

# The Development and Catalytic Uses of N-Heterocyclic Carbene Gold Complexes

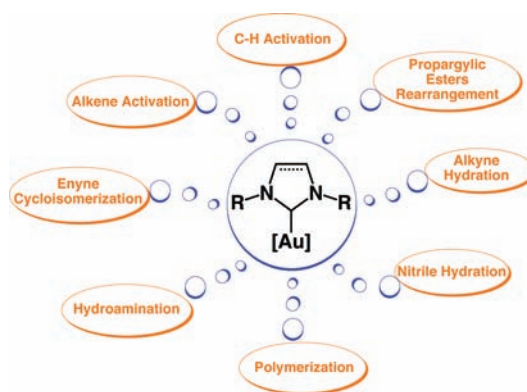
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## CONSPECTUS

Gold has emerged as a powerful synthetic tool in the chemist's arsenal. From the early use of inorganic salts such as AuCl and AuCl<sub>3</sub> as catalysts, the field has evolved to explore ligands that fine-tune reactivity, stability, and, more recently, selectivity in gold-mediated processes. Substrates generally contain alkenes or alkynes, and they usually involve straightforward protocols in air with solvents that can oftentimes be of technical grade. The actual catalytic species is the putative cationic gold(I) complex [Au(L)]<sup>+</sup> (where L is a phosphorus-based species or N-heterocyclic carbene, NHC). The early gold systems bearing phosphine and phosphite ligands provided important transformations and served as useful mechanistic probes. More recently, the use of NHCs as ligands for gold has rapidly gained in popularity. These two-electron donor ligands combine strong σ-donating properties with a steric profile that allows for both stabilization of the metal center and enhancement of its catalytic activity. As a result, the gold–NHC complexes have been used as well-defined precatalysts and have permitted the isolation of reactive single-component systems that are now used instead of the initial [Au(L)Cl]/silver salt method. Because some are now commercially available, NHC-containing gold(I) complexes are gathering increasing interest.



In this Account, we describe the chronological development of this chemistry in our laboratories, highlighting the advantages of this family of gold complexes and reviewing their synthesis and applications in catalysis. We first outline the syntheses, which are straightforward. The complexes generally exhibit high stability, allowing for indefinite storage and easy handling. We next consider catalysis, particularly examining efficacy in cycloisomerization, other skeletal rearrangements, addition of water to alkynes and nitriles, and C–H bond activation. These processes are quite atom-economical, and in the most recent C–H reactions the only byproduct is water. State-of-the-art methodology now involves single-component catalysts, precluding the need for costly silver co-catalysts. Remarkably, the use of an NHC as a supporting ligand has permitted the isolation of [Au(L)(S)]<sup>+</sup> species (where S is a solvent molecule such as a nitrile), which can act as single-component catalysts. Some improvements are still needed, as the single components are most often synthesized with a silver reagent. Owing to the stabilizing effect of NHC coordination, some NHC-containing systems can catalyze extremely challenging reactions (at temperatures as high as 140 °C) and react at very low loadings of gold (ppm levels). Our latest developments deal with C–H bond functionalization and hold great promise.

We close with a selection of important developments by the community with gold–NHC complexes. As demonstrated by the turns and twists encountered during our own journey in the gold–NHC venture, the chemistry described here, combining fundamental organometallic, catalytic, and organic methodology, remains rich in opportunities, especially considering that only a handful of gold(I) architectures has been studied. We hope this Account will encourage young researchers to explore this emerging area, as the adage “the more you do, the more you have to do” surely holds true in gold-mediated catalysis.

## I. Introduction and Background

Gold has taken, in recent years, an unexpected place in the synthetic chemist's arsenal and has opened new avenues for the synthesis of intricate scaffolds.<sup>1,2</sup> In this

context, the design of new catalyst compositions that would achieve better efficiency and selectivity or even permit previously unknown reactivity is a worthwhile endeavor. This is generally best realized through careful

examination of supporting ligands, which can permit one to fine-tune the stability and reactivity in the coordination sphere of the metal center. Interestingly, we realized in early 2004 that the nascent (at that time) field of gold catalysis was mainly examined with “ligandless” systems such as gold(I) and gold(III) chloride salts, with the only exception being the scarce use of PPh<sub>3</sub>-containing species.<sup>1</sup> We had by then examined a number of late transition metal (LTM) systems where the presence of N-heterocyclic carbene (NHC) ligands<sup>3</sup> had brought about beneficial properties to catalysts or precatalysts alike.<sup>4</sup> In the course of studies dealing with the use of NHCs in the development of copper catalysts, we reasoned that a foray down Group 11 might lead to novel complexes possibly possessing improved thermal stability, in a first instance.<sup>5</sup>

This venture ultimately led us to explore the catalytic uses of cationic gold(I) species bearing a NHC ligand. Once in hand, the catalytic results encouraged us to examine the exact nature of the catalytic species and sent us back to the lab to isolate these reactive species. Computational experiments performed in collaboration with colleagues in Salerno and Tarragona also led us to question and explore the synthetic feasibility of isolating organogold species that may be easier to launch in catalysis. These last developments are presently being explored further in our laboratory, but our latest results are presented at the end of this Account to provide a glimpse of the potential of these synthetic avenues.

