

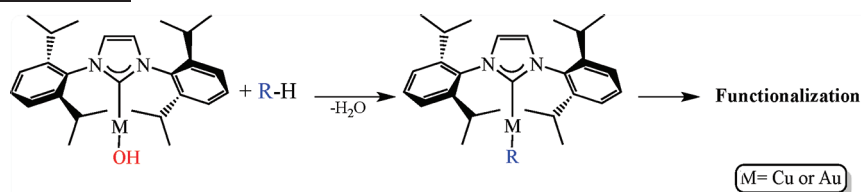
## N-Heterocyclic Carbene Gold(I) and Copper(I) Complexes in C–H Bond Activation

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### CONSPECTUS



**E**nvironmental concerns have and will continue to have a significant role in determining how chemistry is carried out. Chemists will be challenged to develop new, efficient synthetic processes that have the fewest possible steps leading to a target molecule, the goal being to decrease the amount of waste generated and reduce energy use. Along this path, chemists will need to develop highly selective reactions with atom-economical pathways producing nontoxic byproduct.

In this context, C–H bond activation and functionalization is an extremely attractive method. Indeed, for most organic transformations, the presence of a reactive functionality is required. In Total Synthesis, the “protection and deprotection” approach with such reactive groups limits the overall yield of the synthesis, involves the generation of significant chemical waste, costs energy, and in the end is not as green as one would hope. In turn, if a C–H bond functionalization were possible, instead of the use of a prefunctionalized version of the said C–H bond, the number of steps in a synthesis would obviously be reduced. In this case, the C–H bond can be viewed as a dormant functional group that can be activated when necessary during the synthetic strategy.

One issue increasing the challenge of such a desired reaction is selectivity. The cleavage of a C–H bond (bond dissociation requires between 85 and 105 kcal/mol) necessitates a high-energy species, which could quickly become a drawback for the control of chemo-, regio-, and stereoselectivity. Transition metal catalysts are useful reagents for surmounting this problem; they can decrease the kinetic barrier of the reaction yet retain control over selectivity. Transition metal complexes also offer important versatility in having distinct pathways that can lead to activation of the C–H bond. An oxidative addition of the metal in the C–H bond, and a base-assisted metal–carbon bond formation in which the base can be coordinated (or not) to the metal complexes are possible. These different C–H bond activation modes provide chemists with several synthetic options.

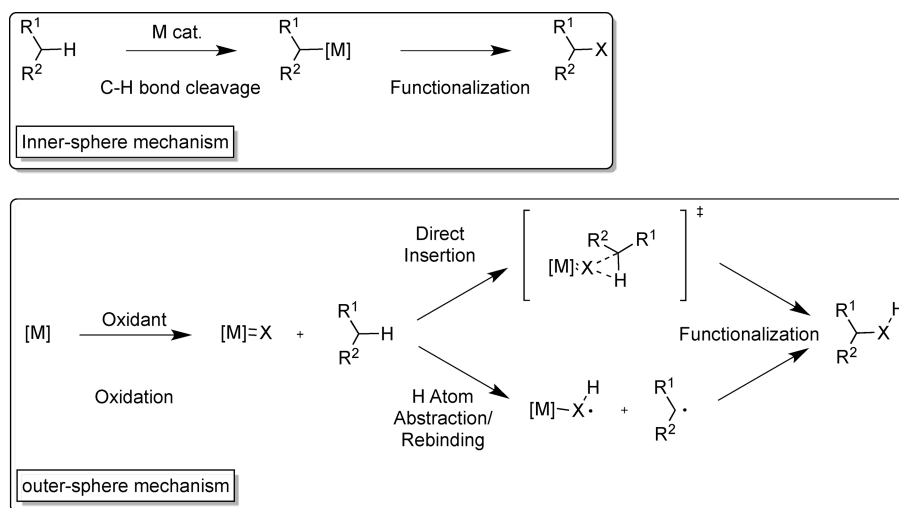
In this Account, we discuss recent discoveries involving the versatile NHC–gold(I) and NHC–copper(I) hydroxide complexes (where NHC is *N*-heterocyclic carbene) showing interesting Brønsted basic properties for C–H bond activation or C–H bond functionalization purposes. The simple and easy synthesis of these two complexes involves their halide-bearing relatives reacting with simple alkali metal hydroxides. These complexes can react cleanly with organic compounds bearing protons with compatible  $pK_a$  values, producing only water as byproduct. It is a very simple protocol indeed and may be sold as a C–H bond activation, although the less flashy “metalation reaction” also accurately describes the process. The synthesis of these complexes has led us to develop new organometallic chemistry and catalysis involving C–H bond activation (metalation) and subsequent C–H bond functionalization. We further highlight applications with these reactions, in areas such as photoluminescence and biological activities of NHC–gold(I) and NHC–copper(I) complexes.

