) \longrightarrow \begin{matrix}[\mathrm{LAuNu^+}]\ \mathrm{X^-}\\ \text{or LAuX}\end{matrix} + \mathrm{AgCl}\downarrow \qquad (1)$$

Nu = any molecule or anion with coordination ability to gold,
X^- = SbF_6^-, NTf_2^-, OTf^-, etc.

of AgCl is normally considered stoichiometric and complete. Therefore, until recently the role of silver in gold catalysis has not been discussed beyond this simple ligand exchange process.

However, recently there has been an increased amount of experimental observations suggesting that silver is not totally innocent in gold catalysis. The first mechanistic evidence was the observation of mixed Au–Ag intermediates in reaction mixtures, briefly reported by Gagné and Weber in 2009.[2] They showed that silver is able to react with the key organogold intermediates to generate new bimetallic intermediates (Scheme 1). The diaurated species **D0** and vinyl gold **B0** react with $AgNTf_2$ to give the argento vinyl gold species **G0**, which was even isolated and characterized by NMR and MS. Unfortunately, no X-ray analysis could be performed and the exact structure remains speculative, on the basis of inspection of previously known examples of various Au/Ag bimetallic

Scheme 1. Reactivity of Vinyl Gold and Diaurated Species toward Ag^+ Observed by Gagné[2]



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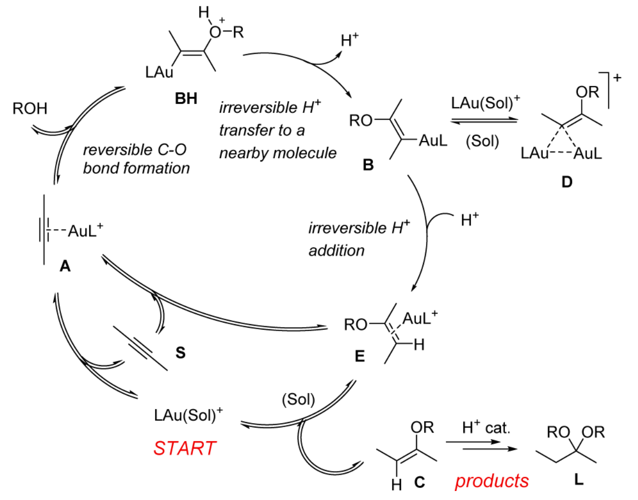
species.[3] This suggests that the structure of **G0** must have much of the planar vinyl gold character with only side-on coordination of silver, with maintenance of a Au−Ag metallophilic interaction. In other words, the three-center−two-electron interaction which was symmetrical in **D0** now is not equal in **G0**, with the C−Au bond dominating the structure.[2] In accordance with this notion we will apply the term "argento vinyl gold" to emphasize the predominant vinyl gold vs vinyl silver character of these species. Furthermore, Gagné and Weber observed **G0** as a resting state of the catalytic reaction, and this remains the only direct evidence of involvement of Au/Ag bimetallic intermediates in gold catalysis. In their case, the reaction was retarded by additions of AgNTf$_2$ (which would be called a "negative silver effect"). In addition, no investigation into the role of **G** in the reaction mechanism was provided.

An extended work reported in 2012 by Shi et al. demonstrated that the rate (and yield) of many gold-catalyzed reactions can be largely influenced by the presence of Ag$^+$ (in addition to already present gold catalyst).[4] These observations not only questioned the innocence of silver in gold catalysis but also questioned fundamental mechanistic principles of gold catalysis at that time. Therefore, an in-depth study seemed necessary to clarify the situation. In the following years there have been increased efforts to investigate and explain this "silver effect" in more detail. Notable examples include recent works from the groups of Echavarren,[5] Hammond, and Hu (to be discussed below).[6] Due to the ambiguous role of silver, several alternative methods for activation of a gold catalyst have been developed that avoid the use of silver salts.[7,8]

In our laboratory we have been involved in mechanistic investigations of gold catalysis. Recently we have reported extensive experimental studies on gold(I)-catalyzed hydroalkoxylation of alkynes (Scheme 2).[9] Herein, using this model reaction with a well-established mechanism, we provide a systematic mechanistic experimental study to disclose the origins of the silver effect. In this work any silver effect is regarded as the influence of silver on the rate of disappearance of the starting alkyne **S**, because formation of enol ether **C** from **S** is a gold-catalyzed step, while formation of acetal **L** from **C** is only a Brønsted acid catalyzed process. On the basis of our observations and the works of others we propose a generalized classification of various origins of the silver effect. This would put in order an understanding of the erratic results associated with this effect.

Scheme 2. Mechanism of Gold-Catalyzed Hydroalkoxylation



2. RESULTS AND DISCUSSION

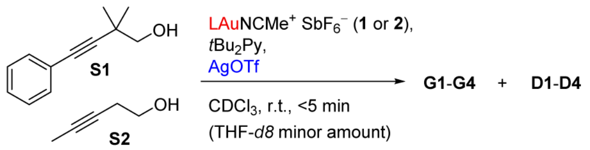
In our experiments we used silver-free gold catalysts Ph$_3$PAuNCMe$^+$SbF$_6^-$ (**1**) and *L2*AuNCMe$^+$SbF$_6^-$ (**2**; *L2* = 2-(di-*tert*-butylphosphino)biphenyl). For the observation of silver effects the reactions were performed in the presence of the silver salts AgOTf and AgSbF$_6$. We found that argento vinyl gold species were involved every time a silver effect took place. Therefore, prior to discussion and explanation of silver effects it is necessary to describe the properties and reactive pathways of this species (sections 2.1−2.3.). The silver effect is then explained for a number of catalytic hydroalkoxylation reactions (section 2.4.). In section 2.5, we propose a generalized picture of silver effects using the knowledge obtained in our research and that of others.

2.1. Synthesis of Argento Vinyl Gold in Situ and Reactions with Nucleophiles.

In 2013 we reported the formation of diaurated species **D** using an alkynol, a gold catalyst, and the non-nucleophilic base 1,8-bis(dimethylamino)-naphthalene (Proton Sponge, PrSp).[10] Using AgOTf as an additional reactant, the same method was initially attempted for the synthesis of the corresponding argento vinyl gold species. However, AgOTf was found to be incompatible with PrSp, causing immediate formation of a black precipitate (reduction of silver). Therefore, *t*Bu$_2$Py was used as a redox-stable base.

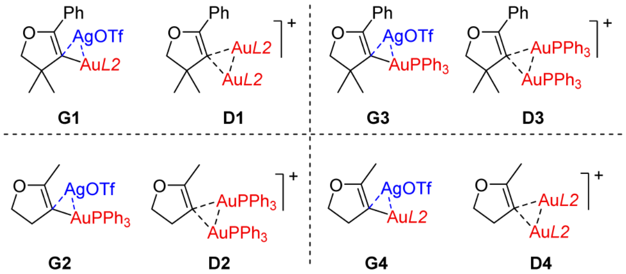
Thus, simple treatment of a concentrated THF-d_8 solution containing a gold catalyst (**1** or **2**) and AgOTf with a CDCl$_3$ solution containing *t*Bu$_2$Py and alkynol (**S1** or **S2**) led to immediate, quantitative formation of the corresponding organometallic species, accompanied by minor competitive enol ether formation. Argento vinyl gold species **G1** and **G4** were formed exclusively (Table 1, entries 1 and 4), while **G2** and **G3** were accompanied by a minor formation of the

Table 1. Stoichiometric Formation of Argento Vinyl Gold in Situ



	reactant (amount in equiv)				
entry	alkynol	gold[a]	*t*Bu$_2$Py	AgOTf	G:D
1	**S1** (1.1)	**2** (1.0)	1.5	1.1	1:0
2	**S2** (2.0)	**1** (1.0)	1.3	1.1	1:0.1
3	**S1** (1.1)	**1** (1.0)	1.6	1.1	1:0.03
4	**S2** (1.5)	**2** (1.0)	2	1.4	1:0

[a] Legend: **1**, L = PPh$_3$; **2**, L = L2 = 2-(di-*tert*-butylphosphino)biphenyl.



corresponding diaurated species **D2** and **D3** (entries 2 and 3). An important requirement for successful formation of argento vinyl gold is that the silver salt should be dissolved prior to the reaction; otherwise, formation of **D** and/or enol ether will predominantly occur. However, AgOTf is negligibly soluble in $CDCl_3$. This is why it was dissolved in a minimum amount of THF-d_8. The synthesis of **G2**−**G4** in $CDCl_3$ occurs under kinetic control, because **D2**−**D4** are thermodynamically favored (to be discussed below). Attempts to isolate any of the argento vinyl gold species in the crystalline state were unsuccessful. Therefore, all characterizations and reactions were performed in solution, using enriched samples prepared in situ.

