

Review

N-heterocyclic Carbene Gold Complexes Active in Hydroamination and Hydration of Alkynes

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Abstract: Until the year 2000, gold compounds were considered catalytically inert. Subsequently, it was found that they are able to promote the nucleophilic attack on unsaturated substrates by forming an Au- π -system. The main limitation in the use of these catalytic systems is the ease with which they decompose, which is avoided by stabilization with an ancillary ligand. N-heterocyclic carbenes (NHCs), having interesting σ -donor capacities, are able to stabilize the gold complexes (Au (I/III) NHC), favoring the exploration of their catalytic activity. This review reports the state of the art (years 2007–2022) in the nucleophilic addition of amines (hydroamination) and water (hydration) to the terminal and internal alkynes catalyzed by N-heterocyclic carbene gold (I/III) complexes. These reactions are particularly interesting both because they are environmentally sustainable and because they lead to the production of important intermediates in the chemical and pharmaceutical industry. In fact, they have an atom economy of 100%, and lead to the formation of imines and enamines, as well as the formation of ketones and enols, all important scaffolds in the synthesis of bioactive molecules, drugs, heterocycles, polymers, and bulk and fine chemicals.

Keywords: N-heterocyclic carbenes; gold complexes; hydroamination; hydration; alkynes

Citation: Mariconda, A.; Sirignano, M.; Troiano, R.; Russo, S.; Longo, P. N-heterocyclic Carbene Gold Complexes Active in Hydroamination and Hydration of Alkynes. *Catalysts* **2022**, *12*, 836. <https://doi.org/10.3390/catal12080836>

Academic Editor: Victorio Cadierno

Received: 6 July 2022

Accepted: 26 July 2022

Published: 29 July 2022

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1. Introduction

Copper, silver, and gold belong to Group 11 (Ib) of the periodic table. The metals of this group have the highest thermal and electrical conductivities. They are the most ductile and malleable and are also commonly called coinage metals. Their use goes back to prehistoric times. The oldest artifacts made with copper date to the Neolithic; silver was used to purify drinking water, and to create jewels and ornaments. In addition, gold was used mainly to make jewelry and to mint coins. For a long time, silver and gold were considered not useful for catalytic purposes; in fact, their use in catalysis is recent.

Nowadays, many complexes of these metals, stabilized by many kinds of ligands, are used as catalysts [1–6]. A class of ligands particularly studied and widely used in catalysis for its excellent chemical properties is constituted by N-heterocyclic carbenes. Their use dates back thirty years, when Arduengo, in 1991, was able to obtain and unequivocally characterize the first stable N-heterocyclic carbene (NHC): the 1,3-diaadamantylimidazol-2-ylidene [7].

Since then, other structurally modified NHC ligands have been synthesized, both cyclic and acyclic, by changing the nature of substituents on nitrogen atoms, or by inserting a heteroatom on the ring core or different substituents on the backbone (Figure 1).

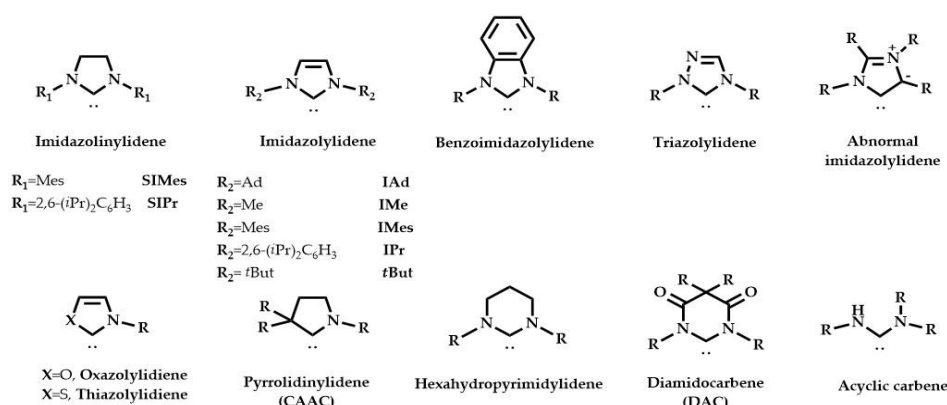


Figure 1. Structure of the most used NHC ligands.

The most commonly used are imidazolinyliidenes, five-membered ring imidazolyliidenes, and triazolyliidenes. NHC ligands have lone-pair electrons on the central carbon atom (sp^2) that can coordinate to a metal. They are strong σ -donating ligands, and the π^* molecular orbital (MO) of the NHCs can accept electron density from the filled d orbitals of the transition metal via a classical $d \rightarrow \pi^*$ back-donation [8,9]. Frequently, NHCs have replaced phosphine ligands in the design and development of efficient catalysts.

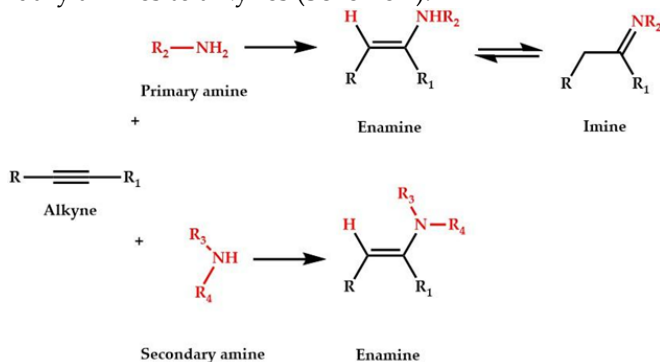
It is worth noting that the chemical–physical properties of metal complexes (M–NHCs), e.g., thermal stability and tolerance against moisture and air, can be modulated by modifying the steric and electronic properties of substituents on the backbone and/or on the nitrogen atoms at the NHC ligand. NHCs are easily obtained upon deprotonation of an imidazolium salt. Their synthesis can be carried out following two methodologies: (i) a multicomponent reaction building up the heterocycle with the appropriate substituents in a one-pot reaction or (ii) nucleophilic substitution at the imidazole heterocycle.

The application of NHCs as ligands able to stabilize metal complexes active in catalysis includes all elements of the d-block from group 3 to group 12 [10]. The two main applications of NHCs–metal catalysts are the ruthenium-catalyzed olefin metathesis and the palladium-catalyzed cross-coupling reactions.

In this review, we describe the development of catalysis carried out using NHC–gold complexes in the hydroamination and hydration of alkynes, pointing out the advantages of using these complexes as catalysts.

2. Hydroamination of Alkynes

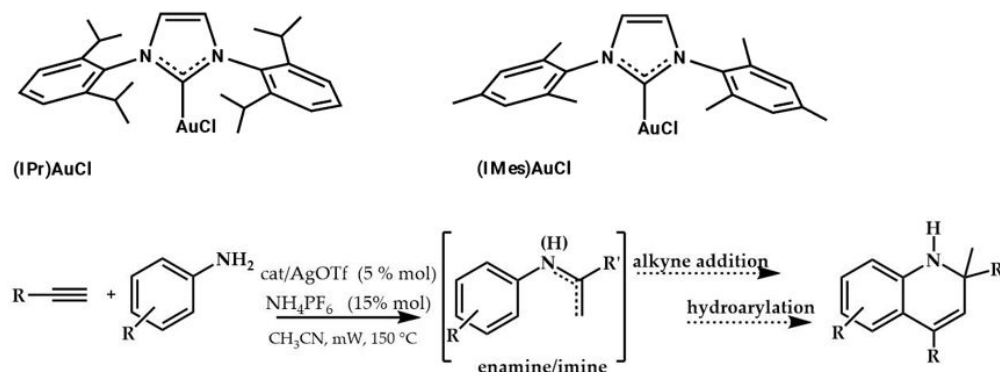
The reaction of hydroamination of alkynes is the addition of ammonia, primary or secondary amines to alkynes (Scheme 1).



Scheme 1. Hydroamination of alkynes.

The enamines and imines produced are useful key molecules for numerous nitrogen-containing compounds of biological, industrial, and agrochemical interest [11]. In general, in the hydroamination of alkynes, using as catalysts metal complexes stabilized by NHC ligands and having halides as counterions, a silver salt is added as co-catalyst, in order to remove the halides coordinated to the gold centers and generate the catalytic active species for substrate coordination.

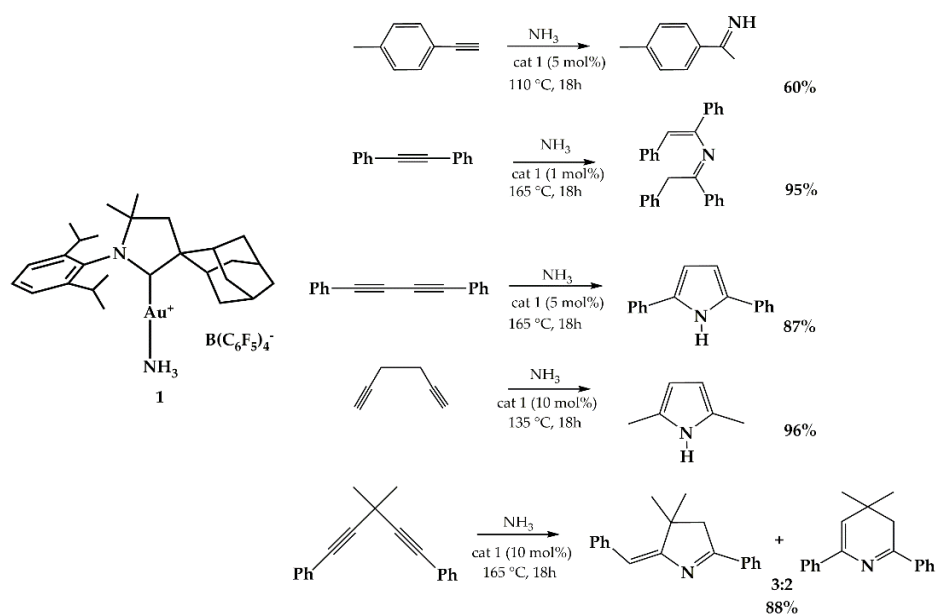
In 2007, Che et al. showed that (IPr)AuCl (Scheme 2) was active in the hydroamination of alkynes with primary arylamines [12].



Scheme 2. NHC–gold(I) catalyzed reactions between primary arylamines and alkynes.

This reaction, in the presence of 5 mol% of NHC–gold catalyst at 80–100 °C, gave 1,2-dihydroquinoline derivatives in up to 80% yields after 12–24 h. Experimental evidence demonstrated that enamine is an intermediate of the reaction. (IPr)AuCl was found to be more efficient than (IMes)AuCl and as active as {(*o*-biphenyl)di-*tert*-butylphosphine}AuCl.

Bertrand et al., in 2008, synthesized and tested in catalysis of hydroamination of alkynes the complex **1** reported in Scheme 3 [13]. The authors obtained pyrroles from diynes for the addition of ammonia. In particular, double hydroamination occurred in the case of diynes.



Scheme 3. Cationic gold-catalyzed hydroamination of alkynes with NH₃.

The study of the reaction mechanism revealed that it proceeds through an intermediate in which both the NH_3 and the alkyne are bound to the acid Lewis gold complex.

In 2009, Bertrand and coworkers reported the catalytic activity of cationic η^2 -toluene gold(I) complex **2** (Figure 2) in the intermolecular hydroamination of alkynes with primary or secondary alkyl amines [14,15].

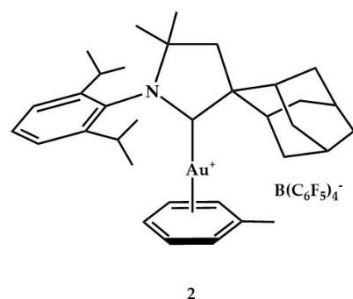


Figure 2. Cationic gold(I) complex **2**.

With the primary amines (2,4,6-trimethylaniline and *tert*-butylamine) and alkynes, using 5 mol% of **2** as catalyst, clean reactions occurred (81%–94% yield) at temperatures between 40 °C and 140 °C and a reaction time between 10 and 24 h. The complex **2** was active (46%–98% yield) also in the hydroaminations with secondary amines (e.g., diphenylamine, *N*-methylaniline, 1,2,3,4-tetrahydroisoquinoline, diethylamine); however, with phenylacetylene and diethylamine the yield was lower (23%). With methylphenylacetylene, the expected mixture of Markovnikov and anti-Markovnikov products was obtained. Instead, it was surprisingly observed that with diethylacetylene, the expected hydroamination adduct was only the minor product (21%–43%) of the reaction, being the major product (79%–57%) an isomer in which the unsaturation has been shifted.

