Silica Immobilized NHC-Gold(I) Complexes; Versatile Catalysts for the Functionalization of Alkynes under Batch and Continuous Flow Conditions

Jeymy T. Sarmiento, Samuel Suárez-Pantiga,[†,§] *Andrea Olmos,* [‡,§]

Teresa Varea and Gregorio Asensio**

Departamento de Química Orgánica, Universidad de Valencia,
Avda. Vicente Andrés Estellés s/n 46100-Burjasot, Valencia, Spain

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ABSTRACT: Immobilized sterically demanding NHC-Au(I) complexes Silica-[(IPr$_R$)Au]Cl and Silica-[(IAdPr$_R$)Au]Cl are synthesized and characterized. These new complexes are suitable catalysts in typical homogeneous Au(I) catalyzed alkyne reactions such as the hydration, hydroamination, hydroarylation or cycloisomerization. The results obtained with the immobilized catalysts in reactions in batch are comparable to those obtained with their homogeneous counterparts with the advantage of easily recovered and recycled in successive

reactions. Their catalytic activity decreases when reused in batch reactions due to crushing associated with magnetic stirring. In contrast, these immobilized catalysts are very effective when used under continuous flow conditions in which the same cartridge can be used to catalyze successively different types of reaction for a long period without noticeable loss of activity.

INTRODUCTION

Gold is a transition metal that is not considered toxic. For example, in the European Union its presence is permitted in food[1] and its concentration in drugs is not limited by law, unlike what happens with other metals used in catalysis.[2] This is a good reason to develop catalysts based on this metal to be applied to the synthesis of organic compounds of interest in foods or medicine. In the last decades, homogeneous catalysis with gold (I) complexes has played a very prominent role in the transformations of organic substrates involving unsaturated carbon-carbon bonds.[3] In these complexes, the carbenes derived from nitrogenous heterocycles (NHC) represent a very interesting alternative to the traditional phosphines as organic ligands, standing out for its good σ donor properties and its great chemical stability against humidity or heat.[4] Of these, carbenes obtained from imidazolium or imidazolinium salts with two groups derived from sterically congested anilines are among the most commonly used today in organometallic catalysis because of their stability and versatility, as well as their facile synthesis.[5] In particular, the so-called IPr, derived from the N, N'-bis-(2,6-diisopropylphenyl)imidazolium cation, forms part of some commercially available gold (I) complexes which have proved their versatility as catalysts in a great variety of transformations.

On the other hand, the immobilization of homogeneous catalysts by the covalent attachment of the ligand on a solid support has been a widely explored research area in the last years in the search of advantages, such as an easy recovery and subsequent reuse of the catalyst or the lower metal contamination of the final products.[6] These alleged advantages have recently been questioned in particular for immobilized palladium and rhodium catalysts.[7] The catalysis with immobilized metals has been directed in most cases to the use of immobilized Pd in cross-coupling or Heck processes and, in the case of other metals, to their use to catalyze hydrogenation reactions. Continuous flow metal catalysis seems to be a methodology suitable to be used with gold better than with other metals since the oxidation state of gold remains unchanged throughout the processes unlike what happens for instance with palladium or rhodium, a change associated to leaching phenomena.[8] The development of immobilized catalysts that combine the performance of homogeneous NHC-Au(I) catalysts and, on the other hand, could be used under continuous-flow conditions, is an attractive idea for their possible use in synthetic processes at multigram scale.

RESULTS AND DISCUSSION

Silica has been the carrier most used to date in the preparation of immobilized NHC-complexes of Au(I)[9] and other metals.[10] The imidazolium nucleus is usually anchored to the support at the nitrogen through an alkyl or benzyl linker. Porous organic polymers with Au(I)-IPr (Au-NHC@POPs) have been synthesized by Li et al.[11] showing superior catalytic activity in batch in alkyne hydration reactions. With the aim of generating a supported catalyst with an activity similar to that of their homogeneous (IPr)AuCl (**1a**) and (IAdPr)AuCl (**1b**) counterparts the silica immobilized complexes **2a** and **2b** were synthesized. It is to be noted that unlike other silica immobilized Au(I)-NHC complexes described so far, complexes **2a** and **2b**, as important differential characteristic, have the 2,6-diisopropyl-4-alkylphenyl moieties linked to silica at the *para* position of the aromatic ring and consequently the metal environment of **2a** is identical to that of the sterically demanding IPr ligand and related ligands,[12] which have been widely used in homogeneous catalysis with many metal complexes in a variety of processes. A bulky 2-adamantyl group was substituted for one of the 2,6-diisopropyl-4-alkylphenyl group in the mixed IAdPr ligand used for the preparation of complex **2b**.

