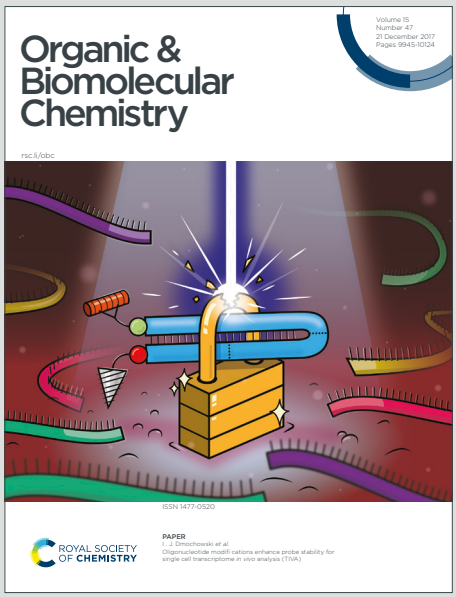
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: V. Marsicano, A. Arcadi, M. Aschi and V. Michelet, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB01598A.






ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB01598A

ARTICLE

# Experimental and Computational Evidences on Gold-Catalyzed Regioselective Hydration of Phthalimido-Protected Propargylamines: An Entry to β-Amino Ketones.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

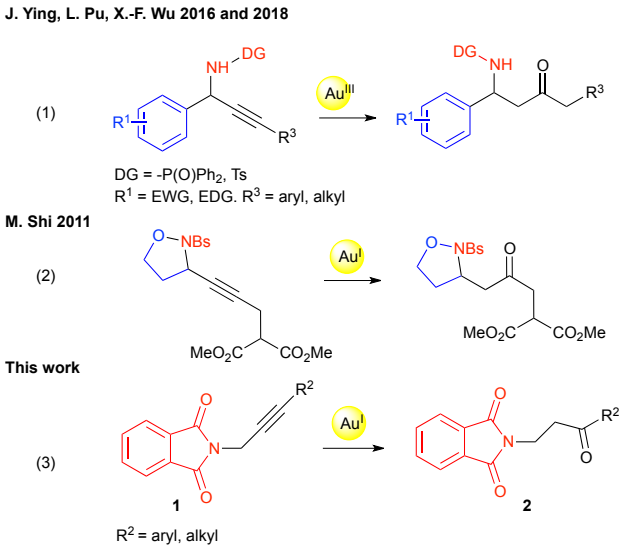
Vincenzo Marsicano,[a,b] Antonio Arcadi,*[a] Massimiliano Aschi,*[a] and Véronique Michelet*[b]

The results of our investigations on Au-catalyzed regioselective hydration reaction of both alkyl- and aryl-substituted *N*-propargyl phthalimides directed to the selective formation of the corresponding β-phthalimido ketones are described. Experimental data, in particular the observed regioselectivity, has been qualitatively supported by Quantum-chemical calculations carried out on model systems in the framework of Density Functional Theory (DFT) followed by quantum theory of atoms in molecules (QTAIMS). Our results suggest that the electronic features of the initial adduct between the propargyl triple bond and the Au(I) catalyst, in particular the character of the gold-triple bond interaction, are essential for the observed regioselectivity. Other effects, such as the presence of the solvent and the formation of a H-bond between the water molecule and the phthalimido moiety, although apparently irrelevent for the regioselectivity, have proved to be kinetically and catalytically rather important.

## Introduction

Propargylic amines are versatile building blocks in organic synthesis[1] and catalytic activation of the C-C triple bond represents a powerful tool to allow for their regioselective functionalization. Especially, the regioselective hydration of propargylamine derivatives by means of gold catalysis instead of toxic mercury reagents[2] provided alternative straightforward and efficient methodologies to generate the corresponding β-amino ketones with excellent regioselectivities under mild conditions.[3] The use of diphenylphosphinoyl and tosyl groups as suitable directing groups in the starting propargylamines allowed the access to the corresponding *N*-protected β-amino ketones by means of regioselective gold(III)-catalyzed hydration reaction (Scheme 1, Eq. 1). In these examples, the amine was functionalized by an aromatic at the propargylic position and either an aryl or alkyl group at the alkynyl position. While a large number of reports have focused on the hydration of an internal general alkyne moiety, [4,5] only limited examples have been reported on the hydration of alkyl or unsubstituted propargylic amine. The group of Shi reported a single example of regioselective hydration of an alkyl-substituted propargylic amine containing an arysulfonyl group on the nitrogen catalyzed by $AuClPPh_3$/ AgOTf, which gave a β-amino ketone in good yield (Scheme 1, Eq. 2).[6] Considering the ubiquitous structural feature of β-amino ketones in nitrogen-containing pharmaceuticals and biologically active compounds,[7,8] and our long interest in gold-catalyzed functionalization of alkynes,[9,10] we envisaged to reach such motifs by hydration of unsubstituted propargylic amines. For this purpose, we have selected phthalimido group [11] as a useful alternative protecting group to direct the regioselective atom economy functionalization of non-symmetrical alkynes by means of gold catalysis. We wish therefore to report therein the results of our investigations on Au-catalyzed regioselective hydration reaction of both alkyl- and aryl-substituted *N*-propargyl phthalimides **1** directed to the selective formation of the corresponding β-phthalimido ketones **2** (Scheme 1, Eq. 3). Experimental data have also been supported by quantum-chemical calculations carried out on model systems in the framework of Density Functional Theory (DFT), which suggested that the regioselectivity is mainly driven by electronic effects.

**Scheme 1.** Regioselective Hydration of Propargylic Amines.




[a] *Dipartimento di Scienze Fisiche e Chimiche Università degli Studi di L'Aquila; Via Vetoio, 67100 Coppito (AQ), Italy*
[b] *University Côte d'Azur, Institut de Chimie de Nice, UMR 7272 CNRS, Parc Valrose, Faculté des Sciences, 06100 Nice, France*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0OB01598A



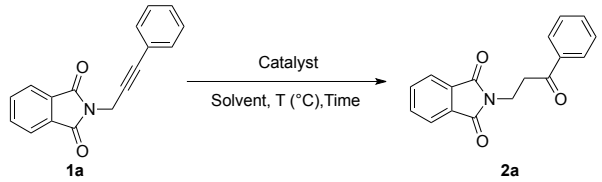
## Computational details

All the calculations were performed in the framework of density functional theory (DFT) using the CAM-B3LYP functional [12] All the structures were first optimized using the 6-31+G* basis set for all the (light) atoms the Los Alamos National Laboratory Effective Core Potential with a double-ζ basis set (lanl2dz) for gold. [13] The same level of theory was employed for calculating the frequencies and, hence, the free energy correction at the temperature of interest (see below) by evaluating for each structure the partition function in the ideal-gas approximation using the geometries and the associated frequencies and considering as a reference state the concentration of 1.0 mole/liter. A larger basis set, 6-311+G*, was then utilized for all the light atoms for performing single point calculations, atomic charge estimations [14] and for calculating the excess free energy, i.e., the effect of the solvent (Acetonitrile at the temperature of 80°C), using a mean-field approach according to the Polarizable Continuum Model (PCM) [15] as implemented in the Gaussian 09 software [16]. Atomic charges were also calculated at the same level of theory, on a selected number of species, using the Natural Bond Order analysis. [17] QTAIMS (quantum theory of atoms in molecules) analysis [18] was finally carried out on the DFT "wavefunction" using the Multiwfn package. [19] All the details of the quantum-chemical calculations and QTAIMS analysis are reported in the Supplementary Information.