^1H NMR spectra of **G1**−**G4** (prepared in situ) exhibit simple patterns, despite the molecules being unsymmetrical. Cooling these solutions to −60 °C led to split spectra in case of **G1**, **G3**, and **G4**. Since **G2** was unstable in solution and equilibrated toward **D2** within several minutes, no clear spectrum was obtained for this species at low temperature. A likely reason for the degeneracy of the CH_2 and $C(CH_3)_2$ protons at room temperature is a fast silver exchange, occurring in the presence of a slight excess of AgOTf. Indeed, when the amount of residual AgOTf was sufficiently low (or excluded), we could observe split spectra of **G1** and **G4**, revealing the unsymmetrical structure even at room temperature. Most reliably this was achieved by fast and quantitative reduction of the residual AgOTf by PrSp. Alternatively, the samples could be slowly reduced by CaH_2 (a routine procedure to dehydrate a solution; **G** stays unreactive). Upon addition of fresh AgOTf (as a solution in minimum THF), the split spectrum is simplified, indicating resumption of the fast silver exchange. The ^1H NMR spectrum of **G1** in the mode of fast and slow silver exchange is shown in Figure 1 as an example. We suppose that the silver exchange might occur either by a nucleophile-assisted dissociative pathway or through a doubly argented intermediate. We prefer the latter scenario, which was also proposed by Gagné to explain the spectrum of **G0**.[2]

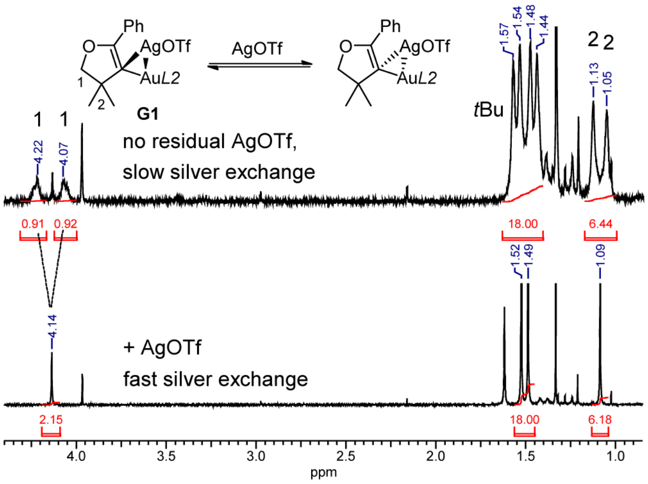


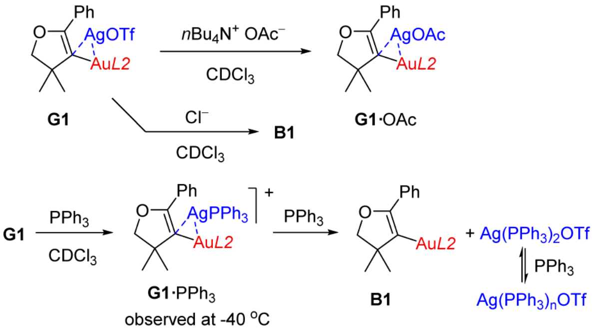
Figure 1. Dynamic behavior of **G1** in the presence of AgOTf.

Complex **G1** was characterized in $CDCl_3$ solution using ^1H, ^{31}P, ^{19}F, ^{13}C and various two-dimensional NMR techniques (these spectra were recorded under conditions of fast silver exchange at room temperature). Using CF_3CO_2Me as an internal standard, the overall 1:1:1 organic core:Au:Ag ratio could be confirmed by ^1H and ^{19}F NMR spectra. Observation of the CAu carbon signal in the ^{13}C NMR spectrum of **G1** is very intriguing, since this signal is often not found. In our case, it could be observed as a doublet at 125.1 ppm (^2J_P = 93.7 Hz). The ^2J phosphorus coupling through the two bonds of the C−Au−P link appears to be greater than the ^1J coupling through the single C_{Ar}−P bond (36.5 Hz). In addition, it is comparable to the value typical for vinyl gold species (ca. 105 Hz) and is more distant from the value typical for diaurated species (ca. 60 Hz).[11] This is in accordance with a planar vinyl gold moiety being only slightly disturbed by the side-on coordination of silver. The enol ether α-carbon atom appeared at 173.3 ppm as a doublet (^3J_P = 9.1 Hz). The coupling to the magnetically active Ag was not observed in any spectrum at room temperature, presumably because of the fast silver exchange in solution.

In order to observe the coupling to Ag, we recorded NMR spectra of **G1** at −20 °C under conditions of slow silver exchange. No evidence was found for coupling in the ^1H spectrum. This is not surprising, since there are no protons located in close proximity to the Ag atom. In contrast, the ^{13}C spectrum was much more indicative. The CAu atom and the enol ether α-carbon atom were additionally split, appearing now as doublets of doublets. The assignment of Ag coupling was made from a comparison of multiplicity in ^{13}C spectra recorded at room temperature and at −20 °C, with the knowledge of the P coupling from the room-temperature spectrum. This way $^1J_{Ag}$ = 46 Hz was determined for the CAu atom and $^2J_{Ag}$ = 4 Hz for the enol ether α-carbon atom. These data are consistent with the assigned structure of **G1**. To the best of our knowledge, this is the first time C−Ag coupling has been determined for any species containing a quaternary CAu(Ag) carbon atom.

Next, we attempted to elucidate the bonding and coordination chemistry at silver and found it very intriguing. To get some insight, we conducted NMR titrations of **G1** at room temperature with various nucleophiles in $CDCl_3$ (Me_2S, Lut = 2,6-lutidine, TMTU = tetramethylthiourea, PPh_3, OAc^-, Cl^-), monitoring ^1H, ^{31}P, and ^{19}F NMR spectra after each addition of the nucleophile. No clear picture about the coordination mode of silver could be obtained in most cases. All reaction mixtures exhibited fast ligand exchange at silver on the NMR time scale, as evidenced by a single set of signals of the enol ether core and the ligands (at room temperature). However, some of these experiments provided useful information. Thus, stoichiometric substitution of the OTf^- ion by 1 equiv of OAc^- at **G1** could be confirmed by the absence of further changes in the ^1H, ^{31}P, and ^{19}F NMR spectra of **G1** at >1 equiv of OAc^- (Scheme 3). The strong

Scheme 3. Stoichiometric Reactions of G1 with Various Nucleophiles (OAc^-, Cl^-, and PPh_3)



nucleophiles PPh_3 and Cl^- caused stoichiometric cleavage of **G1** to form vinyl gold species **B1** and $Ag(PPh_3)_n^+$ ($n = 2-4$) or AgCl precipitate. No evidence for the alternative cleavage to vinyl silver species RAgL and $LAuNu^+$ was obtained; thus, this pathway appears improbable. Whereas the reaction with Cl^- required 1 equiv of the nucleophile for complete cleavage, the reaction with PPh_3 required 2 equiv. This last fact suggests that **G1** can accept 1 equiv of PPh_3 at silver without detachment of **B1**, whereas the second equivalent of PPh_3 causes the cleavage. **G1** was resistant to cleavage in the presence of excess Me_2S, Lut, or OAc^-. Partial cleavage was observed in the presence of 4 equiv of TMTU. In cases where incomplete cleavage of **G1** took place either due to a reversible reaction (TMTU) or reaction before the equivalence point (PPh_3 and Cl^-), the enol ether core exhibited a single set of signals, indicating a fast equilibrium between **G1** and **B1**. This all characterizes argento vinyl gold as a very reactive species, which would undergo fast silver exchange (in the presence of extra Ag^+), fast ligand exchange at silver (in the presence of extra Nu), and fast exchange of the vinyl gold fragment at silver (in the presence of extra vinyl gold).

