

Toward Optimizing the Performance of Homogeneous L-Au-X Catalysts through Appropriate Matching of the Ligand (L) and Counterion (X[−])

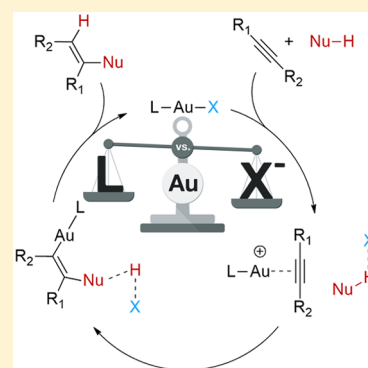
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S Supporting Information

ABSTRACT: The effects of the ligand (L) and counterion (X[−]) are considered the two most important factors in homogeneous gold catalysis, but a rational understanding of their synergy/antagonism is still lacking. In this work, we synthesized a set of 16 gold complexes of the type L-Au-X that differ as follows: (i) L = PPh₃ (**L1**), P(^tBu)₃ (**L2**), tris(3,5-bis(trifluoromethyl)phenyl)phosphine (PArF, **L3**), and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (NHC, **L4**), with the deliberate purpose of varying the electron withdrawing ability of the ligand, and (ii) X[−] = BF₄[−], OTf[−], OTs[−], and TFA[−], which have various coordinating abilities, basicities, and hydrogen bond acceptor powers. All these catalysts were tested in two different model reactions: the cycloisomerization of *N*-(prop-2-ynyl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline and the methoxylation of 3-hexyne. The main results are that the choice of the most efficient L-Au-X catalyst for a given process should not be made by evaluating the properties of L and X[−] alone, but rather based on their best combination. For NHC-Au-X, the noncoordinating and weakly basic anions (such as BF₄[−] and OTf[−]) have been recognized as the best choice for the cycloisomerization of *N*-(prop-2-ynyl)benzamide. On the other side, the intermediate coordinating ability and basicity of OTs[−] provide the best compromise for achieving an efficient methoxylation of 3-hexyne. A completely different trend is found in the case of complexes bearing phosphanes: OTs[−] and TFA[−] have been found to accelerate the cycloisomerization of *N*-(prop-2-ynyl)benzamide, and BF₄[−] and OTf[−] are suitable for the methoxylation of 3-hexyne. A possible explanation of the observed differences between phosphane and NHC ancillary ligands might be found in the higher affinity of the counterion (especially OTs[−]) for the gold fragment for phosphane instead of NHC.



INTRODUCTION

In recent years, homogeneous gold catalysis has received considerable attention and represents a fast growing area of organic chemistry.¹ Most of these reactions can be classified as nucleophilic additions to a carbon–carbon unsaturated bond promoted by L-Au-X compounds (L = an ancillary ligand, and X[−] = a counterion). In essentially all the proposed mechanisms, the gold metal fragment L-Au-X [inner sphere ion pair (ISIP)] acts as a Lewis acid coordinating unsaturated hydrocarbons, i.e., alkyne, in the pre-equilibrium step [Scheme 1, intermediate I, outer sphere ion pairs (OSIP)] that subsequently undergoes nucleophilic attack by a nucleophile (Nu-H), with the formation of organogold intermediates (Scheme 1, intermediate II). The gold–carbon bonds in these intermediates are typically cleaved by a proton, protodeauration, to give the desired products and regenerate the catalyst (Scheme 1). In-depth kinetic and mechanistic studies of gold(I)-catalyzed nucleophilic addition to a carbon–carbon unsaturated bond have been appearing in the literature,² with a goal of understanding the ligand effects in the different steps of the catalytic cycle.³ The ligand electronic structure, in particular its electron donating ability, modulates the

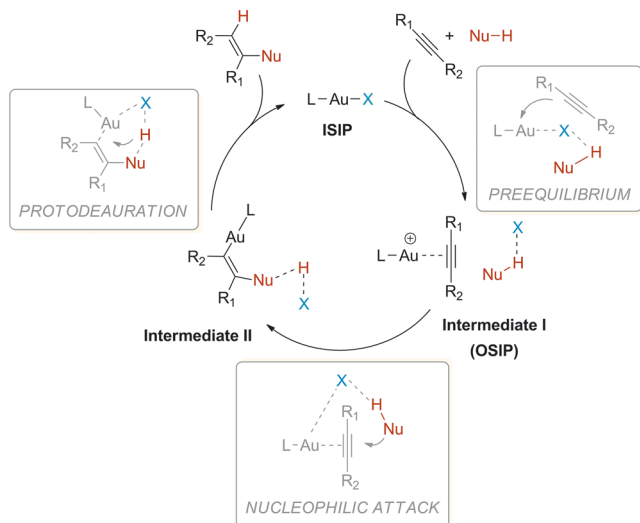
acidic character of the metal fragment in the catalytic cycle and affects the stability of the postulated intermediates^{4,5} (alkene/alkyne gold complexes,⁶ vinyl gold compounds,⁷ carbene gold complexes,⁸ and more or less delocalized carbocationic⁹ complexes).

