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Influence of Carbene and Phosphine Ligands on the Catalytic Activity of Gold Complexes in the Hydroamination and Hydrohydrazination of Alkynes

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Supporting Information Placeholder

ABSTRACT: Through kinetic measurements, catalytic and stoichiometric experiments, as well as DFT calculations, we compare the catalytic activity of gold complexes supported by a variety of ligands (R_3P , NHC, CAAC-5, CAAC-6, BiCAAC) in the hydroamination and hydrohydrazination of alkynes. This study provides a rationale for the superior efficiency of a gold complex bearing a bicyclic (alkyl)(amino)carbene (BiCAAC). We demonstrate that this ligand motif, which is readily available, provides a durable gold catalyst able to compete with sophisticated state-of-the-art phosphine and NHC ligands, which feature secondary interaction capabilities.

KEYWORDS: *cyclic (alkyl)(amino) carbene, gold catalysis, hydroamination, hydrohydrazination, mechanistic study*

The hydroamination of carbon-carbon multiple bonds is the most atom-efficient method for the introduction of nitrogen fragments into organic molecules.¹ Pioneered by Tanaka *et al.*² using $(PPh_3)AuNTf_2$, the field of coinage metal hydroamination catalysis has witnessed an outstanding development in recent years.³ Xu *et al.*⁴ observed a remarkable ligand effect⁵ in the intermolecular hydroamination of phenyl acetylene with aniline, using a set of phosphine ligands. Sophisticated phosphines,^{6,7} such as the WangPhos **L_A**,⁸ or the Lavallo anionic phosphine **L_B**,⁹ allowed to achieve up to 22,000 TON for the hydroamination of phenyl acetylene with aniline. More recently, NHC ligands have become popular replacements for phosphines. As an illustration, César, Michelet and co-workers reported that a gold complex bearing NHC **L_C**,¹⁰ which features a barbituric heterocycle, efficiently promotes the same transformation up to 7600 TON (Scheme 1).

From this short analysis, it appears that phosphines and carbenes, capitalizing on elaborate secondary interactions, afford the most efficient catalysts. However, the presence of these complex motifs clouds an understanding of the electronic contributions from the core of the ligand.¹¹ To better understand, we herein report a detailed investigation of the influence of core ligand structures (R_3P , NHC, CAAC-5, CAAC-6, BiCAAC) on the catalytic performance of gold complexes in the hydroamination and hydrohydrazination of alkynes. For a thorough comparison, *in-situ* kinetic measurements were conducted to determine the order of each reactant and the influence of the electronic properties of the substrates (Hammett plot). Moreover, reactivity studies and DFT calculations enable a

Scheme 1. Comparison of the most efficient tailor-made phosphines and carbenes in the hydroamination of phenyl acetylene with aniline.

rationalization of the catalytic performance of each ligand system. Finally, we show that the readily accessible BiCAAC,¹² which does not feature secondary interactions, competes with state-of-the-art ligands.

Results and Discussion

We have already shown that gold complexes bearing a 5-membered cyclic (alkyl)(amino) carbene (CAAC-5)¹³ are excellent catalysts for the intermolecular hydroamination and hydrohydrazination of alkynes and allenes.^{14,15,16} They survive drastic conditions (up to 200 °C),¹⁷ which allowed the use of ammonia and parent hydrazine that are difficult substrates for transition metal catalysts. Recently, we extended the family of CAACs to the bicyclic version (BiCAAC)¹² and the 6-membered CAAC (CAAC-6),¹⁸ which feature distinct electronic and steric properties (Figure 1).

