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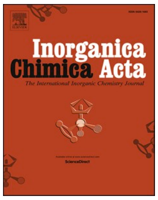

Research paper

# Experimental and theoretical investigation of the cycloisomerization of *N*-propargylcarboxamide catalyzed by NHC-Au-X in green solvents

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## ABSTRACT

For the first time, NHC-Au-X [NHC = (1,3-bis(2,6-di-isopropylphenyl)-imidazol-2-ylidene, $X^- = BF_4^-$, $OTf^-$, $OTs^-$, $TFA^-$] catalysts were tested in the cycloisomerization of N-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline in a wide set of green solvents. We found that most of these solvents (cyclohexanone, isopropyl acetate, MIBK, ethyl lactate, furfuryl alcohol, γ-valerolactone, propylene carbonate and propionic acid) are comparable or better solvents with respect to traditional VOS. Furthermore, the catalyst activity is related to the basic strength of the anion and the performances of the catalysts decrease gradually with increasing basicity and hydrogen-bond acceptor power of $X^-$. Kinetic experiments and DFT calculations seem to indicate that both the characteristic of the solvent and counterion should be taken into account.

## 1. Introduction

In recent years, a fast growing area in organic chemistry is represented by homogeneous gold catalysis [1]. Most of the reactions in which gold catalysts are involved can be classified as nucleophilic additions to a carbon–carbon unsaturated bond promoted by L-Au-X compounds (Scheme 1, ISIP = inner sphere ion pair, L = ancillary ligand and $X^-$ = counterion). The gold metal fragment L-Au-X acts as a Lewis acid coordinating unsaturated hydrocarbons, *i.e.,* alkynes, in the pre-equilibrium step (Scheme 1, **intermediate OSIP** = outer sphere ion pair), which subsequently undergoes nucleophilic attack by Nu-H, with the formation of organogold intermediates (Scheme 1, **intermediate I**). The gold-carbon bonds in these intermediates are typically cleaved by a proton, protodeauration, to give the desired products and regenerate the catalyst. In-depth kinetic and mechanistic studies on gold(I)-catalyzed nucleophilic addition to a carbon–carbon unsaturated bond have been appearing in the literature [2], with the aim to understand the ligand [3–9] and counterion [10–15] effects in the different steps of the catalytic cycle.

A rationalization of the 'counterion effects' is still far from being fully achieved, even if several experimental data in gold catalysis are present in the literature [16]. Both coordination ability and basicity [17] of the counterion may have a great impact on the catalytic performances of gold complexes [16] and some of us [18,19] studied the Au-catalyzed intermolecular methoxylation of alkynes and proposed that the nucleophilic attack of nucleophile is assisted by the anion through the formation of a hydrogen bond [20].

Counterion and ligand effects have been studied by some of us in the cycloisomerization of *N*-propargylcarboxamides [21]. It is a well-studied gold-catalyzed reaction [22] in which protodeauration is considered the slow step (Scheme 1) [3a-d]. A pseudo-first order kinetic with respect to catalyst concentration is observed [23], and the key vinyl gold intermediate [24] (Scheme 1, **intermediate I**) has been identified in the case of NHC-Au(I) [25] and $PPh_3$-Au(I) [2,31] and in the case of gold(III) [26]. These observations induce to believe that the formation of the vinyl gold complex (**intermediate I**) is not the rate-determining step [25]. We have found that the choice of the most efficient L-Au-X catalyst for the cycloisomerization of *N*-propargylcarboxamides should not be