## Results and discussion

At the outset of our investigation, the ready available *N*-propargylphthalimide **1a** [20] was selected as a model substrate for the screening of catalysts and suitable conditions for the synthesis of the β-phthalimido derivative **2a**. The results are summarized in Table 1. The previously reported conditions $NaAuCl_4•2H_2O$ for the gold-catalyzed regioselective hydration of the *N*-diphenylphosphinoyl-/*N*-tosyl propargylic amines [3b] allowed the formation of β-phthalimido ketone **2a** at room temperature, despite in low yield (Table 1, entry 1). The formation of **2a** occurred in 64% yield in the presence of the same catalyst in absolute ethanol at 80 °C. It should be noted that only a single regioisomeric hydration product was isolated along with the recovery of the starting material (12%) (Table 1, entry 2). The use stoichiometric amount of the *p*-toluenesulfonic acid in ethanol was also envisaged and failed to give **2a** in synthetic useful yield (Table 1, entry 3).[21] Pleasingly, the activity of $IPrAuNTf_2$ catalyst resulted in the formation of **2a** under the same reaction conditions in 73% isolated yield (Table 1, entry 4).[22] Further investigation in order to find the more efficient catalytic system showed that both the reaction medium and the choice of the ligand L and anion $X^-$ in complexes L-Au-X can play an effective role in the reaction outcome.[23] Pure water (Table 1, entry 5) proved to be less suitable for the formation of the hydration product. In further optimization on gold catalysts, it was found that the complex $IPrAuNTf_2$ allowed the formation of **2a** in 86% yield in $CH_3CN/H_2O$ (10:1) as the best reaction medium (Table 1, entry 6). Changing the counter anion of this latter cationic gold(I) to $BF_4^-$ resulted in a decreasing yield of **2a** to 60% yield (Table 1, entry 7). The starting alkyne **1a** was recovered unchanged when $AgNTf_2$ was used the catalyst (Table 1, entry 8). By switching to $Ph_3PAuNTf_2$ ($NTf_2$ = bis(trifluoromethanesulfonyl)imide) as the catalyst, the formation of a hydration product **2a** occurred in lower yield (Table 1, entries 9-10). Conversely, the use of $XPhosAu(CH_3CN)SbF_6$ resulted in a very low yield under the same reaction conditions (Table 1, entry 11).

**Table 1.** Optimization of the reaction condition of the hydration of the *N*-propargylphthalimide **1a**.



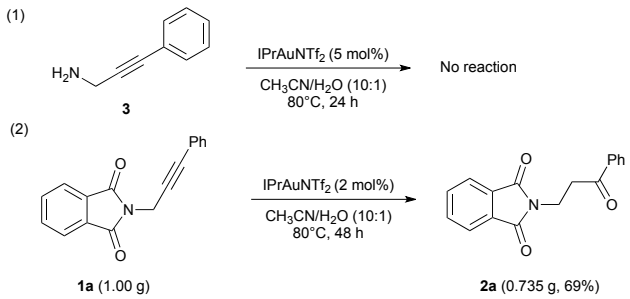

**1a** **2a**

| Entry [a] | Catalyst | Solvent | T (°C) / Time (h) | Yield (%) [b] (Conv.) [c] |
|---|---|---|---|---|
| 1 | $NaAuCl_4•2H_2O$ | $EtOH/H_2O/DCM$ (4:1:1) | r.t. / 24 | 19 (20) |
| 2 | $NaAuCl_4•2H_2O$ | EtOH | 80 / 19 | 64 (88) |
| 3 | *p*-TsOH | EtOH | 80 / 24 | 12 (15) |
| 4 | $IPrAuNTf_2$ | EtOH | 80 / 24 | 73 |
| 5 | $IPrAuNTf_2$ | $H_2O$ | 80 / 24 | 43 |
| 6 | $IPrAuNTf_2$ | $CH_3CN/H_2O$ (10:1) | 80 / 24 | 86 |
| 7 | $IPrAu(CH_3CN)BF_4$ | $CH_3CN/H_2O$ (10:1) | 80 / 24 | 60 |
| 8 | $AgNTf_2$ | $CH_3CN/H_2O$ (10:1) | 80 / 24 | N.R. |
| 9 | $PPh_3AuNTf_2$ | $CH_3CN/H_2O$ (10:1) | 80 / 24 | 60 |
| 10 | $PPh_3AuNTf_2$ | $CH_3CN/H_2O$ (10:1) | r.t. / 24 | 16 |
| 11 | $XPhosAu(CH_3CN)SbF_6$ | $CH_3CN/H_2O$ (10:1) | 80 / 24 | 17 |

[a] Unless otherwise stated, all reactions were performed with 0.191 mmol of 1**a** and 5 mol% of catalyst in 3 mL of solvent. [b] Isolated yield. [c] Conversion. NR = no reaction.

We therefore selected $IPrAuNTf_2$ as the best catalyst in $CH_3CN/H_2O$ (10:1). The pivotal role of the protecting phthalimido group in determining the reactivity and the regiochemical reaction outcome was demonstrated by reacting 3-phenylprop-2-yn-1-amine **3**. When compound **3** was subjected to optimized conditions (Scheme 2, Eq 1), no desired hydration was observed. The application of such transformation was also demonstrated on a larger scale with a smaller amount of catalyst. The hydration of **1a** was conducted on 1 g scale in the presence of 2 mol % of $IPrAuNTf_2$ at 80 °C in $CH_3CN/H_2O$ (10:1) for 48 h and afforded the desired ketone in 69% isolated yield (Scheme 2, Eq 2).

**Scheme 2.** Control experiment and scale-up of the hydration of the *N*-propargylphthalimide **1a**.





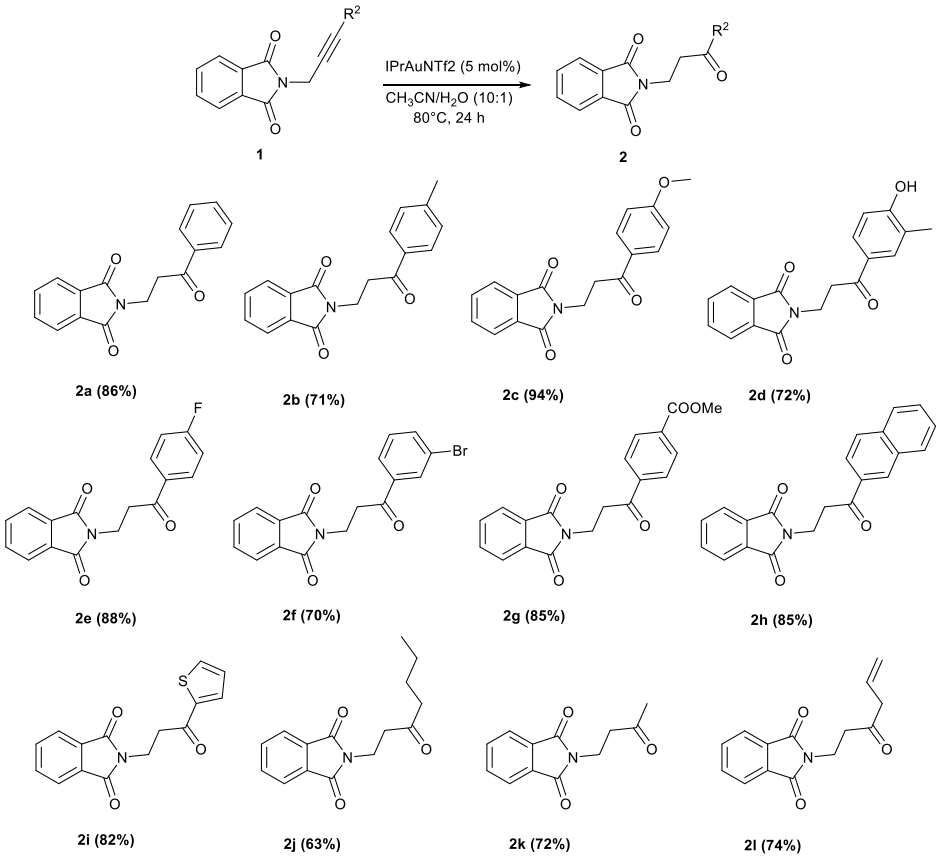
View Article Online
DOI: 10.1039/D0OB01598A





We then decided to study the scope and limitations of this catalytic system. To further extend the generality of the hydration procedure, a variety of *N*-propargylphthalimides with different R groups at the terminal alkynyl position were reacted under the optimized conditions of entry 5 of Table 1 (Scheme 3). Our results showed that both alkyl- and aryl- or heteroaryl-substituted *N*-propargylphthalimides **1a-i** could efficiently undergo hydration to give only the corresponding β-phthalimido ketones **2a-i**. Both electron-donating substituents (*p*-MeO-, *p*-HO- and *p*-Me) and electron-withdrawing ones (*p*-F, *p*-COOMe, *m*-Br) on the aryl moiety were well tolerated. Gratifyingly, compounds bearing a linear alkyl group at terminal alkynyl position also gave the β-phthalimido ketones **2j-k** in 63% and 72% yield, respectively. Additionally, the hydration of **1l** having an allyl group on the triple bond afforded the desired product **2l** in 74% yield.

