

Revisiting the Influence of Silver in Cationic Gold Catalysis: A Practical Guide

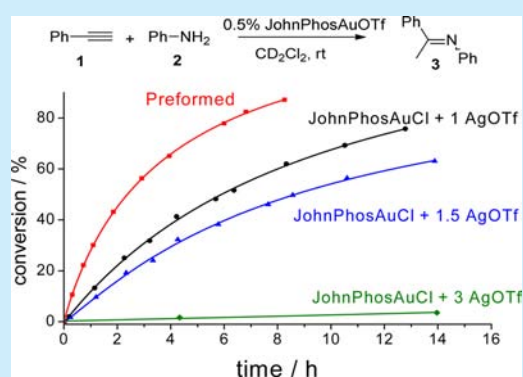
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S Supporting Information

ABSTRACT: An excess amount of silver salt to generate cationic gold from a gold catalyst precursor such as L–Au–Cl almost always has adverse effects on the reactivity of the cationic gold catalyst. A preformed L–Au⁺X[−] complex, generated by sonication followed by centrifugation, increases the reactivity in a gold catalyzed reaction. The adverse silver effect might be caused by the interaction of silver salts with gold intermediates.



Cationic gold is considered among the strongest catalysts for electrophilic activation of alkynes and alkenes.¹ And silver-mediated halide abstraction is regarded as the most common method to generate cationic gold from a gold catalyst precursor (e.g., L–Au–Cl). Recent reports have revealed that the silver based halide abstraction is not a simple process (Scheme 1), possibly because of the high affinity of silver toward gold and the halide atom.

For example, Straub and co-workers have reported that a Au–Ag–Cl complex (type A complex, Scheme 1) can be generated during the silver-based halide abstraction.² More

complex species that contain multiple Au or Ag atoms (e.g., type B complex) can also be formed (Scheme 1).³ Silver may even interact with the gold intermediate in the gold catalytic cycle, giving rise to the formation of a dinuclear gold–silver resting state⁴ (i.e., type C complex, Scheme 1). It has been proposed that silver salts may act as cocatalysts in many gold catalyzed reactions.⁵ All of these findings suggest that silver salts may play a significant role in the efficiency of gold catalyzed reactions in general.

We investigated four modes of cationic gold generating conditions: using a preformed catalyst, or using *in situ* methods and changing the number of AgX equivalents (1.0, 1.5, and 3.0 equiv) (Figure 1).

Most reactions reported in literature are conducted using the *in situ* method. In order to use the *in situ* method, a thorough mixing of AgX and L–Au–Cl is important.⁷ Because AgX is not soluble in most of the organic solvents employed in gold catalysis (e.g., DCM, toluene), we resorted to sonication to mix

Scheme 1. Various Au–Ag Intermediates

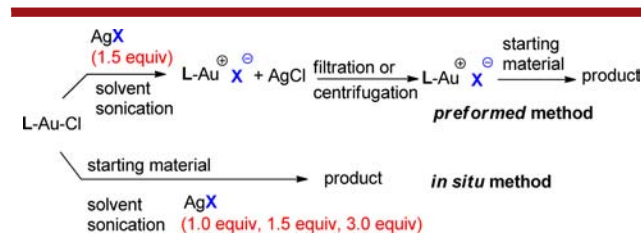
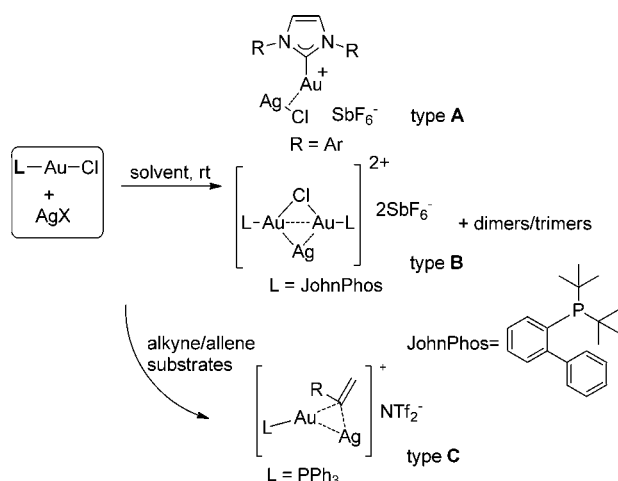


Figure 1. Generation of cationic gold catalysts.

