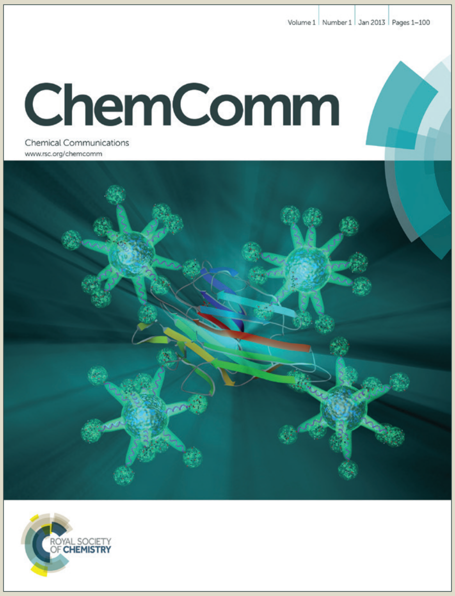

Anomalous ligand effect in gold(I)-catalyzed intramolecular hydroamination of alkynes†

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We analyzed the ligand electronic effect in a gold(I)-catalyzed intramolecular alkyne hydroamination, through a DFT and Charge-Displacement Function (CDF) study. We found that, in the presence of π-electron conjugation between the alkyne and the nucleophilic functionality, electron poor ligands modify the coordination mode and the geometric parameters of the substrate in such a way that, contrary to expectations, the activation barrier of the nucleophilic attack increases. This remarkable effect is due to the competition between alkyne activation and nucleophile deactivation. The general relevance of these findings is highlighted.

Homogeneous catalysis based on gold(I) linear complexes of formula [**L**-Au-**S**]$^{0/+}$ (**L**=auxiliary ligand, **S**=Substrate) has undergone a rapid development in the last decade.[1] One of the most important factors for the optimization of the catalytic performance is obviously the ligand **L**: its choice can be crucial in tuning catalytic activity[2] because it can control the electronic properties of the metallic fragment,[3–5] the anion/cation relative orientation[6] and the outcome of a reaction (including the stereo-regiochemistry).[7,8] The reliable rationalization of ligand effects is therefore crucial for the design *a priori* of new efficient catalysts, but a fully satisfactory understanding is still unattained and, indeed, the development of new catalysts is still mainly based on a trial-and-error procedure.[9] Recently, a few works have tried to rationalize the ligand effect.[10,11] Wang et al.,[11] have found that, when the electronic activation of the unsaturated substrate is the rate determining step (RDS), stronger electron-withdrawing ligands favor the reaction, while the opposite is true when protodeauration is the RDS. A notable example of successful ligand design based on this paradigma is in the recent works by Alcarazo et al., where various cationic ligands have been synthesized[7,12] to increase the electron-withdrawing ability (acidity) of the metal fragment and so to enhance its capacity to activate π systems.

A very helpful way to theoretically quantify the acidity of the [**L**Au]$^+$ fragment, and thus to analyze substrate activation/reactivity correlation, is to use the Charge Displacement Function (CDF) approach,[13] which provides a quantitative picture of the charge transfer between an unsaturated substrate and a metal fragment. The CDF analysis was introduced to study the chemical bond between gold(I) and the noble gases,[13] and subsequently used in several contexts, including excited states[14] and coordination chemistry.[3,5,15,16] We report here a detailed CDF analysis of the electronic effect of the ligand on the gold-catalyzed intramolecular hydroamination of alkynes.[17–20] The reaction we studied is the cyclization of the N,N-dimethyl-2-(methylethynyl)aniline (**S**, see Fig.1a). The reaction mechanism is very simple and seems particularly suitable to selectively study the electronic effect of the ligand on the nucleophilic attack step. The mechanism starts with the coordination of the metal fragment ([**L**Au]$^+$ in Fig.1a) to the triple bond of **S**. Subsequently, the nucleophilic nitrogen attacks the C_2 carbon, leading directly to the product (**P**). Since the reaction proceeds through an *anti*-periplanar attack,[18,21,22] the steric properties of **L** (Figure 1) are expected not to influence the barrier of the attack. Moreover, the presence of two methyl groups prevents the protodeauration step,[18] making this a suitable reaction to study the electronic ligand effect also by experimental investigations.

