Gold(I)-catalyzed 1,3-O-transposition of ynones: Mechanism and catalytic acceleration with electron rich aldehydes

DOI: 10.1021/acscatal.7b04262

Citation for published version (APA):

Published in:
ACS Catalysis

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Gold(I)-catalyzed 1,3-\(O\)-transposition of yrones: 
Mechanism and catalytic acceleration with electron rich aldehydes

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\textbf{ABSTRACT:} The gold-catalyzed 1,3-\(O\)-transposition of yrones occurs intermolecularly via a cyclic organo-gold acetal intermediate formed from the nucleophilic oxo-attack of a second ynone i.e. either starting material or product, on a gold activated ynone. The combination of \(^1\)H NMR monitored kinetic data, analyzed using the Variable Time Normalization Analysis (VTNA) and kinetic modelling, and density functional theory (DFT) was used to elucidate the mechanism. A significant acceleration of the reaction rate could be achieved by the addition of a
substoichiometric amount of electron rich aldehyde as a mediator, allowing the gold-catalyzed 1,3-O-transposition of terminal ynone to ynaldehyde. The mechanism is further supported by NMR characterization of the acetal intermediate and $^{18}$O labeling experiments. A model for predicting the reactivity from aldehydes’ frontier molecular orbital energies is also presented.

KEYWORDS: Gold catalysis, ynone, mechanism, reaction kinetics, DFT

**Introduction**

The $\pi$-philic Lewis acidic metals are versatile and selective tools to activate alkynes for various nucleophiles.\(^1\) Intramolecular carbonyl oxo-nucleophiles, such as aldehydes, ketones, esters, carbonates and amides, are an important sub-class of nucleophiles providing efficient synthetic routes to various O-heterocycles and rearrangement products (Scheme 1). In particular, gold and platinum complexes are frequently used to catalyze the 1,2- and 1,3-migration of propargyl esters and carbonates when preparing allenes and metallocarbenes, respectively.\(^2,3\) Similarly, ynones, which are useful substrates for transition metal\(^{1\text{lab}}\) or organocatalyst mediated synthesis\(^4\text{c}\) and viable starting materials for several natural products,\(^5\) undergo 1,3-O-transpositions in Lewis acidic conditions.\(^6,7\) The mechanism of Lewis acid catalyzed 1,3-O-transposition, however, is not clear.
Recently, Gevorgyan and co-workers reported a gold(I)-catalyzed isomerization of ynones to a thermodynamically more stable structural isomer with more complete $\pi$-bond conjugation (Scheme 2).\textsuperscript{6a} The transposition mechanism has been investigated by $^{18}$O labelling experiments for 1,3-$O$-transposition of ynsulfonamides to ynamides, indicating an intramolecular reaction mechanism through a four-membered oxet-1-ium intermediate, which is a strained four $\pi$-electron $O$-heterocycle.\textsuperscript{8} However, the high computed activation energy of 27 kcal mol$^{-1}$ contradicts the experimentally observed spontaneous catalytic reaction at ambient condition (see SI for full computed energy profile).

Scheme 1. Oxo nucleophile attacks on transition metal (TM) activated alkynes
Here, gold(I)-catalyzed 1,3-\(O\)-transposition of yrones is studied in detail from a combination of kinetic and computational data for isomerization of \(1a\) to \(1b\) (Scheme 2). Our computed values for the reaction thermodynamics are in agreement with the previously published data.\(^6\)a steric hindrance between the \(o\)-methyl substituent and the carbonyl group prevents optimal \(\pi\)-conjugation in \(1a\), while the \(\pi\)-conjugation stabilizes \(1b\) yielding an exergonic 1,3-\(O\)-transposition by \(-3.1\) kcal/mol. Similarly, as for the ynsulfonamides,\(^8\) the calculated activation energy for the gold catalyzed intramolecular transposition of \(1a\) to \(1b\) \textit{via} a 4-ring TS was calculated to be approximately 27 kcal mol\(^{-1}\). Thus, a comprehensive mechanistic analysis was performed to rationalize the observed spontaneous reactivity at RT.

