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Mechanistic Insights into the One-Pot Synthesis of Propargylamines from Terminal Alkynes and Amines in Chlorinated Solvents Catalyzed by Gold Compounds and Nanoparticles

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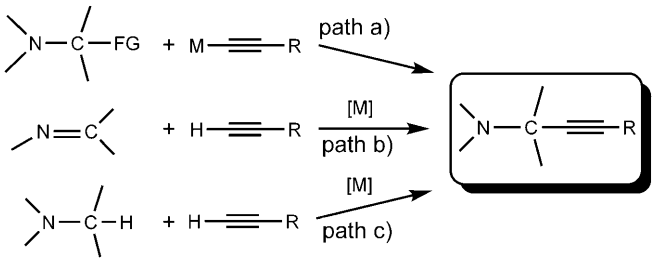
This paper is dedicated to Professor Richard H. Fish on the occasion of his 70th birthday

Abstract: Propargylamines can be obtained from secondary amines and terminal alkynes in chlorinated solvents by a three- and two-component synthesis catalyzed by gold compounds and nanoparticles (Au-NP) under mild conditions. The use of dichloromethane allows for the activation of two C–Cl bonds and a clean transfer of the methylene fragment to the final product. The scope of the reaction as well as the influence of different gold(III) cycloaurated complexes and salts has been investigated. The involvement of gold nanoparticles generated in situ in the process is discussed and a plausible reaction mechanism is proposed on the basis of the data obtained.

Keywords: alkynes · C–C coupling · C–Cl activation · catalysis · gold

Introduction

The synthesis of propargylic amines has attracted considerable attention over the last few years due to their pharmaceutical relevance and their importance as building blocks in the preparation of nitrogen-containing molecules, and as key intermediates for natural product synthesis.[1] There are three main synthetic pathways to obtain propargylamines:[2] 1) by stoichiometric nucleophilic reactions; 2) by transition-metal-catalyzed reactions of imines (or enamines), which can be generated from aldehydes and amines; or 3) by the catalytic coupling of a sp^3 C–H adjacent to nitrogen with a terminal alkyne (Scheme 1). Gold, silver, and copper compounds have also provided efficient catalysts in the imine-, enamine-, or imine-generated addition to alkynes,[3,4] including recyclable gold compounds[5] or nanoparticles.[6] The first example of a Cu^I-catalyzed alkynylation of tertiary amines with terminal alkynes in the presence of *t*BuOOH (Scheme 1, pathway c; through sp^3 C–H activation) was reported.[2]



Scheme 1. Methods available to form propargylamines.[2]

We report herein on a gold-catalyzed three- and two-component synthesis of propargylamines by an alternative route to those outlined in Scheme 1. Gold compounds and nanoparticles (Au-NP) are found to be efficient catalysts for the coupling of secondary amines and terminal alkynes in chlorinated solvents. In dichloromethane, we discovered that the coupling involves the methylene fragment from the solvent, which constitutes an unexpected role for dichloromethane as a CH_2 partner, by a gold-catalyzed C–Cl bond activation.

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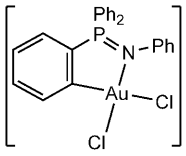
Activation of carbon–halogen bonds by transition-metal compounds is involved in various organic processes, but the activation of the relatively stable C–Cl bond is an important subject in environmental chemistry (due to the possible degradation of harmful chlorinated compounds).[7] The activation of CH_2Cl_2 by late transition metals has been documented for Co^{I},[8] Rh^{I},[9] Rh^{III},[10] Ru^{II},[11] Pd,[12] and Pt^{0}[12] complexes. The activation of the C–Cl bond usually affords M–CH_2Cl or M–CH_2–M organometallic compounds. Dinuclear gold(I) ylide complexes are also known to add CH_2Cl_2 to afford dinuclear Au^{II} derivatives with a methylene bridge.[13] The activation of CH_2Cl_2 (wherein CH_2Cl_2 serves as a CH_2 partner) by early transition metals has also been achieved.[14,15] Cr^{II} complexes are able to promote methylene transfer from CH_2Cl_2 to an alkene (cyclopropanation, but only in 2% yield) and the direct stoichiometric methynelation of ketones and aldehydes has been recorded for a bimetallic Mg/$TiCl_4$/THF system.[15] The heterolytic thermal or photocatalytic degradation of CH_2Cl_2 to HCl and CO under aerobic conditions has been described for heterogeneous catalysts and chlorocuprate ions.[16] The C–Cl bond activation described here represents an elegant example of the activation of CH_2Cl_2, which generates and transfers the methylene fragment catalytically (typically 5 mol% catalyst and amounts as low as 1 mol% for longer reaction times) under mild reaction conditions (50°C). Au^{III} complexes and Ag^{I} salts have proven to be effective in similar C–Cl bond activations,[17] but details of these findings were never published. We report herein on the effects of gold compounds and nanoparticles in different oxidation states in such coupling reactions, and suggest a plausible reaction mechanism.

Although gold-catalyzed reactions have been thoroughly studied in the past decade,[18] the study of reaction mechanisms and the isolation/characterization of gold intermediates and/or catalytically active species has not received the same attention. Clarification of the reaction mechanisms is crucial for the rational design of more efficient molecular catalysts.

We reported on the catalytic and cytotoxic/apoptotic properties[19] of gold(III) compounds containing iminophosphorane ligands (such as **1** and **2**)[19a,c] that catalyzed the addition of 2-methylfuran and electron-rich arenes to methyl vinyl ketone,[19a,b] and the synthesis of 2,5-disubstituted oxazoles through cyclization of *N*-propargylcarboxamides.[19b] Iminophosphoranes ($R_3P{=}NR'$) constitute a class of compounds that can be readily prepared by different synthetic routes,[20] and their electronic and steric properties may be tuned through appropriate choice of R and R′. Not only does the iminophosphorane C,N-backbone confer a marked stability to the metallic center in d^8 square-planar complexes, but also the PR_3 fragment can be used as a spectroscopic marker to follow reactions by ^{31}P NMR spectroscopic analysis. We demonstrated that the real catalytic species in these processes were cationic gold(III) cycloaurated complexes generated by abstraction of the chloride ligands in polar solvents further assisted by silver salts.[19a]



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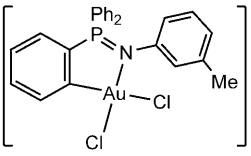

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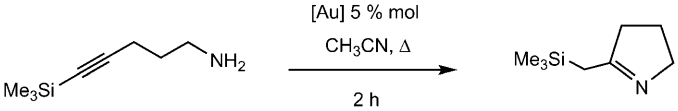
Encouraged by these results, we decided to study hydroamination reactions of alkynes with these and related cycloaurated complexes.

Results and Discussion

Scope of the gold-catalyzed synthesis of propargylamines in chlorinated solvents: Formation and catalytic activity of gold nanoparticles: The cyclization of 5-trimethylsilyl-4-pentynylamine (**3**)[21] was catalyzed by **1**, **2**, and gold(III) salts (Table 1), affording yields of the intramolecular hydroamination product **4** comparable to those reported for Na[$AuCl_4$] with 5-alkynylamines to give tetrahydropyridines (see the Supporting Information).[22]

Table 1. Catalytic preparation of **4** through intramolecular hydroamination of **3**.