On the other hand, the anion plays an important role in gold catalysis, influencing the catalytic activity,¹⁰ the regioselectivity,¹¹ and even the stereoselectivity¹² of the process. Moreover, it has been well established that the structures of the catalyst¹³ and the intermediates¹⁴ are affected by the counterion.^{6,15} Even if several experimental data concerning the “counterion effect” in gold catalysis have been published,¹⁶ its rationalization is still far from being fully obtained, but the idea that coordination ability and basicity of the counterion may have a great impact on the catalytic performance of gold complexes is now accepted.¹⁶ With respect to this topic, very recently, we^{17,18} and others¹⁹ studied the Au-catalyzed intermolecular methoxylation^{20,21} of alkynes and proposed that the nucleophilic attack of methanol is assisted

Received: April 13, 2015

Published: April 24, 2015

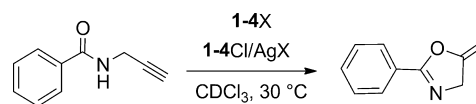
Scheme 1. Proposed Gold Catalytic Cycle



by the anion through the formation of a hydrogen bond. Thus, it is not only a “proton shuttle”, as proposed previously.²²

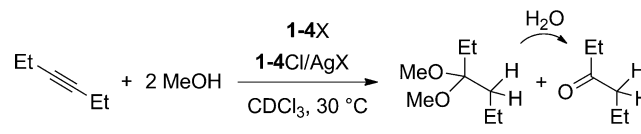
Regardless, both the nature of the ligand^{23,24} and counterion effects are considered the two important factors in gold catalysis, but a rational understanding of their synergy/antagonism is still lacking.

For this reason, we synthesized a set of 16 gold complexes of the type L-Au-X (Scheme 2), differing as follows: (i) L = PPh₃ (L1), P(^tBu)₃ (L2), tris(3,5-bis(trifluoromethyl)phenyl)phosphine (PArF, L3), and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (NHC, L4), with the deliberate purpose of varying the electron withdrawing ability of the ligand, and (ii) X[−] = BF₄[−], OTf[−], OTs[−], and TFA[−], which show various coordinating abilities and basicities.²⁵ All these complexes were tested as catalysts in two different model reactions: the cycloisomerization of *N*-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline (catalysis A, Scheme 3),²⁶ in which the

Scheme 3. Catalysis A, Cycloisomerization of *N*-(Prop-2-ynyl)benzamide to 2-Phenyl-5-vinylidene-2-oxazoline

rate-determining step (RDS) is the protodeauration step,³ and the methoxylation of 3-hexyne in chloroform (catalysis B, Scheme 4), in which the RDS is the nucleophile attack on the

Scheme 4. Catalysis B, Methoxylation of 3-Hexyne in Chloroform



alkyne.^{17,19} Thus, we conducted 16 × 2 independent catalytic tests to assess the best/worst ligand/counterion combination, if any, for both catalytic processes.

Notably, we have found that the catalytic activity of a given L-Au-X complex is strictly related to the L/X[−] combination. In particular, the best settings for catalysis A are PPh₃/OTs[−], P(^tBu)₃/OTs[−], and P(^tBu)₃/TFA[−], while the worst are PArF/TFA[−] and NHC/OTs[−]. Furthermore, for catalysis B, superlative combinations are represented by P(^tBu)₃/OTf[−] and NHC/OTs[−], while PPh₃/TFA[−], P(^tBu)₃/TFA[−], and PArF/TFA[−] have been found to be the poorest.

Thus, in fact, the choice of the most efficient L-Au-X catalyst for a given process should not be made by evaluating the properties of L and X[−] alone, but rather on the basis of their best combination. Most simply, L and X[−] factors must be taken into account together.

Scheme 2. Complete Set of Gold Catalysts Used in This Work^a

L \ X [−]				
BF ₄ [−]	1BF ₄ [a]	2BF ₄ [a]	3BF ₄ [a]	4BF ₄ [a]
	1OTf [a]	2OTf [a]	3OTf	4OTf [17]
	1OTs [28]	2OTs	3OTs	4OTs [17]
F ₃ C-COO [−]	1TFA [29]	2TFA	3TFA	4TFA [17]

^aGenerated *in situ*.