I. Hydroamination reaction

Reaction optimization. Inspired by Blackmond *et al.*,¹⁹ we envisaged the use of *in-situ* kinetic measurements to optimize the catalytic system. Using ¹H NMR spectroscopy, we monitored the formation of imine **1a** in the reaction of aniline with *para*-(methoxyphenyl)

Figure 1. Electronic properties of different families of carbene ligands.

acetylene. The reactions were carried out at room temperature in air, using KBar^F as a chloride scavenger, meanwhile changing the nature of the catalyst (Figure 2a-b), the solvent (Figure 2c), the concentration and catalyst loading (Figure 2d). No reaction was observed with (THT)AuCl and using (Ph₃P)AuCl, we confirmed the accuracy of our kinetic protocol by obtaining comparable results to those reported by Xu *et al.*^{4a} We found that all the carbene ligands that we considered give rise to more active catalysts than PPh₃;

Figure 2. Optimization of the reaction conditions for the hydroamination reaction using ¹H NMR kinetic monitoring.

the order of catalytic activity being BiCAAC (**L**₄) > *N*-heterocyclic carbene IMes (**L**₅) > *Et*CAAC-5 (**L**₁) = *Ad*-CAAC-5 (**L**₃) > *Et*CAAC-6 (**L**₂). Comparing the % buried volumes (%V_{bur}) (**L**₄: 42.1-46.5; **L**₅: 37.5; **L**₁: 43.2; **L**₃: 48.4; **L**₂: 47.4), and the HOMO/LUMO energies of these carbenes (**L**₄: -5.05/-0.05; **L**₅: -5.82/1.00; **L**₁ and **L**₃: -5.35/-0.06; **L**₂: -4.95/-0.04 eV], it appears that neither the steric hindrance nor the electronic factors are decisive on their own. Using DFT calculations, we realized that the steric demands of BiCAAC **L**₄ are variable, due to the rotation of the *iso*-propyl group (Figure 3). Concomitantly, BiCAAC **L**₄ is both

Figure 3. Illustrating the flexible sterics in *IPr*-BiCAACAuCl.

Scheme 2. Substrate scope with amines and alkynes. NMR yields (isolated yields).

more electron donating and withdrawing than the other carbenes, except for CAAC-6 **L**₂ (Figure 1). Thus, we rationalize the superior performance of *IPr*-BiCAAC **L**₄ as a compromise between moderate steric bulk, approaching that of **L**₅, and significant amphiphilicity, nearing **L**₂. With respect to the nature of the solvent (Figure 2c), using **L**₄ we found that the catalytic activity is greatly impaired by strongly coordinating solvents. This is readily rationalized as a competition between the solvent and the substrates for binding to the metal. Finally, we optimized the concentration and the catalyst loading (Figure 2d) and selected 2.5 mol% and 1.5 M, respectively, as a middle point between conversion and reaction time.

Reaction Scope. Using the optimized catalytic system (2.5 mol% of *IPr*-BiCAACAuCl/KBAr^F in benzene - 1.5 M), we evaluated the scope of the hydroamination using a variety of alkynes and anilines (Scheme 2). *p*-Toluidine efficiently added to aryl substituted terminal alkynes; all reactions proceeded within a few hours in very high yields at 20 °C (**1a-1e**). Alkyl substituted terminal alkynes required higher reaction temperatures to achieve high conversions within a reasonable timeframe (**1f-1g**). Note that even with these alkynes, full conversion can still be

achieved at room temperature albeit with a longer reaction time, which is useful for low boiling point substrates such as ethoxyethyne (**1h**). We also found internal alkynes to be more challenging (**1i-1k**) requiring longer reaction times and higher temperatures. We also changed the nature of the aniline (**1l-1p**), and observed very good conversions even with the sterically demanding 2,6-diisopropylaniline (**1m**) and electron-poor perfluorinated aniline (**1o**). Finally, alkyl amines (**1q,r**) proved less reactive but were successfully converted to the desired products by performing the reaction at 80 °C.

Hammett correlation study. We conducted a Hammett correlation study to quantify the electronic influence of the substrates (Figure 4). Both anilines and arylalkynes with electron-donating *para*-substituents showed faster reaction kinetics (ρ value < 0). Electron-rich alkynes favor a forward equilibrium by stabilizing the cationic Au- π complex, whereas electron-rich anilines push a forward equilibrium by favoring the nucleophilic attack on the positively charged carbon. Note, that we observed a nonlinear behavior with the *p*-NMe₂ substituent, likely due to a competitive binding of this group to the gold center.

