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Development of Versatile and Silver-Free Protocols for Gold(I) Catalysis

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Abstract: The use of a versatile *N*-heterocyclic carbene (NHC) gold(I) hydroxide precatalyst, [Au(OH)(IPr)], (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) permits the in situ generation of the $[Au(IPr)]^+$ ion by simple addition of a Brønsted acid. This cationic entity is believed to be the active species in numerous catalytic reactions. ^{1}H NMR studies in several solvent media of the in situ generation of this $[Au(IPr)]^+$ ion also reveal the formation of a dinuclear gold hydroxide intermediate $[\{Au(IPr)\}_2(\mu\text{-}OH)]$, which is fully characterized and was tested in gold(I) catalysis.

Keywords: gold · homogeneous catalysis · N-heterocyclic carbenes

Introduction

Gold-mediated catalysis has emerged as a very versatile synthetic tool that leads to simple as well as complex molecular architectures in a very efficient manner.[1] The ease with which these transformations can be carried out renders them very user-friendly methodologies. Intensive investigations have focused on the design of ligands to stabilize yet support highly active catalytic species.[1c,2] To improve the efficiency of the gold catalyst, the use of weakly coordinating anions,[3] such as fluorinated carboranes, to form cationic gold centers with more Lewis acidic character have also been developed. To this end, a metathetical synthetic route making use of silver salts, to exchange the silver-bound counteranion with the halide originally linked to the gold center, has been extensively employed. However, silver salts are moisture and light sensitive,[4] and are known, as is gold, to be σ- and π-system activating agents, and numerous transformations where the gold catalyst proved to be efficient can be achieved by silver species.[5] However, silver and gold can in some instances act in a cooperative manner.[6] As hydrolysis of the silver salt AgX (X = OTf, BF_4, SbF_6, PF_6) can provide the corresponding Brønsted acid HX,[7] the latter is often suspected of acting as the catalyst in organic reactions.[8] To clarify the ambiguous role of silver salts in gold catalysis, the development of alternative and less expensive activation routes leading to cationic gold(I) species from air- and moisture-stable complexes remains highly desirable. Alternative methods of activation of gold(I) precatalysts are already known. Cationic gold(I) complexes stabilized[9] by an inner sphere counteranion,[4,9a] a solvent molecule,[10] an isocyanate,[11] or an oxonium center[12] have been prepared and proven to be efficient in catalysis. In all instances, their synthesis involves the use of a silver salt. The development of precatalysts that do not involve any silver salt in their synthesis and activation could constitute a significant advance in cationic gold(I) catalysis. One such method, used in the seminal work of Teles and co-workers,[13] employed a protic acid (methanesulfonic acid) acting on the $[Au(CH_3)(PPh_3)]$ complex to liberate methane and generate the $[AuL]^+$ species [Eq. (1)].

$$[Au(CH_3)(PPh_3)] + CH_3SO_3H \longrightarrow [Au(PPh_3)][O_3SCH_3] + CH_4 \quad (1)$$

This protonolysis reaction proved to be very efficient in leading to the formation of an active species that facilitated the addition of alcohols to alkynes with high turnover frequencies and high turnover numbers. However, only one example of $[Au(CH_3)(NHC)]$[14] has been reported and attempts made by Teles and co-workers to synthesize a carbene gold methyl complex reportedly failed.[15] An elegant method to afford a cationic gold(I) complex without silver activation was recently disclosed by Bertrand and co-work-

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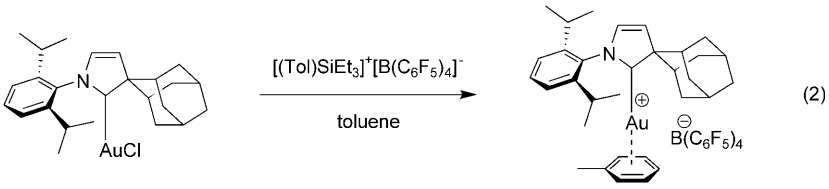
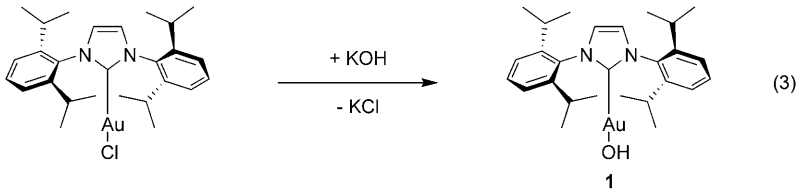
ers[16] who made use of the silylium salt $[(Tol)SiEt_3]^+[B(C_6F_5)_4]^-$, which exhibits halogenophilic properties [Eq. (2)].[17]



(2)

This activation by chloride abstraction appeared to be very efficient in the in situ generation of the active catalytic species for the cross-coupling of enamines and alkynes.[17] A drawback, if one can be cited, is the non-trivial synthesis of the silylium reagent, which requires a strong electrophile.[18] In a recent disclosure of the synthesis of the well-defined air- and moisture-stable [Au(OH)(IPr)] (**1**) complex [Eq. (3)], we highlighted the versatility of **1** in protonolysis reactions leading to a plethora of organogold(I) complexes.[19]



1

(3)

The use of a NHC ligand, in this instance IPr (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene),[20] was initially targeted, as this NHC has often led to the stabilization of reactive species.[21] Juxtaposition of these two concepts, that is, protonolysis of **1** and stabilization of a reactive species by using a NHC ligand, led us to investigate the intriguing possibility of generating $[Au(IPr)][BF_4]$ (**2**) by simply reacting **1** with a protic acid. Moreover, this activation mode would simply yield **2** and water and would be respectful of the principles of green chemistry.[22]

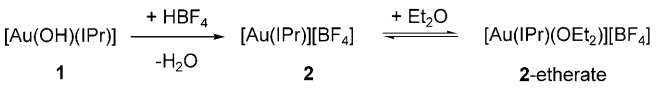
Herein, we report the activation of the air- and moisture-stable precatalyst [Au(OH)(IPr)] by a Brønsted acid. A ^{1}H NMR spectroscopic study of the acid activation of **1** to generate the $[Au(IPr)]^+$ species in situ has been carried out. The catalytic behavior of a number of gold complexes, as isolated complexes or as entities generated in situ, were evaluated in several representative organic transformations to validate our *generation-of-the-catalytically-active-species* hypothesis.

Results and Discussion

The study begins with examining the fate of **1** under various protonolysis protocols relevant to catalytic transformations and elucidating the exact nature of the organogold(I) species generated prior to catalytic involvement.