In 2009, Bertrand et al. synthesized and characterized the complex **3** (Figure 3). The precatalyst was tested in hydroamination of internal alkynes with Et_2NH [16]. The cyclic(alkyl)(amino)carbene (CAAC) ligand provided steric protection to the metal center; in addition, the replacement of one of the nitrogens by a carbon center makes CAACs slightly more nucleophilic, but considerably more electrophilic than NHCs.

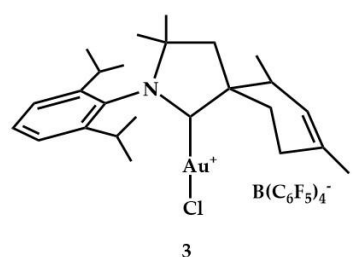


Figure 3. Cationic gold(I) complex **3**.

The precatalyst **3**, in the presence of 1 equiv. of $\text{KB}(\text{C}_6\text{F}_5)_4$, was active for the addition of diethylamine to three internal alkynes: 1,2-diphenylethyne (92% yield), 3-hexyne (93% yield), and 1-phenyl-1-propyne (92% yield). The authors found that **3** was as efficient as **2** (89%–98% yield).

Ghosh et al., in 2010, synthesized a series of gold(I) and silver(I) precatalysts stabilized by *N*-heterocyclic carbenes based on 1,2,4-triazole derivatives (see Figure 4) [17].

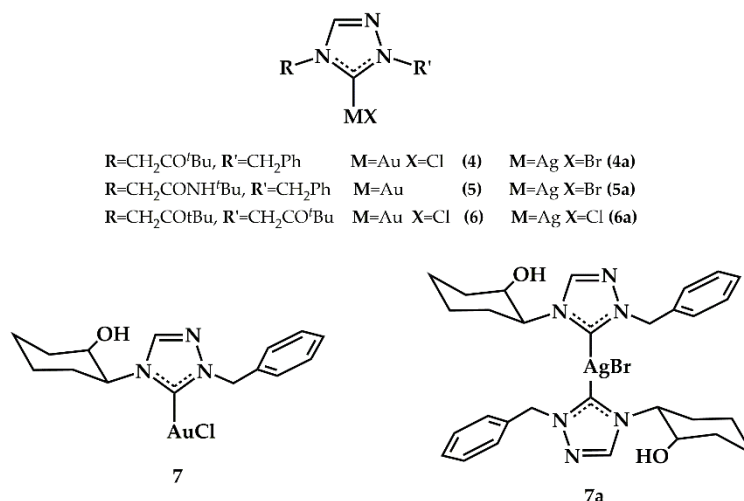
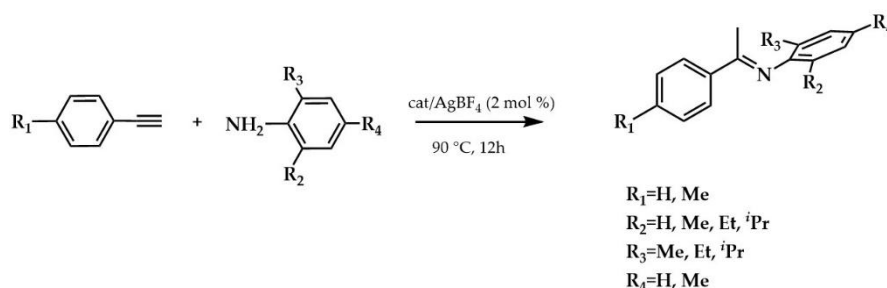


Figure 4. Gold and silver precatalysts of 1,2,4-triazole based NHCs synthesized from Ghosh et al. [17].

The silver(I) **4a–7a** complexes were synthesized from the respective 1,2,4-triazolium halide salts by treatment with silver oxide in 43%–64% yield, while the gold(I) complexes **4–7** were obtained by transmetalation reaction of the silver analogues **4a–7a** with $(\text{Sme}_2)\text{AuCl}$ in 60%–76% yield. The gold(I) **4–7** complexes displayed from good (42%) to high (93%) activity for the intermolecular hydroamination reaction (90 °C for 12 h, in air) of *o/p*-substituted aryl amines (2-methylaniline, 2,6-dimethylaniline, mesitylaniline, 2,6-diethylaniline, and 2,6-di-*i*-propylaniline) with terminal alkynes in CH_3CN (Scheme 4).



Scheme 4. Hydroamination reaction of *o/p*-substituted aryl amines with terminal alkynes.

The yields (%) were determined by GC using diethylene glycol di-*n*-butyl ether as an internal standard. Complex **4** was more efficient in the reaction between 2,6-dimethylaniline or mesitylaniline and 4-ethynyltoluene with a yield of 93%, while complex **6** was more active (92% yield) in the reaction between 2,6-diethylaniline and phenylacetylene. The control experiments performed with $(\text{SMe}_2)\text{AuCl}/\text{AgBF}_4$ and also with the corresponding blank experiment carried out with only AgBF_4 exhibited a significant increase of up to 85% under analogous conditions in the case of the gold **4–7** precatalysts.

The silver(I) **4a–7a** complexes showed lower activity (from 0% to 29% yield) than the analogous gold(I) **4–7** complexes did. The reaction of hydroamination showed, for all the alkyne substrates, a Markovnikov-type N–H addition. The results obtained in this work underline the importance of gold complexes with respect to silver analogs in catalysis.

In 2011, Bertrand and coworkers reported that the two complexes in Figure 5 catalyzed the addition of hydrazine (H_2NNH_2) to a variety of non-activated alkynes and allenes to afford a diverse array of acyclic and cyclic nitrogen-containing compounds [18].

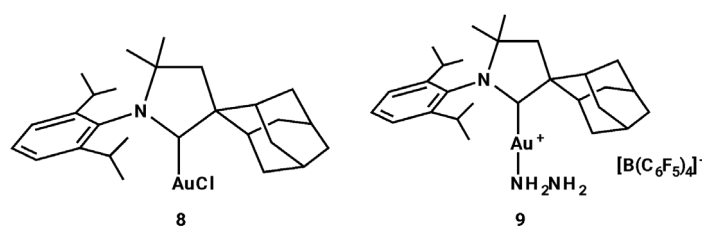


Figure 5. Complexes studied from Bertrand.

The solid-state structure of **9** was determined by X-ray diffraction, which confirmed that only one amino group is coordinated to the cationic gold(I) to give a η^1 Werner-like complex. The catalytic hydroamination of *p*-methoxyphenylacetylene with hydrazine, both complexes **8** and **9** to 5.0 mol% in the presence of $\text{KB}(\text{C}_6\text{F}_5)_4$, led to the formation of hydrazone, which is the tautomer of the enamine resulting from a Markovnikov-type addition (yield 95%, at 100 °C for 30 min). By lowering the amount of complex **8** to 0.1 mol%, 95% conversion was observed when the reaction mixture was heated at 150 °C for 6 h. The reaction of hydrazine with terminal alkynes, i.e., *n*-butyne, benzyl acetylene, and 6-midazole6-ylene, using complex **8** (5 mol%) as catalyst, produced after 3 h at 100 °C the hydrazones resulting from a Markovnikov-type addition in high yields: 89%, 95%, and 92%, respectively. Both complexes **8** and **9** (5 mol%) gave high yields even in the reaction of 1,2-diphenylethyne with H_2NNH_2 , although a longer reaction time (14 h) was required. Both complexes were also active in the catalysis of diynes with H_2NNH_2 for the synthesis of heterocycles.

In 2012, Lavoie et al. achieved a highly stereoselective Markovnikov-type addition of phenylacetylene to 2,6-dimethylaniline using gold(I) complexes of 1-[1-(2,6-dimethylphenylimino)alkyl]-3-(mesityl) 6-midazole-2-ylidene ($\text{C}^{\wedge}\text{ImineR}$), 1,3-dimesitylimidazol-2-ylidene (Imes) and the corresponding thione derivatives ($\text{S}^{\wedge}\text{ImineR}$ and ImesS) complexes (Figure 6) [19].

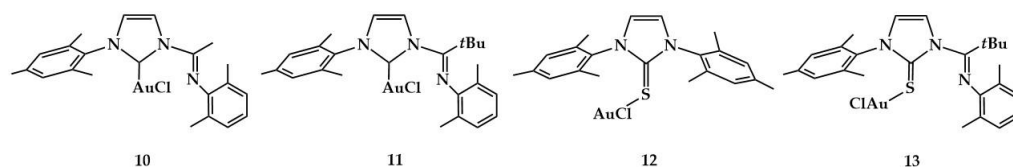
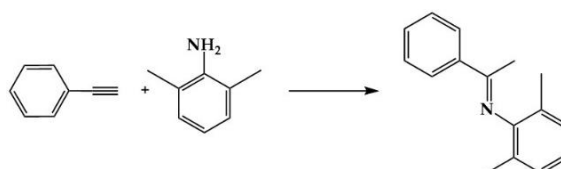


Figure 6. Complexes of Lavoie et al. [19].

The activity in catalysis of the gold complexes in the hydroamination of phenylacetylene with 2,6-dimethylaniline was evaluated and compared to control catalyst systems such as $\text{Au}(\text{Sme}_2)\text{Cl}$ (**14**), benchmark (Imes) AuCl , and AgBF_4 (Table 1).

Table 1. Catalyst screening for the hydroamination of phenylacetylene with 2,6-dimethylaniline.



Entry ^a	Complex	Conversion (%) ^b
1	14	35
2	13	85
3	12	57
4	11	>98
5	11 ^c	37

6	10	71
7	(Imes)AuCl	98
8	AgBF₄^d	42

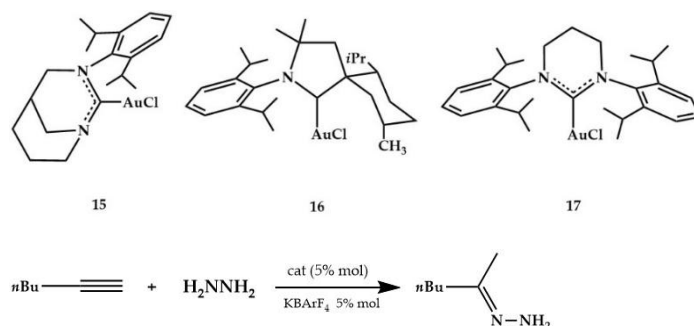
^a Reaction conditions: phenylacetylene (1.0 equiv.), 2,6-dimethylaniline (1.1 equiv.), catalyst (5 mol% Au), AgBF₄ (10 mol%), CD₃CN (0.6 mL) at 70 °C, 20 h. ^b Percentage conversion determined by ¹H-NMR spectroscopy based on the amount of phenylacetylene in solution. ^c Reaction performed in the absence of AgBF₄ under otherwise identical conditions. ^d Reaction performed with AgBF₄ (10 mol%) in the absence of any gold complex but under otherwise identical conditions.

The highest conversions were obtained with **11** (entry 4) and (Imes)AuCl complexes. All catalysts tested exclusively produced the product Markovnikov obtained for addition of the aniline with subsequent tautomerization of the enamine.

The different activity of complexes **11** and **10** found in catalysis suggested that the steric effects of the ligand play a relevant role. The **10**, **11**, and **13** gold complexes were used to study the steric and electronic effects of the substituents of the anilines (2,4,6-trimethylaniline, 2-*tert*-butylaniline, 2,6-diisopropylaniline, aniline, *para*-methylaniline, *para*-anisidine, *para*-(trifluoromethyl)aniline, *para*-nitroaniline) on the catalysis. The order of reactivity found was to be **11** > **13** > **10** using either sterically or electronically demanding anilines.

Ghosh et al., in 2012, studied the coordination pathways between two representative substrates, MeC≡CH and PhNH₂, in the hydroamination reaction of gold(I) complex, namely, [1,3-dimethylimidazol-2-ylidene]gold chloride, using the density functional theory (DFT) [20]. The study found that the lowest activation barrier is for amine coordination compared to alkyne coordination. Furthermore, it was calculated that the hydroaminated enamine PhNHMeC=CH₂ is more stable in its tautomeric imine form, PhN=Cme₂.

Bertrand et al., in 2013, synthesized the (carbene)gold chloride **15** (Scheme 5), which was isolated in 57% yield, and fully characterized also by a single-crystal X-ray diffraction study [21]. This catalyst promoted the hydroamination of 1-hexyne with hydrazine at room temperature.



Scheme 5. Hydroamination of 1-hexyne with hydrazine.

The reactions were carried out in different solvents, i.e., chloroform, dichloromethane, tetrahydrofuran, and benzene (entry 4). The latter gave the best results: 91% conversion after 3 h (Table 2).

Table 2. Catalytic hydroamination of 1-hexyne with hydrazine.

