

# Gold Catalysis

# Unexpected Anion Effect in the Alkoxylation of Alkynes Catalyzed by N-Heterocyclic Carbene (NHC) Cationic Gold Complexes

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Abstract: The intermolecular alkoxylation of alkynes is the oldest application of cationic gold(I) catalysts; however, no systematic experimental data about the role of the anion are available. In this contribution, the role of the anion in this catalytic reaction as promoted by a N-heterocyclic carbene-based gold catalyst, [(NHC)AuX] (X = BARF<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, OTf<sup>-</sup>, OTs<sup>-</sup>, TFA<sup>-</sup>, or OAc<sup>-</sup>) is analyzed, through a combined experimental (NMR spectroscopy) and theoretical (DFT calculation) approach. The most important factor seems to be the ability to abstract the proton from the methanol during the nucleophilic attack, and such ability is related to the anion basicity. On the other hand, too high coordination power or basicity of the anion worsens the catalytic performance by preventing alkyne coordination or by forming too much free methoxide in solution, which poisons the catalyst. The intermediate coordinating power and basicity of the OTs<sup>-</sup> anion provides the best compromise to achieve efficient catalysis.

Homogeneous gold catalysis has received considerable attention in recent years and great efforts have been made to optimize known reactions and find new catalytic applications.<sup>[1]</sup> Recently, in-depth kinetic and mechanistic studies on the gold(I)catalyzed nucleophilic addition to a carbon–carbon unsaturated bond have been published, with the aim to understand the ligand effect<sup>[2]</sup> and to isolate and characterize the intermediates involved in the catalytic cycle.<sup>[3,4]</sup> However, also the anion

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can influence the catalytic activity,<sup>[5]</sup> the regioselectivity,<sup>[6]</sup> and even the stereoselectivity<sup>[7]</sup> of the process. Moreover, it has been observed that the anion can influence the structure of the catalyst<sup>[8]</sup> and of the intermediates in the catalytic cycle.<sup>[9]</sup> Although the importance of the anion is well recognized, its role in each individual step of the reaction mechanism is still largely unknown. One of the crucial pieces of information that may contribute to the comprehension of such an effect is the relative orientation of the anion/cation in solution. In the past years, we studied the ion-pair structure of different [(L)Au(S)]X salts, where S is an unsaturated organic substrate (alkene or alkyne) and L represents a series of ligands commonly used in catalysis.<sup>[10,11]</sup> Our results showed that the position of the anion can be finely modulated by the choice both of the ligand L and the substrate S.<sup>[12]</sup>

The intermolecular alkoxylation of alkynes and similar reactions (hydration and hydrophenoxylation) are among the oldest applications of gold(I) catalyst.<sup>[13]</sup> From the seminal work of Teles,<sup>[14]</sup> several other studies on these classes of reaction have been published, in order to find highly active catalysts<sup>[15]</sup> and to shed more light on the reaction mechanism.<sup>[3b,16]</sup>

Maier and Zhdanko have shown that when the typical N-heterocyclic carbene [NHC, (1,3-bis(2,6-di-isopropylphenyl)-imidazol-2-ylidene)] is used as the ancillary ligand, the catalyzed addition of methanol to 3-hexyne is pseudo-zero order in relation to 3-hexyne and pseudo-first order in relation to methanol and the catalyst.<sup>[16a]</sup>

The gold metal fragment acts as a Lewis acid, coordinating 3-hexyne (Scheme 1, OSIP = outer sphere ion pair), which subsequently undergoes a nucleophilic attack from MeOH, with the formation of an organogold intermediate (Scheme 1, intermediate I). The gold—carbon bond in the intermediate is typically cleaved by a proton (protodeauration) to give the vinyl



Scheme 1. Steps in the alkoxylation of 3-hexyne with [(NHC)AuX].

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ether and regenerate the catalyst (Scheme 1, ISIP = inner sphere ion pairs).