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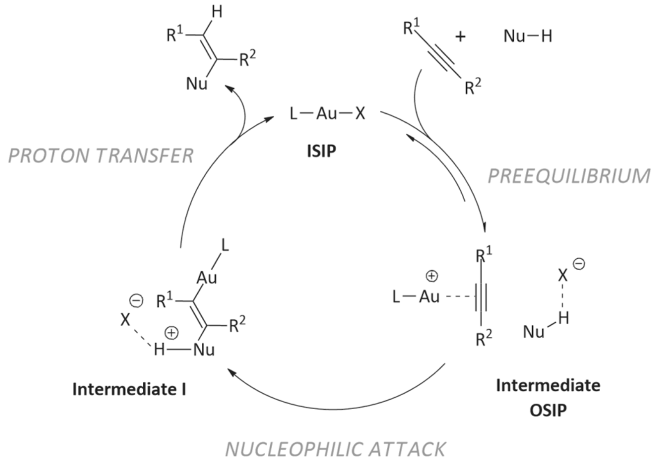


**Scheme 1.** Proposed gold catalytic cycle.

done by evaluating the properties of L [27] and $X^-$ alone, but rather on the basis of their best combination.

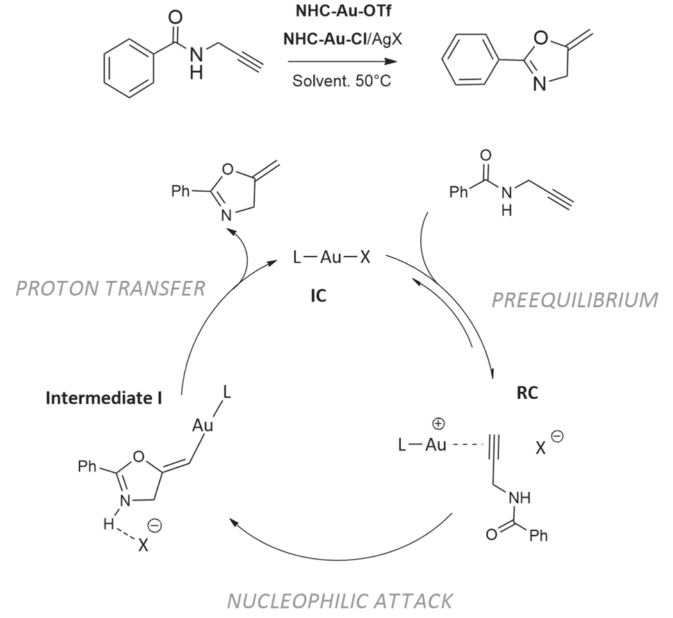
On the other hand, most of the protocols that employ gold(I) complexes as catalysts, are unsustainable from a green chemistry point of view [28]: high catalyst loading, use of volatile organic solvent (VOS), silver salts as halide scavenger, and non-recyclable catalysts represent the major drawbacks [29]. A great effort was done in the area of neat and silver-free gold catalyzed reactions [30–32].

Recently, some of us investigated the activity of NHC-Au-X [NHC = (1,3-bis(2,6-di-isopropylphenyl)-imidazol-2-ylidene, $X^-$ = $BArF^-$, $BF_4^-$, $SbF_6^-$, $ClO_4^-$, $OTf^-$, $NTf_2^-$, $OTs^-$, and $TFA^-$), $BArF^-$ = tetrakis(3,5-bis(trifluoro-methyl)phenyl)-borate] as catalysts in solvent-, acid- and silver-free hydration of alkynes at room/mild temperature and with suitable ionic additives [33].

Replacement of VOS with green solvents [34] is a key topic in organic synthesis, and in many transition metal catalyzed organic process bio-based solvents [35] such as water [36], γ-valerolactone (GVL) [37], glycerol [38], lactic acid and its derivatives [39], d-limonene and *p*-cymene [40] are employed instead of VOS. Other green solvents such as biodiesel [41], $scCO_2$ [42], perfluorinated hydrocarbons [43], polyethylene glycol (PEG) [44], Deep Eutectic Solvent (DES) [45] and ionic liquid (IL) [46] also find frequent use in organic synthesis. Use of green solvents instead of VOS is rare in gold catalysis [47–49].