Entry ^a	Complex	Solvent	Time (h)	Conversion (%) ^b
1	15	CDCl ₃	3	42
2	15	CD ₂ Cl ₂	3	56
3	15	THF-d ₈	3	68
4	15	C ₆ D ₆	3	91
5	8	C ₆ D ₆	4	22

6	16	C ₆ D ₆	16	10
7	17	C ₆ D ₆	16	>5

^a Reaction conditions: solvent (0.4 mL), 1,4-di-*tert*-butylbenzene (0.05 mmol), alkyne (0.5 mmol), anhydrous NH₂NH₂ (0.5 mmol) in a J Young NMR tube at room temperature. ^b Determined by ¹H-NMR with 1,4-di-*tert*-butylbenzene as internal standard.

Its catalytic activity was compared with the three benchmark metal complexes (**16**, **17**, and **8**) shown in the Scheme 5 and Figure 5, respectively. Under the same experimental conditions, only a 22% conversion was observed after 4 h with the complex **8** (entry 5), whereas complex **16** gave 10% conversion after 16 h (entry 6) and complex **17** proved to be even less effective (entry 7). In Table 3, the efficiency of the catalyst **15** using alkyl substituted terminal alkynes is reported. The catalytic activity decreased when the steric hindrance of the substrates increased.

Table 3. Catalytic hydroamination of alkynes with hydrazine.

$$\text{R}-\text{C}\equiv\text{C}-\text{R}' + \text{H}_2\text{NNH}_2 \xrightarrow[\text{Benzene}]{\text{KBu}_4\text{F}_4 \text{ 5 \% mol}, \text{15 (5 \% mol)}} \text{R}-\text{C}(\text{CH}_2\text{R}')=\text{N}-\text{NH}_2$$

Entry ^a	R, R'	Temperature (°C)	Time (h)	Conversion (%) ^b	Yield (%)
1	<i>n</i> Butyl, H	rt	3	91	83
2	Cyclohexyl, H	rt	18	78	71
3	Benzyl, H	rt	4	87	83
4	<i>tert</i> Butyl, H	rt	36	29	-
5	<i>tert</i> Butyl, H	90	6	88	79
6	Phenyl, H	rt	12	<5	-
7	Phenyl, H	90	3	100	87
8	4-Methoxyphenyl, H	90	4	100	95
9	1-Cyclohexenyl, H	75	6	100	77
10 ^c	Ph, Ph	110	6	100	82

^a Reaction conditions: solvent (0.4 mL), 1,4-di-*tert*-butylbenzene (0.05 mmol), alkyne (0.5 mmol), anhydrous NH₂NH₂ (0.5 mmol) in a J Young NMR tube. ^b Determined by ¹H-NMR with 1,4-di-*tert*-butylbenzene as internal standard. ^c CDCl₃ was used as the solvent.

Peris et al. prepared a rigid, planar tris (NHC) based on a triphenylene core coordinated to palladium and gold [22].

The obtained trimetallic gold **18** and **19** complexes (Figure 7) were tested in the hydroamination of phenylacetylene with several substituted anilines (see reaction of Table 1 and results in Table 4). Their catalytic activity was compared with **20** complex (Figure 7).

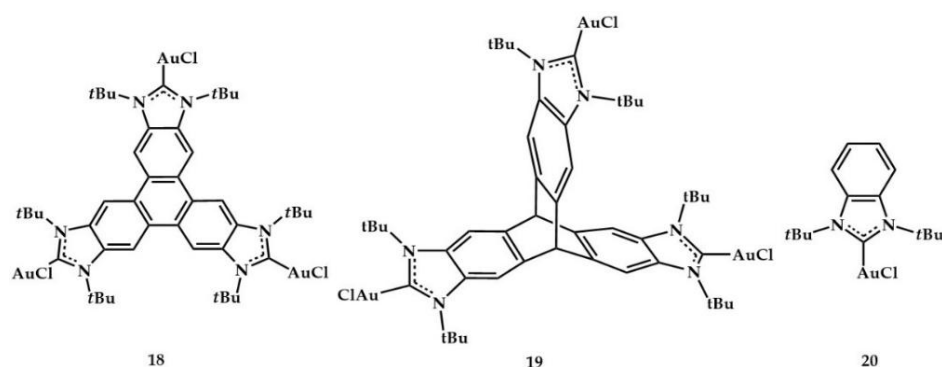


Figure 7. Trimetallic gold **18** and **19** complexes and monometallic **20** complex.

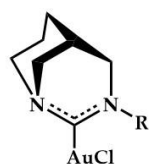
Table 4. Hydroamination of phenylacetylene with substituted anilines.

Entry ^a	Aniline	Complex	Yield (%) ^b
1	2,4,6-Me ₃ C ₆ H ₂	18	94
2	2,4,6-Me ₃ C ₆ H ₂	19	87
3	2,4,6-Me ₃ C ₆ H ₂	20	89
4	2,6- <i>i</i> Pr ₂ C ₆ H ₃	18	95
5	2,6- <i>i</i> Pr ₂ C ₆ H ₃	19	54
6	2,6- <i>i</i> Pr ₂ C ₆ H ₃	20	82
7	Ph	18	95
8	Ph	19	82
9	Ph	20	91
10	2-MeC ₆ H ₄	18	99
11	2-MeC ₆ H ₄	19	86
12	2-MeC ₆ H ₄	20	85
13 ^c	2-MeC ₆ H ₄	18	96
14 ^c	2-MeC ₆ H ₄	19	81
15 ^c	2-MeC ₆ H ₄	20	83
16 ^d	2-MeC ₆ H ₄	18	87
17 ^d	2-MeC ₆ H ₄	19	62
18 ^d	2-MeC ₆ H ₄	20	85
19	4-MeC ₆ H ₄	18	91
20	4-MeC ₆ H ₄	19	60
21	4-MeC ₆ H ₄	20	70

^a Reaction conditions: 0.5 mmol phenylacetylene, 0.55 mmol amine, 1 mol% [Au], 2 mol% AgBF₄, 1 mL of MeCN at 90 °C, 6 h. ^b Yields determined by GC using anisole (0.5 mmol) as internal standard. ^c Used 0.5 mmol hexafluorobenzene. ^d Used 2 mmol hexafluorobenzene.

All the reactions catalyzed by the trimetallic complex **18** provided excellent yields (>90%), while the catalytic activity of the monometallic complex **20** was higher than that shown by the trimetallic complex **19**, except for in the reactions carried out with *o*-methylaniline, for which the activities were similar.

Bertrand and coworkers, in 2016, reported the catalytic activity of gold complexes bearing anti-Bredt di(amino)carbenes ligands **21a–d** (Figure 8) in the hydroamination of phenylacetylene with phenyl hydrazine or aniline (for reaction, see Table 1) [23].



R= 2,4,6-Me₃(C₆H₂) (**21a**)
R= Ph (**21b**)
R= 4-Me(C₆H₄) (**21c**)
R= 4-Me(C₆H₄)SO₂CH₂ (**21d**)

Figure 8. Gold complexes with anti-Bredt ligands.

These ligands are significantly more π -accepting than classical N-heterocyclic carbenes are, while retaining their strong σ -donation to the metal [24]. The **21a** complex (5 mol%) and potassium tetrakis(pentafluorophenyl)borate (KB(C₆F₅)₄) were active in the reaction of phenylhydrazine with some arylacetylenes and 1-ethynylcyclohexene to afford quantitatively (84%–99%) hydrazones at room temperature, after 24 h. The authors studied the hydroamination of phenylacetylene with aniline of the **21a–d** complexes. Data in Table 5 show that all complexes were found to be very active at room temperature using

KB(C₆F₅)₄ as co-catalytic salt. The reaction rate proved to be insensitive to the N-substituent of the ligand.

Table 5. Hydroamination of phenylacetylene with aniline.

Entry ^a	Complex	Time (h)	Conversion (%) ^b
1	21a + TosylAg	3	35
2	21a + AgSbF ₆	3	44
3	21a + KB(C ₆ F ₅) ₄	3	75
4	22a	3	0
5	21a + KB(C ₆ F ₅) ₄	24	>99
6	21b + KB(C ₆ F ₅) ₄	24	>99
7	21c + KB(C ₆ F ₅) ₄	24	>99
8	21d + KB(C ₆ F ₅) ₄	24	>99

^a Reaction conditions: 0.5 mmol phenylacetylene, 0.55 mmol aniline, 5 mol% catalyst, 0.6 mL C₆D₆, room temperature. ^b Determined by NMR.

The catalytic system **21a**/KB(C₆F₅)₄ was also tested in the reaction of aryl alkynes and 1-ethynylcyclohexene with various anilines bearing electron-withdrawing or electron-donating substituents. In all cases, almost complete conversion was observed after 24 h at room temperature.

In 2017, Peris et al. coordinated to gold a D_{3h}-symmetry tris-N-heterocyclic carbene ligand that contains an electron-poor hexaazatriphenylene (HAT) core [25]. The tris-Au(I) **22** complex (Figure 9) was tested in the hydroamination of phenylacetylene with substituted anilines (for reaction, see Table 1) and in the three-component Strecker reaction.

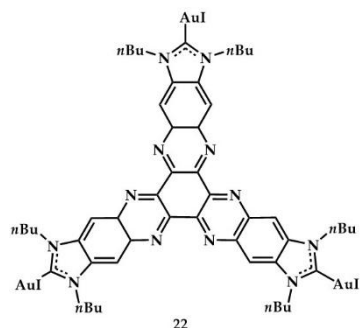


Figure 9. Gold complex with hexaazatriphenylene core.

The catalytic activity in the hydroamination reaction was compared with that of the benchmark complex **20** (Table 6). The latter can be considered as one of the gold-containing branches of **22**, but without the electron-poor pyrazine ring. With both gold complexes, AgBF₄ was added as a chloride scavenger in order to activate the catalysts.

Table 6. Hydroamination of phenylacetylene with substituted anilines.

Entry ^a	ArNH ₂ (Ar)	Complex	Yield (%) ^b
1	2,4,6-Me ₃ C ₆ H ₂	22	82
2	2,4,6-Me ₃ C ₆ H ₂	20	68
3	2,6- <i>i</i> Pr ₂ C ₆ H ₃	22	81
4	2,6- <i>i</i> Pr ₂ C ₆ H ₃	20	64
5	Ph	22	92
6	Ph	20	72

7 ^a	2-MeC ₆ H ₄	22	98
8	2-MeC ₆ H ₄	20	80
9	4-MeC ₆ H ₄	22	91
10	4-MeC ₆ H ₄	20	72

^a Reaction conditions: 0.5 mmol phenylacetylene, 0.55 mmol amine, 1 mol% catalyst (based on concentration of Au active sites), 2 mol% AgBF₄, 1 mL of MeCN at 90 °C, 6 h. ^b Yields determined by GC using anisole as internal standard.

In 2017, Peris and coworkers also synthesized three gold(I) complexes bearing NHC ligands with fused polycyclic aromatic hydrocarbons (Figure 10) [26].

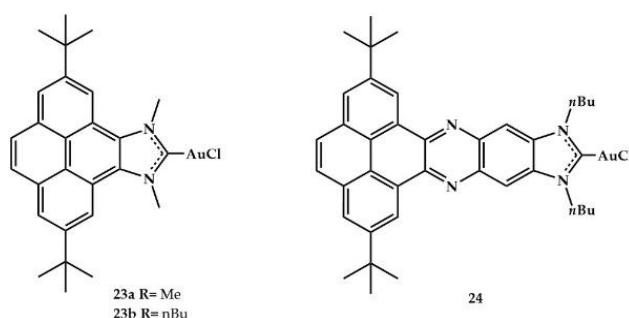


Figure 10. Gold(I) complexes with fused polycyclic aromatic hydrocarbons as ligands.

The **23a–b** and **24** complexes were tested as catalysts for the hydroamination of phenylacetylene (Table 7) with substituted anilines (for reaction see Table 1).

Table 7. Hydroamination of phenylacetylene with substituted anilines.

Entry ^a	ArNH ₂ (Ar)	Complex	Yield (%) ^b
1	2,4,6-Me ₃ C ₆ H ₂	23a	41
2	2,4,6-Me ₃ C ₆ H ₂	23b	68
3	2,4,6-Me ₃ C ₆ H ₂	23b^c	82
4	2,4,6-Me ₃ C ₆ H ₂	24	37
5	2,4,6-Me ₃ C ₆ H ₂	24^c	40
6	2,6- <i>i</i> Pr ₂ C ₆ H ₃	23a	39
7	2,6- <i>i</i> Pr ₂ C ₆ H ₃	23b	62
8	2,6- <i>i</i> Pr ₂ C ₆ H ₃	23b^c	77
9	2,6- <i>i</i> Pr ₂ C ₆ H ₃	24	54
10	Ph	23a	44
11	Ph	23b	88
12	Ph	23b^c	99
13	Ph	24	21
14	Ph	24^c	36
15	2-MeC ₆ H ₄	23a	70
16	2-MeC ₆ H ₄	23b	90
17	2-MeC ₆ H ₄	23b^c	92
18	2-MeC ₆ H ₄	24	55
19	2-MeC ₆ H ₄	24^c	60
20	4-MeC ₆ H ₄	23a	50
21	4-MeC ₆ H ₄	23b	80
22	4-MeC ₆ H ₄	23b^c	84
23	4-MeC ₆ H ₄	24	29

^a Reaction conditions unless specified otherwise: 0.5 mmol of phenylacetylene, 0.55 mmol of amine, 1 mol% of [cat.], 2 mol% of AgBF₄, 1 mL of MeCN, 90 °C, 6 h. ^b Yields determined by GC using anisole (0.5 mmol) as internal standard. ^c Addition of 0.05 mmol of pyrene.