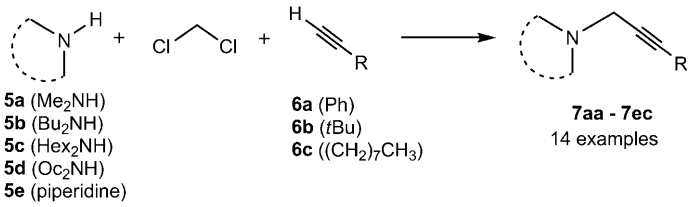
3 **4**

Entry	Catalyst ([mol%])	Ag^+ ([mol%])	Time [h]	Yield [%][a]
1	$AuCl_3$ (5)	–	2	64
2	Na[$AuCl_4$] (5)	–	2	85
3	**1** (5)	–	2	61
4	**1** (5)	AgOTf (11)	2	80
5	**1** (5)	AgOTf (6.1)	2	73
6	**1** (5)	–	2	65
7	**2** (5)	AgOTf (11)	2	79
8	**2** (5)	AgOTf (6.1)	2	70

[a] Isolated yields.

Abstract in Spanish: *Se han obtenido propargilaminas a partir de aminas secundarias y alquinos terminales en disolventes clorados a través de una síntesis de dos o tres componentes catalizada por compuestos de oro y nanoparticulas (Au-NP) en condiciones de reacción suaves. El uso de diclorometano permite la activación de dos enlaces C–Cl y la posterior trasferencia del fragmento metileno al producto final. El alcance de la reacción así como la influencia de diferentes compuestos ortometalados y sales de oro(III) han sido investigados. Los resultados obtenidos son la base de la discusión sobre la participación de nanopartículas de oro generadas in situ en el proceso así como del posible mecanismo de reacción.*

We have also studied the catalytic activity of **1** in intermolecular hydroamination processes with terminal alkynes and secondary amines. However, when Bu_2NH (**5b**) was added to HC≡CPh (**6a**) in either THF or toluene in the presence of **1** (5 mol%, 50°C, 24 h), the expected intermolecular hydroamination product was not obtained and the unreacted starting materials were recovered instead (Scheme 2). Surprisingly, when CH_2Cl_2 was employed we obtained propargylamine **7ba**. This compound comes from a three-component coupling of the amine **5b**, the alkyne **6a** and the CH_2 fragment from the solvent CH_2Cl_2 as will be demonstrated below.



Scheme 2. Three-component synthesis of propargylamines.

We explored the scope of the reaction for the cycloaurated gold compound **1** as a catalyst under the same reaction conditions (alkyne (2 mmol), amine (2 mmol), **1** (5 mol%), 24 h, 50°C) for three different terminal alkynes and for five different secondary amines (Table 2). No reaction was observed between 1-decyne and $HNMe_2$. Better yields were obtained with Bu_2NH than with Me_2NH, probably due to the high volatility of the dimethylamino derivatives. The reaction seems to be very sensitive to the nature of the amine because no reaction was observed between the above-mentioned alkynes and Ph_2NH, Cy_2NH, iPr_2NH, or MeBnNH. Amines with linear N-alkylic chains are best tolerated and we observed that more basic amines such as Bu_2NH and piperidine also gave better results (dimethylamino derivatives were more volatile and gave lower isolated yields). The reaction is also sensitive to the nature of the solvent: whereas CH_2Br_2 can be used instead of CH_2Cl_2, other chlorinated solvents, such as $CHCl_3$ or $(ClCH_2)_2$, did not give detectable coupling products (see below). Preliminary reactions with a higher catalyst loading (10 mol%) and a 1:1.2 molar ratio of alkyne to amine afforded higher yields (Table 3 below and Table 1 in the Supporting Information), but the reaction conditions were subsequently optimized to lower the amount of catalyst and to use a 1:1 molar ratio (alkyne/amine).

Table 2. Three-component synthesis[a,b] of propargylamines in CH_2Cl_2 with **1** as the catalyst (Scheme 2).

Amine	**6a** [%]	**6b** [%]	**6c** [%]
5a	15 (**7aa**)	17 (**7ab**)	0 (**7ac**)
5b	58 (**7ba**)	71 (**7bb**)	57 (**7bc**)
5c	22 (**7ca**)	21 (**7cb**)	30 (**7cc**)
5d	70 (**7da**)	36 (**7db**)	51 (**7dc**)
5e	60 (**7ea**)	70 (**7eb**)	55 (**7ec**)

[a] Isolated yields. [b] Reaction conditions: cat. **1** (5 mol%), CH_2Cl_2 (5 mL), alkyne (2 mmol), amine (2 mmol), 24 h, 50°C.

Table 3. Synthesis of progargylamines **7ba**, **7bd**, and **8bd** in CH_2Cl_2 with isolated Au-NP (nano-**12**) synthesized by the Brust[26] method. A comparison with $K[AuCl_4]$ is given in the table.

Cat.	**7bd**+**8bd** [%]	**7ba** [%]
Nano-**12**[a]	94 (**7bd**/**8bd**, 1:0.5)	75
$K[AuCl_4]$[a]	93 (**7bd**/**8bd**, 1:0.5)	75
Nano-**12**[b]	90 (**7bd**/**8bd**, 1:0.05)	76
$K[AuCl_4]$[a]	91 (**7bd**/**8bd**, 1:0.08)	83

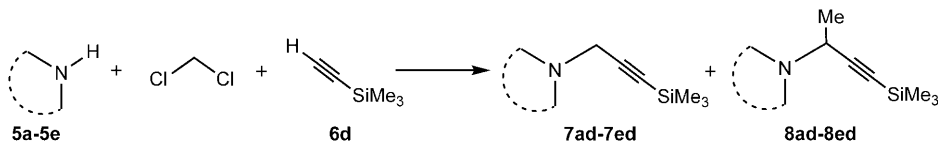
[a] Reaction conditions: cat. (10 mol%), solvent (5 mL), 50°C, 24 h, alkyne/amine (1:1). [b] Reaction conditions: cat. (1 mol%), solvent (5 mL), 50°C, 72 h, alkyne/amine (1:1.2).

The nature of the alkyne has a critical influence over the general process, as depicted in Scheme 3. The reaction of $Me_3SiC{\equiv}CH$ (**6d**) with R'_2NH (**5a–e**) in CH_2Cl_2 under the same conditions gave two different propargylamines (Table 4). The main product of the mixture was the CH_2Cl_2 activation product (**7ad–ed**), whereas the minor product (**8ad–ed**) arose from the formal coupling of one R'_2N fragment, one $Me_3SiC{\equiv}C$ unit, and a CH(Me) group that comes from a second $Me_3SiC{\equiv}CH$ alkyne molecule (see below). The nature of the silyl substituent is crucial for the synthesis of compound **8**. For instance, the terminal alkyne $Me_3CC{\equiv}CH$ (**6b**) did not afford propargylamines of the type **8** with a $Me_3CC{\equiv}C$ unit.

