

Unveiling the complexity of the dual gold(I) catalyzed intermolecular hydroamination of alkynes leading to vinylazoles

Md Bin Yeamin^{a,b}, Josep Duran^b, Sílvia Simon^b, Nikolaos V. Tzouras^c, Steven P. Nolan^{c,*}, Albert Poater^{b,*}

^a Department of Physical and Inorganic Chemistry, Universitat Rovira i Virgili, c/ Marcel···Li Domingo 1, Campus Sescelades, Tarragona 43007, Spain

^b Institut de Química Computacional i Catalisi and Departament de Química, Universitat de Girona, c/ Maria Aurèlia Capmany 69, Girona 17003, Catalonia, Spain

^c Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Building S3, Krijgslaan 281, Ghent 9000, Belgium

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ABSTRACT

The conversion of alkynes into functionalised alkenes catalyzed by Au(NHC) complexes (NHC = *N*-heterocyclic carbene) is a fundamental and atom-economical transformation yet its mechanistic understanding is limited. In order to shed light on such catalytic reaction mechanisms, computational tools are utilized to gain insights into the gold catalyzed intermolecular hydroamination of internal alkynes. The combination of alkynes and benzotriazole leads to vinylazoles via a solvent free, gold(I) mediated hydroamination. DFT permits an in-depth discussion of single versus dual metal catalysis in this transformation. The role of the triflate anion is studied, being essential for the protodeauration and it helped to clarify the rate determining step, that consists of the gold-tiazolyl nucleophilic attack to the gold-alkyne π -complex.

Introduction

Among privileged scaffolds in the pharmaceutical industry, *N*-functionalized azoles are frequently encountered structural motifs displaying activities against bacterial and fungal infections [1–3], and are used as anxiolytic [4], analgesic, antidepressant drugs, and even as anticancer agents [5]. Even though the synthesis of azole derivatives centers around cycloaddition and multicomponent reactions [6–10], the hydroamination of alkynes, but also alkenes or alkynyl sulfamides [11], proves more step-economical. One of the lacking incarnations of the latter approach (although it has been used in inter- and intramolecular hydroamination of terminal alkynes [12–14]) is the intermolecular hydroamination of alkenes [15]. In addition, the intermolecular hydroamination of internal alkynes with primary amines has been successfully catalyzed mainly by titanium (IV) based catalysts [16–23], while dialkylamines or heterocycles fail as nucleophiles. On the other hand, the hydroamination of internal alkynes under solvent free conditions has been found feasible [24].

In seminal efforts in this direction, Schaffer succeeded in achieving a selective anti-Markovnikov hydroamination of terminal and internal alkynes with *N*-silylamines, leading to primary amines with a bis

(amidate)bis(amido)titanium(IV) catalyst [25,26]. Subsequent efforts focused on rhodium(I) catalysts [27,28], here, Dong and Sunoj developed the hydroamination of internal alkynes via tandem metal catalysis to yield *N*-allyl indolines [29] and branched *N*-allylic amines, whereas Breit and coworkers accomplished the rhodium(I) catalyzed chemo-, regio-, and enantioselective allylation of triazoles and pyrazoles with internal alkynes [30]. Zhao and coworkers explored the hydroamination combined with C–H activation in a highly selective [4 + 2] imine/alkyne annulation leading to multi-substituted 3,4-dihydroisoquinolines [31]. Additionally, looking beyond rhodium, silver(I) and copper (II) complexes were found to be active in the regioselective intermolecular hydroamination of internal alkynes, functionalized with electron-withdrawing groups [32,33], while gold(I) catalysts enabled catalytic additions to C–C bonds leading to intramolecular reactions [34–43]. Mechanistic insights were provided for intermolecular reactions including the hydroamination of alkynes with ammonia, hydrazine and amines catalyzed by gold complexes with cyclic(alkyl)(amino)carbenes [44,45]. The same synthetic methodology led to 1,2-dihydroquinolines [46,47], here insights shed light on the stereo and regioselective hydroamination of internal alkynes using dialkylamines [48,49], and the intermolecular hydroamination of internal

; DFT, Density Functional Theory; GGA, gradient generalized approximation; NHC, *N*-heterocyclic carbene.

* Corresponding author.

E-mail addresses: steven.nolan@ugent.be (S.P. Nolan), albert.poater@udg.edu (A. Poater).