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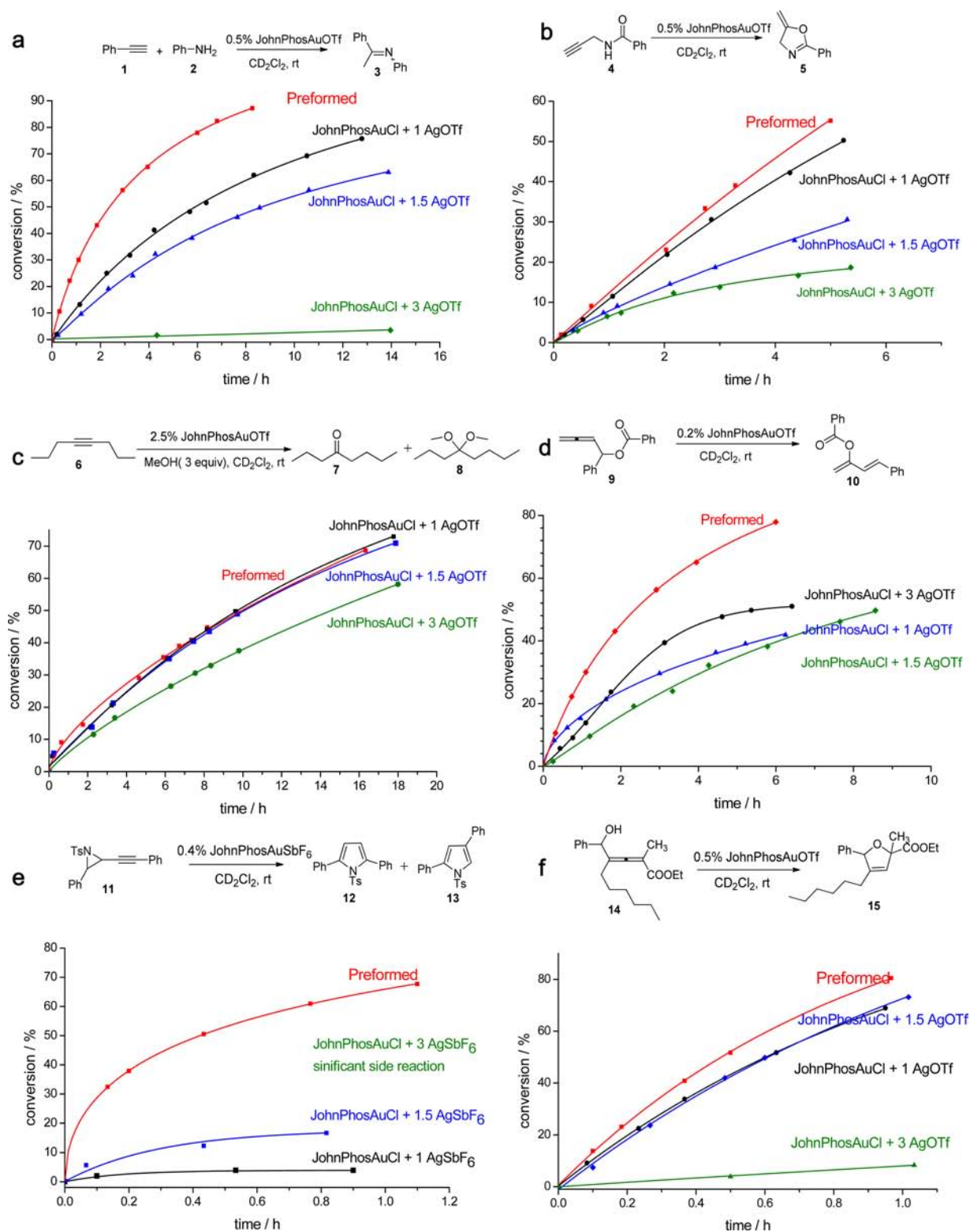


Figure 2. Effects of silver on reactivity of cationic gold catalyzed reactions.

AgX with L–Au–Cl. We found sonication was much more efficient than stirring. We also found that some basic components present in filtration aids (e.g., Celite) may poison the reactive cationic gold catalyst,^{6f} a problem that can be avoided by centrifugation.

We discovered that an excess amount of silver salt actually retarded the reactions studied (Figure 2), in all cases the

preformed catalysts exhibited the highest reactivity. Some reactions were especially sensitive toward additional amounts of silver salts. For example, in the hydroamination reaction and the cyclization of propargyl amide (Figure 2a and Figure 2b), higher amounts of silver led to a significantly slower reaction rate. In other reactions, there was no direct correlation between reactivity and the number of equivalents of silver, although in

all cases the preformed gold catalyst exhibited the highest reactivity. In the cycloisomerization of aziridine **11**, a large amount of silver (3 equiv vs gold) led to significant amounts of side products (Figure 2 e). This result is consistent with a literature report that found that the presence of silver caused side reactions.⁸

The adverse effects of silver were further confirmed by the addition of a silver salt during the course of the cyclization of propargylic amide **4**.⁹ When a preformed gold catalyst was used, the kinetics of this reaction was close to zero-order when the conversion was less than 90%. We allowed the reaction to proceed for the first hour using a preformed gold catalyst, and afterward we added additional AgOTf to the system. We noticed that the reaction still followed a zero-order kinetics, but at a much slower rate (Figure 3).