Compound **8ed** was not formed under the reaction conditions. Compound **8bd** was obtained as the exclusive product under similar reaction conditions in chlorinated solvents, such as $CHCl_3$ or $ClCH_2CH_2Cl$, with yields of 90%. A similar reaction between Et_2NH and acetylene (13.6 atm) to afford 3-diethylaminobut-1-yne, catalyzed by CuBr (20 mol%) in THF at 100°C, was described as early as 1949.[23]

We tested other gold(III) derivatives with different charges, such as the simple gold(III) salt $K[AuCl_4]$ (anionic) and new cationic cycloaurated phosphane-containing derivatives **9** and **10** (Scheme 4).

The synthesis and characterization of **9** and **10** are described in the Experimental Section. Mono- and dicationic derivatives **9** and **10**, respectively, are cleanly obtained from

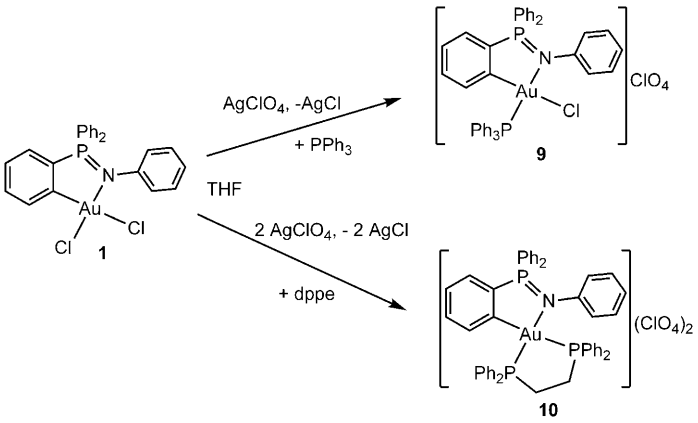


Scheme 3. Two- versus three-component synthesis with trimethylsilylacetylene.

Table 4. Two- versus three-component synthesis[a,b] of propargylamines in CH_2Cl_2 with **1** as the catalyst (Scheme 3).

Amine	**6d** [%]
5a	55 (**7ad/8ad**, 1:0.2)
5b	95 (**7bd/8bd**, 1:0.5)
5c	39 (**7cd/8cd**, 1:0.05)
5d	40 (**7dd/8dd**, 1:0.3)
5e	65 (**7ed/8ed**, 1:0.0)

[a] Isolated yields. [b] Reaction conditions: cat. **1** (5 mol%), CH_2Cl_2 (5 mL), alkyne (2 mmol), amine (2 mmol), 24 h, 50°C.



Scheme 4. Synthesis of new cationic cycloaurated *endo* derivatives **9** and **10** with phosphane ligands. Dppe = 1,2-bis(diphenylphosphino)ethane.

the organometallic gold(III) *endo* derivative **1**[19a] by removal of one or two chloride ligands with a silver salt and addition of a mono- (PPh_3) or bis-phosphane (dppe), respectively.

With the salt $K[AuCl_4]$ as a catalyst, we studied the addition reaction of the secondary amines **5a–e** to the terminal alkynes **6a–c** in CH_2Cl_2 (Scheme 2, Table 5). The results

Table 5. Three-component synthesis[a,b] of propargylamines in CH_2Cl_2 with $K[AuCl_4]$ as the catalyst (Scheme 2).

Amine	**6a** [%]	**6b** [%]	**6c** [%]
5a	35 (**7aa**)	30 (**7ab**)	0 (**7ac**)
5b	76 (**7ba**)	80 (**7bb**)	60 (**7bc**)
5c	32 (**7ca**)	30 (**7cb**)	35 (**7cc**)
5d	61 (**7da**)	41 (**7db**)	73 (**7dc**)
5e	78 (**7ea**)	80 (**7eb**)	68 (**7ec**)

[a] Isolated yields. [b] Reaction conditions: cat. $K[AuCl_4]$ (5 mol%), CH_2Cl_2 (5 mL), alkyne (2 mmol), amine (2 mmol), 24 h, 50°C.

were comparable to those obtained with the cycloaurated derivative **1** (slightly higher yields in this case). More basic amines gave better isolated yields. We could also reduce the catalyst loading to 1 mol% without loss of conversion (83%), at the expense of longer reaction times (72 h), to obtain propargylamine **7ba** (Table 3 below).

Moreover, the catalytic activity and selectivity of $K[AuCl_4]$ was similar to that of **1** when amines were added to the terminal alkyne $Me_3SiC{\equiv}CH$ (**6d**) (Table 6 and Scheme 3). With more basic amines, the selectivity towards the CH_2Cl_2 activation product was higher. Again **8ed** (with piperidine) could not be obtained under these reaction conditions.

Table 6. Two- versus three-component synthesis[a,b] of propargylamines in CH_2Cl_2 with $K[AuCl_4]$ as the catalyst (Scheme 3).

Amine	**6d** [%]
5a	60 (**7ad/8ad**, 1:0.3)
5b	90 (**7bd/8bd**, 1:0.1)
5c	46 (**7cd/8cd**, 1:0.05)
5d	42 (**7dd/8dd**, 1:0.8)
5e	73 (**7ed/8ed**, 1:0.0)

[a] Isolated yields. [b] Reaction conditions: cat. $K[AuCl_4]$ (5 mol%), CH_2Cl_2 (5 mL), alkyne (2 mmol), amine (2 mmol), 24 h, 50°C.

With $K[AuCl_4]$, the catalyst load (Table 3) could be reduced to 1 mol% (for amine **5b** and alkyne **6d**) to give the mixture of products in 91% yield in a similar ratio **7bd/8bd** (1:0.08) but after longer reaction times (72 vs. 24 h). Exchanging CH_2Cl_2 with other chlorinated solvents resulted in the clean synthesis of product **8bd**; with $CHCl_3$ or $ClCH_2CH_2Cl$ the yields of isolated product were 90 and 93%, respectively. In the case of the reaction of amine **5b** and alkyne **6d** in nonchlorinated solvents, such as THF or CH_3CN, the C–Cl activation product **7bd** was clearly not observed and, instead, the chiral product **8bd** was obtained in low yields (40 and 10%, respectively) together with starting materials and some unidentified amine derivatives.

The results of our study on the catalytic activity of the mono- and dicationic cycloaurated derivatives **9** and **10** are collected in Table 7. We investigated the standard reaction in CH_2Cl_2 and the particular case of the $Me_3SiC{\equiv}CH$ alkyne (**6d**) with n-Bu_2NH (**5b**). The catalytic activity was similar to that observed for **1** and $K[AuCl_4]$ for phenylacetylene (**6a**), but decreased for the other alkynes. In the case of trimethylsilylacetylene (**6d**), the propargylamine obtained was exclusively derived from CH_2Cl_2 activation (**7ba**).

Table 7. Two- versus three-component synthesis[a,b] of propargylamines derived from n-Bu_2NH (**5b**) in CH_2Cl_2 with cationic cycloaurated gold(III) derivatives **9** and **10** as catalysts (Equations 2 and 3).

Cat.	**6a** [%]	**6b** [%]	**6c** [%]	**6d** [%]
9	80 (**7ba**)	60 (**7bb**)	47 (**7bc**)	34 (**7bd/8bd**, 1:0.0)
10	75 (**7ba**)	65 (**7bb**)	43 (**7bc**)	30 (**7bd/8bd**, 1:0.0)

[a] Isolated yields. [b] Reaction conditions: cat. **9** or **10** (5 mol%), CH_2Cl_2 (5 mL), alkyne (2 mmol), amine (2 mmol), 24 h, 50°C.