The formation of vinyl ether is the key gold-catalyzed step, although the addition of the second molecule of methanol, leading to the final product (acetal), seems to be very fast<sup>[16b]</sup> and is considered to be a classical proton-catalyzed process.<sup>[16a]</sup> To the best of our knowledge, no systematic experimental data about the role of the anion are available. In this contribution, we analyze in detail the role of the anion in different steps of this catalytic cycle through a combined experimental/theoretical approach. The mechanistic framework is largely simplified if one chooses [(NHC)AuX] species as catalysts: the stability of the species [(NHC)Au(S)]X and the absence of gem-diaurated species [(NHC-Au)<sub>2</sub>S]X under the catalytic conditions are known.<sup>[16a]</sup> We have considered a series of anions with increasing coordination ability:<sup>[17]</sup> tetrakis(3,5-bis(trifluoro-methyl)phenyl)-borate (BARF<sup>-</sup>), tetrafluoroborate (BF<sub>4</sub><sup>-</sup>), trifluoromethanesulfonate (OTf<sup>-</sup>), p-toluensolfonate (OTs<sup>-</sup>), trifluoroacetate (TFA<sup>-</sup>) and acetate (OAc<sup>-</sup>).

All the catalysts [(NHC)AuX] (1X) were synthesized from [(NHC)AuCl] through anion metathesis procedures, but in the case of BARF<sup>-</sup> and BF<sub>4</sub><sup>-</sup> the complexes are not stable enough and so [(NHC)Au( $\eta^2$ -3-hexyne)]X complexes (1 BARF and **1**BF<sub>4</sub><sup>[18]</sup> respectively) have been used as catalysts (see the Supporting Information for details and characterization of new complexes).

The results for the alkoxylation of 3-hexyne with MeOH are shown in Figure 1 and Table 1.<sup>[19]</sup> The most active catalyst is complex 1OTs, followed by 1OTf, 1BF4, 1BARF, then 1TFA,



Figure 1. Rate of alkoxylation of 3-hexyne with [(NHC)AuX].

which led to complete conversion of 3-hexyne in 17, 33, 40, 48, and 266 min, respectively (entries 1, 4, 5, 6 and 7 in Table 1). The values of the turnover frequencies (TOF) are 5.6, 2.9, 2.4, 2.0, and 0.4 min<sup>-1</sup> for 1 OTs, 1 OTf, 1 BF<sub>4</sub>, 1 BARF, and 1TFA, respectively (Table 1). 1OAc does not show any catalytic activity.

Very surprisingly, the trend of the TOF values does not reflect the coordinating power<sup>[17]</sup> of the anions. Usually, when the first catalytic step involves competition between the substrate and the anion for the metal coordination vacancy,

Table 1. Alkoxylation of 3-hexyne with [(NHC)AuX].					
Entry	Conditions	Anion	Conv. [%]	t [min] <sup>[e]</sup>	TOF <sup>[f]</sup> [min <sup>-1</sup> ]
1	[a]	OTs <sup>-</sup>	99	17	5.6
2 <sup>[c]</sup>	[a]	OTs <sup>-</sup>	99	20	4.8
3 <sup>[d]</sup>	[a]	OTs <sup>-</sup>	99	22	4.3
4	[a]	OTf <sup>-</sup>	99	33	2.9
5	[a]	$BF_4^-$	99	40	2.4
6	[a]	BARF <sup>-</sup>	99	48	2.0
7	[a]	TFA <sup>-</sup>	99	266	0.4
8	[a]	$OAc^{-}$	0	-	-
9	[b]	OTs <sup>-</sup>	99	18	5.3
10	[b]	OTf <sup>_</sup>	99	47	2.0
11	[b]	$BF_4^-$	99	64	1.5
12	[b]	BARF <sup>-</sup>	99	89	1.1
[a] 30 °C, 3-hexyne (100 $\mu$ L), <b>1X</b> loading (1 mol%), CH <sub>3</sub> OH (143 $\mu$ L). [b] 30 °C, 3-hexyne (100 $\mu$ L), <b>1X</b> loading (1 mol%), CH <sub>2</sub> OD (143 $\mu$ L) in					

CDCl<sub>3</sub> (400 µL). [c] With 5% NBu<sub>4</sub>OTs as additive. [d] With 15% pTsOH as additive. Conversions were determined by <sup>1</sup>H NMR spectroscopy, using TMS as internal standard, as average of three runs. [e] Time for 95% conversion. [f] TOF = ([acetal]/[1 X])/t at 95% of conversion.