RESULTS AND DISCUSSION

Synthesis and Characterization of Gold Catalysts.

Neutral compounds 3,4OTf, 1–4OTs, and 1–4TFA (Scheme 2) were synthesized according to a literature procedure (see the Supporting Information for details). Novel complexes 2OTs, 2TFA, 3OTf, 3OTs, and 3TFA have been isolated in high yield by reacting 2Cl or 3Cl precursors with a slight excess of the appropriate silver salt. All the proton and carbon resonances belonging to the different fragments were assigned via ^1H , ^{13}C , ^{19}F , and ^{31}P NMR spectroscopy (see the Supporting Information). With regard to complexes 2X, the coordination of OTs $^-$ or TFA $^-$ to the $[(\text{L}2)\text{Au}]^+$ fragment causes a deshielding of the ^{31}P resonance from 96.5 ppm (2Cl) to 89.1 ppm (2OTs) and 87.4 ppm (2TFA). A similar behavior was observed for complexes 3X; thus, the ^{31}P NMR resonance changes from 36.8 ppm (3Cl) to 30.5 ppm (3OTf), 32.4 ppm (3OTs), and 30.7 ppm (3TFA). These variations in the ^{31}P chemical shift with respect to 1Cl were previously observed for 1OTf, 27 1OTs, 28 and 1TFA 29 (see the Supporting Information).

Catalysis. All complexes 1–4X (Scheme 2, $\text{X}^- = \text{BF}_4^-$, OTf $^-$, OTs $^-$, and TFA $^-$) have been tested as catalysts in catalysis A (Scheme 3 and Table 1). The isolated species were employed in

Table 1. Gold(I)-Catalyzed Cyclization of *N*-(Prop-2-ynyl)benzamide a

entry	catalyst	time (min)	conversion b (%)	TOF b (min $^{-1}$)
1	1BF $_4$	114	>98	1.88
2	2BF $_4$	84	>98	1.94
3	3BF $_4$	120	55	1.25
4	4BF $_4$	99	>98	1.86
5	1OTf	120	78	1.40
6	2OTf	120	83	0.92
7	3OTf	120	50	0.74
8	4OTf	120	89	1.29
9	1OTs	63	>98	4.16
10	2OTs	40	>98	3.67
11	3OTs	120	53	0.76
12	4OTs	120	65	0.84
13	1TFA	120	63	1.07
14	2TFA	73	>98	3.89
15	3TFA	120	22	0.13 d
16	4TFA	120	56	0.54

a Catalysis A conditions: 30 $^\circ\text{C}$, *N*-(prop-2-ynyl)benzamide (80 mg, 0.5 mmol), 1 mol % catalyst (or 1:1 L-Au-Cl/AgX) in CDCl_3 (500 μL). b Conversions and TOF $_i$ determined by ^1H NMR spectroscopy as the average of three runs. c TOF $_i = (n_{\text{product}}/n_{\text{catalyst}})/\text{time}$ (at 30% conversion). d To calculate the TOF $_i$ value, the catalytic process was followed until 30% conversion was reached.

the case of all *p*-toluenesulfonates, trifluoroacetates, and 3–4OTf, whereas in all other cases, the catalyst was prepared *in situ* in a NMR tube by mixing equimolar amounts of precursor 1–4Cl and the appropriate silver salt in CDCl_3 .

A typical catalytic run was performed by mixing *N*-(prop-2-ynyl)benzamide in the presence of 1 mol % catalyst (or 1:1 L-Au-Cl/AgX) at 30 $^\circ\text{C}$ in CDCl_3 . The progress of the reaction was monitored by NMR spectroscopy (see the Supporting Information for details). Quantitative (>98%) conversion of the substrate into 2-phenyl-5-vinylidene-2-oxazoline was reached in 114, 84, and 99 min by using 1BF $_4$, 2BF $_4$, and 4BF $_4$, respectively (Table 1, entries 1, 2, and 4). Much less efficiently,

3BF $_4$ promoted the formation of the reaction product in only 55% yield after 120 min (Table 1, entry 3).

By changing the anion from BF $_4^-$ to OTf $^-$, we observed a slight decrease in the catalytic efficiency for all the catalysts (Table 1, entries 5–8 vs entries 1–4). Again, the complex bearing PARf (3OTf) proved to be the less active catalyst within the series 1–4OTf (Table 1, entry 7).

To verify that “silver effects” 30 are negligible under our catalytic conditions, isolated 1OTf was also employed as catalyst giving similar conversion of 1Cl/AgOTf (see Table S1 of the Supporting Information).