In contrast to our previous studies with gold(III) complexes, for which we demonstrated that the catalytically active species were discrete gold(III) derivatives,[19] it seems that the real catalytically active species here are gold nano-

particles (Au-NP) generated in situ at the beginning of the reaction by reduction of the gold precursors with the amine. We always observed an immediate change of the color of the gold(III)-containing solutions from yellow to deep red upon addition of the amine in all reactions. Au-NP were reported to be formed by reduction of gold(III) salts with amines.[24] Moreover, Au^I halides, AuCl, and AuBr can also generate Au-NP with narrow size distribution under mild conditions (60 °C)[25] similar to those used in the catalytic conditions reported herein (50 °C).

We have been able to characterize these deep-red solutions to test for the presence of gold colloids in the formation of **7ba** with $K[AuCl_4]$ (nano-**11**). Indeed, TEM analysis of these gold materials (aliquot of the solution deposited onto a carbon-coated copper grid and blotted) as well as X-ray diffraction studies (from the powdered sample after removal of all solvents) confirmed the formation of homogeneous nanoparticles with a 3 nm radius (see the Supporting Information). As expected, isolable gold nanoparticles prepared by literature methods (nano-**12**),[26] were also catalytically active in CH_2Cl_2 in the reactions described herein (Table 3) and the yields of products **7ba** and **7bd**/**8bd** obtained were similar to those achieved with $K[AuCl_4]$.

Reaction mechanism: We have elucidated the origin of the CH_2 (in propargylamines of type **7**) and C(H)Me (in propargylamines of type **8**) fragments. NMR spectroscopy experiments proved that the CH_2 fragment in **7ba** comes from the CH_2Cl_2 solvent. When the $K[AuCl_4]$-catalyzed reaction of PhC≡CH (**6a**) and Bu_2NH (**5b**) was performed in CD_2Cl_2, the signal in the ^1H NMR spectra corresponding to the CH_2 fragment at $\delta = 3.63$ ppm in the final product ([D_2]**7ba**) disappeared (Figure 1). The fact that the new isolated compound incorporated deuterium (CD_2 fragment) was further confirmed by ^2H NMR analysis and mass spectrometry (see the Supporting Information).

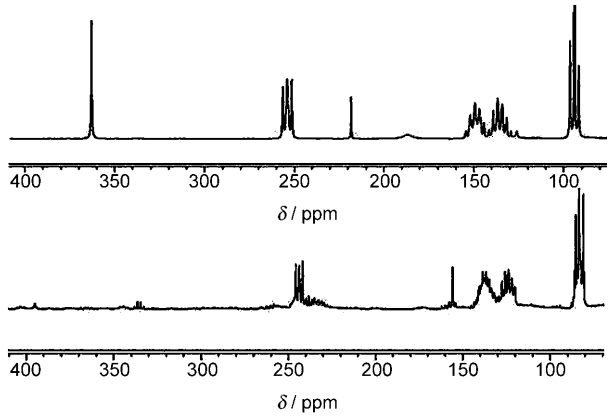
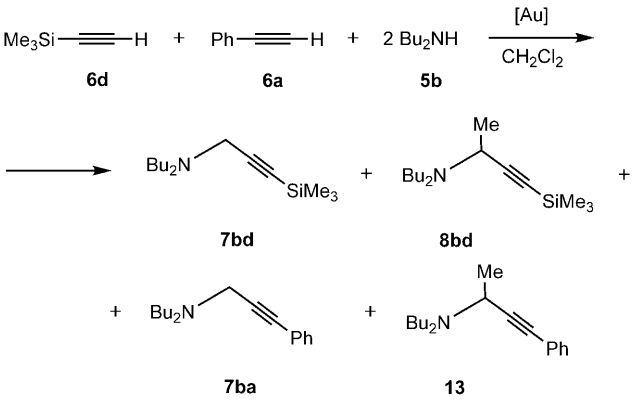


Figure 1. ^1H NMR spectra of: a) **7ba** and b) [D_2]**7ba**.

In the case of the C(H)Me fragment, we excluded the theoretical possibility of participation by the solvent by performing an experiment with $Me_3SiC{\equiv}CH$ (**6d**) and Bu_2NH (**5b**) in $CDCl_3$; as expected, compound **8bd** did not show incorporation of ^2H in the C(H)Me unit. The generation of the C(H)Me unit can be explained by a desilylation reaction of the starting alkyne. The reaction of an equimolar mixture of $Me_3SiC{\equiv}CH$ (**6d**) and PhC≡CH (**6a**) with two equivalents of Bu_2NH (**5b**) in CH_2Cl_2, gave the cross-coupling product PhC≡C-C(H)Me-NBu_2 (**13**) in 15% yield, together with the expected products **7ba** (4%), **7bd** (41%), and **8bd** (40%) (see Scheme 5 and the Supporting Information). This result clearly showed that the incorporation of the C(H)Me unit is related to the presence of the silylalkyne in the starting mixture because the reaction of PhC≡CH (**6a**) with Bu_2NH (**5b**) gave only **7ba**.



Scheme 5. Gold-catalyzed cross-coupling reaction of Bu_2NH (**5b**) with two different alkynes (trimethylsilylacetylene (**6d**) and phenylacetylene (**6a**)) in CH_2Cl_2.

The definitive proof of the origin of the C(H)Me fragment came from the reaction of isotopically enriched alkyne $Me_3Si^{13}C{\equiv}^{13}CH$ (^{13}C-**6d**) with Bu_2NH (**5b**) (CH_2Cl_2, 24 h, 50 °C). The $^{13}C\{^1H\}$ NMR spectrum of the resulting mixture shows unambiguously the presence of a spin system due to the $^{13}C{\equiv}^{13}C{-}^{13}C(H){-}^{13}CH_3$ skeleton: the signal at about $\delta =$ 50 ppm, which was assigned to the ^{13}CH carbon, appears as a ddd by coupling with the other three ^{13}C nuclei (^{13}C-**8bd**, see Figure 2 and detailed assignment of signals in the Sup-

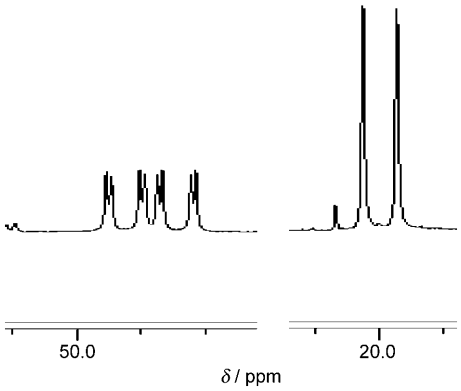
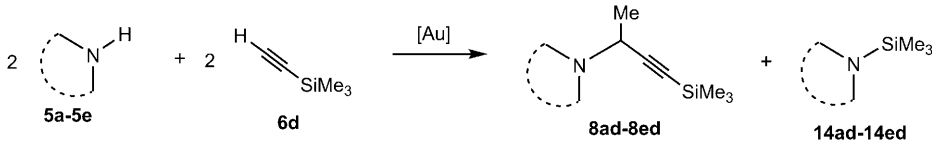


Figure 2. ^{13}C NMR spectrum of ^{13}C-**8bd** showing the $^{13}C{\equiv}^{13}C^{13}CH^{13}CH_3$ spin system (CH and CH_3 signals).

porting Information). A proposal to account for the formation of propargylamines of the type **8** is outlined in Scheme 6.



