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Referee report

On the doctoral thesis by MARIAROSA ANANIA, entitled

Mechanisms of metal-catalyzed reactions: an electrospray ionization mass spectrometry approach

In Prague, August 31st, 2020

The dissertation thesis by Mariarosa Anania summarizes the development and application of mass spectrometry techniques in studies of gold-catalysed reactions, namely the formation of gold-acetyl complexes and hydration of alkynes. The unique properties of Au(I) complexes together with their catalytic activity make them a research topic of high scientific relevance.

The thesis is based on three publications which are published in renowned international journals. The candidate is the first author of two publications published in *Org. Biomol. Chem.* and *Chem. Sci.* and a co-author of one publication published in *J. Am. Chem. Soc.* The thesis reveals that the candidate used a variety of methods ranging from mass spectrometry and IRPD to GC, kinetic modelling to quantum chemical computations for the description of mechanisms of metal-catalysed reactions. The thesis is of a predominantly experimental character, but a considerable part of the text is dedicated to the kinetic modelling and development of delayed reactant labelling (DRL) technique.

The dissertation thesis contains five chapters, the introduction parts about the chemistry of gold and mass spectroscopy techniques are followed by description of DRL and kinetic modelling methods. The last two chapters describe the candidate's publications on the formation of gold-acetyl complexes and hydration of substituted acetylenes. The bibliography of the work contains 271 references and sufficiently covers the studied field.

The theoretic introduction describes the used techniques and state-of-the-art overview of Au(I) chemistry. Most of the graphical content of the thesis (figures, schemes) is directly reproduced from published work with designated permission of the publisher. Besides the advantageous fact that the graphical content already successfully underwent a review process, this brings inconsistency in formatting, style and, most importantly, numbering of molecules and reaction intermediates. The intermediates are often denoted with empirical formulae (e.g. $[(PPh_3)_2Au_2(CD_2COCD_3)]^+$) where information about the constitution of the molecule is lost. This is practical for the assignment of mass signals of a certain m/z value, but it complicates the orientation of the reader. Generally, the text could have gone through more detailed proof-reading as it contains numerous typographical and factual errors. Here, I attach a list of my findings:

p. 1: *essential to addressing* instead of *essential for addressing*

p. 3: *complexes*³⁴, instead of *complexes*.³⁴

p. 3: *Chen has been studying* instead of *Chen has studied*

p. 3: *Rh*⁴⁴, instead of *Rh*.⁴⁴

p. 4: *Morita Bayles Hillman* instead of *Morita Baylis Hillman*

p. 4: *for the first time*⁵², instead of *for the first time*.⁵²

p. 4: *water*⁵⁶, instead of *water*.⁵⁶

p. 4: *reactivity*.^{57, 58} *Their* instead of *reactivity*.^{57, 58} *Their*

p. 4: *complex*⁷¹, instead of *complex*.⁷¹

p. 7: Scheme 1.1: plus sign is missing for the LAu species below the arrow going from 1-2 to 1-3

p. 7: Scheme 1.1: the product **1-4** should be consistent with the notation and should contain C= Nu⁺ instead of a C=O group.

p. 7: In the discussion the Fukuda's and Utimoto's work the turnover number of the catalyst should be mentioned if it is known.

p. 9: Scheme 1.5: the curly arrows in the transition state **1-10** do not follow the general rules.

p. 11: Figure 1.1: it is unclear why the compound shown in the figure is relevant for the discussion of the reaction mentioned in Chapter 1.2.2.1.

p. 11: *alkyne lowest unoccupied molecular orbital* instead of *alkyne's lowest unoccupied molecular orbita*

p. 12: Scheme 1.9: the curly arrow in intermediate **9** does not follow the general rules.

p. 12: the text should also discuss the pathways B) and C) shown in Scheme 1.10.

p. 14: Scheme 1.11: *American* instead of *American Chemical Society*

p. 19: **1-16** instead of **1-16**

p. 19: Scheme 1.19: the numbering of the compounds should follow the order of their first mentioning in the text (the compound **1-23** is not mentioned in the text).

p. 19: the work by Roithová and co-workers is mentioned in the theoretical introduction of the thesis and it is unclear if the candidate collaborated on the described project and if it should therefore be included in the experimental part of the thesis.

p. 23: Figure 1.4: oxygen atom is missing in structure **B**

p. 24: Figure 1.5: *kuzmina* instead of *Kuzmina*

p. 24: Scheme 1.22 b): the starting NHC-complex is missing one double bond

p. 25: acetone deprotonation does not lead to the formation of its tautomer, but it forms acetone anion

p. 25: Scheme 1.23: the curly arrow does not follow the general rules.

p. 31: the abbreviation NCE should be introduced in the text and listed in the list of abbreviations

p. 39: the text about DLR should contain a reference.

p. 39: *kinetic model* instead of *Kinetic model*

p. 42: Figure 3.2 (it should not be a figure but a scheme) *b-H-elimination* instead of *β-H-elimination*

p. 42: Figure 3.2: the curly arrow does not follow the general rules.

p. 44: the units of k' of ~0.063 are missing.

p. 45: Scheme 3.2: the process assigned as rearrangement is a tautomeric equilibrium

p. 48: Figures 3.7 and 3.8: the assignment of the curves in the figure and in the text does not correspond to each other.

p. 48: *intermediate H⁺* instead of *intermediate **1H⁺***

p. 49: *shown in Figure 3.7* instead of *shown in Figure 3.9*

p. 50: *is converted into either benzylmethylketone (B) or ethylphenylketone (C)* instead of *is converted into benzylmethylketone (B) and ethylphenylketone (C)*

p. 51: Figure 3.11: the phase correction of the ¹H NMR spectrum was not done properly.