### Introduction and Background

In recent years, C–H bond activation or the C–H bond functionalization reactions catalyzed by transition metals

have become the subject of intensive studies by the chemical community.<sup>1</sup> Indeed, the addition of a functional group at a C–H bond position represents a great advance in

SCHEME 1. C–H Bond Functionalization Mechanisms



synthetic methodology and presents a greener approach to molecular assembly protocols.

C–H bond activation has historically been observed to occur at very high temperature, but observations of agostic bonding<sup>2</sup> present in some transition metal complexes highlighted the possibility that such reactions might proceed under milder reaction conditions. Even if this strategy of an already coordinated ligand reacting with the metal center to form an additional bond to the metal was not the best for catalytic C–H bond activation, these, at first, isolated examples suggested that intermolecular alkane activation might take place.<sup>3</sup> Using organometallic complexes designed to be stable after C–H bond activation of alkanes, several new complexes were isolated providing the *proof of concept*.<sup>4</sup> In terms of mechanism, Labinger and Bercaw<sup>1b</sup> defined five classes of C–H bond activation pathways: (i) oxidative addition; (ii)  $\sigma$  bond metathesis; (iii) metalloradical activation; (iv) 1,2-addition; (v) electrophilic activation. The first two cases were noted to be the most frequently encountered, while pathways iii and iv were less common. The fifth case was reported as a transient organometallic species.

More recently, a simpler vision on the most common C–H bond activation pathways was provided by Sanford who described these as “inner-sphere” and “outer-sphere” mechanisms. Crabtree defined them as “organometallic” and “coordination” mechanism, respectively (Scheme 1).<sup>5</sup>

As defined by Sanford, the “inner-sphere” mechanism comprises two steps that involve the cleavage of the C–H bond leading to the formation of a transition metal alkyl or

aryl derivative and the functionalization of this intermediate by an external reagent (or the metal center) to lead to final product. Concerning the “outer-sphere” mechanism, the first species formed is a high oxidation state metal complex containing an activated ligand (e.g., a carbene). This reactive species can evolve by two different pathways, one is the direct insertion in the C–H bond and the second is a hydrogen atom abstraction/radical rebound furnishing the C–H bond functionalization product.

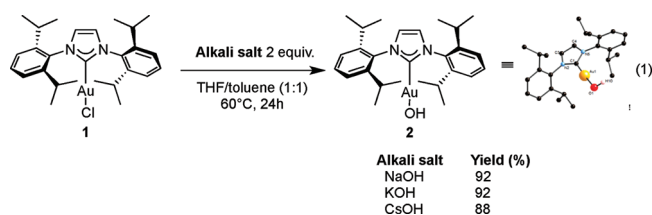
With these mechanism and reactivities in mind, our interest in this area began as studies in organogold chemistry was initiated in our laboratories. Gold catalysis has become an extremely prolific area of research, emphasized by numerous reviews on different applications in catalysis,<sup>6</sup> organometallic chemistry,<sup>7</sup> Total Synthesis,<sup>8</sup> mechanism,<sup>9</sup> and biochemistry.<sup>10</sup> Copper, the cheaper group XI congener, has also been widely studied in these areas in order to replace the more costly gold systems.<sup>11</sup> Studies on gold- and copper-mediated C–H bond activation and functionalization<sup>12</sup> owe much to the seminal work of the early 1930s by Kharasch and Isbell who first observed the C–H bond activation of benzene by auric acid.<sup>13</sup>

As part of our studies on organometallic complexes involving NHCs, we have developed numerous NHC–gold and –copper complexes.<sup>14</sup> This led us to contribute to the development of (NHC)gold<sup>15</sup> and (NHC)copper<sup>16</sup> chemistries. The stabilization of metal complexes brought about by the use of NHCs as ancillary ligands is also present for Cu and Au complexes.<sup>17</sup> With this important library of potential

active catalysts on hand, we were interested in evaluating some of these complexes for such challenging reactions as C–H bond activation and C–H bond functionalization. In this Account, we will present our latest findings dealing with C–H bond activation involving (NHC)gold(I) and (NHC)copper(I) complexes. Moreover, applications of these complexes to photoluminescence and medicinal uses will be presented.