Some of us [50] investigated the alkoxylation and hydration of alkynes in a wide set of green solvents using NHC-Au-OTf as catalyst and we found that polarity and functionalities present in the solvent influence the three steps of the reaction pathway (pre-equilibrium, nucleophilic attack, and protodeauration).

Building on this state of the art, we investigate here the activity of NHC-Au-X ($X^-$ = $BF_4^-$, $OTf^-$ $OTs^-$, $TFA^-$) catalysts in the cycloisomerization of N-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline (Scheme 2) conducted in green solvents. We found that most of these solvents are comparable or better solvents with respect to traditional VOS. Kinetic experiments coupled with DFT calculations have allowed us to shed light on the mechanism of cycloisomerization in green conditions. The results presented here show that the anion properties, both coordination ability and basicity (hydrogen-bond acceptor power), should have a great impact on its "proton shuttle ability".



**Scheme 2.** Cycloisomerization of N-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline.

**Table 1**
NHC-Au-X catalyzed N-(2-Propynyl)benzamide isomerization at 50 °C.[a]

| Entry | Solvent | Conv.[b] % | TOF[c] ($h^{-1}$) | $\varepsilon_r$[d] |
|---|---|---|---|---|
| | **VOS** | | | |
| 1 | Chloroform | 90 | 354 | 4.81 |
| 2 | Dichloromethane | 89 | 406 | 8.93 |
| 3 | Acetone[e] | 10 | 43 | 21 |
| 4 | 3-Nitrotoluene | 65 | 281 | 22.2 |
| 5 | Nitromethane | 67 | 274 | 35.87 |
| | **Green** | | | |
| 6 | Cyclohexanone | 47 | 206 | 2.02 |
| 7 | p-Cymene | 15 | 63 | 2.24 |
| 8 | Limonene[e] | 11 | 50 | 2.4 |
| 9a | Propionic acid | 94 | 431 | 3.35 |
| 9b | Propionic acid[f] | 16,7 | 65 | 3.35 |
| 9c | Propionic acid[g] | 39,6 | 154 | 3.35 |
| 9d | Propionic acid[h] | 90,9 | 354 | 3.35 |
| 10 | Cyrene | 23 | 94 | 3.4 |
| 11 | Anisole[e] | 13 | 56 | 4.3 |
| 12 | Isopropyl acetate | 49 | 223 | 6.3 |
| 13 | MIBK | 62 | 250 | 13.1 |
| 14 | Ethyl Lactate | 73 | 317 | 15.4 |
| 15 | Furfuryl alcohol | 39 | 148 | 16.85 |
| 16 | Propionitrile[e] | 12 | 50 | 27.7 |
| 17 | γ-Valerolactone | 47 | 192 | 36.9 |
| 18 | DMSO | 5 | 21 | 46.7 |
| 19 | Propylene carbonate | 49 | 180 | 64 |
| 20 | BMIM-OTf | 28 | 120 | – |
| 21 | Methyl levulinate | 21 | 90 | – |

[a] Catalysis conditions: NHC-Au-OTf (0.0025 mmol, 1.8 mg), N-(2-Propynyl)benzamide (0.5 mmol, 79.6 mg), solvent (200 μL).
[b] Determined by 1H NMR; average value of three measurements after 30 min.
[c] $TOF = (mol_{product}/mol_{catalyst})/t$ calculated after 30 min.
[d] $\varepsilon_r$ = dielectric constant.
[e] slightly or not soluble.
[f] NHC-Au-Cl (0.0025 mmol, 1.6 mg), 1.1 eq AgOTs.
[g] NHC-Au-Cl (0.0025 mmol, 1.6 mg), 1.1 eq AgTFA.
[h] NHC-Au-Cl (0.0025 mmol, 1.6 mg), 1.1 eq $AgBF_4$.