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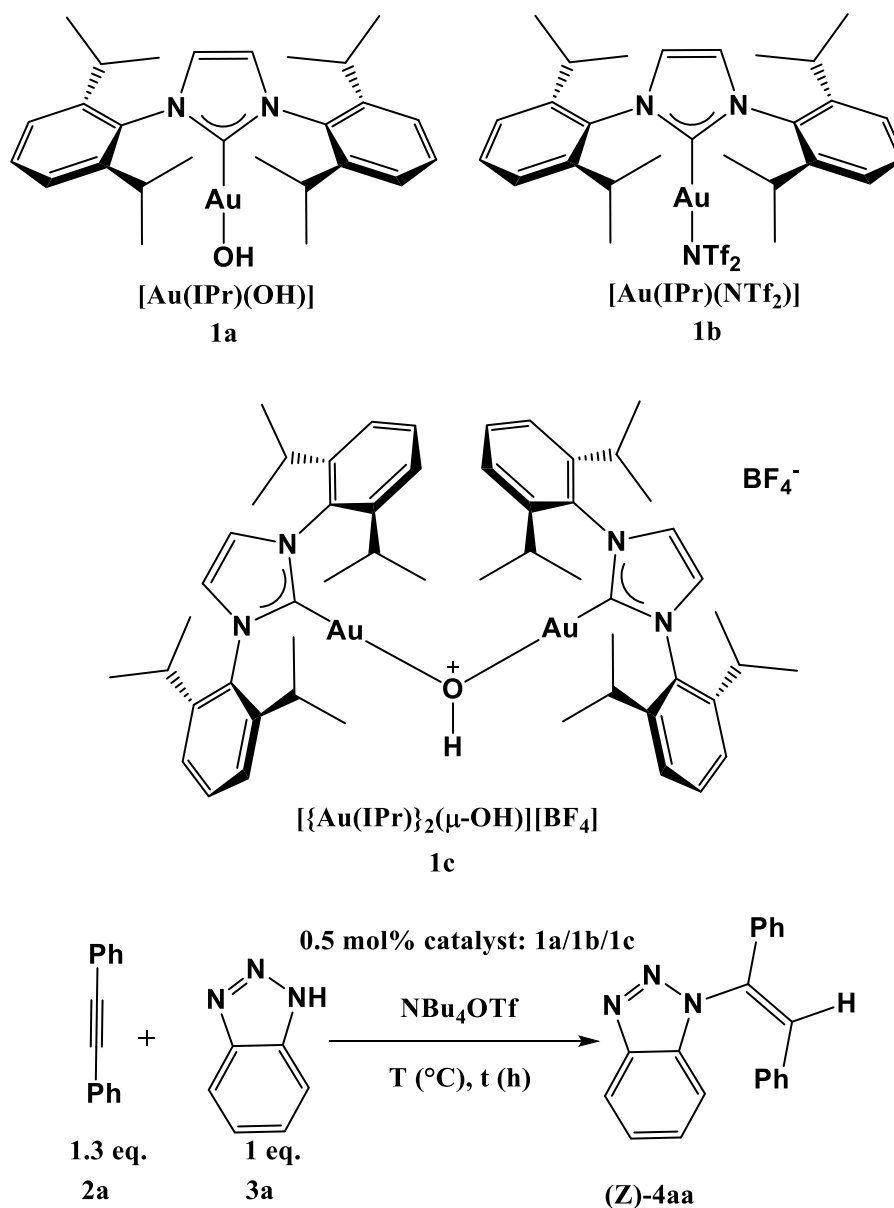


Fig. 1. Catalytic reaction of alkynes and benzotriazole to *N*-functionalized azole (a sand bath at 100 °C for 72 h; $a = 0.22$ mmol of **3a**; $b = 1.10$ mmol of **3a**) [54].

alkynes with primary amines, using an acid co-catalyst [50]. Interestingly, the latter methodology led to vinyl-substituted triazoles [51], and pyrazoles [52].

Among the catalysis for azide-alkyne cycloaddition reactions [53], in 2019, Michon, Nolan and coworkers developed a gold(I)-catalyzed intermolecular hydroamination strategy to couple internal alkynes and benzotriazole for the effective synthesis of functionalized vinylazoles [54], in high yields and high regio-, chemo-, and stereoselectivity, under solvent free conditions. The synthetic methodology proved simple and scalable (See Fig. 1), using standard thermal heating or more convenient microwave heating. However, the reaction mechanism was not probed in detail, despite recent synthetic efforts [55,56].

Actually, this difficulty in studying the mechanism was also an issue for the gold(I)-catalyzed hydroamination of alkenes by Michon and coworkers [57–61], or the gold(I)-catalyzed hydroalkoxylation, hydrophenoxylation, and hydrocarboxylation of alkynes by Nolan and coworkers [62–65]. In collaboration with the latter experimental group, Poater and coworkers have provided evidence for the dual gold catalyzed hydrophenoxylation of alkynes [66,67]. The main conclusion of

this study was that not only is a gold(I) center needed to activate the alkyne, but that an additional gold is required to activate the phenol substrate as well [68,69]. Houk, Toste and collaborators reached the same conclusion, nearly one decade ago, for the cycloisomerization of allenyne mediated by a digold catalyst [70], i.e. including a nucleophilic addition to the allene double bond to a cationic phosphinegold(I)-complexed phosphinegold(I) acetylide. This was followed by a series of experiments [71–73], and seminal calculations [74].

