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Efficient Generation and Increased Reactivity in Cationic Gold via Brønsted Acid or Lewis Acid Assisted Activation of an Imidogold Precatalyst

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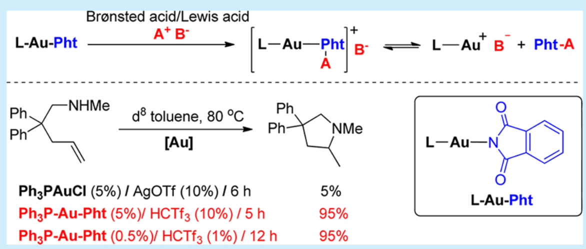
S *Supporting Information*

ABSTRACT: Brønsted or Lewis acid assisted activation of an imidogold precatalyst (**L-Au-Pht**, Pht = phthalimide) offers a superior way to generate cationic gold compared with the commonly used silver-based system. It is also broadly applicable for most common gold-catalyzed reactions. For reactions that require milder conditions, milder acids can be used for optimized efficiency.



Cationic gold catalysis is an important addition to the field of organic synthesis.[1] Silver-mediated halogen abstraction is the most preferred method to generate cationic gold from a gold catalyst precursor (e.g., L−Au−Cl) because of the mild conditions needed and the relative availability of silver activators (AgX, X= OTf^-, SbF_6^-, NTf_2^-, etc.). However, the use of silver activators is not problem free. First, some of the preferred silver activators are either relatively expensive (e.g., $AgNTf_2$),[2] commercially unavailable, or troublesome to prepare (e.g., $Ag[B(C_6F_5)_4]$).[3] Second, the presence of silver may cause side reactions.[4] Indeed, recent reports have revealed that the silver mediated halogen abstraction is not as simple a process as initially thought (Figure 1). Possibly because of the high affinity of silver

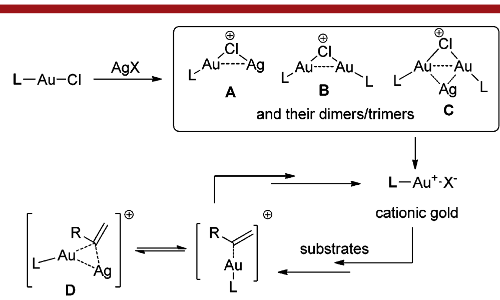
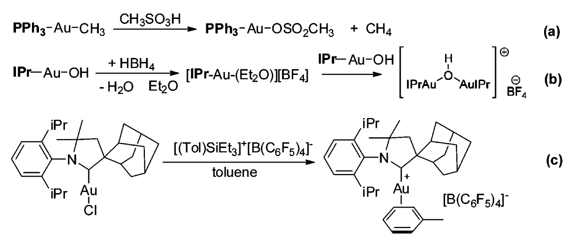


Figure 1. Various Au−Ag intermediates.

toward gold and halogen, various Au−Ag intermediates (**A**,[5] **B**,[6] **C**[7]) are formed during the halogen abstraction step (Figure 1). The presence of silver could also have an additional deleterious effect: the formation of a dinuclear gold−silver resting state (i.e., intermediate **D** in Figure 1).[8] Although silver activators do not always negatively affect the system, using preformed $L{-}Au^+X^-$ complexes with weakly coordinating anions often can avoid the problems described in Figure 1.[9]

There are alternative ways to generate cationic gold.[10] Teles and others[11] reported the protonolysis of $Ph_3PAu{-}CH_3$ in the hydration and amination of alkynes with good turnover numbers (Scheme 1a). Nolan and co-workers reported a Brønsted acid

Scheme 1. Selected Silver-Free Cationic Gold Generation



activation of NHC−Au−OH that generated cationic $[NHC{-}Au]^+$ or $[Au{-}O{-}Au]^+$ species (Scheme 1b).[12] Bertrand and co-workers generated cationic gold taking advantage of the high affinity of silica toward chloride (Scheme 1c).[13] Recently, Lafolle and Gandon reported the use of $Cu(OTf)_2$ to activate L−AuCl.[14]