## 2. Results and discussion

Gold complexes were synthesized according to literature procedures (see Supporting Information for details). All complexes NHC-Au-X (Scheme 2, $X^-$ = $BF_4^-$, $OTf^-$, $OTs^-$, $TFA^-$) have been tested as catalysts in the cycloisomerization of N-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline (Scheme 2 and Table 1). Isolated NHC-Au-OTf was directly employed, whereas in all other cases the catalyst was prepared *in situ* in an NMR tube by mixing equimolar amounts of the precursor NHC-Au-Cl and the appropriate silver salt (Scheme 2 and Table 1). Interestingly, all the solvents were used as delivered without further purification.

A typical catalytic run was performed by dissolving N-(prop-2-ynyl) benzamide (0.5 mM) in the presence of 0.5 mol% of NHC-Au-OTf (or 1:1 L-Au-Cl/AgX) at 50 °C in the appropriate solvent (0.2 mL). The progress of reaction was monitored by NMR spectroscopy (see Supporting Information for details).

Most reactions reached more than 90% of conversion within 8 h (see Table S2 in the Supporting Information) except those run in acetone, limonene, anisole and proprionitrile (Table 1, entries 3, 8, 11, and 16) in which N-(prop-2-ynyl)benzamide resulted slightly soluble or even insoluble, and in dimethyl sulfoxide (Table 1, entry 18) due to its strong coordinative capability, as previously observed [50].

In order to compare the catalytic activity in different solvent, the values of the initial turnover frequency, TOFi (Table 1) were calculated.

Chloroform and dichloromethane showed the best performance among the volatile organic solvents (VOS) giving a $TOF_i$ of 354 and 406 $h^{-1}$, respectively (Table 1, entries 1 and 2). Less efficiently, NHC-Au-OTf promoted the formation of the reaction product with a very similar $TOF_i$ of 281 and 274 in the higher polar solvents 3-nitrotoluene and nitromethane (Table 1, entries 4 and 5). Finally, the very low value of 43 was obtained in acetone (Table 1, entry 3).

Turning into green solvents, very different catalytic performances were observed, and although the green solvents showed, on average, slower conversion with respect to VOS, propionic acid resulted to be the best among all solvents with a $TOF_i$ of 431 $h^{-1}$ (Table 1, entry 9). Medium $TOF_i$ values in the range 150–300 $h^{-1}$ were obtained in cyclohexanone, isopropyl acetate, MIBK, ethyl lactate, furfuryl alcohol, γ-valerolactone, and propylene carbonate (Table 1), while lower catalytic performances ($TOF_i$s in the range 90–150 $h^{-1}$) were observed for p-cymene, BMIM-OTf and methyl levulinate (Table 1). Finally, limonene, cyrene, anisole, propionitrile and DMSO gave the worst catalytic performances ($TOF_i$s below 90 $h^{-1}$) owing to coordination of the solvent to the metal fragment (propionitrile in addition to DMSO) or low solubility of the starting material.

These results confirm our previous results concerning the hydration and alkoxylation of alkynes: a sustainable production of chemicals with homogeneous gold catalysts in green solvents is reachable [51] and exploration of the use of gold catalysts in other nucleophilic addition reactions on substrates with unsaturated bonds (especially alkynes) in green solvents is mandatory.

In order to verify the importance of the acid-base nature and hydrogen-bond acceptor powers of the counterion in this reaction we have just considered (Fig. 1) the catalytic properties of NHC-Au-X ($X^- = BF_4^-$, $OTf^-$, $OTs^-$, and $TFA^-$) in $CDCl_3$ [21] The catalyst activity is related to the basic strength of the anion and the performances of the catalysts decrease (Fig. 1) gradually with increasing basicity and hydrogen-bond acceptor power of $X^-$ (basic strength: $BF_4^- < OTf^- < OTs^- < TFA^-$). The plausible scenario for NHC-Au-X is that too basic anions with higher hydrogen-bond acceptor power ($OTs^-$ and $TFA^-$) do not easily release the proton to gold thus slowing down the reaction rate.