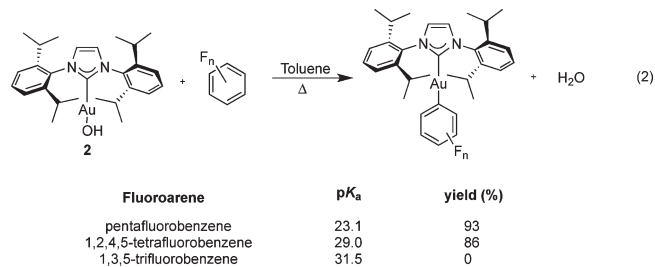
## The Discovery of (NHC)gold(I) and (NHC)copper(I) Hydroxide Complexes

Our journey into the gold and copper hydroxide chemistry area begins with theoretical calculations. As often in the group, DFT calculations were performed on mechanistic aspects of a metal-catalyzed organic transformation developed in our laboratories. This was initially simply to gain insight into possible mechanistic pathways leading to the formation of conjugated enones and enals catalyzed by (NHC)gold(I).<sup>18</sup> From these calculations, a [Au(OH)(NHC)] complex was found to be a “stable” species along the reaction pathway. After some thought on how to attack this synthetic problem and a move from Spain to Scotland, studies aimed at isolating [Au(OH)(IPr)] (**2**) (IPr = *N,N'*-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene) were initiated.<sup>19</sup> This air-stable **2** was readily prepared from the commercially available [AuCl(IPr)]<sup>20</sup> (**1**) in the presence of a simple alkali metal hydroxide in a mixture of THF/toluene (1:1) in 92% yield if potassium or sodium hydroxide are used (eq 1).

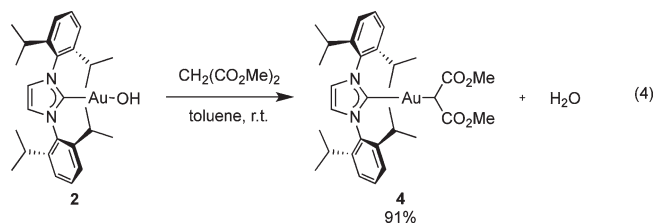
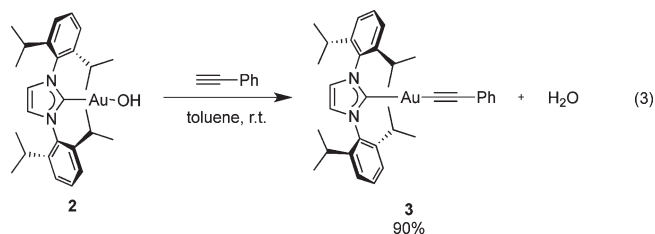


With **2** in hand, the catalytic activity of this complex in the formation of enones and enals from propargyl acetate was investigated and found to be lower than *in situ* generated cationic gold(I) species.<sup>21</sup> Most often, DFT calculations help explain the stability of intermediates and this also often drives synthetic chemists toward further advances. In this case, the poor catalytic activity of **2** proved a bit disappointing. Further examination of the reaction chemistry of **2**, rapidly showed that **2** was a versatile synthon for X–H and C–H bond activations. Our preliminary investigations on C–H bond activation, by deprotonation of various fluoroarenes,<sup>22</sup> permitted us to evaluate the  $pK_a$  of proton on C–H bond required to

react with the Au–OH bond in **2** to be between 29 and 31  $pK_a$  units (eq 2).



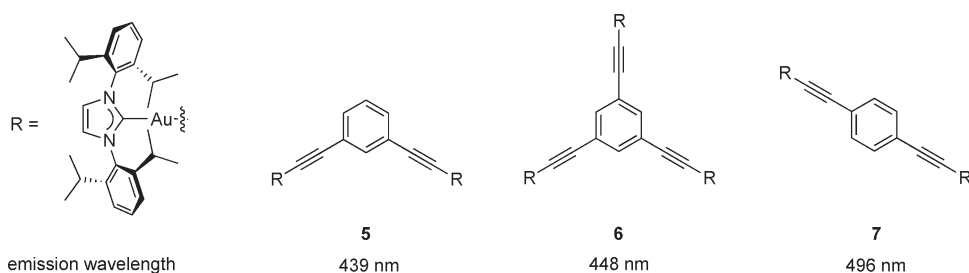
Keeping in mind this *estimated* value, we began to examine some applications employing the Brønsted basic character of **2** in organometallic chemistry. Complex **2** was therefore reacted with substrates bearing proton having  $pK_a$  values lower than this 29–31 range. Substrates such as phenylacetylene ( $pK_a = 28.7$ )<sup>23</sup> and dimethylmalonate ( $pK_a = 16.4$ )<sup>23</sup> lead to, respectively, complexes **3** and **4** in high yields and produced water as sole byproduct (eqs 3 and 4).



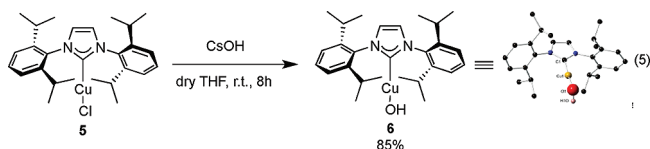
At this point, this methodology was found very interesting in terms of green chemistry because the reaction is quite atom economical and the only byproduct is water. Furthermore, no heat is required to perform the reaction, which can be carried out in technical grade solvents under air. One caveat to this simple protocol is the required exclusion of acidic impurities in these technical grade solvents, which can react with the basic Au–OH bond and poison the desired reaction. Additionally, depending of the  $pK_a$  value of the proton, O–H, N–H, and S–H bonds can also be activated.