They showed moderate-to-good conversion to products (21%–90%). It was observed that the activities of the catalysts were enhanced by the addition of a little amount of pyrene, this was attributed to the formation of π - π stacking aggregates between the molecules of pyrene and the catalyst, which in turn partially prevents self-assembly of the catalyst.

In 2017, Messerle et al. reported the synthesis of an Au(III) complex containing a hemilabile bis-pyrazole carbene ligand, namely, (1,3-bis((1H-pyrazol-3-yl)methyl)-2,3-dihydro-1H-imidazole) [27].

The **25** Au(III) complex was tested in dihydroalkoxylation, spirocyclization of alkynyl diols, and intra/intermolecular hydroamination reactions in the presence of sodium tetrakis(pentafluorophenyl)borate ($\text{NaB}(\text{C}_6\text{F}_5)_4$). Its catalytic activity was compared with the analogous **26** gold(I) complexes (Figure 11) in the intramolecular hydroamination reactions (Table 8) and for hydroamination of phenylacetylene with aniline (Table 9) (for reaction see Table 1).

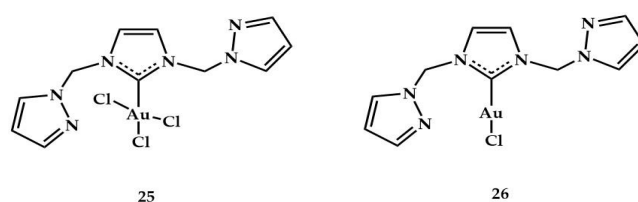
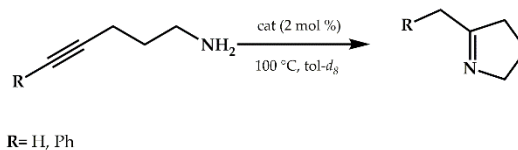


Figure 11. Au(III) and Au(I) complexes synthesized by Messerle et al. [27].

Table 8. Intramolecular hydroamination reaction.



Entry ^a	R	Complex	Time (h)	Conversion (%) ^b
1	H	25	13	97
2	H	26	18	93
3	Ph	25	24	98
4	Ph	26	24	96

^a Reaction conditions: 0.2 mmol of substrate, 2 mol% of [cat.], 2.2 mol% of NaBAR^{F} , 0.6 mL of toluene- d_8 in a Young's NMR tube, 100 °C. ^b Conversions were determined by integration of the product resonances relative to the substrate resonances.

Table 9. Gold-catalyzed intermolecular hydroamination reactions of phenylacetylene with Ar-NH₂.

Entry ^a	Ar-NH ₂	Complex	Time (h)	Conversion (%) ^b
1	Ph	25	0.33	26
2	Ph	26	1	30
3	2,4,6-Me ₃ C ₆ H ₂	25	16	61
4	4-CF ₃ C ₆ H ₄	25	16	49

^a Reaction conditions: 0.2 mmol of phenylacetylene, 0.2 mmol of amine, 2 mol% of [cat.], 2.2 mol% of NaBAR^{F} , 0.6 mL of toluene- d_8 in a Young's NMR tube, 100 °C. ^b Conversions were determined by integration of the product resonances relative to the substrate resonances.

The catalytic system showed a good performance. The gold-catalyzed intermolecular hydroamination reactions between phenylacetylene and some substituted anilines were studied.

The intermolecular hydroamination between phenylacetylene and aniline gave a low conversion for both catalytic systems, 26% and 30% for **25** and **26**, respectively. The complex **25** also promoted the reaction between phenylacetylene and mesitylamine or

(trifluoromethyl)aniline, giving 61 and 49% conversion to product, respectively. Thus, the catalysts **25** and **26** proved more active for intra- than for intermolecular hydroaminations.

Peris, in 2018, reported the synthesis and the X-ray analysis of digold(I) complex with a pyrenebis(imidazolylidene) ligand (Figure 12) and its catalytic activity in the presence of AgBF_4 in hydroamination of phenylacetylene (for reaction see Table 1) [28]. The authors studied the effects on the catalytic activity of **27** in the presence of a coronene.

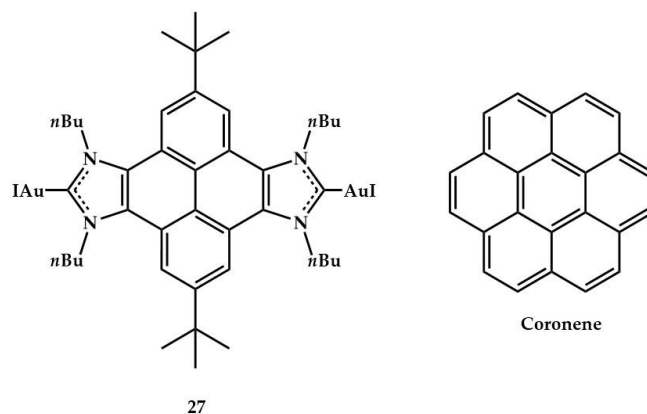


Figure 12. Digold(I) complex **27** and coronene.

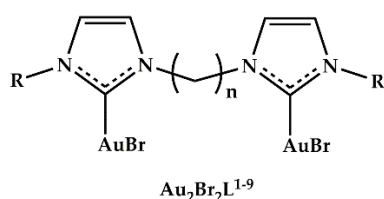
The results are given in Table 10.

Table 10. Hydroamination of phenylacetylene with substituted anilines.

Entry ^a	Ar-NH ₂	Complex (mol%)	Conversion (%) ^b	Yield (%) ^b
1	Ph	0.5	98	66
2	4-MeC ₆ H ₄	0.5	93	65
3	2,4,6-Me ₃ C ₆ H ₂	0.5	99	86
4	Ph	0.05	34	26
5 ^c	Ph	0.05	58	50
6	4-MeC ₆ H ₄	0.05	41	33
7 ^c	4-MeC ₆ H ₄	0.05	45	40
8	2,4,6-Me ₃ C ₆ H ₂	0.05	45	36
9 ^c	2,4,6-Me ₃ C ₆ H ₂	0.05	51	44

^a Reaction conditions: 0.5 mmol of phenylacetylene, 0.55 mmol of amine, 0.2 or 2 mol% AgBF_4 (depending on the catalyst loading), 1 mL of MeCN, 90 °C, 6 h. ^b Conversions and yields were determined by GC using anisole (0.5 mmol) as an internal standard. ^c Upon the addition of 0.05 mmol of coronene. As expected, yields were higher with the addition of coronene of about 20–30%.

In 2018, Baron et al. investigated, in alkyne hydroamination and Suzuki cross-coupling reactions, the catalytic performance of dinuclear gold(I) complexes with bridging di(N-heterocyclic carbene) (diNHC) ligands of the general formula $\text{Au}_2\text{Br}_2\text{L}^{1-9}$ (Figure 13) [29].



28a L^1 $n=1$, $\text{R}=\text{Me}$

28b L^2 $n=2$, $\text{R}=\text{Me}$

28c L^3 $n=3$, $\text{R}=\text{Me}$

28d L^4 $n=1$, $\text{R}=\text{Mesityl}$

28e L^5 $n=2$, $\text{R}=\text{Mesityl}$

28f L^6 $n=3$, $\text{R}=\text{Mesityl}$

28g L^7 $n=1$, $\text{R}=2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$

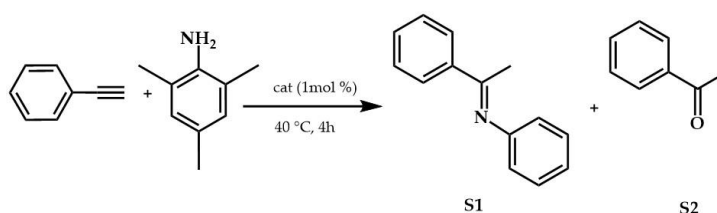
28h L^8 $n=2$, $\text{R}=2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$

28i L^9 $n=3$, $\text{R}=2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$

Figure 13. Gold(I) diNHC complexes $\text{Au}_2\text{Br}_2\text{L}^{1-9}$ of Baron et al. [29].

Single-crystal X-ray diffraction analyses have been made for $\text{Au}_2\text{Br}_2\text{L}^4$, $\text{Au}_2\text{Br}_2\text{L}^5$, and $\text{Au}_2\text{Br}_2\text{L}^6$. The authors used **28i** complex to optimize the reaction conditions of hydroamination of phenylacetylene with 2,4,6-trimethylaniline. The best reaction conditions found were neat conditions, 4 h and 2 mol% AgSbF_6 as co-catalyst. The results are reported in Table 11. The catalytic activity of synthesized $\text{Au}_2\text{Br}_2\text{L}^{1-9}$ complexes was compared with that of the benchmark (IPr)AuCl complex. Better performances were recorded with the N-methyl-substituted complexes (**28a–c**), which, together with benchmark (IPr)AuCl, reached complete alkyne conversions and very high hydroamination yields within the 4 h reaction time.

Table 11. Hydroamination reaction of phenylacetylene with 2,4,6-trimethylaniline.



Entry ^a	Complex	Yield S1(%)	Yield S2(%)
1	28a	93	7
2	28b	94	6
3	28c	94	6
4	28d	64	3
5	28e	75	9
6	28f	72	10
7	28g	73	2
8	28h	75	2
9	28i	70	6
10	(IPr)AuCl ^b	88	11

^a Reaction conditions: 1 mmol amine, 1 mmol phenylacetylene, 1 mol% Au catalyst, 2 mol% AgSbF_6 , 40 °C, 4 h. ^b 2 mol% Au catalyst.

The reaction produced also a small amount of acetophenone. Its formation probably proceeded through two steps: (i) Au-catalyzed hydroamination of phenylacetylene and (ii) hydrolysis of the hydroamination product by water brought into the system with the silver salt co-catalyst, which is quite hygroscopic. It is worth noting that no hydroamination product was obtained with internal alkynes, i.e., phenylpropyne and diphenylacetylene and N-methylaniline (secondary arylamines), or with cyclohexylamine and morpholine (primary/secondary alkylamines), except with complexes bearing the N-2,6-diisopropylphenyl substituent.

In 2019, the group of Nolan reported the hydroamination reactions with the catalysts in Figure 14 [30].

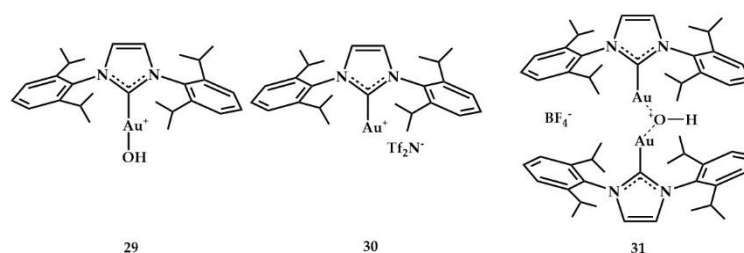
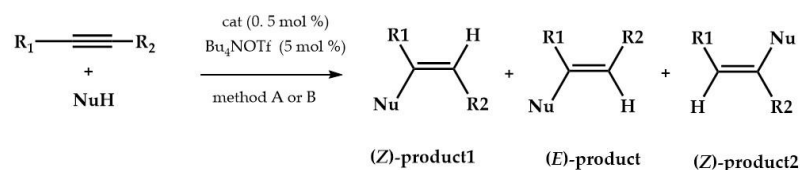


Figure 14. Complexes tested by Nolan et al. in the hydroamination of internal alkynes.

The **29–31** complexes (0.5 mol%) were used to establish the best catalytic conditions in hydroamination of phenylacetylene with *1H*-benzo[*d*][1,2,3]triazole; two methods were used: (i) a sand bath at 100 °C for 72 h and (ii) using microwave heating at 150 °C for 0.75 h. Complex **31** provided the best yields with both methods (66% and 96%, respectively, in neat conditions and in the presence of 5 mol% of Bu₄NOTf as co-catalyst).