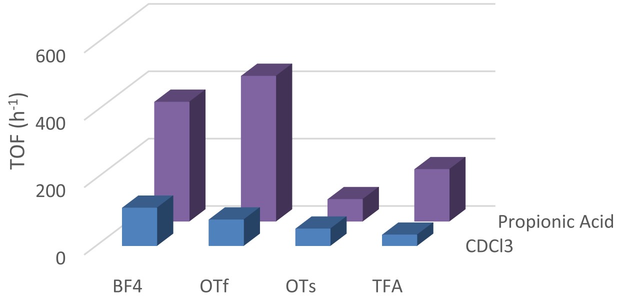


**Fig. 1.** $TOF_i$ values for the cycloisomerization of N-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline catalyzed by NHC-Au-X ($X^- = BF_4^-$, $OTf^-$, $OTs^-$, and $TFA^-$) in $CDCl_3^{21}$ and propionic acid.

In addition, the higher coordination ability of $TFA^-$ versus the NHC-$Au^+$ fragment probably favors the formation of the precatalyst NHC-Au-TFA during the catalysis.

In the case of propionic acid, $OTf^-$ shows the best performance followed by $BF_4^-$. $OTs^-$ exhibited the lower activity according to the previous study [21]. On the other hand, the most basic anion $TFA^-$ shows better results probably due to the acid environment that is able to protonate $TFA^-$ disfavouring the formation of NHC-Au-TFA.

Summarizing, the experimental catalytic activity trend found here for the cyclization of propargylamides, namely, $TFA^- < OTs^- < OTf^- < BF_4^-$, shows that the performances of the catalysts increase gradually with decreasing coordinating ability and hydrogen-bond acceptor power of $X^-$ (basicity and coordinating strength: $BF_4^- < OTf^- < OTs^- < TFA^-$), with $TFA^-$ being by far the worst counterion. Thus, the results presented here show that the anion properties, both coordination ability and basicity (hydrogen-bond acceptor power), should have a great impact on its “proton shuttle ability”. To elucidate the gold(I) catalytic activity in the cyclization of propargylamide, the NHC-Au-X (NHC = 1,3-dimethylimidazol-2-ylidene; $X^- = BF_4^-$, $BF_4^-/H_2O$, $OTf^-$, $OTs^-$) complexes have been considered as catalysts and N-(prop-2-ynyl)benzamide as the substrate for the calculations (Scheme 2). On the basis of $BF_4^-$ instability to $H^+$ with respect to the HF elimination and its low-coordinating nature, an additional water molecule has been included in the calculations to explore the catalytic activity of this anion ($BF_4^-/H_2O$). The calculated reaction energy profiles for the nucleophilic attack step are shown in Fig. 2.

The NHC-Au-X initial complex (IC), with the N-(prop-2-ynyl)benzamide in the second coordination sphere, has been considered as zero energy reference structure for all the three anions. The displacement of the coordinated anion has been calculated to be a thermodynamically favorable process for $BF_4^-$ (−13.9 kcal/mol), $BF_4^-/H_2O$ (−14.1 kcal/mol), and $OTf^-$ (−5.7 kcal/mol), leading to the corresponding reactant