Scheme 6. Formation of propargylamines of type **8** from trimethylsilylacetylene (**6d**).

At this point, we considered what role the gold nanoparticles could play in the catalytic process. One important factor is the oxidation state of the gold-containing species (mainly nanoparticles) that are generated in situ by reduction of the gold(III) complexes by the secondary amine before the addition of the terminal alkyne and subsequent catalytic reaction. To gain some insight into this aspect of the reaction, we ran an X-ray photoelectron spectroscopy (XPS) experiment (see explanations in the Supporting Information) on the solution generated by the reduction of $K[AuCl_4]$ with Bu_2NH (**5b**) in CH_2Cl_2 (nano-**14**). The XPS spectrum (Figure 3) shows the typical doublet (due to spin–orbital

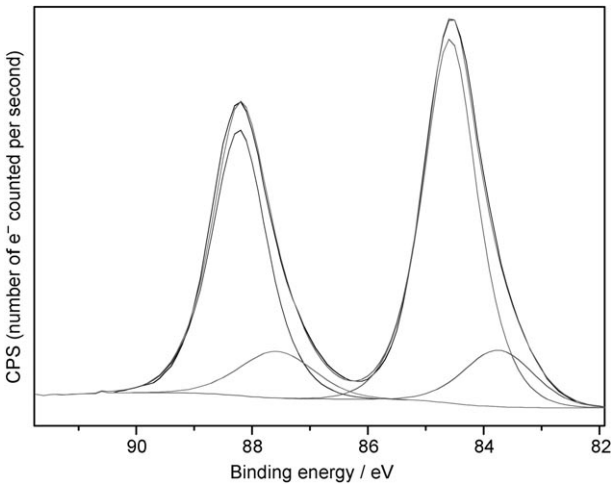


Figure 3. XPS deconvolution spectra from nano-**14** generated by reduction of $K[AuCl_4]$ by amine (Scheme 2, Table 5, Table 8).

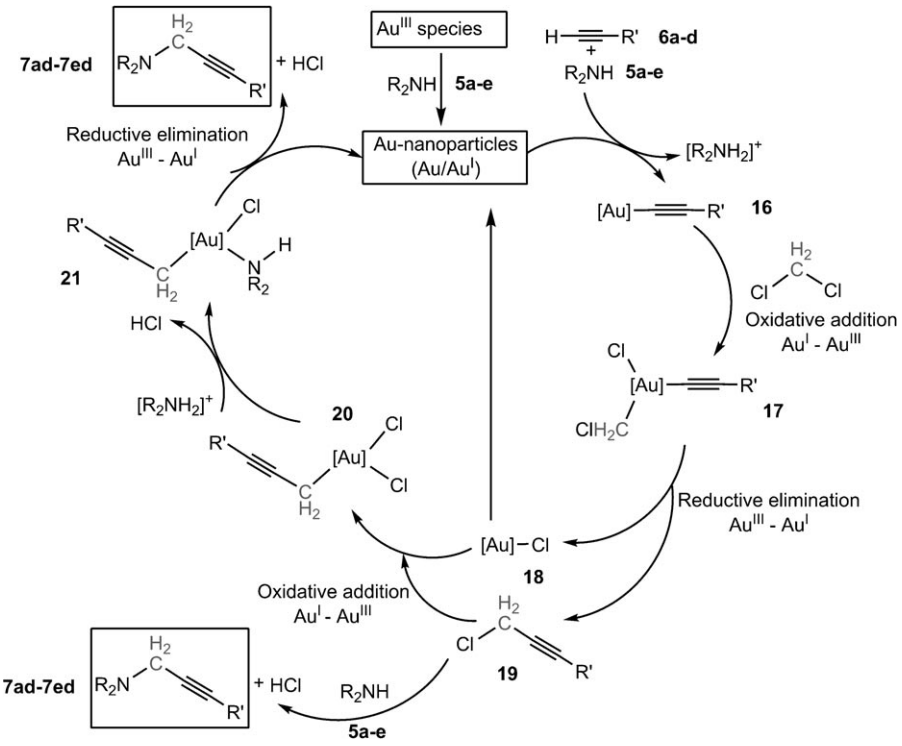
splitting) for an electron on a 4f level of gold. Each component of the doublet is called 4f7/2 and 4f5/2. The deconvolution of the resulting signal indicates that two different oxidation states are contributing to each component of the doublet, and the values for the binding energy for each peak are in good agreement with the presence of gold in the oxidation states 0 and +1. The subsequent assignment of oxidation states in these colloids is shown in Table 8.

Most of the gold species (84%) were found to be in the oxidation state +1, and 16% in oxidation state 0. The XPS technique can measure the composition of the examined surface up to a depth of 10 nm. We can assume that, in a homogeneous sample such as this one (see Figure SI 1 in the Supporting Information), the composition in the surface is representative of the whole sample. Thus, no gold(III) was found in these solutions or in the nanoparticles. In the three-component coupling of aldehydes, terminal alkyne, and amine catalyzed by supported Au-NP on CeO_2 or ZrO_2, it was demonstrated that the catalytic activity was directly related to the content of Au^{III} in these nanoparticles.[5a] The authors claimed that the support led to stabilization of the gold(III) species and allowed its reduction to gold(I) or metallic gold and a higher catalytic activity. However, gold(III) and gold(I) derivatives and unsupported Au-NP were also catalytically active in these couplings.[4,5b,c,6] In Scheme 7, we propose a plausible reaction mechanism for the formation of propargylamines of type **7** (Scheme 2) in CH_2Cl_2.

Table 8. Assignation of oxidation states in the XPS deconvolution experiment from nano-**14** (Figure 3).

Assignation	Binding energy [eV] 4f7/2	4f5/2	Area [%]
Au^0	83.8	87.7	16
Au^I	84.6	88.3	84

The first step of the proposed catalytic cycle is the reduction of all gold(III) complexes and salts by the amine to Au-NP in the oxidation states Au^I–Au^0. The working hypothesis here is that the Au^I fragments are the catalytically active species in this process. The next step is the addition of the terminal alkynes and the formation of alkynylgold(I) species. The synthesis of ethynyl(arene)gold compounds from gold(I) derivatives such as $[AuCl(SMe_2)]$ with terminal alkynes and NEt_3 as a base has been previously reported.[27] Moreover, the formation of alkynylgold(I) and alkynylgold(III) species has been proposed as the first step in the A^3 coupling reaction of terminal alkynes, amines, and aldehydes to afford propargylamines.[4,5] The alkynylgold(I) species **16** should react with the CH_2Cl_2 and give the Au^{III} species **17** by oxidative addition of the CH_2Cl_2 through activation of one C–Cl bond. Such an oxidative addition has been reported for dinuclear gold(I) ylide derivatives in the formation of dinuclear gold(II) complexes with the methylene group as a bridge ligand.[13] The addition of CH_2X_2 with X = Br or I to dinuclear gold(I) derivatives is also known[28,29] to afford either dinuclear gold(II) complexes with the methylene bridging the gold centers[28] or to mononuclear gold(III) derivatives.[29] Subsequent reductive elimination of highly reactive **17** would afford the corresponding propargylchloride **19** and gold(I) species **18**. Reductive eliminations on alkynylgold(III) derivatives have been described before to afford RC≡C-containing products and gold(I) complexes.[30] The reaction of propargylchloride with an amine may



