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ROYAL SOCIETY OF CHEMISTRY

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DOI: 10.1039/C7CC06065C

Journal Name

ARTICLE

Received 00th January 20xx,

An ambiphilic phosphine/H-bond donor ligand and its application to the gold mediated cyclization of propargylamides

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We describe the synthesis of an ambiphilic phosphine/H-bond donor ligand featuring a trifluoroacetamide functionality, its coordination to gold(I) chloride, and its application as a self-activating catalyst for the cyclization of propargylamides.

Access to electrophilic transition metal catalysts is typically achieved through the use of a Lewis acid that activates the metal centre by abstraction of an anionic ligand.[1] This strategy has been applied to diverse areas including olefin polymerization catalysis where the role of the Lewis acids is usually fulfilled by strongly Lewis acidic fluorinated boranes.[1-2] The same principles apply to electrophilic late transition metal catalysts which are typically activated by abstraction of a halide anion using a silver salt.[3] While the exposed nature of the resulting cationic transition metal center is usually desired for high catalytic activity, it can also be a source of instability and a conduit for catalyst decomposition, especially in the case of late transition metals that are prone to reduction.[4] For this reason, alternative activation methods are being actively pursued, for example with the use of milder Lewis acids.[5] It has also been argued that improved catalyst stability could derive from the presence of an ancillary Lewis acidic site positioned within the ligand architecture.[6] This idea, combined with recent advances in the field of anion-pairing organocatalysis using hydrogen-bond donor systems,[7] has led us to question whether an intramolecular hydrogen-bond donor functionality could also be used to activate an organometallic catalyst via interaction with a metal-bound anionic ligand.

To explore this possibility, we decided to first synthesize an ambiphilic ligand in which the role of the acidic functionality is fulfilled by a hydrogen bond donor group. Reaction of *o*-lithiotrifluoroacetanilide with Ph_2PCl followed by acidic work up produced *o*-(diphenylphosphino)trifluoroacetanilide (**1**) as a pale yellow solid. The ligand (**1**) was characterized by ^{1}H, ^{19}F and ^{31}P NMR spectroscopy and also by ESI^{-}/MS. Salient spectroscopic features include a ^{1}H NMR resonance at 8.81 ppm corresponding to the the amide hydrogen atom and a ^{31}P NMR resonance at -21.9 ppm. The trifluoroacetamide functionality also gives rise to a ^{19}F NMR signal at -76.1 ppm.

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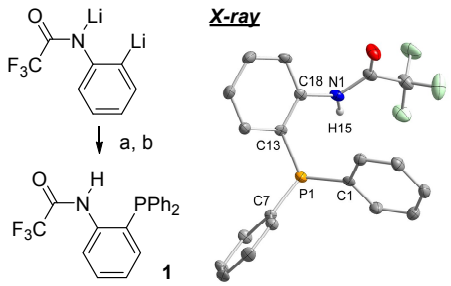
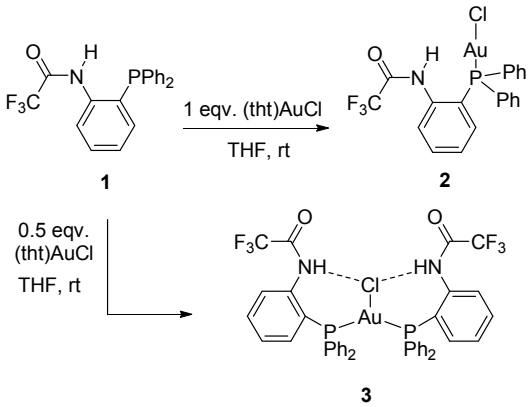
† Electronic Supplementary Information (ESI) available: General experimental details and characterization data for all the reported complexes are included in the ESI. CCDC 1566425- 1566427 contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center.

The structure of **1** was also confirmed by X-ray analysis which revealed that the N-H hydrogen atom is not interacting with the phosphorus atom.



Scheme 1. Left: Synthesis of **1**. (a) 1. nBuLi, 2. 2 eqv. *t*BuLi., 3.Ph_2PCl, (b) HCl (1M in Et_2O) in THF at -78° C. Right: Crystal structure of **1**.

