Gold Catalysis

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Mechanistic Study of Gold(I)-Catalyzed Hydroamination of Alkynes: Outer or Inner Sphere Mechanism?**

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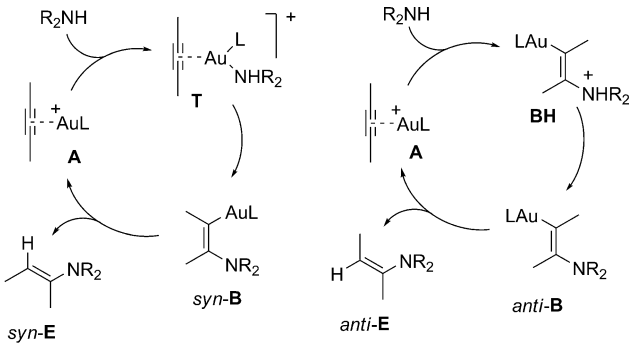
Abstract: *An experimental mechanistic study of the gold(I)-catalyzed hydroamination shows the formation of conformationally flexible auro-iminium salts* ***Au-Im****, which originate from the protonation of a vinyl gold species. Rotation around the C–CAu bond is the reason for the loss of stereospecificity of protodeauration, which explains the stereochemical result of the Stradiotto reaction. The ambiguity about inner or outer sphere mechanism is thus resolved in favor of the outer sphere mechanism.*

Gold(I)-catalyzed hydroamination of alkynes is an important synthetic tool for the functionalization of C≡C bonds.[1] Like some other processes in gold catalysis, it was already described in 1987,[2] but did not receive much attention until around 2000, when the interest in gold catalysis started to rise. Nowadays, the scope of gold(I)-catalyzed hydroamination of alkynes is not limited to the synthesis of imine or enamine structures by the formal addition of various N–H reagents onto the C≡C bond.[3,4] Rather, a number of complex cascade reactions were reported, using this addition as one step within a complicated multistep process.[5] However, the hydroamination reaction often requires harsh conditions, which limits its scope. Last but not least, the development of the method is also limited because of the lack of understanding of the reaction mechanism. In several studies gold–amine complexes $[LAu(amine)]^+$ were identified as reaction intermediates. This fact, together with the stereoselective formation of *syn*-**E** in the intermolecular reaction described by Stradiotto and co-workers, was considered as sufficient evidence for the inner sphere mechanism (Scheme 1).[3a,6] However, ionic organo–gold complexes formed upon intramolecular 5-*endo-dig* and 5-*exo-dig* addition of a tertiary amine moiety described by Bertrand and co-workers[7] as well as a single vinyl–gold complex described by Hashmi and co-workers,[8] provided evidence for the outer sphere mechanism. It should be stressed, that according to the current understanding of protodeauration, the outer sphere mechanism should lead to the product of *anti*-addition (*anti*-**E**), which is in contradiction to the formation of *syn*-**E** described by Stradiotto and co-workers.[3a] As it stands, there is still an unresolved ambiguity: should the reaction generally be considered as proceeding through an inner or outer sphere mechanism (Scheme 1)?



Scheme 1. Short representation of inner and outer sphere mechanism proposed for the hydroamination of alkynes.

As part of our studies on mechanisms of gold catalysis,[9] we report herein an experimental NMR investigation of the mechanism of the gold(I)-catalyzed hydroamination of alkynes. We describe the key organo–gold intermediates originating from catalysts $[Ph_3PAuNCMe]^+$ SbF_6^- (**1**) and $[L2AuNCMe]^+$ SbF_6^- (**2**) (*L2* = *o*-(di-*tert*-butylphosphino)biphenyl) as well as the chemistry of gold complexes relevant to the process, leading to a consensus: the gold(I)-catalyzed hydroamination reaction is best described by the outer sphere mechanism, whereas the inner sphere mechanism cannot be accepted anymore as an explanation.