Using a more basic and coordinating anion such as OTs $^-$, very different catalytic performances were observed within the series 1–4OTs. Thus, a complete conversion was obtained in the case of 1OTs and 2OTs after 63 and 40 min, respectively (Table 1, entries 9 and 10). On the other hand, 3OTs and 4OTs gave performances comparable to that of 3OTf (Table 1, entries 7, 11, and 12). It is worth noting that the catalytic activity of 4OTs is very similar to that of 3OTs, while when the anion is BF $_4^-$, 4BF $_4$ shows the same high efficiency of 1BF $_4$ and 2BF $_4$, different from that of 3BF $_4$ (Figure 1).

Finally, in the case of TFA $^-$, the most coordinating and basic anion of the four screened in this work, generally low catalytic performances were observed, with the exception of 2TFA, which

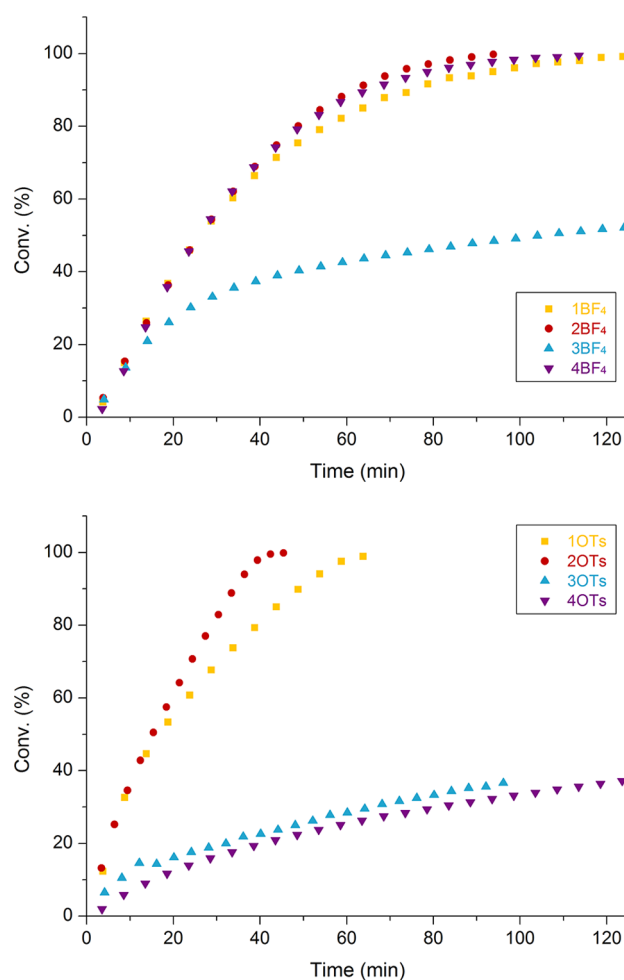


Figure 1. Catalysis A performed by 1–4BF $_4$ (top) and 1–4OTs (bottom) complexes.

allows complete formation of 2-phenyl-5-vinylidene-2-oxazoline in a short reaction time.

Comparing the value of the initial turnover frequency, TOF_i (Table 1 and Figure 2), one can see that for catalysts bearing

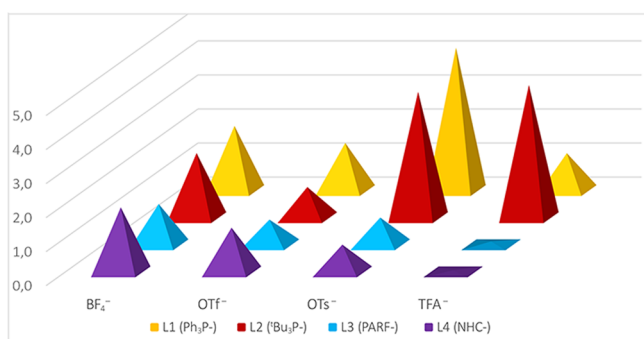


Figure 2. TOF_i values for catalysis A promoted by 1–4X ($X^- = \text{BF}_4^-$, OTf^- , OTs^- , and TFA^-).

triphenylphosphane (Table 1, entries 1, 5, 9, and 13) the best anion is OTs^- followed, in order, by BF_4^- , OTf^- , and TFA^- . The range of TOF_i values varies from 1.07 to 4.16 min^{-1} . With the exception of 2TFA, an analogous trend can be observed for catalysts 2X (Table 1, entries 2, 6, and 10). Different from 1TFA, complex 2TFA exhibits approximately the same high performance as 2OTs, their TOF_i values being 3.67 and 3.89 min^{-1} , respectively. By contrast, for 3X and 4X series, the catalytic activity decreases following exactly the increasing basicity of the anion. In fact, the TOF_i values are 1.25, 0.74, 0.76, and 0.13 min^{-1} for 3 BF_4 , 3 OTf , 3 OTs , and 3TFA, respectively, and 1.86, 1.29, 0.84, and 0.54 min^{-1} for 4 BF_4 , 4 OTf , 4 OTs , and 4TFA, respectively.