During the last decade, the area of dual gold catalysis has seen evolutions on going from phosphinegold(I) catalysts to (NHC)gold(I) catalysts (NHC = N-heterocyclic carbene) [75,76]. In addition to DFT calculations that validated the dual gold catalyzed hydrophenoxylation of alkynes, mass spectrometry (MS) experiments by Roithová and coworkers showed that these digold species were not simple catalyst reservoirs [77,78], being particularly active in the synthesis of functionalized alkenes [79–81], including especially (*Z*)-vinyl ethers [82,83]. Reek and coworkers subsequently confirmed that encapsulation of the gold catalysts enhanced the dual gold catalyzed hydrophenoxylation [84,85]. Furthermore, the heterobimetallic catalytic

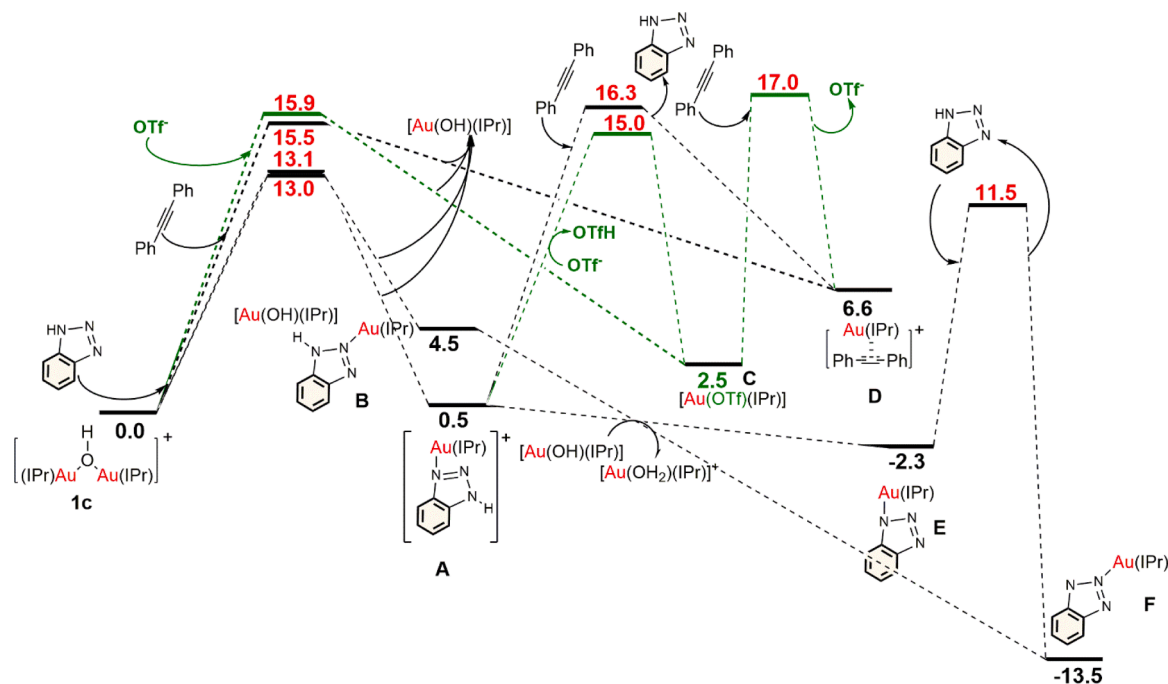


Fig. 2. Computed stationary points calculated at the M06/TZVP~x223Csd(ccpm)//BP86/SVP~x223Csd level of theory for the reaction pathways referred to **1c** catalyst using diphenylacetylene and benzotriazole as the substrates (Gibbs energies are given in kcal/mol, in red labels the relative values for the transition states, in green the direct participation of OTf⁻).

system with two different metal moieties, including gold and copper, showed enhanced catalytic activity in the same reaction, confirming the dual metal catalysis concept to not be limited to homobimetallic systems [86,87]. However, the discussion of mono vs. dual catalysis remains an ongoing topic of debate for various transformations, including water oxidation catalysis as a paradigmatic case [88–90]. Of note, this discussion continues especially because not all kinetic experiments match the dual gold catalysis model [91,92], with additional controversy for other dual metal catalyzed reactions [93–95]. The crucial role of the counterion in dual catalysis has also been addressed and highlights the complex nature of the mechanistic issues [96–102].