NMR spectroscopic study:[23] Investigation of the possible activation of **1** with a Brønsted acid began with monitoring the evolution of a stoichiometric mixture of **1** and tetrafluoroboric acid–etherate ($HBF_4{\cdot}OEt_2$) by ^{1}H NMR spectroscopy in CD_2Cl_2 at 298 K. Complex **1** was rapidly transformed into another species that was presumed to be the cationic $[Au(IPr)]^+$ species. A resonance at $\delta = 2.49$ ppm, is attributed to the C*H* of the isopropyl group of the ancillary ligand IPr, and shifts by 0.09 ppm compared to **1**. Interestingly, the signal of the IPr backbone protons at $\delta = 7.17$ ppm for complex **1** shifts and broadens to overlap with the doublet of the C*H* aromatic signal at $\delta = 7.37$–7.35 ppm. This shift denotes a loss of electronic density in the heterocyclic system, due to a delocalization of the π-electrons toward the more acidic gold center.

^{1}H NMR experiments were then performed at low temperature to examine if the broad signal observed in the spectrum was a result of a possible coalescence of several forms of the species **2**. At 203 K, the broad signal attributed to the protons of the backbone, evolved into two singlets at $\delta = 7.48$ and 7.38 ppm.[23] The broad signal, observed at room temperature, corresponds to an average of signals assigned to species **2** and $[Au(IPr)(OEt_2)][BF_4]$, the etherate complex of **2**. We suspect that the stability of species **2** is due to the NHC ligand[21] and to the weak coordination of diethyl ether under the reaction conditions, as is indicated by broad signals associated to diethyl ether in the ^{1}H NMR spectra ($\delta =$ 3.48–3.39 (m, 4H), 1.05 ppm (br t, 6H)).[23] Species **2** is surprisingly long-lived under these conditions, and ^{1}H NMR spectroscopic analysis highlighted no visible decay of this species over the course of several hours. Numerous examples of stabilized **2** with solvents,[10a,11,16,24] alkenes,[25] or alkynes[26] are already known.[27] Herrmann et al. have postulated a correlation between the chemical shift of the carbenic carbon atom of the NHC and the acidity of the coordinated metal center.[28] In CD_2Cl_2 at 203 K, the ^{13}C NMR shift of the carbenic carbon of IPr was found at $\delta = 159.0$ ppm for **2** and $\delta = 159.8$ ppm for the etherate complex of **2**. To the best of our knowledge, the most upfield signal of the carbenic carbon in cationic gold(I) complexes for IPr was observed at $\delta = 159.7$ ppm for $[Au(IPr)(THF)][PF_6]$ and is in good agreement with the one observed for both **2** and its etherate complex.[10a,29] Based on the NMR data, the transformation proceeds as illustrated in Scheme 1.



1 2 2-etherate

Scheme 1. Protonolysis of **1** leading to **2**.

After several days in the NMR tube, the solution containing a mixture of species **2** decomposed partially into another complex and yielded a pink solution, which appears to be due to the presence of gold(0) nanoparticles. The decomposition of **2** into gold(0) appears to proceed with concomitant release of IPr and leads to the formation of $[Au(IPr)_2][BF_4]$ (**3**), which was independently prepared by deprotonation of IPr·HBF_4 with **1**.[30]

As $HBF_4{\cdot}OEt_2$ is a fuming acid, the more easily handled aqueous HBF_4 solution was investigated as a possible activator for **1**. An NMR-scale reaction involving **1** and one equivalent of aqueous HBF_4 led to the formation of $[Au(IPr)][BF_4]$ (**2**) with concomitant formation of a new complex. Addition of water to the reaction mixture (same reaction mediated in a mixture of 10:1 of CD_2Cl_2/D_2O) appeared to promote the formation of this new complex. ^{19}F NMR spectroscopy confirmed the presence of a BF_4^- counterion, suggesting that the complex was a cationic gold complex. To establish the unequivocal atomic composition and connectivity in this complex, single crystals were grown by slow diffusion of pentane into a saturated dichloromethane solution. X-ray diffraction revealed a new cationic dinuclear hydroxygold(I) complex, $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ (**4**; see Figure 1).

Similar μ-OH dinuclear complexes to **4** have been reported for platinum; for example $[Pt(cod)(OTf)_2]$ (cod = cyclooctadiene), which, when crystallized in wet dichloromethane, led to the formation and characterization of $[\{Pt(cod)(OTf)\}_2(\mu\text{-OH})][OTf]$.[31] Complex **4** is analogous to the gold(I) complexes $[\{LAu\}_2X]Y$ (L = phosphine, X = halide, Y = dissociated counterion) reported initially by Laguna et al.[32] and later by Schmidbaur and co-workers.[33] For a better comparison to multinuclear gold(I) μ-O complexes, trigoldoxonium complexes $[(LAu)_3(\mu_3\text{-O})][BF_4]$ (with L = phosphines or phosphites) can be cited,[34] in which the Au–O bond lengths were reported to range from 2.023 to 2.078 Å. A monocationic dinuclear gold(I) complex bearing the 8-quinolinate ligand has also been reported by Schmidbauer and co-workers.[35] However, the Au–O bond lengths in the 8-quinolinate gold(I) complex are quite different (2.033(6) and 2.575(6) Å) due to the presence of the aromatic nitrogen atom and its ability to coordinate to the cationic gold center. The Au1–O1 and Au2–O1 bond lengths in **4** (see Figure 1) were found to be quite similar (2.070(5) and 2.072(5) Å, respectively). They are in good agreement with the lengths reported for $[(LAu)_3(\mu_3\text{-O})][BF_4]$ complexes, but they are surprisingly close to the one observed in **1** (2.078(6) Å) despite the fact that **1** is a neutral complex. The $Au{-}C_{carbene}$ distances in **4**, for Au1–C1 and Au2–C31, were determined to be 1.957(7) Å 1.948(7) Å, respectively. These distances are in good agreement with the $Au{-}C_{carbene}$ distances in neutral **1** (1.935(6) Å), and in cationic **3** (2.027 and 2.031 Å). These average values between a neutral and cationic gold(I) complexes highlight the dual nature of the metal centers in **4**, which can be viewed as a combination of **1** and **2**. Finally, the tendency of gold(I) to become engaged in secondary Au–Au bonding, also coined "aurophilicity", usually favors the formation of trigoldoxonium complexes. These complexes have Au–Au distances between 2.9320 and 3.0968 Å, but this does not appear to be the case in **4**, where the Au1–Au2 distance is 3.746(1) Å, which supports the assigned oxidation state of the two gold centers as +1.[36]

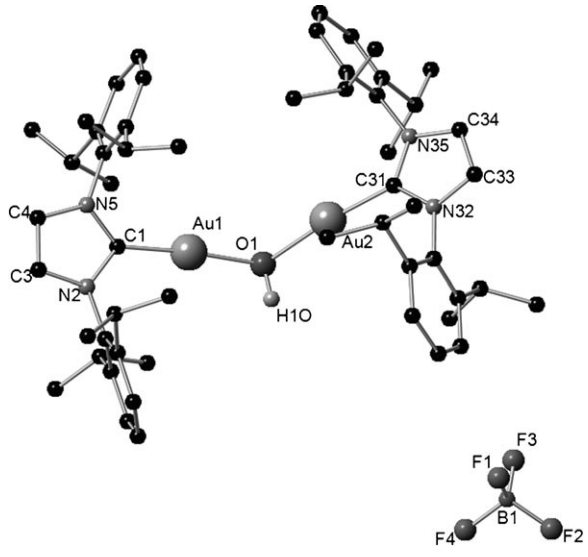
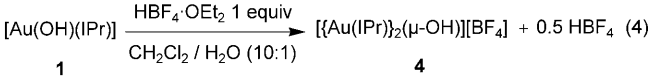


Figure 1. Ball-and-stick representation of $[Au(IPr)_2(\mu\text{-OH})][BF_4]$ (**4**). H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°] for **4**: Au1–Au2 3.746(1), Au1–O1 2.070(5), Au2–O1 2.072(5), Au1–C1 1.957(7), Au2–C31 1.948(7); Au1-O1-Au2 129.5(3), Au1-O1-H1O 105(5), Au2-O1-H1O 107(5), C1-Au1-O1 174.2(2), C31-Au2-O1 173.8(2).