Scheme 2. The gold(I) catalyzed 1,3-\(O\)-transposition of \(1a\) to \(1b\) was studied as a model reaction both experimentally and computationally

**Materials and methods**

**Kinetic measurements and reaction progress profiling**

Kinetic profiles were measured by continuous \(^1\)H NMR. The reaction orders were determined using the Variable Time Normalization Analysis (VTNA).\(^9\) The kinetic modeling was performed using COPASI, a software for simulation analysis of reaction networks and their dynamics.
**Computational methods**

Density functional theory (DFT) computations were performed using TPSS\textsuperscript{10} functional with zero-damped D3 dispersion correction from Grimme.\textsuperscript{11} Geometries were optimized using def2-SVP basis sets and the final energies were computed using def2-TZVP basis sets.\textsuperscript{12} Solvent effects were accounted for using COSMO with dielectric constant of dichloromethane (8.9).\textsuperscript{13} For full computational details, see SI.

**Results and discussion**

**Reaction order analysis**

To elucidate the order of the reaction in all reaction components, we monitored the progress of four reactions with different initial concentrations of each of the component we wanted to evaluate the effect of. The first reaction had the same initial concentrations as the standard reactions and the second, third and fourth reaction had changes only in [1a]_o, [1b]_o and [IPrAuNTf₂]_o, respectively. The progress reaction profiles of all four reactions were investigated using the VTNA.\textsuperscript{9} All the original reaction progress profiles (Figure 1a) overlay on a straight line when the correct orders are used in the normalization: 1.5 in 1a, 0.15 in 1b and 1.0 in the gold catalyst (Figure 1b). The modification of any of the orders in the reaction components from their correct values causes the divergence of the profile of the reaction with a different initial concentration of the corresponding component. Figure 1c shows that the normalized profile of the reaction with different initial concentration of 1a diverges from the profiles of the other reactions when the order in 1a is modified to 1.5±0.3. Similar divergences of the corresponding normalized profiles of the reactions with different initial concentration of 1b and gold catalyst are shown in Figures 1d and 1e when their orders are modified to 0.15±0.3 and 1.0±0.3, respectively. In addition to the
The divergence of specific reaction profiles, the loss of linearity is also informative of the reaction orders. The reaction progress profiles in Figure 1c and 1d lose their linearity due to the use of wrong orders in 1a and 1b, whose concentrations change during the course of the reaction.

**Figure 1.** a) Original reaction progress profiles for the four reactions. b) The best overlay of all four reaction progress profiles happens with orders 1.5 in 1a, 0.15 in 1b, and 1.0 in IPrAuNTf₂. c) Divergence of the reaction profiles when the order in 1a is modified ±0.3 from 1.5. d) Divergence
of the reaction profiles when the order in 1b is modified ±0.3 from 0.15. e) Divergence of the reaction profiles when the order in gold catalyst is modified ±0.3 from 1.0.

The order in 1a, higher than one, and the positive order in 1b prove that, in addition to one molecule of 1a and one molecule of gold, the mechanism of the reaction also involves a second molecule of either 1a or 1b to form the final product (pathways a and b of Scheme 3, respectively). Nevertheless, the orders of the reaction do not completely rule out the possibility of an intramolecular competitive pathway involving the 1,3-O-transposition of ynones. To investigate further the relative importance of the intramolecular pathway c versus the pathways with the assistance of a second molecule of either 1a or 1b, we analyzed the experimental reaction profiles with the kinetic modeling program COPASI.

Scheme 3. Catalytic cycles deduced from VTNA analysis. Pathway a and b are for 1a and 1b mediated reactions, respectively. Pathway c represents the intramolecular pathway.

The parameter estimation for the kinetic constants of the reaction network shown in Scheme 3 led to the best fitting to the experimental profiles when the contribution of the intramolecular pathway...
was negligible in front of the pathway mediated by 1a or 1b. Any attempt to find a set of kinetic constants with a significant contribution of the intramolecular pathway led to much worse fittings to the experimental reaction progress profiles. These modelling results prove that the experimental kinetic profiles can be perfectly explained by only considering the intermolecular pathways involving a second molecule of either 1a or 1b and suggest that the contribution of the intramolecular pathway to the overall reaction is insignificant. From this result we derived a plausible reaction mechanism which was computationally investigated and the energy profile for the mechanism is presented in Figure 2.