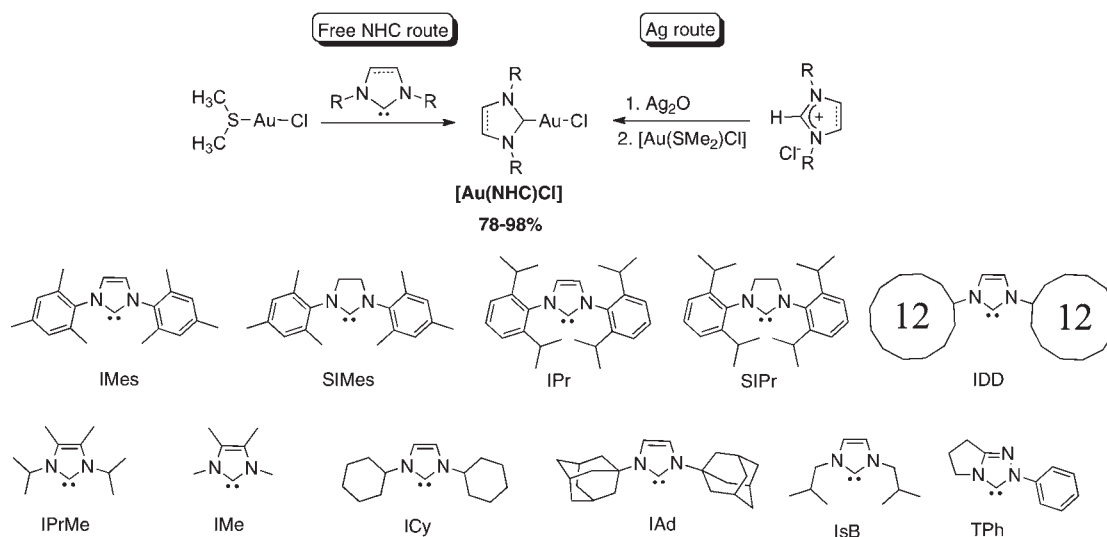
## II. Synthetic Routes to NHC–Au Complexes

As often is the case now in the group, our studies on gold–NHC complexes involved the methodical synthesis of a series of gold(I) complexes bearing various members of the NHC family. This approach usually allows us to gain a better understanding of the catalytic behavior of organometallic species as a function of ancillary ligands. This provides information dealing with very practical aspects of organometallic chemistry such as complex stability, reactivity, storage, and so forth. This approach becomes very useful during the optimization stage of a given transformation, since it provides access to a wide range of catalysts with diverse steric and electronic properties. Hence, as shown in Scheme 1, a series of [Au(NHC)Cl] complexes was initially synthesized<sup>6</sup> using (1) the silver oxide route developed by Lin and co-workers<sup>7</sup> to generate the appropriate [Ag(NHC)Cl] complexes that are used as NHC transfer agents when reacted with the [Au(DMS)Cl] precursor (DMS = dimethylsulfide)<sup>8</sup> or (2) the free NHC in a simple ligand substitution reaction.

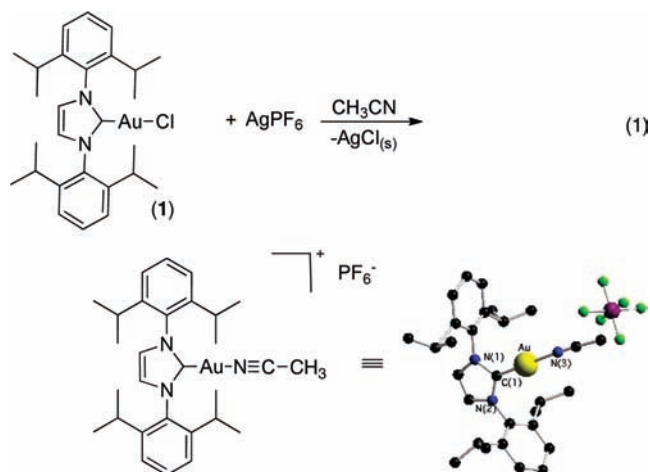
As catalytic studies proceeded and our understanding of the nature of the reactive species evolved, we reasoned that the stabilization imparted by NHC in the numerous transition-metal systems previously investigated could also be beneficial in a possible isolation of the putative [Au(L)]<sup>+</sup> species. This entity is still most often generated in situ by combining a [Au(L)Cl] (L = phosphine or NHC) complex with a silver additive which acts as a halide abstractor.

The approach was really straightforward (as are most things with hindsight), and it involved the simple use of a

**SCHEME 1.** Synthesis of a Series of [Au(NHC)Cl] Complexes



silver reagent acting on our favorite NHC bearing gold species, namely,  $[\text{Au}(\text{IPr})\text{Cl}]$  (**1**) (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) (eq 1):



The unequivocal atom connectivity and stability of the cationic complex was confirmed by X-ray diffraction results<sup>9</sup> and proved surprising to us as literature reports hinted at the instability of such a species.<sup>10</sup> This was indeed surprising, but more surprises were in store...