The aforementioned nonsilver activation methods have limitations though. First, gold precatalysts like $L{-}Au{-}CH_3$ and L−Au−OH have only been synthesized successfully for a limited set of ligands.[11a,15] This limitation is a constraint in gold catalysis because different gold-catalyzed reactions usually require different ligands for optimal efficiency.[16] Second, for each of the activation methods reported, only a limited set of gold-catalyzed reactions has been tested.[10a] Third, the relative reactivity of the nonsilver based system viz a viz the equivalent silver-based system has not been aptly compared. Fourth, L−

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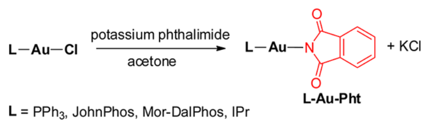
Au−CH_3/acid system has been reported to be very unstable in some solvents.[17]

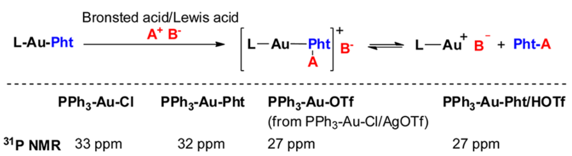
In our continuing effort to improve the efficiency of gold catalysis,[18] we found that a gold phthalimide complex (**L−Au−Pht**) can be easily synthesized from L−Au−Cl and potassium phthalimide for a diversity of ligands (Scheme 2).[19] **L−Au−Pht** in itself is not an active gold catalyst due to strong an Au−N bond. But due to the affinity of **Pht** toward Brønsted acid and Lewis acid, we can generate cationic gold using **L−Au−Pht**/acid combination. The reactivity of the **L−Au−Pht**/acid system could be fine-tuned by readily available Brønsted acids/Lewis acids, each of which with a unique acid strength and counterion.

Scheme 2. Synthesis of L-Au-Pht



^{31}P NMR is a good indicator of the electronic properties of gold complexes, which may relate to catalytic reactivity. Treatment of **Ph_3PAu−Pht** with TfOH does generate a cationic gold species system similar to the commonly used Ph_3PAu−OTf (Scheme 3).

Scheme 3. Brønsted/Lewis Acid Activation of L-Au-Pht



We used the hydroamination of alkynes[10b,11b] as a model system and found the reactivity of the **L−Au−Pht**/acid system was superior to the traditional silver halide removal protocol (Figure 2). We measured the initial reaction rate for each activator at a given concentration (Table 1). We found that weak acids like benzoic acid did not promote this reaction and stronger acids were more effective ($HCTf_3$ > $HNTf_2$ > TfOH).[20] Most Lewis acids also worked well. The counterions of Brønsted acids or Lewis acids played an important role (rate: CTf_3^- > NTf_2^- > TfO^- > BF_4^-). We also evaluated other gold catalyst precursors (Ph_3PAuCl, Ph_3PAu−Sac, Ph_3PAu−OAc, Table 1, entries 8−10) and found them less effective. The data in Table 1 also demonstrate that we have many more options to choose from compared to silver activators. For example, if a strong acid cannot be tolerated, then we can replace it with a milder acid, such as $Yb(OTf)_3$ (Table 1, entry 13, its aqueous solution is close to neutral) or $AgCTf_3$ (Table 1, entry 18).[21]

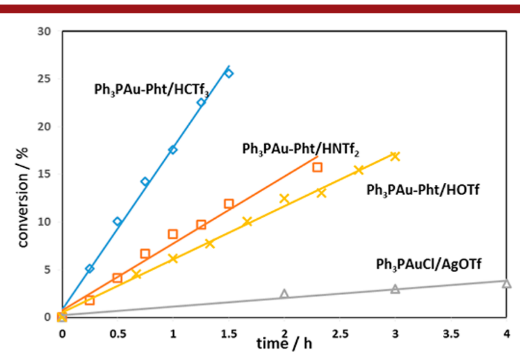
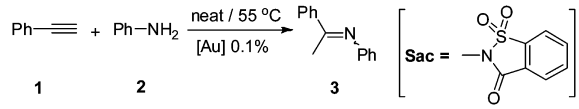


Figure 2. Effects of acids on hydroamination of **1**.