The cycloisomerization of *N*-propargylcarboxamides is a well-studied gold-catalyzed reaction in which protodeauration is considered the slow step (Scheme 1).^{3a–d} A pseudo-first-order kinetics with respect to the catalyst concentration is observed,³¹ and the key vinyl gold intermediate (Scheme 1, intermediate II) has been identified in the case of $\text{NHC-Au(I)}^{26c,d}$ and $\text{PPh}_3\text{-Au(I)}^{2,31}$ by the groups of Hashmi and Hammond, respectively, and by Ahn³² and co-workers in the case of gold(III). These observations make us believe that the formation of the vinyl gold complex (intermediate II) is not the rate-determining step.

In intermediate II, the gold–carbon bond is cleaved by a proton (protodeauration, RDS) to give the final product and regenerate the catalyst (Scheme 1, ISIP). Accordingly, it was found that the additives that are good hydrogen bond acceptors increase the efficiency of this reaction, because they can act as a proton shuttle.³³

To confirm that the organogold intermediate is actually present in our catalytic mixture, ³¹P NMR spectra have been recorded during the catalysis for complexes 1–3X ($X^- = \text{BF}_4^-$, OTf^- , OTs^- , and TFA^-). ³¹P NMR monitoring indicated that the resting state for the gold catalyst is a vinyl gold complex, intermediate II. At high conversions, also the coordination of the product is observed (see the Supporting Information for details). Therefore, it is reasonable to assume that the protodeauration step is slow, and consequently, it is the RDS for all 1–4X catalysts under our reaction conditions (Table 1).

In the literature, it is suggested that two important factors should be taken into account to rationalize the activity of L–Au–X compounds: (i) the breaking of the Au–C bond, which is related to the nature of the ligand L,^{2,34} and (ii) the ability of the

counterion to promote the proton shuttle,²² which is related to the acid–base nature³⁵ and hydrogen bond acceptor powers of X^- .³³

With regard to the first point, if we compare the results obtained using 1–4 BF_4 catalysts (BF_4^- is a poor basic and noncoordinating anion³⁶) we observe that compound 3 BF_4 , bearing the most electron-withdrawing ligand (PARF), is by far the worst catalyst within the series (Table 1, entry 3 vs entries 1, 2, and 4), presumably because it renders the Au–C bond more stable.³ On the other hand, 1 BF_4 , 2 BF_4 , and 4 BF_4 showed higher activity, but with almost negligible differences in their performance.³⁷

To verify the importance of the acid–base nature and hydrogen bond acceptor powers of the counterion (second point), we can consider the series of complexes 4X ($X^- = \text{BF}_4^-$, OTf^- , OTs^- , and TFA^-). It can be seen that the catalyst activity is related to the basic strength of the anion (Table 1, entries 4, 8, 12, and 16). Performances of the catalysts decrease gradually with the increasing basicity and hydrogen bond acceptor power of X^- (basic strength: $\text{BF}_4^- < \text{OTf}^- < \text{OTs}^- < \text{TFA}^-$). The plausible scenario for 4X is that anions that are too basic with higher hydrogen bond acceptor powers (OTs^- and TFA^-) do not easily release the proton to gold, thus slowing the reaction rate.

In the case of phosphane complexes 1–2X ($X^- = \text{OTf}^-$, OTs^- , and TFA^-), the catalytic activity of each compound follows the basicity scale of X^- , and medium to highly basic and hydrogen bond acceptor OTs^- and TFA^- anions give better results (Table 1, entries 9, 10, 13, and 14).

A possible explanation can be found in the coordination properties (affinity) of medium to highly coordinative OTs^- and TFA^- anions toward Au.³⁸

In the case of complexes 1X and 2X, the best anions are by far OTs^- and TFA^- , respectively, probably because during the proton shuttle the anion can interact with the Au atom. This interaction weakens both Au–C and H–X bonds simultaneously, accelerating the reaction (Scheme 1, protodeauration). A similar trend was recently observed by Xu and Hammond.³³ They observed that the addition of NaOTs or HCOONa to a catalytic chloroform solution of 1OTf and *N*-propargylcarboxamides enhances the catalytic performance 3.9- and 1.4-fold, respectively. Unlike OTs^- , there are not many examples in gold catalysis in which TFA^- becomes the best choice.^{11d}

Finally, the behavior of 3X is similar to that of the related NHC complexes (4X). In this case, the interionic structure of OSIP [$\text{PARF-Au(2-hexyne)BF}_4$] shows that the anion has a strong tendency to interact with the highly positively charged *ortho* proton of the aryl fragment (3,5- $\text{CF}_3\text{-C}_6\text{H}_3$) rather than with the gold atom.^{14b} This evidence suggests that Au...X interaction is less probable during protodeauration.