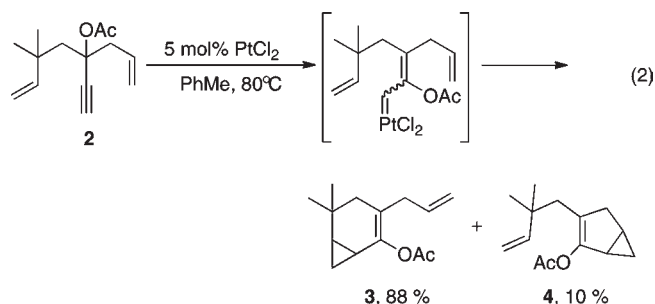
As a number of organic reactions could be mediated by Au(III) salts, we also endeavored to synthesize and characterize  $[\text{Au}(\text{NHC})\text{X}_3]$  (X = halide) complexes. The synthetic approach made use of the  $[\text{Au}(\text{NHC})\text{Cl}]$  lessons, and the  $[\text{Au}(\text{NHC})\text{Br}_3]$  complexes were initially targeted (this for entirely practical purposes). A series of new NHC–gold(III) carbene complexes was synthesized by simple oxidative addition to Au(I) complexes.<sup>11</sup> A series of  $[\text{Au}(\text{NHC})\text{Cl}_3]$  congeners was also more recently synthesized.<sup>12</sup> These Au(III) complexes were precatalysts in the addition of water to alkynes, but both series of complexes show a high propensity for spontaneous reduction to Au(I) species.

Once these gold–NHC complexes were in hand (neutral at first and then cationic), we set out to examine their catalytic potential. This Account describes our exploration of gold catalysis, which, with a combination of mechanistic hypothesis, observation, and serendipitous discovery, keeps us humble and reminds us that research is *not* a linear process.

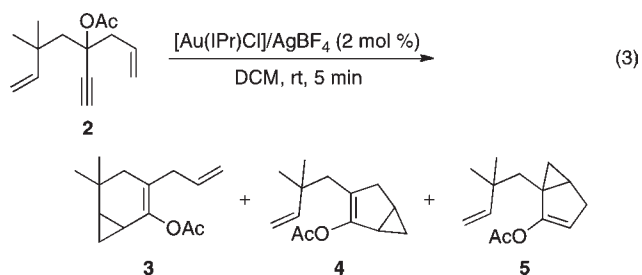
### III. Reactivity of Enynes Bearing a Propargylic Ester

Our journey into gold catalysis began with the apparently complex enyne cycloisomerization reaction. It appeared as an obvious choice at that time, notably in view of a number

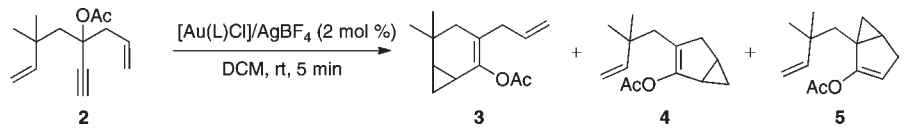
of groundbreaking studies on the outstanding activity of gold catalysts toward enynes published in the course of 2004.<sup>13</sup> Our primary focus was not (yet) to uncover novel reactivity but rather modestly to test our NHC–Au catalysts. So we sought an already published enyne cycloisomerization reaction in which we could apply our new catalysts. In the process, we teamed up with the research groups of Professors Malacria and Fensterbank in Paris. Their previous experience of cycloisomerization chemistry was welcome, and we were interested in a reaction they had previously described in 2002.<sup>14</sup> As depicted in eq 2, the reaction consists of the formation of a  $[n-2.1.0]$  bicyclic derivative from a linear  $1,n$ -enyne with concomitant 1,2-migration of the acetate; a reaction that revitalized research activity on the peculiar reactivity of propargylic esters<sup>15</sup> following seminal studies from the Firmenich laboratories.<sup>16,17</sup> The diyne substrate **2** designed by Fensterbank and Malacria presents the particularity of containing two enyne moieties that differ by the length of their tether. Hence, upon electrophilic activation of the alkyne, either the 1,5- or the 1,6-enyne can react and leads to two products.<sup>18</sup>



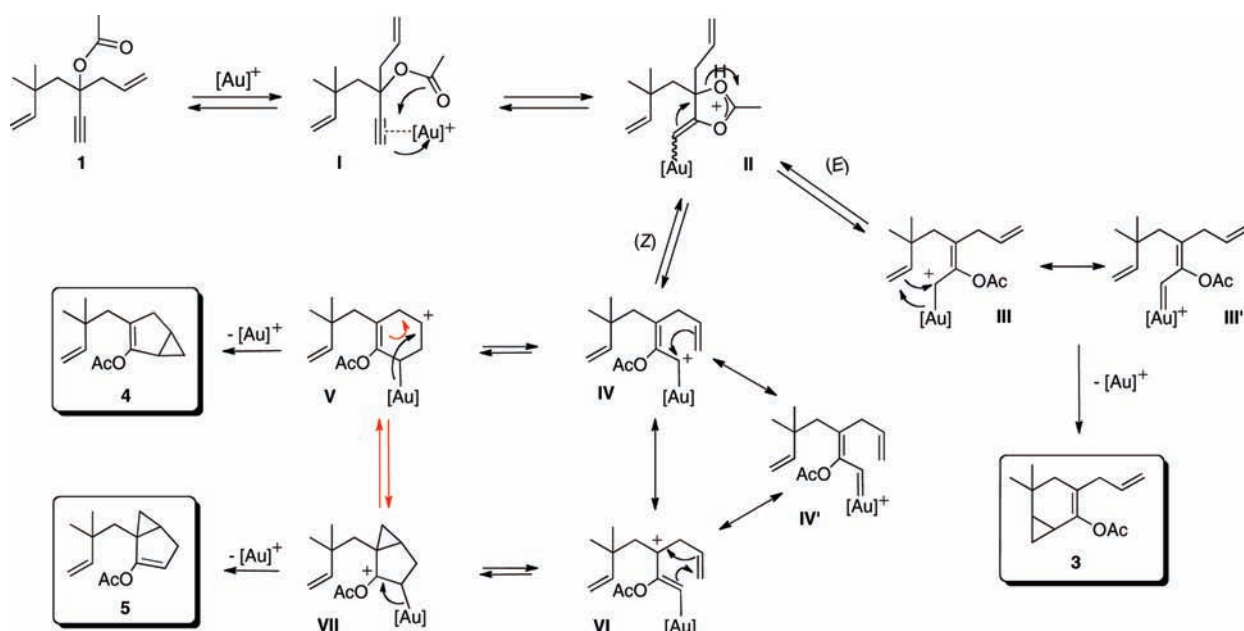
In the initial Pt mediated reaction (eq 2), only two products were observed and we were surprised to observe that neither of the reported 5- nor 6-membered carbocycles were the main product in the gold–NHC reaction but a novel 5-membered carbocycle (**5**) was formed in 42% isolated yield (eq 3).