strongly coordinating anions reduce the catalytic activity.[20] Indeed, from the mechanism depicted in Scheme 1, we may expect that non-coordinating anions should maximize the catalytic rate. On the other hand, the trend of the TOF values does not reflect the basicity of the anions<sup>[21]</sup> towards the abstraction of the alcoholic proton of the methanol before or after the nucleophilic attack, either. As a matter of fact, the best performing anion, OTs-,[22] possesses intermediate coordinating and basicity properties in the considered series of counterions. To get a deeper insight into these intriguing results, we analyzed the effect of the anion in the ISIP/OSIP pre-equilibrium step (Scheme 1). The equilibrium [(NHC)AuX]+3hexyne $\leftrightarrow$ [(NHC)Au( $\eta^2$ -3-hexyne)]X between the ISIP and the OSIP (Scheme 1) is shifted to the right when weakly and noncoordinating  $OTf^-$ ,  $BF_4^-$ , and  $BARF^-$  anions are considered.<sup>[18]</sup> This means that the concentration of ISIP is constant during the reaction, leading to a linear profile of the conversion against time (Figure 1).

In contrast, for 1TFA (Figure 1), the reaction rate is not constant, but decreases after about 90 min. Recording the <sup>19</sup>F NMR spectrum of the reaction mixture at different reaction times, we observed the disappearance of a broad resonance at -74.8 ppm and the simultaneous formation of a sharp new resonance at -76.2 ppm (assigned to trifluoroacetic acid, TFAH, see the Supporting Information). Dissolving 1TFA in CDCl<sub>3</sub> with 400 equivalents of methanol, the same phenomenon is observed, with the total disappearance of the NMR signal corresponding to 1TFA within one hour. If 3-hexyne is added to the solution after three hours (at complete formation of TFAH), no catalytic activity was observed. These experimental results can be explained by assuming an acid-base reaction between TFA<sup>-</sup> and MeOH, giving TFAH and MeO<sup>-</sup>, which, in turn, probably poisons the catalyst by forming the catalytically inert [(NHC)Au(OMe)] species.[16]

For 1OAc, which shows no catalytic activity (Figure 1), the reaction with MeOH is very slow (30% of acetic acid in 48 h).

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In this case, the ISIP is predominant in solution owing to the strong coordinating ability of the anion (see the Supporting Information).

Finally, for the <sup>1</sup>H NMR spectra recorded during the catalysis with **1 OTs**, the resonances of the tosylate anion closely resemble those of NBu<sub>4</sub>OTs (see the Supporting Information), which indicates that the anion is not coordinated to the metal. As the pre-equilibrium is completely shifted toward the ISIP in absence of methanol (see the Supporting Information), we can surmise that methanol may help the de-coordination of the anion, probably through the formation of a hydrogen bond.<sup>[23]</sup> The importance of the pre-equilibrium step is demonstrated by the fact that the addition of an external salt, such as NBu<sub>4</sub>OTs (5%), reduces the TOF to 4.8 min<sup>-1</sup>, probably because of the shift of the ISIP/OSIP equilibrium toward the ISIP.