The addition of catalyst **2** (4 mol%) to alkyne-amine **S1** in $CDCl_3$ led to a sluggish catalytic reaction. Monitoring by ^1H NMR spectroscopy showed the immediate formation of two organo–gold species **Au1** and **Au2**, but after a few minutes only **Au2** remained (Scheme 2). After 8 h 60–70% conversion of **S1** was achieved, giving a mixture of enamines **E1**/**E2** as the main product.[10] In a stoichiometric study, 1.5 equiv of **S1** reacted with 1 equiv of **2** in $CDCl_3$ instantly giving complex **Au2** which was isolated in its individual state (80% yield, 100% yield in situ) and fully characterized by NMR spectroscopy and X-ray analysis. However, reaction of a slight excess of **2** with **S1** led to the immediate formation of **Au1** (>90% in situ). Reaction of the sterically less hindered catalyst **1** led to a mixture of diaurated species **D1** and **Au3**.

Complexes **Au1**–**Au3** are depicted as auro-iminium salts and not as gold enamine π-complexes. This structure assignment and understanding of bonding follows from the NMR

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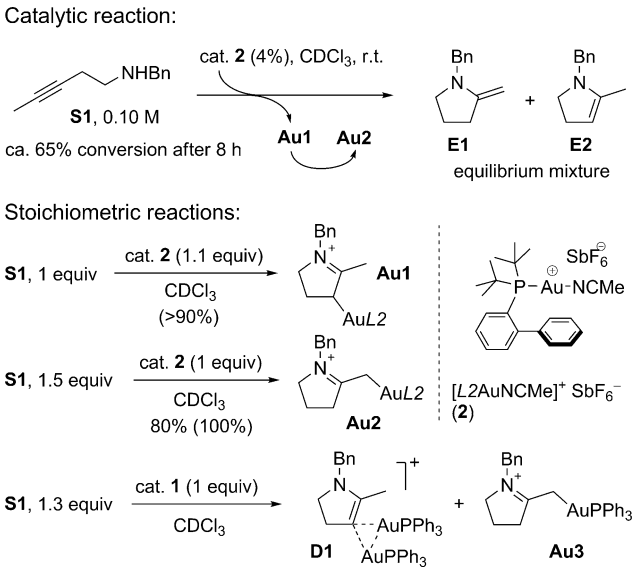


Scheme 2. Reactions of amine **S1** with catalysts **1** and **2**.

spectra in solution and X-ray analysis. The ^{1}H NMR spectrum of pure **Au2** in CD_2Cl_2 at room temperature contains simple signals (including the doublet at 1.91 ppm, $J_P = 8.9$ Hz of the CH_2Au group), but at low temperature the spectrum shows a complicated pattern (Figure 1). Structural parameters determined from the solid structure of **Au2** are between the typical values for known gold–enol ether complexes and gold–ene-1,1-diamine complexes (Figures 2 and 3).[11] This unambiguously characterizes the alkyl enamine **E1** as a ligand with a high degree of slippage when coordinated to gold.

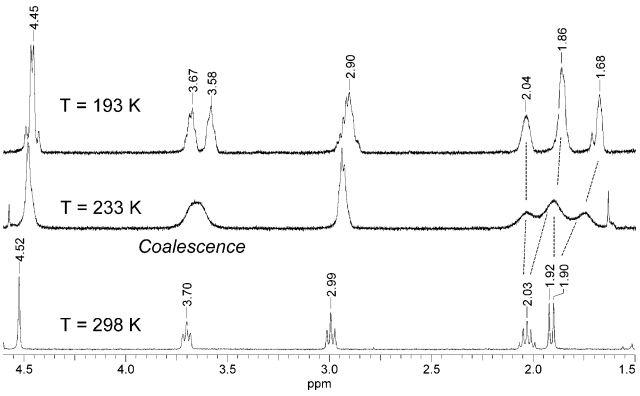


Figure 1. ^{1}H NMR spectra of **Au2** at various temperatures in CD_2Cl_2.

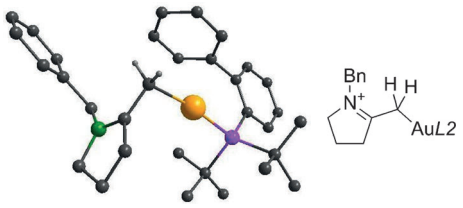


Figure 2. Structure of the **Au2** cation in the solid state. All hydrogens are omitted except for the CH_2Au fragment.