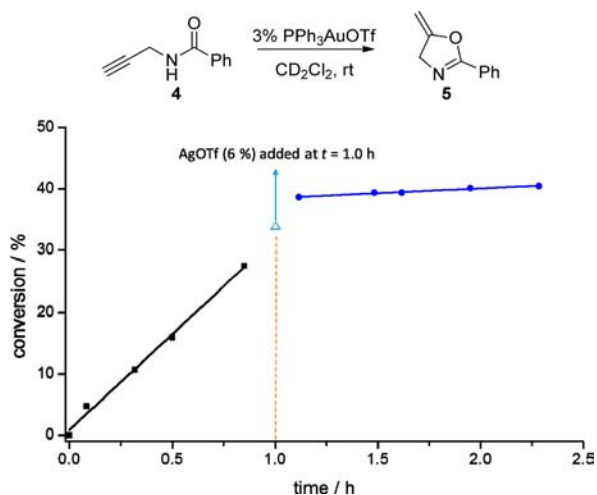
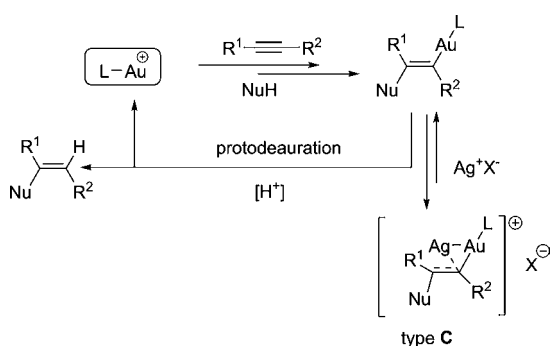


Figure 3. Addition of silver during the reaction.

As explained in the introductory paragraph, various Ag–Au complexes (e.g., type A, type B, type C) can be formed in gold catalyzed reactions (Scheme 1). Both, type A and type B complexes contain chloride. The presence of chloride may hinder the reactivity of type A and type B complexes, but because type A and type B complexes are not very stable, they tend to lose AgCl over time.^{2,10} Therefore, we believe that type A or type B complexes do not play a major role in the deactivation of gold catalysts. Instead, we believe that the deleterious effect caused by excess silver is caused by its interaction with a key gold intermediate such as the vinyl gold complex in the gold catalytic cycle shown in Scheme 2.

Scheme 2. Role of Silver in Gold Catalytic Cycle



The above statement is supported by the fact that silver salts can affect the reactivity of a preformed gold catalyst when they are added during the course of the reaction. This statement is also consistent with Gagné and co-workers' finding that excess amounts of AgNTf₂ slowed down the preformed L–Au–NTf₂ catalyzed intramolecular hydroarylation reaction.⁴

Gagné and co-workers isolated the type C complex **Au-1** (Figure 4).⁴ We investigated the interaction of isolable vinyl

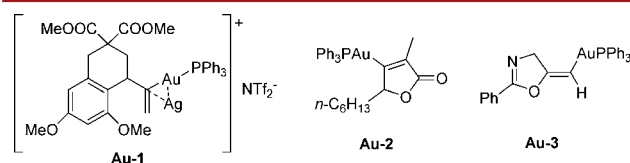


Figure 4. Interaction of vinyl gold intermediates and silver salts.

gold intermediates **Au-2**¹¹ and **Au-3**^{6h,12} with silver salts. Both **Au-2** and **Au-3** exhibited sharp peaks in their ³¹P NMR spectra, but after treating **Au-2** and **Au-3** with silver salts we observed significant changes in their chemical shifts and peak broadenings in their ³¹P NMR spectra (see Supporting Information). Although we are not certain about the structures of the **Au-2**/AgX or **Au-3**/AgX adducts, our NMR experiments indicated that vinyl gold complexes interacted with silver salts.

Many silver-free methods have been reported in gold catalyzed reactions,^{6g,13} so the presence of silver is not indispensable. The findings presented herein demonstrate that the presence of silver salts may be even harmful for some reactions. Based on our investigations on the influence of silver, our recommended method to generate cationic gold is the preformed method (Figure 5). Accordingly, L–Au–Cl and



Figure 5. Recommended preformed method to conduct gold catalyzed reactions.

AgX are first mixed in the solvent chosen to conduct the reaction. A slight excess of AgX (e.g., 1.5 equiv) can be used to make sure that enough AgX is present. Because AgX is not soluble in solvents commonly used in gold catalysis (e.g., DCM, toluene), the excess AgX can be removed easily later. Sonication is recommended for mixing L–Au–Cl and AgX. Echavarren and co-workers found that simple stirring often leads to incomplete removal of Cl, generating a less reactive [(L–Au)₂Cl]⁺ species.⁷ We found that the problem of insufficient mixing can be overcome by sonication and usually only 5 min sufficed. We also noticed that centrifugation can be used to remove the AgCl precipitate and excess AgX (X = OTf, SbF₆, etc.). The last step in the preformed method is the addition of the substrate to start the reaction. This protocol usually leads to fast reaction rates and avoids the side reactions caused by excess silver salts.

In summary, we have found that the presence of silver activators almost always have adverse effects in many gold catalyzed reactions. Using a preformed L–Au⁺X[−] complex by removing excess AgX before the reaction generally avoids this problem. The deleterious silver effect may be caused by the

interaction of silver salts with key gold intermediates such as a vinyl gold complex in the gold catalytic cycle.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b02224](https://doi.org/10.1021/acs.orglett.5b02224).

General experimental procedures and additional kinetic data (PDF)

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Notes

The authors declare no competing financial interest.

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