Reaction of **1** with one equivalent of (tht)AuCl (tht = tetrahydrothiophene) in THF at room temperature afforded **2** as a light-sensitive white solid. A peak at 22.2 ppm in the ^{31}P NMR spectrum, downfield to the peak corresponding to the free ligand, confirmed the formation of the gold(I) complex. The ^{1}H NMR resonance corresponding to the N-*H* is observed as a broad singlet at 8.54 ppm. The structure of **2** indicates



Scheme 2. Synthesis of **2** and **3.**

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that the complex exists as a dimer held by an aurophilic interaction of 2.997(7) Å.[8] The dimer also benefits from two hydrogen-bonds connecting the N-*H* proton of one molecule to the chlorine atom of the other one. The presence of these hydrogen bonds is supported by N-H•••Cl hydrogen bonds as confirmed by the Cl1-N1 and Cl1-N1 separations of 3.199(8) Å and 3.164(8) Å which fall in the expected range.[9] The structure of **2** shows no evidence for a hydrogen-bonding interaction involving the gold atom.[10]

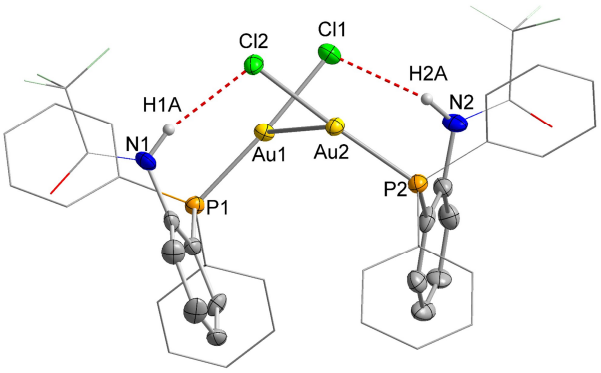

Figure 1. Crystal structure of **2**. Displacement ellipsoids are scaled to the 50% probability level. All the hydrogen atoms except the amide hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (deg) for **2**: Au1-Au2 2.9976(7), Au1-Cl1 2.314(2), Au2-Cl2 2.316(2), N1-H1A 0.8800, N2-H2A 0.8800, H1A---Cl2 2.3802(22), H2A---Cl1 2.4050(24); P1-Au-Cl1 171.93(8), P2-Au2-Cl2 172.94(7).

Next, we decided to investigate the molecularity of **2** in solution using the pulse gradient spin-echo (PGSE) NMR method, which has proved to be well adapted for organometallic compound molecular size determination.[11] PGSE measurements were carried out using a solution of **2** in CD_2Cl_2 and its diffusion was compared to that obtained with 1,3,5-tri-tert-butylbenzene (**A**), a molecule that we used as an internal standard. This molecule was chosen because of its apolar nature and inertness toward **2**. Its molecular size ($V_{X\text{-}ray}$(**A**) = 454 Å^3)[12] is also close to that of monomeric **2** ($V_{X\text{-}ray}$(**2**) = 504 Å^3). A quantitative treatment of the diffusion data obtained with a 36 mM solution of **2** in CD_2Cl_2 afforded a molecular volume of V_{PGSE}(**2**, 36 mM) = 865 Å^3. This value, which is higher than the value of $V_{X\text{-}ray}$(**2**) = 504 Å^3 but smaller than that of the dimer (1008 Å^3) was taken as an indication that the gold complex undergoes a monomer-dimer equilibrium in solution. To confirm this hypothesis, the same PGSE measurement was repeated after a three-fold and nine-fold dilution of the sample. These measurements afforded V_{PGSE}(**2**, 12 mM) = 747 Å^3 and V_{PGSE}(**2**, 4 mM) = 648 Å^3. The observed volume decrease is consistent with increasing dissociation of the dimer upon dilution, thus supporting the hypothesis that **2** is indeed in a monomer-dimer equilibrium. The PGSE data could also be fitted to this monomer-dimer equilibrium, affording an association constant *K* of 1020(±100) M^{-1} (see SI). We also found that solutions of compound **2** in CH_2Cl_2 are non-conducting, thus ruling out the possibility of an equilibrium involving the formation of $[L_2Au]^+[AuCl_2]^-$ as a salt (See SI). Finally, VT ^{31}P NMR spectroscopy shows that the chemical shift of **2** (12 mM) in CD_2Cl_2 shows only a downfield shift of 0.8 ppm upon elevation of the temperature from -30°C to 50°C. We interpret these last results as an indication that the nuclearity of the complex has little impact on the ^{31}P NMR chemical shift.