The isolation, derivatization, and complete characterization of **5** confirmed the atom connectivity. A screening of

**TABLE 1.** Cycloisomerization of **2** Mediated by Cationic Gold(I) Species<sup>a</sup>


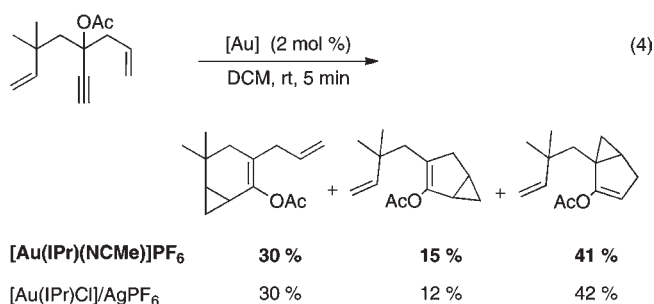
| entry | L                | <b>3</b> | <b>4</b> | <b>5</b> |
|-------|------------------|----------|----------|----------|
| 1     | IMes             | 26%      | 12%      | 40%      |
| 2     | SIMes            | 23%      | 9%       | 40%      |
| 3     | IPr              | 30%      | 12%      | 42%      |
| 4     | SIPr             | 41%      | 13%      | 36%      |
| 5     | IAd              | 54%      | 6%       | 35%      |
| 6     | ITM              | 52%      | 8%       | 12%      |
| 7     | PPh <sub>3</sub> | 50%      | 2%       | 12%      |

<sup>a</sup>NMR yields, average of two runs.**SCHEME 2.** Proposed Mechanism for the Cycloisomerisation of **2**

NHC–gold catalysts highlights the influence of the nature of the NHC bound to gold on the efficiency and selectivity of the cycloisomerization reaction; see Table 1.<sup>19</sup> Entry 7 in Table 1 highlights the influence of various bulky NHCs and a typical phosphine on directing product distribution.

The active role of the putative cationic species was confirmed in this study when the isolated cationic species [Au(IPr)(NCMe)]<sup>+</sup>BF<sub>4</sub><sup>−</sup> was used as catalyst; an experiment that leads to the same product distribution as when it is generated in situ (eq 4).

Mechanistically, the product distribution was proposed to proceed through a series of accessible pathways illustrated in Scheme 2.<sup>20,21</sup> Results from this cycloisomerization represent, as far as we are aware, the first example of important reactivity/selectivity differences between platinum and gold complexes in such reaction types.



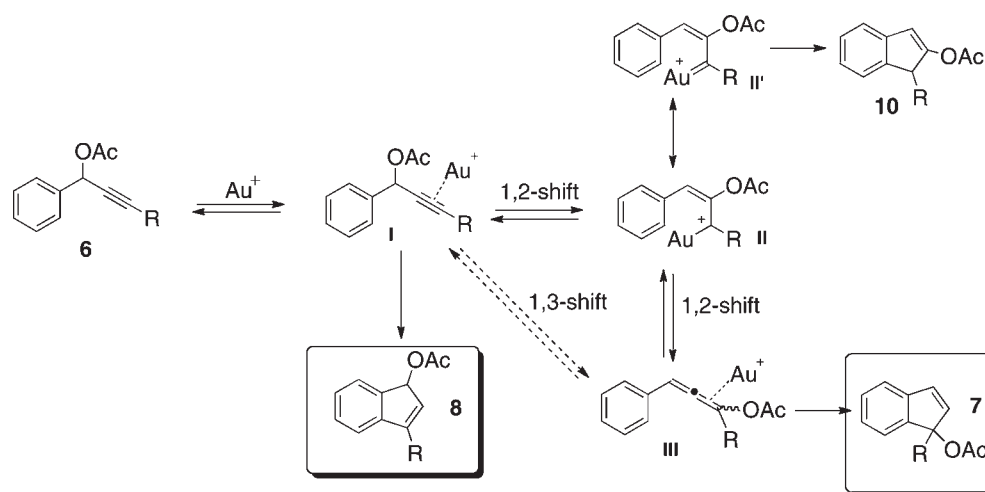
#### IV. Tandem $\pi$ -Activation–Carboxylate Migration

The dienyne substrate **2** is actually a fairly complex starting point to attempt to understand the activity of gold in such transformations. To hopefully better understand the behavior of our gold catalysts, we next examined simpler systems