In order to get a more detailed insight into these fast exchange reactions, we performed some of them at low temperature. NMR titration of **G1** with PPh_3 at −40 °C revealed the formation of an intermediate that was assigned to the 1:1 adduct **G1**·PPh_3. A ^{31}P NMR spectrum of **G1**·PPh_3 at low temperature exhibited one signal for *L2* and a pair of doublets due to a single PPh_3 group coupled to the two silver isotopes ($^1J(^{31}P-^{109}Ag) = 641$ Hz, $^1J(^{31}P-^{107}Ag) = 555$ Hz). Integration of ^{31}P as well as ^1H NMR spectra confirmed the molecular composition of **G1**·PPh_3. Upon further PPh_3 addition **G1**·PPh_3 was cleaved to yield **B1**, which was also observed separately at this temperature (Scheme 3). Similar NMR titration of **G1** with TMTU at −40 °C did not reveal the formation of a separate species, because even at this temperature the exchange processes were fast.

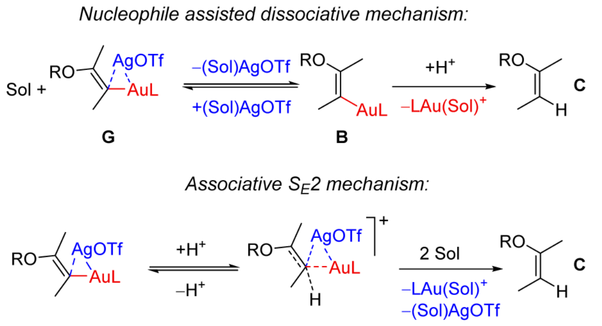
These observations suggest that silver in **G1** has a coordination number of 2. Therefore, OTf^- must be covalently bound to silver in a $CDCl_3$ solution of **G1** in the absence of sufficiently strong nucleophiles. Rather, in CD_3OD solution **G1** appears to be a cationic complex. This follows from the observation of a ^{19}F resonance at a constant shift of −80.1 ppm, the same as that with AgOTf, $PrSpH^+OTf^-$, and TfOH, unambiguously indicating complete dissociation of OTf^- from silver in CD_3OD.

2.2. Mechanism of Protodeauration of Argento Vinyl Gold.

In order to understand the role of argento vinyl gold in the catalytic cycle, it is necessary to ascertain the mechanism by which it can be protodemetalated, releasing gold and silver back into solution. Similarly to what was previously described for diaurated species, also here there is a choice between the nucleophile-assisted dissociative mechanism and bimolecular S_E2 mechanism (Scheme 4).

Preliminary experiments were conducted with the argento vinyl gold species **G1** generated in situ. Thus, TfOH, CF_3CO_2H, and $tBu_2PyH^+OTf^-$ all caused instant (<5 min) protodemetalation of this compound in MeOD at room temperature (**G1** was stable toward $tBu_2PyH^+OTf^-$ in $CDCl_3$, however). Reaction with AcOH occurred more slowly and was found to be inhibited in the presence of additional AgOTf but accelerated in the presence of Me_2S. These results already suggest the nucleophile-assisted dissociative mechanism. However, it was difficult to find suitable conditions to allow accurate determination of chemical kinetics that would prove this mechanism more rigorously. Therefore, we turned to a catalytic study instead.

Scheme 4. Possible Mechanisms of Protodemetalation of Argento Vinyl Gold



Theoretical analysis of a gold-catalyzed hydroalkoxylation in the case of complete and immediate formation of argento vinyl gold as a single resting state comes to different results depending on whether it undergoes protodemetalation by a nucleophile-assisted dissociative mechanism or an S_E2 mechanism. An analysis of the kinetics with the anticipated nucleophile-assisted mechanism is shown in Scheme 5. Using the steady-state approximation for vinyl gold species **B** (always present in undetectable amounts, eq 5) and the steady-state approximation for **G** (always present in full amount, keeping all the gold of the system, eq 6), one easily comes to the following expression for **B** (eq 7). Putting this into the reaction rate (eq 8) gives the following final expression for the rate law (eq 9). According to this analysis, the reaction should be zero order in substrate, first order in gold, first order in acid, and minus first order in silver. An analysis of the kinetics that would take place in the case of an S_E2 mechanism is given in the Supporting Information. It leads to zero order in substrate, first order in gold, first order in acid, and zero order in silver. Therefore, the order in silver in a catalytic process would be indicative of the actual mechanism of protodemetalation of argento vinyl gold.

Scheme 5. Derivation of the Rate Law for a Catalytic Reaction Having G as a Single Resting State

$$\mathbf{A} \xrightarrow{k_1} \mathbf{B} + H^+ \qquad (2)$$

$$\mathbf{B} + Ag(Sol)^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{G} + Sol \qquad \left(\frac{k_2}{k_{-2}} = K_{Ag}\right) \qquad (3)$$

$$\mathbf{B} + H^+ \xrightarrow{k_3} E \xrightarrow[ROH]{\sim H^+} Acetal \qquad (4)$$

$$\begin{cases} \dfrac{d[\mathbf{B}]}{dt} = k_1[\mathbf{A}] - k_3[\mathbf{B}][H^+] - \underbrace{k_2[\mathbf{B}][Ag^+] + k_{-2}[\mathbf{G}]}_{=0} = 0 & (5) \\ \dfrac{d[\mathbf{G}]}{dt} = k_2[\mathbf{B}][Ag^+] - k_{-2}[\mathbf{G}] = 0 & (6) \end{cases}$$

$$[\mathbf{B}] = \frac{[\mathbf{G}]}{K_{Ag}[Ag^+]} \qquad (7)$$

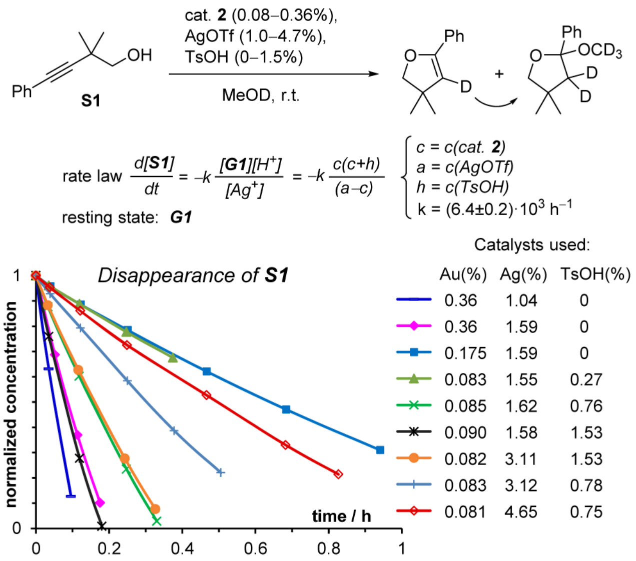
$$\text{overall reaction rate:} \quad -\frac{d[\mathbf{S}]}{dt} = k_1[\mathbf{A}] = k_3[\mathbf{B}][H^+] \qquad (8)$$

$$\frac{d[\mathbf{S}]}{dt} = -\frac{k_3[\mathbf{G}][H^+]}{K_{Ag}[Ag^+]} \qquad (9)$$

Then we experimentally determined the kinetics of cyclization of **S1** in the presence of various amounts of catalyst

2, AgOTf, and TsOH in CD_3OD (Scheme 6). In each run gold rested as the single species **G1**, directly observable by ^1H NMR.