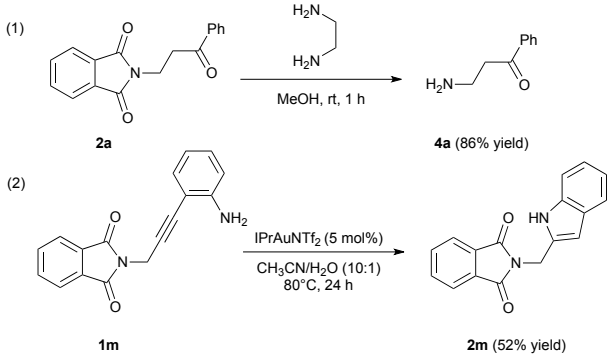
**Scheme 3.** Substrate scope of the Gold-catalyzed hydration of *N*-propargylphthalimides.




[a] Unless otherwise stated, all reactions were performed with 0.140-0.180 mmoles of **1a-l** in 3 mL of $CH_3CN/H_2O$ (10:1). [b] Isolated yields.

We also got interested in further applications through the deprotection of the protective group and also the competition with other gold-catalyzed transformations such as hydroamination.[24] The phthalimido-protected product **2a** could be easily transformed into the corresponding primary amine derivative **4a** in the presence of ethylenediamine in MeOH at room temperature (Scheme 4, Eq. 1).[25] Interestingly, the 2-aminophenyl substituted N-propargylphthalimide **1m** underwent the gold-catalyzed intramolecular hydroamination instead of the intermolecular hydration to afford the 2-((1H-indol-2-yl)methyl)isoindoline-1,3-dione **5m** in 52 % yield (Scheme 4, Eq. 2).

**Scheme 4.** Applications.

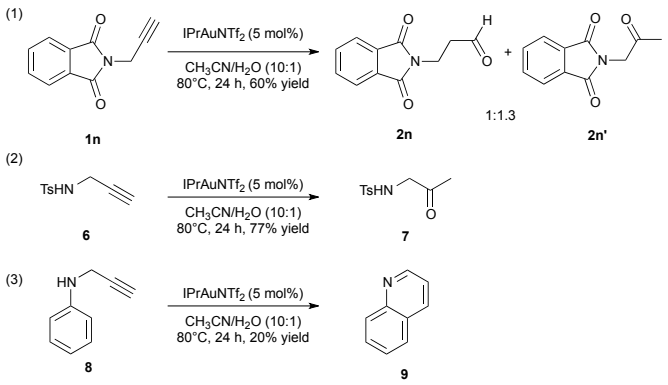


View Article Online
DOI: 10.1039/D0OB01598A



To investigate the mechanism of the reaction, we also studied the reaction of the non-substituted *N*-propargylphthalimide **1n** under the standard reaction conditions. A lack of regioselectivity was observed and the reaction afforded a mixture of **2n** and **2n'** in a 1:1.3 ratio in 60% yield (Scheme 5, Eq. 1). Anticipating that this unusual regioselectivity could be due to the protective group, we prepared the *N*-tosyl protected compound **6**.

**Scheme 5.** Effect of Directing Group.




Conversely, a total regioselectivity leading to the formation of only the α-tosylamido ketone **7** occurred in 77% yield by starting from the *N*-tosyl propargyl amine **6** (Scheme 5, Eq. 2). The *N*-phenyl propargyl amine **8** underwent under the same reaction conditions a sequential intramolecular hydroarylation/oxidation to give the quinoline **9** although in low yield (Scheme 5, Eq. 3).[26]

Concerning the mechanistic aspect, some theoretical papers aimed at understanding the mechanism of action of the gold catalyst in protic solvents and under acidic conditions have appeared in the literature.[27] DFT calculations coupled with kinetic experiments allowed to shed light on the mechanism of alkyne hydration, under apolar, aprotic, and neutral conditions.[28] A variety of complexes and plausible intermediates have been suggested to explain the regioselective gold-catalyzed hydration of the *N*-diphenylphosphinoyl-/*N*-tosyl propargylic amines.[3] Nonetheless, we envisaged that further computational calculations should shed the light on the key factors determining the regioselective outcome of the gold catalyzed hydration of the *N*-protected propargylic amines. Thus, we underwent a computational investigation aimed at trying to provide a rationale for some of our experimental results. In particular we decided to study the following model reactions in acetonitrile at 80°C: (a) gold-catalyzed hydration of *N*-propargylphthalimide **1a** (with $R_2$ = phenyl); (b) gold-catalyzed hydration of *N*-propargylphthalimide **1n** (with $R_2$ = H) (c) gold-catalyzed hydration of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide **6**; (d) gold-catalyzed hydration of *N*-(prop-2-yn-1-yl)aniline **8**; (e) gold-catalyzed hydration of 3-phenylprop-2-yn-1-amine **3**. Note that in all the systems we employed the complex of Au(I) with 1,3-dimethyl-imidazol-4,5-2-ylidene, as simplified but still realistic model of the $IPrAuNTf_2$ catalyst utilized in most of the experiments. It is also important to remark that in all the subsequent analyses we schematically indicate with $R_1$-Au-X the initial adduct between the propargyl triple bond and the $R_1$-Au$^+$ species. Results of reaction (a) are reported in Figure 1.

The starting $R_1$-Au-X adduct, indicated with **A1** in the Figure 1, turned out to be in the singlet magnetic state, as indeed in all the cases addressed in this study, revealing much more stable than the triplet one. The reaction was initiated by the water addition either on the α or β propargyl position of the substrate through the transition structures **TSAα** and **TSAβ**. Our results indicated that this initial step, the only plausibly responsible of the reaction regioselectivity, was characterized by a very different free energy barriers with the β-addition appearing therefore as, by far, the kinetically more favoured. Such a difference was also observed in the gas-phase calculations, i.e. in the absence of the solvent effect, hence suggesting that its origins should be related to intrinsic, i.e. electronic or steric, effects. The presence and hence the possible involvement of **A1** cyclization product in the whole mechanism [29] was discarded because of the positive free energy (ΔG° of +40 kJoule/mole at 80°C, at the same level of theory) associated with the related reaction. A further interesting aspect to remark was the presence, in the intermediate complexes **A2** and **A3**, of a sharp H-bond between the water molecule and the phthalimido moiety actually producing a zwitterionic species in both the cases. This feature appeared as kinetically relevant. As a matter of fact, such a proton was then transferred, through **TSA1** or **TSA2** (showing the same free energy barrier), to the propargyl position to irreversibly produce the protonated form of the final product, i.e. the β-phthalimido ketone. Therefore, the H-bond with phthalimido-group appeared a key catalytic event for the whole process even though, apparently, it did not play any relevant role in the observed regioselectivity hence requiring a more in-depth analysis (see below). A slightly different scenario was observed (see Figure 2) when the phenyl group was substituted by a H-atom (reaction (b)). In this case we observed a similar (although not identical, see below) initial $R_1$-Au-X complex and, most importantly, the same mechanism characterized by the similar shuttling role of the phthalimido-group. However, the relative height of the two barriers turns out to be lower and also reversed with respect to reaction (a). This finding, in nice qualitative agreement with experimental results, suggests for this reaction a reduced regioselectivity. It is important to note that in this case the formation of a cyclized product from the R1-Au-X complex also showed a positive formation free energy ΔG° (+18 kJoule/mole) which again makes this species not mechanistically relevant.[29]