p. 51: Figure 3.11: the text says: *The δ scale was referenced to the solvent residual peak at δ = 3.31 ppm*. No solvent residual peak can be observed at 3.31 ppm.

p. 53: *Jašikova* instead of *Jašíková*

p. 54: *1H⁺* instead of ***1H⁺***

p. 55: *C-H bonding formation* instead of *C-H bond formation*

p. 60: *to remove precipitated AgX* instead of *to remove precipitated AgCl*

p. 60: a general procedure for the preparation of reaction mixtures would have been enough for the description of experimental procedure.

p. 61: the masses of AgNTf₂ differ each time for the preparation of different Au(I) complexes despite the fact the text states that 6 μmol has been used in each case. There must be a mistake in calculation of the used mass.

p. 67: **(1)** and **(2)** should be depicted in Scheme 4.1

p. 71: the text promises to show the KIEs as a function of different gold complexes containing ligands PMe₃, PPh₃ and JohnPhos (Figure 4.10 – 4.13) but the captions below Figure 4.10 – 4.13 do not correspond to that.

p. 76: the term *overnight solution* is generally not acceptable.

p. 79: Figure 4.21: the caption does not correspond to the content of the figure

p. 99: Figure 5.7: the compound description in the caption does not correspond to the compound description in the Figure

Besides this, I attach a list of my comments and remarks that should be discussed in the disputation:

- 1) Please, explain the following statement: *As such, the catalytic process is any cyclic process in which the catalyst is both a reactant and a product of the reaction.* (p. 2)
- 2) p. 8: Scheme 1.4: the bonding of in the molecule **1-8** exceeds standard valency of carbon atom. How can this be explained?
- 3) The statement: *These experiments showed that the gold and silver cations preferentially coordinate to gold acetylides rather than to nonactivated CC triple bonds.* (p. 14) is in contradiction with Scheme 1.11 where the second equivalent of gold cation coordinates to the (sterically hindered) CC triple bond rather than to the gold acetylide (**M** to **N**). Could the candidate briefly comment on this?
- 4) The text contains too detailed information about experimental methods (such as: *The reaction was performed under air and using technical grade solvents.* mentioned in the theoretical introduction of the thesis, p. 25, reaction conditions description in Chapter 4 etc.) and other details (such as structural information about Au-NHC complex on page 25) which are irrelevant for the topic of the thesis.
- 5) Some parts of the text describe too trivial facts which do not need to be mentioned in a dissertation thesis, such as: *Gas chromatography (GC) is a chromatographic technique used for analytical purposes.* or *To operate efficiently, gases must be pure and free of organic material, and their flow rates must be optimized for the particular detector and analyte.* (p. 35)
- 6) The text about DRL (p. 39) should discuss the case when a kinetic isotope effect is involved which might complicate the analysis of the measured data and influence the ratio of labelled and unlabeled intermediate at $t = \infty$.
- 7) Could the candidate derive the equations 3.3 and 3.4 from the steady-state approximation scenario mentioned in equation 3.1? It is not obvious from the text how the kinetic equations 3.3 and 3.4 were derived.
- 8) Could the candidate estimate the relative affinity of the gold catalyst to the substrate vs. to the product of the reaction mentioned in Scheme 3.2 (p. 45)?
- 9) Figure 3.4 (p. 46) shows integrated ^1H NMR spectrum with relative ratio of the triplet signals of $\sim 6:17$. This corresponds to the conversion of $\sim 85\%$ and not 92% as it is mentioned in the figure.
- 10) The fit of the experimental data shown in Figure 3.9 (p. 49) is inaccurate at short times. What is the reason for that?
- 11) How was the KIE calculated for the C-H bond formation and protodeauration (p. 55)?
- 12) Is the ratio of the products of hydration of 1-phenylpropyne influenced by the ionic strength/additive presence (p. 55)?
- 13) How did the candidate assign which ion at $m/z = 643$ (Figure 3.18, p. 59) has a higher ion mobility?
- 14) Figure 4.1c) (p. 63): why does the relative abundance of signals at $m/z = 603$ and 608 differ so much when the monoaurated species ($m/z = 331$ and 337) appear almost in the same concentration?
- 15) Why is the region between $800 - 1000 \text{ cm}^{-1}$ in Figure 4.3c) not shown despite the fact that it should contain signals important for the structural assignment of the ion?
- 16) The experiment mentioned on page 84 and its conclusions should be discussed in the disputation.

- 17) The text mentions that the complex $[(L)_2Au_2OH]^+$ is a strong base. What is the expected pK_{aH} of the digold hydroxide studied in the thesis? How does the nature of the ligand and the counterion influence its basicity?
- 18) Is the effect of the glass vial vs plastic vial shown in Figure 5.15 (p. 114) of any statistical relevance? The data seem to be quite scattered.
- 19) How do you explain the statement: *The conversion of digold hydroxide into digold-acetonyl is larger if the solution contains a larger amount of water?* (p. 117) How do water molecules assist the formation of digold-acetonyl?

Besides the listed errors and the partial lack of discussion of some experimental findings, I find this thesis to be highly scientific relevant and I declare that it demonstrates the candidate's potential to perform an independent creative scientific work and to cooperate effectively in international scientific teams. I therefore **recommend the thesis to be accepted** by the committee of the Faculty of Science of the Charles University.



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