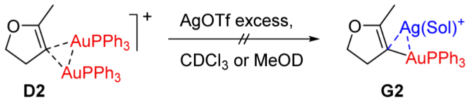
Scheme 6. Kinetics of Gold Catalyzed Reaction in the Presence of Ag^+ and H^+



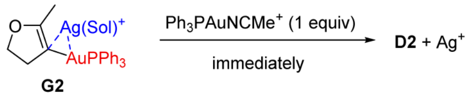
Protodemetalation of **G1** becomes visible only upon complete consumption of **S1** (the signal of $L2Au(Sol)^+$ appears). [**S1**] decreased almost linearly with time; therefore, zero order in substrate was accepted for further analysis (Supporting Information). The analysis indicated first order in gold, first order in acid, and, importantly, *minus first order in silver*. This finding is fully consistent with a nucleophile-assisted dissociative mechanism and not with the an associative S_E2 mechanism. Accordingly, argento vinyl gold must be essentially considered as an off-cycle intermediate, with clear resemblance to the known properties of diaurated species.[12]

2.3. Reactivity of Silver Salt toward Diaurated Species.

Following the work of Gagné,[2] we studied the transmetalation of diaurated species by silver salts. To our surprise, diaurated species **D2** did not exhibit any appreciable reactivity, giving no argento vinyl gold **G2** species (eq 10).



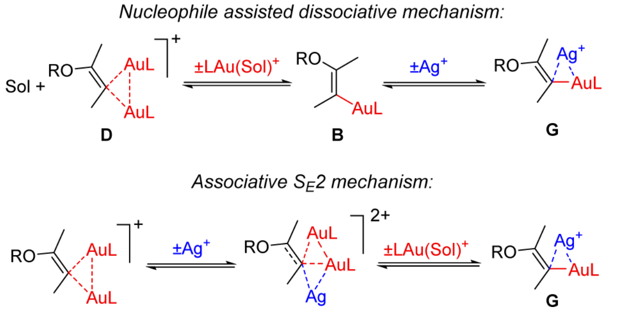
(10)



(11)

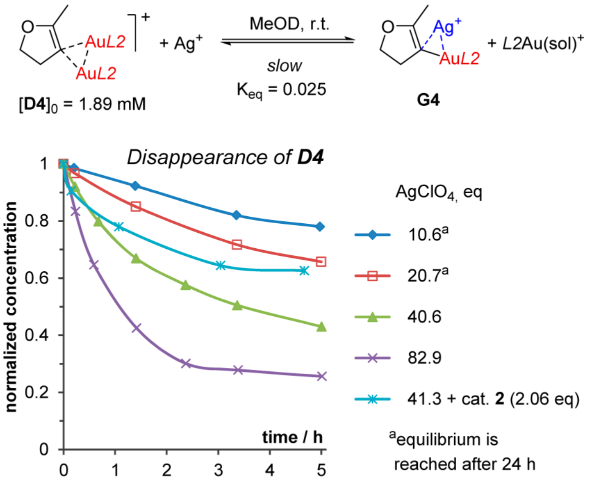
Rather, the opposite reaction was found to occur immediately (eq 11). In contrast, the less stable diaurated species **D4** slowly reacted with Ag^+ in methanol, affording **G4**. This transformation can be described by two mechanisms: a nucleophile-assisted dissociative mechanism and a bimolecular S_E2 mechanism (Scheme 7). In contrast to protodeauration of diaurated species that occurs only by the nucleophile-assisted mechanism, here also the S_E2 mechanism appears likely (the transition state would be stabilized by multiple metallophilic interactions). It is easy to see that the transmetalation must be considered a reversible process (if the strong preference for one of the sides is not known beforehand).

Scheme 7. Possible Mechanisms of Transmetalation of Diaurated Species



We hoped that the slow reaction of **D4** with Ag^+ would give us insight into the actual reaction mechanism. This reaction was performed at a constant initial concentration of **D4** using various amounts of Ag^+ (10–80 equiv) and catalyst **2** (0–2 equiv) in MeOD (Scheme 8). Unfortunately, the kinetics of this reaction could not be analyzed to differentiate between the two possible mechanisms, because the reaction appeared to be reversible and did not reach 100% conversion even in the presence of 80 equiv of Ag^+. However, as a small reward, we were able to determine the equilibrium constant ($K_{eq} = 0.025 \pm 0.005$). Since **D2** is >1000 times more stable than **D4**, it is not surprising that **D2** does not show any signs of transmetalation even in the presence of a large excess of a silver salt.[13]

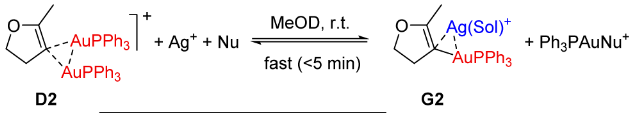
Scheme 8. Slow and Reversible Transmetalation of D4



We found that the equilibrium between diaurated species **D** and argento vinyl gold species **G** can be strongly influenced by the addition of a nucleophile (Scheme 9). Thus, using Me_2S, Lut, TMTU, and PPh_3 it is possible to entirely shift the equilibrium toward **G** even if it was completely on the side of **D** before the addition of a nucleophile. The main driving force is provided by binding gold to form $LAuNu^+$. Clearly, there is the opposite driving force provided by binding silver to form $Ag(Nu)_n^+$ (n = 2–4), but it does not play a role, being dominated by gold, as indicated by a model study of the binding preferences.[14] The stability of $LAuNu^+$ increases in the order Nu = Me_2S < Lut < TMTU < PPh_3;[15] therefore, the ability of a nucleophile to shift the equilibrium between **D** and **G** increases in the same order.

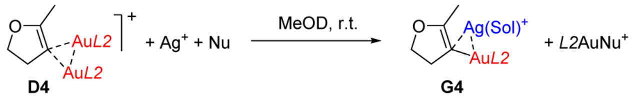
These findings allow the conclusion that not every diaurated species **D** can be transmetalated by silver salts. This appears to

Scheme 9. Influence of a Nucleophile on Transmetallation of Diaurated Species



	Ag$^+$, eq	Nu, equiv	**D2/G2**
1	12^a	none	1:0
2	12^a	Lut, 15.5	0.47:0.53
3	10^a	TMTU, 3.6	0.46:0.54
4	10^a	TMTU, 13	0:1
5	1.1^a	PPh$_3$, 2.0	0:1

(Sol = MeOD, Nu)



	Ag$^+$, eq	Nu, equiv	conversion
1	1.76^a	Me$_2$S, 11.8	92% in 2h
2	1.3^a	TMTU, 2.7	ca 40% in 15 min
3	1.3^a	TMTU, 3.6	100% <5 min