View Article Online
DOI: 10.1039/D0OB01598A

ARTICLE

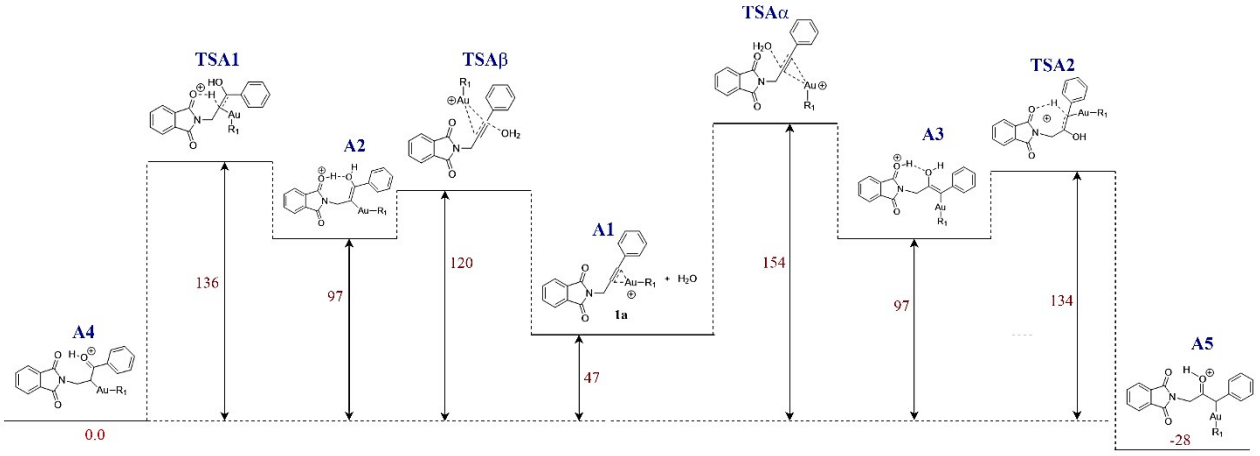



**Figure 1.** Free energy (kJoule/mole) diagram at 80°C in acetonitrile for the gold-catalyzed hydration of *N*-propargylpthalimide (**1a** with $R_2$ = phenyl).

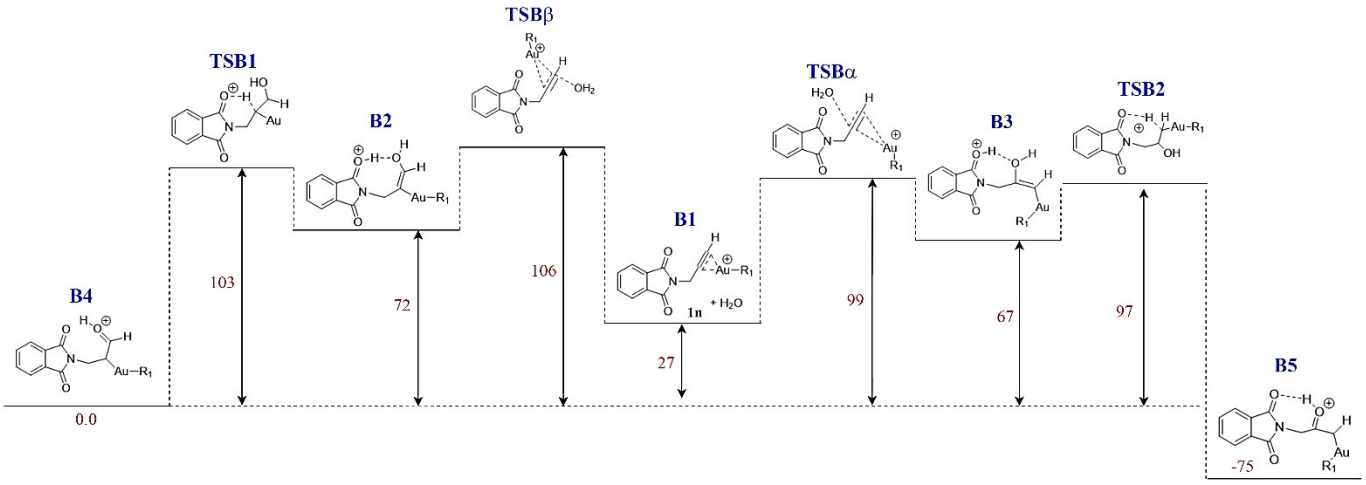



**Figure 2.** Free energy (kJoule/mole) diagrams at 80°C in acetonitrile for of gold-catalyzed hydration of *N*-propargylpthalimide (**1n** with $R_2$ = H).

View Article Online
DOI: 10.1039/D0OB01598A



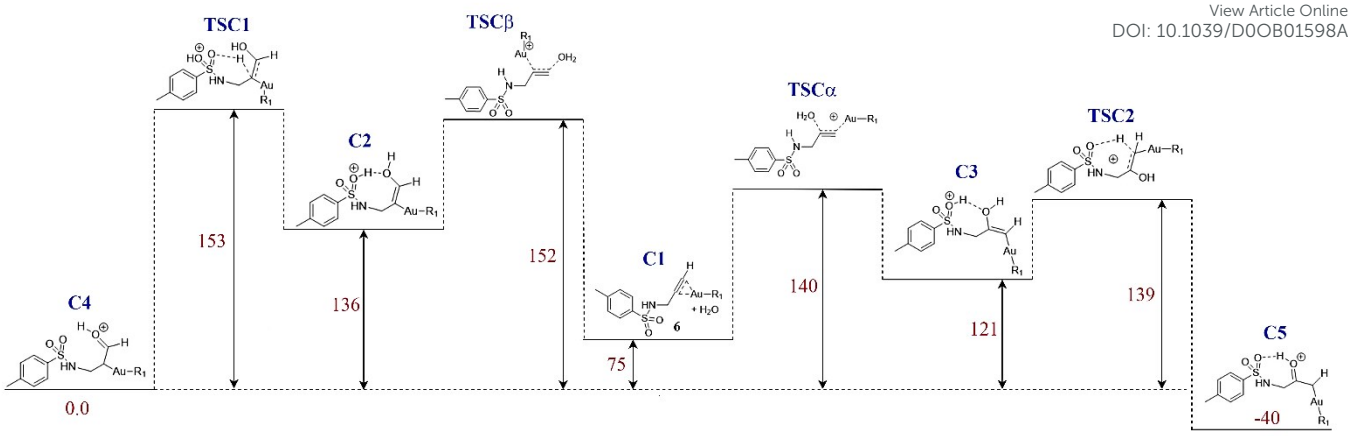



**Figure 3.** Free energy diagrams at 80°C in acetonitrile (kJoule/mole) for the reaction gold-catalyzed hydration of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide.

In the case of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide **6** (reaction (c), Figure 3) we found a free energy profile qualitatively resembling the previous case. Interestingly, also in this case, the presence of the shuttling effect appeared as crucial for the whole reaction kinetic and thermodynamic outcome. The catalytic role of the basic group acting as a proton-shuttle in the hydration mechanism was even reinforced by the outcome of the next step of our computational investigation concerning the hydration of N-(prop-2-yn-1-yl)aniline **8** (reaction (d)). For this substrate, we located a stable R1-Au-X initial adduct with the same previously observed initial complex features, but we could not find any low-energy TS concerning the water addition to the propargyl group. On the other hand, we could easily find a TS connecting the initial substrate to the cyclic structure according to the following route described in Figure 4.