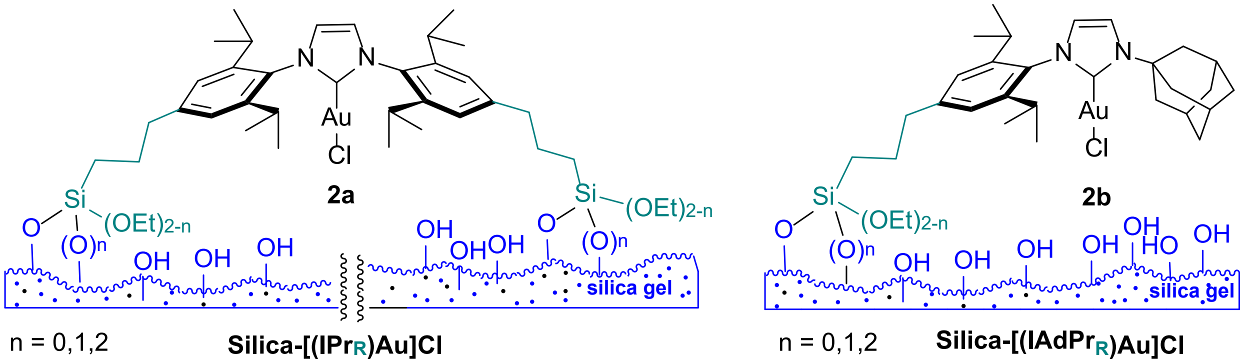
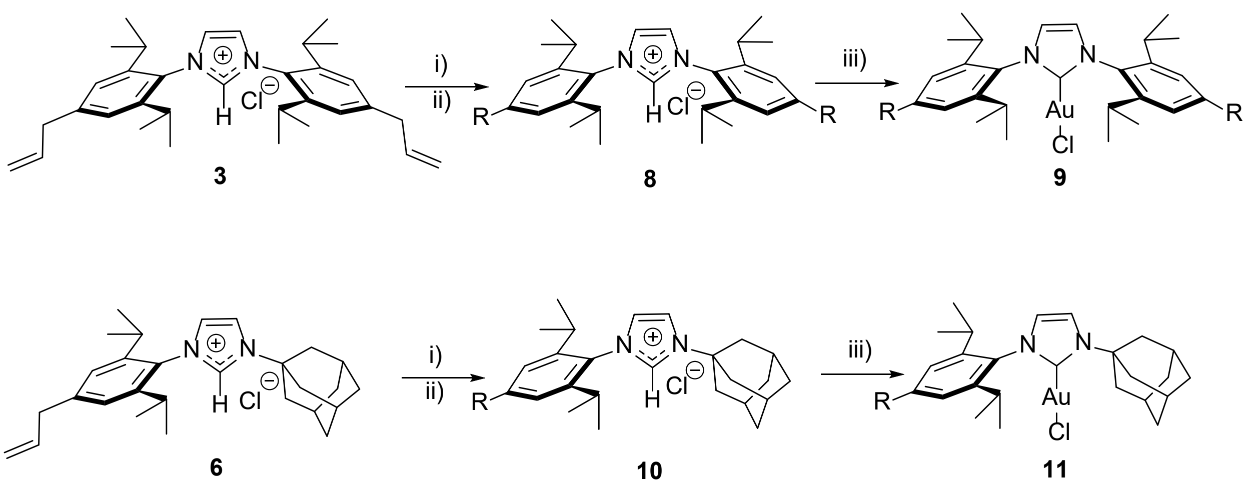


Chart 1. Silica immobilized catalysts **2a** and **2b**.

As shown in Scheme 1, two different methodologies were used for the preparation of the necessary symmetrical and unsymmetrical imidazolium salts used as carbene precursors.[13] Symmetrical 1,3-bis-(4-allyl-2,6-diisopropylphenyl)imidazolium chloride (**3**)[14] was synthesized by reacting N,N'-bis-(4-allyl-2,6-diisopropylphenyl)ethane-1,2-diimine (**4**),[15] obtained by condensation of glyoxal and two equivalents of 4-allyl-2,6-diisopropylaniline (**5**),[16] with formaldehyde (for experimental details see SI). 1,3-(adamant-1-yl)-(4-allyl-2,6-diisopropylphenyl) imidazolium chloride (**6**) was synthesized by a multicomponent reaction from amine **5**, 1-adamantylamine (**7**), glyoxal and an aqueous solution of formaldehyde in acetic acid following the procedure described by Baslé and Mauduit[17] for other unsymmetrical unsaturated imidazolium salts (for experimental details see SI). Catalytic hydrosilylation of the terminal double bonds of **3** and **6** using catalytic $PtCl_4$ and trichlorosilane followed by ethanolysis with ethanol/triethyl amine afforded the corresponding triethoxysily substituted imidazolium salts **8** and **10** (Scheme 1).

Scheme 1. Preparation of silylated gold complexes **9** and **11**.



R = $CH_2CH_2CH_2Si(OEt)_3$

i) $HSiCl_3$, $PtCl_4$, CH_2Cl_2, 60°C, 24h; ii) Et_3N, EtOH; iii) K_2CO_3/Au(DMS)Cl, Acetone, 60°C

To obtain the corresponding supported complexes we tested two alternative strategies that differ in the order in which the formation of the gold complex and the anchoring process is carried out. First, imidazolium salts **8** or **10** were anchored on silica and then treated with Au(DMS)Cl/K_2CO_3 but complexes **2a** or **2b** could not be obtained. The use of Au(THT)Cl/ KOtBu was also inefficient.

By contrast, gold complexes **2a** and **2b** were readily synthesized when the processes of grafting and complexation were performed in the reverse order. Accordingly, silylated NHC-Au complexes **9** (64% yield) and **11** (90% yield) were respectively obtained following the improved general protocols reported by Nolan and Gimeno[18] by treatment of **8** or **10** respectively with Au(DMS)Cl and K_2CO_3 in acetone.

The immobilized catalysts **2a** and **2b** (designated as Silica-[(IPr$_R$)Au]Cl and Silica-[(IAdPr$_R$)Au]Cl respectively) were obtained by grafting the silylated gold complex **9** or **11** on activated silica in toluene under reflux using a Dean-Stark apparatus. The gold loading found per gram of silica immobilized complex, determined by atomic absorption spectrometry, was 12,37 mg (0,063 mmol) and 9,85 mg (0,05 mmol) in solids **2a** and **2b** respectively (for experimental details see SI).

Characterization of hybrid silica materials **2a** and **2b**.

Hybrid silica materials **2a** and **2b** were analyzed by ^{13}C and ^{29}Si CP-MAS NMR spectrometry, ^{13}C CP-MAS spectra are displayed in Figures 1 and 2. Spectra of silylated gold complexes **9** and **11** in solution are shown for comparison. Good accordance between the chemical shift values of the precursor gold carbene complexes and the resulting hybrid materials can be observed in both cases. Complete disappearance of the signals at $\delta = 57{,}7$ and 18,6 ppm corresponding to the triethoxy groups occurs during the grafting reactions as expected.