Table 1. Relative Rate of Intermolecular Hydroamination

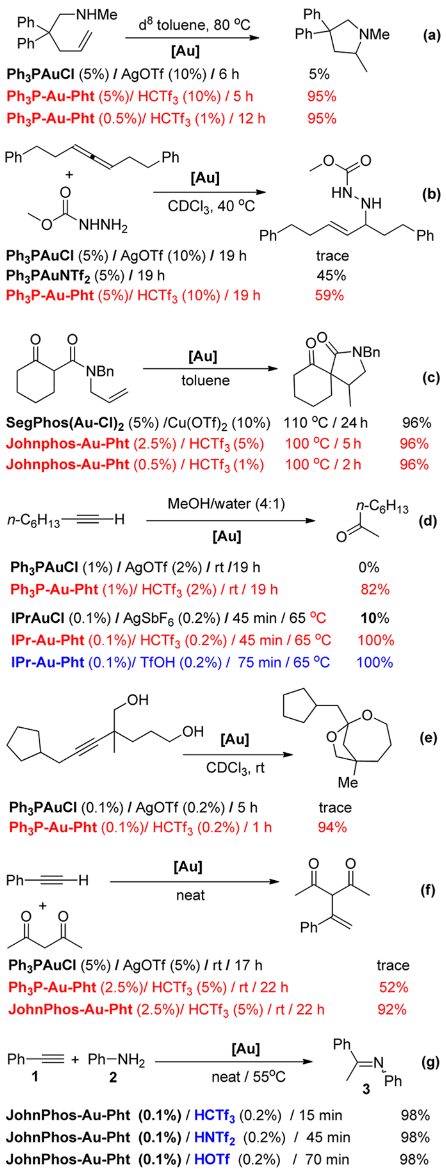


entry	catalyst	relative rate
1	**Ph_3PAuCl** / AgOTf (0.2%)	1.0
2	**Ph_3P-Au-Pht** / no acid	0
3	**Ph_3P-Au-Pht** / PhCOOH (0.2%)	0
4	**Ph_3P-Au-Pht** / HBF_4 (0.2%)	2.4
5	**Ph_3P-Au-Pht** / TfOH (0.2%)	6.3
6	**Ph_3P-Au-Pht** / $HNTf_2$ (0.2%)	7.4
7	**Ph_3P-Au-Pht** / $HCTf_3$ (0.2%)	19.1
8	**Ph_3P-Au-Cl** / $HCTf_3$ (0.2%)	3.3
9	**Ph_3P-Au-OAc** / $HCTf_3$ (0.2%)	11.8
10	**Ph_3P-Au-Sac** / $HCTf_3$ (0.2%)	18.6
11	**Ph_3P-Au-Pht** / $Sc(OTf)_3$ (0.2%)	2.6
12	**Ph_3P-Au-Pht** / $In(OTf)_3$ (0.2%)	2.5
13	**Ph_3P-Au-Pht** / $Yb(OTf)_3$ (0.2%)	2.5
14	**Ph_3P-Au-Pht** / $Cu(OTf)_2$ (0.2%)	2.1
15	**Ph_3P-Au-Pht** / $In(CTf_3)_3$ (0.2%)	28.4
16	**Ph_3P-Au-Pht** / $Yb(CTf_3)_3$ (0.2%)	27.2
17	**Ph_3P-Au-Pht** / AgOTf (0.2%)	0.5
18	**Ph_3P-Au-Pht** / $Ag(CTf)_3$ (0.2%)	6.4
19	**Ph_3P-Au-Pht** / Nafion	0