Based on NMR and XRD data, the transformation appears to proceed as illustrated in [Eq. (4)].



1 4

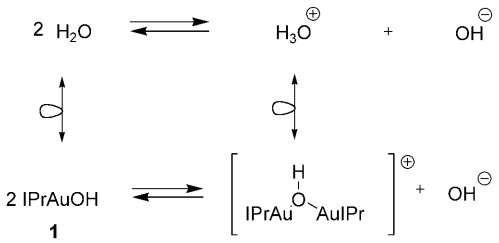
Noteworthy in Equation (4), 0.5 equivalents of HBF_4 is released. To understand the behavior of this in situ generated species, protonolysis of **1** was undertaken with different amounts of $HBF_4{\cdot}OEt_2$ and aqueous HBF_4 solution. Water appears to assist in the formation of **4**. Nevertheless, the amount of water liberated by the protonolysis of complex **1** with 1 or 1.5 equivalents of $HBF_4{\cdot}OEt_2$ is not enough to obtain complex **4** as observed when a 10:1 mixture of CD_2Cl_2/D_2O was used. So far, the best conditions to form in situ complex **4** is to use **1** in the presence of 0.5 equivalents of aqueous HBF_4.[23] To exclusively produce species **2**, the use of an excess of $HBF_4{\cdot}OEt_2$ with respect to **1** is best.[23] Noteworthy, when complex **4** was treated with 0.5 equivalents of $HBF_4{\cdot}OEt_2$ in dry CD_2Cl_2, the formation of **2** was observed. To summarize these experiments, in dry dichloro-

methane, the first half equivalent of acid affords complex **4** and if more acid is added, the formation of **2** is observed. Nevertheless, when a biphasic system of water/dichloromethane is used, only complex **4** is obtained and the excess HBF_4 rests in the aqueous layer.

Interestingly, the chemical shift of the two protons of the IPr backbone can be correlated to the Lewis acidic character of the gold(I) center and shows that the more Brønsted acid is added to **1**, the stronger the Lewis acidic character of the resultant species. Indeed, if a Lewis acid character ranking is established using ^{13}C NMR chemical shift data for the carbenic carbon ($\delta = 171.6$ ppm in **1**, $\delta = 162.6$ ppm in **4**, $\delta = 159.8$ ppm in ethereal species **2**, and $\delta = 159.0$ ppm in **2**) the following order is found: **2** > **2·ether** > **4** > **1**.[28,29] In the ^1H NMR spectra, the chemical shift of the two protons found at $\delta = 7.20$ ppm in **1**, $\delta = 7.22$ ppm in **4**, $\delta = 7.38$ ppm in the ethereal species **2**, and $\delta = 7.48$ ppm in **2** in dry CD_2Cl_2, shows that a more downfield shifted signal correlates to a stronger Lewis acid character of the gold(I) center.

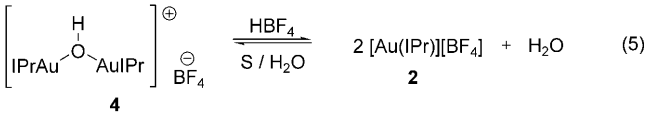
As the presence of water is important for the formation of **4** and as water is used in several reactions involving cationic gold(I) catalysis, the behavior of the catalytic species generated by acid activation of **1** was investigated in mixtures of water and water-miscible organic solvents. A 1:1 mixture of [D_8]THF/D_2O was first selected to mimic the previously developed reaction conditions for nitrile hydration.[37] ^1H NMR spectra of well-defined **1** and **4** were recorded in a 1:1 mixture of [D_8]THF/D_2O. In both cases, the spectra showed the presence of another complex. Assuming that the major product observed was the starting complex, the ^1H NMR spectrum of **1** revealed it to be in equilibrium with another species which exhibits signals similar to those found for **4**. A similar reaction using well-defined **4** reveals features that can be attributed to the cationic species **2**. Based on computational results, Toste and co-workers previously proposed an equilibrium that exists in the case of tris[phosphinegold(I)]oxonium in the presence of an allenyne as substrate in cycloisomerization processes.[38] This gold(I) oxonium species can be in equilibrium with a dinuclear gold hydroxide and a gold acetylide complex with the allenenyne. These species can also be in equilibrium with a gold hydroxide complex and a cationic species coordinated to the alkyne of the acetylide complex. Moreover, as $[LAu]^+$ is considered isolobal with H^+[39] and as water is miscible with [D_8]THF, an analogy to the equilibrium involving the hydroxonium with water could be envisaged with complex **1** and a bis[(IPr)Au(I)] hydroxide (Scheme 2).

Noteworthy, when complex **1** was treated with 0.33 equivalents of HBF_4, no trigold(I) or tetragold(I) complexes were observed like the phosphine gold(I) complexes reported by Schimdbaur and co-workers.[40] The activation of **1** in a [D_8]THF/D_2O mixture by acid addition was next attempted, and when 0.5 equivalents of aqueous HBF_4 were added to **1**, formation of **4** was observed with **2** as the minor product. Then with a stoichiometric amount of acid, a 4:1 ratio of **2** and **4** was observed. Finally, increasing the amount of acid



Scheme 2. Equilibrium of **1** in aqueous medium.

relative to **1** (1.5 equivalents) led to the nearly exclusive formation of **2**, with only traces of **4**. Cleary, a difference in reactivity appeared between THF and dichloromethane solutions. Since HBF_4 is more soluble in water than in organic solvents, and as **4** appears to be a stable form of **2**, we propose that, in the case of an immiscible mixture, complex **4** is initially formed and that the excess acid migrates to the aqueous layer. However, in the case of a miscible solvent system, the acid remains available and **4** is in equilibrium with species **2** [Eq. (5)].

