## A Highly Efficient and Broadly Applicable Cationic Gold Catalyst\*\*

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**Abstract:** Gold catalysts capable of promoting reactions at low-level loadings under mild conditions are the exception rather than the norm. We examined reactions where the regeneration of cationic gold catalyst (e.g., protodeauration) was the turnover limiting stage. By manipulating electron density on the substituents around phosphorus and introducing steric handles we designed a phosphine ligand that contains two electron-rich ortho-biphenyl groups and a cyclohexyl substituent. This ligand formed a gold complex that catalyzed common types of gold-catalyzed reactions including intra- and intermolecular X-H (X = C, N, O) additions to alkynes and cycloisomerizations, with high turnover numbers at room temperature or slightly elevated temperatures ( $\leq 50^{\circ}C$ ). Our new ligand can be prepared in one step from commercially available starting materials.

Gold catalysis is a landmark addition to the field of organic synthesis.<sup>[1]</sup> Gold's synthetic usefulness notwithstanding, the relatively large catalyst loading needed in many gold-catalyzed applications is impractical in large-scale synthesis or multistep syntheses because gold is an expensive metal and the catalyst is difficult to recycle. Catalyst loadings in the ppm range have been reported for a narrow set of gold-catalyzed reactions.<sup>[2]</sup> Notable examples include the [(NHC)Au<sup>I</sup>]-catalyzed (NHC = N-heterocyclic carbene) alkyne hydration, reported by Nolan and co-workers;<sup>[3]</sup> the [(NHC)Au<sup>I</sup>]-catalyzed intramolecular addition of diol to alkyne, reported by Hashmi and co-workers;<sup>[4]</sup> the hydroamination of alkynes with a hyperhalogenated carba-closo-dodecaborate anionic ligand, reported by Lavallo and co-workers;<sup>[5]</sup> and the ester assisted hydration of alkynes catalyzed by small gold clusters, reported by Corma and co-workers.<sup>[6]</sup> In some exceptional cases, even higher turnovers have been achieved but at the cost of employing relatively high temperatures (e.g. 120 °C).<sup>[3]</sup>

Our goal is to develop a broadly applicable, readily prepared cationic gold catalyst that is efficient at ppm loading levels and reaction temperatures equal or below 50 °C. The use of relative low temperatures is important for the synthesis of complex target molecules, which usually contain sensitive functional groups. To design such a gold catalyst we focused

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on the three major factors that account for the high loading of gold catalysts. These factors are: the decay of the gold catalyst during the reaction, the formation of off-cycle gold species, and the mismatch of electronic effects within the gold ligand. We used the intermolecular hydroamination of phenyl acetylene **1** with aniline as a study model.<sup>[7]</sup> As seen in Figure 1, a popular ligand like  $Ph_3P$  is not a good choice in the



Figure 1. Ligand effect in hydroamination of 1.

reaction of **1** because the reaction is relatively slow (20% conversion after 18 h). The low reaction rate could have been caused by the electronic effect mismatch in the ligand, as this reaction needs an electron-rich ligand; furthermore, the gradual deactivation of the catalyst contributed to the low rate of the reaction. By replacing one phenyl ring in  $Ph_3P$  with an *o*-biphenyl group (**L2** in Figure 1) the reaction rate increased significantly. Keeping the biphenyl group and increasing the electron density of ligand by introducing two electron-rich *t*Bu groups (**L3**, JohnPhos) produced an even higher rate and full conversion to product.

These experiments underscore the importance of *ortho*substitution and electronic density matching within the ligand, both of which were discussed in an earlier paper from our group.<sup>[7]</sup> In that paper we suggested that: 1) the proximity of the *o*-phenyl to the gold center may prevent the deactivation of gold(I)<sup>[7]</sup> (see **A** in Figure 2), and 2) the turnover limiting stage in the majority of gold-catalyzed reactions is the regeneration of the cationic gold catalyst from the gold  $\sigma$ -complex intermediate (e.g., vinyl gold complex **A**, Figure 2) via protodeauration. An electron-rich ligand capa-

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Figure 2. Ligand design for gold catalysis.

ble of supplying electronic density to the gold metal center would facilitate the regeneration of the cationic gold catalyst.

Two significant literature reports should be noted: Widenhoefer and co-workers'<sup>[8]</sup> finding that the off-cycle gold species bis-Au-vinyl species **B** may reduce turnover, and Buchwald and co-workers' development of phosphine ligands with an o-biphenyl dialkylphosphine backbone (e.g., John-Phos, XPhos), which are widely used in transition metal catalysis.<sup>[9]</sup> With the above findings as preamble, we hypothesized that two sterically demanding biaryls on the phosphine ligand could surround the gold center further and discourage the formation of **B** (Figure 2). Thus, we designed ligand L1 (Figure 2) that featured two electron-rich and sterically demanding ortho-biphenyl groups and one electron-rich cyclohexyl group. We prepared L1 in a single step from commercially available starting materials<sup>[10]</sup> (see Supporting Information). The crystallographic structure of L1-AuCl (Figure 2)<sup>[11]</sup> demonstrated that the two ortho-biphenyl motifs were able to surround or embed the gold center.

A comparison between our new ligand L1 and other benchmark ligands is shown in Table 1. We chose the carbenebased gold catalyst L4 as a vardstick because of its proven efficiency towards gold catalyzed reactions. L1 was the most reactive ligand (Table 1). A ligand with three o-biphenyl motifs (L14) was less effective, probably because of its lower electronic density. The importance of the ligand electronic density on the rate of hydroamination became apparent when we kept the o-biphenyl motif unchanged and modulated the electron densities of the two remaining groups connected to phosphorus (L5 to L8). In this subset, electron-richer ligands produced higher reaction rates. Substituting the o-biphenyl group with ferrocene decreased the reaction rate significantly (Table 1, L8 and L9). The merits of L1 were further assessed in other gold-catalyzed intermolecular and intramolecular reactions with C, N, or O nucleophiles so as to determine the reaction conditions needed to achieve the highest possible turnover for each of the reactions tested.