**Computed intermolecular reaction pathways**

![Image of reaction pathways](image)

**Figure 2.** The computed intermolecular 1,3-\(O\)-transposition reaction pathways mediated with 1a or 1b. Pathway mediated by 1a and 1b is plotted in blue and red, respectively. The energies were
calculated using TPSS-D3/def2-TZVP//TPSS-D3/def2-SVP with COSMO (DCM, $\epsilon = 8.9$) for geometries and energies.

In Figure 2, the reaction is self-mediated by another substrate molecule \textit{1a} or by product \textit{1b} in accordance with the kinetic analysis and the formation of an intermediate combining one molecule of \textit{1a}, gold, and \textit{1a}/\textit{1b} is the rate limiting step. The intermolecular carbonyl oxo-nucleophilic attack on gold activated ynone produces a cyclic organo-gold acetal intermediate (\textbf{Int-4}, Figure 2) of lower energy than oxet-1-iium intermediate of the intramolecular reaction pathway (SI). Moreover, the \textbf{Int-4} is energetically quite similar to the 2–alkyne coordination complexes \textbf{Int-1} and \textbf{Int-2}. Computationally, the TS-1 energies for the nucleophilic attack are also reasonable for a reaction done at room temperature, being 13.5 and 14.4 kcal mol$^{-1}$ for \textit{1a} and \textit{1b}, respectively. The Scheme 4 illustrates the pathways deduced from kinetic (Scheme 3) analysis updated with computationally studied mechanistic details: the gold coordination on \textit{1a} C-C triple bond initiates the reaction, thereafter cyclic acetal intermediate is formed either by addition of \textit{1a} (Pathway a, blue) or \textit{1b} (Pathway b, green) to be released after oxygen atom interchange.
Scheme 4. Catalytic cycle derived from the results of kinetic and computational studies. Pathway a (blue) and Pathway b (green) depict cycles mediated by 1a and 1b, respectively.

Aldehyde mediators in ynone transposition

As a consequence of the results of the kinetic and computational studies, we investigated if the transposition rate could be accelerated by another nucleophilic species to yield a synthetic route for electron poor ynones, which are inactive in transposition. For this, transposition kinetics were monitored with several carbonyl compound additives, for the most part aldehydes (Scheme 5). Figure 3 illustrates $^1$H NMR monitored kinetics with 0.1 equiv. of benzaldehyde (3a), $p$-anisaldehyde (3b), $m$-anisaldehyde (3c), $p$-(dimethylamino)benzaldehyde (3d), 2,4,5-trimethoxybenzaldehyde (3e) and pivalaldehyde (3f) additives (Scheme 5). Amongst these, the aliphatic pivalaldehyde caused a distinct inhibition of the reaction, whereas the benzaldehyde
slightly decreased the reaction rate. However, a notable rate acceleration could be observed with electron rich aromatic aldehydes as 3b, 3d and 3e provided a substantial rate of acceleration for the reaction.

Scheme 5. The set of aldehydes used in the reactions

Figure 3. Monitoring of reaction progress with \([1a]_0 = 0.1\) M, 10 mol % loadings of IPrAuNTf₂ and aldehyde additives 3a-3f in \(d_2\)-DCM and at 27 °C: Concentration of 1b versus time evolution
Computational reaction pathway with aldehyde additives

Analogous mechanistic pathways to self-mediated reaction (Figure 2) were calculated for the aldehyde mediated reactions (Table 1 and SI). The reaction profiles differ drastically from the 1a/1b mediated ones: The stationary points Int-3, TS-2, TS-3 and Int-5 could only be located for 3d and 3e aldehydes (SI). The energetically most relevant intermediates, Int-1 and Int-4, and TSs, TS-1 and TS-4, for aldehyde mediated reactions are shown Table 1 for aldehydes 3a-3f.