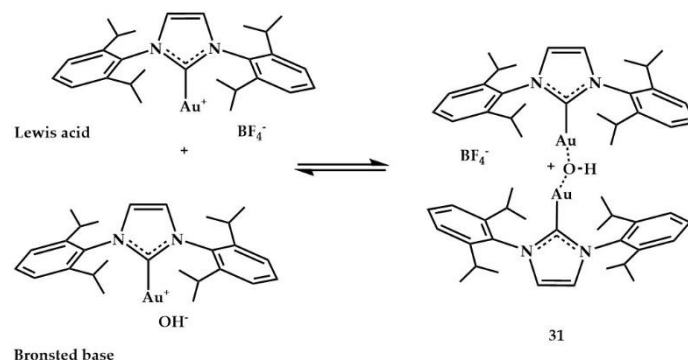
Subsequently, the authors used complex **31** with some alkynes (i.e., 1,2-diphenylethyne, dimethyl but-2-ynedioate, ethyl 3-phenylpropiolate, 3-phenylpropionitrile, prop-1-yn-1-ylbenzene, oct-4-yne) and azole nucleophiles (i.e., *1H*-benzo[*d*][1,2,3]triazole, 4,5-dihydro-*1H*-1,2,3-triazole, 1-methylimidazolidin-2-one, *1H*-pyrazole, *2H*-indazole, *1H*-1,2,4-triazole, *1H*-imidazole) using both methods previously tested (Scheme 6).



Scheme 6. Hydroamination reactions.

The products obtained in almost all catalysis reactions were (*Z*)-enamines, as established on observing the NOE profiles after the full assignment of ¹H/¹³C/¹⁵N chemical shifts.

Concerning the reaction mechanism using complex **31** as catalyst, the authors suggested that the Lewis acid [Au(IPr)][BF₄] could coordinate to the alkyne and the Brønsted base [Au(IPr)(OH)] could deprotonate the azole nucleophile to generate the corresponding gold–azole complex and release a water molecule (Scheme 7).



Scheme 7. Species hypothesized for reaction mechanism.

Recently, Huynh et al. synthesized and characterized the first gold(III) complexes bearing expanded-ring NHCs (erNHCs) by oxidative addition of bromine to the respective gold(I) erNHC precursors (Figure 15) [31].

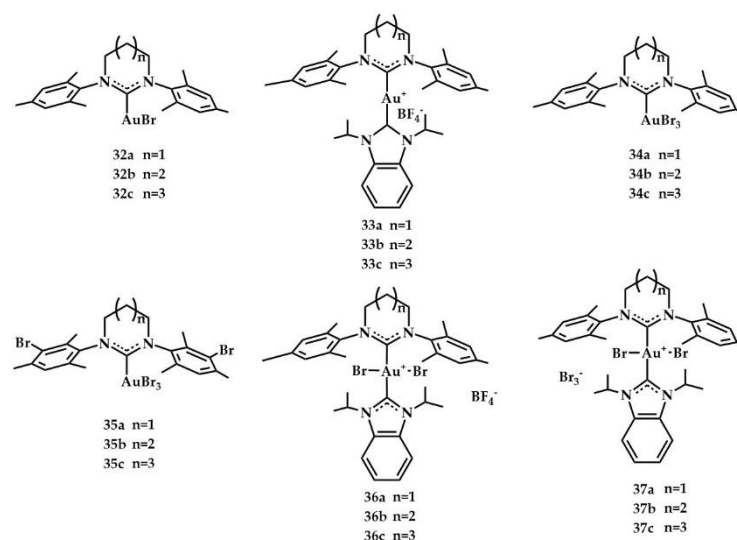


Figure 15. Complexes synthesized by Huynh et al. [31].

All Au erNHC complexes **32a–37a–c** have been tested as precatalysts for the hydroamination of phenylacetylene with 2,4,6-trimethylaniline (for reaction, see Table 1). The simplest precatalyst, **32a**, was chosen for the exploration of the best reaction conditions: phenylacetylene (0.3 mmol, 1.5 equiv.), 2,4,6-trimethylaniline (0.2 mmol, 1 equiv.), AgSbF₆ (0.004 mmol, 2 mol%), and Au NHC (0.004 mmol, 2 mol%) in CH₃CN (~1 mL) heated at 90 °C in a screw cap tube under air for 14 h. Complex **32c** was found to be the most active with 98% conversion (Table 12).

Table 12. Hydroamination reaction.

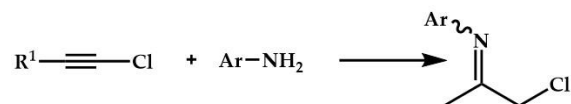
Entry ^a	Complex	Conversion (%) ^b
1	32a	91
2	32b	96
3	32c	98
4	33a	86
5	33b	88
6	33c	90
7	34a	80
8	34b	74
9	34c	80
10 ^c	36a	13

^a Reaction conditions: phenylacetylene (0.3 mmol, 1.5 equiv.), 2,4,6-trimethylaniline (0.2 mmol, 1 equiv.), AgSbF₆ (0.004 mmol, 2 mol%), Au NHC (0.004 mmol, 2 mol%) in CH₃CN (~1 mL) heated at 90 °C in a screw cap tube under air. ^b GC/GC-MS conversion to product. ^c Without AgSbF₆.

Notably, all cationic heterobis (carbene) complexes **36a–37a–c** were inactive regardless of the gold oxidation state, the nature of the counteranion, and the presence of the halide scavenger. The authors hypothesized that inactivity was due to two strong Au–NHCs bonds and the increased steric hindrance. Further, the complex **32c** was tested in the intermolecular hydroamination of different alkynes (phenylacetylene, 4-methoxyphenylacetylene, 4-methylphenylacetylene, 4-fluorophenylacetylene, 4-(dimethylamino)-phenylacetylene, 1-hexyne) and amines (2,4,6-trimethylaniline, aniline, 2,6-diisopropylaniline, 4-methoxyphenylamine, 1-naphthylamine, butylamine). In all

catalytic reactions, the complex **32c** proved to perform well, except for in the hydroamination of phenylacetylene with butylamine and 1-hexyne with 2,4,6-trimethylaniline.

In 2022, Olmos and coworkers reported the synthesis of α -chloromethylketimines by hydroamination of aromatic and aliphatic 1-chloroalkynes with aromatic amines with (IPr)AuCl (Scheme 8) [32].



Scheme 8. Hydroamination of aromatic and aliphatic 1-chloroalkynes with aromatic amine.

The authors optimized the reaction conditions using 1 mol% 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (IPr)AuCl activated by 1.5 mol% sodium tetrakis [3,5-bis(trifluoromethyl)phenyl]-borate (NaBARF) as catalyst in toluene (0.42 M) at 120 °C for 0.5 h. These selected conditions were used for the reaction of 1-chloroethynylbenzene with a series of primary amines. Efficiency was demonstrated by the excellent result obtained with the strongly hindered 2,6-diisopropylaniline (yield 98%) and with 4-aminophenol (yield 97%). The authors studied the reactivity of different 1-chloroalkynes (i.e., 2-(chloroethynyl)-1,3,5-trimethylbenzene, 1-(chloroethynyl)-4-methoxybenzene, 1-(chloroethynyl)-4-(trifluoromethyl)benzene, 1-chlorodec-1-yne and 2-(chloroethynyl)pyridine) with aniline. Excellent to very good yields were obtained in all cases, except for one, in which the presence of a pyridine inhibited the reaction.

Peris et al., in 2022, synthesized and characterized a gold complex with a naphthalene-di-imide-functionalized NHC ligand (Figure 16) [33].

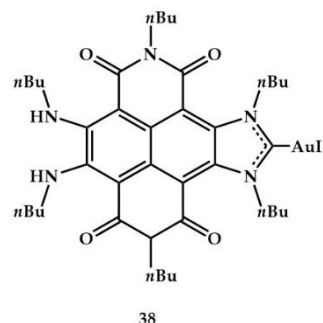


Figure 16. Complex 38 of Peris et al. [33].

The catalytic activity of complex **38** was tested in the hydroamination of phenylacetylene with four different amines (Table 13).

Table 13. The activity of complex in the hydroamination of phenylacetylene with arylamine.

Entry ^a	Ar-NH ₂	Cat. Load (%)	Additive	Time (h)	Yield (%) ^b
1	Ph	1	none	8	82.5
2	2-MeC ₆ H ₄	1	none	8	77.2
3	4-MeC ₆ H ₄	1	none	8	75.3
4	2,4,6-Me ₃ C ₆ H ₂	1	none	8	76.9
5	Ph	0.5	none	8	49.2
6	Ph	2	none	5	90.0
7 ^c	Ph	1	[CoCp ₂]	8	0

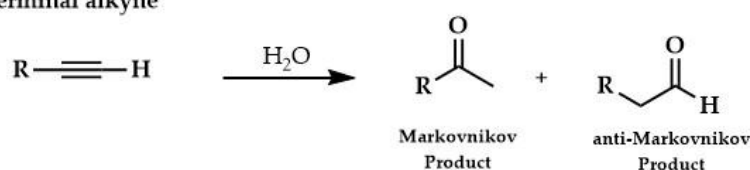
^a Reaction conditions: 0.5 mmol phenylacetylene, 0.55 mmol aryl amine, 1 mol% **3**, and 2 mol% NaBARF in 1 mL of CH₃CN at 90 °C. ^b Yields calculated by GC using anisole (0.5 mmol) as the internal standard. Final yields were also confirmed by ¹H-NMR spectroscopy. ^c One equivalent of cobaltocene was added related to the amount of the catalyst.

After 8 h of reaction, using a catalyst loading of 1 mol% produced yields of the imine products in the range of 75%–82%. For the case of the reaction between phenylacetylene and aniline, a reduction of the catalyst loading to 0.5 mol% produced a significant decrease in the yield down to 49% (entry 5), while doubling the amount to 2 mol% increased the product yield up to 90% in just 5 h (entry 6).

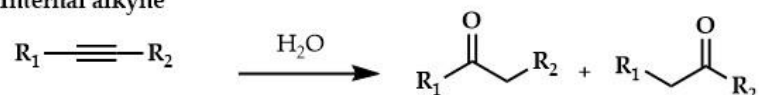
3. Hydration of Alkynes

A synthetic method for generating carbonyl compounds is the hydration reaction of alkynes. This reaction is considered an example of both atom economy and an environmentally friendly synthetic method [34,35]. It is based on the addition of water to terminal alkynes giving either methyl ketone (Markovnikov addition) or an aldehyde (anti-Markovnikov addition; Scheme 9a), in addition, nonsymmetrical internal alkynes may give two regioisomeric ketones (Scheme 9b).

a) Terminal alkyne



b) Internal alkyne

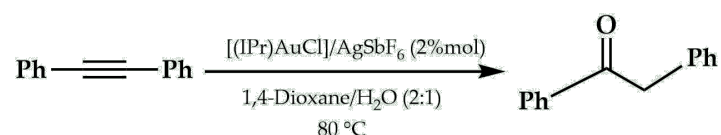


Scheme 9. Hydration of (a) terminal and (b) internal alkynes.

The use of a catalyst is required, because it promotes the attack of water to the alkyne unit. Among the catalytic systems used, gold-based compounds occupy a prominent place due to their high versatility. In fact, they can act as σ - and π -Lewis acids, which has allowed the activation of a wide diversity of functional groups, including unsaturated carbon systems (i.e., alkenes, allenes, and alkynes).

The hydration of alkynes can be promoted by L–Au–X compounds (L = an ancillary ligand, and X[−] = a counterion). In this review, we focused on N-heterocyclic carbenes (NHCs) [36,37] as neutral ligands, because they have already proven to be particularly effective in stabilizing gold complexes used in homogeneous catalysis [38,39], and they have resulted in the development of highly efficient systems at very low catalyst loadings [40–42] under mild conditions.

In 2008, Nolan and coworkers reported an in-depth investigation of a catalytic system for the hydration of alkynes [43]. They concentrated on the study of the hydration of diphenylacetylene with (NHC)AuCl complexes (NHC = IPr or IMes or ItBu), examining different parameters, such as temperature, concentration, solvent, water/alkyne ratio, and the nature of silver(I) salt, used as co-catalyst, and finally, of the NHC ligand. The reaction conditions were optimized (Scheme 10).



Scheme 10. Optimization of the reaction of hydration.

Among the NHC ligands used, IPr was the most reactive, especially in equimolar quantities of (IPr)AuCl and AgSbF₆, with a conversion of 97%. Other silver salts (AgBF₄

and AgOAc) are less active compared to AgSbF₆. 1,4-dioxane, in a 2:1 ratio with water, turned out to be the best solvent. Moreover, (IPr)AuCl at 0.1 mol%, at 120 °C, gave a ketone yield of 77%.