We have determined the order of reaction with respect to 1 OTs as first-order (see the Supporting Information). Note that the same order has been measured in the case of non-coordinating anions.<sup>[16a]</sup> Consequently, only one gold atom is involved in the rate-determining step (RDS) of the reaction. However, the RDS can be either the nucleophilic attack or the protodeauration (Scheme 1). Different catalytic conditions have been tested. In the presence of HOTs (15%), the reaction is decelerated and the TOF changes from 5.6 to 4.3 min<sup>-1</sup> (entries 1 and 3, Table 1). In addition, by using CH<sub>3</sub>OD instead of CH<sub>3</sub>OH, we observe a slight reduction in the TOF, which shifts from 5.6 to 5.3 min<sup>-1</sup> (compare entries 1 and 9, Table 1), giving a kinetic isotopic effect (KIE)^{[24]} equal to 1.1. For  $1\,OTf,\ 1\,BF_4,\ \text{and}$ 1BARF, the KIE was equal to 1.4, 1.6, and 1.8, respectively (entries 4 vs. 10, 5 vs. 11, and 6 vs. 12, Table 1). These values of KIE point out that, under our conditions, the turnover-limiting step is the nucleophilic attack of the methanol.<sup>[25]</sup> However, the small increase in the KIE on going from a more coordinating anion (OTs<sup>-</sup>) to a non-coordinating one (BARF<sup>-</sup>) may indicate that the importance of the protodeauration step in the mechanism increases from OTs<sup>-</sup> to OTf<sup>-</sup>, from OTf<sup>-</sup> to BF<sub>4</sub><sup>-</sup>, and from BF<sub>4</sub><sup>-</sup> to BARF<sup>-</sup>. In agreement with our findings, Zhdanko and Maier showed clearly that the reaction rate of the hydroalkoxylation of 3-hexyne by methanol (in methanol) is independent from the amount of acid, excluding the protodeauration as the rate-limiting step.<sup>[16a]</sup> We also note that the turnover-limiting step strongly depends on the reaction conditions and on the reactants. In a recent paper by Straub and co-workers,<sup>[26]</sup> a KIE of 3-5 is observed for the hydration of terminal alkyne conducted in methanol, and the group of Gagné and Widenhoefer reported a KIE of 5.3 for the gold-catalyzed intramolecular hydroalkoxylation of 2,2-diphenyl-4,5-hexadien-1-ol to a 2-vinyltetrahydrofuran derivative.<sup>[27]</sup> These authors suggest that protonolysis of the gold-carbon bond was the turnoverlimiting step in both cases.

From a computational point of view, the role of the anion has usually been recognized only in the protodeauration step,<sup>[28]</sup> where it acts as a "proton shuttle", or forms weak interactions with the substrate, in order to explain the enantioselectivity.<sup>[29]</sup> However, as the nucleophilic attack is the rate-determining step under our catalytic conditions, an active role of the anion is also expected within this step. We focused our study on the addition of the first methanol molecule, as we mentioned the addition of the second molecule of methanol is shown to be fast.<sup>[16b]</sup> We selected the complex [(NHC')AuOTs], (NHC' = 1,3-dimethylimidazol-2-ylidene) with 2-butyne and methanol as models for the catalyst, substrate, and nucleophile, respectively. In particular, we decided to investigate the OTs<sup>-</sup> anion because, unexpectedly, it is the most efficient in spite of its stronger coordinating ability with respect to BF<sub>4</sub><sup>-</sup> and BARF<sup>-</sup>. According to recent benchmark papers, we used density functional theory (DFT) in combination with the BP86 exchange-correlation functional to optimize the geometries and the double-hybrid functional B2PLYP to compute the corresponding energy.<sup>[30,31]</sup>

For the pre-equilibrium state, the electronic energy of the complex [(NHC')AuOTs]·(2-butyne) is 3.6 kcal mol<sup>-1</sup> lower than that of  $[(NHC')Au(\eta^2-2-butyne)]OTs$ , a fact that indicates that the alkyne substitution of the coordinated OTs<sup>-</sup> is somewhat unfavorable. Interestingly, when one molecule of methanol is introduced into the system, the difference between [(NHC')AuOTs]·(2-butyne)·(MeOH) (A\_ISIP) and [(NHC')Au( $\eta^2$ -2butyne)]OTs•(MeOH) (A\_NR) lowers to 1.8 kcalmol<sup>-1</sup> thanks to hydrogen-bond formation between the methanol and the anion ( $O_{OTs}$ - $H_{MeOH}$ =1.722 Å). In the **A\_NR** configuration, the anion weakly interacts with the gold (Au-O<sub>OTs</sub>=3.133 Å) and the methanol is positioned nearly over the gold. However, a different local minimum configuration has been found, with the methanol still interacting with the anion, but located at the opposite side of the alkyne with respect to the gold (A\_RC, Au– $O_{OTs}$  = 3.283 Å,  $O_{OTs}$ – $H_{MeOH}$  = 1.780 Å). The energy of **A\_RC** is only 0.9 kcal mol<sup>-1</sup> higher than that of **A\_NR** (Figure 2). **A\_RC** is a particularly suitable reactant complex configuration for the anti-periplanar addition of the nucleophile, which is the most favored mechanism according to previous studies.<sup>[32]</sup>