Because we are also interested in copper chemistry, the translation of this gold chemistry to copper was obvious. The synthesis of [Cu(OH)(IPr)] (**6**) was attempted and successfully achieved using [CuCl(IPr)] (**5**) in the presence of CsOH in dry

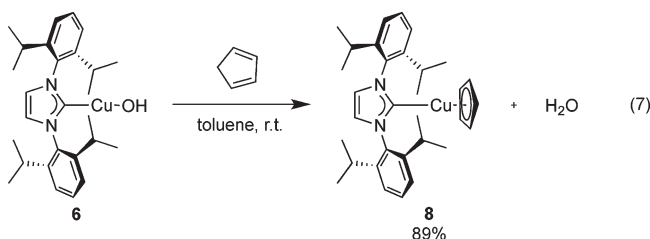
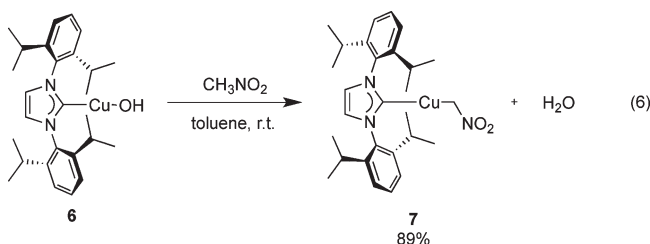
SCHEME 2. Emission Wavelengths of Selected Poly-(IPr)gold(I) Arylacetylide Complexes



and degassed THF (eq 5).<sup>24</sup> The synthesis of **6** is even more attractive because the precursor **5** can be isolated in a one-pot reaction as recently disclosed by Cazin.<sup>25</sup>



Interestingly, in addition to fluoroarene, malonate, and terminal alkyne derivative C–H bond activation, **6** revealed to be basic enough to deprotonate nitromethane and cyclopentadiene, yielding, respectively, complexes **7** and **8** in 89% isolated yield (for both) (eqs 6 and 7).

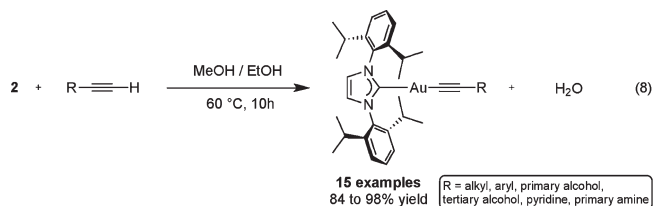


Here again, the C–H bonds are not the only ones that can be activated by complex **6**, P–H, O–H, N–H, S–H, and Mo–H bonds have also revealed reactivity.

Once these two preliminary studies were completed, we realized that the simple methodology involving acid–base reactions by the “inner-sphere” mechanism defined by Sanford (Scheme 1) would yield numerous opportunities.<sup>5a</sup> Indeed, this exploration had just begun, yet we felt it held an intriguing and exciting potential.

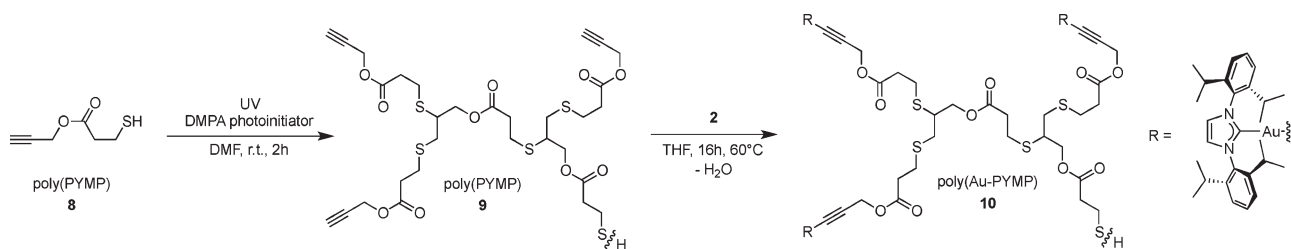
## C–H Bond Activation of Terminal Alkynes

Taking advantage of the easy procedure of our C–H activation of phenylacetylene furnishing **3** under very mild conditions (eq 3), we turned our attention to gold acetylide derivatives and their applications, especially in photoluminescence.<sup>26</sup> Indeed, a series of (NHC)gold(I) acetylide complexes<sup>27</sup> was readily prepared by simply mixing **2** with terminal alkynes affording 15 complexes in excellent yields ranging from 84% to 98% (eq 8).