Using methanol as solvent, instead of 1,4-dioxane, Nolan obtained very interesting results with terminal alkynes. In fact, while with diphenylacetylene the conversion into ketone was much slower in methanol than it was with 1,4-dioxane, with terminal alkynes, such as phenylacetylene, this relation was the opposite. Probably, these results were due to different mechanisms, and methanol could play an active role in this reaction. To verify this hypothesis, the reactivity of several terminal alkynes was investigated, and a faster conversion was obtained when the reactions were performed in methanol instead of in 1,4-dioxane.

In 2016, Silvestri and coworkers developed new NHC–gold complexes **39–43** (Figure 17) soluble in water and able to catalyze the hydration of alkynes [44,45].

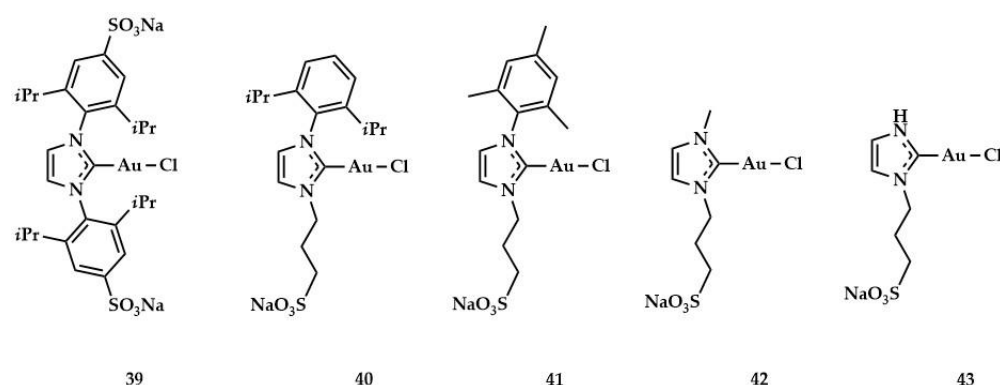
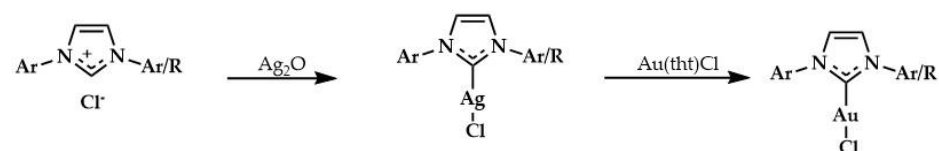


Figure 17. Structure of gold(I) sulfonated NHC complexes of Silvestri et al. [44,45].

The synthesis of gold complexes was obtained by reaction between imidazolium compounds and silver oxide [46,47], then the Au complexes were obtained via transmetalation, using [AuCl(tht)] (tht = tetrahydrothiophene) as gold precursor [48] (Scheme 11).



Scheme 11. Synthesis of Gold(I) sulfonated NHC complexes.

The study started with the hydration of phenylacetylene using complex **39** as catalyst and pure water as solvent. The results are reported in Table 14. When carrying out the reaction at 80 °C with 1 mol% of **40**, acetophenone in a quantitative yield was obtained after 5 h (entry 1). The effects of some parameters such as the use of silver salts [49], the catalyst load, and the reaction temperature were studied. No improvement was obtained by adding 1 mol% of AgSCN (entry 2), but the time of reaction was reduced when using 2 mol% of AgSCN or when increasing the amount of catalyst (2 mol%, entry 3 and 4) or increasing the temperature (entry 6 and 7). Instead, the addition of 1 mol% of AgSCN and AgSbF₆, at 100 °C, caused a decrease in the catalytic activity (entry 8 and 9), while the time of reaction was reduced to 30 min when the reaction was carried out with 2 mol% of catalyst, without silver salt, at 100 °C in pure water.

Table 14. Hydration of phenylacetylene promoted by complex **39**.

Entry ^a	Complex 39 (mol%)	AgX Salt (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%) ^b
1	1	-	H ₂ O	80	5	100
2	1	SCN (1)	H ₂ O	80	5	100
3	1	SCN (2)	H ₂ O	80	4	100
4	2	SCN (1)	H ₂ O	80	3	98
5	2	-	H ₂ O	80	3	70
6	1	-	H ₂ O	90	3	100
7	1	-	H ₂ O	100	1.17	100
8	1	SCN (1)	H ₂ O	100	0.5	55
9	1	SbF ₆ (1)	H ₂ O	100	0.5	68
10	2	-	H ₂ O	100	0.5	100
11	1	-	H ₂ O:MeOH	100	0.5	100
12	1	-	H ₂ O:MeOH	80	0.75	100
13	2	-	H ₂ O:MeOH	100	0.25	100
14	1	SCN (1)	H ₂ O:MeOH	100	0.66	100
15	1	OTs (1)	H ₂ O:MeOH	100	0.33	100
16	1	SbF ₆ (1)	H ₂ O:MeOH	100	0.13	100
17 ^c	1	-	MeOH ^d	100	0.5	83 ^e

^a Reaction conditions: 0.5 mmol of phenylacetylene, in 3.0 mL of water or 1.5 mL water:methanol. ^b Isolated yield. ^c A quantitative yield was obtained after 40 min. ^d Stoichiometric amount of pure water. ^e Together with 4% of (1-methoxyvinyl)benzene.

An analogous study was performed by carrying out the reaction in a mixture of methanol and water (1:1) [50] and analyzing the effects of temperature, different loadings of catalyst, and the addition of silver salts on reaction time. The decrease in temperature (from 100 to 80 °C) caused an increment in the reaction time (from 30 to 45 min, entry 11 and 12). Instead, when using 2 mol% of catalyst, the reaction time was reduced to 15 min (entry 13), while the introduction of 1 mol% of AgSbF₆ and 1 mol% **39** decreased the reaction time to 8 min (entry 16). Considering that the reactions in water were slower than those in water:methanol 1:1, Silbestri and coworkers carried out the reaction in methanol with stoichiometric amounts of water; however, the time was increased, and the amount of ketone was reduced (entry 17). To evaluate the effects of the catalyst, a series of experiments were carried out both in water and in water:methanol, at 100 °C, reducing the amounts of catalyst (from 1 to 0.05 mol%), in the absence of silver salts. The results are shown in Table 15.

Table 15. Optimization of catalyst loading.

Entry ^a	Complex 39 (mol%)	Solvent	Time (h)	Yield (%) ^b
1	1	H ₂ O	1.17	100
2	0.5	H ₂ O	2	100
3	0.25	H ₂ O	4	100
4	0.10	H ₂ O	8	100
5	0.05	H ₂ O	13	100
6	1.0	H ₂ O:MeOH	0.5	100
7	0.5	H ₂ O:MeOH	1	100
8	0.25	H ₂ O:MeOH	2	100
9	0.10	H ₂ O:MeOH	4	100
10	0.05	H ₂ O:MeOH	7	100

^a Reaction conditions: 0.5 mmol of phenylacetylene; water (3 mL); water:methanol (1.5 mL:1.5 mL); heating (oil bath). ^b Isolated Yield.

In all cases, the catalyst was found to be active, and when halving the catalyst loading, it was necessary to double the reaction time to obtain the same results. As already noted from the previous results, the reaction carried out in water (from 1.17 to 13 h, entries 1–5) was slower than that in water:methanol (from 30 min to 7 h, entries 6–10). Another important aspect is that the catalyst was active at 0.5 mol% and it was recycled and reused five times without losing its activity.

Other studies have investigated the steric effect of NHC ligands on catalyst activities, focusing on the hydration of phenylacetylene with less bulky NHC–gold complexes (**40**–**43**) using 1 mol%. All reactions were carried out in pure water and water:methanol, in both the presence and absence of silver salts, with opportune temperature. The results are shown in Table 16. No complexes exhibited activity in water. Furthermore, complexes **40** and **42** did not react, despite the longer time reaction (24 h) and increasing the loads of Au (5 mol%) or adding different silver salts (entries 1–5, 18–22). Complexes **41** and **42** were unstable in water; in fact, they totally decomposed in 3 h and 5 h, respectively, as they did when using a lower temperature (30 °C) or when loading 10 mol% of silver salt (entries 10 and 11). On the other hand, all reactions in water:methanol gave positive results. In fact, when using only 1 mol% of **40**, the reaction was quantitative in 13 h (entry 6), while adding 1 mol% of silver salts (AgOTs and AgSbF₆) caused the reaction time to decrease (6 h and 7.5 h, respectively) (entries 7–8); this effect was probably due to counterion with gold(I) catalysts [51,52]. Complex **41** showed a good yield after 48 h, and the addition of silver salts [AgSCN, AgOTs, and AgSbF₆] did not determine beneficial effects on conversion (35%, 80%, and 56%, respectively) in the same reaction time (entries 13–15). Regarding complexes **42** and **43**, they gave a moderate conversion in 60 h. The addition of silver salts did not produce any benefit for the reaction with complex **42**, while with complex **43** it produced a positive effect (entries 23–25, 29–31).

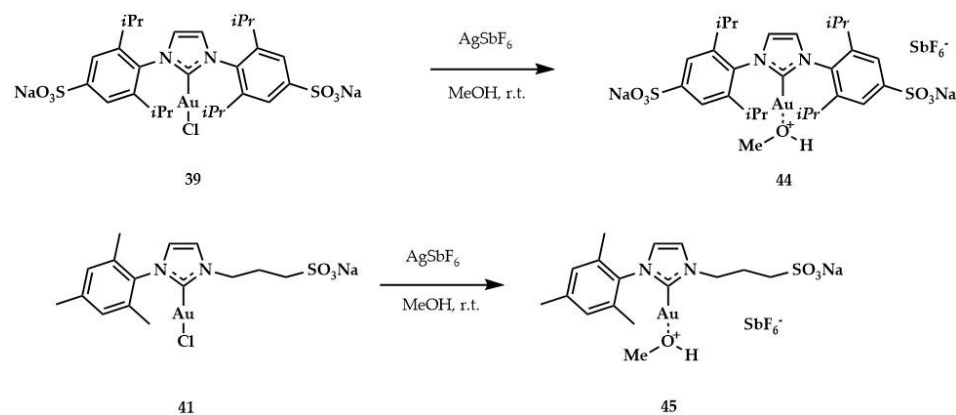
Table 16. Hydration of alkynes catalyzed by **40**–**43**.

Entry ^a	Complex	AuNHC (mol%)	AgX Salt (mol%)	Solvent	Temperature (°C)	Time (h)	Yield ^b (%)
1	40	1	-	H ₂ O	100	24	0
2	40	1	SCN (1)	H ₂ O	100	24	0
3	40	1	SbF ₆ (1)	H ₂ O	100	24	0
4	40	5	-	H ₂ O	100	24	0
5	40	5	SbF ₆ (10)	H ₂ O	30	24	0
6	40	1	-	H ₂ O:MeOH	100	13	100
7	40	1	OTs (1)	H ₂ O:MeOH	100	6	100
8	40	1	SbF ₆ (1)	H ₂ O:MeOH	100	7.5	100
9	40	1	-	TMS	80	24	0
10	41	1	SbF ₆ (1)	H ₂ O	80	3	0
11	41	5	SbF ₆ (10)	H ₂ O	30	3	0
12	41	1	-	H ₂ O:MeOH	80	48	95
13	41	1	SCN (1)	H ₂ O:MeOH	80	48	35
14	41	1	OTs (1)	H ₂ O:MeOH	80	48	80
15	41	1	SbF ₆ (1)	H ₂ O:MeOH	80	48	56
16	41	1	-	H ₂ O:MeOH	100	24	44
17	41	1	-	TMS	80	48	0
18	42	1	-	H ₂ O	80	24	0
19	42	1	SCN (1)	H ₂ O	80	24	0
20	42	1	SbF ₆ (1)	H ₂ O	80	24	0
21	42	5	-	H ₂ O	80	24	0
22	42	5	SbF ₆ (10)	H ₂ O	30	24	0
23	42	1	-	H ₂ O:MeOH	80	60	62

24	42	1	OTs (1)	H ₂ O:MeOH	80	60	52
25	42	1	SbF ₆ (1)	H ₂ O:MeOH	80	60	48
26	42	1	-	H ₂ O:MeOH	100	24	14
27	42	1	-	TMS	80	24	0
28	43	5	SbF ₆ (10)	H ₂ O	30	0.5	0
29	43	1	-	H ₂ O:MeOH	80	60	20
30	43	1	SbF ₆ (1)	H ₂ O:MeOH	80	60	35
31	43	1	-	H ₂ O:MeOH	100	24	19

^a Reaction conditions: 0.5 mmol of phenylacetylene; water (3 mL); water:methanol (1.5 mL:1.5 mL); heating (oil bath). ^b Isolated yield.