We also tested the 2:1 reaction of **1** and (tht)AuCl. This reaction affords the corresponding bis(phosphine) complex **3** (Scheme 2). Complex **3** gives rise to a broad ^{31}P NMR resonance at 35.78 ppm. In the ^{1}H NMR spectrum, the N-*H* proton resonates at 10.55 ppm, indicating its involvement in a hydrogen-bonding interaction. The solid state structure of **3** confirms the formation of the expected complex. The gold center adopts a trigonal planar geometry. The short contact between the amide nitrogen atoms and the gold-bound chlorine atom (Cl2-N1 = 3.224(5) Å and Cl1-N2 = 3.197(5) Å) are consistent with the presence of N-H•••Cl interactions. A further evidence for the presence of this interaction comes from the Au-Cl bond distance of 2.6614(14) Å which is significantly longer than that in $(PPh_3)_2AuCl$ (2.526(10) Å).[13] It is also interesting to note that, as a result of this hydrogen bonding motif, the P1-Au-P2 angle in **3** (144.95(5)°) is significantly wider than that in $(PPh_3)_2AuCl$ (136.4(3)°).[13] Complex **3** did not show any luminescence at room temperature or at 77 K when irradiated with a hand-held UV lamp.

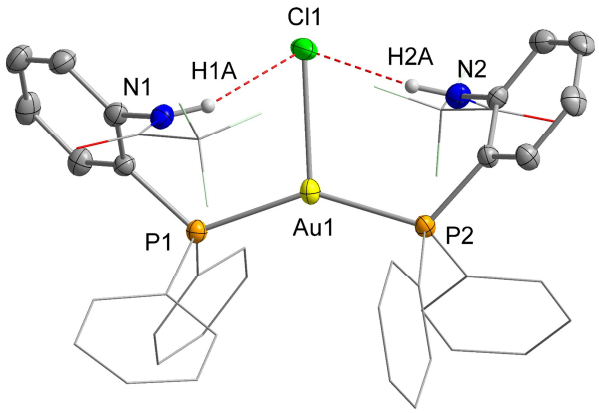

Figure 2. Crystal structure of **3**. Displacement ellipsoids are scaled to the 50% probability level. All the hydrogen atoms except the amide hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (deg) for **2**: Au1-Cl1 2.6614(14), N1-H1A 0.8800, N2-H2A 0.8800, P1-Au-P2 144.90(5), Cl1-A12-P2 108.32(5), Cl1-A12-P2 106.74(5).

Given the demonstrated ability of the trifluoroacetamide functionality to form a hydrogen bond with a gold-bound chloride anion, we questioned whether such an interaction would be sufficiently strong to render the gold center of these complexes catalytically active. With this in mind, we decided to investigate the catalytic activity of **2** and **3** in the cycloisomerization of propargylamides, without addition of a silver activating agent. Initially , both complexes were tested at

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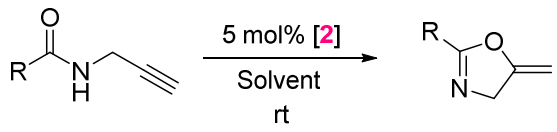
room temperature in $CDCl_3$ using *N*-(prop-2-yn-1-yl)benzamide as a substrate. While no cyclisation was observed when **3** was employed as a catalyst, ^{1}H NMR and gas chromatography monitoring showed smooth conversion when **2** was added to the reaction. In all cases, the reactions were accompanied by the slow production of purple gold particles, raising doubt about the nature of the catalytically active species. For this reason, we decided to use a different solvent. We found that **2** is stable in dichloromethane, with no sign of decomposition after 24h as confirmed by visual inspection of the solution and ^{31}P NMR spectroscopy. The catalysis in dichloromethane was monitored by GC and the results are compiled in Table 1. Formation of only one isomer of the cyclized oxazole was observed consistent with the presence of a reactive gold(I) catalytic center.[14] A comparison of the percentage conversion of the different starting materials after 24 h, revealed that the reaction occurs faster in the case of electron rich *N*-(prop-2-yn-1-yl)-4-methoxybenzamide in line with the amide functionality acting as the nucleophile toward the activated alkyne. In the case of *N*-(prop-2-yn-1-yl)-2-methylbenzamide, the relatively slow progress of the reaction can be attributed to the steric hindrance resulting from the *o*-Me group.