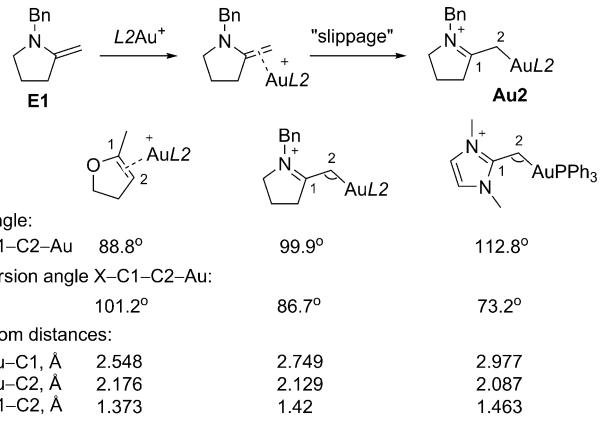
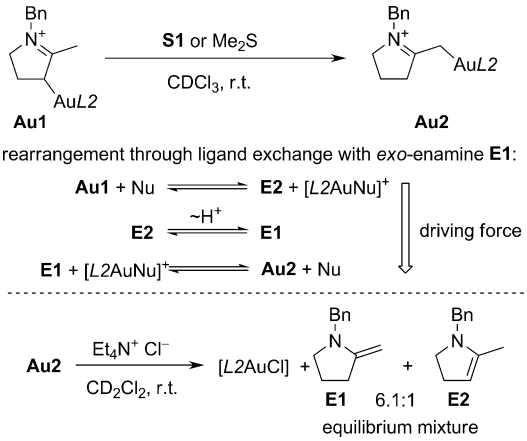


Figure 3. Slippage mechanism and structure comparison of representative gold–enol ether,[11a] gold–enamine, and gold–ene-1,1-diamine complexes.[11b]

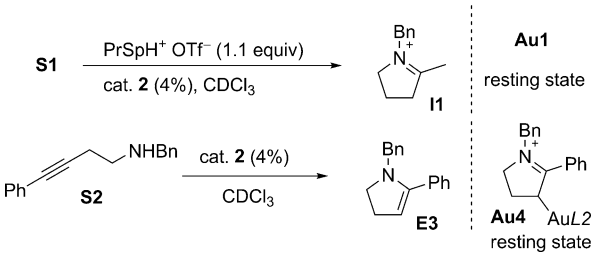
Correspondingly, **Au2** exhibits a high degree of η^1-coordination mode to gold and a predominant loss of the double-bond character of the C1–C2 bond; this enables easy rotation around this bond and therefore **Au2** should rather be considered an alpha auro-iminium salt than a π-alkene complex. This property is the key to understand the stereochemical outcome of alkyne hydroamination reactions (see below).

In order to conclude about the role of auro-iminium salts in the hydroamination mechanism, the origin of these species has to be established. First, the chemistry of **Au1** and **Au2** was studied. The addition of free **S1** to a solution of **Au1** led to the rapid rearrangement of **Au1**, thereby forming **Au2** (with concomitant slow catalytic reaction). The same occurs upon addition of a moderately strong nucleophile (Me_2S) to **Au1**. However, the addition of Cl^- as a strong nucleophile either to **Au1** or **Au2** led to complete liberation of [*L2*AuCl] and the formation of free enamines **E1**/**E2** as an equilibrium mixture (Scheme 3). It becomes clear that the rearrangement of **Au1** to **Au2** is simply a ligand exchange with free **E1**, giving the thermodynamically more stable **Au2**. This process can be considered as catalytic in enamine (or another nucleophile).