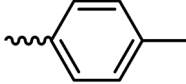

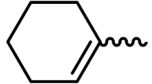

Other information about the influence of steric hindrance around a metal center was given by kinetic experiments, by means of which Silbestri and coworkers confirmed the importance of this parameter both in the stability and in the catalytic activity of gold (I) complexes. The bulkier NHC complexes were the most effective catalysts in these reactions. Other authors reported similar results in different reactions carried out in conventional organic solvents [53–56]. The lower activity of complexes **40** and **43** was due to sulfonated moiety, which may coordinate the metal or interfere with the reaction center. These limitations could be eliminated at an acidic pH; for example, the complex **43** was more active at pH = 2 than at a pH between 6.4 and 7.2. This achievement supports the hypothesis that there was a coordination between the metal and the sulfonate group. The influence of methanol is no less important. In fact, the use of methanol as a co-solvent could lead to a more active precatalyst being obtained. In support of this hypothesis, two other complexes with methanol coordinated were synthesized (**44** and **45**, Scheme 12), according to the procedures described [57,58].



Scheme 12. Synthesis of the catalysts **44** and **45** by corresponding gold sulphonated NHC complexes.

Comparing the catalytic activity of **39** and **44** and of **41** and **45**, either in water or water:methanol, it was observed that **44** was more active than **39** was in water (85% vs. 42%), but they showed similar activity in water:methanol (90% vs. 88%). The same results were obtained with **45** vs. **41**. Considering the excellent activity of complex **39**, Silbestri and coworkers studied the reactivity of selected terminal and internal alkynes in water at 100 °C, without silver salts (see Scheme 9). The results are shown in Table 17. The hydration of terminal alkynes gave the corresponding Markovnikov ketone in quantitative yields and in an acceptable reaction time (entries 1–6). On the other hand, the reactions with internal enyne gave a mixture of ketone (entry 7). Finally, the reaction conducted with prop-2-yn-1-ol and but-3-yn-1-ol, in the same condition (100 °C), did not give the expected ketone, but the corresponding hydroxy ketone was obtained when carrying out the reaction with AgSbF₆ at 60 °C.

Table 17. Hydration of terminal and internal alkynes promoted by complex **39** in water.

Entry ^a	R ¹	R ²	Time (h)	Yield (%) ^{b,c}
1	-C ₅ H ₁₁	H	1.17	100 (96)
2	-C ₃ H ₇	H	1.17	100 (97)
3	Ph	H	1.17	100 (99)
4		H	2	100 (96)
5		H	2	100 (98)
6		H	2	100 (97)
7		-C ₂ H ₅	6	23 ^d 40 ^e
8 ^f	HO-CH ₂ -	H	2	100 (99)
9 ^f	HO-(CH ₂) ₂ -	H	2	100 (99)

^a Reaction conditions: 0.5 mmol of alkyne; 1 mol% of **39**; water (3.0 mL); heating (oil bath). ^b Quantified by GC, using the external standard method. ^c Isolated yield between brackets. ^d Anti Markovnikov ketone. ^e Markovnikov ketone. ^f Heating 60 °C with addition of AgSbF₆ (1 mol%).

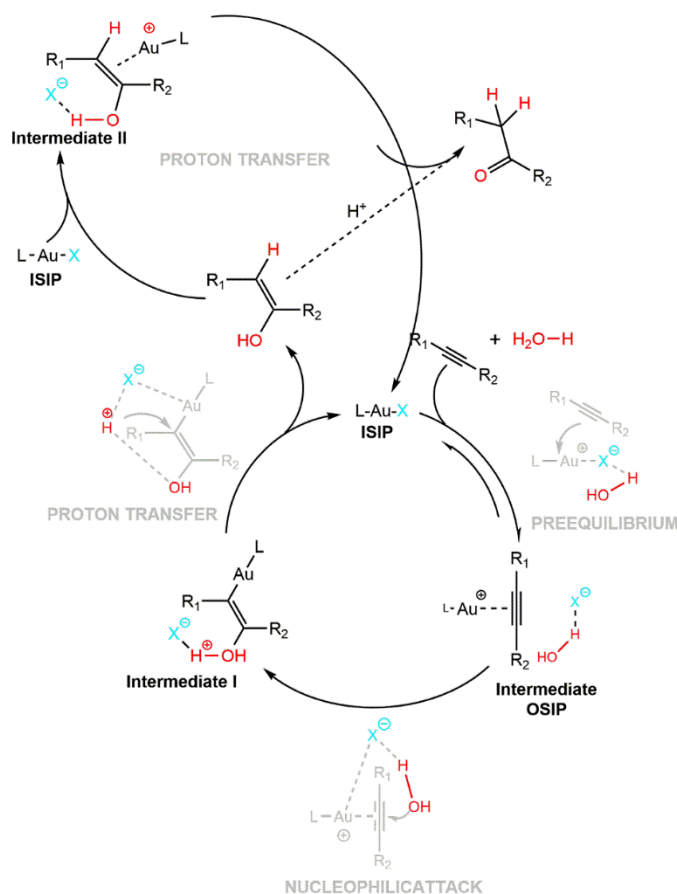
Zuccaccia et al., in 2016, developed an efficient methodology for the hydration of alkynes by NHC gold complexes using solvent-, silver-, and acid-free conditions, focusing their attention on the pivotal role of the counterion [59]. They analyzed the activity of (IPr)Au-X (X⁻ = BArF⁻, BF₄⁻, SbF₆⁻, ClO₄⁻, OTf⁻, NTf₂⁻, OTs⁻, TFA⁻, BArF = tetrakis(3,5-bis(trifluoromethyl)-phenyl) borate) complexes in neat condition and without using silver salts in the hydration of alkynes at room/mild temperature, with suitable ionic additives. The synthesis of complexes was carried out according to literature procedures [60], and they studied the hydration of internal and terminal alkynes. Some experiments carried out on 3-hexyne (see Scheme 9b, R₁=R₂=Et, Table 18) showed that the complexes in which the counterions were BArF⁻, BF₄⁻, SbF₆⁻, ClO₄⁻, OTs⁻, and TFA⁻ did not promote the reaction after 24 h; probably it was due to the poor basic properties and low coordinating ability of BArF⁻, BF₄⁻, SbF₆⁻, and ClO₄⁻ or to strong coordinating ability and basic properties of OTs⁻ and TFA⁻ (entries 1–3 and 6–8). Instead, OTf⁻ and NTf₂⁻ gave a quantitative conversion (entries 4 e 5).

Table 18. Hydration of 3-hexyne catalyzed by (IPr)Au-X complexes.

Entry ^a	Temperature (°C)	X ⁻	Time (h) / [TOF] ^b	Conversion (%) ^c
1	30	BF ₄ ⁻	24	<1
2	30	SbF ₆ ⁻	24	<1
3	30	ClO ₄ ⁻	24	<1
4	30	OTf ⁻	16/[64]	>99
5	30	NTf ₂ ⁻	16/[64]	>99
6	30	OTs ⁻	24	<1
7	30	TFA ⁻	24	<1
8	30	BArF ⁻	24	<1
9	50	BF ₄ ⁻	24	<1

^a Reaction conditions: 1.75 mmol of 3-hexyne and H₂O (1.92 mmol). ^b TOF = (n_{product}/n_{catalyst})/(t(h)) at reported conversion. ^c Determined by ¹H-NMR.

Moreover, the TOF value ((TOF (h^{-1}) = (mol of product)/(mol of catalyst) (time elapsed)); Table 18)] obtained by NHC–Au–OTf and NHC–Au–NTf₂ was about 64 h^{-1} higher than those reported in the literature under neat conditions and at room temperature [61]. The theoretical mechanisms proposed by Zuccaccia and coworkers for an alkyne hydration reaction catalyzed by [NHC–Au]⁺ catalyst in the presence of the OTf[−] emphasizes the importance of the counterion role (Scheme 13).



Scheme 13. Mechanism of hydration of Au(I)NHC. Reprinted with permission from Ref. [59]. Copyright 2016 American Chemical Society.

They showed that, during nucleophilic attack, the anion plays two useful roles: (i) it locks the water molecule in the correct position for the outer-sphere addition; (ii) it increases the nucleophilicity of the attacking water through the HOH \cdots OTf[−] hydrogen bond, which in turn polarizes the oxygen.

Zuccaccia and coworkers, afterwards, paid attention to the importance of the ligand and understanding its effect during different steps in the hydration of alkynes [60,62]. For this purpose, they synthesized several L–Au–X complexes where L = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene {IPrNHC}, tris(3,5-bis(trifluoromethyl)phenyl)phosphine {PArF}, bis(imino)acenaphthene-supported-1,3-bis(2,6-diisopropylphenyl) dihydroimidazol-2-ylidene {BIAN}, 1,3-bis-(2,6-di-isopropylphenyl)dihydroimidazol-2-ylidene {NHCCH₂}, bis(tert-butylamino)methylidene {NAC}, 2-di-tertbutyl(o-diphenyl)phosphine {JohnPhos}, tricyclohexylphosphine {PCy₃}, triphenylphosphine {PPh₃}, tris(2,4-di-tertbutylphenyl) phosphite {POR₃} (Figure 18) and X[−] = Cl[−], OTf[−], OTs[−]. The structure of the ligand modulates the acidic character of the metal center and influences the stability of intermediates [3,63–65].

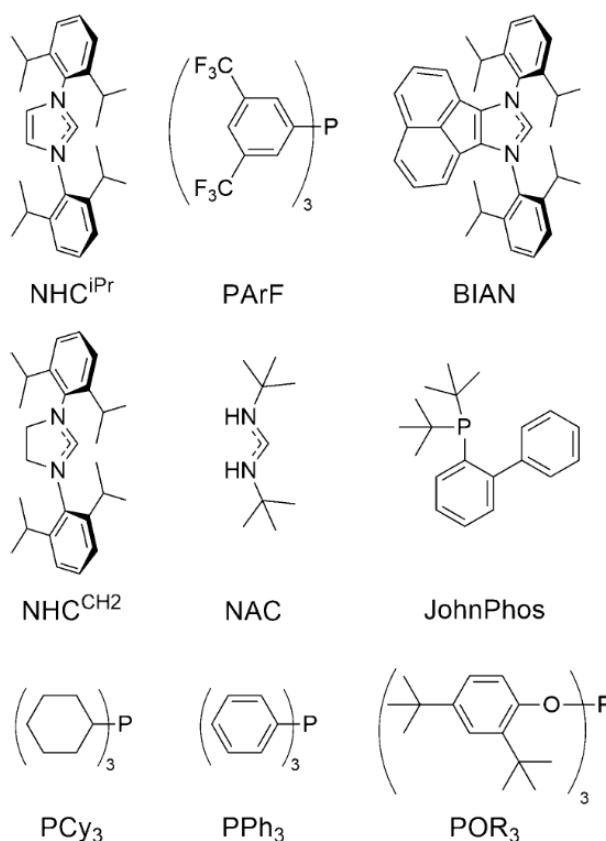


Figure 18. Structure of ligands used by Zuccaccia et al. Reprinted with permission from Ref. [60] Copyright 2016 American Chemical Society.

Furthermore, they examined the effect of ionic additive compounds (for example, NBu_4OTf), silver salts, and the temperature on the hydration of alkynes. Their principal aim was the development of an efficient methodology for the hydration of unreactive diphenylacetylene in neat condition and without silver salt and acid using only 0.1 mol% of catalyst. The complexes were tested as catalysts in the hydration of 3-hexyne and diphenylacetylene (Tables 19 and 20) in solvent- and acid-free conditions.

Table 19. L–Au–X (0.1 mol%) catalyzed hydration of 3-hexyne at 30 °C in the presence of NBu_4OTf .

Entry ^{a,b}	Ligand	Conversion (%) ^g	Time (h)/[TOF] ^{h,i}
1 ^c	NHC ^{iPr}	>99	2/[495]
2 ^{d,f}	NHC ^{iPr}	70	2/[350]
3 ^{d,f}	BIAN	76	2/[380]
4 ^{d,f}	NHC ^{CH2}	76	2/[380]
5 ^{d,f}	NAC	0	24
6 ^{d,f}	JohnPhos	75	4/[188]
7 ^{d,f}	PCy ₃	0	24
8 ^{d,f}	PArF	0	24
9 ^{d,f}	PPh ₃	0	24
10 ^{d,f}	POR ₃	0	24
11 ^e	NHC ^{iPr}	>99	3.5/[285]
12 ^e	BIAN	>99	4/[248]
13 ^e	NHC ^{CH2}	98	8/[122]
14 ^e	NAC	9	24/[4]

15 ^e	JohnPhos	74	5/[148]
16 ^e	PCy ₃	6	24/[3]
17 ^e	PArF	0	24
18 ^e	PPh ₃	3	24/[1]
19 ^e	POR ₃	17	24/[7]
20 ^c	BIAN	>99	2/[495]
21 ^c	NHC ^{CH2}	>99	4/[248]

^a Reaction conditions: 3-hexyne (1.75 mmol), 5 mol% NBu₄OTf (0.087 mmol), H₂O (1.92 mmol), L–Au–X (0.1 mol%) and AgOTf (0.1 mol%) when indicated. ^b mol% = (mol of catalyst/mol of alkyne) × 100. ^c X = OTf. ^d X = Cl[−]. ^e X = OTs[−]. ^f With AgOTf 0.1 mol%. ^g Determined by ¹H-NMR; average value of three measurements. ^h Time necessary to reach the reported conversion. ⁱ TOF = (*n*_{product}/*n*_{catalyst})/time at the reported conversion.