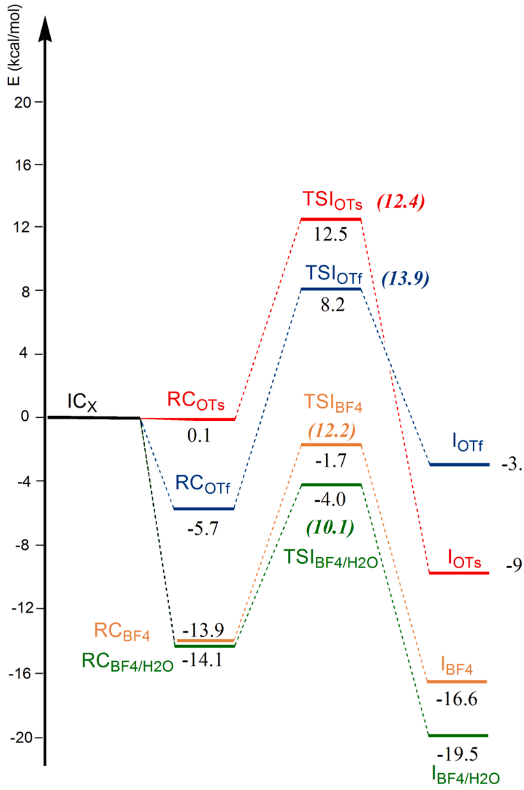


**Fig. 2.** Energy profiles for the nucleophilic attack step of the cycloisomerization of *N*-propargylcarboxamides reaction mechanism catalyzed by NHC-Au-X ($X^- = BF_4^-$, $BF_4^-/H_2O$, $OTf^-$, and $OTs^-$). Energy values (kcal/mol) refer to the corresponding $IC_X$ taken as zero.

complexes $RC_{BF4}$, $RC_{BF4/H2O}$ and $RC_{OTf}$, where N-(prop-2-ynyl)benzamide is coordinated to gold and the anion is in the second coordination sphere weakly interacting with the NH moiety of the substrate through a hydrogen bond. The $OTs^-$ replacement with the substrate is instead a thermoneutral process, yielding a $RC_{OTs}$ (0.1 kcal/mol) through a calculated energy barrier of 7.8 kcal/mol and a tri-coordinated transition state where both N-(prop-2-ynyl)benzamide and $OTs^-$ are bound to gold (see Fig. S3 in the SI). The optimized geometries of all species are shown in Figs. S4–S7. In all the RC complexes the counterion $X^-$ is placed above gold, weakly interacting with the metal center with at least one basic atom and forming a hydrogen bond with substrate NH group. Starting from these RC adducts, the oxygen atom of the substrate CO group intramolecular nucleophilic attack to one carbon atom of the activated triple bond can easily occur, with relativity low energy barriers (12.2, 10.1, 13.9 and 12.4 kcal/mol for $BF_4^-$, $RC_{BF4/H2O}$, $OTf^-$ and $OTs^-$, respectively) (Fig. 2).

Formation of the vinyl gold complex (intermediate I) from this step is an exergonic process for all the anions (Fig. 2). In the intermediate I, the anion, still forming a hydrogen bond with the substrate NH group, moves from the gold center, localizing in the second coordination sphere. The acidic NH hydrogen should then be transferred to the *C*2 carbon atom coordinated to Au by the anion, acting as proton shuttle. To calculate the overall path starting from NH proton detachment, due to the very large number of different conformations involved, molecular dynamics simulations would be needed, which are beyond the scope of this work.

However, starting our analysis of the protodeauration step from **intermediate I**, a transition state for the final proton transfer from the anion to *C*2 (TSII) has been located, which allows to completely rationalize the experimental findings.

Energy profiles for the protodeauration step are shown in Fig. 3.

The energy barrier calculated from I follows the trend $BF_4^-/H_2O < OTf^- < OTs^-$ (21.8, 25.0 and 27.4 kcal/mol, respectively).