Noteworthy, unprotected propargylic alcohols and amines were compatible in these reaction conditions. The functionalization of several terminal alkyne frameworks bearing alkyl or aryl fragments was also successfully achieved. A selection of three complexes was synthesized with the aim to examine their absorption and emission spectra. These compounds exhibited emission wavelengths in the blue-green and blue regions of the visible spectrum that are of interest (Scheme 2).

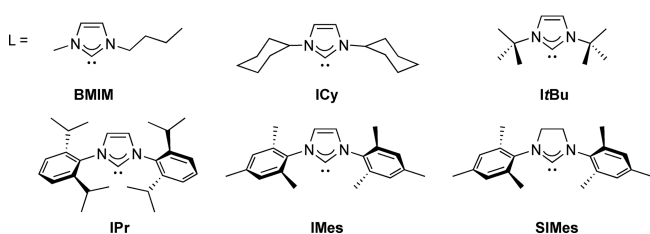
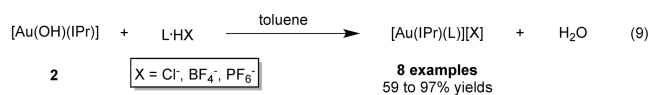
While these studies were being carried out, the group of Perrier published the synthesis of a hyper-branched polymer called polyPYMP (PYMP = prop-2-ynyl-3-mercaptopropionate) by a simple thiol–yne reaction.<sup>28</sup> Such a polymer could offer numerous potential anchoring points for gold centers if a simple method to charge the gold were available. The aim of such a procedure would be to potentially increase the chance of multiple “aurophilic”<sup>26c,29</sup> interactions in the polymer structure that could confer interesting photoluminescent properties to this organometallic material. This idea led to a collaboration between our groups and culminated in a joint report on the reaction between **2** and polyPYMP **9** affording quantitatively a new organometallic polymer named poly(Au-PYMP) **10** incorporating multiple gold atoms (Scheme 3).<sup>30</sup>

**SCHEME 3.** Synthesis of Poly(Au-PYMP) **10** by C–H Bond Activation of the Poly(PYMP) **9** by **2**

The absorption and emission of this new poly(Au-PYMP) **10** material was measured. Solution of **10** in chloroform, irradiated at 365 nm showed blue-violet luminescence with the emission spectrum showing two distinct bands at 382 nm in the UV region and 402 nm in the visible region.

### C–H Bond Activation of Heterocyclic Derivatives

The journey continues with the C–H bond activation of heterocyclic derivatives. Because fluoroarenes were easily deprotonated by **2** and **6**, the evolution of this reaction to include heterocyclic derivatives was also envisaged. In parallel with the C–H functionalization of terminal alkynes, we began the exploration of the C–H activation of heterocyclic compounds bearing an acidic proton with a compatible  $pK_a$  value, with [Au(OH)(NHC)] and [Cu(OH)(NHC)] complexes. We initially investigated the reactivity of imidazolium salts aiming to form cationic bis(NHC)gold(I) complexes having two different NHCs on the metal center. Indeed, the usual syntheses of bis(NHC)gold(I) complexes are performed by transmetalation<sup>31</sup> from the corresponding silver(I) complexes or by substitution<sup>32</sup> of AuCl(DMS) (DMS = dimethylsulfide) using 2 equiv of the free NHC. So, the strategy was to have an NHC already on the gold center and then to exchange the halide atom by a hydroxide ligand for the deprotonation of another imidazolium salt. This was again successfully achieved affording a series of cationic bis(NHC)gold(I) complexes with good to excellent yield (eq 9).<sup>14f</sup>

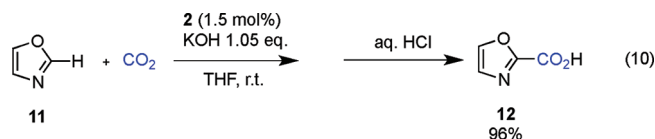


Here, limitation to the reaction scope can be explained by the steric hindrance brought about by the N-substituents of the NHC. Indeed, a complete structural study on these complexes has been performed showing that the percent buried volume<sup>33</sup> ( $\%V_{\text{Bur}}$ ), using the SambVca method developed by Cavallo and co-workers,<sup>34</sup> associated with the two NHCs around gold can reach a maximum of 81.3%, and this corresponds to the most sterically encumbered coordination sphere, a complex obtained with the lowest yield (59%). Interestingly, phosphonium salts can also be deprotonated by **2** to afford heteroleptic cationic phosphine–NHC gold(I) complexes. This procedure circumvents the use of air-sensitive trialkylphosphines and makes use of the easily handled phosphonium salts derivatives.