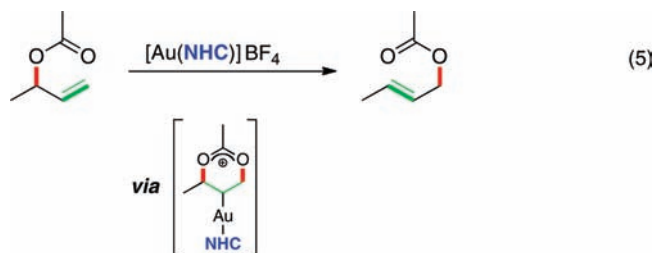


**TABLE 2.** Cycloisomerization of **6** Mediated by Cationic Gold(I) Species

| entry | [catalyst] (2 mol %)         | time      | <b>7</b> | <b>7</b> (%) | <b>8</b> (%) | <b>9</b> (%) |
|-------|------------------------------|-----------|----------|--------------|--------------|--------------|
| 1     | (IPr)AuCl/AgBF <sub>4</sub>  | 5 min     |          | 92           |              |              |
| 2     | (IPr)AuCl                    | overnight |          | no reaction  | no reaction  | no reaction  |
| 3     | AgBF <sub>4</sub>            | 30 min    |          |              |              | 87           |
| 4     | (IPr)AuCl/AgPF <sub>6</sub>  | 5 min     |          | 90           |              |              |
| 5     | (IPr)AuCl/AgSbF <sub>6</sub> | 5 min     |          | 73           |              |              |
| 6     | (SIPr)AuCl/AgBF <sub>4</sub> | 5 min     |          | 88           | 5            |              |
| 7     | (IMes)AuCl/AgBF <sub>4</sub> | 5 min     |          | 76           | 3            |              |
| 8     | (ITM)AuCl/AgBF <sub>4</sub>  | 5 min     |          | 54           | 23           |              |
| 9     | (IAd)AuCl/AgBF <sub>4</sub>  | 15 min    |          | 89           |              |              |

**SCHEME 3.** Proposed Mechanism for the Cycloisomerisation of **6**

and tackled allylic acetates as substrates. In this gold-mediated transformation, eq 5, a series of [Au(NHC)Cl] complexes in conjunction with Ag salts were examined for activity in a sigmatropic rearrangement.<sup>22</sup> The reaction proceeds very well and a mechanism was postulated based on computational analysis.<sup>23</sup>



A system very closely related to substrate **2** was next examined. This system, although arguably a simpler molecular architecture than **2**, leads to the formation of three possible products under gold catalysis<sup>24</sup> (Table 2).

Under these simple experimental conditions, indenenes can be generated in ca. 5 min. Mechanistically, the formation of product is proposed to proceed through the intermediacy of an allene, followed by rearrangement and migration as proposed above for substrate **2**; see Scheme 3.

The intermediacy of the allene was confirmed by using isolated allenes as starting material for the rearrangement/cyclization reactions (eq 6).<sup>22</sup>

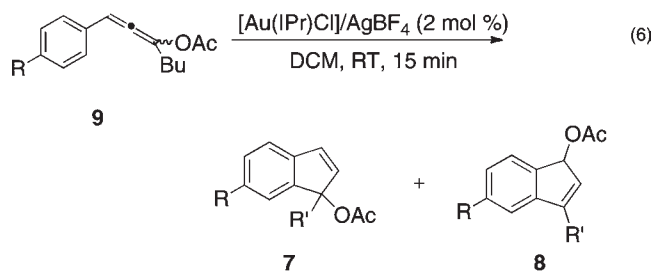
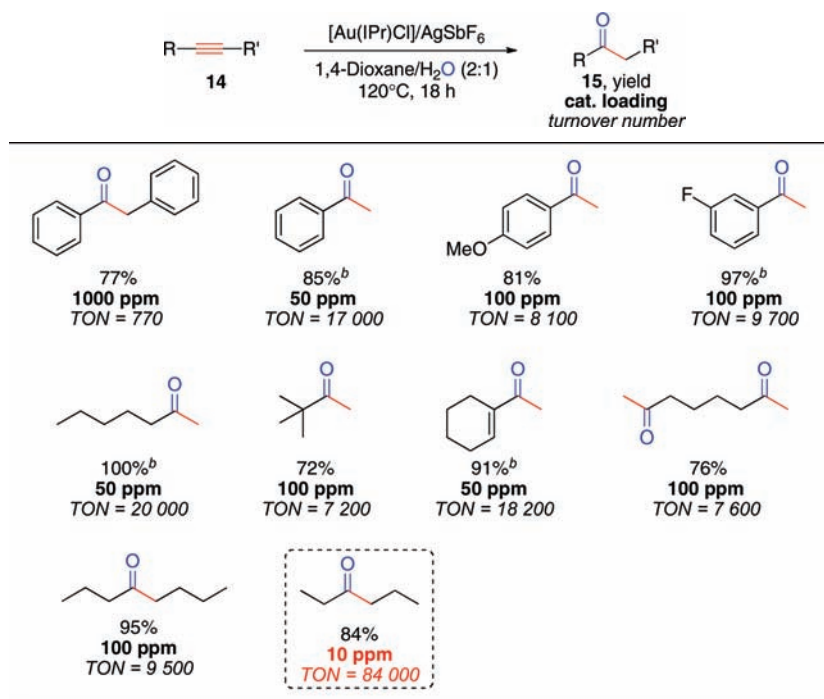


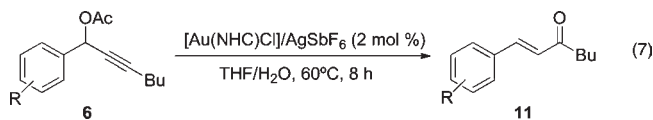
TABLE 3. Alkyne Hydration Mediated by Cationic Gold(I) Species



<sup>a</sup><sup>1</sup>H NMR yields against benzaldehyde as internal standard. Yields are average of at least two runs. <sup>b</sup>Reaction performed with MeOH instead of 1,4-dioxane.