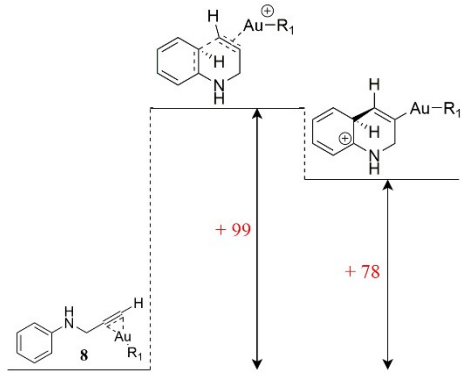



**Figure 4.** Free energy diagrams at 80°C in acetonitrile (kJoule/mole) for the cyclization gold-catalyzed reaction of of N-(prop-2-yn-1-yl)aniline

However, in this system, and differently from the previous reported examples, we also located a very stable N-Au complex,[30] which revealed 15 kJ/mole more stable than the R1-Au-X complex but unable of generating a kinetically accessible hydration route. This finding turned out to be crucial in the final example concerning the hydration of the 3-phenylprop-2-yn-1-amine, experimentally found to be completely inefficient.

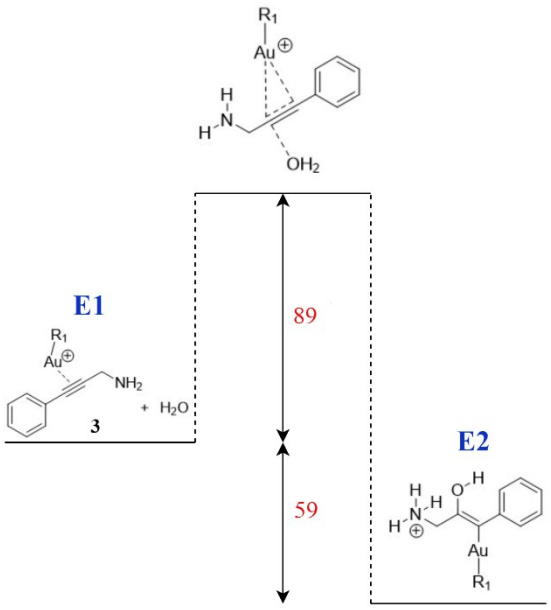



**Figure 5.** Free energy diagrams at 80°C in acetonitrile (kJoule/mole) for gold-catalyzed hydration reaction of of 3-phenylprop-2-yn-1-amine.

As a matter of the fact, the analysis of the free-energy diagram reported in Figure 5 actually indicated that hydration reaction could be considered as kinetically feasible through a relatively low-energy-barrier α-addition and the stabilizing effect of the basic $NH_2$ group in the intermediate E2. However, for this system, the Au-*N*-complex, for which we could not locate any low-energy route for hydration reaction, revealed 75 kJoule/mole more stable than the $R_1$-Au-X



View Article Online
DOI: 10.1039/D0OB01984A

complex at 80°C in acetonitrile. It is important to note that the reason for the above huge free energy difference was found to be entirely due to non-intrinsic electronic effects and, in particular, to the higher polarity of Au-*N*-complex whose dipole moment, 4.0 Debye, was exactly twice the dipole moment of π-complex. Therefore, the presence of any solvent, in particular polar solvents, unavoidably stabilized for electrostatic effects the more polar species essentially resulting in a hydration inhibition. Results so far illustrated, although able of showing the importance of the presence of moieties able to establish a H-bond with the entering water, do not shed light on the possible origin of the observed regioselectivity. At this purpose we decided to carry out a comparative investigation, making use of both Natural Bond Order QTAIMS analysis, of the main electronic features of the initial $R_1$-Au-X adduct and the hydration TSs previously described. In Figure 6 we report a concise description of the final outcome whose details can be found in the Supplementary Information.

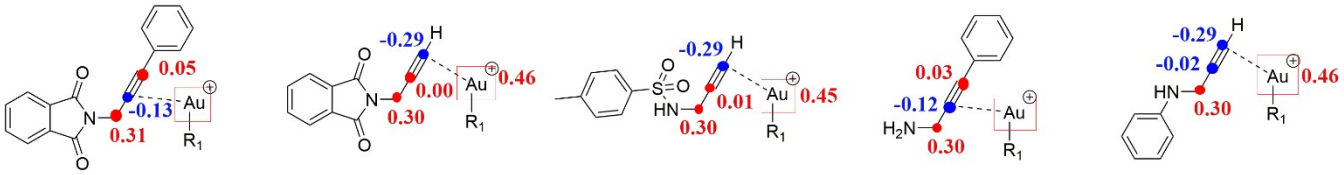



**Figure 6.** Schematic picture of the NBO charges (in atomic units) for the $R_1$-Au-X atoms mainly involved in the hydration process (see Figures 1-5). The presence or the absence of a dotted line between gold atom and the alkyne carbon atoms indicates the presence or the absence of an interaction as emerged from QTAIMS analysis.

It is important to initially focus our attention on the results of QTAIMS analysis on the hydration TSs for which we have systematically observed : (i) a sharp increase (order of 10-15%), with respect to the initial adduct, of the distance between Gold(I) and the carbon atom undergoing water addition: (ii) a scarce covalent character of the water-carbon interaction clearly indicating an *early* character of all the TSs. This information suggests that most of the observed mechanistic features should rely on the actual electronic features of the $R_1$-Au-X adducts in part schematically reported in the Figure 6. Gold(I) atom, beyond a non-covalent (order of 6-10 kJoule/mole) and probably kinetically irrelevant interaction with the oxygen atom of the phthalimido or benzensulfonamide group, was systematically found to interact, through a transit interaction [18] (order of 50-60 kJoule/mole) only with the $C_\beta$ atom and only with the $C_\alpha$ atom in the lack and in the presence of the phenyl substituent, respectively (see also Figure 6). As a consequence the carbon atom not interacting with gold(I), and also characterized by a weak positive charge, turns out to be (i) more electrophilic toward water and (ii) more inclined to suffer the increase of the distance from Gold(I) observed upon water addition. For this reason, such a carbon atom always shows the kinetically more accessible hydration site generating the observed regioselectivity. It is also interesting to note that, for some not emerged reason, in the case of *N*-(prop-2-yn-1-yl)aniline none of the carbon atoms shows a net positive charge. Although these electronic/electrostatic effects cannot explain more conclusive evidences concerning the physico-chemical nature of the observed activation free-energy differences, in some cases are very high (Figure 5) and in some other cases less pronounced (Figures 2 and 3), we feel that they are particularly significant and certainly deserve further investigation in the future.

## Conclusions

In conclusion, we have therefore extended the methodology of the gold-catalyzed reactions by studying the hydration process of *N*-propargylphthalimides. After optimization of the reaction conditions, we found that the commercially available $IPrAuNTf_2$ was effective to promote regioselective hydration of protected propargylic amines, regardless of the substituents of the alkynyl moiety. Both alkyl- and aryl- or heteroaryl-substituted *N*-propargylphthalimides could efficiently be transformed to β-amino ketones. The results of the computational investigation carried out on five model systems were found in satisfactory agreement with the experimental findings. Electronic effects appeared as the most relevant ones for the reaction mechanism. In particular, the combination of intrinsic electronic features – such as the electrophilicity of carbon atoms presented in the initial substrate or the electronic density distribution in the water addition TS – or external electronic features such as the solvent effect seemed to play a relevant role in the reaction outcome. The presence in the substrate of moieties able to establish a H-bond with the entering water appeared as kinetically relevant for the irreversibility of the formation of the final product. Further studies will focus on other applications of *N*-propargylphthalimides such as the combination of hydration with other atom economical processes.

## Conflicts of interest

There are no conflicts to declare.