Since the dual metal catalyzed reaction mechanism is usually omitted in DFT calculations, we wish to correct this situation and provide details for the transformation of internal alkynes and benzotriazole for the effective synthesis of functionalized vinylazoles where two gold moieties must be in proximity for the reaction to proceed and therefore should involve, a dual metal catalytic scheme [103,104]. However, the effort for finding dual metal catalyzed mechanisms should not be biased [105,106], and it should be understood that most processes do not follow this dual model [107–109].

Materials and methods

Geometry optimizations have been carried out by means of DFT calculations with Gaussian09 [110]. The gradient generalized approximation (GGA) BP86 functional of Becke and Perdew was used [111, 112]. The electronic configurations of the molecular systems were described with the standard split-valence basis set including the polarization function of Ahlrichs and coworkers for hydrogen, carbon, nitrogen, an oxygen (SVP keyword in Gaussian09) [113], whereas for gold we used the quasi-relativistic Stuttgart/Dresden effective core potential with the associated valence basis set (standard sdd keyword in Gaussian09) [114–116]. The stationary points were characterized by analytical frequency calculations.

On the BP86/SVP~x223Csd optimised geometries, single-point calculations were performed using the M06 functional [117] with the triple- ζ basis set of Weigend and Ahlrichs for main-group atoms (TZVP

keyword in Gaussian) [118], and for gold the sdd pseudopotential and basis set. In those latter calculations, the polarizable conductor calculation model (CPCM) was also used to model the solvent effects (pyridine) [119–121]. The reported free energies in this work include energies obtained at the M06/TZVP~x223Csd level of theory corrected with zero-point energies, thermal corrections and entropy effects evaluated at 298 K with the BP86/SVP~x223Csd method in the gas phase, omitting corrections of entropy and standard state of 1 M concentration in solution [122].

Results and discussion

The reaction between the alkyne and the benzotriazole substrates described in Fig. 1 is catalyzed by $[\{Au(IPr)\}_2(\mu-OH)][BF_4]$ **1c**, with the assistance of the triflate anion. Apart from the greater coordinating capacity of the triflate anion, the BF₄ anion was not taken into account according to previous computational studies [66]. To dissect the exact mechanism at play, first it is necessary to determine which is, or which are, the catalytically active species when two metal moieties are involved in the catalytic cycle.

In Fig. 2, on the basis of previous mechanistic studies, we propose the cationic $[\{Au(IPr)\}_2(\mu-OH)]^+$ as a simplification of $[\{Au(IPr)\}_2(\mu-OH)][BF_4]$, since the latter neutral complex is isoenergetic with respect to both, $[\{Au(IPr)\}_2(\mu-OH)]^+$ and BF₄⁻, bearing a nearly complete ionic link between the two moieties. However, there are several potential dissociation routes available to the hydroxide bridged complex. If this gem-digold complex coordinates to the alkyne to form π -complex D, the Brønsted base $[Au(IPr)(OH)]$ is generated. This step needs to overcome an energy barrier of 15.5 kcal/mol and is thermodynamically unfavored by 6.6 kcal/mol, whereas when benzotriazole opens the bridge, the energy barrier is 2.4 kcal/mol, and leads to a rather stable intermediate A. However, the benzotriazole has two N atoms which can coordinate the metal center. If the benzotriazole binds gold, the corresponding energy barrier is nearly identical via the external or middle nitrogen (0.1 kcal/mol more favored for the middle nitrogen), whereas the thermodynamics favours by 4.0 kcal/mol the external coordination, thus not leading to the less stable intermediate B. Nevertheless, both