Computed energy pathways for aldehydes are in good agreement with the kinetic studies. In comparison to the 1a/1b-mediated reaction, the lowered energy barriers were found for the pathways mediated with aldehydes 3b, 3d and 3e. The activation energy barrier TS-1 – Int-1 associated with nucleophilic addition of 3f in entry 8 (Table 1) is slightly higher compared to 1a/1b whereas the barrier from Int-4 to TS-4 increases to 22 kcal mol\(^{-1}\). In addition, the barrier for the reverse reaction from Int-4 to Int-1 becomes even greater, 25 kcal mol\(^{-1}\). The higher barriers explain the experimental observation that shows inhibition effect by 3f (Figure 3) due to the partial monopolization of the gold catalyst in an overall slower pathway.\(^{16}\)

Table 1. \(\Delta G\) energies (TPSS-D3/def2-TZVP//TPSS-D3/def2-SVP in DCM) for two the key-steps for substrate, product and aldehyde mediated pathways in kcal mol\(^{-1}\).
entry | additive | ΔG(TS-1 - Int-1) | ΔG(Int-4 - Int-1) | ΔG(TS-4 - Int-4) |
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<td>1.5</td>
<td>8.9</td>
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<tr>
<td>2</td>
<td>1b</td>
<td>14.4</td>
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<td>12.8</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
<td>3d</td>
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<td>3f</td>
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**Trapping of acetal intermediate and $^{18}$O labelling**

Both experimental results (Figure 3) and computational findings (Table 1) guided the attempt to verify the proposed mechanism by trapping the corresponding intermediate (Int-4) in 3f mediated reaction with substrate (1a) and gold (Figure 4). A set of new signals were identified as belonging to the cyclic acetal 4 (Figure 4). A characteristic proton resonance at 5.0 ppm could be assigned to
the acetal bridge (HA, Figure 4). This proton showed ROE correlations to the o-tolyl and t-butyl groups (Figure 4). Additionally, the HMBC experiment showed correlations, e.g. from the acetal bridge proton to the CO carbons (at 187.95 and 192.52 ppm), that further confirmed that acetal 4 is most likely present in the reaction mixture (SI). The proposed cyclic organogold acetal is an unreported intermediate in gold catalysis, even though it has some structural similarity with the gold-oxocarbenium cation species (Figure 4b) characterized earlier by Fürstner and coworkers.\textsuperscript{17,18}

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{a) Part of 2D ROESY spectrum that shows the NOE from the acetal proton (H\textsuperscript{A}) to the protons of the methyl (H\textsuperscript{C}), phenyl (H\textsuperscript{D}) and t-butyl groups (H\textsuperscript{B}), b) The structurally relative gold-oxocarbenium cation characterized by Fürstner \textit{et al.}\textsuperscript{17}}
\end{figure}

To further confirm the intermolecular reaction mechanism, a crossover experiment was performed using an \textsuperscript{18}O-labelled aldehyde. The IPrAuNTf\textsubscript{2} (10 mol \%) catalyzed transposition of 1a mediated with a stoichiometric amount of C=\textsuperscript{18}O labelled (70\% \textsuperscript{18}O) 2,4,5-trimethoxybenzaldehyde (3e') was performed in DCE at RT (Scheme 6). The mass analysis of the reaction mixture implied that
50% of the $^{18}$O label was transferred into the ynone product, which is consistent with the mechanistic hypothesis (SI).

Scheme 6. $^{18}$O labelling experiment with $^{18}$O-2,4,5-trimethoxybenzaldehyde, 3e’

From these kinetic, experimental and computational results we formulated the catalytic cycle for the system (Scheme 7). The free gold species coordinates to the ynone C-C triple bond and (the rate limiting step of) the nucleophilic addition of an additive (substrate/product or aldehyde) follows. The free gold species is regenerated by the liberation of the same additive molecule and the product.
Scheme 7. Schematic diagram of the full catalytic cycle with additives. Left-hand side is a combined catalytic cycle for 1a/1b and Pathway d is the same cycle for aldehyde (3) mediators. Coefficients $k_2, k_3, k_4,$ and $k_5$ are same as in Scheme 3 and 4.

**Predictive model for aldehyde reactivity**

The reactivity of the aldehyde mediated reaction could be straightforwardly predicted by the computed reaction pathways (Table 1, Figure 2 and SI). However, this procedure is rather laborious in particular if only the reactivity of the aldehyde is to be predicted. Thus, we investigated if the reactivity can be straightforwardly predicted from the electronic structure of the aldehyde.
First, we investigated if the computed oxygen charge of the carbonyl group correlates with their nucleophilicities and would provide a simple model for prediction. The computed NBO charges show some correlation against the energy barriers for the nucleophilic attack ($\Delta G(\text{TS-1 - Int-1})$ values in Table 1 and Figure S22, SI), but not with the rate limiting energy barrier. The NBO charges consider the population associated to the complete atom, and thus are not suitable in this case to predict the reactivity rising from specific π-orbital.