Scheme 3. Catalytic cyclization of propargylic amides by **2**.

Table 1. Catalytic conversion of the propargylic amides by 2 (5 mol%) in CH_2Cl_2 monitored by GC

R	Solvent	Time (h)	Conversion (%) by GC
Ph	CH_2Cl_2	24	36
o-Tolyl	CH_2Cl_2	24	35
p-F-C_6H_4	CH_2Cl_2	24	37
p-OMe-C_6H_4	CH_2Cl_2	24	53

To understand if the presence of an intramolecular hydrogen bond donor group is a prerequisite for catalysis, we also tested the cyclisation of *N*-(prop-2-yn-1-yl)benzamide using $PhNHCOCF_3$ and PPh_3AuCl but observed no cyclization products even after 48 hours using CD_2Cl_2 or $CDCl_3$ as a solvent. This experiment shows that the presence of a trifluoroacetamide functionality within the catalyst structure is essential for activity. The lack of activity noted in the case of **3** shows that coordination of a second phosphine ligand to the gold center is also incompatible with substrate activation as previously described.[6e] The same explanation may be invoked to rationalize the fact that no reaction is observed when the reactions are carried out in donor solvents such as MeCN and THF. These donor solvent may coordinate to the activated gold center therefore preventing substrate activation. Finally, we note that, while catalysis is observed, the activity is moderate. We also failed to observe any activity in the hydroamination of phenylacetylene with *p*-toluidine or in the cyclization of dimethyl 2-allyl-2-(2-propynyl)malonate.

In summary, we describe a phosphine gold chloride complex which acts as a self-activating catalyst for the cyclization of propargylamide. Although the activity of the catalyst is low, our results provide proof-of-concept evidence that the self-activating nature of the catalyst originates from the presence of a hydrogen bond donor group which activates the gold atom, presumably by interaction with the chloride anion. While the results are compelling, we have not yet been able to ascertain the nuclearity of the catalyst which we presume could be either monomeric or dimeric as suggested by the solid state structure and the PGSE studies. We are currently working on clarifying this point through mechanistic and kinetic analyses.

Acknowledgements

This work was supported by the National Science Foundation (CHE-1566474), the Welch Foundation (A-1423), and Texas A&M University (Arthur E. Martell Chair of Chemistry). We thank Ms. Chia-Hsiu Chen for her assistance with the PGSE measurements. We are grateful to Prof. Christian Hilty for his invaluable suggestions and for allowing us to use his NMR facilities.

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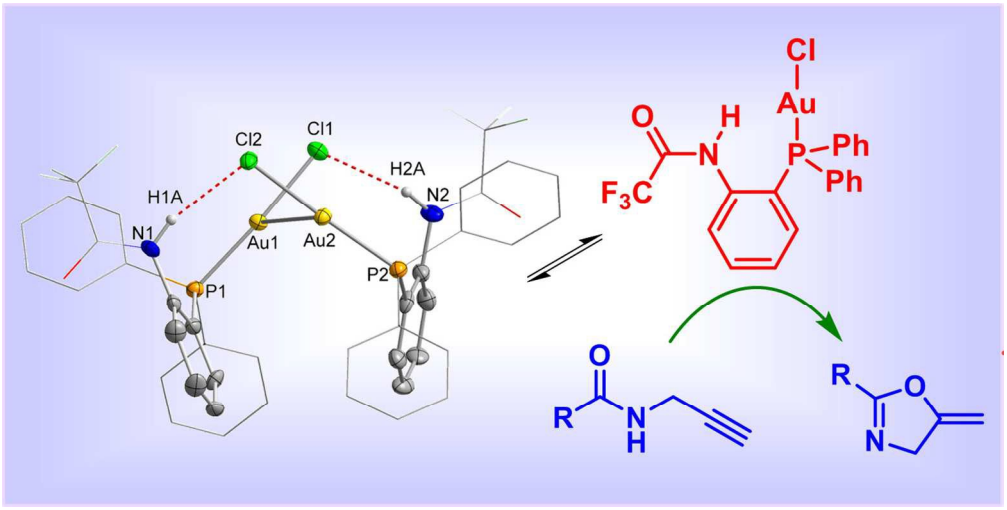

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