Scheme 7. Proposed reaction mechanism for the gold-catalyzed synthesis of propargylamines of type **7** in CH_2Cl_2.

render the final product **7**. The catalytic cycle can close because the Au^I species **18** could further react with more alkyne to give **16**. Alternatively, the cycle could be closed by further oxidative addition of propargyl chloride to the gold(I) species **18** to afford gold(III) species **20**. By reaction with quaternary ammonium salts, compound **20** would generate a gold(III) intermediate **21** containing the propargylic fragment and the amine, which, by reductive elimination, would afford propargylamines **7ae**–**7de** and the gold(I) species that is able to restart the catalytic cycle.

We performed a set of experiments to provide evidence for some steps of this proposed mechanism. We tested the catalytic activity of gold(I) derivatives such as [AuCl(tht)] (tht = tetrahydrothiophene) and [AuCl(PPh_3)] in the formation of propargylamines **7ba** and **7bd**–**8bd** in CH_2Cl_2 under the standard reaction conditions (alkyne (2 mmol), amine (2 mmol), cat. (5 mol%), 24 h, 50°C) and found that both compounds were able to catalyze the reactions (Table 9). However, slightly lower yields were obtained: a 40–65% yield of **7ba**, compared with an average value of 75% using gold(III) precursors, and a 52–60% yield of the mixture **7bd**–**8bd** compared with an average value of 90% using neutral or anionic gold(III) compounds. In the case of trimethylsilylacetylene, complete selectivity towards the CH_2Cl_2 activation product **7bd** was found when [AuCl(PPh_3)] was used as the catalyst. Interestingly, the catalytic reactions performed with Au^I complexes did not develop the deep-red color observed in reactions using Au^{III} complexes. Since we have shown that gold(I) catalyzes efficiently the formation of propargylamines, we wondered about the presence of NP in these reaction mixtures. Transmission electron microscopy (TEM) analysis of the mixture of [AuCl(tht)] and $HNBu_2$ (**5b**) shows a very small amount (almost zero) of very small nanoparticles (approximately 2–3 nm, see TEM image of **22** in the Supporting Information). The influence of the ligand coordinated to the Au^I–Cl, either tetrahydrothiophene or PPh_3, on the stability of the Au^I compound must be strong. Gold(I) halides without other stabilizing ligands are able to afford stable nanoparticles of 12 nm radius by reduction with alkylamines.[25] In our case, it seems that the Au^I derivatives with other stabilizing ligands do not produce Au-NP under the reaction conditions (50°C) in the presence of alkylamines.

Table 9. Synthesis of progargylamines **7ba**, **7bd**, and **8bd** in CH_2Cl_2 with gold(I) compounds.

Cat.[b]	**7bd**+**8bd** [%][a]	**7ba** [%][a]
[ClAu(tht)]	52 (**7bd**/**8bd**, 0.7:1)	65
[ClAuPPh_3]	60 (**7bd**/**8bd**, 1:0.0)	40

[a] Isolated yields. [b] Reaction conditions: cat. (5 mol%), solvent (5 mL), 50°C, 72 h, alkyne/amine (1:1.2).

The interaction of the Au-NP with the alkyne should result in a plausible alkynyl–Au^I compound that could also be catalytically active. We have checked this possibility, and have found that the complex [$Ph_3PAuC{\equiv}CPh$][31] efficiently catalyzes the coupling between Bu_2NH (**5b**) and PhCCH (**6a**), giving the propargylamine **7ba** in 61% yield, and providing proof that the alkynyl species could be involved in the catalytic cycle.

The next step is the oxidative addition of CH_2Cl_2 to the formed alkynyl–Au^I complex. In this respect, we have performed a comparative study of the reaction of Ph$C{\equiv}$CH (**6a**) with Bu_2NH (**5b**) in either CH_2Cl_2 or CH_2Br_2. Monitoring the reaction leading to **7ba** by NMR spectroscopic analysis, revealed that the process is more rapid for CH_2Br_2 (see the Supporting Information). This fact strongly suggests that incorporation of the solvent onto the gold catalyst proceeds through an oxidative addition reaction. At this point, we can consider two ways to close the catalytic cycle, as proposed before. In the first, a reductive elimination in **17** gives propargyl chloride and an Au^I species **18**, which could restart the catalytic cycle. We found that the reaction between propar-

gylchloride (from Aldrich) and Bu_2NH (**5b**) to afford propargylamine **7ba** proceeds cleanly in CH_2Cl_2 without the assistance of a catalyst (with a slight excess of amine, and a 1:1.2 molar ratio of propargylchloride/alkylamine). This indicates that the key step of the catalytic process may indeed be the activation of CH_2Cl_2 by an alkynyl–gold(I) species (mono or polynuclear) formed in situ by reduction of gold(III) complexes by the amine, and subsequent reaction of the gold(I) species with terminal alkynes in basic media. An alternative way to close the catalytic cycle involves the oxidative addition of propargylchloride to Au^I species **18**, amine coordination, further C–N coupling, and reductive elimination. With the data thus far obtained, we cannot yet discriminate between these two pathways.

The fact that the more basic amines give better yields in these processes confirms our hypothesis that gold(III) has to be reduced to lower oxidation states to achieve higher catalytic activity. $K[AuCl_4]$ and cyclometalated **1** give similar yields, whereas the more cationic species with phosphane derivatives give lower yields of product. This may arise from a combination of factors, such as the higher stability of the cationic pincer derivatives towards reduction and/or the ease of formation/stability of the alkynylgold derivatives formed in situ. The nanoparticle size may also play an important role. It has been demonstrated that in the A^3 coupling of aldehyde, terminal alkyne, and aldehyde by recyclable gold nanoparticles, a size of 20 nm was optimal to afford high yields of products at 75–80 °C in 12 h, with a catalyst load of 10 mol % Au-NP.[6] We think that cationic derivatives may afford Au-NP with a lower content of Au^I and/or a different size, and that this may be the reason for the lower yield. We have already seen that, although gold(I) compounds have proven to be catalytically active in the formation of propargylamine **7ba**, the yields of isolated product are lower; this could be correlated to the fact that they did not produce considerable amounts of nanoparticle under the reaction conditions (see TEM image of **22** in the Supporting Information). What seems clear is that the key steps in the catalytic process involve the reduction of gold(III) complexes to gold(I)-containing nanoparticles, and the production of catalytically active species able to activate C–Cl bonds in the CH_2Cl_2.