## V. Hydration-Type Reactions

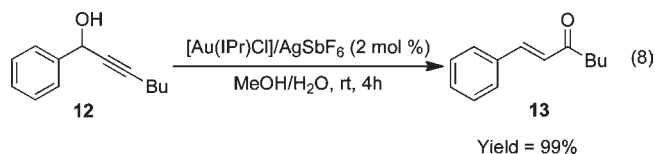
While studying the indene forming reaction, and while the chemistry was being completed at the University of Ottawa (during our 8 months there), we encountered issues of reproducibility. What was observed as a minor product (usually <5%) and was usually easily separated from the desired indene product became a major byproduct (as much as 20%). This indene yield erosion had to be explained, and we launched a large-scale reaction (10 mmol) to separate, isolate, and fully characterize this pesky byproduct. We also noticed that heating the reaction under the cyclization conditions led to an increase in yield of this side-product. The reaction and byproduct are presented in eq 7.



The enone **10** can be generated in excellent yields and to the exclusion of the indene product if water is present and the reaction is heated.<sup>25</sup> Various enones, aryl and alkyl bearing, can be generated using this simple protocol. Although the optimum NHC was identified as I<sup>t</sup>Bu, the IPr congener can be used to conduct this reac-

tion with comparably good results. These reaction conditions also show that the gold–NHC catalysts can tolerate thermal treatment, a reoccurring property of LTM–NHC complexes.<sup>3b</sup> This thermal tolerance issue will reappear shortly.

This initial negative results transformed into a veritable opportunity to synthesize straightforwardly  $\alpha,\beta$ -unsaturated ketones. We then followed this lead and examined a closely related substrate and whether gold could facilitate the Meyer–Schuster reaction (eq 8).<sup>26</sup>

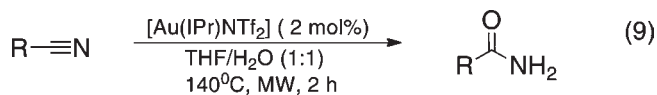


Catalysis was performed in a 2:1 mixture of methanol and water at 60 °C and afforded good yields even for tertiary alcohols and sterically demanding substrates. Thorough evaluation of the optimized catalytic system showed it was unsuitable for terminal alkynes and primary alcohols.

Following this theme of water as a reagent, we next turned to a previously examined reaction mediated by cationic gold–phosphine complexes, namely, the hydration of alkyne reaction. The seminal work of Teles encouraged us to examine the

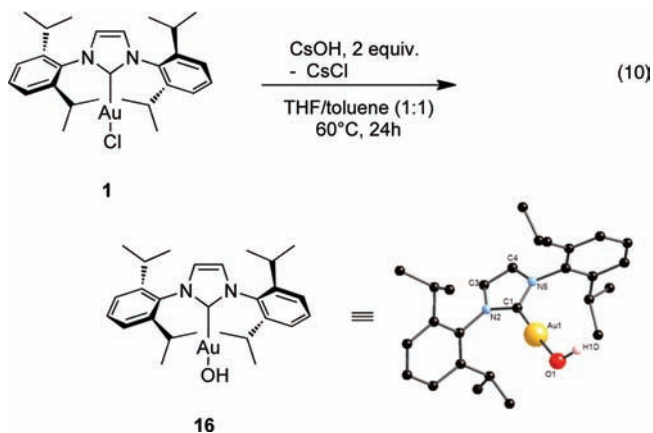
limits of reactivity displayed by our gold–NHC systems. Alkyne hydration reactions at low catalyst loadings<sup>27</sup> were next performed, and results again show that these systems are extremely active and very tolerant of thermal treatment (Table 3).<sup>28</sup>

The reactivity of this *sp* hybridized carbon function suggested to us that possibly other *sp* hybridized functions could react in this manner, and so we next targeted nitriles. Indeed, on examining the literature, we were surprised to find out that, among the numerous metals able to hydrate nitriles, gold was absent. In addition, the nitrile function has a special role in cationic gold catalysis as it is used as a stabilizing ligand in cationic species.<sup>7,29</sup> The possibility of involving this spectator entity in catalysis was intriguing. After a short exploratory optimization study, we realized that indeed the nitriles could be more than spectators in gold catalysis and that amides could be formed although under fairly forcing conditions (eq 9).<sup>30</sup> A variety of nitriles (aromatic and heteroaromatic) can be involved in a reaction that is performed under microwave irradiation at 140 °C. The optimum catalyst found in this reaction is of the Gagosz-type, bearing an NTf<sub>2</sub> (NTf<sub>2</sub> = bis(trifluoromethanesulfonyl)imide) counterion in the metal inner coordination sphere.<sup>31</sup>