We started our analysis by optimizing the geometry of the [**L**Au-**S**]$^{0/+}$ complex (Reactant Complex, **RC**), with **L** covering a wide range of ligands (Fig.1b), from strongly electron-withdrawing (such as the dicationic phosphine ACPP[7]) to electron-donating ones (such as the anionic ligands).[23] Geometry optimizations have been performed using Density Functional Theory (DFT) with a TZ2P basis set for all atoms and the BP86 functional.[24] Energies have then been computed at the optimized geometries with the B2PLYP functional.[25] Recent benchmark studies show that this procedure yields accurate geometries and energies of typical intermediates in gold(I)-catalyzed reactions.[26] All computational details, including optimized structures, are given in the ESI.†

Our first noteworthy finding is that the alkyne coordination

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† Electronic Supplementary Information (ESI) available: computational details, additional Figures, Tables and coordinates of all the optimized complexes . See DOI: 10.1039/b000000x/

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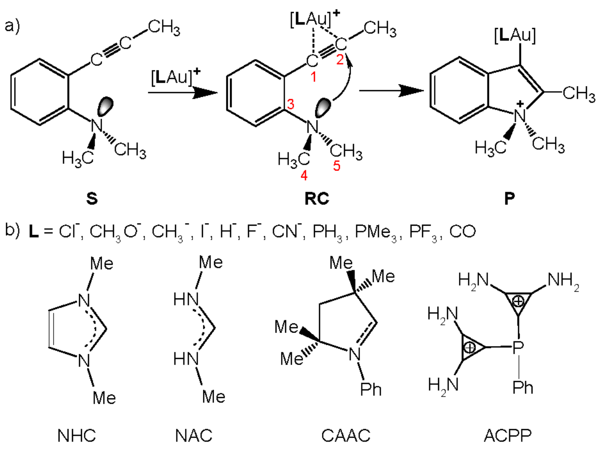

Fig. 1 a) Schematic representation of the studied reaction leading from the substrate (**S**) to the product (**P**). b) List of the investigated ligands. For the NHC, NAC, CAAC and ACPP ligands, a graphical representation is also shown.

arrangement in the RC varies for different ligands. Fig. 2a shows for example that the coordination is η^2 for ClAuS, it is non-symmetric (with a slippage of the metal towards C_2) for (NAC)AuS and it is η^1 for (CO)AuS. The slippage of coordination mode in metal-alkyne complexes is typically much less pronounced than we found here.[27] Recent studies did find 'slipped' coordination modes in some cationic gold(I) enol ether[27,28] or enamine complexes.[29] However, the strong dependence we find here of the coordination mode on the ancillary ligand is surprising and, to our knowledge, has not been evidenced before.

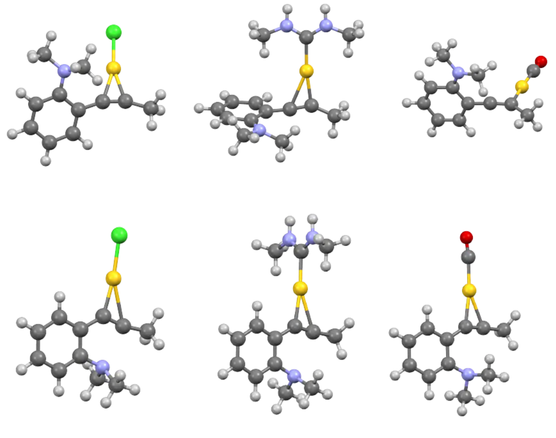

Fig. 2 Structure of a) Reactant Complex RC (LAuS_RC) and of b) Transition State TS (LAuS_TS) for three ligands (**L** = Cl^-, NAC and CO).

Table 1 Some relevant geometrical parameters of the substrate: C_1C_2-Au angle, C_1C_2 and NC_3 bond lengths and $NC_3C_4C_5$ dihedral angle. Angles are in degrees, distance in Å.

Ligand	C_1C_2Au	C_1C_2	NC_3	$NC_3C_4C_5$
NO CAT	–	1.217	1.404	157.2
CH_3O^-	75.2 (η^2)	1.262	1.400	157.5
F^-	75.2 (η^2)	1.261	1.397	158.1
Cl^-	76.1 (η^2)	1.257	1.396	159.0
I^-	76.9 (η^2)	1.255	1.395	159.0
CN^-	77.5 (η^2)	1.248	1.393	159.6
CH_3^-	78.7 (η^2)	1.244	1.396	159.4
H^-	79.1 (η^2)	1.242	1.394	160.1
CAAC	90.0 (η^2)	1.255	1.371	170.7
NHC	91.1 (η^2)	1.260	1.367	172.1
NAC	91.6 (η^2)	1.260	1.366	172.2
$P(CH_3)_3$	105.3 (η^1)	1.269	1.361	174.3
PH_3	107.0 (η^1)	1.276	1.357	175.4
None (Au^+)	107.5 (η^1)	1.286	1.350	177.0
CO	107.6 (η^1)	1.283	1.353	176.3
PF_3	109.6 (η^1)	1.281	1.354	176.2
ACPP	118.8 (η^1)	1.291	1.347	176.8