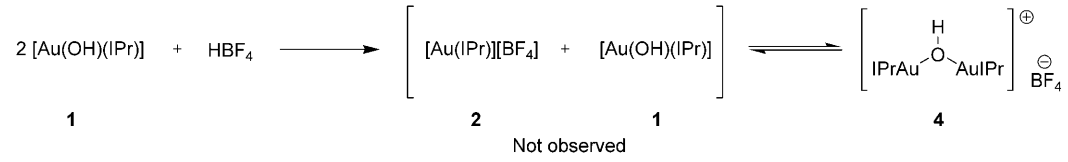


S = water miscible organic solvent

Importantly, this equilibrium is shifted towards **2** when excess acid is present. A similar ^1H NMR investigation was undertaken using a 10:1 mixture of CD_3OD/D_2O. These conditions are relevant to previous catalytic studies dealing with the Meyer–Schuster rearrangement.[41] The same equilibrium phenomenon between complexes **1**, **4**, and species **2** was observed [Eq. (5)]. Noteworthy, when only one equivalent of aqueous HBF_4 is used, the equilibrium is already shifted to the almost exclusive formation of **2**. Indeed, in a 10:1 CD_3OD/D_2O mixture, **1** when reacted with one equivalent of acid led to less than 4% (versus 9% in THF/water conditions) of **4**.

In summary, formation of complex **4** can be viewed as occurring in two consecutive steps. First, the addition of 0.5 equivalents of HBF_4 to **1** leads to the formation of the species **2** by simple protonolysis. In a second step, the binding of **2** to unreacted **1** affords complex **4** (Scheme 3).

Catalytic studies: As **1**, **3**, and **4** were isolated and can be generated in situ under well determined conditions (vide infra), the catalytic activity of these complexes (acid-activated or not) was evaluated in a number of important organic transformations. A broad range of previously reported cationic gold(I)-catalyzed reactions were targeted, such as the hydration of nitriles[37] and alkynes,[42] the synthesis of enones via the isomerization of propargylic acetates,[43] skeletal rearrangements,[1o,m,10c,44] and alkoxycyclization[9a,44] of

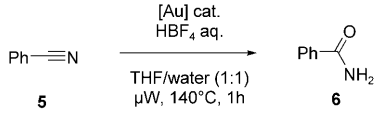


Scheme 3. Proposed formation of **4** by acid activation of **1**.

enynes. Beyond reactions involving triple bonds, reactions involving alkenes such as the allylic acetate rearrangement[45] and the hydroamination of alkenes[46] were also examined. To complete the study, the Beckmann-type reaction was also investigated.[47] In every case, the substrates used were the usual benchmarks employed in the development of these transformations. In all reactions, the behavior of **1**, **3**, and **4** was tested. For protocols requiring the activation of **1** and **4**,[48] an aqueous solution of HBF_4 was used instead of $HBF_4{\cdot}OEt_2$ when water was involved in the organic transformation.

Nitrile and alkyne hydration: Nitrile hydration has been extensively studied with late transition metals (LTM) as catalysts but only one report has disclosed this reaction catalyzed by cationic gold(I). Nolan et al. used the well-defined Gagosz-type complex $[Au(IPr)(NTf_2)]$[4] (2 mol%) in a 1:1 mixture of water/THF under microwave irradiation at 140°C for 2 h to convert benzonitrile **5** into benzamide **6**.[37] Results of nitrile hydration of **5** catalyzed by **1**, **3**, and **4** with or without acid activation are summarized in Table 1.

Table 1. Hydration of benzonitrile **5** catalyzed by gold complexes.[a]



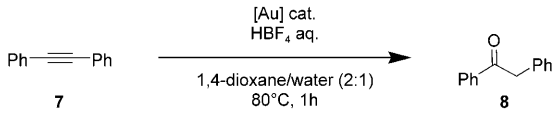
Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	5	0
2	**3** (5)	0	0
3	**1** (5)	0	23
4	**1** (5)	2.5	>99
5	**1** (5)	5	98
6	**1** (5)	7.5	98 (90)[c]
7	**4** (2.5)	0	>99
8	**4** (2.5)	2.5	>99

[a] Reaction conditions: benzonitrile **5** (1 mmol), gold complexes (based on gold, 5×10^{-2} mmol) with different amounts of aqueous HBF_4 in a 1:1 mixture of THF/water (1 mL) irradiated under microwave at 140°C for 1 h. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

Complete conversion of nitrile **5** into amide **6** was achieved when using **4** as catalyst or when **1** was activated with 0.5 equivalents of aqueous HBF_4 (entries 4 and 7, Table 1). Noteworthy, the use of **1** without activation afforded a 23% conversion of **5** into **6**. The catalytic activity of **1** in this reaction can reasonably be explained by the equilibria observed by ^1H NMR spectroscopy (vide supra) between complex **1** and **4** (ratio between complex **1** and **4** was 6.4:1) and complex **4** with species **2** (ratio between species **4** and **2** was 2.8:1). Finally, the cationic species **2** and complex **4** are expected to display catalytic activity, whereas **1** is expected to act as a precatalyst in this reaction and under these reaction conditions.

In the alkyne hydration reaction, a related reaction also involving the addition of water across a triple bond, the catalytic activity of the various entities examined and synthesized so far were tested. In 2002, Tanaka et al.[42b,c] reported the first alkyne hydration catalyzed by $[Au(Me)(PPh_3)]$ activated by H_2SO_4. Later, Nolan and co-workers reported the use of [AuCl(IPr)] activated by $AgSbF_6$ at low catalyst loading in a 2:1 mixture of 1,4-dioxane/water.[42a] Results on the gold-catalyzed hydration of diphenylacetylene (**7**) into ketone **8** mediated by **1**, **3**, and **4** with or without activation are summarized in Table 2.

Table 2. Hydration of diphenylacetylene **7** catalyzed by gold complexes.[a]



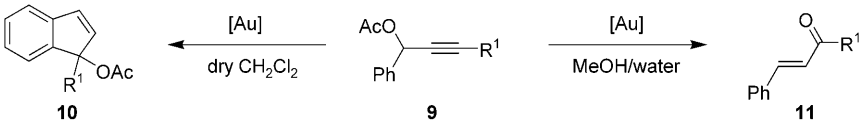
Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	2	0
2	**3** (2)	0	0
3	**1** (2)	0	12
4	**1** (2)	1	90
5	**1** (2)	2	>99 (93)[c]
6	**1** (2)	3	>99
7	**4** (1)	0	88
8	**4** (1)	1	>99

[a] Reaction conditions: diphenylacetylene **7** (0.5 mmol), gold complexes (based on gold, 1×10^{-2} mmol) with different amounts of aqueous HBF_4 in a 2:1 mixture of 1,4-dioxane/water (1 mL) at 80°C for 1 h. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

The best result in this reaction was obtained when **1** was activated with an equimolar amount of aqueous HBF_4 to furnish the ketone **8** in 93% isolated yield (entry 5, Table 2). Compared to the Tanaka procedure, our catalytic system provided better yield (93% versus 53%), in less time (1 h versus 5 h) and with less acid (2 mol% versus 50 mol%). Interestingly, the use of **4** alone, without activation, also leads to the successful 88% conversion to product (entry 7, Table 2) in 1 h (97% conversion in 1.5 h). The in situ generation of the active species from **1** and half an equivalent of aqueous HBF_4 also provided good activity, achieving a 90%

conversion within 1 h (entry 4, Table 2) and 96% conversion in 1.5 h. In this reaction, complex **1** alone exhibited low catalytic activity with 12% conversion of the alkyne **7** into ketone **8** (entry 3, Table 2). For the same reasons as the one evoked in nitrile hydration, complex **1** is in equilibrium with an analogue of complex **4** that was able to catalyze the reaction. To complete this reactivity vignette, complex **3**, which results from the decomposition of gold catalyst, did not show any activity in alkyne and nitrile hydration (entry 2, Table 1 and entry 2, Table 2).