Table 20. NHC^{IPr}–Au–OTf-catalyzed hydration of diphenylacetylene.

Entry ^a	Loading (mol%) ^d	Temperature (°C)	Conversion (%) ^e	Time (h) / [TOF] ^{f,g}
1 ^b	0.1	65	82	8/[102]
2 ^b	0.05	80	42	8/[105]
3 ^b	0.05	120	94	4/[470]
4 ^b	0.025	120	85	8/[435]
5 ^b	0.01	120	27	5/[560]
6 ^{b,h}	0.05	120	88	8/[220]
7 ^c	0.05	120	7	8/[17]

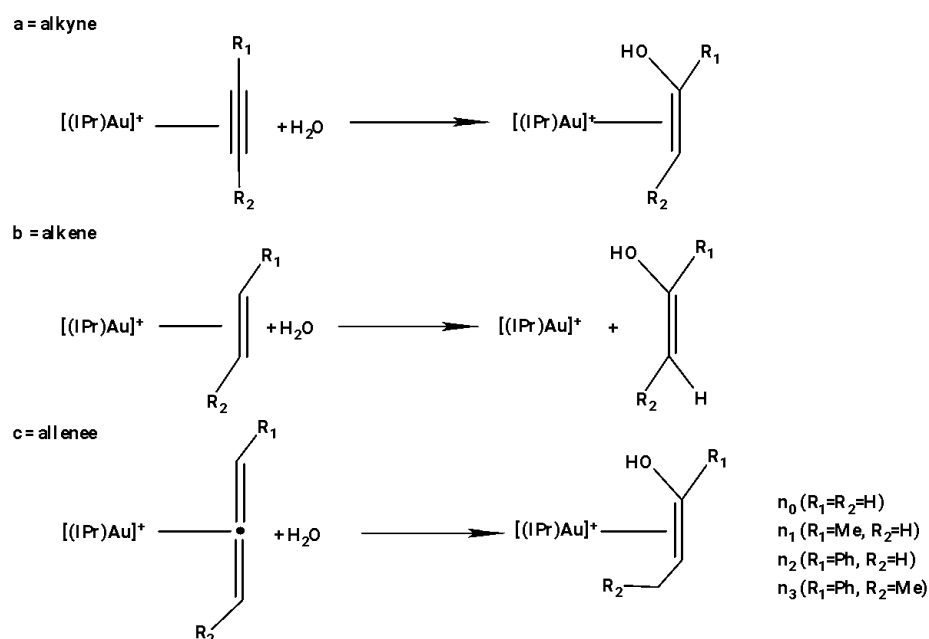
^a Reaction conditions: diphenylacetylene (1.75 mmol), 5 mol% NBu₄OTf (0.087 mmol), H₂O (1.92 mmol), L–Au–X (0.1 mol%). ^b X[−] = OTf. ^c X[−] = OTs[−]. ^d mol% = (mol of catalyst/mol of alkyne) × 100. ^e Determined by ¹H-NMR; average value of three measurements. ^f Time necessary to reach the reported conversion. ^g TOF = (*n*_{product}/*n*_{catalyst})/time at the reported conversion. ^h With D₂O instead of H₂O.

When utilizing L–Au–Cl/AgOTf systems, where L is PCy₃, PArF, POR₃, PPh₃, and NAC (Table 19, entries 5 and 7–10), no formation of product was observed within 24 h, because the decomposition of catalyst in neat conditions occurred [66]. In addition, the complexes having NHC ligands showed a decomposition process promoted by silver salt in neat and acid-free conditions. Under silver-free conditions, the complexes with phosphine-based ligands were also decomposed (entries 16–19), except for JohnPhos (conversion of 74% in 5 h, entry 15). The complexes with NHC ligands and –OTf (IPrNHC–Au–OTf) were more active compared to IPrNHC–Au–OTs (entry 1 vs. 11), because the coordinating ability of OTs[−] was higher than that of OTf[−].

The same results were obtained in the hydration of diphenylacetylene; in fact, the IPrNHC–Au–OTf was more effective compared to the analogous complex with OTs[−] as counterion (Table 20, entries 3–7). In this work, it was possible to reduce, for the first time, the catalyst loading to 0.01 mol% in solvent-, silver-, and acid-free conditions, with high TON (3400) and TOF (435 h^{−1}) thanks to the synergy effect of ligand and counterion [67]. The neat conditions are not applicable when the reagents are solid or viscous.

For this reason, in a recent work, Zuccaccia et al. focused on the use of green solvents in the hydration of alkyne [68]. In the literature, many organic processes, promoted by transition metals, were carried out in bio-based solvents [69] (i.e., water [70], glycerol [68], D-limonene and p-cymene [71,72], γ -valerolactone (GVL) [73,74], lactic acid and its derivatives [75]) instead of in volatile organic solvents. They found that the reaction of hydration of alkynes promoted by (IPr)Au–OTf proceeded very well in some of the alternative solvents, such as ethyl lactate, glycerol, propylene carbonate, D-limonene, γ -valerolactone, and p-cymene. In addition, they noted that the activity of the catalyst, in terms of TOF, seemed to be inversely related to the polarity of the solvent. In fact, when

increasing the dielectric constant, the equilibrium between the ion pair and free ions was shifted toward free ions, and this reduced the useful effect of OTf during the nucleophilic attack of methanol (water). The presence of proton acceptor/donor functionalities in some solvents (e.g., cyclohexanone and glycerol) increased the rate of the reaction, even if their dielectric constant was medium–high. At the same time, solvents having coordinated functional groups (e.g., D-limonene C=C, propionitrile C≡N, and DMSO) decreased the rate of reaction due to their coordination to the metal center. More recently, the Ujaque group [76] studied the reaction mechanism for the hydration to some alkynes (terminal and internal), alkenes, and allenes catalyzed by (IPr)Au⁺ complex (see Scheme 2) by means of DFT calculations. In Scheme 14, the reactions studied are summarized [77].



Scheme 14. IPrAu⁺-catalyzed hydration of alkynes, alkenes, and allenes.

The catalytic cycle for the three substrates can be described by three steps: (i) π coordination of reactant to the Au(I) complex, (ii) nucleophilic addition of water, and (iii) protodeauration (this is the step with subtle differences among the reactants). DFT calculations showed that alkynes and allenes undergo the reaction of hydration without any problems, while the alkenes show a scarce reactivity. This different reactivity is not due to the nucleophilic attack of water, although it goes with different energies (lower energies with alkynes and allenes, higher energy for alkenes), but is attributed to the high-energy intermediate formed in the protodeauration step. However, it could be argued that the terminal functional groups are always more reactive compared to the internal functional groups as they are often difficult to access; unsubstituted alkyne (ethyne, a0) and alkene (ethene, b0) have higher barriers to water addition compared to the species with terminal groups, this effect being due to the favorable presence of the Me and Ph substituents on the Markovnikov addition [78]. Regarding regioselectivity, addition on the most substituted carbon (Markovnikov addition) was always favorable for all unsaturated functional groups evaluated. Regarding alkenes, the situation becomes more complicated, because nucleophilic addition was significantly higher in terms of the Gibbs energy barrier than it was in the case of alkynes and allenes. The high energy of this species is related to the strength of the C–O bond in the presence or absence of a π -bond in the organic fragment and not to the Au(I)–CC system interaction.

Asachenko and coworkers studied the effect of ring sizes and substituents in NHC ligands in some (NHC)Au(I) complexes in the reaction of hydration of alkynes, especially

focusing their study on regioselectivity of asymmetrical diarylacetylene and alkylarylacetylenes [79]. The results are reported in Table 21.

Table 21. Results of Au(I) NHC precatalysts with different ring size.

R = <i>p</i>-Tolyl			
Entry ^a	NHC	A:B (%)	Yield
1	IMes ^b	-	-
2	SIMes ^b	-	-
3	6-Mes	33.3:66.7	18
4	7-Mes	28.6:71.4	49
5	IPr ^b	29.4:70.6	99
6	SIPr ^b	25.6:74.4	80
7	IPr ^b	37:63	91
8	6-Dipp	22.7:77.3	79
9	7-Dipp	28.6:71.4	95
R = <i>n</i>-Hexyl			
10	IMes ^b	-	<2
11	SIMes ^b	-	<2
12	6-Mes	11.1:88.9	62
13	7-Mes	11.1:88.9	82
14	IPr ^b	27.8:72.2	93
15	SIPr ^b	25:75	87
16	IPr ^b	20:80	76
17	6-Dipp	8.3:91.7	70
18	7-Dipp	7.1:92.9	67

6-Dipp =

6-Mes =

7-Dipp =

7-Mes =

^a Reaction conditions: acetylene (1.00 mmol), (NHC)AuCl (0.01 mmol), AgOTf (0.01 mmol), H₂O (15 mmol) in 1,4-dioxane (1 mL). ^b See Figure 1.

In both hydration reactions, the 7-DippAuCl demonstrated the best regioselectivity, even if its efficiency was not outstanding. The results show that Au(I) complexes having Dipp (2,6-diisopropylphenyl) as NHC ligands are more active than those with Mes (2,4,6-trimethylphenyl) substituted. However, in this kind of reaction, the regioselectivity was almost independent of the NHC ligand; in fact, all complexes demonstrated low selectivity towards the Markovnikov product. The complex 7-DippAuCl was used to investigate the effect of different substituents in the aromatic rings (i.e., 1-methyl-4-(phenylethynyl)benzene, 1-methyl-2-(phenylethynyl)benzene, 1,3,5-trimethyl-2-(phenylethynyl)benzene, 1-methoxy-4-(phenylethynyl)benzene, 1-(phenylethynyl)-3-(trifluoromethyl)benzene) of the alkynes on the regioselectivity of the hydration reaction. They obtained always Markovnikov products. However, in the study of the reaction of alkylarylacetylenes, under the same condition, the regioselectivity was anti-Markovnikov and highly controlled by the ligand. These results are more important because it is very difficult to obtain anti-Markovnikov products by other methods, so this reveals the synthetic importance of this research [80]. More probably this unusual selectivity is due

to the difference in steric repulsion between aryls of arylalkylacetylenes and the NHC ligand in the transition state of the water addition step.

4. Conclusions

Ever since Arduengo isolated the first N-heterocyclic carbene, the use of these ligands in the organometallic field has received a lot of attention from the scientific community. NHC complexes of gold, unlike other transition metals, have received interest only more recently. Many works have shown that NHC gold (I/III) complexes are powerful catalysts for intermolecular and intramolecular hydroamination and hydration of terminal and internal alkynes, through π activation of the CC multiple bond.

This review highlighted the catalytic activity of the NHC complexes of gold (I/III) in the formation of C–N and C–O bonds, by adding amines and water to the alkynes. The high focus on this type of reaction is attributable to the atom economy and sustainable conditions. Despite all these studies, there is still work to be done, focusing, for example, on the following: (1) achieving low-loadings catalytic NHC systems; (2) enhancing the catalytic activity of gold catalysts turned on by ligands and counteranions. Furthermore, given the interesting results obtained by (NHC)Au(III) complexes in hydroamination reactions, it is also possible to imagine that new higher-performing gold (III) complexes will be designed and tested in these and other types of reactions.

The aim of this review was to summarize the most interesting results obtained by the Au(I/III) NHC complexes in the addition of amines and water to alkynes, and secondly, to encourage the synthesis of new N-heterocyclic carbene ligands for the development of increasingly active gold catalysts.

Author Contributions: Conceptualization and supervision: P.L. and A.M.; writing—original draft preparation: A.M. and R.T.; review, editing, and schemes: A.M., M.S., R.T., S.R. and P.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research required no external funding.

Data Availability Statement: This study did not report any data.

Acknowledgments: The authors are grateful to the Department of Science of Basilicata University and to the Department of Chemistry and Biology of Salerno University, Italy, for facilities of this research.

Conflicts of Interest: The authors declare no conflict of interest.

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