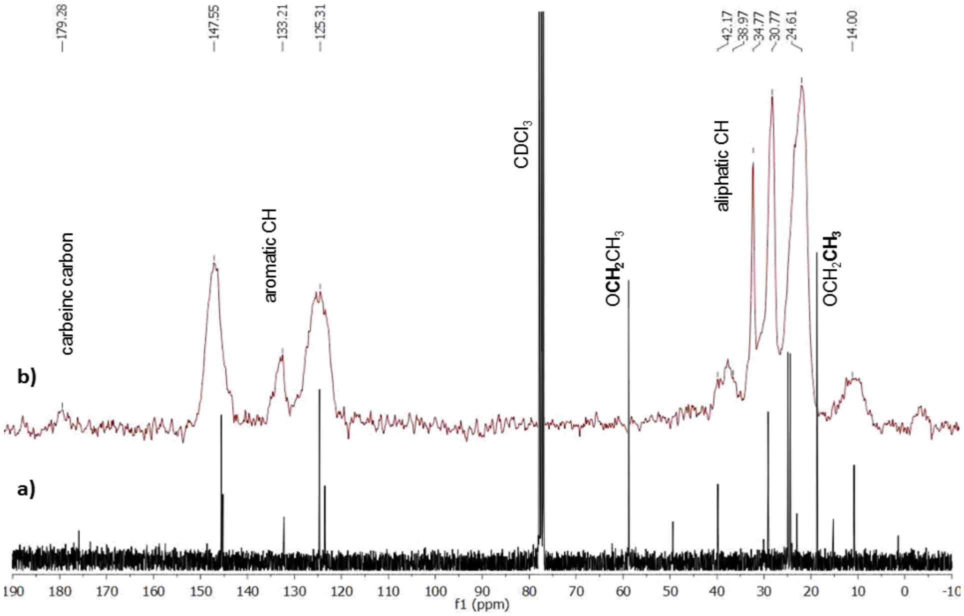


Figure 1. a) ^{13}C NMR spectrum of complex **9** in $CDCl_3$ solution; b) ^{13}C CP-MAS NMR spectrum of hybrid material Silica-[(IPr$_R$)Au]Cl (**2a**).

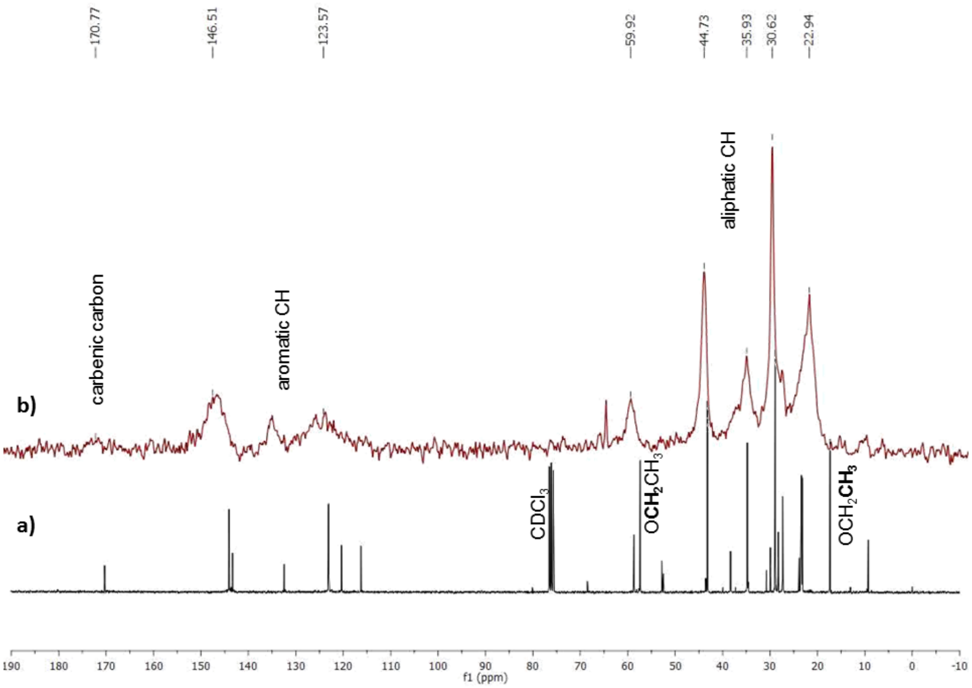


Figure 2. a) ^{13}C NMR spectrum of complex **11** in $CDCl_3$ solution; b) ^{13}C CP-MAS NMR spectrum of hybrid material Silica-[(IAdPr$_R$)Au]Cl (**2b**).

In the ^{29}Si CP-MAS spectra new signals can be observed between -56 and -68 δ ppm corresponding to T^2 and T^3 silicon atoms as well as a decrease of the Q^2 signal demonstrating the covalent bonding of the ligand to the silica surface (Figure 3).