Rate order. We established the rate order in the alkyne and the amine under pseudo first-order conditions (excess of the spectator substrate; Figure 5). In both cases, we found first order dependence on these substrates which suggests that both of them are involved in the rate-limiting step.

II. Hydrohydrazination reaction

Hydrazines are inherently more challenging than amines due to their propensity to generate inert gold(0) nanoparticles²⁰ or unreactive Werner complexes.^{21,22} We have shown that (CAAC-5)AuCl in the presence of KBar^F is active for the hydrohydrazination of a variety of alkynes at rather high temperatures (90-150 °C).¹⁴ Although the scope of applications is much narrower, gold complexes bearing the saturated abnormal NHC (*sa*NHC)²³ or the *anti-Bredt*-NHC,^{24,25} which are π -accepting carbenes, promote this transformation under milder conditions.

Reaction conditions: As we did for amines, we began our investigation with a kinetic survey using ¹H NMR spectroscopy to monitor the formation of **2c** in the reaction of phenyl hydrazine with *para*-methoxy-phenyl acetylene at room temperature. We varied the nature of the catalyst (Figure 6a-b), the solvent (Figure 6c), the concentration and the catalyst loading (Figure 6d). Here again using KBar^F as a chloride scavenger we confirmed the accuracy of our kinetic protocol by verifying that (Ph₃P)AuCl is not an efficient catalyst for

Figure 4. Hammett correlations of rates and substituents on either alkyne (a) or amine (b).

Figure 5. Rate dependence of the hydroamination on the concentration of alkyne (a) and amine (b).

this transformation.⁴ Upon comparing the catalytic activity of the CAAC complexes, we found that the smaller *Et*CAAC-5 (**L**₁, %V_{bur}: 43.2) was deactivated by hydrazines in marked contrast with the bulkier *Ad*-CAAC-5 (**L**₃, %V_{bur}: 48.4) and *Et*CAAC-6 (**L**₂, %V_{bur}: 47.4). We attribute this peculiar result to the propensity of **L**₁ to favor disproportionation to a catalytically inactive bis-ligated (**L**₁)₂Au⁺ in polar solvents.²⁶ Apart from **L**₁, the order of activity **L**₃ < **L**₂ < **L**₅ < **L**₄ resembles that observed for the hydroamination, with the Bi-CAAC **L**₄ gold complex being the most active catalyst. As in the case of amines, we found that the catalytic activity is greatly impaired by strongly coordinating solvents (Figure 6c). Moreover, the early precipitation of the product prevented accurate reaction monitoring in benzene. Thus, using chloroform, we evaluated the concentration and the catalyst loading (Figure 6d). We selected 0.5 mol% and 1.8 M as a middle point between conversion and reaction time.

Reaction Scope: Using the optimized conditions obtained from our kinetic study (0.5 mol% of **L**₄AuCl/KBar^F in CHCl₃ - 1.8 M), we evaluated the scope of the reaction using a range of alkynes and

Figure 6. Optimization of the reaction conditions of the hydrohydrazination reaction using ^1H NMR kinetic monitoring

Scheme 3. Substrate scope with hydrazines. NMR yields (isolated yields)

hydrazines (Scheme 3). With phenylhydrazine, we found this catalytic system to be very efficient with aryl substituted terminal alkynes at room temperature (**2a-2e**). With 3-ethynylpyridine (**2f**), however, the reaction was much slower, requiring 2.5 mol% catalyst loading and 80 °C for 10 h. Similarly, in the case of alkyl substituted terminal alkynes, as well as internal alkynes, higher reaction temperatures were required to reach high conversion within a reasonable timeframe (**2g-2k**). While both mono-substituted and parent hydrazine were readily converted under mild conditions (**2l-2m**), we found 1,1-disubstituted hydrazines (**2o**²⁷ and **2p**) to be much less reactive.