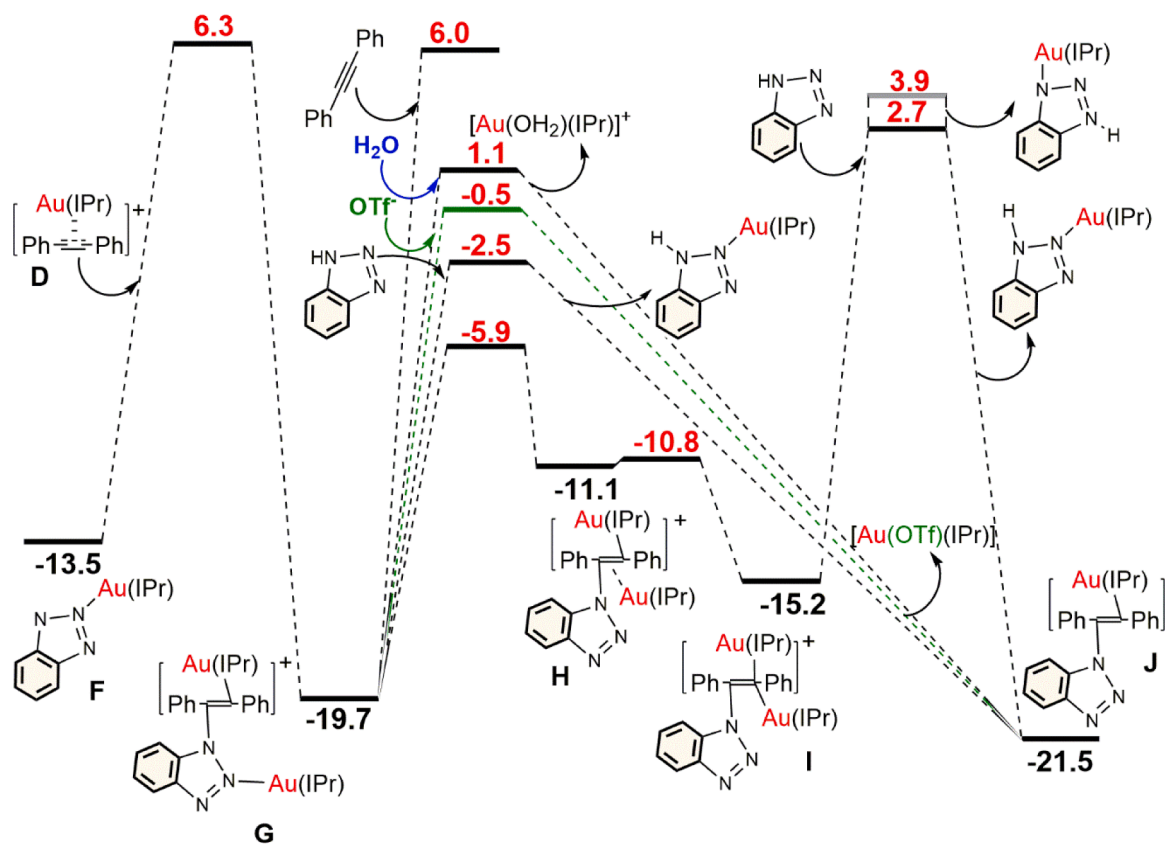


Fig. 3. Computed stationary points from intermediates F to G calculated at the M06/TZVP~x223Csdd(cpcm)//BP86/SVP~x223Csdd level of theory referred to 1c catalyst for the dual gold-catalyzed hydroamination (Gibbs energies are given in kcal/mol, in red labels the relative values for the transition states, in green the direct participation of OTf⁻).