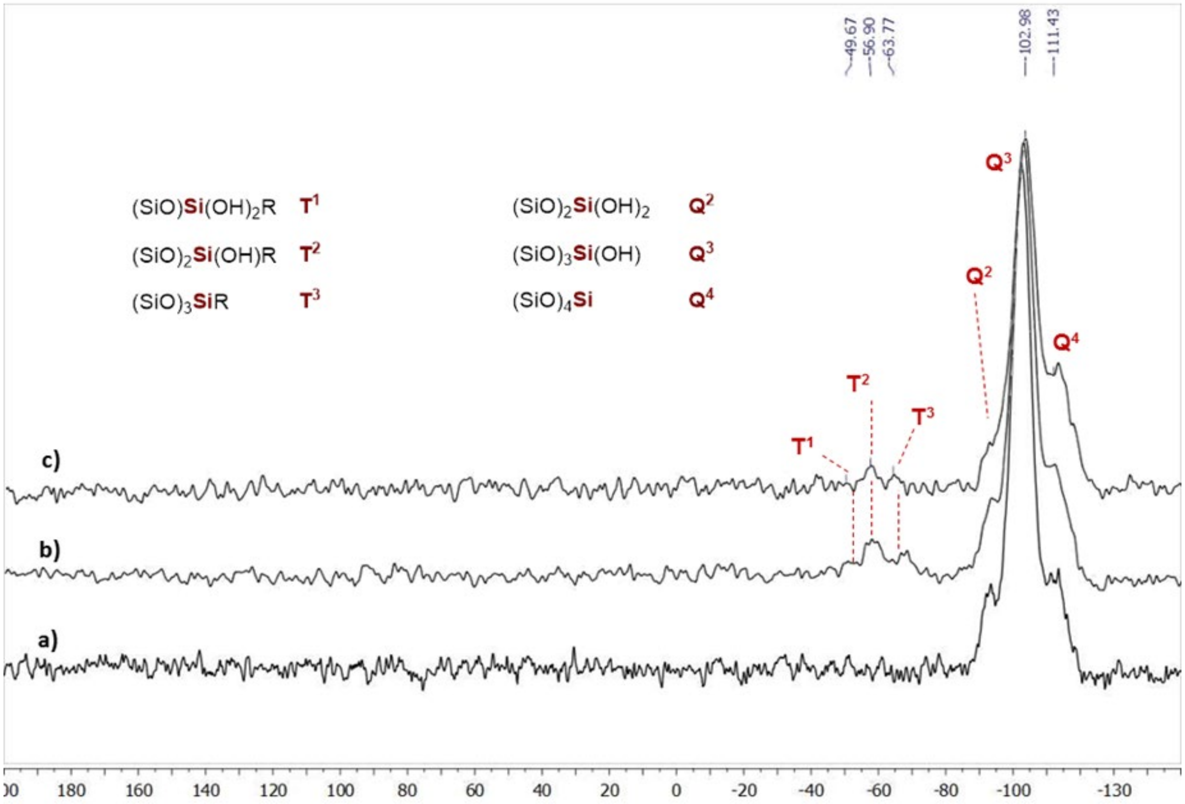


Figure 3. ^{29}Si CP-MAS spectra of: a**)** activated silica; b**)** hybrid silica material **2a** and c**)** hybrid silica material **2b**.

SEM images of the hybrid materials were also acquired. Figure 4a shows the typical laminar morphology of silica particles before grafting. A significant reduction of particle size due to sintering during stirring in the grafting reaction is observed in the silica immobilized complexes **2a** and **2b** (Figures 4b and 4c).

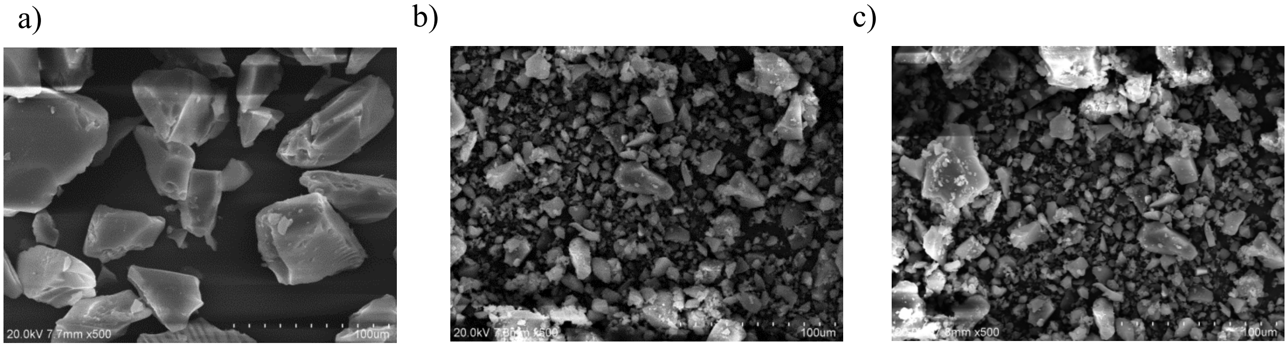
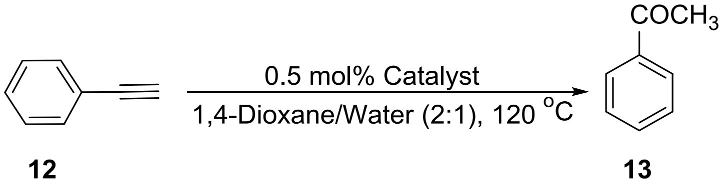


Figure 4. SEM images of a) activated silica before grafting; b) hybrid silica material **2a**; c) hybrid silica material **2b**.

Four typical gold catalyzed nucleophilic addition reactions to alkynes (Scheme 2) were selected to test the catalytic activity of the hybrid materials compared to that of their homologous complexes (IPr)AuCl (**1a**) and (IAdPr)AuCl (**1b**) under homogeneous conditions. $AgSbF_6$ was used in all the cases to obtain the corresponding cationic Au(I) catalysts (see supporting information).

The hydration of alkynes with gold catalysts[19] is perhaps one of the most studied reactions in the chemistry of this metal, due to its great potential in sustainable chemical transformations. It implies only water as the reagent and a low catalyst loading. Phenylacetylene (**12**) was selected as the substrate to test the activity of the immobilized catalysts in this transformation. Different reaction conditions have been described for the Au(I)-catalyzed hydration of alkynes in homogeneous phase. Long reaction times (*c.a.*20 h) were required to achieve complete conversion into the corresponding ketone when the water addition to the alkyne was carried out using a 2:1 methanol/water mixture as the solvent at 65 ºC and 0.5 mol% loading of the silica supported catalysts.[20] Hydration reactions catalyzed by **2a** proceeded slightly faster than those carried out using **2b** as the catalyst. A similar result was obtained when 1,4-dioxane was substituted for methanol as the solvent. However complete conversion of the alkyne was achieved in only 2 h in 2:1 dioxane/water solution with the same catalyst load when the temperature was raised to 120 ºC (Table 1, entries 1 and 2). Reactions were monitored by gas chromatography using benzaldehyde as the standard. Although both silica supported catalysts were efficient to promote the expected transformation and could be recovered by filtration, the reactions performed at 65 ºC seem to be too slow to allow the design of neither *practical* recycling process nor their use under continuous flow conditions.

Table 1. Hydration of **12** catalyzed by silica immobilized NHC gold complexes **2a** and **2b**



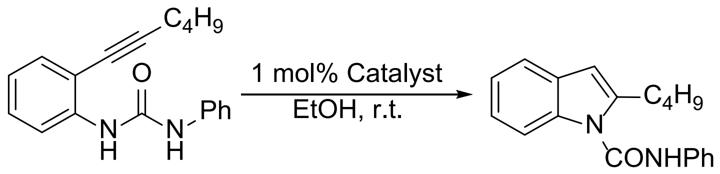
entry	Cycle	Catalyst[a]	Time,[b] yield %					
			1h	2h	3h	4h	5h	20h
1	1	**2a**	77	>99				
2	1	**2b**	57	>99				
3	2	**2a**		73	>99			
4	2	**2b**		57	97			
5	3	**2a**			70	87	>99	
6	3	**2b**				80	87	>99
7	4	**2a**					80	>99
8	4	**2b**					80	>99
9	5	**2a**					76	>99
10	5	**2b**					73	>99

[a] $AgSbF_6$ was used in all the cases to obtain the corresponding cationic Au(I) catalysts. [b] The first conversion was monitored in each case at the time required to achieve full conversion in the previous cycle.