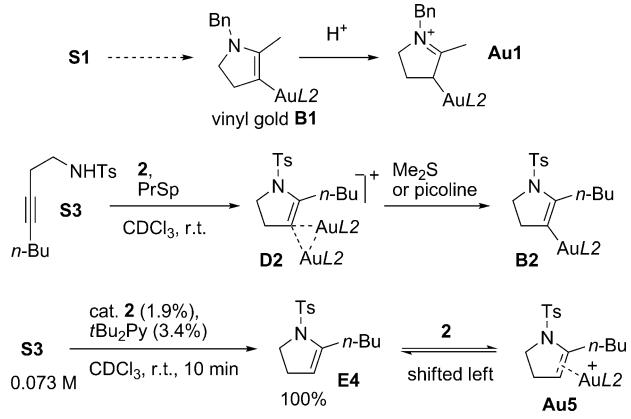
Scheme 3. Reaction of auro-iminium salts with nucleophiles.

To confirm that **Au2** arises as a product of ligand exchange and not as a direct participant of the catalytic cycle, we performed the hydroamination of **S1** in the presence of an acid (1,8-bis(dimethylamino)naphthalene triflate salt, $PrSpH^+ \cdot OTf^-$). Under these conditions the formed enamines are immediately protonated, giving iminium salt **I1** as a single final product (Scheme 4).[12] Because of the negligible concentration of free enamine at all times, the rearrangement of **Au1** to **Au2** should be suppressed. Indeed, gold was exclusively present as **Au1** (directly evidenced from NMR spectra). This confirms that **Au1** is the primary organo–gold intermediate, originating from pure 5-*endo-dig* cyclization, and that **Au2** is a thermodynamically more stable isomer originating from ligand exchange with free **E1**. In addition, the application of phenyl-substituted alkyne-amine **S2** leads to single enamine **E3**. Accordingly, the single auro-iminium salt **Au4** was observed as a resting state (Scheme 4).



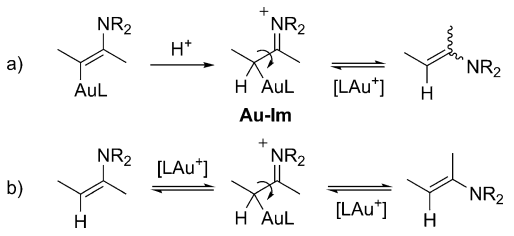
Scheme 4. Observation of resting states.

In the next step the mechanism of the formation of the auro-iminium salt was analyzed. Since the 5-*endo-dig* cyclization cannot be triggered by a proton, we hypothesized that the auro-iminium salt **Au1** forms as a result of the protonation of vinyl–gold complex **B1**, which itself is undetectable because of its very high affinity to protonation (Scheme 5). Indeed, attempts to deprotonate **Au2** to generate *exo*-vinyl–gold failed, suggesting that this species is highly basic (and definitely more basic than simple enamines). To confirm the vinyl–gold complex as an essential organo–gold intermediate, we studied substrate **S3** having a sulfonamide functionality to reduce the basicity of the relevant species. When **S3** was treated with 1,8-bis(dimethylamino)naphthalene (PrSp) and catalyst **2**, the diaurated species **D2** was generated as the single organo–gold product. Upon treatment with K_2CO_3, Me_2S, or picoline, **D2** readily gives rise to **B2** (Scheme 5). In addition, diaurated species were found in the aforementioned reaction of **S1** with catalyst **1** (**D1**, Scheme 2). Even though **B1** or **B2** cannot be directly observed under normal catalytic conditions, the formation of the diaurated species confirms that vinyl–gold indeed has to be an intermediate of the hydroamination process, because diaurated species are known to be the product of trapping vinyl–gold intermediates with an LAu^+ unit.[13,9] Correspondingly, the auro-iminium salt is considered to be the product of protonation of the vinyl–gold species.



Scheme 5. Origin of auro-iminium. Confirmation of the intermediacy of vinyl–gold.