On the basis of all these observations, a general trend can be drawn as follows. When the coordination of the anion to gold during the protodeauration step (Scheme 1) is not favored, the catalytic performances follow the basicity of the anion. This is the case for complexes 3X and 4X (Figure 2). As a confirmation, the interionic structure of $\text{NHC-Au(3-hexyne)BF}_4$ OSIP, determined by a ¹⁹F–¹H HOESY experiment and explained by the DFT calculation of Coulomb potential, suggests that the counterion does not easily interact with the gold fragment.^{14d} On the other hand, when coordinated of X^- to gold is possible, a balance between basicity and hydrogen bond acceptor power versus coordination ability of the anion is observed. This is the case for complexes 1X and 2X, where the ion pair structures of

strictly related compounds **L1**-Au-(η^2 -Me-styrene)BF₄ and **L2**-Au-(η^2 -3-hexyne)BF₄ suggest that the counterion can interact with the gold atom.^{14a,c}

The results presented here show that the anion properties, both coordination ability and basicity (hydrogen-bond acceptor power), have a great impact on the “proton shuttle ability”²² of the counterion, and more importantly, this ability depends on the ligand **L** present in the cationic gold fragment.

In summary, the catalytic results obtained studying the gold-catalyzed cycloisomerization of *N*-(prop-2-ynyl)benzamide show that ligands with weaker electron withdrawing ability generally accelerate the reaction, but the exact order cannot be trivially anticipated because of the match/mismatch of ligand and anion properties. Taking into account the most used catalysts **1X** and **4X**, we can conclude that the intermediate coordinating ability and hydrogen bond power of OTs[−] provide the best results within the **1X** series (PPh₃ ligand), while BF₄[−] or OTf[−] is the best choice for the **4X** series (NHC ligand).

Very recently, we¹⁷ and others¹⁹ found a complete inverse trend for the intermolecular alkoxylation of 3-hexyne with methanol: whereas OTf[−] is the best compromise for PPh₃, OTs[−] is the most suitable anion for NHC-containing catalysts. To complete and rationalize these findings, complexes **1–3X** (Scheme 2) have been tested as catalysts in catalysis B (Scheme 4 and Table 2) under the same experimental conditions

Table 2. Gold(I)-Catalyzed Methoxylation of 3-Hexyne in Chloroform

entry	catalyst	time (min)	conversion ^b (%)	TOF _i ^{b,c} (min ^{−1})
1	1 BF ₄	120	36	0.31
2	2 BF ₄	118	>98	2.72
3	3 BF ₄	120	>98	1.43
4	4 BF ₄	42	>98	2.86 ¹⁷
5	1 OTf	120	84	0.97
6	2 OTf	61	>98	5.84
7	3 OTf	52	>98	3.45
8	4 OTf	33	>98	3.46 ¹⁷
9	1 OTs	120	70	0.69
10	2 OTs	120	82	2.43
11	3 OTs	120	94	2.37
12	4 OTs	18	>98	5.06 ¹⁷
13	1 TFA	120	5	0.05 ^d
14	2 TFA	120	4	0.04 ^d
15	3 TFA	120	1	0.03 ^d
16	4 TFA	120	72	0.60 ¹⁷

^aCatalysis B conditions: 30 °C, 3-hexyne (100 μL, 0.88 mmol), 1 mol % catalyst (or 1:1 **L**-Au-Cl/AgX), CH₃OH (143 μL, 4 equiv), in CDCl₃ (400 μL). ^bConversions and TOF_i determined by ¹H NMR spectroscopy as the average of three runs. ^cTOF_i = (*n*_{product}/*n*_{catalyst})/time (at 30% conversion). ^dTo calculate the TOF_i value, the catalytic process was followed until 30% conversion was reached.

described previously.¹⁷ A typical catalytic run was performed by mixing 3-hexyne and methanol in the presence of the active catalyst (X[−] = OTs[−] and TFA[−]) or the catalyst precursor **1–3**Cl and the appropriate silver salt (X[−] = BF₄[−] and OTf[−]), at 30 °C in CDCl₃. In Table 2, the already published results¹⁷ concerning complexes **4X** have been added for useful comparison.