Conclusion

Reduction of gold(III) compounds and salts in situ generates gold(I)-containing nanoparticles that are efficient catalysts for the one-pot synthesis of propargylamines from alkynes and amines in chlorinated solvents under mild conditions. Importantly, we have shown that CH_2Cl_2 can be activated by these nanoparticles, and some other gold(I) species, to serve as a CH_2 partner that could lead to potentially relevant gold-catalyzed chemical processes.

Experimental Section

General methods: Solvents and amines were dried and distilled under argon by using standard procedures before use. Elemental analyses were carried out with a Perkin–Elmer 2400-B microanalyser. Infrared spectra (4000–200 cm^{-1}) were recorded with a Perkin–Elmer Spectrum One IR spectrophotometer from nujol mulls between polyethylene sheets. The ^1H, ^2H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded in $CDCl_3$, CD_2Cl_2, or CH_2Cl_2 ([D_2]**7ba**) at 25 °C with Bruker ARX-300, AvanceII-300, Avance-400, or Avance-500 spectrometers (δ, ppm; J, Hz); ^1H and $^{13}C\{^1H\}$ were referenced by using the solvent signal as internal standard; $^{31}P\{^1H\}$ was externally referenced to H_3PO_4 (85 %). The mass spectra (MALDI+) and (ESI+) were recorded from solutions in CH_2Cl_2 or MeOH with a MALDI-TOF MICROFLEX (Bruker) spectrometer (DCTB as matrix). Compounds **1**,[18a] **3**,[20] nano-**12**,[26] [Au(C≡CPh)(PPh$_3$)],[31] [AuCl(tht)],[32] and [AuCl(PPh$_3$)][33] were synthesized as reported before. All other chemicals and reagents were commercially available and used without further purification.

Propargylamines 7 and 8: Typical optimized procedure: The gold catalyst (**1**, $K[AuCl_4]$, **9**, **10**, nano-**12**, [AuCl(tht)], [AuCl(PPh$_3$)], or [Au(C≡CPh)(PPh$_3$)]; 5 mol %) was added to a solution of amine **5a–e** (2 mmol) in CH_2Cl_2 (5 mL). The corresponding alkyne **6a–d** (2 mmol) was subsequently added to the resulting mixture, which was stirred at 50 °C for 24 h. Subsequent filtration through Celite and complete removal of the solvent gave the crude mixture, which afforded the final products after purification by column chromatography on silica gel. Details of the purification procedures used for the different propargylamines, as well as spectroscopic data and selected spectra, are provided in the Supporting Information.

Experiments with deuterated CH_2Cl_2 and CD_2Cl_2 to give [D_2]7ba: Catalyst $K[AuCl_4]$ (5 mol %) was added to a solution of Bu_2NH (**5a**; 2 mmol) in $CDCl_2$ (5 mL), then phenylacetylene (**6b**; 2 mmol) was added to the resulting mixture, which was stirred at 50 °C for 24 h. Subsequent filtration through Celite and complete removal of the solvent gave a crude mixture that afforded pure [D_2]**7ba** after purification by column chromatography on silica gel (*n*-hexane/AcOEt, 95:5). Yield: 60 %. MS (ESI+): m/z (%): 246 (100) $[M]^+$. For the relevant spectra, see Figure 2 and the Supporting Information.

Reaction with CH_2Br_2 to give 7ba: Catalyst $K[AuCl_4]$ (5 mol %) was added to a solution of Bu_2NH (**5a**; 2.4 mmol) in CH_2Br_2 (5 mL), followed by phenylacetylene (**6b**; 2 mmol). The resulting mixture was stirred at 50 °C for 24 h. Subsequent filtration through Celite and complete removal of the solvent gave a crude mixture that afforded the final product **7ba** after purification by column chromatography on silica gel (*n*-hexane/AcOEt, 95:5). Yield: 73 %. For NMR spectra, see the Supporting Information.

Gold-catalyzed cross-coupling reaction of Bu_2NH (5b) with trimethylsilylacetylene (6d) and phenylacetylene (6a) in CH_2Cl_2: Catalyst $K[AuCl_4]$ (5 mol %) was added to a solution of Bu_2NH (**5a**; 3.1 mmol) in CH_2Br_2 (5 mL), followed by either phenylacetylene (**6a**; 1.6 mmol) or trimethylsilylacetylene (**6d**; 1.6 mmol). The resulting mixture was stirred at 50 °C for 24 h. Subsequent filtration through Celite and complete removal of the solvent gave a crude mixture that afforded the products **7ba**, **7bd**, **8bd**, and **13** after purification by column chromatography on silica gel (*n*-hexane/AcOEt, 80:20).

Experiments with ^{13}C-enriched trimethylsilylacetylene (^{13}C-6d) to give ^{13}C-8bd: Catalyst $K[AuCl_4]$ (5 mol %) was added to a solution of Bu_2NH (**5a**; 1 mmol) in CH_2Br_2 (5 mL), followed by ^{13}C-enriched trimethylsilylacetylene (1 mmol). The resulting mixture was stirred at 50 °C for 24 h. Subsequent filtration through Celite and complete removal of the solvent gave a crude mixture of products ^{13}C-**7bd** and ^{13}C-**8bd**.

Synthesis of [9: Catalyst $AgClO_4$ (0.074 g, 0.36 mmol) was added to a solution of orthoaurated complex **1** (0.201 g, 0.32 mmol) in anhydrous THF (20 mL). The resulting suspension was stirred for 30 min at RT with exclusion of light, and then filtered through a Celite pad to remove the insoluble AgCl formed. The freshly prepared solution was treated with PPh_3 (0.085 g, 0.32 mmol) and stirred for 2 h at RT. The solvent was sub-

sequently evaporated to a small volume and the residue was treated with Et_2O (20 mL). Further stirring resulted in the precipitation of **9** as an orange solid that was filtered and vacuum-dried. Yield: 0.193 g (63.1%). ^1H NMR ($CDCl_3$): $\delta = 6.91–7.00$ (m, 5H; $H_o + H_p$, NPh H-5 + H-6, C_6H_4), 7.09 (t, $^3J(H,H) = 7.1$ Hz, 2H; H_m, NPh), 7.29–7.34 (m, 2H; H-3 + H-4, C_6H_4), 7.54 (m, 6H; H_m, PPh_3), 7.60–7.70 (m, 13H; H_m, $PPh_2 + H_p + H_o$, PPh_3), 7.77–7.85 ppm (m, 6H; $H_p + H_o$, PPh_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 123.9$ (d, $^1J(P,C) = 67.7$ Hz; C_i, PPh_3), 124.4 (d, $^1J(P,C) = 93.3$ Hz, C_i, PPh_2), 125.9 (s; C_p, NPh), 128.4 (s; C_m, NPh), 129.0 (C_o, NPh + C-4 + C-5, C_6H_4 overlapped), 129.6 (d, $^3J(P,C) = 12.6$ Hz; C_m, PPh_3), 130.0 (d, $^3J(P,C) = 12.7$ Hz; C_m, PPh_2), 131.5 (d, $^2J(P,C) = 17.6$ Hx; C_3, C_6H_4), 133.6 (d, $^2J(P,C) = 10.7$ Hz; C_o, PPh_2), 133.9 (d, $^4J(P,C) = 3.1$ Hz; C_p, PPh_3 + C-6, C_6H_4 overlapped), 135.0 (d, $^4J(P,C) = 2.8$ Hz, C_p, PPh_2), 135.1 (d, $^4J(P,C) = 10.8$ Hz; C_o, PPh_3), 136.1 (d, $^1J(P,C) = 126.1$ Hz; C-2, C_6H_4), 143.2 (d, $^2J(P,C) = 2.2$ Hz; C-1′, NPh), 151.6 ppm (d, $^2J(P,C) = 14.8$ Hz; C-1, C_6H_4); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 40.46$ (PPh_3), 60.09 ppm (PPh_2). IR: $\tilde{\nu} = 1277$ ($\nu_{P=N}$) cm^{-1}; MS (MALDI+): *m/z* (%): 846 (100) $[M-ClO_4]^+$; elemental analysis calcd (%) for $C_{42}H_{34}AuCl_2NO_4P_2$ (946.54): C 53.29, H 3.62, N 1.48; found: C 53.09, H 3.45, N 1.21.