An orbital dependent nucleophilicity model for aldehydes has been recently introduced by Pratihar.\textsuperscript{19} In this model, the “nucleophilicity factors” are based on computed HOMO-LUMO gaps of the aldehydes, which correlate well with the experimental oxidation of the aldehydes using KMnO$_4$. While the HOMO-LUMO gaps correlate to some degree with the computed $\Delta G$ values for our set of aldehydes (see SI), an individual examination of aldehyde MOs is necessary to localize the populated MO in which the MO is localized to the nucleophilic orbital, i.e., the π-orbital of the carbonyl oxygen (Figure S25, SI).\textsuperscript{20} When the energy gap was computed based on these energies ($(\text{HOMO-X}) - \text{LUMO}; N(\text{MO}))$,\textsuperscript{21} the predicted reactivity shows highly linear correlation when compared against $\Delta G$ values (Figure 5). This means that among the aldehydes, the orbital based inspection of the mediator molecular orbitals provides a cost-efficient tool for predicting the reactivity rather than demanding complicated analysis of the reaction pathway for each mediator (Table 1).
Figure 5. Computed activation energies (ΔG) vs. nucleophilic HOMO energies. N(MO) = (3(HOMO-X)-LUMO)²/(8((HOMO-X)-LUMO)). Energies were calculated on TPSS-D3/def2-TZVP//TPSS-D3/def2-SVP level in DCM.

The expediency of the aldehyde additive in the gold-catalyzed 1,3-O-transpositions is demonstrated with conversion of terminal alkyne 5a to aldehyde 5b (Scheme 8). The ynone 5a was cleanly converted (>95% conversion) in 20 h to aldehyde 5b with 3e as additive at RT. In contrast, without the additive, 5b was generated slowly with lower final yields and concomitant formation of side products. The simple inspection of frontier MOs (SI, Figure S25 and Table S2) reveals that for both 5a and 5b the critical nucleophilic MOs are low energy orbitals. The low energy orbitals of 5a and 5b indicates that the starting material or product mediation of the reaction is unlikely in this case and underlines the essential nucleophilic role of the mediator.
Scheme 8. Activation of 5a

Conclusions

The kinetic monitoring of the gold catalyzed ynone 1,3-\(O\)-transposition proved the intermolecular character of the reaction with respect to the ynone substrate. Further, the reaction rate was notably accelerated by using electron rich aldehyde additives as mediators. Computational studies confirmed the intermolecular oxo attack of keto or aldehyde carbonyl to be favored over the intramolecular one and moreover, the observed reaction rate acceleration by aldehyde additives could be rationally explained. The identification of the nucleophilic MOs of aldehydes and the comparison of their MO energies correlated well with computational energy barriers as well as the order of experimental reaction rates, thus providing a simple model to predict the reactivity. It is anticipated that beyond the transposition reaction, the established bimolecular reaction pathway might inspire catalyst researchers to look for new reactivity for ynones.

Supporting Information.

The following files are available free of charge.

Experimental methods: preparation of substrates, \(^{18}\)O labeling experiment, synthesis and
characterization of acetal intermediate 4, kinetic studies, NMR spectra for substrates and products, computational data and procedures (PDF)

**Acknowledgements**

The Financial support from Academy of Finland [project no. 129062 (J.H.)] is acknowledged. The Finnish National Centre for Scientific Computing (CSC) is recognized for computational resources.

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**Notes**

The authors declare no competing financial interest.

**References**


14. Details of the kinetic modeling are provided in the SI.

15. A ketone test reaction was also performed with acetophenone but no significant difference to structurally similar benzaldehyde was detected.


20. Molecular orbital pictures and energies in addition to the calculated N(MO)-values are presented in SI.

TOC graphics:

- Kinetic analysis indicates involvement of a second molecule in the reaction
- Aldehydes \( (R_4=H) \) can accelerate or inhibit the reaction
- Cyclic acetal intermediate identified in NMR
- \(^{18}\text{O} \) labelling supports intermolecular transfer of the carbonyl oxygen