This reaction occurs at room temperature and can be conveniently monitored by NMR spectroscopy (see the Supporting Information for details). Under these conditions, it is known that the enol–ether intermediate, resulting from the

first attack of methanol on 3-hexyne, is very reactive and quickly undergoes the attack of a second molecule of methanol, leading to the formation of 3,3-dimethoxyhexane. It should be noted also that 3-hexanone, arising from 3,3-dimethoxyhexane hydrolysis due to traces of water, was detected in solution.

Complexes **2**BF₄ and **3**BF₄ promoted full conversion of the precursors within 120 min (Table 2, entries 2 and 3), whereas catalyst **1**BF₄ in the same reaction time promoted only 36% conversion (Table 2, entry 1).

When the catalytic process was conducted using **1–3**OTf as the catalysts, an overall neat increase in the reaction rate was observed. Again, the complex bearing PPh₃ (**1**OTf) gave the poorest result, as only 84% conversion was reached within 120 min. By contrast, the reaction catalyzed by **2**OTf and **3**OTf reached full conversion in 61 and 52 min, respectively (Table 2, entries 5–7).

When OTf[−] is replaced with a more coordinating and basic anion such as OTs[−], lower activity was exhibited by all catalysts (**1–3**OTs). Thus, 70, 82, and 94% conversions were recorded for **1**OTs, **2**OTs, and **3**OTs, respectively, after a reaction time of 120 min (Table 2, entries 9–11, respectively).

Finally, using TFA[−] as a counterion, the reaction rate for all catalysts **1–3**TFA slowed further, and only small amounts of product (<5%) were detected after 120 min (Table 2, entries 13–15).

Comparing the values of initial turnover frequency TOF_i (Table 2 and Figure 3), one can observe that all complexes

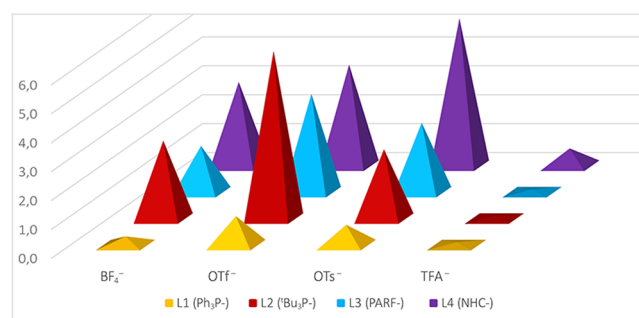


Figure 3. TOF_i values for catalysis B promoted by **1–4X** (X[−] = BF₄[−], OTf[−], OTs[−], and TFA[−]).

bearing phosphanes (**1–3X**) follow the same trend, although with different magnitudes. While only a slight difference has been observed upon replacement of BF₄[−] with OTs[−], OTf[−] derivatives showed a 2–3-fold increase in catalytic activity. **1–3**TFA are the worst catalysts, as judged by their extremely low TOF_i values. On the other hand, complexes **4X** follow a different trend,¹⁷ as the performance increases upon going from BF₄[−] to OTf[−] and then to OTs[−], but it finally collapses in the case of TFA[−] (entries 4, 8, 12, and 16 in Table 2 and Figure 3).

The alkoxylation of alkynes has been deeply studied by several groups,³⁹ and the accepted mechanism is shown in Scheme 1. In the presence of certain phosphanes, the formation of the gem-diaurated species⁴⁰ was observed, which causes a different kinetic profile of the reaction for different **L** ligands. The detailed study of the kinetic profile has led to the conclusion that, in the catalytic cycle, only one gold atom is involved and that the RDS of the reaction is the attack of methanol on the ISIP (Scheme 1) for both phosphane and NHC ligands.^{17,19} A notable anion effect was observed, particularly in the initial steps of the reaction: pre-

equilibrium ISIP–OSIP and activation of methanol during the nucleophile attack (Scheme 1).^{17,19}

In the nucleophilic attack step, the anion acts as a template, holding the methanol in the right position for the outer sphere attack and as a hydrogen bond acceptor, improving the nucleophilicity of the attacking methanol.

In particular for NHC complexes, the intermediate coordinating ability and basicity of OTs[−] afford the best compromise for achieving an efficient catalyst. Thus, in the presence of this anion, the pre-equilibrium is shifted toward the OSIP and its characteristic basicity promotes the nucleophilic attack (much better than less basic BARF[−] {tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate}, BF₄[−], and OTf[−] anions). With regard to 1X, it has been found that OTf[−] is the best anion, and it has been suggested that OTs[−] is too coordinating to 1⁺, reducing the amount of OSIP in solution.¹⁹

Via analysis of our results, it should be noted that for all 1–4X complexes the catalytic performances improve upon replacement of BF₄[−] with OTf[−], as expected, because of the higher basicity and hydrogen bond acceptor powers of the latter. However, if the basicity of the anion is further increased (OTs[−]), opposite trends in the function of the ligand L can be observed. Thus, while a decrease in catalytic efficiency was measured for all species bearing phosphanes (1–3), a significant increase was obtained for NHC.