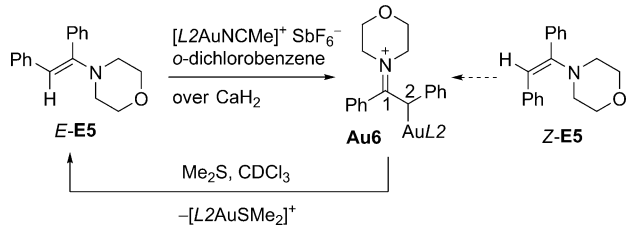
After the work of Bertrand and co-workers,[7] these observations further confirm the outer sphere mechanism at least for intramolecular gold-catalyzed hydroamination reactions since the formation of vinyl–gold complex **B** as an essential intermediate is simply not possible by an inner sphere mechanism. However, there is no reason to assume the mechanism to be different for the intermolecular version.[14] So far, the stereochemical outcome of the intermolecular hydroamination reaction as described by Stradiotto and co-workers[3a] was the only experimental evidence which was seemingly inconsistent with the outer sphere mechanism. However, from now on with the knowledge of the nature of auro-iminium salts, it is possible to correctly explain these experimental results also with regard to this mechanism. Thus, even though the *anti*-addition of an amine onto a gold–alkyne complex would lead to vinyl–gold in a stereospecific manner, this stereochemical information is completely lost upon formation of the conformationally flexible auro-iminium salt **Au-Im**, which makes the overall protodeauration process no longer stereospecific, unlike it is generally considered for other vinyl–gold species (Scheme 6a). It is clear, that via **Au-Im**, gold will also catalyze the isomerization of one geometrical isomer of an enamine into another until the thermodynamic equilibrium is reached, regardless of the exact stereochemical outcome of the ligand exchange itself (Scheme 6b).[15] Likewise, the isomerization of enamines will additionally occur through the classical protonation/deprotonation pathway promoted by traces of Brønsted acid in the reaction mixture. In literature, the *E*-enamine is known to be thermodynamically more stable than the *Z*-enamine, and this simple fact explains the selective formation of *E*-enamine in the reaction described by Stradiotto and co-workers.[16] The



Scheme 6. a) Loss of stereoselectivity due to protodeauration and b) isomerization of enamines through auro-iminium salt **Au-Im**.

overall stereochemical outcome of the reaction is thus determined solely by the thermodynamics of the final enamines. With this explanation, the consensus is reached that gold-catalyzed hydroamination reactions should be described by the outer sphere mechanism, same as other hydrofunctionalization reactions of alkynes.[17]

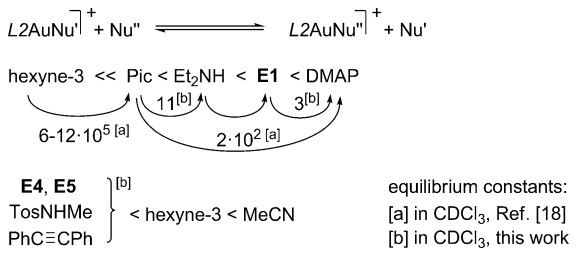
To confirm this conclusion experimentally, we generated auro-iminium salt **Au6** from the corresponding *E*-**E5**. The ^{1}H NMR spectrum of **Au6** exhibits a similar temperature dependence as was described above for **Au2**, confirming the rotation around the C1–C2 bond (see the Supporting Information). Addition of Me_2S to a solution of **Au6** regenerates *E*-**E5** with >95% stereoselectivity, Scheme 7.



Scheme 7. Preparation of an enriched sample of **Au6** and its conversion back to *E*-**E5**.

The fast rotation of the C1–C2 bond in **Au6** implies that the formation of this compound is independent of the initial geometric configuration of the double bond at the enamine. Therefore, the same compound would be formed from the corresponding *Z*-isomer of **E5**. This argument together with the stereoselective regeneration of *E*-**E5** from **Au6** confirms the mechanism of enamine isomerization which is proposed in Scheme 6 and that our explanation of the stereochemical outcome of the intermolecular hydroamination reaction is consistent with the outer sphere mechanism.

To gain a deeper understanding of the course of the hydroamination process, we determined the binding affinity of the *L2*Au$^+$ unit to representative neutral compounds using the ligand exchange with auxiliary nucleophiles with known binding affinities (Scheme 8).[18] From the ligand strength series it is clear that simple alkyl amines and alkyl enamines would be $\gg 10^5$ stronger ligands than the alkyne substrate. Not surprisingly, [LAu(amine)]$^+$ complexes were previously as well as in our research observed as resting states. It appears that the ligand exchange equilibrium strongly disfavors the formation of the activated gold–alkyne complex **A**. This is the principal reason why hydroamination reactions often require