Then, we examined the possibility of reusing **2a** or **2b** to catalyze the hydration of **12** in 2:1 dioxane/water solution at 120 ºC. Five successive reaction cycles were essayed by recovering each time the catalyst by filtration after the complete conversion of the alkyne had been achieved prior to the catalyst reuse in the next cycle (see Table 1).

The catalyzed intramolecular hydroamidation of 1-(*o*-akynylaryl)ureas with 5 mol% of (IPr)AuCl (**1a**) in DMF at 60 ºC leads to indoles in 1 h.[21] The immobilized catalysts Silica-[(IPr)Au]Cl (**2a**) and Silica-[(IAdPr)Au]Cl (**2b**) activated with $AgSbF_6$ were found to be fairly active in this transformation.

Table 2. Cyclization of 1-(*o*-akynylaryl)urea **14** catalyzed by silica immobilized gold NHC complexes **2a** and **2b**.



14 **15**

entry	Cycle	Catalyst[a]	Time,[b] conversion %					
			1 h	2 h	3 h	4 h	5 h	6 h
1	1	**1a**	>99					
2	1	**1b**	70	100				
3	1	**2a**	56	>99				
4	1	**2b**	67	85	>99			
5	2	**2a**		78	84	>99		
6	2	**2b**			75	83	>99	
7	3	**2a**				59	83	>99
8	3	**2b**				50	78	90[c]
9	4	**2a**					50	70[d]
10	4	**2b**					30	50
11	5	**2a**						64[d]
12	5	**2b**						30

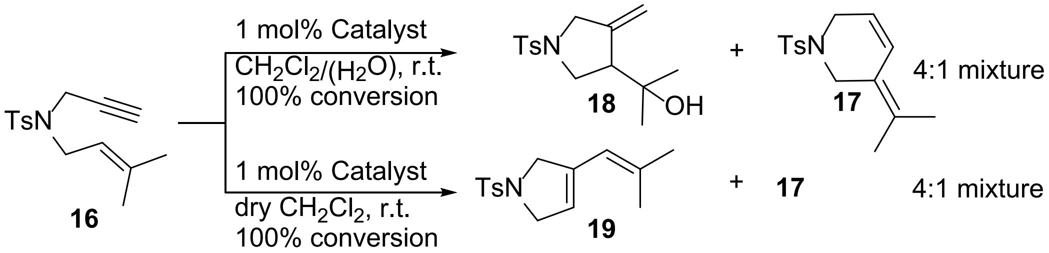
[a] $AgSbF_6$ was used in all the cases to obtain the corresponding cationic Au(I) catalysts. [b] The first conversion was monitored in each case at the time required to achieve full conversion in the previous cycle. [c] Complete conversion was attained after 10 h. [d] Complete conversion was observed after 18 h.

The reaction conditions were optimized using ethanol as the solvent at room temperature and a catalyst load of 1 mol% percent. Complete conversion was observed to take place after 2 or 2.5 h respectively and both catalysts could be recovered by filtration. Reaction times were slightly longer using immobilized catalysts instead of their homogeneous analogous **1a** and **1b** under the optimized conditions (Table 2, entries 1-4).

Five successive reaction cycles were essayed by recovering each time the catalyst by filtration after the complete conversion of the alkyne had been achieved for reuse in the next cycle (see Table 2).

We then selected the cycloisomerization reaction of enynes to continue testing the activity and selectivity of the silica immobilized catalysts **2a** and **2b**. This reaction has found numerous applications both in the synthesis of carbocyclic and heterocyclic structures as well. Besides its practical interest, the reaction offers different alternatives from the mechanistic point of view with and without skeletal rearrangement and, consequently, several reaction paths can be followed along the cyclization processes. Gold-catalyzed homogeneous cycloisomerization reaction with catalysts containing a variety of phosphine and NHC ligands have been extensively studied and reviewed.[22] Interestingly, Yu *et al.* reported[23] the use of two recyclable polystyrene-supported gold catalysts in the cycloisomerization of 1,6-enyne **16** to give tetrahydropyridine **17** and alcohol **18** with a 6 mol% catalyst load. Then, the product selectivity of these PS-immobilized gold catalysts resembles to that of homogeneous phosphine complexes.[24] Different results were obtained from this substrate using **2a** or **2b** depending on whether the reactions were performed under strictly anhydrous conditions or water was not completely excluded. In our preliminary experiments carried out in wet CH_2Cl_2, the cycloisomerization of **16** catalyzed by 1 mol% **2a** led to a 4:1 mixture of the 5-*exo-dig* hydroxicyclization alcohol **18** and the tetrahydropyridine **17** resulting from a 6-*endo-dig* cyclization of the enyne precursor. Complete conversion was reached in methylene dichloride at room temperature in only 15 min. The cycloisomerization of **16** with 5 mol% of silver activated **1a** and **1b** in a 6:1 mixture CH_2Cl_2:H_2O at room temperature was essayed for comparison leading to a 4:1 mixture of **18** and **17** with complete conversion of the substrate in 5 h and 4h, respectively. Accordingly, silica-immobilized **2a** and **2b** behave under these conditions as their homogeneous counterparts as expected being even more active in this transformation. In a new series of experiments **2a** and **2b** were carefully dried under vacuum in a desiccator using P_2O_5 as drying agent and cycloisomerization reactions were carried out at room temperature in previously dried CH_2Cl_2 under Ar atmosphere (see SI for details). Complete conversion of **16** into a 4:1 mixture of dienes **19** and **17** respectively took place now in 15 min with a catalyst load of 1 mol% (Scheme 2).