Some characteristic geometrical parameters of the complexes are reported in Table 1. The C_1C_2 bond length, which is commonly related to the degree of activation of the alkyne, ranges from 1.217 Å, for the substrate without gold, to 1.291 Å with the highly acidic ACPP ligand. The C_1C_2Au angle varies from about 75° for the anionic ligands (indicating a clear η^2 alkyne coordination) to about 90-110° for the neutral ligands and to 120° for the dicationic ACPP (indicating a η^1 alkyne coordination). The Table also shows that the geometrical variations induced by the ligand reach the distant site of the nucleophile -$N(CH_3)_2$ group. Indeed, the NC_3 bond length is shorter than that of the free substrate and the largest displacements are found for the cationic complexes. The $NC_3C_4C_5$ dihedral angle (Table 1), which is a measure of the nitrogen pyramidality, follows the opposite trend. Finally, the NC_3 bond length correlates well with both the C_1C_2 distance and the $NC_3C_4C_5$ dihedral angle, since it shortens as both the C_1C_2 distance and the $NC_3C_4C_5$ dihedral angle increase (Fig. S1 and S2, respectively, ESI†).

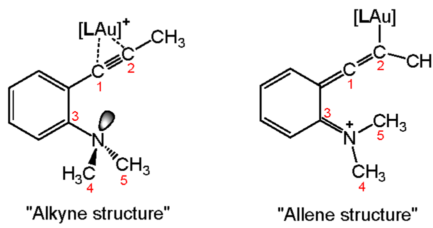

Fig. 3 Two possible limit structures for the substrate-catalyst RC complex.

The above findings indicate that the geometry of these complexes vary along a continuum between two limit structures, which we refer to as the "alkyne" and the "allene" one, respectively, which display different bonding (Fig. 3). The former possesses an alkyne triple bond and a single NC_3 bond, while in the latter an allene bond and a double NC_3 bond with a positively charged sp^2 N atom are present. The alkyne structure is predominant with the anionic ligands, while the allene structure prevails for electron-withdrawing ones. It is noteworthy that cationic gold(I) enamine complexes with phosphine ligands display a highly distorted coordination mode that is consistent with a stable iminium ion structure,[29] such as is found in the allene structure.

What we then set out to investigate is if there is a recognizable quantitative relationship between the varying $[\mathbf{L}Au]^+$ coordination mode we have just discussed and its acidity. For this, we resorted to the CDF approach, which allows us to quantitatively estimate the charge transfer (CT) from the alkyne to the $[\mathbf{L}Au]^+$ fragment (Table S1, ESI†). This is a measure of $[\mathbf{L}Au]^+$ acidity, which, in turn, depends on the electron donating power of **L**. We found, as may be expected, that the anionic ligands induce small CT values (below 0.07 e), whereas the cationic $[(ACPP)Au]^{3+}$ (0.55 e) and Au^+ (0.62 e) reach the highest CT values. As it turns out, a clear quantitative relation exists between the acidity of $[\mathbf{L}Au]^+$ and alkyne coordination mode: CT is directly proportional to the C_1C_2Au angle and inversely proportional to the NC_3 distance (Fig. S3 and Fig. S4, respectively, ESI†).

Our next focus has been to ascertain how ligand acidity and the coordination mode of the metal fragment influence the actual substrate activation, with an eye to verifying if the practical rule mentioned earlier (i.e.: strong electron withdrawing metal fragments favour the nucleophilic attack) holds in this case. We thus computed the activation energies ($\Delta E^\ddagger$) for the nucleophilic attack by transition state calculations for all the considered ligands (Table S1, ESI†), and set this against the $\mathbf{S}\rightarrow$Au CT values. What we found is that the $\Delta E^\ddagger$ vs CT plot (reported in Fig.4 and labeled as '**S**') displays an unexpected "V" shape: the barrier is high when the $[LAu]^+$ acidity is either very low (14.1 kcal/mol for CH_3O^-) or very high (15.9 kcal/mol for ACPP), while it presents a minimum for the carbene and alkyl phosphines (5.3 kcal/mol for CAAC). (The same trend is also found using the BP86 functional.) Interestingly, however, if one considers just the η^2 systems, the trend is the expected one and the barrier decreases when the electron-withdrawing power of **L** (as measured by the sustrate-to-metal CT) increases. For the η^1 systems, the trend is the opposite.