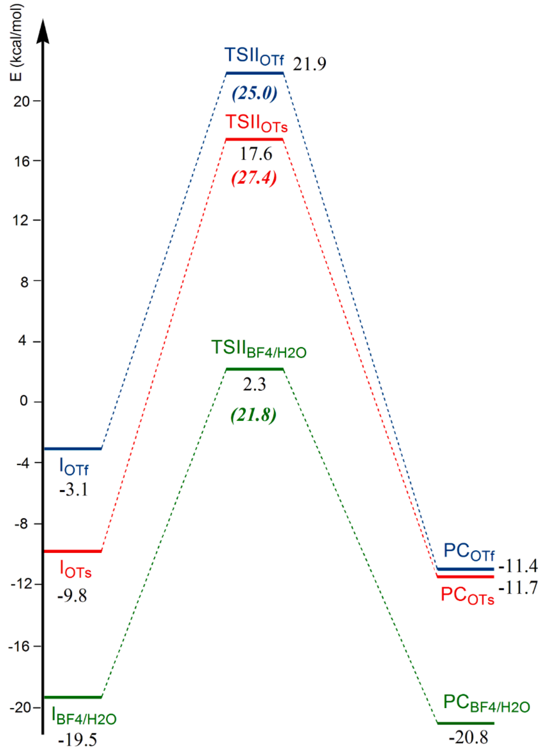


**Fig. 3.** Energy profiles for the protodeauration step of the cycloisomerization of *N*-propargylcarboxamides reaction mechanism catalyzed by NHC-Au-X ($X^-$ = $BF_4^-/H_2O$, $OTf^-$, and $OTs^-$). Energy values (kcal/mol) refer to corresponding $IC_X$ (Fig. 2) taken as zero.

As it can be seen, this step requires a higher energy barrier than that of the nucleophilic attack step for all the three anions, in full agreement with the experimental observations. The geometries of TSII are compared in Fig. 4, whereas PC structures are reported in Fig. S8 in the SI.

The protodeauration energy barrier trend exactly matches both that of the catalytic performances, and that of the anion basicity and hydrogen-bond acceptor power ($BF_4^- < OTf^- < OTs^-$), thus suggesting an impact of the anion in controlling the reaction rate through abstraction of the proton from the NH moiety and its releasing to the *C*2 atom bond to gold. Interestingly, inspection of the TSII structures in Fig. 4 reveals that both the coordinating ability trend (Au…O = 3.523 Å for $OTs^-$, Au…O = 3.611 Å for $OTf^-$, and Au…F = 3.914 Å for $BF_4^-/H_2O$) and the hydrogen-bond acceptor power (H…*C*2 = 3.079 Å for $OTs^-$, H…C = 2.984 Å for $OTf^-$, and H…C = 2.288 Å for $BF_4^-/H_2O$) are able to account for the energy barrier trend. In addition, hydrogen abstraction from substrate NH appears to be hindered by the coordinating capability of the anion (H…N = 2.328 Å for $OTs^-$, H…N = 2.498 Å for $OTf^-$, and H…N = 4.444 Å for $BF_4^-/H_2O$). Thus, the anion basicity seems to be mainly responsible for the energy activation barrier value. Overall, these results suggest that too basic anions, with higher hydrogen-bond acceptor power ($OTs^-$), do not easily abstract and transfer the proton, thus slowing the reaction rate, consistently with experimental findings, where the anion “proton shuttle ability” is found to be crucial for the catalytic activity. Finally, a calculation has been performed on the overall reaction path for NHC-Au-OTf, using the full ligand (NHC = 1,3-bis(2,6-di-isopropylphenyl)-imidazol-2-ylidene), to test the reliability of the results previously obtained with the model NHC. The optimized structures of IC, RC, TSI, I, TSII and PC and their relative energies are reported in the SI (Fig. S9). The results show that the interactions of the anion with the bulky NHC ligand do not affect the energetics of the whole path, particularly at the transition states, which show comparable energies with respect to the corresponding IC (for model NHC E ($TSI_{OTf}$) = 8.2 kacl/mol, E($TSII_{OTf}$) = 21.9 kcal/mol vs. full NHC E($TSI_{OTf}$) = 6.3 kcal/mol, E($TSII_{OTf}$) = 21.6 kcal/mol).