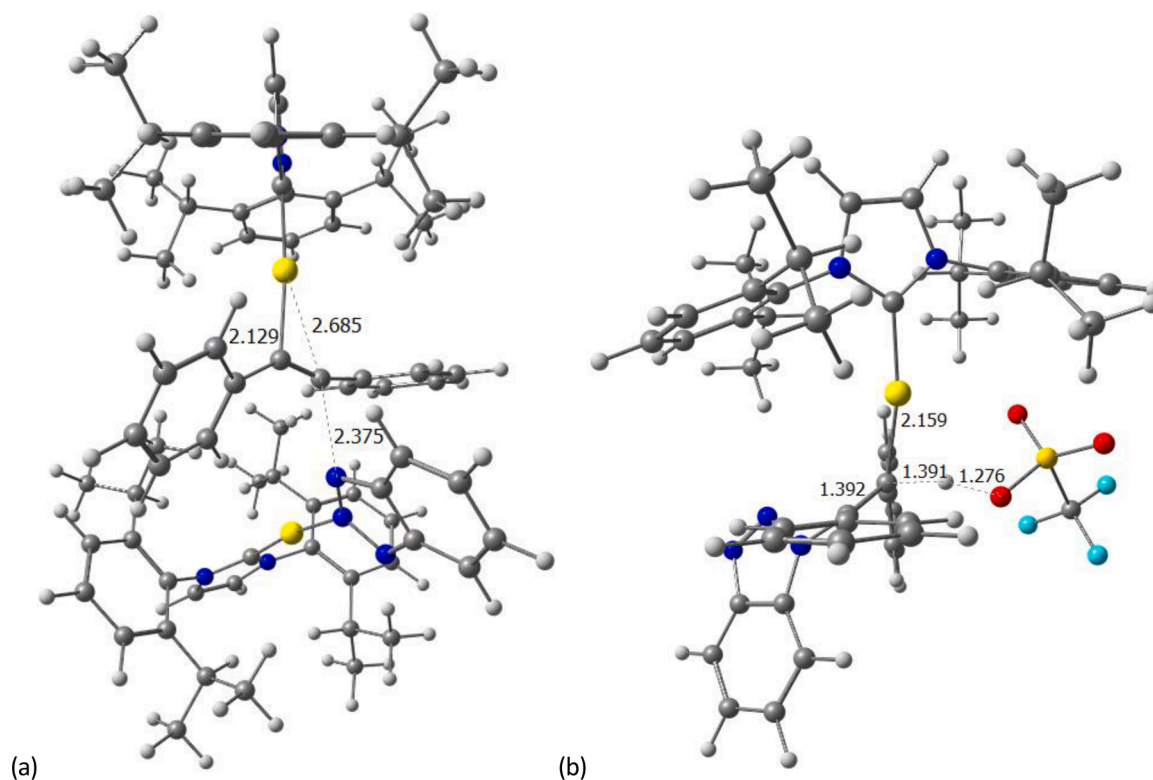


Fig. 4. Transition states (a) F-G and (b) J-K assisted by triflate (selected distances given in Å).

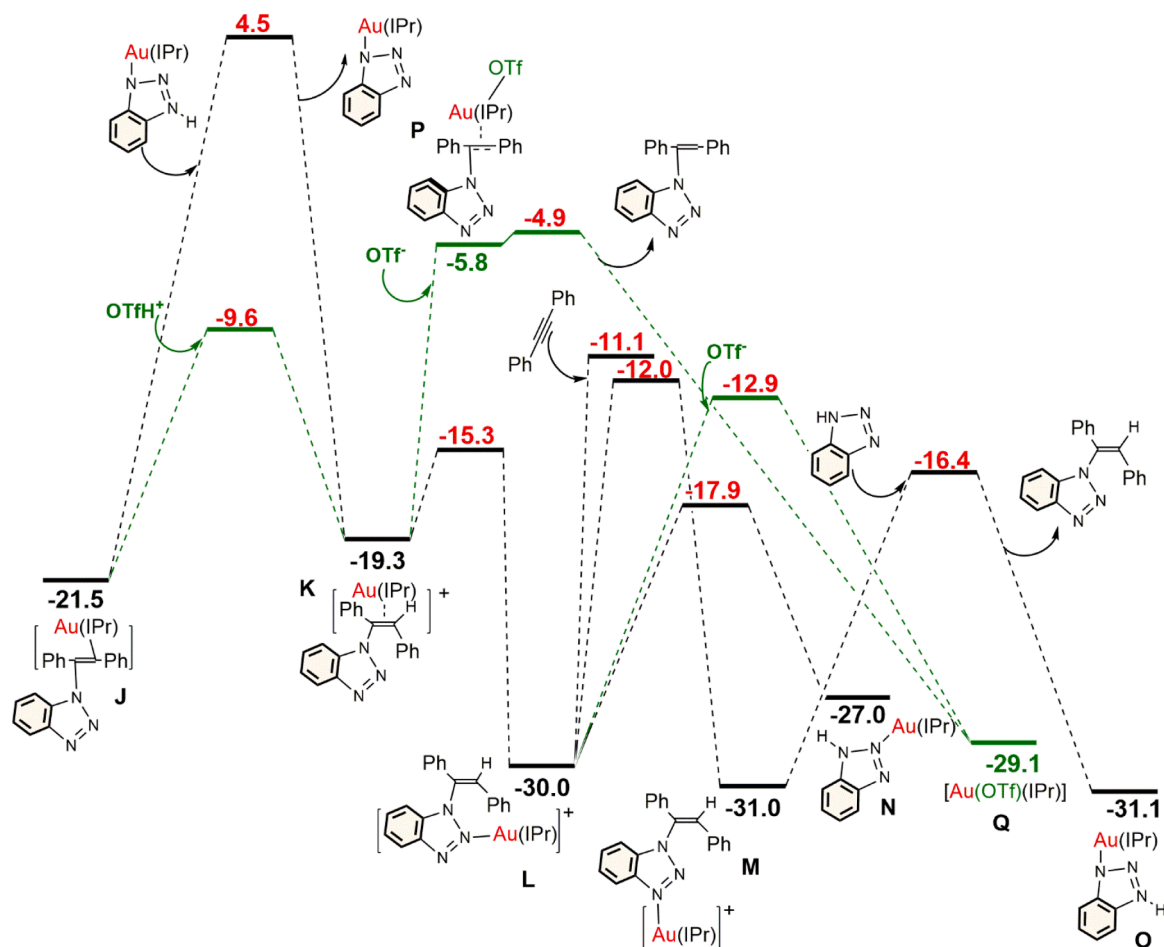


Fig. 5. Computed stationary points from intermediates J to O calculated at the M06/TZVP~x223Csdd(cpcm)//BP86/SVP~x223Csdd level of theory referred to 1c catalyst for the dual gold-catalyzed hydroamination (Gibbs energies are given in kcal/mol, in red labels the relative values for the transition states, in green the direct participation of OTf⁻).