[a] Ag$^+$ exists as an undetermined Ag(Nu)$_n^+$ (n = 2 - 4) or their mixture

Background equilibriums:

$$\mathrm{Ag(Nu)_{n-1}^+ + Nu \rightleftharpoons Ag(Nu)_n^+}$$

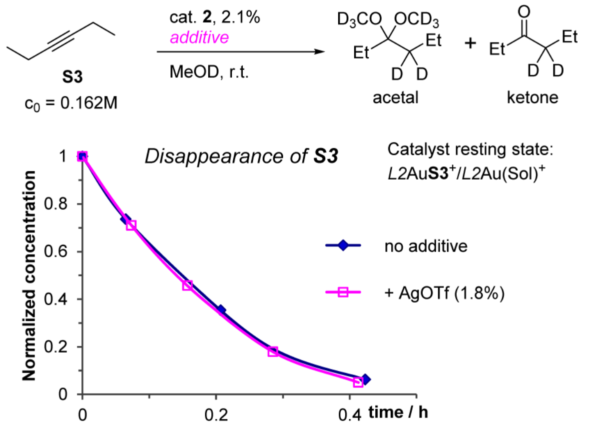
$$\mathbf{D}\mathrm{ + Nu \rightleftharpoons }\mathbf{B}\mathrm{ + LAuNu^+}$$

be a reversible reaction that obviously depends on the thermodynamic stability of **D** and **G**. In most cases **D** would be reluctant to undergo transmetalation; rather, the opposite reaction would be favored. In the case where **D** is highly destabilized by the steric bulk of the LAu, formation of **G** would be more favored (the stability of **G** is obviously less sensitive to the steric bulk of the LAu moiety and the enol ether core in comparison to that of **D**). In addition, binding of LAu$^+$ by an additional nucleophile provides a driving force that may shift this equilibrium toward **G** (this may take place under catalytic conditions; see below).

2.4. Influence of Silver Additives on Catalysis by Gold Catalysts. Having briefly described the properties of argento vinyl gold, we turn to an explanation of silver effects in catalysis. Here MeOD was used as a solvent to ensure complete solubility of the catalytic system and also to eliminate any counterion effects. We performed a series of catalytic runs with and without silver additives and monitored the reaction progress directly by NMR. Particular attention was given to the observation of catalytic intermediates in situ during the whole process. Using these observations as well as a knowledge of the properties of argento vinyl gold (sections 2.1–2.3.) and the mechanism of gold-catalyzed hydroalkoxylation (shown in Scheme 2) it was possible to unambiguously define the role of silver and explain the silver effect in every case.

At first, it is most convenient to describe and explain a silver effect for a reaction where transition from π-complex **A** to vinyl gold species **B** is rate limiting, because for this easy case there is no need to consider any off-cycle intermediates (**D** or **G**), protodemetalation, and concentration of acid in the system. At the same time this reaction type allows probing the role of silver in the initial steps of the gold catalytic cycle. A suitable reaction is intermolecular hydroalkoxylation of hexyne-3 (**S3**), which was previously investigated.[9] Repeating this reaction in the presence of AgOTf did not reveal any detectable silver effects (Scheme 10). The resting state of the catalyst in both

Scheme 10. No Silver Effect on Hydroalkoxylation of S3 Catalyzed by 2

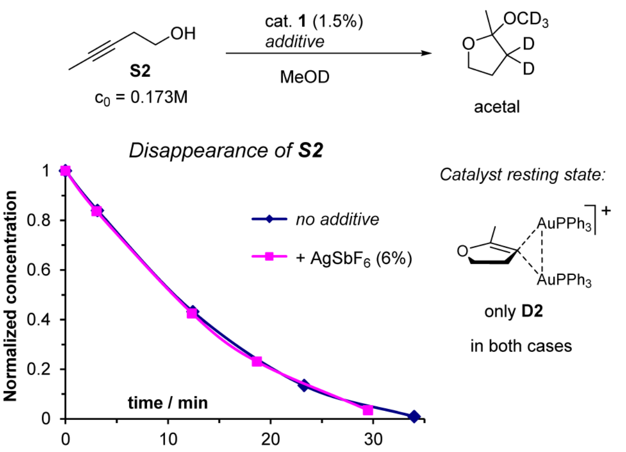


cases was a $L2\mathrm{Au}(\mathbf{S3})^+/L2\mathrm{Au(Sol)}^+$ mixture. This indicates that silver has no affect on changing the rate-limiting step (that is, vinyl gold **B** formation) and on changing the $L2\mathrm{Au}(\mathbf{S3})^+/L2\mathrm{Au(Sol)}^+$ ratio. This unambiguously proves that silver does not cooperate with gold and that all catalytic activity is exclusively due to the gold catalyst alone. This conclusion was additionally confirmed in the intramolecular cyclization of 6-phenylhexyn-5-ol-1 ($\mathrm{PhC{\equiv}C(CH_2)_4OH}$), which also did not exhibit any significant silver effect (see the Supporting Information).

This finding suggests that a possible way for silver to influence a gold-catalyzed hydroalkoxylation is through formation of the off-cycle argento vinyl gold species **G**. This conclusion is corroborated in a series of further experiments. In addition to organogold resting states, here we need to consider the concentration of concomitant acid because all the reactions described below are acid dependent (in the absence of silver they are characterized by the formation of **B** or **D** as a resting state).

Next we investigated the cyclization of 3-pentyn-1-ol (**S2**) in $\mathrm{CD_3OD}$ in the presence of catalyst **1** (Scheme 11). No silver effect was observed. In the absence of any additives this reaction is characterized by complete formation of **D2** (leaving only undetectable steady-state concentrations of other gold species).[9] NMR examination confirmed that the same situation

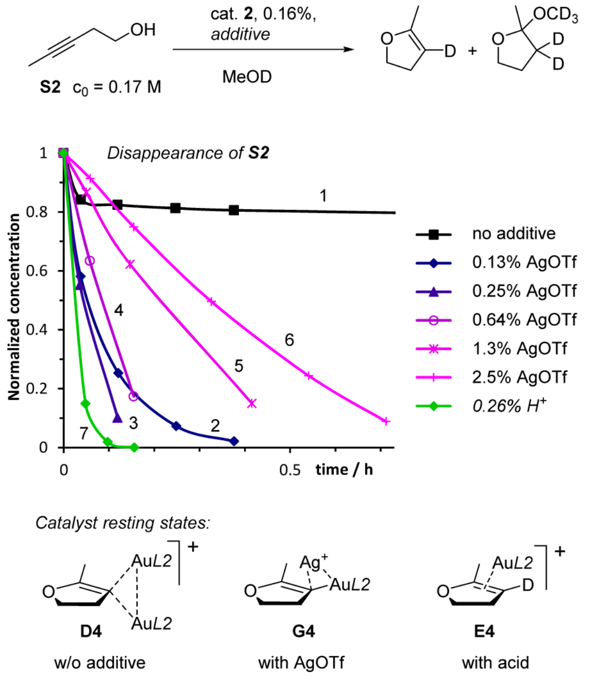
Scheme 11. Absence of Acid and Silver Effects on Cyclization of S2 in the Presence of Catalyst 1



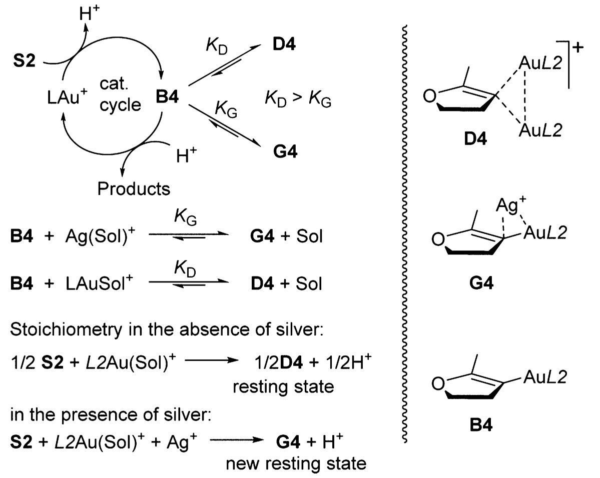
is observed in the presence of silver additive. Given the aforementioned stability of **D2** in comparison to **G2** (section 2.3.) it is not surprising that silver was unable to form **G2** and influence the distribution of gold intermediates in any appreciable way. In other words, if the diaurated species is too stable, the silver effect does not take place.