## 3. Conclusion

In this work, we extended our previous works studying the cycloisomerization of N-propargylcarboxamides promoted by NHC-Au-X complexes in green solvents from an experimental and theoretical point of view. At first, we investigated the effect of the solvent employed. As a primary and important goal, we found that the reaction proceeds very well in most of the alternative solvents employed, such as cyclohexanone, isopropyl acetate, MIBK, ethyl lactate, furfuryl alcohol, γ-valerolactone and propylene carbonate. TOFs are comparable or even better with respect to those obtained using VOS. On the other hand, when the reaction is performed in DMSO or propionitrile the TOFs are much lower, owing to the presence of a coordinating functional group (>S=O and —C≡N, respectively) that upon coordination to the metal centre affords inactive NHC-Au(solvent)OTf species. We also observed that the use of propionic acid resulted in a speed up of the reaction, according to the view that protodeauration is the RDS.

Secondarily, we found, according to our previous work, that the activity of the catalyst in propionic acid (in terms of TOF) seems to be inversely correlated to the coordinating ability and hydrogen-bond acceptor power of $X^-$ (basic and coordinating strength: $BF_4^- < OTf^- < OTs^- < TFA^-$), with $TFA^-$ being by far the worst counterion. This behaviour is consistent with the active role of the counterion in all the three steps of the reaction pathway (pre-equilibrium, nucleophilic attack and protodeauration).

DFT calculations corroborate these peculiar experimental kinetic findings showing an excellent agreement, and the proposed mechanism fully rationalizes the experimental reactivity, which is highly dependent on both anion and solvent effects.

These results are indeed remarkable and suggest that a sustainable

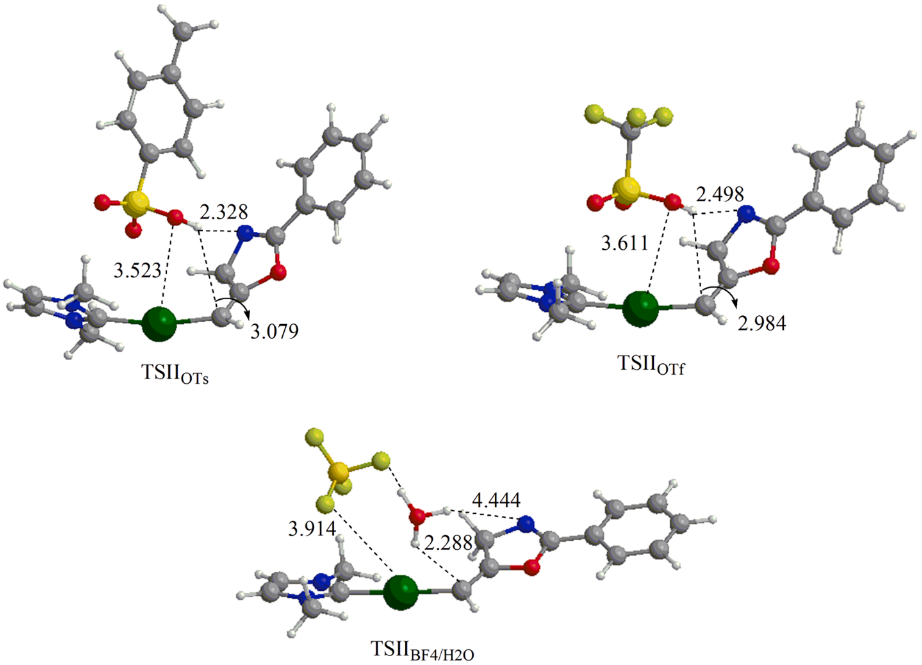


**Fig. 4.** Transition state (TSII$_X$) geometries for the protodeauration step of the cycloisomerization of N- propargylcarboxamides reaction mechanism catalyzed by NHC-Au-X ($X^- = BF_4^-$,$BF_4^-/H_2O$, OTf$^-$, and OTs$^-$). Bond lengths are in Å.

production of 2-phenyl-5-vinylidene-2-oxazoline promoted by gold catalysts can be pursued if both the solvent and counterion effects are carefully taken into account.

## Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2021.120372.

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