To assess the generality of our approach, we screened other common gold-catalyzed reactions and compared our results with standard silver-based methods. We began by investigating the most common type of gold-catalyzed reaction, namely the X−H (X = O, N, C) addition to C−C unsaturated compounds (Scheme 4). The addition of a basic alkyl amine to an alkene (Scheme 4a) is a very demanding reaction in gold catalysis not only because the basic amine binds strongly to cationic gold[3] but also because the basic amine may inhibit protodeauration by quenching any acid present in the system.[22] Hartwig and co-workers have used cationic rhodium complexes (2.5% loading) of a biaryldialkylphosphine (DavePhos) to catalyze this reaction.[15] A commonly used gold catalytic system such as PPh_3PAu/AgOTf gives very low conversion (5%) even at high catalyst loading (Scheme 4a). Instead, our Ph_3P−Au−Pht/$HCTf_3$ system gives very good yields under the same conditions (Scheme 4a) using a much lower loading (0.5%), and a simple Ph_3P ligand. Our L−Au−Pht/acid system also showed good reactivity in the intermolecular hydroamination of allene[23] (Scheme 4b), whereas the silver-based system is less efficient. Lafolle and Gandon reported the use of $Cu(OTf)_2$ to activate L−AuCl directly in the intramolecular C−H addition of alkene[14] (Scheme 4c); our L−Au−Pht/$HCTf_3$ also worked well in this reaction.

Next, we investigated the hydration of alkynes; Ph_3PAuCl/AgOTf was not efficient at relatively low temperature and catalyst loading, but our Ph_3P−Au−Pht/$HCTf_3$ performed nicely (Scheme 4d). The IPr−Au−Cl/$AgSbF_6$[24] system was slow at lower temperature (60 °C), but IPr−Au−Pht/$HCTf_3$ system was capable of completing the reaction in less than 45 min (Scheme 4b). A similar outcome took place in the cyclization of homopropargylic diols (Scheme 4e).[25] Ph_3PAuCl/AgOTf was able to complete the reaction in less than 0.5 h using a relatively high loading (2%), but at low loading (0.1%) only trace amounts of product were observed after 5h. In contrast, our Ph_3P−Au−Pht/$HCTf_3$ furnished the product in high yield after only 1 h.

Scheme 4. Addition of X−H (X = O, N, C) to Alkyne/Alkene

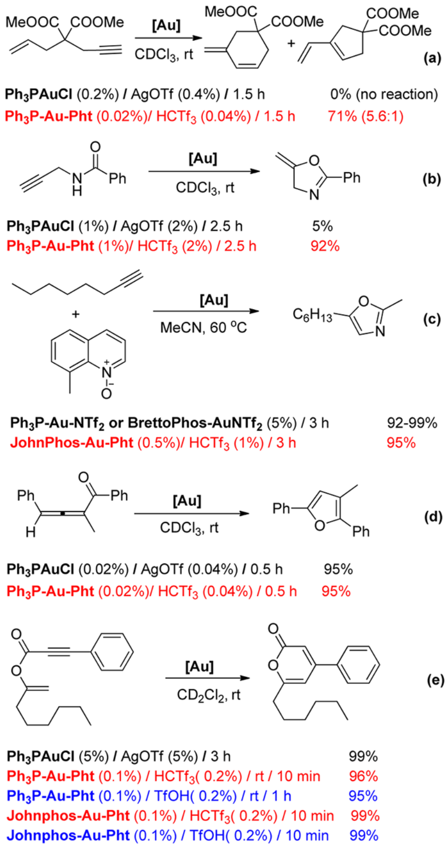


Furthermore, our L−Au−Pht/$HCTf_3$ system worked well in the C−H addition to alkynes (Scheme 4f),[26] whereas the silver-based system only gave trace amounts of product under the same conditions. We also revisited the hydroamination reaction using a more electron-rich ligand (JohnPhos); the reaction was completed in only 15−70 min (Scheme 4g).