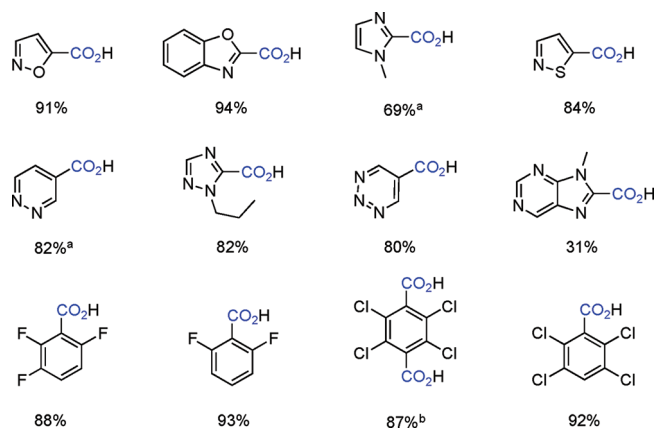
With the invaluable assistance of our biologist and collaborators (Professor Andrew Riches and his group), we explored a worthwhile application of these complexes obtained by simple C–H bond activation/metalation. Indeed, inspired by the biological study of Berners-Price, Filipovska, and co-workers,<sup>32c,35</sup> our cationic bis(NHC)gold(I) complexes were subjected to biological testing. A series of eight cationic bis(NHC)gold(I) complexes were found efficient for the mitochondrial apoptosis of a prostate carcinoma cell line (LNCaP) and a breast carcinoma cell line (MDA MB231).<sup>36</sup> Noteworthy, complex **2** has shown a slightly lower activity than the cationic bisNHCgold(I) complexes, but complex **2** still possesses a lower  $\text{IC}_{50}$  value than cisplatin for the two cell lines cited above. With the highlighted specific basic properties of **2**, questions about the exact nature of the gold entity exhibiting anticancer activity and the mechanism of action are presently being addressed in St Andrews.

After our preliminary results on the C–H bond activation of heterocyclic and aromatic compounds by **2** and **6**, we thought that a small molecule such as  $\text{CO}_2$  could be inserted in the metal–carbon bond, and we turned our attention to carboxylation reaction of aromatic derivatives. We demonstrated that reaction performed with oxazole **11** in the presence of 1.5 mol % of **2**, 1.05 equiv of KOH, and 1.5 bar pressure of carbon dioxide led to the carboxylated

product **12** with 96% yield after a postcatalytic protonolytic treatment (eq 10).<sup>37</sup>



During the course of this study, we synthesized other (NHC)gold(I) hydroxides and performed titration experiments to determine precisely the  $pK_a$  value of our complexes in DMSO. The experimental measurement for **2** revealed a  $pK_a$  value of 30.3 units (between 29 and 31 had previously been estimated from reaction chemistry, see above). The scope of the reaction was extended to several aromatic heterocycles and fluoroarenes with yields up to 96%. Noteworthy, the higher basicity of [Au(OH)(*ItBu*)] (**13**) (*ItBu* = 1,3-*di-tert*-butylimidazol-2-ylidene) permitted the extension of the reaction scope to less reactive compounds (when complex **2** was used) such as pyridazine, 1-methylbenzimidazole, and 1-methylimidazole (Figure 1).

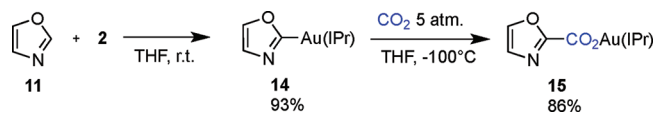


**FIGURE 1.** Selected examples of carboxylated products obtained by [Au(OH)(NHC)] catalysis. (a) Reaction performed with [Au(OH)(*ItBu*)] **13**. (b) Reaction performed with 2 equiv of KOH.

The mechanism of the carboxylation reaction involving aromatic heterocycles is supported by stoichiometric reactions involving well-defined Au–C complexes. The (NHC)gold(I) complex **14** bearing oxazole was prepared from **2** and oxazole **11** and then subjected to 5 bar of carbon dioxide affording complex **15** (Scheme 4).

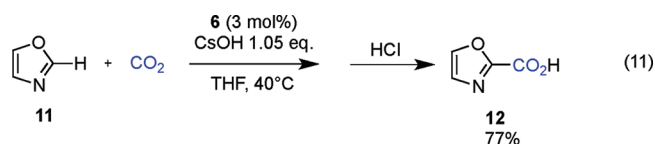
The two (NHC)gold(I) complexes **14** and **15** have shown high catalytic activities for the carboxylation of **11** both giving **12** in high yield confirming their role in the catalytic cycle. Noteworthy, higher turnover frequencies can be achieved at lower temperature, which is simply explained by an improved solubility of carbon dioxide at lower

**SCHEME 4.** Isolation of Intermediate of the C–H Bond Carboxylation of Aromatic Derivatives



temperatures. The insertion of carbon dioxide into the Au–C bond appears rate-limiting in the catalytic cycle. Interestingly, recycling of catalyst **2** was achieved six consecutive times with high retention of the catalytic activity giving a cumulative turnover number of 78.