A completely different situation was observed in a similar study of the cyclization of 3-pentyn-1-ol (**S2**) in CD_3OD in the presence of catalyst **2** (Scheme 12). In the absence of silver additive this reaction is also accompanied by formation of the corresponding diaurated species (**D4**).[9] However, because of the low catalyst loading (0.16% of **2**) and the lower stability of **D4** in comparison with that of **D2**, the diaurated species does not form instantly but accumulates gradually during the first few minutes of the reaction, resulting in appearance of the rush period on the kinetic curve (curve 1). When it was performed in the presence of various amounts of AgOTf additive, this reaction exhibited a positive silver effect (curves 2−6). NMR examination indicated that **D4** was (almost) completely replaced by the corresponding argento vinyl gold **G4**, which was observed as a single resting state. Since the formation of **G4** is immediate, the rush period disappears. For an explanation of this effect it is necessary to consider the material balance of the catalytic system. Thus, in the presence of silver we have 1 equiv of **G4** and 1 equiv of H^+ instead of 1/2 equiv of **D2** and 1/2 equiv of H^+ before (per 1 equiv of LAu^+ as the reference, Scheme 13). Second, $K_D > K_G$ because **D4** is more stable than **G4** (see section 2.3).[16] This means that **G4** must be a less detrimental off-cycle resting state for the reaction than **D4**. As a consequence, the gold/silver-catalyzed reaction benefits from having a higher fraction of in-cycle organogold intermediates and a higher concentration of H^+. This adds together to account for the overall positive silver effect. For comparison we also determined the effect of a Brønsted acid additive (curve 7), which appeared to be considerably stronger than a silver effect.

Scheme 12. Positive Acid and Silver Effects on Cyclization of S2 in the Presence of Catalyst 2



Scheme 13. Changes in the Catalytic System Caused by Addition of Ag^+



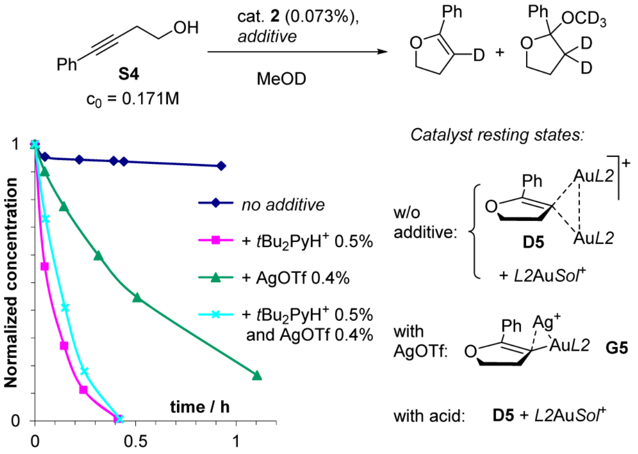
In this case the reaction is not accompanied by formation of any detrimental off-cycle intermediates at all (which means that the gold catalysis runs at its full possible power) and yet the concentration of H^+ is directly increased. This observation supports our explanation about the positive silver effect being associated with favorable changes in material balance of the catalytic system.

Furthermore, the kinetics of the silver-assisted reaction and the influence of the amount of AgOTf additive on the strength of the silver effect were analyzed. It is clear to see that the strength of the positive silver effect initially increases (going from 0 until 0.25% Ag, curves 1−3) and then decreases as more silver is present (from 0.25 until 2.5% Ag, curves 3−6). This is associated with the interplay of negative and positive factors. The initial gradual increase of the positive effect must be associated with the favorable changes in material balance of the catalytic system (replacement of **D4** by **G4** as a resting state, hence, the increase of in-cycle organogold and H^+). However, once the formation of **G4** is stoichiometrically complete (which in our case takes place already at 0.25% Ag, curve 3), addition of more silver no longer benefits the reaction this way. Rather, the excess of silver shifts the equilibrium K_G further toward **G4**, now reducing the total amount of in-cycle organogold, albeit not affecting H^+ (Scheme 13). This explanation is supported by establishing the minus first order in silver, taking place from 0.25 until 2.5% Ag, as shown in curves 3−6 (see the Supporting Information for calculations), which is the same result as was obtained in Scheme 6. In addition, the zero order in **S2** is obeyed with a moderate accuracy for this range of silver additive.

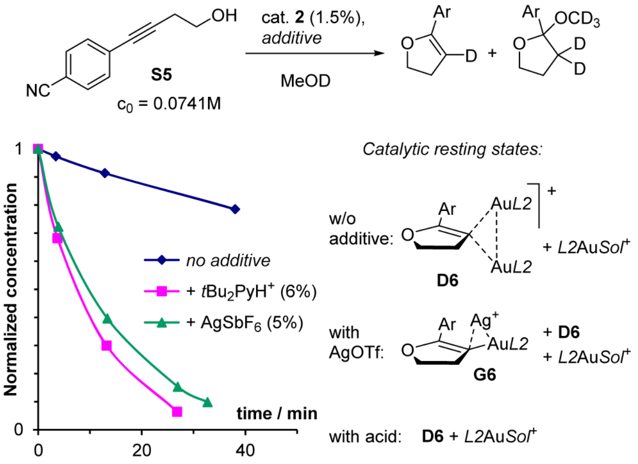
Similar explanations can be applied to explain the positive acid and silver effects that were observed in the cyclizations of 4-phenylbut-3-yn-1-ol (**S4**) and 4-(4-cyanophenyl)-butyn-3-ol-1 (**S5**) in the presence of catalyst **2** (Schemes 14 and 15) and the cyclization of **S2** catalyzed by diaurated species **D4** (Supporting Information). In the case of **S4** the resting state was entirely changed from **D5** to **G5** upon addition of silver, resembling the situation explained for alcohol **S2** above. Only partial changes in resting states were noted in the case of alcohol **S5** (see the Supporting Information for more details).

As a further case we examined the reaction of 2,2-dimethyl-4-phenylbut-3-yn-1-ol (**S1**), which is unable to form diaurated species with catalyst **2** because of steric reasons associated with

Scheme 14. Acid and Silver Effects on Cyclization of S4



Scheme 15. Acid and Silver Effects on Cyclization of S5



such a bulky substrate/ligand combination. In the absence of any additives this reaction is characterized by complete formation of vinyl gold **B1**, having protodeauration as the rate-limiting step.[9] Application of silver should bind this vinyl gold into argento vinyl gold. In complete accordance with our expectations, a *negative* silver effect was indeed observed (Scheme 16). As expected, vinyl gold completely disappeared and argento vinyl gold **G1** was observed by NMR as the only species. The kinetics of this reaction was analyzed in section 2.2.

The findings allow the conclusion that silver effects described in this section are caused only by changes of the concentrations of in-cycle organogold intermediates and H$^+$, induced by the formation of the new off-cycle intermediate **G**, and that silver has no direct role in the catalytic cycle itself.