Transformation of propargylic acetates into enones: Another relevant example of the crucial role of water in gold catalysis was reported in the isomerization of propargylic acetates **9**,[49] which can lead to the formation of indenes **10**, when the reaction is carried out under anhydrous conditions,[50] but can afford enones **11** in methanol/water solvent mixtures (Scheme 4).[43]

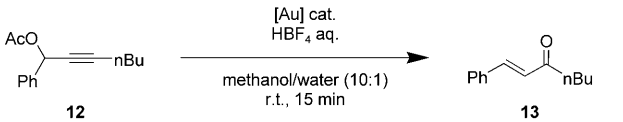


Scheme 4. Products obtained by cationic gold catalysis from propargylic acetate **9** depending on the presence or absence of water.

As water is generated in the acid activation protocol, the conversion of the propargylic acetate **12** into the corresponding enone **13** was examined under methanol/water conditions to evaluate the catalytic activity of complexes **1** and **4** (see Table 3).[51] In this context, Zhang et al. reported the formation of α,β-unsaturated ketones **11** from propargylic acetates **9** catalyzed by [Au(PPh$_3$)][NTf$_2$] (2 mol%) in acetone or 2-butanone as solvent at room temperature in 16 h.[43c] In the same year, Nolan and co-workers reported alternative conditions for this reaction with the use of [AuCl(I*t*Bu)] (2 mol%) (I*t*Bu = 1,3-bis-*tert*-butylimidazol-2-ylidene) activated by AgSbF$_6$ (2 mol%) in a 10:1 mixture of THF/water at 60°C for 8 h and reached 98% conversion of propargylic acetate **13**.[43b] Results of the formation of enone **13** from propargylic acetate **12** under conditions discussed above are summarized in Table 3.

Optimal results were obtained with complex **1** (2 mol%) and activation with 1.5 equivalents (based on gold) of aqueous HBF$_4$ to afford the enone **13** in 91% isolated yield (entry 6, Table 3). Here again, both the independently synthesized and in situ generated complex **4** displayed excellent catalytic activity with 99% and 90% conversion, respectively (entries 4 and 7, Table 3). In comparison to the previously reported method,[44b] the acid activation requires no heating (60°C was previously necessary) and occurs in a considerably shorter reaction time (15 min versus several hours). Noteworthy, complex **1** does not show any activity under these conditions (entry 3, Table 3). ^{1}H NMR spectroscopic studies revealed that complex **1** in this solvent mixture leads to the formation of complex **4** in less than 2% and therefore helps rationalize the poor activity of **1** under these specific operating conditions.[23]

Table 3. Enone **13** synthesis from propargylic acetate **12** catalyzed by gold complexes.[a]



12 13

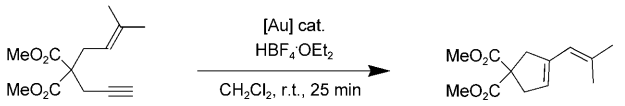
Entry	Catalyst (mol%)	HBF$_4$ [mol%]	Conv. [%][b]
1	none	2	0
2	**3** (2)	0	0
3	**1** (2)	0	0
4	**1** (2)	1	>99
5	**1** (2)	2	>99
6	**1** (2)	3	>99 (91)[c]
7	**4** (1)	0	90
8	**4** (1)	1	>99

[a] Reaction conditions: propargylic acetate **12** (0.2 mmol), gold complexes (based on gold, 4×10^{-3} mmol) with different amounts of aqueous HBF$_4$ in a 10:1 mixture of methanol/water (3.3 mL) at room temperature for 15 min. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

Skeletal rearrangement and alkoxycyclization of enynes: Skeletal rearrangement and cycloisomerization catalyzed by cationic gold(I) are useful tools to synthesize five-membered rings.[1m,f] To examine the versatility of the acid activation procedure, the catalytic activities of **1**, **3**, and **4** were investigated in these important transformations. Echavarren et al. observed the skeletal rearrangement of enyne **14** into cyclopentene **15** catalyzed by [Au(biphenyldi-*tert*-butylphosphine)(CH$_3$CN)][SbF$_6$] (2 mol%) in dry dichloromethane at room temperature in 5 min.[10c] Gagosz and coworkers took advantage of the weakly coordinating counterion bis(trifluoromethanesulfonyl)imidate to perform this transformation at very low catalyst loadings (0.01 mol%) in a reasonable reaction time (30 min.).[4,9a] Results from the skeletal rearrangement of enyne **14** with the ensemble of catalytic systems examined above are summarized in Table 4.

Enyne **14** was fully converted into the vinylcyclopentene **15** with 95% isolated yield when **1** was activated with 1.5 equivalents (based on Au) of HBF$_4$·OEt$_2$ (entry 6, Table 4). As expected in this reaction, which needs to be carried out under anhydrous conditions, **2** appears to be the active catalytic species. In this transformation, complex **4** showed moderate catalytic activity with 38% conversion (entry 7, Table 4) and its in situ generation left the enyne **14** unreacted (entry 4, Table 4). A plausible reason explaining these relative reactivities could be associated with the lower Lewis acidic character of the gold center in **4** when compared to that of **2**, as deduced from the ^{1}H NMR chemical shifts of the two protons of the backbone of IPr. When **4**

Table 4. Skeletal rearrangement of enyne **14** catalyzed by gold complexes.[a]



14 **15**

Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	2	<2
2	**3** (2)	0	0
3	**1** (2)	0	0
4	**1** (2)	1	0
5	**1** (2)	2	>99
6	**1** (2)	3	>99 (95)[c]
7	**4** (1)	0	38
8	**4** (1)	1	>99

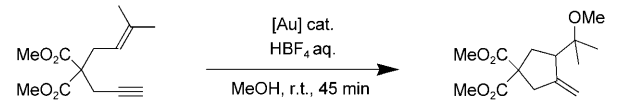
[a] Reaction conditions: enyne **14** (0.21 mmol), gold complexes (based on gold, 4.2×10^{-3} mmol) with different amounts of $HBF_4{\cdot}OEt_2$ in dry dichloromethane (2 mL) at room temperature for 25 min. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

was activated with one equivalent of acid (amount based on **4**) to form **2**, excellent catalytic activities were observed (entry 8, Table 4).[38]

An alternative reactivity involving **14** that was reported by the Echavarren group consists of an alkoxycyclization of enyne in methanol, a net cyclization, and addition of a solvent molecule.[44a] This initial study made use of $[Au(CH_3)(PPh_3)]$ (3 mol%) activated by HBF_4 (6 mol%) to afford the *exo*-methylenecyclopentane **16** by incorporation of a molecule of methanol in 4 h at room temperature with a 97% isolated yield. Gagosz and co-workers obtained similar yields with several phosphine gold triflimidate catalysts using lower catalyst loadings (1 mol%) and shorter reaction times (20 min).[4,9a] The alkoxycyclization of enyne **14** into **16** under conditions mentioned above, is summarized in Table 5.