Moving to copper chemistry, carboxylation of organoboronic esters catalyzed by (NHC)copper complexes was initially reported by Hou,<sup>38</sup> and DFT studies on the mechanism by Lin, Marder, and co-workers<sup>39</sup> demonstrated that an arylcopper(I) complex was an intermediate in the catalytic cycle. Because we demonstrated that the analogous organogold(I) complex was an intermediate in this carboxylation reaction and because we and the Cazin group were interested in copper chemistry, we examined whether the (NHC)gold(I) hydroxide chemistry could also be performed by an (NHC)copper(I) congener.<sup>40</sup> In this study, [Cu(Cl)(IPr)] **5** could be employed as catalyst. Nevertheless, an induction time of 200 min to form the active species [Cu(OH)(IPr)] **6** was required. Importantly, the  $pK_a$  associated with **6** was determined to be 27.7, which is 2.6  $pK_a$  units less than that of the analogous gold(I) and therefore slightly diminishes the number of compatible substrates. The reaction can be performed with 3 mol % of **6** in the presence of CsOH. The carboxylate salt formed during the reaction was isolated as a carboxylic acid **12** by quenching the salt with aqueous solution of HCl (eq 11).

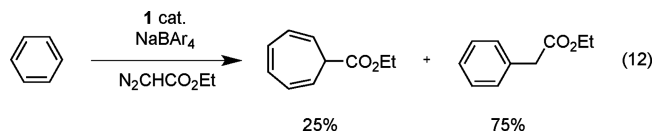


In addition to the C–H bond carboxylation of aromatic substrates, we also demonstrated that the N–H carboxylation of *N*-heterocycles was also possible and their carboxylate salts could be quenched with iodomethane affording the corresponding methyl ester.

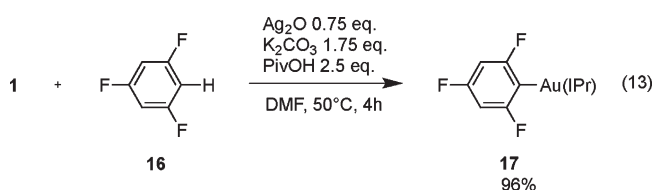
The carboxylation reaction study with copper(I) catalyst **6** presents the advantage of low cost but due to its sensitivity to oxygen, its handling and recyclability are more difficult than demonstrated with its (NHC)gold(I) congener **2**. Moreover, complex **6**, because of its lower basicity, reacts with less acidic substrates than **2**.

## Outlook

The chemistry developed in the above-mentioned studies was based on simple Brønsted acid–base principles. Nevertheless, C–H bond activation can also occur through the “outer sphere pathway” with gold catalysis. An example of this was reported in the course of a study dealing with carbene insertion chemistry in 2005 (eq 12).<sup>20,41</sup> We expect more of this type of reactivity to emerge because numerous gold– and copper–NHC complexes are now commercially available.<sup>42</sup>

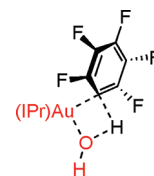


Returning to the “inner sphere” pathway,  $pK_a$  measurements of complexes **2** and **6** have permitted us to predict the limitation of the reaction scope in terms of the nature of the C–H bond acting in carboxylation and C–H bond activation/metalation. In this context and with this information in hand, we were amazed by a report from the Larrosa group<sup>43</sup> describing the synthesis of phosphine–gold(I) fluoroarene complexes. In this work, one particular example attracted our attention. Indeed, the authors succeeded in activating the C–H bond of the 1,3,5-trifluorobenzene (**16**) ( $pK_a = 31.5$ ) using complex **1** affording the aryl–IPr–gold(I) complex **17** under the somewhat involved conditions depicted in eq 13.



The authors proposed a mechanism for the reaction occurring via two different pathways: (i) a concerted metalation/deprotonation where pivalate ligand acts as a proton acceptor via a six-member transition state; (ii) an oxidative addition mechanism where a transient gold(III) hydride species is formed. Using our more defined system, the second pathway can be excluded, and a concerted deprotonation involving a four-membered transition state is, we believe, more likely (Figure 2).