We revisited the hydroamination reaction because it is a representative example of a C–N bond forming reaction where nitrogen is the nucleophile. Tanaka and co-workers Table 1: Relative rates of hydroamination for various ligands.



reported an efficient gold-catalyzed intermolecular hydroamination of alkynes using the precatalyst  $[PPh_3AuCH_3]$  in the presence of  $H_3PW_{12}O_{40}$  acting as acidic promoter.<sup>[12]</sup>

Using an acidic promoter is fitting in hydroamination because protodeauration is the rate-limiting step.<sup>[7]</sup> Shi and co-workers reported an even higher turnover using a Ph<sub>3</sub>PAuOTf/benzotriazole/H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> system (Scheme 1 a).<sup>[13]</sup> When we used Tanaka's acidic promoter with our L1-AuCl precatalyst and the alkali salt of the bulky counterion  $\text{CTf}_3^{-[14]}$  we found that the catalytic loading could be reduced to 0.0025 % (25 ppm) and the reaction still reached an impressive TON of 31 200. To the best of our knowledge, no other catalyst system has matched this provess at such low temperature (50 °C). Our catalyst system also worked equally well in relatively larger scales (10 mmol).

We chose the gold-catalyzed intermolecular addition of N-hydroxy benzotriazole **4** to an alkyne as our model system for O–H addition.<sup>[15]</sup> We were able to reduce the catalytic loading to 0.1% (Scheme 1b). This result is a significant improvement over the original literature report (Scheme 1b), which needed 5% catalyst loading.

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Scheme 1. Use of L1-AuCl in X-H (X = N, O) addition to alkynes.

We also tested the intramolecular version of X–H addition to alkyne, which is, in general, more efficient than the intermolecular version. For example, in the gold-catalyzed cyclization of homopropargylic diols,<sup>[16]</sup> we observed that L1-AuCl needed only 20 ppm to yield 92% of product **7** after 24 h at room temperature (Scheme 1 c). This result was significantly better than the 2% catalyst loading cited in the literature.<sup>[16]</sup> L1-AuCl was also efficient in the intramolecular cyclization of 4-pentynoic acid **8** (Scheme 1 d), as demonstrated by the TON of 9900 achieved at room temperature. This result was far better than the available literature report (Scheme 1 d).<sup>[17]</sup>

Since C–C bond formation is the most important class of reactions in synthesis, we studied several gold catalyzed C–H additions to alkynes. We evaluated the Conia–ene reaction of  $\beta$ -ketoester **10** first<sup>[18]</sup> (Scheme 2 a). Again, L1-AuCl worked very well in this reaction: it needed only 0.004% (40 ppm) catalyst loading at room temperature to furnish the product in 95% yield. The use of an acidic promoter enhanced the reactivity, just as it was the case in the hydroamination reaction described earlier.

L1-AuCl also worked well in the intermolecular version of the Conia–ene reaction (Scheme 2b); very good to excellent



Scheme 2. C-H additions to alkynes (C-C bond formations).

yields could be achieved in this reaction using low catalyst loadings in the presence of a co-catalyst,  $Ga(OTf)_3$ .<sup>[19]</sup> L1-AuCl also performed efficiently in the synthesis of  $\alpha$ -pyrone (Scheme 2 c). We obtained the pyrone product **15** in 95% yield at 50°C using only a catalyst load of 0.05% (500 ppm) whereas the corresponding reaction cited in the literature<sup>[20]</sup> needed a 5% loading.<sup>[21]</sup> We reduced the catalyst loading to 0.02% (200 ppm) and still managed to obtain a respectable 80% yield (Scheme 2 c). To broaden the applicability of our gold catalyst L1-AuCl we chose another example of a C–H addition to an alkyne, namely the hydroarylation of **16**<sup>[22]</sup> (Scheme 2 d). The product, 2*H*-chromene **17**, was obtained in 95% yield at room temperature using a catalyst loading of 0.05% (500 ppm).

Envne cycloisomerization is a class of reactions where gold catalysis has proved its efficiency.<sup>[23]</sup> Using 1,6-envne **18** as model substrate, we found that our gold catalyst needed only a loading of 0.02% (200 ppm) to drive the envne cycloisomerization to completion, furnishing **19** in almost

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Scheme 3. Enyne and allenone cycloisomerization.

quantitative yield (Scheme 3 a). In contrast, a similar reaction reported in the literature<sup>[23]</sup> needed a 2% catalyst loading. We also investigated the cycloisomerization of allenone **20**, first reported by Hashmi and co-workers<sup>[24]</sup> and later refined by Che and co-workers (Scheme 3b).<sup>[25]</sup> Using 0.01% (100 ppm) of our catalyst L1-AuCl, we obtained the desired furan **16** in quantitative yield after 7 h at room temperature; this result corresponded to a TON of 10000.

In summary, we have found a broadly applicable cationic gold catalyst system that is highly efficient at extremely low loadings and relatively low temperatures. Our reactions were conducted in open-air containers using commercial solvents that needed no prior purification. The catalyst L1-AuCl is now available from Aldrich under the name BisPhePhos XD gold(I) chloride (catalog no. L511846).

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cationic gold catalyst was developed that works at extremely low loading and relatively low temperature. The new gold catalyst containing a bis(biphenyl) phosphane ligand was tested in many

common types of gold-catalyzed reactions including intra- and intermolecular X–H (X=C, N, O) additions to alkynes (see example) and cycloisomerizations of enyne and allenone.

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