Enyne **14** was fully converted when **1** was activated by 1.5 equivalents (based on gold) of aqueous HBF_4 to yield **16**

Table 5. Alkoxycyclization of enyne **14** catalyzed by gold complexes.[a]



14 **16**

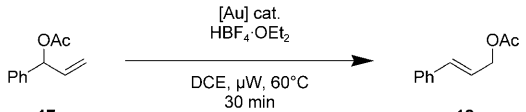
Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	2	0
2	**3** (2)	0	0
3	**1** (2)	0	0
4	**1** (2)	1	16
5	**1** (2)	2	90
6	**1** (2)	3	>99 (97)[c]
7	**4** (1)	0	30
8	**4** (1)	1	>99

[a] Reaction conditions: enyne **14** (0.21 mmol), gold complexes (based on gold, 4.2×10^{-3} mmol) with different amounts of aqueous HBF_4 in methanol (2 mL) at room temperature for 45 min. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

in 97% isolated yield (entry 6, Table 5). Nolan and co-workers previously reported that a terminal alkyne could be deprotonated by **1**.[19] Here, an acetylide complex was observed in the ^1H NMR analysis of the crude reaction mixture when **1** was employed as catalyst, which explained its inactivity (entry 3, Table 5). Noteworthy, with the use of technical grade methanol and aqueous HBF_4, low activity was observed with **4** (entry 7, Table 5). In this reaction, the Lewis acid character of **4** appears to be insufficient to catalyze the reaction, and **2** turned out to be more efficient. Finally, for both reactions involving enyne **14**, no catalytic activity was observed with HBF_4 or when **3** were used (entries 1 and 2, Tables 4 and 5).

3,3′-Rearrangement of allylic acetates: As triple bonds proved to be active substrates using our various well-defined and/or activation protocols, we next turned our attention to the reactivity of double bonds with the systems in hand. One example of C=C double bond reactivity is the 3,3′-rearrangement of allylic acetate **17** previously examined by Nolan and co-workers who performed this transformation with [AuCl(IPr)] (3 mol%) activated by $AgBF_4$ (2 mol%) in dichloroethane (DCE) at 80°C for 12 min.[45] Results of the rearrangement of acetate **17** and the conditions used for this transformation are summarized in Table 6.

Table 6. 3,3′-Rearrangement of allylic acetate **17** catalyzed by gold complexes.[a]



17 **18**

Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	2	10[c]
2	**3** (2)	0	0
3	**1** (2)	0	0
4	**1** (2)	1	0
5	**1** (2)	2	43
6	**1** (2)	3	>99 (93)[d]
7	**4** (1)	0	4
8	**4** (1)	1	>99

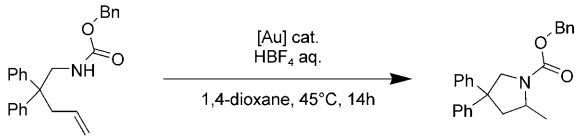
[a] Reaction conditions: allylic acetate **17** (0.3 mmol), gold complexes (based on gold, 6×10^{-3} mmol) with different amounts of $HBF_4{\cdot}OEt_2$ in DCE (3 mL) in microwave at 60°C for 30 min. [b] Conversions are an average of two runs. [c] Full conversion was observed, but only around 10% of the expected product was formed, along with decomposition products. [d] Isolated yield is an average of two runs.

Acetate **17** was fully converted when **1** was activated with 1.5 equivalents (based on gold) of $HBF_4{\cdot}OEt_2$ to afford the acetate **18** in 93% isolated yield (entry 6, Table 6). Noteworthy, the control experiment with $HBF_4{\cdot}OEt_2$ exhibits 10% conversion into the desired product **18** along with concomitant decomposition of the remaining starting material to unidentified products. This reaction is typically catalyzed by **2**, and activation of **1** required an excess of $HBF_4{\cdot}OEt_2$ but did not lead to the formation of decomposition products. Com-

pared to the previous reaction conditions described by Nolan et al.,[45] decreasing the temperature allowed a cleaner reaction but the reaction time needed to be extended to 30 min. Complex **3** displayed no catalytic activity in the 3,3′-rearrangement (entry 2, Table 6).

Intramolecular hydroamination of alkene: As olefins could be activated with the investigated complexes, a reaction involving a nucleophile attack on a double bond was envisaged. Intramolecular hydroamination[1q,52] is a one-step process that affords interesting heterocycles. In this transformation, amines protected as carbamates or ureas react more easily than the corresponding ammonium salts or tosylated amines. Indeed, for ammonium and tosylated amino substrates, the reaction is usually carried out with [AuCl(L)] (5 mol%) (L=phosphine ligand) activated by AgOTf (5 mol%) in toluene at 80°C for 18–24 h.[46c,d] When urea is used, the reaction is performed with [AuCl(IPr)] (5 mol%) activated by AgOTf (5 mol%) in dioxane at 45°C for 15 h.[46b] In the case of carbamate, published reaction conditions made use of 5 mol% [AuCl(PPh_3)] with 5 mol% AgOTf in dioxane at 60°C for 18 h to afford the cyclic amine **20** in a 97% isolated yield.[46a] This transformation was examined and results dealing with the intramolecular hydroamination of **19** catalyzed by complex **1**, **3**, and **4** (activated or not) are summarized in Table 7.

Table 7. Intramolecular hydroamination of alkene **19** catalyzed by gold complexes.[a]



19 **20**

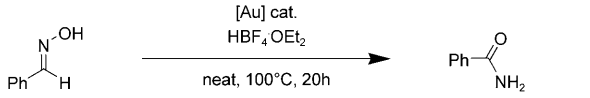
Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	5	0
2	**3** (5)	0	0
3	**1** (5)	0	0
4	**1** (5)	2.5	0
5	**1** (5)	5	61
6	**1** (5)	7.5	>99 (98)[c]
7	**4** (2.5)	0	0
8	**4** (2.5)	2.5	58

[a] Reaction conditions: amine **19** (0.05 mmol), gold complexes (based on gold, 2.5×10^{-3} mmol) with different amounts of $HBF_4{\cdot}OEt_2$ in 1,4-dioxane (2 mL) at 45°C for 14 h. [b] Conversions are an average of two runs. [c] Isolated yield is an average of two runs.