Scheme 2. Cycloisomerization of enyne **16** catalyzed by silica immobilized gold NHC complexes **2a** and **2b**.



The catalysts were readily recovered by filtration under inert atmosphere after completion of each cycle for subsequent reuse. Five cycles were run in dry CH_2Cl_2 as the solvent with the catalysts recovered leading in all the cases to an 4:1 mixture of **19** and **17**. The progress over time of the conversion of **16** into the products was monitored for each cycle by GC (see Table 3).

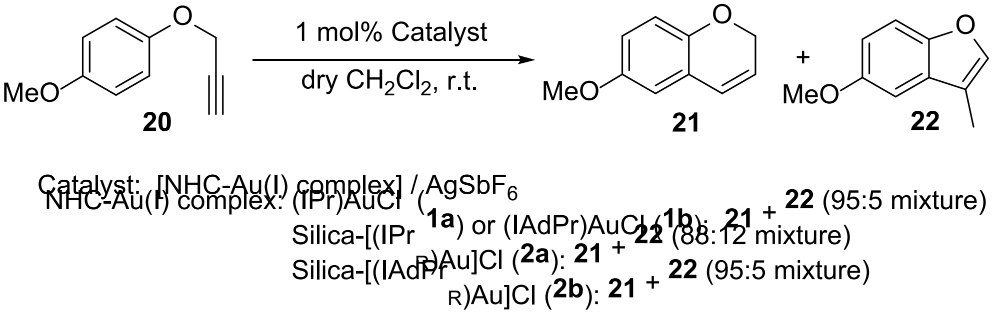
Table 3. Progress over time of the conversion of **16** into an 4:1 mixture of **19** + **17** in dry CH_2Cl_2 at r.t.

entry	Cycle	Catalyst[a]	Time,[b] conversion %				
			5 min	10 min	15 min	30 min	45 min
1	1	**1a**	80	>99			
2	1	**1b**	>99				
3	1	**2a**	60	80	>99		
4	1	**2b**		74	>99		
5	2	**2a**			>99		
6	2	**2b**			80	>100	
7	3	**2a**			>99		
8	3	**2b**			60	87	>99
9	4	**2a**			76	>99	
10	4	**2b**			57	87	99
11	5	**2a**				90	>99
12	5	**2b**					80

[a] $AgSbF_6$ was used in all the cases to obtain the corresponding cationic Au(I) catalysts. [b] The first conversion was monitored in each case at the time required to achieve full conversion in the previous cycle.

Gold complexes catalyze the intermolecular hydroarylation of alkynes.[25] In an intramolecular version of this reaction, aryl propargyl ethers under homogeneous conditions with low catalyst loadings (1 mol%) were shown to provide a mild an easy entry to 2*H*-chromenes, coumarins and benzofurans, their formal 6-*endo-dig* or 5-*exo-dig* cyclization products. In the syntheses reported,[26] Au(I) complexes containing phosphine ligands were used to obtain 2*H*-chromenes and benzofurans in a variable ratio depending on the substitution pattern at the aryl ether precursor. Only the 2*H*-chromene is obtained from (prop-2-yn-1-yloxy)benzene (**20**)[26b,c] and this reaction was selected to test the catalytic activity of silica supported complexes **2a** and **2b**. Unfortunately, no reports were found for comparison on the hydroarylation of **20** using NHC-Au(I) complexes. For this reason, first of all we essayed this reaction under homogeneous conditions with 1 mol% of the silver activated complexes (IPr)AuCl (**1a**) and (IAdPr)AuCl (**1b**) as the catalyst, in CH_2Cl_2 solution at room temperature. The reaction was very selective giving in both cases a 95:5 mixture of 2*H*-chromene **21** and benzofurane **22** (Scheme 3). Interestingly, the hydroarylation reaction with the complex **1b** was faster and complete conversion was achieved in just 7 minutes while **1a** required 15 min under these conditions (Table 4, entries 1 and 2).

Scheme 3. Hydroarylation of arylalkyne **20** catalyzed by activated gold NHC complexes



The cyclization of **20** catalyzed with silver activated immobilized **2a** (1 mol%) or **2b** (1 mol%) was somewhat slower than that under homogeneous conditions with the analogue catalyst and it took place in dry CH_2Cl_2 at room temperature with complete conversion of **20** in 30 min (Table 4, entries 3 and 4). The *exo/endo* selectivity in the cyclization was slightly lower for **2a** giving in this case an 88:12 mixture of **21** and **22** while **2b** showed the same selectivity as that found with the homogeneous catalysts (Scheme 3).

The reactions become progressively slower, to a lesser or greater extent depending on the nature of the substrate, when using recycled catalysts in all the cases, what at first was attributed to catalyst leaching. The loss of activity was investigated, and the metal content in the filtrate resulting from recovery and washing the catalyst for reuse was quantified by ICP. It was found to be <1% of the initial gold content of the catalyst in any case. This allows ruling out leaching to justify the progressive deactivation of the silica supported catalysts along the successive reaction cycles. It should also be noted that color changes associated with the presence of gold nanoparticles were never observed.

Table 4. Progress over time of the conversion of **20** into the mixture **21** + **22** in dry CH_2Cl_2 at r.t

entry	Cycle	Catalyst[a]	Time min,[b] Conversion %								
			10	15	30	60	90	120	180	240	360
1	1	**1a**	52	>99							
2	1	**1b**	>99								
3	1	**2a**	43	84	>99						
5	1	**2b**		70	>99						
6	1	**2b**[c]		95	>99						
7	2	**2a**			61			>99			
8	2	**2b**			34			>99			
9	2	**2b**[c]		70	92	>99					
10	3	**2a**						70		90	>99
11	3	**2b**						70		85	>99
12	3	**2b**[c]				71	94				
13	4	**2a**								57	80[d]
14	4	**2b**								40	60[d]
15	4	**2b**[c]						82	96		

[a] $AgSbF_6$ was used in all the cases to obtain the corresponding cationic Au(I) catalysts. [b] The first conversion was monitored in each case at the time required to achieve full conversion in the previous cycle. [c] Orbital shaker. [d] Complete conversion was attained after 10 h.