isomers, **A** and **B**, collapse into intermediate **F** by action of the [Au(IPr)(OH)] intermediate, which is able to deprotonate the charged azole-gold intermediates **A** and **B**, with barrierless and highly favored thermodynamic processes (2.8 and 13.5 kcal/mol, respectively). However, after the deprotonation from the gold-azole **A** to its neutral form **E**, an additional step is required, overcoming an energy barrier of 13.8 kcal/mol the coordination atom of the former azole is changed, from the central or any of the terminal N atoms, assisted with an additional benzotriazole molecule.

On the other hand, the potential active role of the triflate anion, as well as water molecule that is formed as a by-product, was explored for the cleaving of $[\{Au(IPr)\}_2(\mu-OH)]^+$, with energy barriers of 15.9 and 16.4 kcal/mol, respectively, thus neither is the best starting reagent to cleave the digold species, despite stabilizing the cationic gold moiety. The triflate leads to intermediate **C** that can replace the alkyne overcoming an energy barrier of 14.5 kcal/mol, and leads to the cationic intermediate **D**. Of note, in the absence of OTf⁻ anion the formation of the Au-alkyne species would not be diminished. Even though the dimer is only cleaved by the triazole, the OTf⁻ anion could facilitate the formation of the π -complex **D** in a stepwise process, first with the exchange of the triazole by the OTf⁻ anion with the next exchange of the anion by the alkyne, with an upper barrier of 16.5 kcal/mol. However, the direct formation of the π -complex **D** from the Au-azole species **A** has an energy barrier lower by 0.7 kcal/mol. Thus, the presence of OTf⁻ is not mandatory for the initiation step to take place.

The neutral Au-azole species **F**, where Au is bound to the azole through its central nitrogen atom, is the active species in the catalytic

cycle (see Fig. 3). The subsequent nucleophilic attack of the gold-azole **F** toward π -complex **D** would lead to the formation of the diaurated species **G**. The formation of the C–N bond involves a kinetic cost of 19.8 kcal/mol (see Fig. 4a), but exergonically, with an energy gain of 6.2 kcal/mol.

To point out that the absence of gold with benzotriazole is disadvantaged kinetically by 10.5 kcal/mol, in agreement with past studies [15]. Then a benzotriazole molecule could displace the second gold center overcoming an energy barrier of 17.2 kcal/mol, leading to intermediate **J**. However, the simple rearrangement of the di-gold species could proceed with less kinetic cost with the migration of this second gold moiety. Regardless, this process needs to overcome three energy barriers since intermediates **H** and **I** are also present along the reaction coordinate. The first two energy barriers are lower than that of the external triazole attack, by 3.4 and 8.3 kcal/mol, respectively, while the third is 5.2 kcal/mol more kinetically demanding. On the other hand, the OTf⁻ anion could also compete with the external triazole but this is less favored by 2.0 kcal/mol. Alternatively, the nucleophilic attack of gold-azole **F** toward π -complex **D** in an anti-fashion would lead to the formation of a *gem*-diaurated species, however all of those off-cycle species were found to be disfavored either thermodynamically and/or kinetically.

From intermediate **J**, the protonation of the former alkyne group leads to the alkene product (see Fig. 5). The formation of the vinylazole product would be favored if the cationic $[Au(OH_2)]^+$ species was available [66,123], but this strategy is not right since we never enjoy the presence of water to generate it. Then the second option is the protonation by means of the cationic Au-azole moiety with a cost of 26.0