In the intramolecular hydroamination of unactivated alkenes, **4** clearly appeared inactive (entries 4 and 7, Table 7). The best conversion of **19** was obtained in the presence of **1** activated by 1.5 equivalents (based on gold) of $HBF_4{\cdot}OEt_2$ to generate **2** and provided the cyclic amine **20** in 98% isolated yield (entry 6, Table 7). This excess of $HBF_4{\cdot}OEt_2$ appears to be crucial to generate **2**. Indeed, when **4** was activated with 0.5 equivalents of acid, the reaction afforded only 58% conversion (entry 8, Table 7). This is in contrast to other reactions studied where these conditions appeared to be compatible to activate the gold center. Control experiments with separately, $HBF_4{\cdot}OEt_2$ and **3**, did not show any conversion of the starting material (entries 1 and 2, Table 7).

Beckmann-type rearrangement: As oximes can be dehydrated to give nitriles and water, and as nitriles can be hydrated in the presence of gold catalysts,[37] Beckmann-type rearrangements that are believed to proceed through a discrete nitrile intermediate when catalyzed with late transition metals, were then investigated. Nolan et al. have reported the first version of this reaction catalyzed by cationic gold complexes with the assistance of silver.[47] The Beckmann-type rearrangement of benzaldoxime **21**, which was carried out with [Au(IPr)Cl] (5 mol%) and $AgBF_4$ (10 mol%) without solvent at 100°C for 20 h, yielded the benzamide **6** in 92% isolated yield. Results of the Beckmann-type rearrangement of benzaldoxime **21** into benzamide **6** under various conditions are summarized in Table 8.

Table 8. Beckmann-type rearrangement of benzaldoxime **21** catalyzed by gold complexes.[a]



21 **6**

Entry	Catalyst (mol%)	HBF_4 [mol%]	Conv. [%][b]
1	none	5	0 (48)[c]
2	**3** (5)	0	0
3	**1** (5)	0	17 (5)[c]
4	**1** (5)	2.5	46 (5)[c]
5	**1** (5)	5	81 (4)[c]
6	**1** (5)	7.5	92 (4)[c] (72)[d]
7	**4** (2.5)	0	25 (6)[c]
8	**4** (2.5)	2.5	90 (6)[c]

[a] Reaction conditions: benzaldoxime **21** (0.41 mmol), gold complexes (based on gold, 2.05×10^{-2} mmol) with different amounts of $HBF_4{\cdot}OEt_2$ in neat condition at 100°C for 20 h. [b] Conversions are an average of two runs. [c] Conversion of **21** into benzaldehyde and/or benzonitrile. [d] Isolated yield is an average of two runs.

The control reaction with $HBF_4{\cdot}OEt_2$ as catalyst allowed 48% conversion of the starting material into benzaldehyde and nitrile (entry 1, Table 8). This was not surprising as Brønsted acids are known to dehydrate oximes into nitriles.[53] Benzamide **6** was obtained in 72% isolated yield when the reaction was performed with **1** (5 mol%) and 1.5 equivalents (based on gold) of $HBF_4{\cdot}OEt_2$ under solvent-free conditions at 100°C for 20 h (entry 6, Table 8). Interestingly, **4** showed moderate catalytic activity with a 25% conversion of the benzaldoxime **21** (entry 7, Table 8). This result, in the context of solvent-free reaction conditions, might suggest an alternative mechanistic pathway for this transformation.[54]

All organic transformations involving **1** activated by HBF_4 are summarized in Scheme 5.

The results presented here highlight species **2** as the active species in most of the transformations investigated. It

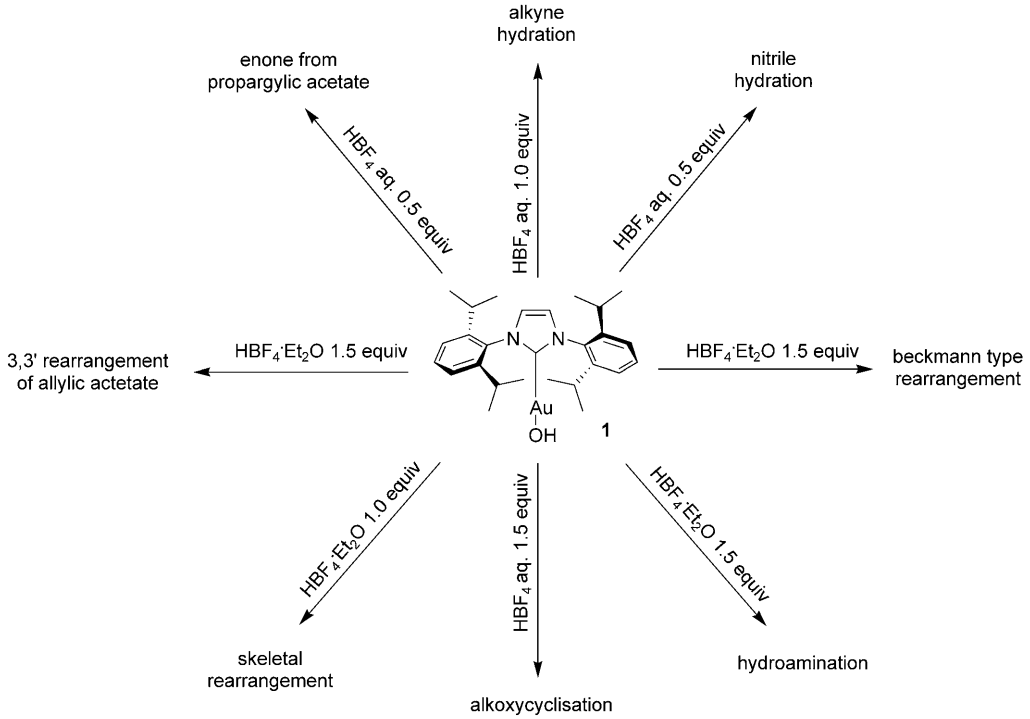
also appears clear that, during the formation of **2** by activation of **1**, **4** is generated by the first half equivalent of acid, and that **4** is in equilibrium with species **2** in water-containing reaction mixtures when more acid is added. Then, these equilibria are apparently solvent dependent; for example, when **1** is activated with 1.0 equivalent of acid, species **2** is almost exclusively generated in dry dichloromethane, whereas in a 10:1 mixture of dichloromethane/water, **4** is the only species formed. With polar and water-miscible solvents such as THF and methanol, the acid activation of **1** leads to an equilibrium between **1**, **4**, and **2**.

This highlights the fact that the in situ generation of cationic gold(I) **2** by using a combination of silver salts and gold(I) halide must be carefully examined because the nature of the solvent, the presence or the absence of water, the presence of any excess silver salt as a function of gold, which can lead to the formation of acid when hydrolysis occurs, can lead to various equilibria between complexes **1**, **4**, and **2**, which is ultimately responsible for the catalytic activity observed. One must never forget the importance of control experiments in such silver activation of gold catalysts.