In the protocol followed to recover the catalysts all operations were performed under inert atmosphere and the same dry solvent in which the reactions were carried out was used in each case to wash the solid. Since all the reactions were carried out with magnetic stirring, it was considered that the solid support could be crushed during the stirring time modifying its structure. This mechanical effect should not affect the covalent bonds between the silica support and the ligand nor promote the dissociation of the metal complex.

To test this hypothesis the hydroarylation of **20** was carried out again with **2b** using now an orbital shaker. The catalyst was recovered by filtration following the same protocol as described above. In this way all cycles were faster than the corresponding cycle carried out with magnetic stirring (see Table 4 entries 6, 9, 12 and 15). SEM images of the catalysts after being used in several cycles in selected reactions were acquired for comparison. Indeed, a severe reduction of the particle size could be observed in **2a** and **2b** after several cycles of magnetically stirred reactions as expected (compare Figures 5a and 5b with Figures 4b and 4c, respectively). By contrast, the particle size of **2b** did not decrease when the reactions were carried out using an orbital shaker as observed in Figure 5c.

This clearly points to crushing of the solid as responsible, at least in part, of the progressive loss of activity observed in **2b** in the successive cycles essayed under batch reactions. Aimed by this idea we decided to test the performance of **2b** under flow conditions since in this way any stirring or manipulation of the catalyst is avoided. The hydroarylation reaction of **20** was first selected for the flow experiments provided that this transformation is quite fast at room temperature under batch conditions as shown above although the catalytic activity of **2b** decreases along the successive cycles.

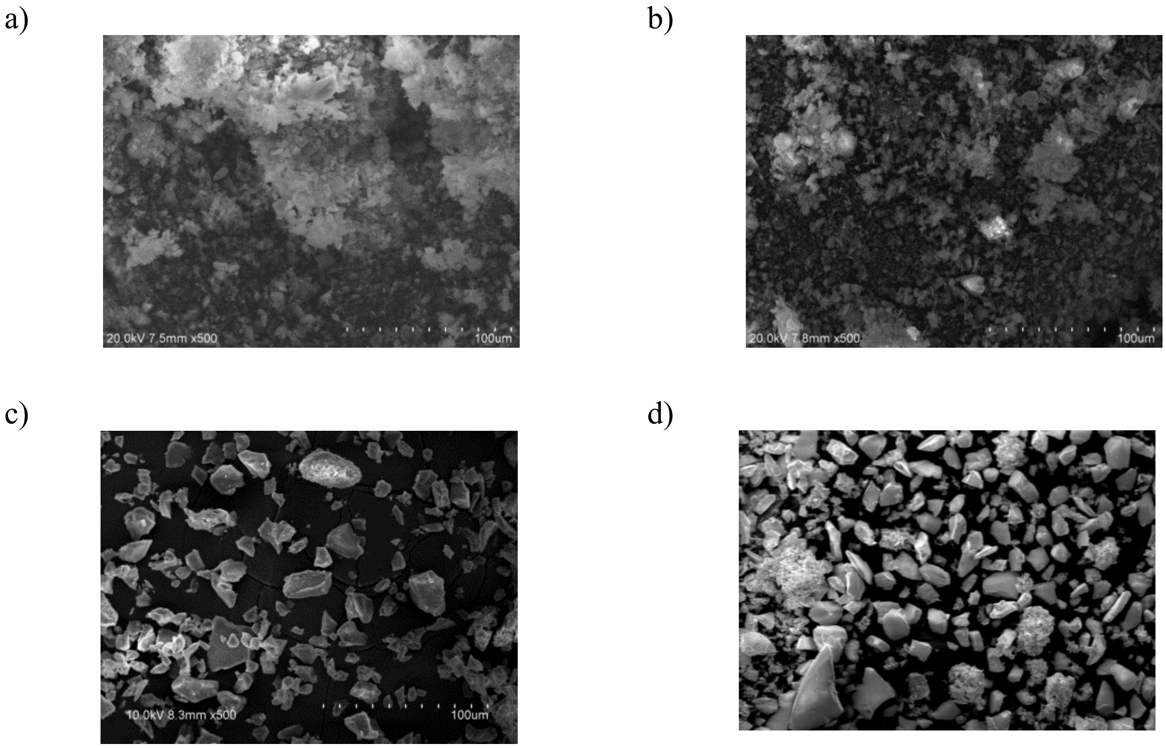


Figure 5. SEM images of a) hybrid silica material **2a** after 12 cycles of hydration reaction; b) hybrid silica material **2b** after 4 cycles of hydroarylation reaction; c) hybrid silica material **2b** after 4 cycles of catalysis using an orbital shaker; d) hybrid silica material **2b** after all the experiments carried out under continuous flow conditions.

The flow reactions were carried out using a H-Cube Pro (ThalesNano) instrument equipped with a micro HPLC pump which allows to control a 0,3-3 mL/min flow rate with increasing intervals of 0,01 mL/min. The cartridge containing the catalyst was charged with previously activated **2b** (98 mg, 0,0049 mmol Au). Alumina and Celite were placed at both ends of the cartridge to prevent any eventual removal of catalyst by the solvent to complete a total solid charge of 120 mg. Different concentrations of **20** in dry CH_2Cl_2 and flow rate were essayed to optimize the flow conditions. Optimal conditions to reach complete conversion of the substrate were achieved by using a 0,05 M solution of **20** in dry CH_2Cl_2 and a 0,5 mL/min flow rate. Separate samples were collected during 40 min with 4 min intervals each one corresponding to the transformation of 0,1 mmol of substrate. The activity of **2b** remained unaltered in the cartridge along the complete flow experiment and hence complete conversion of 1 mmol of **20** into a 95:5 mixture of 2*H*-chromene **21** and benzofurane **22** was attained in 40 min. This conversion rate would correspond to a productivity of 306 $mmol_{product}.mmol_{Au}^{-1}.h^{-1}$.