Hammett correlation study. A Hammett correlation study was performed to quantify the electronic influence of the substrates in the gold catalyzed hydrohydrazination of alkynes (Figure 7). Faster reaction kinetics were obtained for alkynes bearing electron donating phenyl *para*-substituents (ρ value < 0), as observed in the hydroamination. The reverse is observed with phenyl-hydrazine, with decreasing rates obtained for electron donating substituents (ρ value > 0). This observation is in good agreement with the experimental results (**2l-2o**), and could be due to the higher binding affinity of the most basic hydrazines to the gold center. However, a computational study by Ujaque, Lledós *et al.*²⁸ showed that the catalytic cycle of hydrohydrazination of alkynes does not depend on the energy barrier for the nucleophilic addition of the hydrazine on the Au- π complex, but rather relies on hydrazine assisted intermolecular proton transfer. As a result, it is likely that the increased hydrazine N-H bond acidity with electron-withdrawing phenyl substituents favors the reaction.

Figure 7 Hammett correlations of rates and substituents on either alkyne (a) or hydrazine (b).

Rate order. We established the rate order in the alkyne and the hydrazine under pseudo first-order conditions (excess of the spectator substrate; Figure 8). We found first order dependence for both reactants

supporting that both alkyne and hydrazine are involved in the rate-limiting step. Together with the results obtained for the hydroamination, our data are in good agreement with both processes falling into the category of reactions involving nucleophilic attack of an amine on a gold activated carbon-carbon triple bond, followed by nucleophile assisted nitrogen to carbon atom proton transfer.^{4,28}

Figure 8. Rate dependence of the hydrohydrazination on the concentration of alkyne (a) and hydrazine (b).

III. Rationalizing the ligand effect

Catalyst stability. As already mentioned, low turnover numbers in gold catalysis often originate from catalyst degradation giving unreactive Au⁰ nanoparticles or unreactive (L)₂Au⁺ species. Xu and coworkers disclosed that the decay of cationic gold [(R₃P)Au⁺(π -alkyne)][OTf⁻] in solution is phosphine dependent.⁴ Buchwald-type biphenyl phosphine ligands were shown to afford very stable cationic gold complexes,^{5,4} likely owing to secondary coordination to the distal phenyl substituent of the biphenyl unit.²⁹ To estimate the propensity of CAAC ligands to stabilize cationic gold (L)Au⁺(π -alkyne) under pseudo-catalytic conditions, we performed a similar study. We examined the rate of decay at room temperature in cationic gold species bearing L₁-L₄ ligands, as well as the smaller *Me*BiCAAC L₆ and Ph₃P, in the presence of excess *n*-hexyne (Figure 9). As expected, we found *Et*CAAC-5 L₁, *Ad*CAAC-5 L₃, and *IPr*BiCAAC L₄ to yield very stable cationic gold species over a period of 4 days, whereas a rapid decay was observed with *Et*CAAC-6 L₂, *Me*BiCAAC L₆ and PPh₃. For L₂ and PPh₃, we attributed the decomposition to the formation of gold(0) nanoparticles as highlighted by the observation of insoluble black deposits on the NMR sample.³⁰ Because of the very different lifetime of (*IPr*BiCAAC)AuCl and (*Me*BiCAAC)AuCl, we took a closer look at their behavior under catalytic conditions. As shown in Figure 10, in both hydroamination and hydrohydrazination, we

Figure 9. Ligand effects on the decay of $[\text{LAu}(\text{alkyne})]^+[\text{BARF}^-]$.

found that $(i\text{PrBiCAAC})\text{AuCl}$ outperforms $(\text{MeBiCAAC})\text{AuCl}$. We next attempted to isolate the putative intermediates of the catalytic cycle (Scheme 4). Complex $(\text{L}_4)\text{AuCl}$ reacted with a terminal or an internal alkyne affording stable $(\text{L}_4)\text{Au}^+(\text{alkyne})$ adducts with either BF_4 or BARF^- anions. One of these complexes was characterized by X-ray crystallography. In contrast, even with a large excess of alkyne, $(\text{L}_6)\text{Au}^+(\text{alkyne})$ can only be characterized by NMR spectroscopy. After 2 days at room temperature, this complex disproportionates into the bis-ligated $(\text{L}_6)_2\text{Au}^+$ (characterized by X-ray crystallography) and gold nanoparticles. Note that the predisposition of MeBiCAAC L_6 over $i\text{PrBiCAAC}$ L_4 to favor the formation of such bis-ligated complexes has already been observed with copper.¹²

Scheme 4. Behavior of BiCAACAu^+ toward alkynes, amines and hydrazines under stoichiometric conditions. For the X-ray structures of gold complexes, only the cations are shown.