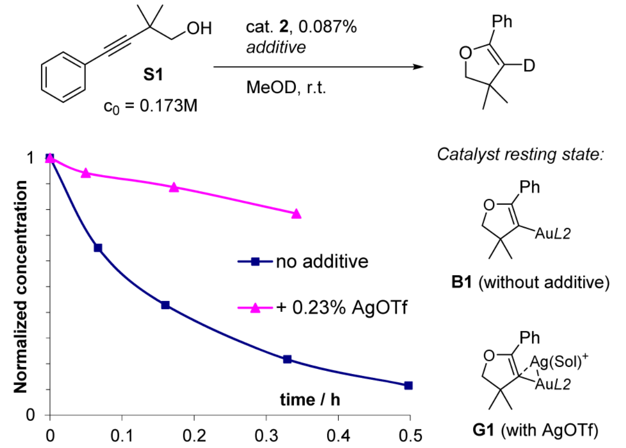
2.5. Classification of Silver Effects.

Our research and the topical reports found in the literature indicate that the silver effect may be encountered in many situations. However, it is not always "silver" in nature (that is, silver is not involved in the catalytic process itself). In order to eliminate confusion around the interpretation of various silver effects, we discuss briefly the silver effects found by other researchers in this area and demonstrate that all effects have, in their essence, a common origin.

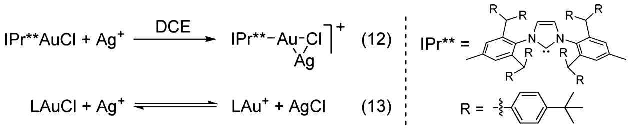
2.5.1. Silver Effect Associated with Incomplete Halogen Exchange (Eq 1).

Under certain conditions the halogen abstraction reaction may not reach completion, leading to

Scheme 16. Negative Silver Effect on the Cyclization of S1 in the Presence of Catalyst 2



other gold complexes instead. In 2012 Straub et al. performed a reaction of a very bulky IPr**AuCl with AgSbF$_6$ under almost non-nucleophilic conditions and isolated [IPr**AuClAg]$^+$, where silver is adjacent to the Au−Cl bond (eq 12).[17] This finding shows that an ideal halogen exchange reaction (eq 13) would be reversible under virtually non-nucleophilic conditions.[14] This complex is considered as the very early intermediate of eq 1.



$$\text{IPr**AuCl} + \text{Ag}^+ \xrightarrow{\text{DCE}} \left[\text{IPr**}\text{−}\underset{\text{Ag}}{\text{Au−Cl}}\right]^+ \quad (12)$$

$$\text{LAuCl} + \text{Ag}^+ \rightleftharpoons \text{LAu}^+ + \text{AgCl} \quad (13)$$

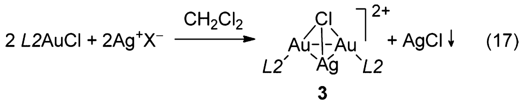
In 2013 Echavarren et al. described the formation of bridged chloronium complexes (LAu)$_2$Cl$^+$ as products of incomplete halogen abstraction (eq 14).[5] Since (LAu)$_2$Cl$^+$ is a precatalyst that has to react through a ligand exchange equilibrium (eq 15), it is clear that the best theoretical performance of 1 equiv of (LAu)$_2$Cl$^+$ (with regard to gold) cannot be higher than the activity of 0.5 equiv of formal LAu$^+$. We estimated the equilibrium constant of ligand exchange of ($L2$Au)$_2$Cl$^+$ with MeCN (eq 16), which indicates that ($L2$Au)$_2$Cl$^+$ would be slightly more stable toward reaction with a substrate than $L2$AuNCMe$^+$.

$$2L2\text{AuCl} + \text{Ag}^+\text{X}^- \xrightarrow{\text{CH}_2\text{Cl}_2} (L2\text{Au})_2\text{Cl}^+ + \text{AgCl}\downarrow \quad (14)$$

$$(L2\text{Au})_2\text{Cl}^+ + \text{Substr} \rightleftharpoons L2\text{AuSubstr}^+ + L2\text{AuCl} \quad (15)$$

$$(L2\text{Au})_2\text{Cl}^+ + \text{MeCN} \underset{\text{CDCl}_3}{\overset{K_{\text{eq}}\approx 0.4}{\rightleftharpoons}} L2\text{AuNCMe}^+ + L2\text{AuCl} \quad (16)$$

In 2013 yet another complex was identified by Jones et al. as a component of LAuCl/Ag$^+$ mixtures: the mixed silver−gold chloride complex **3** eq 17.[18] It also exists under almost non-



$$2\,L2\text{AuCl} + 2\text{Ag}^+\text{X}^- \xrightarrow{\text{CH}_2\text{Cl}_2} \mathbf{3} + \text{AgCl}\downarrow \quad (17)$$

$$\mathbf{3} + 2\ \text{Substr} \longrightarrow 2\ L2\text{Au(Substr)}^+ + \text{AgCl}\downarrow \quad (18)$$

nucleophilic conditions and immediately precipitates AgCl if a nucleophile (e.g., a substrate) is added to a solution of **3** (eq 18). A combination of eqs 17 and 18 completes the stoichiometry of eq 1.

From these findings it is easy to conclude that precipitation of AgCl and the presence of a nucleophile (even a weak one, such as H_2O or MeCN) or a counterion able to bind gold are the two driving forces which are simultaneously required for the halogen exchange (eq 1) to be complete.

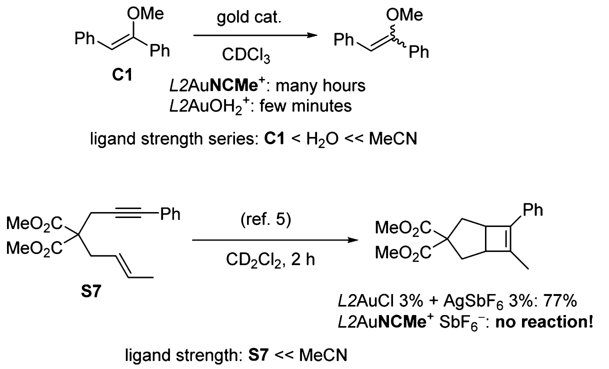
Furthermore, yet another factor should be taken into account: the simple solubility of the starting AgX salt. This idea came to mind after examination of the paper by Echavarren, where they observed incomplete halogen abstraction with $AgNTf_2$ and AgOTf in CH_2Cl_2.[5] Presumably, the low solubility of these salts in CH_2Cl_2 or $CHCl_3$ alone might be the likely reason for the incomplete reaction: a certain part of AgX may remain in the precipitate. In our own practice, we always dissolved silver salts in a minimum amount of acetone or MeCN prior to a halogen abstraction reaction. It never failed under these conditions. In particular, *L2*AuOTf was synthesized in quantitative yield from *L2*AuCl and AgOTf taken in a 1:1 ratio.

Without giving it any further investigation, we propose the following condition for reliable and 100% complete halogen exchange to use in laboratory practice: use the starting silver salt not as a solid but as a solution in a minimum amount of a *weakly* coordinating solvent (acetone, MeOH, THF, or MeCN). This ensures immediate and complete reaction strictly according to eq 1, avoiding accumulation of any intermediate complexes such as $[LAuClAg]^+$, $(LAu)_2Cl^+$, and **3**.

2.5.2. Silver Effect Associated with Reactivation of a Gold Catalyst That Was Poisoned by Impurity or Celite Filtration. It was demonstrated that the reactivity of gold catalysts generated in situ from a LAuCl/AgX system can be dramatically decreased if they are filtered through Celite prior to the reaction.[4,19] Hammond and Hu nicely explained that this has nothing to do with silver itself but with poisoning of a gold catalyst by traces of high gold/proton affinity impurities in Celite.[6] They described reactivation of a gold catalyst by using H^+, Ag^+, and other Lewis acids as sacrificial electrophiles to bind possible catalyst poisons and set the gold catalyst free.