In a second experiment a new cartridge was packed as described above to further explore the life-time of **1b** under flow conditions in this transformation. The same concentration of **20** in CH_2Cl_2 and flow rate were also used but in this case the progress of the reaction was followed by GC with 1 h intervals. (see Figure 6). After 12 h, 18 mmol of the mixture of hydroarylation products were obtained with complete conversion of the substrate in this time. However, in the sample analyzed after 13 h the activity of the catalyst had diminished and the conversion was only 86%. The apparent loss of activity of **2b** could be reverted by washing the cartridge with 45 mL of dry CH_2Cl_2 at a 1 mL/min flow rate**.** Afterwards, the flow reaction was continued by using the same cartridge and now 4 mmol of **20** were synthesized in 160 min with complete conversion of the alkyne **20**. At this point of the transformation, the TON value was 4753 and the experiment was discontinued. These results show that silica supported gold catalyst **2b** is suitable to perform hydroarylation reactions under flow conditions without loss of activity, maintaining a productivity value of 300 h^{-1} approximately.

To further assure the suitability of **2b** to be used under flow conditions we decided to reuse this same cartridge to carry out a different transformation. The above cartridge was washed with CH_2Cl_2 for 30 minutes at a flow rate of 1 mL/min and then tested to catalyze the cycloisomerization reaction. Enyne **16** (1 mmol) was dissolved in 20 mL of a 6:1 CH_2Cl_2/water mixture and passed through the recycled cartridge at 1 mL/min flow rate (see Figure 6). Complete conversion of the substrate into a 4:1 mixture of compounds **18** and **17** was attained in 20 min. Then, the productivity for this transformation was at least 612 h^{-1}, twice the observed value in the hydroarylation reaction. At this point the flow experiment was discontinued. The supported solid was then removed from the cartridge and SEM images of the hybrid material were acquired as above described confirming that its structure remains practically unchanged during the hydroarylation and cycloisomerization experiments performed under flow conditions as expected (see Figure 5d).

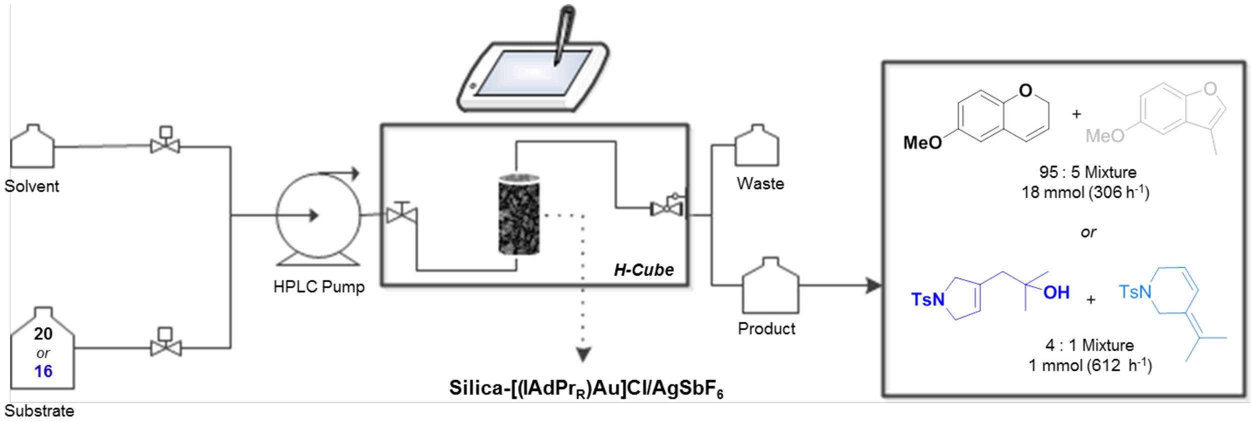


Figure 6. Hydroarylation and cycloisomerization carried out sequentially under continuous flow conditions catalyzed by **2b**. Productivities in $mmol_{product}.mmol_{Au}^{-1}.h^{-1}$ are shown in brackets.

CONCLUSIONS

Strongly hindered symmetrical or unsymmetrical NHC ligands derived from two amines of well-differentiated basicity are readily synthesized by condensation reactions from conventional products. Both types of ligand can be easily anchored on silica when they possess one or two unsaturated chains in the *para* position of the aromatic amine from which they derive by hydrosilylation with subsequent grafting. The preparation of the corresponding immobilized Au(I) complexes requires forming the metal complex prior to the grafting. The immobilized complexes have been shown to be excellent catalysts that replicate and sometimes even exceed the activity of their homologues in homogeneous phase in the typical reactions involving the activation of the alkynes tested. The immobilized catalysts studied are easily recovered by simple filtration and can be reused in batch reactions in successive cycles, keeping constant its metal content demonstrating that they do not undergo leaching processes. However, a loss of catalytic activity occurs after several cycles due to degradation of the original surface of the solids by crushing induced by magnetic stirring. The degradation of the catalysts occurs more slowly by using an orbital shaker in the reactions. These immobilized catalysts have been shown to be particularly suitable in reactions under continuous flow conditions which take advantage of the fact that the metal complex is bound to the surface of the solid support by a strong covalent bond. In addition, the surface of the catalysts does not undergo mechanical degradation due to the absence of stirring. The immobilized gold complexes have shown to be highly stable against leaching compared to those derived from other transition metals most likely because the oxidation state of gold remains constant throughout the catalytic process. Excellent productivities were attained using activated Silica-[(IAdPr$_R$)Au]Cl (**2b**) as the catalyst under continuous flow conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:xxxxxxxxxxxxx.

Experimental part including general information, procedures for the synthesis of unsymmetrical gold(I) complex **1b** and immobilized gold (I) complexes **2a** and **2b**, general procedures for catalytic reactions in batch and recycling procedure, experimental procedure for the reactions under flow conditions, characterization data for new compounds and cold complexes and NMR spectra.

■ AUTHOR INFORMATION

Corresponding Author

*Email: gregorio.asensio@uv.es

*Email: maria.t.varea@uv.es

Present address

[†]Departamento de Química, Universidad de Burgos, Pza. Misael Bañuelos s/n 09001-Burgos, Spain

[‡]Laboratorio de Catálisis Homogénea, CIQSO-Centro de Investigación en Química Sostenible, Universidad de Huelva, 21007-Huelva, Spain

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. [§]These authors contributed equally.

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Notes

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