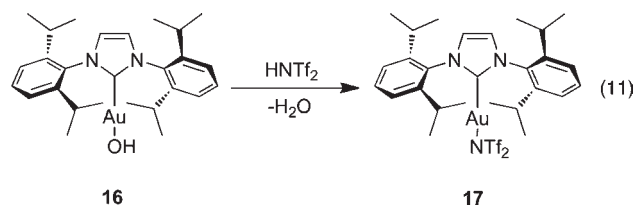
## VI. Novel Well-Defined Precatalysts

In the course of investigations dealing with reactions implicating water, our computational colleagues suggested that a [Au(NHC)OH] species might prove exceptionally stable. As we pondered this possibility and as we busied ourselves moving to Scotland, on arrival, we took up the synthetic challenge of isolating such a complex. After a short screening of bases and reaction conditions, the desired [Au(IPr)OH] (**16**) complex was isolated in excellent yields according to eq 10.<sup>32</sup>



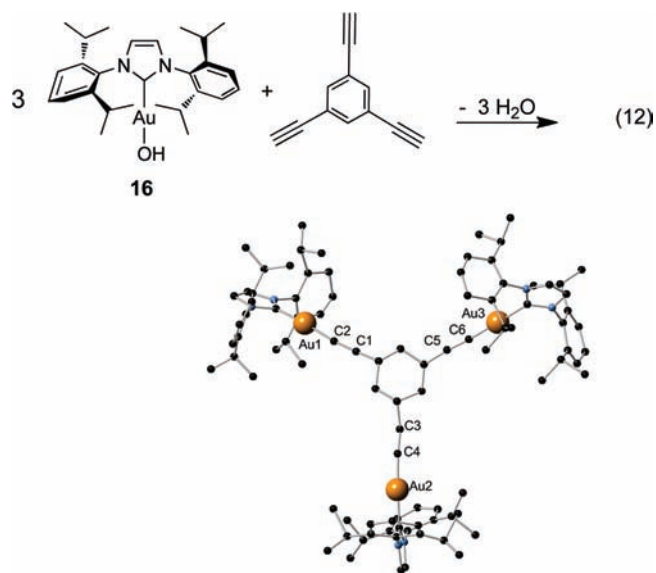
We feel this synthetic development is a veritable advance as the use of silver in all precursor steps has been eliminated.

This is clearly illustrated in the straightforward synthesis of the Gagosz-type complex (**17**) that is simply made from **16** and the HNTf<sub>2</sub> according to eq 11.



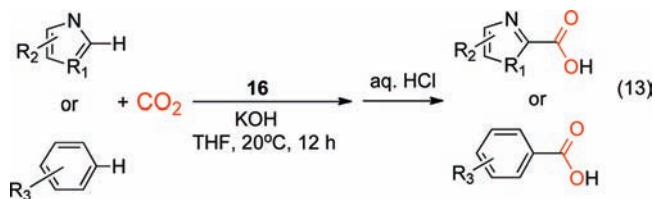
The basicity of **16** was gauged chemically by examining the *p*K<sub>a</sub> of C–H bonds in fluoroarene compounds. As these values are known, they permit one to establish that the *p*K<sub>a</sub> of **16** falls between 29 and 31 *p*K<sub>a</sub> units (see Table 4). Of note, this series of reactions also represents relatively facile C–H activation processes.<sup>33</sup>

Following this early study on C–H activation, we recently reported on the ease with which terminal alkyne C–H bonds can be activated and lead in high yields to a variety of gold–alkynyl complexes by simple water elimination reaction.<sup>34</sup> An example is presented in eq 12.



The lesson taught by the gold–hydroxide complex **16** is that simple acid–base principles guide the chemistry. At this point, it appears this simple. Others have reported the synthesis of alkynyl complexes requiring other routes,<sup>35</sup> and the present pathway appears to be the simplest and most cost efficient. As C–H bond *activation* now proved possible as illustrated by eq 12, we most recently turned our attention toward C–H bond *functionalization*. Our most recent report deals with the carboxylation of C–H bonds under fairly mild conditions using **16** as catalyst (eq 13).<sup>36</sup>

We are now exploring multiple uses of **16** as a synthon and as a precatalyst.

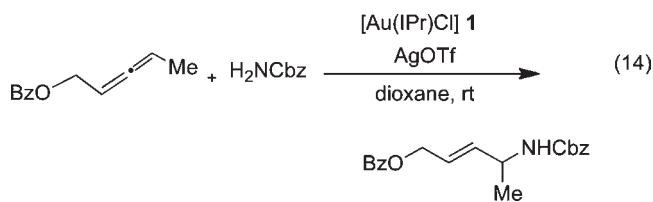


If the Reader has come this far, one of the questions that might be honestly asked is: Are NHCs simply tertiary phosphine mimics? This question is one that is deserving of an answer; and based on our observations and findings so far dealing with gold–NHC versus gold–PR<sub>3</sub> catalysis, we can state that in many instances they appear to behave as phosphine mimics. However, in numerous other cases, they are distinct as they lead to different reactivity/selectivity and the resulting complexes, because of their improved thermal stability, can mediate transformations requiring harsher reaction conditions. The last example (eq 13) is a noteworthy one as we have been so far unable to synthesize phosphine analogues of **16**, and ongoing studies examining the possible involvement of Au–PR<sub>3</sub> complexes in a transformation such as the carboxylation of C–H bonds have proven frustrating thus far. The Au–NHC complexes are special, and how special is a question continued research and time should hopefully clearly answer.