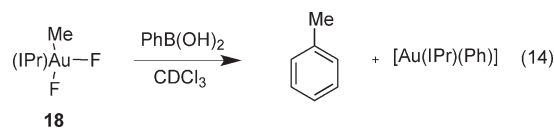
If an intermediate of form  $[\text{Au}(\text{OPiv})(\text{IPr})]$  is considered for the reaction reported in the Larrosa study, (formation of this intermediate is compatible with his reaction conditions), the reaction should follow the same pathway using the pivalate as ligand as a reaction using **2**. The difference of reactivity



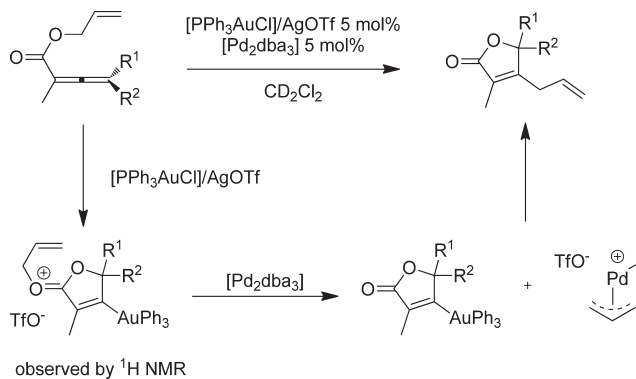
**FIGURE 2.** Transition state proposed for the C–H bond activation involving **2**.

between the procedure reported by Larrosa *et al.* and ours can be explained first by the basic character of the anionic ligand. Nevertheless, another possible reason for this difference in reactivity could be the nature of the solvent, which could slightly change the acidity of the aromatic proton. The last and the most interesting reason could come from the presence of  $\text{Ag}_2\text{O}$ , which we believe acts as a  $\pi$ -system activator of the aromatic ring. Indeed,  $\text{Ag}_2\text{O}$  is well-known to be used in electrophilic substitution of aromatic rings.<sup>44</sup> This activation could diminish the  $pK_a$  of the aromatic proton, which could react with the basic pivalate ligand.<sup>45</sup> This is an important result, and the Larrosa work, although not completely clear mechanistically, raises hope that the range of C–H bonds possibly activated by the gold systems could reach higher  $pK_a$  values by use of additives. Finally, a hopefully enlarged reaction scope could also come by modulation of the NHC ligands.

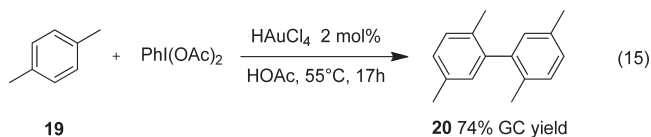
The studies discussed above in the context of C–H bond activation of aromatic derivatives with the isolation of stable organogold(I) and organocopper(I) complexes are of interest in view of already reported coupling reactions.<sup>46</sup> The mechanisms proposed for several C–H bond activation reactions combined with coupling reactions catalyzed by gold or copper complexes involve the  $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ <sup>12c,44</sup> or  $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$  redox couples.<sup>12e</sup> This was recently very nicely demonstrated by Toste and Mankad who showed that the methylgold(III)–NHC difluoride (**18**) is an efficient mediator of C–C bond formation in the presence of boronic acid (eq 14).<sup>47</sup>



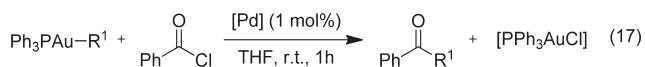
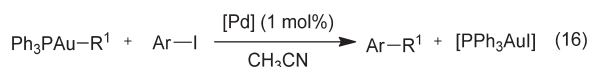
Noteworthy, the authors informed the readers that the two key factors to observe intermediate in this reaction are the use of NHC as ancillary ligand and fluoride as halide for the anionic ligands. An oxidant is most often needed to oxidize the metal center in these instances, and the reaction takes advantage of the different substrate affinity and reactivity as a function of the metal oxidation state. One example

**SCHEME 5.** Proposed Mechanism by Shi for the Dual Gold–Palladium Catalysis

illustrating the need for an oxidant for C–H bond functionalization is the direct oxidative coupling of nonactivated arenes catalyzed by  $\text{HAuCl}_4$  in presence of  $\text{PhI}(\text{OAc})_2$  (eq 15).<sup>48</sup>



An interesting alternative in cross coupling reactions will be the use of other transition metal reagents in a transmetalation step instead of the use of an oxidant for the oxidation of the gold center. Indeed, stoichiometric amounts of organogold(I) can react with organic electrophile in the presence of a catalytic amount of palladium(0) complexes (eq 16 and 17).<sup>49</sup>



With combination of the metalation step to generate an organogold complex and use of palladium in a separate transmetalation step, cooperative catalysis involving gold and other transition metals such as palladium could be successfully achieved. Indeed, Blum and co-workers have reported a cooperative catalysis using an allyl allenolate with a catalytic amount of both gold and palladium (Scheme 5).<sup>50</sup>

These studies and proofs-of-concept about the “coupling reaction” combined with our studies on metalation of organic derivatives by protonolysis with our  $[\text{AuOH}(\text{NHC})]$  or  $[\text{CuOH}(\text{NHC})]$  permit one to envisage a variety of partners for new coupling reactions. Finally, we feel confident that the

potential of this chemistry and of these catalyst precursors has not yet been realized.

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