In terms of the mechanism, the identification of **4** as a potentially active catalytic species in selected transformations creates a new working hypothesis in gold(I) catalysis. Indeed, Toste, Houk and co-workers have described in a detailed computational study, the role of a $[\{Au(PH_3)\}_3O]^+$ species as a reservoir for the $[Au(PH_3)]^+$ species and a source of $[Au(OH)(PH_3)]$.[38] The reservoir analogy in the context of the observed equilibria involving **4** is quite germane to the present study. Moreover, gold(I) hydroxide complexes have to be considered as potential strong Brønsted bases (pK_a between 29 to 31 for **1**), which can interact with substrate acidic protons.[19] The synthetically useful potential of **4** to deliver **2** acting as a σ- and π-system activating agent and a strong base simultaneously allows the consideration of new mechanistic pathways in gold (I) catalysis. These possibilities are presently being explored in our laboratory.

Conclusion

We have developed a practical and efficient method to generate the $[Au(IPr)][BF_4]$ species (**2**) from the easily synthesized [Au(OH)(IPr)] (**1**). This method represents a unique synthetic route where no silver reagent is used, at any stage.[55] The simple acid-assisted in situ generation of species **2** from the air- and moisture-stable complex **1** could have important repercussions on gold synthetic and catalytic applications. Along with economical and environmental considerations, this activation mode provides a very attractive alternative to silver activation protocols. With silver no longer being required for activation, the present protocol should lead to more straightforward gold-mediated transformations where the possible involvement of the silver activator is no longer suspect. The straightforward generation of $[[Au(IPr)]_2(\mu\text{-}OH)][BF_4]$ (**4**) is disclosed. The use of well-defined **4** or its generation in situ when **1** is activated by the addition of one-half equivalent of acid, can be viewed as a stable reservoir of species **2**. Also worthy of mention is the



Scheme 5. Summary of transformations catalyzed by **1** activated with HBF_4.

intriguing possibility of **4** acting as a reservoir of **1**, which is a strong Brønsted base.

Experimental Section

General considerations: All reactions were carried out in air unless otherwise stated. In such exceptions, experiments were performed by using standard Schlenk techniques using inert atmosphere of dry argon or in a MBraun glovebox containing dry argon and less than 1 ppm oxygen. Anhydrous solvents were either distilled from appropriate drying agents or purchased from Aldrich and degassed prior to use by purging with dry argon and kept over molecular sieves. Solvents for NMR spectroscopy were degassed with argon and dried over molecular sieves. NMR spectra were recorded on a 400 MHz Varian Gemini spectrometer. Elemental analyses were performed by St Andrews analytical services.

Preparation of $[Au(IPr)_2](BF_4)$ (3): Complex **1** (100 mg, 0.166 mmol) and IPr·HBF_4 (79.1 mg, 0.166 mmol) were introduced into a vial containing toluene (1.6 mL). The reaction mixture was stirred at 70 °C for 48 h. Pentane (2 mL) was then added and the resulting precipitate was collected on a frit. The solid was washed with pentane (3×3 mL) and dried under vacuum to afford **3** as a white microcrystalline solid (168 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (t, J = 7.8 Hz, 2H, C*H* aromatic IPr), 7.11 (s, 2H, C*H* imidazole IPr), 7.09 (d, J = 7.8 Hz, 4H, C*H* aromatic IPr), 2.27 (sept, J = 6.9 Hz, 4H, C*H*(CH_3)$_2$), 1.04 (d, J = 6.9 Hz, 12H, CH(C*H*$_3$)$_2$), 0.83 ppm (d, J = 6.9 Hz, 12H, CH(C*H*$_3$)$_2$); ^{19}F NMR (282 Hz, $CDCl_3$): δ = −151.0 (s, BF_4), −151.1 ppm (s, BF_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2 (s, C carbene), 145.0 (s, *C* aromatic IPr), 133.9 (s, *C* aromatic IPr), 130.7 (s, *C*H aromatic IPr), 125.2 (*C*H imidazole IPr), 124.3 (s, *C*H aromatic IPr), 28.5 (s, *C*H(CH_3)$_2$), 24.2 (s, CH(*C*H$_3$)$_2$), 24.0 ppm (s, CH(*C*H$_3$)$_2$); elemental analysis calcd (%) for $C_{54}H_{72}AuBF_4N_4$: C 61.13, H 6.84, N 5.28; found: C 60.95, H 6.80, N 5.31.

Preparation of $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (4): Complex **1** (97 mg, 0.160 mmol) and tetrafluoroboric acid–diethyl ether complex (11.0 μL, 0.080 mmol) were added to benzene (2 mL). The reaction mixture was stirred at room temperature for 4 h. Pentane (5 mL) was then added to the reaction mixture to precipitate the product as a white solid. The crude white product was crystallized from CH_2Cl_2/pentane to give complex **4** as a white microcrystalline solid (92 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (t, J = 7.8 Hz, 4H, C*H* aromatic IPr), 7.26 (s, 4H, C*H* imidazole IPr), 7.24 (d, J = 7.8 Hz, 8H, C*H* aromatic IPr), 2.39 (sept, J = 6.9 Hz, 8H, C*H*(CH_3)$_2$), 1.19 (d, J = 6.9 Hz, 24H, CH(C*H*$_3$)$_2$), 1.11 ppm (d, J = 6.9 Hz, 24H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6 (s, C carbene), 145.4 (s, *C* aromatic IPr), 133.6 (s, *C* aromatic IPr), 130.7 (s, *C*H aromatic IPr), 124.2 (s, *C*H aromatic IPr), 124.1 (s, *C*H aromatic IPr), 28.6 (s, *C*H(CH_3)$_2$), 24.4 (s, CH(*C*H$_3$)$_2$), 23.8 ppm (s, CH(*C*H$_3$)$_2$); ^{19}F NMR (185 Hz): δ = −154.90, −154.85 ppm; IR (KBr): $\tilde{\nu}$ = 3621, 3167, 3137, 3084, 2964, 2928, 2871, 1596, 1553, 1472, 1421, 1386, 1365, 1329, 1215, 1058, 947, 807, 762, 707, 581, 455 cm^{-1}; elemental analysis calcd (%) for $C_{54}H_{73}Au_2BF_4N_4O$: C 50.87, H 5.77, N 4.39; found: C 51.06, H 5.47, N 4.36.

CCDC-773700 (**3**) and CCDC-761375 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[55] This statement refers to the use of no silver in all synthetic steps leading to the isolation of the final complex whether it involves the synthesis of the [AuCl(IPr)] or [Au(OH)(IPr)] (**1**). Most silver-free catalysts, such as [Au(NTf_2)(IPr)] and [Au(IPr)](CH_3CN)][X], are synthesized by using a silver reagent, see: reference [9a] and [10].

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