Synthesis of 10. Catalyst $AgClO_4$ (0.135 g, 0.65 mmol) was added to a solution of **1** (0.184 g, 0.30 mmol) in anhydrous THF (20 mL). The resulting suspension was stirred for 30 min with exclusion of light, and then filtered through a Celite pad to remove the insoluble AgCl formed. Dppe (0.118 g, 0.30 mmol) was added to the freshly prepared solution and the resulting pale-yellow solution was stirred at RT for 2 h. After the reaction time, the solvent was evaporated to a small volume (ca. 1 mL) and Et_2O (30 mL) was added. By continuous stirring, compound **10** was obtained as a yellow solid that was filtered and vacuum-dried. Yield: 0.133 g (39.2%). ^1H NMR ($CDCl_3$): $\delta = 6.41$ (t, $^3J(H,H) = 7.6$ Hz, 2H; H_m, NPh), 6.55 (t, $^3J(H,H) = 7.3$ Hz, 1H; H_p, NPh), 6.62 (d, $^3J(H,H) = 7.6$ Hz, 2H; H_o, NPh), 7.04 (td, $^4J(H,P) = 3.0$ Hz, $^3J(H,H) = 7.3$ Hz, 1H; H-4, C_6H_4), 7.23–7.31 (m, 3H; H-3 + H-5 + H-6, C_6H_4), 7.46–7.52 (m, 10H; $H_m + H_p + H_o$, Ph_2-dppe), 7.59–7.63 (m, 4H; H_m, PPh_2- C_6H_4), 7.67–7.75 (m, 12H; $H_m + H_p$, Ph_2-dppe + $H_p + H_o$, PPh_2- C_6H_4), 7.99–8.05 ppm (m, 4H; H_o, Ph_2-dppe); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 28.9$ (d, $^1J(P,C) = 36.8$ Hz; CH_2, dppe), 30.6 (d, $^1J(P,C) = 41.6$ Hz; CH_2, dppe), 120.7 (d, $^1J(P,C) = 63.8$ Hz; C_i, PPh_2-dppe), 121.8 (d, $^1J(P,C) = 54.0$ Hz; C_i, PPh_2-dppe), 123.8 (d, $^1J(P,C) = 94.0$ Hz; C_i, PPh_2-C_6H_4), 126.0 (s; C_p, NPh), 128.6 (s; C_m, NPh), 128.9 (d, $^3J(P,C) = 4.5$ Hz; C_o, NPh), 129.9 (d, $^3J(P,C) = 12.7$ Hz; C_m, PPh_2-dppe), 130.3 (d, $^3J(P,C) = 11.9$ Hz; C_m, PPh_2-C_6H_4), 1310.0 (d, $^3J(P,C) = 12.6$ Hz; C_m, PPh_2-dppe), 131.3 (s; C_6H_4), 133.5–133.8 (C_p, PPh_2-dppe + C_p, PPh_2-C_6H_4 + C_p, PPh_2-dppe + C_o, PPh_2-dppe overlapped), 134.2 (d, $^2J(P,C) = 11.4$ Hz; C_o, PPh_2-dppe), 134.8 (d, $^2J(P,C) = 28.4$ Hz; C_o, PPh_2-C_6H_4 + C-4, C_6H_4 overlapped), 137.0 (C_6H_4), 137.19 ppm (C_6H_4). Signals due to C-1′ (NPh) and C-1, C-2 (C_6H_4) were not observed, in spite of long time accumulation trials. $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 61.01$ (d, $^4J(P,P) = 2.4$ Hz; PPh_2), 64.75 (d, $^3J(P,P) = 14.8$ Hz; dppe), 72.38 ppm (dd, $^3J(P,P) = 14.8$ Hz, $^4J(P,P) = 2.4$ Hz; dppe); IR: $\tilde{\nu} = 1284$ ($\nu_{P=N}$) cm^{-1}; MS (MALDI+): *m/z* (%): 1046 (95) $[M-ClO_4]^+$; elemental analysis calcd (%) for $C_{50}H_{43}AuCl_2NO_8P_3$: C 52.37, H 3.78, N 1.22; found: C 51.91, H 3.50, N 1.05.

Preparation and X-ray/TEM characterization of gold nanoparticles nano-11: An aliquot of nano-**11** (1 mL), generated from a solution of nBu_2NH (2 mmol) in CH_2Cl (5 mL) with $K[AuCl_4]$ (5 mol%), after stirring for 5 min at RT, was applied to a glow-discharged carbon-coated copper grid and blotted. The specimen was imaged with a JEOL-2000FXII high-resolution transmission electron microscope (point-to-point resolution: 0.28 nm) and images were recorded with a Gatan MSC-794 camera, by using the Digital Micrograph software (from Gatan). A step-scanned powder diffraction pattern of nano-**11** was collected at RT by using a Siemens D500/501 diffractometer with a Cu X-ray tube. The diffractometer was operated at 30 mA and 35 kV and a graphite monochromator was used to select the $Cu_{K\alpha 1,2}$ radiation. Data were collected from 5 to 80° with a step size of 0.03° and a counting rate of 2 s/step.

Preparation and TEM characterization of gold nanoparticles 22: An aliquot of **22** (1 mL) generated from a solution of nBu_2NH (2 mmol) in CH_2Cl (5 mL) with [AuCl(tht)] (5 mol%), after stirring for 5 min at RT, was applied to a glow-discharged carbon-coated copper grid and blotted. The specimen was imaged with a JEOL-2000FXII high-resolution transmission electron microscope (point to point resolution 0.28 nm) and images were recorded on a Gatan MSC-794 camera, by using the Digital Micrograph software (from Gatan).

X-ray photoelectron spectroscopy: XPS measurements of nano-**14**, which was prepared by reduction of $K[AuCl_4]$ with Bu_2NH (**5b**), were taken with a Kratos AXIS Ultra DLD (Kratos Tech.) spectrometer. Samples were prepared under a cover of argon gas and placed in a vacuum before measurement. While collecting the survey scans, the following parameters were used: $Al_{K\alpha}$ monochromatic excitation source (1486.6 eV) working at 15 kV and 10 mA, pass energy = 120 eV. To confirm the oxidation state of the various gold species, high-resolution scans were also taken by using a pass energy of 20 eV.

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