Starting from A\_RC, the methanol can approach the carbon atom coordinated to the gold, passing through a transition state (**TS\_attack**) with an activation barrier of 15.6 kcal mol<sup>-1</sup> (computed with respect to A\_RC). Note that on removing the anion from the catalytic cycle, the  $\sigma$ -coordinated gold(I) vinyl ether (B-like structure of Figure 2) is not stable. In the transition-state geometry, the distance between the methanol and the carbon atom is 2.084 Å (Figure 2, right), with the anion facilitating the attack in two ways: it acts as a template, keeping the reactive methanol molecule in the right position for addition, and, simultaneously, it "activates" the nucleophile through a hydrogen bond that is shorter than in  $A_RC$  ( $O_{OTS}-H_{MeOH}=$ 1.538 Å). The product of the attack is a metal  $\sigma$ -coordinated vinyl ether (B), with the hydrogen atom of the methanol completely transferred to the anion  $(O_{OTs}-H_{MeOH}=1.035 \text{ Å})$ , giving a neutral molecule of *p*-toluenesulfonic acid. The acid easily donates its hydrogen atom to the carbon coordinated to the gold (TS\_proto), thereby acting as an efficient proton shuttle between the methanol and the substrate (activation barrier 4.7 kcalmol<sup>-1</sup> with respect to **B**). The product of the protodeauration step is a  $\pi$ -coordinated vinyl ether (C). In C, the gold is not equidistant from the two carbon atoms, but instead is further away from the carbon that underwent the nucleophilic attack (Au-C2=2.209 Å, Au-C1=2.430 Å). The same

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Figure 2. Left: DFT-calculated profile for the reaction between 2-butyne and methanol, catalyzed by (NHC')AuOTs. The structures of the species are also shown. The protons of 2-butyne have been omitted for clarity. Right: Geometric structure of **TS\_attack**, with relevant distances [Å].

asymmetry has been experimentally observed, too.<sup>[33]</sup> Finally, the vinyl ether can de-coordinate and be substituted by another molecule of alkyne.<sup>[34]</sup>

From the structure of **TS\_attack**, the experimentally observed anion effect (Figure 1) can be rationalized on the basis of the coordinating and basicity properties of the different anions. The most important factor seems to be the ability to abstract the proton from the methanol, and this ability is proportional to the anion basicity. Consistent with this picture, the performances of **1BF**<sub>4</sub> and **1BARF** are worse than that of **1OTs** because such anions have more difficulty forming the corresponding acids HBF<sub>4</sub> and HBARF. On the other hand, too high coordination or basicity power of the anion worsens the catalytic performance, preventing alkyne coordination (as in the case of OAc<sup>-</sup>) or forming too much free MeO<sup>-</sup> in solution, which poisons the catalyst (as in the case of TFA<sup>-</sup>).

In conclusion, we have shown that the anion properties, both coordination ability and basicity, have a great and underevaluated impact on the catalytic performance of gold complexes, and the "classical" non-coordinating anions (such as BF<sub>4</sub><sup>-</sup>) may be not always the best choice. Intermediate coordinating and basicity power of the anion OTs<sup>-</sup> provides, under the specific experimental conditions employed, the best compromise to achieve an efficient catalyst: the pre-equilibrium with this anion is shifted toward the OSIP, deactivation of catalyst to a gold-methoxide is prevented, and its characteristic basicity promotes the nucleophilic attack. This study clearly demonstrates that the anion can play an effective role in different steps of the catalytic cycle, including the overall important nucleophilic attack.<sup>[35]</sup> A more comprehensive study, both computational and experimental (including high-throughput experimentation methods), of the anion's role in the mechanistic steps are clearly required and are underway in our laboratory.

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Unexpected Anion Effect in the Alkoxylation of Alkynes Catalyzed by N-Heterocyclic Carbene (NHC) Cationic Gold Complexes



6

**Goldilocks and the six anions**: The role of the anion in the intermolecular alkoxylation of alkynes catalyzed by [(NHC)AuX] is analyzed with a combined experimental and theoretical approach. The anion plays a role in the abstraction of the proton from the methanol during the nucleophilic attack, in the coordination of alkyne, and in the deactivation of the catalyst. Intermediate coordinating power and basicity of the OTs<sup>-</sup> anion gives the best catalytic performance.

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