To understand these differences, at first we deeply investigated the ISIP–OSIP equilibrium (Scheme 1) during the reaction, recording ³¹P NMR spectra at different reaction times. We found that OTs[−] tends to re-enter gradually in the first coordination sphere of gold (ISIP) while the reaction proceeds and the amount of alkyne and methanol is decreasing (Figure 4 and the

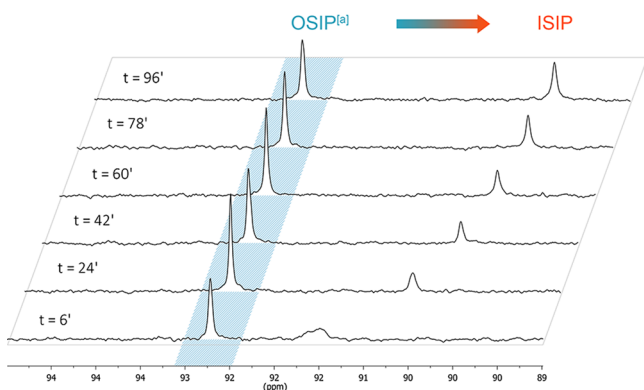


Figure 4. ³¹P NMR spectra recorded at different reaction times for catalysis B conducted with 2OTs. [a] and/or gem-diaurated.^{39a}

Supporting Information). We can ascribe the different catalytic behavior observed for 1–3OTs, with respect to that of 4OTs, to the higher coordination power of OTs[−] when phosphanes rather than NHC are bound to gold. However, it is also possible that OTs[−] shows a different ability to act as a template (holding the methanol for the outer sphere attack and as a hydrogen bond acceptor) when NHC is replaced with phosphanes.

Finally, the very strong tendency of TFA[−] to coordinate to gold and its high basicity deeply undermine catalyst efficiency for all species bearing phosphanes (1–3), preventing alkyne coordination and forming free MeO[−] in solution, which poisons the catalyst (Supporting Information) as observed for 4X.^{17,18}

CONCLUSION

From the results reported here, it is evident that the correct choice of the ligand L, to improve the performances of L–Au–X complexes in catalysis, strongly depends on the nature of the anion X[−] and vice versa.

For NHC compounds, noncoordinating and weakly basic anions (such as BF₄[−]) may be the best choice for a reaction in which the RDS is protodeauration, as in the case of the cycloisomerization of *N*-propargylcarboxamides. On the other side, the intermediate coordinating ability, basicity, and hydrogen bond acceptor property of OTs[−] provide the best compromise for achieving an efficient catalyst in the methoxylation of 3-hexyne, where the RDS is the nucleophilic attack helped by the counterion. In the case of complexes bearing phosphanes, a completely different behavior has been outlined. Thus, an intermediate to high coordination ability of the anion combined with its relatively high basicity and hydrogen bond acceptor property (OTs[−] and TFA[−]) has been found to accelerate the cycloisomerization of *N*-(prop-2-ynyl)benzamide. Instead, a medium to low coordination power and a weak basicity of the anion (BF₄[−] and OTf[−]) are suitable for the methoxylation of 3-hexyne. A possible explanation can be found in the higher affinity of the counterion (especially OTs[−]) for the gold fragment when the ancillary ligand L is a phosphane with respect to NHC: a higher gold affinity accelerates the reaction in which the RDS is the protodeauration but inhibits it when the RDS is the nucleophilic attack, because of the shift of the ISIP–OSIP equilibrium (Scheme 1) in favor of ISIP.

This study clearly demonstrates that the interplay between the ligand nature and anion effect is crucial in different steps of the catalytic cycle. The multiple roles played by counterions and L–Au⁺ fragments in chemical transformations require more comprehensive computational and experimental studies of the ligand/anion correlation. These studies are underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

General procedures and materials, synthesis and characterization of novel compounds, catalysis plot, and ³¹P NMR spectra of 1–3X for catalysis A and catalysis B. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. P. Martinuzzi for helping in NMR measurements. This work was supported by grants from the MIUR (Rome, Italy) and the FIRB-Futuro-in-Ricerca project RBFR1022UQ [“Novel Au(I)-based molecular catalysts: from know-how to know-why (AuCat)”].

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