Then we proceeded to examine a wider range of gold-catalyzed reactions (Scheme 5). In the gold-catalyzed cycloisomerization of 1,6-enyne, the silver-based system catalyzed a fast conversion to product using a relatively high loading (2%), but at a lower loading (0.2%) the reaction was sluggish (Scheme 5a). However, our Ph_3P−Au−Pht/$HCTf_3$ system was very efficient even at 0.02% catalyst loading.

A similar result occurred during the cycloisomerization of propargyl amide: the Ph_3PAuCl/AgOTf system was very slow at low catalyst loadings whereas our Ph_3P−Au−Pht/$HCTf_3$ system was very fast. We also tested an oxygen-transfer reaction recently reported by Zhang and co-workers (Scheme 5c);[27] the authors used L−Au−NTf_2 (5% loading, L = Ph_3P or BrettPhos, prepared from L−Au−Cl and $AgNTf_2$). Our system worked equally well

Scheme 5. Other Examples of Gold-Catalyzed Reactions

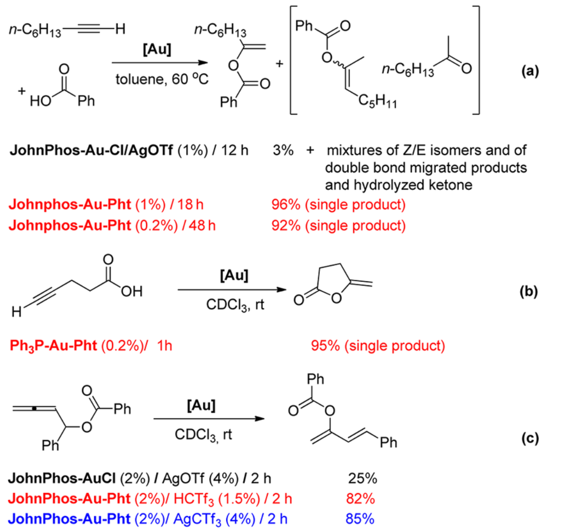


but needed only a 10-fold lower catalyst loading (0.5%). In our study, the only reaction in which our silver-free method and the conventional silver-based method worked equally well was in the cycloisomerization of allenone (Scheme 5d).[9,28] In in the synthesis of α-pyrone (Scheme 5e), we obtained the pyrone product in 99% yield using only a catalyst load of 0.1%, whereas the same reaction cited in the literature[29] needed a 5% loading.

The activation of **L−Au−Pht** by stronger acids usually gives better reactivity, but in some reactions, the starting material or the product may not withstand the strong acids. An added feature of our approach is that it allows us to either reduce the amount of acid activator or use a weaker acid instead. For example, the addition of a carboxylic acid to an alkyne could produce a useful intermediate, a functionalized vinyl acetate (Scheme 6a),[30] but a silver-based cationic gold generation protocol produces a mixture of double-bond migration products and the hydrolysis byproduct 2-octanone (Scheme 6a). The weak carboxylic acid is able to activate the **L−Au−Pht** precatalyst. In this manner, we obtained the single product exclusively. The same approach was used successfully in the intramolecular version of the reaction (Scheme 6b).

Although in most of the aforementioned reactions we used 2 equiv (vs gold catalyst) of acid activator, we can reduce the amount of acid activator further (e.g., 0.9 equiv vs gold) and foster milder conditions. For example, in the gold(I)-catalyzed isomerization of allenyl carbinol ester,[31] the resulting product can be hydrolyzed by the trace water present in the presence of acid. But we can overcome this problem by simply using less than 1 equiv of acid activator or by choosing a milder Lewis acid (Scheme 6c).

Scheme 6. Reactions That Benefit from Milder Conditions



In summary, the Brønsted acid or Lewis acid activation of imido gold precatalyst (**L−Au−Pht**) is a superior way to generate cationic gold, compared to a silver-based activator. Our silver-free system led to higher reactivity and higher turnover number in a large variety of gold-catalyzed reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure. 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.

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