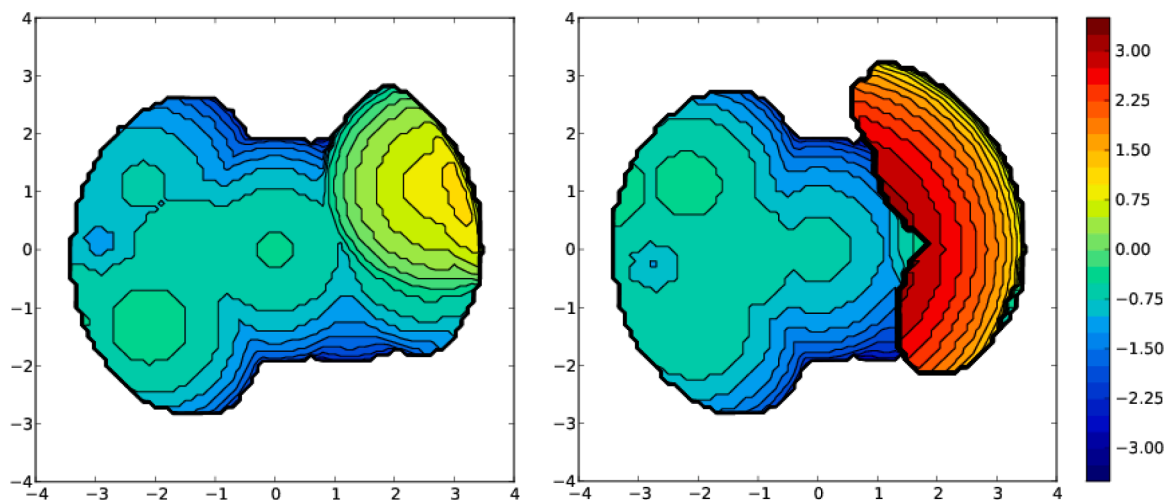


Fig. 6. Steric maps (plane xy) with the linking N in the center, the linking C in the z axis, and the C bonded to Au on the X axis, of the TS F-G (left) and the corresponding TS for the cis attack (right), with a radius of 3.5 Å.

kcal/mol, and thus this would be the rate determining step (rds) [124]. However, this is not dramatic, as a third option, the protonated OTf⁻ anion can carry out this protonation, overcoming a rather low energy barrier of 11.9 kcal/mol (see Fig. 4b). Then the next steps to release the product are simple rearrangements of the gold center, which is finally removed by a triazole ligand, delivering the organic product.

Alternative pathways were explored, including the one leading to the cis-alkene product, but none being competitive in energy (see Fig. S1), since the cis attack involves an increase in steric pressure in an area of the space between the two metal moieties in the homologous transition state F-G [66,125]. What is most affected is the distortion that is reflected with the C—C—N angle moving from 106.1 to 113.8° when passing from the trans attack to the cis. However, using the sterical hindrance index developed by Cavallo and coworkers [126], there is also a clear worsening of the steric part in the cis attack (from 33.0 to 34.3% V_{bur}) [127], and observing Fig. 6 can be seen in the steric maps [128,129] (see Figs. S2 and S3 for further details). There is a much more sterically occupied area in the cis attack [130], due to the fact that the metal moiety bound to the alkyne is close [131,132]. In addition, to make sure that the rds barrier, i.e. of the F-G step, is not an artifact of the method, it was found that the use of BP86 in geometry optimization was not decisive, as the inclusion of dispersion with the Grimme GD3 model [133], i.e. BP86-D3, led to an energy barrier increase of only 0.9 kcal/mol, whereas 4.3 kcal/mol reoptimizing the geometries. On the other hand, the use of M06L or M06L-D3 decreased by 2.4 kcal/mol [134], and neither did the functional hybrids significantly change the results, with an increase in the energy barrier in 1.1 and 1.8 by B3LYP and B3LYP-D3 [135–137], respectively.

Results included in Figs. 3 and 5 validate the hypothesis that two metal moieties must be in close proximity for the reaction to occur [138, 139]. Thus, the digold catalyst **1c** in Fig. 1, where both metals are linked by a hydroxide ligand facilitates the preparation of both metal moieties that must assist the hydroamination reaction, similarly to other gold catalyzed reactions [140,141]. In particular, the digold-hydroxides had been synthesized some years ago [141], and even though some subsequent *gem*-di-aurated compounds were considered as potential off-cycle catalytic species [64,142,143], they behave as a combination of a Lewis acid and a Brønsted base [144]. In detail, the cationic gold fragment with the alkyne bonded to gold is considered as a Lewis acid whereas the neutral gold hydroxide as a Brønsted base [145,146]. However, the latter species is transformed to the neutral species with the deprotonated azole, i.e. another Brønsted base [147].

Conclusions

The synthetic efforts that provided the gold(I)-catalyzed regio- and stereoselective intermolecular hydroamination of internal alkynes, under solvent free conditions, leading to functionalised vinylazoles, were computationally studied here by DFT calculations. Calculations not only provided the reaction mechanism, but they led to the identification of the key role of the triflate anion, without which the final vinylazole product could not be obtained. This is because the triflate anion is essential for protodeauration which would otherwise be kinetically very demanding. In the reported system which does utilize a triflate anion, the rate-determining step is the addition of the gold-tiazolyl nucleophile to the gold-alkyne π -complex.

CRediT authorship contribution statement

Md Bin Yeamin: Investigation, Data curation. **Josep Duran:** Investigation, Data curation. **Sílvia Simon:** Investigation, Data curation. **Nikolaos V. Tzouras:** Investigation, Data curation. **Steven P. Nolan:** Supervision, Conceptualization, Writing – review & editing. **Albert Poater:** Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

There are no conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2021.112090.

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