## VII. Outlook

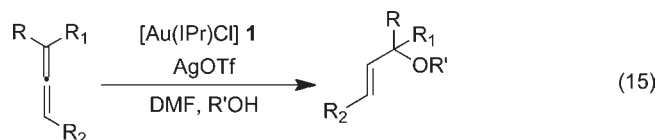
Since [Au(IPr)Cl] (**1**) is now commercially available,<sup>37</sup> a number of groups have also examined **1**-mediated catalysis. In this initial “outlook” section, I feel it important to look outward and discuss the uses of **1** made by colleagues. The list is not exhaustive, and I do apologize in advance for any omission.

The Widenhofer group has made extensive uses of **1** as a catalyst precursor (in conjunction with silver salts) in facilitating hydroamination-type reactions,<sup>38</sup> an example is illustrated in eq 14.



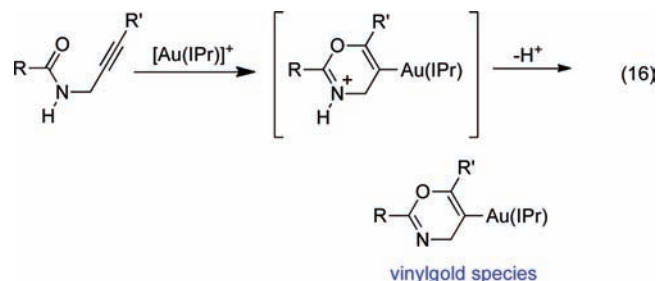
Using a similar hydroamination approach, quinolines have been synthesized from aromatic amines and alkynes

by Che and co-workers.<sup>39</sup> The involvement of alkynes and allenes in gold catalysis continues to evolve, and numerous reports of cyclization reactions mediated by **1** as a cocatalyst have appeared.<sup>40</sup> A very recent example of regioselective synthesis of allylic ethers mediated by **1** and a silver salt was reported by Hadfield and Lee<sup>41</sup> (eq 15) that was supported by a computational study<sup>42</sup> by the Maseras group.



Toste et al. reported a series of oxidative rearrangements catalyzed by a **1**/Ag salt combination in 2007.<sup>43</sup> Pérez and Nolan found this report made use of diazo compounds as starting reagents and these proved useful in functionalizing alkanes in 2005.<sup>44</sup> The versatility of [Au(IPr)Cl] **1** was further demonstrated, as it was found active in polymerization reactions.<sup>45</sup>

The NHC ligands continue to assist chemists in understanding reaction mechanisms as they are able to stabilize otherwise “unstable” species.<sup>46</sup> A recent example reported by the Hashmi group describes the stabilization imparted by the IPr NHC to permit the isolation of vinylgold derivatives<sup>47</sup> which have been invoked as intermediates in gold-catalyzed addition of nucleophiles to C–C multiple bonds (eq 16).



Another example of stabilization brought about by the use of NHC ligands is illustrated in the series of complexes generated from the versatile [Au(IPr)H] synthon reported by Tsui in 2008.<sup>48</sup> The Fürstner group has recently reported on NHCAu–alkyne complexes that were characterized by single crystal diffraction studies and analyzed by density functional theory calculations.<sup>49</sup> The same group has recently reported that NHCs can be more backdonating than previously recognized which can provide a certain element of reaction control in the course of certain gold-catalyzed reactions.<sup>50</sup>

To finally illustrate the breadth of applications and uses of the [Au(NHC)] complexes, some have been synthesized

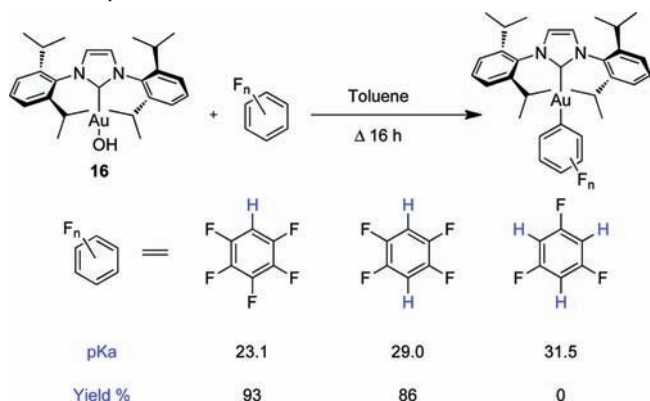


bearing biocompatible entities<sup>51</sup> and a number of these have been reported to possess important anticancer activity.<sup>52</sup>

In closing, it should be said that our journey into gold chemistry and catalysis evolved in a series of challenges and failures that were transformed into opportunities (i.e., the water story being a *salient* example). The work was obviously not performed in a vacuum, and any progress we have made surely rests on the *shoulders* and seminal findings of *giants* that preceded us.

The water analogy follows us as the *Golden Synthon*, [Au(IPr)OH] **16**, is, through the isolobal analogy, equivalent to water. Our exploration of gold catalysis led us from complexity to more fundamental systems aimed at understanding the basics. Our voyage took us from the United States to Canada to Spain and finally to Scotland. Through these changes, gold continues to surprise us through its versatility, complexity, and, in the end, elegant simplicity.

**TABLE 4.** pKa Determination and Activation of Fluoroarene C–H Bond



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#### FOOTNOTES

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