View Article Online
DOI: 10.1039/D0OB01842J





## Acknowledgements

This work was supported by the Università dell'Aquila, the Centre National de la Recherche Scientifique (CNRS) and the University Côte d'Azur. We gratefully acknowledge the Università dell'Aquila for grant to VM. This study was partly supported by research funding from the Canceropôle PACA, Institut National du Cancer and Région Sud. CINECA is acknowledged for the use of the supercomputing facilities in the framework of an ISCRA-C project.

## Notes and references

1 (a) E. Vessally, M. Babazadeh, A. Hosseinian, L. Edjlali and L. Sreerama, Recent Advances in Synthesis of Functionalized β-Lactams through Cyclization of *N*-Propargyl Amine/Amide Derivatives, *Curr. Org. Chem.*, 2018, **22**, 199-205; (b) K. Lauder, A. Toscani, N. Scalacci and D. Castagnolo, Synthesis and Reactivity of Propargylamines in Organic Chemistry, *Chem. Rev.*, 2017, **117**, 14091-14200; (c) S. Arshadi, E. Vessally, L. Edjlali, R. Hosseinzadeh-Khanmiri and E. Ghorbani-Kalhor, *N*-Propargylamines: versatile building blocks in the construction of thiazole cores**,** *Beilstein J. Org. Chem.*, 2017, *13*, 625-638; (d) E. Vessally, L. Edjlali, A. Hosseinian, A. Bekhradnia and M. D. Esrafili, Novel Routes to Quinoline Derivatives from *N*-Propargylamines, *RSC Adv.*, 2016, **6**, 49730-49746; (e) E. Vessally, A New Avenue to the Synthesis of Highly Substituted Pyrroles: Synthesis from *N*-Propargylamines, *RSC Adv.*, 2016, **6**, 18619-18631.

2 (a) A. Suneja, V. Bisai and V. K. Singh, Asymmetric Synthesis of Medicinally Important Isoindolinones (*S*)-PD 172938, (*R*)-JM 1232, and Related Structures. *J. Org. Chem.*, 2016, **81**, 4779-4788; (b) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli and G. Celentano, Very Mild, Enantioselective Synthesis of Propargylamines Catalyzed by Copper(I)-Bisimine Complexes. *J. Org. Chem.*, 2006, **71**, 2064-2070.

3 (a) J. Ying, H. Wang, X. Qi, J.-B. Peng and X.-F. Wu, Gold-Catalyzed Regiospecific Hydration of *N*-Tosyl Propargylic Amines. *Organometallics*, 2018, **37**, 2837-2841; (b) J. Ying and L. Pu, Regiospecific Hydration of *N*-(Diphenylphosphinoyl) propargyl Amines: Synthesis of β-Amino Ketones by Au(III) Catalysis, *J. Org. Chem.*, 2016, **81**, 8135-8141; (c) W. E. Brenzovich, Gold in Total Synthesis: Alkynes as Carbonyl Surrogates, *Angew. Chem., Int. Ed.*, 2012, **51**, 8933-8935.

4 (a) L. Hintermann and A. Labonne, Catalytic Hydration of Alkynes and Its Application in Synthesis, *Synthesis* 2007, **2007**, 1121-1150. (b) M. Beller, J. Seayad, A. Tillack and H. Jiao, Catalytic Markovnikov and anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368- 3398. (c) F. Alonso, I. P. Beletskaya and M. Yus, Transition-Metal-Catalyzed Addition of Heteroatom-Hydrogen Bonds to Alkynes, *Chem. Rev.*, 2004, **104**, 3079-3159.

5 (a) M. Heidrich, M. Bergmann, D. Müller-Borges and H. Plenio, Bispentiptycenyl-*N*-Heterocyclic Carbene (NHC) Gold Complexes: Highly Active Catalysts for the Room Temperature Hydration of Alkynes, *Adv. Synth. Catal.*, 2018, **360**, 3572-3578; (b) M. Gatto, W. Baratta, P. Belanzoni, L. Belpassi, A. Del Zotto, F. Tarantelli and D. Zuccaccia, Hydration and Alkoxylation of Alkynes Catalyzed by NHC-Au-OTf, *Green Chem.*, 2018, **20**, 2125-2134; (c) M. Gatto, A. Del Zotto, J. Segato and D. Zuccaccia, Hydration of Alkynes Catalyzed by L–Au–X under Solvent- and Acid-Free Conditions: New Insights into an Efficient, General, and Green Methodology, *Organometallics*, 2018, **37**, 4685-4691; (d) P. Klumphu, C. Desfeux, Y. Zhang, S. Handa, F. Gallou and B. H. Lipshutz, Micellar Catalysis Enabled Sustainable ppm Au-Catalyzed Reactions in Water at Room Temperature, *Chem. Sci.*, 2017, **8**, 6354-6358; (e) J. T. Sarmiento, S. Suárez-Pantiga, A. Olmos and T. Varea, G. Asensio, Silica-Immobilized NHC-Gold(I) Complexes: Versatile Catalysts for the Functionalization of Alkynes under Batch and Continuous Flow Conditions, *ACS Catal.*, 2017, **7**, 7146-7155; (f) M. N. Pennell, M. Kyle, S. M. Gibson, L. Male, P. G. Turner, R. S. Grainger and T. D. Sheppard, Intercepting the Gold-Catalysed Meyer-Schuster Rearrangement by Controlled Protodemetallation: A Regioselective Hydration of Propargylic Alcohols, *Adv. Synth. Catal.*, 2016, **358**, 1519-1525; (g) R. E. Ebule, D. Malhotra, G. B. Hammond and B. Xu, Ligand Effects in the Gold Catalyzed Hydration of Alkynes, *Adv. Synth. Catal.*, 2016, **358**, 1478-1481; (h) M. Trinchillo, P. Belanzoni, L. Belpassi, L. Biasiolo, V. Busico, A. D'Amora, L. D'Amore, A. Del Zotto, F. Tarantelli, A. Tuzi and D. Zuccaccia, Extensive Experimental and Computational Study of Counterion Effect in the Reaction Mechanism of NHC-Gold(I)-Catalyzed Alkoxylation of Alkynes, *Organometallics*, 2016, **35**, 641-654; (i) L. Biasiolo, A. Del Zotto and D. Zuccaccia, Toward Optimizing the Performance of Homogeneous L-Au-X Catalysts through Appropriate Matching of the Ligand (L) and Counterion ($X^-$), *Organometallics*, 2015, **34**, 1759-1765; (j) Y. Xu, X. Hu, J. Shao, G. Yang, Y. Wu and Z. Zhanga, Hydration of Alkynes at Room Temperature Catalyzed by Gold(I) Isocyanide Compounds, *Green Chem.*, 2015, **17**, 532-537; (k) L. Biasiolo, G. Ciancaleoni, L. Belpassi, G. Bistoni, A. Macchioni, F. Tarantelli and D. Zuccaccia, Relationship Between the Anion/Cation Relative Orientation and the Catalytic Activity of Nitrogen Acyclic Carbene–Gold Catalysts, *Catal. Sci. Technol.*, 2015, **5**, 1558-1567; (l) A. Zhdanko and M. E. Maier, Explanation of Counterion Effects in Gold(I)-Catalyzed Hydroalkoxylation of Alkynes, *ACS Catal.*, 2014, **4**, 2770-2775; (m) L. Biasiolo, M. Trinchillo, P. Belanzoni, L. Belpassi, V. Busico, G. Ciancaleoni, A. D'Amora, A. Macchioni, F. Tarantelli and D. Zuccaccia, Unexpected Anion Effect in the Alkoxylation of Alkynes Catalyzed by *N*-Heterocyclic Carbene (NHC) Cationic Gold Complexes, *Chem. Eur. J.*, 2014, **20**, 14594-14598; (n) A. Zhdanko and M. M. Maier, The Mechanism of Gold(I)-Catalyzed Hydroalkoxylation of Alkynes: An Extensive Experimental Study, *Chem. Eur. J.*, 2014, **20**, 1918-1930; (o) H. He, C. Qi, X. Hu, Y. Guan and H. Jiang, Efficient Synthesis of Tertiary α-Hydroxy Ketones through $CO_2$-Promoted Regioselective Hydration of Propargylic Alcohols, *Green Chem.*, 2014, **16**, 3729-3733.