Scheme 8. Binding affinity scale for *L2*Au$^+$ (pic = 4-picoline).

elevated temperature. However, the situation improves significantly when amide substrates with a reduced binding affinity to gold are used. For example, the reaction of **S3** takes only a few minutes (or less), whereas the reaction of **S1** requires many hours (Schemes 5 and 2). The same accounts for the reactivity series established by Tanaka and co-workers (anilines with electron-deficient substituents react faster).[3b]

In summary, the gold-catalyzed hydroamination reaction is described by the outer sphere mechanism which is also the case for other hydrofunctionalization reactions of alkynes. The process includes the formation of gold–enamine complexes as intermediates. These complexes exhibit a loss of the double bond character, which enables an easy rotation around the C–CAu bond, and therefore they are viewed as auro-iminium salts. Because of the rotation, the liberation of an enamine from the auro-iminium salt upon ligand exchange is not stereospecific. This is responsible for the fact that the protodeauration of enamine-derived vinyl–gold complexes **B** is not stereospecific, thereby constituting the fundamental difference from other protodeaurations known to occur with retention of the configuration at the double bond.[19] Via intermediate auro-iminium salts, gold will also catalyze the isomerization of one geometrical isomer of an enamine into the other until the thermodynamical equilibrium is reached. Furthermore, the positional rearrangement of the enamine double bond can occur as a Brønsted-acid-catalyzed process. It can be concluded, that the gold-catalyzed hydroamination reaction yields enamines as a thermodynamically controlled mixture of isomers and can only be selective if the dominant isomer is considerably more stable than the other. The overall mechanism of the gold-catalyzed hydroamination reaction appears to be similar to hydroamination reactions catalyzed by other transition metals (e.g. palladium(II)[20] and iridium-(III)[21]).

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[1] For general reviews about the hydroamination reaction of multiple bonds, see: a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–703; b) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892; c) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555–4563.

[2] a) Y. Fukuda, K. Utimoto, H. Nozaki, *Heterocycles* **1987**, *25*, 297–300; b) Y. Fukuda, K. Utimoto, *Synthesis* **1991**, 975–978.

[3] a) K. D. Hesp, M. Stradiotto, *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029; b) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349–3352; c) J.-E. Kang, H.-B. Kim, J.-W. Lee, S. Shin, *Org. Lett.* **2006**, *8*, 3537–3540; d) S. L. Crawley, R. L. Funk, *Org. Lett.* **2006**, *8*, 3995–3998; e) Y. Zhang, J. P. Donahue, C.-J. Li, *Org. Lett.* **2007**, *9*, 627–630; f) L.-A. Schaper, X. Wei, S. J. Hock, A. Pöthig, K. Öfele, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Organometallics* **2013**, *32*, 3376–3384; g) V. Lavallo, J. H. Wright, F. S. Tham, S. Quinlivan, *Angew. Chem.* **2013**, *125*, 3254–3258; *Angew. Chem. Int. Ed.* **2013**, *52*, 3172–3176.

[4] Addition of hydrazine: R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2011**, *123*, 5674 – 5677; *Angew. Chem. Int. Ed.* **2011**, *50*, 5560 – 5563.

[5] a) H. Wu, Y. P. He, L. Z. Gong, *Adv. Synth. Catal.* **2012**, *354*, 975 – 980; b) Y.-P. He, H. Wu, D.-F. Chen, J. Yu, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 5232 – 5237; c) S. Fleischer, S. Werkmeister, S. Zhou, K. Junge, M. Beller, *Chem. Eur. J.* **2012**, *18*, 9005 – 9010; d) X.-Y. Liu, C.-M. Che, *Org. Lett.* **2009**, *11*, 4204 – 4207; e) P. P. Sharp, M. G. Banwell, J. Renner, K. Lohmann, A. C. Willis, *Org. Lett.* **2013**, *15*, 2616 – 2619; f) X. Chen, H. Chen, X. Ji, H. Jiang, Z.-J. Yao, H. Liu, *Org. Lett.* **2013**, *15*, 1846 – 1849; g) J. Han, B. Xu, G. B. Hammond, *Org. Lett.* **2011**, *13*, 3450 – 3453; h) J. Han, B. Xu, G. B. Hammond, *J. Am. Chem. Soc.* **2010**, *132*, 916; i) X. Wang, Z. Yao, S. Dong, F. Wei, H. Wang, Z. Xu, *Org. Lett.* **2013**, *15*, 2234 – 2237; j) X. Wang, S. Dong, Z. Yao, L. Feng, P. Daka, H. Wang, Z. Xu, *Org. Lett.* **2014**, *16*, 22 – 25.