Figure 10. Comparison of the catalytic activity of L_4 and L_6 in the hydroamination (a) and hydrohydrazination (b) reactions

Reaction of $(\text{L}_4)\text{Au}^+(\text{TolCCH})$ with an excess of tolylamine or tosyl-hydrazine led to the expected formation of the corresponding imine **1b** and hydrazone **2q**. More interestingly, these experiments also showed the concomitant formation of the Werner adducts $(\text{L}_4)\text{Au}^+(\text{TolNH}_2)$ and $(\text{L}_4)\text{Au}^+(\text{TosNHNH}_2)$ which further illustrates that $i\text{PrBiCAAC}$ L_4 is capable of stabilizing the gold center at every step of the catalytic cycle.

Rationalizing the ligand effects by DFT: All calculations were performed with the Gaussian09 program suite³¹ using ultrafine³² (99,590) integration grids.³³ All structures were optimized with the ω B97X-D³⁴ functional and 6-31g**³⁵ basis set for all atoms except Au, which was treated with the SDD³⁶ basis set and ECP. Solvent was treated as a polarizable continuum of benzene.³⁷ Ujaque, Lledós *et al.* computationally demonstrated that the energy of the transition state for substrate exchange between the Werner complex (catalyst resting state) and the active species (η^2 - π complex) follows the order of stability of the π -complex,²⁸ meaning that the more stable the π -complex, the lower the barrier for a given ligand. Using their work as a guiding principle we compared the energy differences between the Werner complexes of aniline and phenylhydrazine and the η^2 - π complex of phenylacetylene for (L)Au⁺ complexes bearing ligands **L**₁ to **L**₄ (Figure 11). Our DFT study clearly shows that in both cases the *IPr*BiCAAC **L**₄ affords the most accessible

Figure 11. Energy profiles of substrate ligand exchanges as a function of **L**₁-**L**₄.

η^2 - π adducts. As highlighted previously,²⁸ the barrier determining the rate of the catalytic cycle is not the barrier for the nucleophilic attack on the π -complex but rather the protonolysis of the migrated Au-amide bond.³⁸ In their report, Ujaque, Lledós *et al.* noted the trend of increasing barrier height for proton transfer with increasing donor-strength of the ligand (barrier height: CAAC > saNHC). This principle provides a conundrum for chemists designing catalysts,³⁹ where there is a trade-off between the strength of the ligand to metal (L-M) bonds allowing for more durable catalysts and lower barriers to promote proton transfer.⁴⁰ Unarguably, the most ambiphilic ligands provide the strongest L-M bonds (*i.e.* **L**₂ > **L**₄ > **L**₁ = **L**₃) at the expense of an increased barrier for proton transfer. This could also explain why **L**₂ performs much worse than several carbenes despite having the strongest M-L bond and a sterically flexible backbone. A good illustration of this statement is given by NHC **L**₅ which performs surprisingly well compared to the more

ambiphilic carbenes thanks to its relatively weak donor-ability resulting in a low barrier for proton transfer. Altogether, our data suggest that *IPr*BiCAAC **L**₄ occupies the “sweet spot”, featuring both a strong M-L bond and a relatively low barrier for proton transfer.

IV. Benchmarking *IPr*BiCAAC **L**₄ against state-of-the-art ligands

The stability of gold complexes under prolonged reaction times and high temperatures is a prototypical limitation of most gold catalytic reactions. Capitalizing on the robustness of the **L**₄-Au bond, we envisaged that this complex should survive the experimental conditions used in the hydroamination of alkynes with the state-of-the-art phosphines **L**_A and **L**_B, and NHC **L**_C gold complexes, namely between 50 and 80 °C.^{8,10} We were pleased to witness a catalytic activity reaching nearly 17,000 TON in 19 h at 80 °C (Figure 12). We also evaluated the (*IPr*BiCAAC)AuCl complex in the hydrohydrazination reaction, and obtained, under the same conditions, up to 27,000 TON.