6 L. Wu and M. Shi, $Yb(OTf)_3$- or $Au^I$-Catalyzed Domino Intramolecular Hydroamination and Ring-Opening of Sulfonamide-Substituted 1,1-Vinylidenecyclopropane diesters, *Chem. Eur. J.*, 2011, **17**, 13160-13165.

7 (a) D. Dutt, V. Goel, N. Garg, D. Choundhury, D. Mallick and V. Tyagi, Biocatalytic Aza-Michael Addition of Aromatic Amines to Enone Using α-Amylase in Water, *Adv. Synth. & Catal.*, 2020, **362**, 858-866; (b) B. Yasa, B. Hsdemir and O. Erken, *β*-Amino Carbonyl Compounds from Iodine-Catalyzed Three Component Mannich Reactions and Evaluation of Their Antioxidant Activity, *Org. Prep. Proc. Int.*, **2019**, **51**, 537-546; (c) J.-T. Xu, G.-Q. Xu, Z.-Y. Wang and P.-F. Xu, Visible Light Photoredox-Catalyzed α-Alkylation of Cyclic Tertiary Arylamines, *J. Org. Chem.*, 2019, **84**, 14760-14769 and references therein.

8 For selected methods to prepare β-amino ketones, see: (a) P. Raundal, R. Watpade, P. Patil and J. Aher, Synthesis, Characterization of ß-Amino Carbonyl Complexes via Mannich Reaction and Study of their Antibacterial Activity, *Der Pharma Chemica*, 2016, **8**, 27-30; (b) M. S. Taylor, D. N. Zalatan, D. A. M. Lerchner and E. N. Jacobsen, Highly Enantioselective Conjugate Additions to α, β-Unsaturated Ketones Catalyzed

View Article Online
DOI: 10.1039/D0OB01598A



by a (Salen)Al Complex, *J. Am. Chem. Soc.*, 2005, **127**, 1313-1317; (c) M. L. Kantam, V. Neeraja, B. Kavita, B. Neelima and S. Hussain, $Cu(acac)_2$ Immobilized in Ionic Liquids: A Recoverable and Reusable Catalytic System for Aza-Michael Reactions, *Adv. Synth. Catal.*, 2005, **347**, 763-766; (d) P. Aschwanden, L. Kværnø, R. W. Geisser, F. Kleinbeck and E. M. Carreira, Reduction of 2,3-Dihydroisoxazoles to β-Amino Ketones and β-Amino Alcohols, *Org. Lett.*, 2005, **7**, 5741-5742; (e) A. Dondoni, A. Marra and A. Boscarato, Stereoselective Conjugate Addition of Nitrogen and Carbon Nucleophiles to Sugar-Derived Enones: Synthesis of Sialic Acid Analogues, *Chem. Eur. J.*, 1999, **5**, 3562-3572; (f) S. Kobayashi and H. Ishitani, Catalytic Enantioselective Addition to Imines, *Chem. Rev.*, 1999, **99**, 1069-1094; (g) M. Arend, B. Westermann and N. Risch, Modern Variants of the Mannich Reaction, *Angew. Chem. Int. Ed.*, 1998, **37**, 1044-1070. (h) S. G. Davies and T. D. McCarthy, An Asymmetric Synthesis of *N*-Protected β-Amino Aldehydes and β-Amino Ketones, *Synlett*, 1995, 700-702. (i) D. J. Hart and D. C. Ha, The Ester Enolate-Imine Condensation Route to β-Lactams, *Chem. Rev.*, 1989, **89**, 1447-1465.

9 (a) N. D. Rode, A. Arcadi, A. Di Nicola, F. Marinelli and V. Michelet, Gold-Catalyzed Cascade Reaction of β-(2-Aminophenyl)-α,β-ynones with Ynamides: A Sequential Route to Polysubstituted 2-Aminoquinolines, *Org. Lett.*, 2018, **20**, 5103-5106 ; (b) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli and V. Michelet, Sequential Silver-Catalyzed Oxidative Cyclization Reactions of Unprotected 2-Alkynylanilines to Anthranils, *Eur. J. Org. Chem.*, 2017, **16**, 2214-2222 ; (c) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli and V. Michelet, Silver- *versus* Gold-Catalyzed Sequential Oxidative Cyclization of Unprotected 2-Alkynylanilines with Oxone, *Chem. Commun.*, 2016, **52**, 1458-1461; (d) A. Arcadi, E. Pietropaolo, A. Alvino and V. Michelet, One-Pot Gold-Catalyzed Aminofluorination of Unprotected 2-Alkynylanilines, *Org. Lett.*, 2013, **15**, 2766-2769.

10 (a) R. Laher, C. Marin and V. Michelet, When Gold Meets Perfumes: Synthesis of Olfactive Compounds via Gold-Catalyzed Cycloisomerization Reactions, *Org. Lett.*, 2020, **22**, 4058-4062; (b) Y. Tang, I. Benaissa, M. Huynh, L. Vendier, N. Lugan, S. Bastin, O. Belmont, V. César and V. Michelet, An Original L-shape, Tunable N-Heterocyclic Carbene Platform for Efficient Gold(I) Catalysis, *Angew. Chem. Int. Ed.*, 2019, **58**, 7977-7981. (c) X. Chen, S. Martini and V. Michelet, A Mild and Regioselective Synthesis of α-Fluoroketones *via* Gold and Selectfluor Partnership, *Adv. Synth. Catal.*, 2019, **361**, 3612-3618.

11 For selected examples of the reactions of propargyl phthalimidic derivatives, see: (a) H. P. Deng, X. Z. Fan, Z. H. Chen, Q. H. Xu and J. Wu, Photoinduced Nickel-Catalyzed Chemo- and Regioselective Hydroalkylation of Internal Alkynes with Ether and Amide α-Hetero C($sp^3$)-H Bonds, *J. Am. Chem. Soc.*, 2017, **139**, 13579-13584; (b) M. V. Pham, B. Ye and N. Cramer, Access to Sultams by Rhodium(III)-Catalyzed Directed C-H Activation, *Angew. Chem. Int. Ed.*, 2012, **51**, 10610-10614; (c) T. Achard, A. Lepronier, Y. Gimbert, H. Clavier, L. Giordano, A. Tenaglia and G. Buono, A Regio- and Diastereoselective Platinum-Catalyzed Tandem [2+1] / [3+2] Cycloaddition Sequence, *Angew. Chem. Int. Ed.*, 2011, **50**, 3552-3556; (e) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, Rhodium(III)-Catalyzed Arene and Alkene C-H Bond Functionalization Leading to Indoles and Pyrroles, *J. Am. Chem. Soc.*, 2010, **132**, 18326-18339; (f) G. Hilt, A. Paul and J. Treutwein, Cobalt Catalysis at the Crossroads: Cobalt-Catalyzed Alder-Ene Reaction versus [2 + 2] Cycloaddition, *Org. Lett.*, 2010, **12**, 1536-1539; (g) H. Gerhard, F. Galbiati and K. Harms, A Modular Approach for the Synthesis of Dibenzoazepine Derivatives, *Synthesis*, 2006, 3575-3584. (h) H. Gerhard and F. Galbiati, Cobalt(I)-Catalysed Neutral Diels-Alder Reactions of Nitrogen-Functionalised Alkynes, *Synlett*, 2005, 829-833.

12 T. Yanai, D. P. Tew and N. C. Handy, A New Hybrid Exchange-Correlation Functional Using the Coulomb-Attenuating Method (CAM-B3LYP), *Chem. Phys. Lett.*, 2004, **393**, 51-57.