2.5.3. Silver Effect Wrongly Associated with the Negative Role of MeCN. In connection with the use of a LAuCl/AgX system instead of a commercially available family of silver-free catalysts $LAuNCMe^+X^-$ we especially stress that for some substrates the LAuCl/AgX system would work more efficiently than $LAuNCMe^+$ but that this is not necessarily a silver effect! This might be the effect of the absence of MeCN in the system. In fact, many alkynes and alkenes have very weak binding affinity to the catalyst, and for them even MeCN ligand would be like a catalyst poison. This is nicely exemplified by cis/trans isomerization of enol ether **C1** (Scheme 17), which is much more efficiently catalyzed by a gold hydrate, a catalyst lacking MeCN.[20] Another example is a reaction of enyne **S7** taken from the literature (the authors did not interpret this effect).[5] We believe the confusing role of MeCN is encountered (but overlooked) in many gold-catalyzed reactions of substrates with very low binding affinity to gold. Those reactions would have $LAuNCMe^+$ as a resting state, and often they would not involve any neutral organogold intermediates in their mechanism. It is clear to see that this phenomenon has nothing to do with silver itself. Simply, the LAuCl/AgX system provides the activated $LAuS^+$ (S = substrate) complex more easily (eq 19) than does $LAuNCMe^+$ (eq 20). The gold hydrate can be quantitatively prepared by rotary evaporation of a commercial $LAuNCMe^+$ catalyst from EtOH (two times) and then from $CDCl_3$ (one time), as exemplified in eq 21. This procedure can be considered as a simple way to boost a silver-free gold catalyst.

Scheme 17. Negative Effect of MeCN on Reaction Rate Should Not be Confused with a Silver Effect



$$S + LAuCl + AgX \rightarrow LAuS^+X^- + AgCl\downarrow \qquad (19)$$

$$S + LAuNCMe^+ \rightleftharpoons LAuS^+ + MeCN \qquad (20)$$

$$\textit{L2}AuNCMe^+\ SbF_6^- \xrightarrow[\text{MeCN}\uparrow]{\text{1) evap. from EtOH} \atop \text{2) evap. from CDCl}_3} \underset{100\%}{\textit{L2}AuOH_2^+\ SbF_6^-} \qquad (21)$$

2.6. Outlook. The knowledge obtained in our research (sections 2.1−2.4) and the literature (section 2.5) adds together to explain the origin of silver effects within the mechanism of gold-catalyzed hydroalkoxylation (Scheme 18). This scheme illustrates two main conclusions. (1) Ag^+ is found to be essentially innocent with regard to the mechanism of the catalytic process. (2) The silver effect (positive or negative) occurs only if silver induces variations of concentrations of in-cycle organogold intermediates and H^+, which can be associated with formation of the new off-cycle intermediate argento vinyl gold **G**, incomplete halogen abstraction by Ag^+, or reactivation of a poisoned catalyst by Ag^+. The steps that cause these variations are shown in blue.

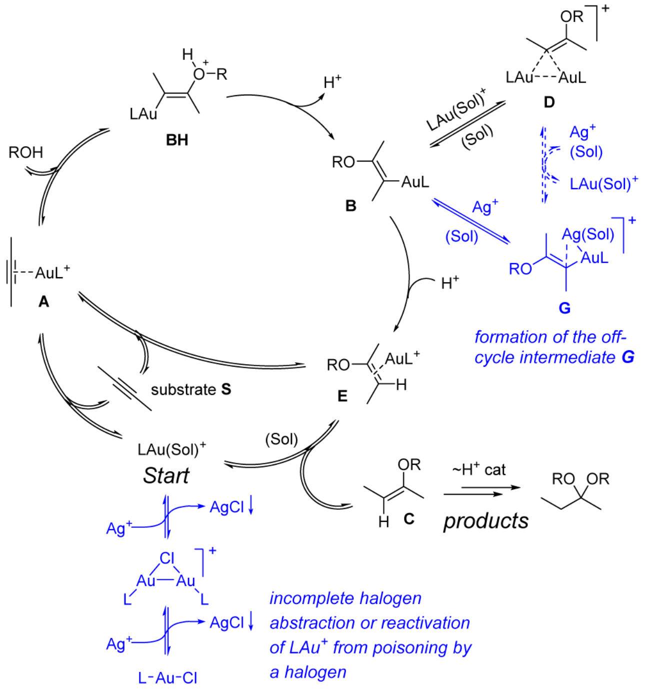
3. CONCLUSION

The research initiated by Gagné (Scheme 1) was expanded to complete the explanation of the silver effect (Scheme 18). In situ NMR monitoring of gold-catalyzed hydroalkoxylation in the presence of a silver salt revealed the formation of argento vinyl gold **G** in all cases when a silver effect was operative.

Stoichiometric studies indicated argento vinyl gold **G** to be a reactive species, undergoing in the presence of Ag^+, Nu, or vinyl gold **B**, correspondingly, fast silver exchange, fast ligand exchange at silver, and fast vinyl gold exchange at silver. Sufficiently strong nucleophiles will cause cleavage of **G** to yield **B**.

Protodemetalation of **G** was found to occur by the nucleophile-assisted dissociative mechanism (through **B**). Therefore, **G** is considered as an off-cycle intermediate of the catalytic process (the same as diaurated species **D**). Considering the material balance of the catalytic system, it

Scheme 18. Mechanism of Gold(I)-Catalyzed Hydroalkoxylation (in Black) Showing the Steps Responsible for the Silver Effect (in Blue)



was demonstrated that formation of **G** will induce changes in the concentrations of in-cycle organogold intermediates and H^+, and only these changes are responsible for the observed effect (not silver itself). The effect can be positive or negative (see explanations in the main text). No silver effect takes place if there is no accumulation of **G** in the reaction mixture. We foresee that the formation of mixed silver−gold acetylide complexes $[RC{\equiv}C(AuL)(Ag)]^+$ might contribute to a silver effect in reactions of some terminal alkynes.[21] This subclass remains to be explored.

Despite the ability to influence the rate of gold-catalyzed hydroalkoxylation, Ag^+ is found to be essentially innocent with regard to the mechanism of the catalytic process itself. This is thought to be valid for many reaction types, including those for which the simultaneous presence of silver and gold components was previously (erroneously) suggested to be crucial.[4] Some reactions that are separately catalyzed either by silver or by gold are beyond the scope of this conclusion (for those reactions a "true" silver effect associated with direct participation of silver in the catalytic process would indeed take place).[22]

In addition to the formation of **G**, a silver effect may be associated with an incomplete eq 1 or reactivation of a gold catalyst by silver from halide poisoning. Whatever reason applies, the chemical sense of a silver effect is the same: a change (decrease or increase) in the concentration of nonsilver catalytic cycle participants. Therefore, a gold catalysis practitioner should not think of silver as a necessary component of the catalytic cycle but rather must take care of speciation of the catalytic system to ensure the maximum concentration of catalytic cycle participants.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01493.

Complete experimental procedures and detailed NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Formation of **G4** in place of the more stable **D4** should not be misleading, because under the catalytic reaction conditions **G4** may become kinetically or even thermodynamically favored. For example, note that **G4** forms immediately and is reluctant to equilibrate to **D4**. The equilibration toward the more stable **D4** may be strongly retarded because there are always negligible concentrations of free vinyl gold **B4** and free $LAu(Sol)^+$. In addition, this does not necessarily contradict the thermodynamics, because an additional driving force is certainly provided by binding LAu^+ by the reactive substrate, eventually turning both gold and silver into **G4**, disfavoring formation of **D4** to some extent (Le Chatelier's principle). This driving force, however, was unable to cause any changes in resting state in the aforementioned reaction with catalyst **1** (**D2** forms quickly and is simply much more stable than **G2**).

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