[6] a) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5302 – 5306; *Angew. Chem. Int. Ed.* **2008**, *47*, 5224 – 5228; b) N. Nishina, Y. Yamamoto, *Angew. Chem.* **2006**, *118*, 3392 – 3395; *Angew. Chem. Int. Ed.* **2006**, *45*, 3314 – 3317.

[7] X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2010**, *122*, 954 – 957; *Angew. Chem. Int. Ed.* **2010**, *49*, 942 – 945.

[8] A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971 – 975.

[9] a) A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2013**, *19*, 3932 – 3942; b) A. Zhdanko, M. E. Maier, *Organometallics* **2013**, *32*, 2000 – 2006; c) A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2014**, *20*, 1918 – 1930.

[10] The ratio of enamines cannot be accurately established due to the broad signals in the spectrum, which are presumably caused by the fast isomerization rate. However, the ratio was easily measured in another experiment performed at a lower concentration (Scheme 3). Isomerization of *endo*-enamine to *exo*-enamine is catalyzed by acid but not by gold, as proven in the Supporting Information.

[11] a) For enol ether complexes, see: Y. Zhu, C. S. Day, A. C. Jones, *Organometallics* **2012**, *31*, 7332 – 7335; b) For ene-1,1-diamine complexes, see: A. Fürstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chem.* **2008**, *120*, 3254 – 3258; *Angew. Chem. Int. Ed.* **2008**, *47*, 3210 – 3214.

[12] In contrast to the enamine, **S1** is predominantly not protonated in the presence of $PrSpH^+$. In the presence of a stronger acid (tBu_2PyH^+) both, enamine and **S1**, are protonated and the reaction is even slower because of the deactivation of the amine as a nucleophile.

[13] a) D. Weber, M. A. Tarselli, M. R. Gagne, *Angew. Chem.* **2009**, *121*, 5843 – 5846; *Angew. Chem. Int. Ed.* **2009**, *48*, 5733 – 5736; b) G. Seidel, C. W. Lehmann, A. Fürstner, *Angew. Chem.* **2010**, *122*, 8644 – 8648; *Angew. Chem. Int. Ed.* **2010**, *49*, 8466 – 8470.

[14] Being unable to confirm this statement experimentally, we appeal to the fact that both inter- and intramolecular hydroalkoxylation of alkynes occur through the same outer sphere mechanism. Furthermore, it is generally accepted that the addition of a nucleophile onto an activated gold–alkyne complex leads to the *anti*-adduct.

[15] It is possible that the ligand exchange gives the geometrical isomers of enamines in a ratio different from the ratio of the enamines at thermodynamic equilibrium.

[16] M. E. Munk, Y. K. Kim, *J. Org. Chem.* **1965**, *30*, 3705 – 3710.

[17] The hypothetical tricoordinate species **T** (Scheme 1), the key intermediate of the inner sphere mechanism, is only accepted as intermediate or transition state of a ligand exchange at gold, which is commonly known to proceed through an associative S_N2 mechanism. See: a) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun.* **2009**, 6451 – 6453; b) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 6350 – 6351.

[18] A. Zhdanko, M. Ströbele, M. E. Maier, *Chem. Eur. J.* **2012**, *18*, 14732 – 14744.

[19] A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360 – 5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232 – 5241.

[20] a) T. E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter, Y.-K. Yan, *Organometallics* **2000**, *19*, 170 – 183; b) T. E. Müller, M. Berger, M. Grosche, E. Herdtweck, F. P. Schmidtchen, *Organometallics* **2001**, *20*, 4384 – 4393.

[21] X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree, *Org. Lett.* **2005**, *7*, 5437 – 5440.