13 P. J. Hay and W. R. Wadt, "Ab Initio Effective Core Potentials for Molecular Calculations - Potentials for K to Au Including the Outermost Core Orbitals," *J. Chem. Phys.*, 1985, **82** 299-310.

14 C. B. Breneman and K. B. Wiberg, Determining Atom-Centered Monopoles from Molecular Electrostatic Potentials. The Need for High Sampling Density in Formamide Conformational Analysis, *J. Comput. Chem.*, 1990, **3**, 361-373.

15 (a) S. Miertuš and J. Tomasi, Approximate Evaluations of the Electrostatic Free Energy and Internal Energy Changes in Solution Processes, *Chem. Phys.*, 1982, **65**, 239-245 (b) V. Barone, M. Cossi, and J. Tomasi, A New Definition of Cavities for the Computation of Solvation Free Energies by the Polarizable Continuum Model, *J. Chem. Phys.*, 1997, **107**, 3210-3221.

16 Gaussian 09, Revision A.02, M. J. Frisch et al. Gaussian, Inc., Wallingford CT, 2016.

17 F.P. Foster and F. Weinhold, Natural Hybrid Analysis, J. *Am. Chem. Soc.* 1980, **102**, 7211-7218.

18 R. Bader, A Quantum Theory of Molecular Structure and its Applications, *Chemical Reviews*, 1991, **91**, 893-928.

19 T. Lu and F. Chen, Multiwfn: a Multifunctional Wavefunction Analyzer, *J. Comput. Chem.*, 2012, **33**, 580-592. It is important to note that all the calculations reported in this study suffer from some intrinsic limitations. As a matter of fact, the limited size of the basis set adopted for the optimizations as well as the use of the ECP for Au do not allow to extract a fully quantitative information from the obtained free-energy profiles and from QTAIMS analysis which should be then considered as a semi-quantitative (if not qualitative) support to the experimental observations.

20 S. Sakthivel, A. Sharma and R. Balamurugan, Silver-Catalyzed Synthesis of Substituted Pyridine Derivatives from *N*-Propargylic α-Enamino Esters, *Eur. J. Org. Chem.*, 2017, 3941-3946.

21 L. Politanskaya and E. Tretyakov, *p*-Toluenesulfonic Acid Induced Conversion of Fluorinated Trimethylsilylethynylanilines into Aminoacetophenones: Versatile Precursors for the Synthesis of Benzoazaheterocycles, *Synthesis*, 2018, 555-564 and references therein.

22 (a) P. Nun, R. S. Ramon, S. Gaillard and S. P. Nolan, Efficient Silver-Free Gold(I)-Catalyzed Hydration of Alkynes at Low Catalyst Loading, *J. Organomet. Chem.*, 2011, **696**, 7-11; (b) N. Marion, R. S. Ramón and S. P. Nolan, [(NHC)$Au^I$]-Catalyzed Acid-Free Alkyne Hydration at Part-per-Million Catalyst Loadings, *J. Am. Chem. Soc.*, 2009, **131**, 448-449; (c) N. Marion, R. Gealageas and S. P. Nolan, [(NHC)$Au^I$]-Catalyzed Rearrangement of Allylic Acetates, *Org. Lett.*, 2008, **10**, 1037-1037.

23 (a) D. Zuccaccia, A. Del Zotto and W. Baratta, The Pivotal Role of the Counterion in Gold Catalyzed Hydration and Alkoxylation of Alkynes, *Coord. Chem. Rev.*, 2019, **396**, 103-116. (b) M. Jia and M. Bandini, Counterion Effects in Homogeneous Gold Catalysis, *ACS Catal.*, 2015, 5, 1638-1652.

24 (a) A. Arcadi, Gold-Catalyzed Synthesis of Nitrogen Heterocyclic Compounds via Hydroamination Reactions, *Top Heterocycl Chem*, 2016, **46**, 53-86; (b) G. Abbiati, F. Marinelli, E. Rossi, A. Arcadi, Synthesis of Indole Derivatives from 2-Alkynylanilines by means of Gold Catalysis, *Israel J. Chem.*, 2013, 53, 856-868; (c) I. Ambrogio, A. Arcadi, S. Cacchi, G. Fabrizi and F. Marinelli, Gold-Catalyzed Synthesis of 2-Substituted, 2,3-Disubstituted and 1,2,3-Trisubstituted

View Article Online
DOI: 10.1039/D0OB01598A



Indoles in [bmim]$BF_4$, *Synlett*, 2007, 1775-1779; (d) A. Arcadi, G. Bianchi and F. Marinelli, Gold(III)-Catalyzed Annulation of 2-Alkynylanilines: a Mild and Efficient Synthesis of Indoles and 3-Haloindoles, *Synthesis*, 2004, 610-618.

25 Q. Wang, Y. Jiang, R. Sun, X.-Y. Tang and M. Shi, Gold-Catalyzed Fluorination-Hydration: Synthesis of α-Fluorobenzofuranones from 2-Alkynylphenol Derivatives, *Chem. Eur. J.*, 2016, **22**, 14739 -14745.

26 M. Alfonsi, A. Arcadi, M. Chiarini and F. Marinelli, Sequential Alkylation/Gold-Catalyzed Annulation Reactions of Anilines with Propargylic Bromide Derivatives, *Tetrahedron Lett.*, 2011, **52**, 5145-5148.

27 (a) J. Cordón, G. Jiménez-Osés, J. M. López-de-Luzuriaga, M. Monge, M. E. Olmos and D. Pascual, Experimental and Theoretical Study of Gold(III)-Catalyzed Hydration of Alkynes, *Organometallics*, 2014, **33**, 3823-3830; (b) D. Zuccaccia, L. Belpassi, F. Tarantelli and A. Macchioni, Ligand Effects on Bonding and Ion Pairing in Cationic Gold(I) Catalysts Bearing Unsaturated Hydrocarbons, *Eur. J. Inorg. Chem.*, 2013, 4121-4135; (c) G. Mazzone, N. Russo and E. Sicilia, Gold(I)-Catalyzed Hydration of 1,2-Diphenylacetylene: Computational Insights, *J. Chem. Theory Comput.*, 2010, **6**, 2782-2789.; (d) C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, A New Insight into Gold(I)-Catalyzed Hydration of Alkynes: Proton Transfer, *ChemCatChem*, 2010, **2**, 1226-1230.

28 M. Gatto, P. Belanzoni, L. Belpassi, L. Biasiolo, A. Del Zotto, F. Tarantelli and D. Zuccaccia, Solvent-, Silver-, and Acid-Free NHC-Au-X Catalyzed Hydration of Alkynes. The Pivotal Role of the Counterion, *ACS Catal.*, 2016, **6**, 7363-7376.

29 (a) J. A. Goodwin and A. Aponick, Regioselectivity in the Au-Catalyzed Hydration and Hydroalkoxylation of Alkynes, *Chem. Commun.*, 2015,**51**, 8730-8741; (b) J. Jeong, D. Ray and C. H. Oh, Cationic Gold-Catalyzed Regioselective Hydration of 1-Arylalkynes through Carbonyl Group Participation, *Synlett*, 2012, 897–902; (c) W. Wang, B. Xu and G. B. Hammond, Efficient Synthesis of *γ*-Keto Esters through Neighboring Carbonyl Group-Assisted Regioselective Hydration of 3-Alkynoates, *J. Org. Chem.* 2009, **74**, 1640-1643.

30 (a) G. Kovács, A. Lledòs and G. Ujaque, Hydroamination of Alkynes with Ammonia: Unforeseen Role of the Gold(I) Catalyst, *Angew. Chem. Int. Ed.*, 2011, **50**, 11147-11151; (b) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, and Guy Bertrand, Homogeneous Catalytic Hydroamination of Alkynes and Allenes with Ammonia, *Angew. Chem. Int. Ed.*, 2008, **47**, 5224-5228.