In order to cast light on these findings, an analysis of the transition state (TS) structures (ESI†) is particularly revealing and in Fig.2b we show, as examples, the TS structures for the Cl^-, NAC and CO ligands. Unlike the RCs, all TS structures, irrespective of the ligand **L**, show the same η^2 coordination (slightly slipped towards the C_1 carbon) and a pyramidalized nitrogen (as in the "alkyne" structure of Fig.1). As is easily understood, a pyramidalized nitrogen is essential for an effective nucleophilic attack, since the lone pair of the nitrogen is a more efficient nucleophile than the iminium ion of the allene structure. In addition, in the allene structure, the π system is not activated by the metal and C_2 is less prone to a nucleophilic attack. In conclusion, it appears that, if in the RC alkyne coordination tends to η^1, some energy has to be spent in order to restore the η^2 coordination that facilitates the attack.

We can thus recognize that, for this electronically conjugated substrate, there are two conflicting effects on the reaction barrier, and thus on the catalyst effectiveness: on the one hand, decreasing the electron donating power of **L** has the effect of enhancing the metal fragment acidity and thus increasing its substrate activation power; on the other hand, it also has the effect of progressively shifting the RC towards the allene structure, where the reactivity of both the nucleophile and of the site of attack is diminished. These two effects, which we may concisely describe as substrate activation and nucleophile deactivation, produce a minimum barrier when the right compromise between them is reached, with the carbene-type ligands. Indeed, Bertrand and coworkers discovered that using $[(CAAC)Au(C_6H_6)]$BARF the reaction is practically instantaneous.[20]

The deactivation of the nucleophilic functionality is due to the π electron conjugation assisted by the phenyl group. Indeed, when we considered an aliphatic version of the substrate, with the phenyl ring substituted by the C_2H_4 group (**S2**), we found that the alkyne coordinates η^2 in the RC with any ligand, and larger values of CT correlate with lower energy barriers (Fig.4, data labeled as '**S2**'). Actually, using strong electron-withdrawing ligands, the nucleophilic attack takes place even without barrier (see details in ESI†). For the anionic ligands, the aromatic or aliphatic nature of the substituents hardly affects either CT or $\Delta E^\ddagger$ (Fig. 4). For example, with $\mathbf{L} = Cl^-$ CT increases from 0.04 to 0.07 e on going from the phenyl to the ethyl substituent, while the activation barrier slightly decreases from 11.5 to 11.2 kcal/mol. Conversely, for neutral ligands both CT and $\Delta E^\ddagger$ are quite different for the aromatic or aliphatic substrate. For the CO ligand, the CT decreases from 0.41 to 0.33 e, while the activation barrier drops from 10.6 to 0.0 kcal/mol. The observed difference in CT is consistent with the different substrate coordination, since a σ-bonded carbon is expected to donate more electronic density to the metal.

In summary, we have studied a typical $[\mathbf{L}Au]^+$-catalyzed intramolecular hydroamination of alkynes and found an interesting and unforeseen effect. Purely due to electronic effects, the coordination of the gold complex to the substrate, which contains both the amino nucleophile and the alkyne,

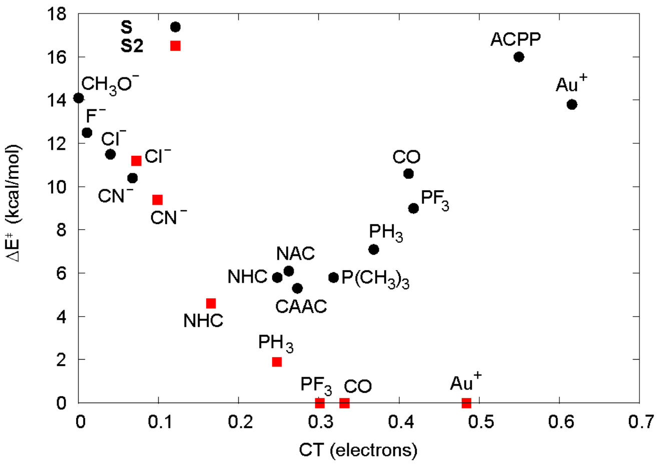

Fig. 4 Reaction barrier versus CT for the aromatic and aliphatic substrates (see text).

can switch from η^2 to η^1 mode depending on the ligand **L**. The allene (η^1) structure prevails with electron withdrawing ligands, whereas the alkyne (η^2) structure is preferred with electron donor ligands. Since the nucleophilic attack is possible only in the latter configuration, high activation barriers are found for strong electron withdrawing ligands, in contrast with the common view. The "normal" behavior, i.e., the occurrence of smaller barriers with stronger electron withdrawing ligands, is restored if no π-electron conjugation is present in the substrate. The present findings, while calling for experimental verification of the discovered trend of reaction barriers, are of broad relevance, since cyclizations of this type are very common, and there are examples in the literature that can potentially be controlled by the effects discussed here.[20,30] Our results also emphasize that efficient ligand design for metal catalysts is a complex task where details of the bonding may have unexpected effects not easily foreseen without reliable theoretical guidance, especially in cases where two or more substrate functionalities are present and may interplay.

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