Conclusions

In summary, we have reported a comprehensive study highlighting the reactivity of CAAC gold complexes in the hydroamination and hydrohydrazination of alkynes. Our kinetic measurements demonstrate that the *IPr*BiCAAC **L**₄ provides a very active catalysts for these transformations, which is rationalized through mechanistic and DFT studies. We propose that the unique steric and electronic environment provided by the **L**₄ ligand singlehandedly shields the metal from degradation. Concomitantly it stabilizes the key π -alkyne complex active intermediate, and favors a low barrier for proton transfer. High TONs were obtained in the hydroamination and hydrohydrazination of alkynes, competing with recently reported, highly sophisticated phosphine and NHC complexes. Contrad-

Figure 12. Benchmarking the catalytic activity of *IPr*BiCAAC gold chloride (**L**₄AuCl) against state-of-the-art ligands.

icting a general consensus that gold catalysts must be improved through the design of tailored secondary interactions, we have provided compelling evidence that there is still much to be gained in controlling the ligand and core – that is, the metal-ligand bond itself. The remarkable progress made in the past 30 years in the design of stable carbenes have taught us that these species provide an exceptional handle for the tuning of the electronic and steric environment of a metal, including now the readily available BiCAAC ligands,¹² one of the most recent additions to the CAAC family.

Experimental Section

All the catalytic experiments were performed in air using commercial grade solvents and reagents unless otherwise noted. All the kinetic experiments were performed three times to verify the reproducibility of the results. All other manipulations were performed using standard glovebox and Schlenk techniques. Glassware was dried in an oven overnight at 150 °C or flame-dried before use. Benzene, diethyl ether, and n-pentane were freshly distilled over Na/benzophenone. Hexanes, dichloromethane, and chloroform were freshly distilled over CaH₂. Deuterium-labeled solvents were purchased from Cambridge Isotope Laboratories. NMR: Multinuclear NMR data were recorded on a Varian INOVA 400 and 500 MHz or a Bruker Avance 300 and 600 MHz. Single-crystal X-ray structure determinations were carried out at low temperature on a Bruker P4, Platform, or Kappa diffractometer equipped with a Mo ($\lambda = 0.71073$ Å) or Cu ($\lambda = 1.54178$ Å) radiation source and a Bruker APEX detector. Crystals were selected under oil, mounted on nylon loops, then immediately placed in a cold stream of nitrogen. All structures were solved by direct methods with SIR 2004 or SHELXS and refined by full-matrix least-squares procedures utilizing SHELXL within the Olex 2 small-molecule solution,⁴¹ refinement, and analysis software package.

General method for the hydroamination

In air, a scintillation vial (3 mL) was charged with IPrBiCAAC)AuCl/ KBarF (2.5 mol%), C₆H₆ (1 mL) and the alkyne (1.163 mmol, 1.0 eq.). After stirring for two minutes, the amine (1.163 mmol, 1.0 eq.) was added as a solution in C₆H₆ (0.5 mL). The mixture was then set stirring according to reaction time and temperature listed in scheme 3. The products were purified by column chromatography using Florisil and eluting with a gradient mixture of DCM/hexane.

General method for the hydrohydrazination

In air, a scintillation vial (3 mL) was charged with IPrBiCAAC)AuCl/ KBarF (0.5 mol% for 2a-2e; 2.5 mol% for 2f-2p), C₆H₆ (200 μ L) and the alkyne (0.357 mmol, 1.0 eq.).

After stirring for two minutes, the amine (0.357 mmol, 1.0 eq.) was added as a solution in C₆H₆ (200 μ L). The mixture was then set to stir according to the reaction time and the temperature listed in scheme 4. The products were purified by column chromatography using Florisil and eluting with a gradient mixture of DCM/hexane. NB: Air sensitive products were purified under argon using dried Florisil.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/>

Experimental procedures and characterization data, X-ray crystallographic data and computational details.

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