



HAL
open science

Study of electronic effects in organometallic complexes using mass spectrometry and their application in medicinal chemistry

Clément Soep, Yanis Laghsal, Marie Chatel Niemann, Benoît Bertrand, Denis Lesage, Héloïse Dossmann

► To cite this version:

Clément Soep, Yanis Laghsal, Marie Chatel Niemann, Benoît Bertrand, Denis Lesage, et al.. Study of electronic effects in organometallic complexes using mass spectrometry and their application in medicinal chemistry. 39ème Journées Françaises de Spectrométrie de Masse (JFSM 2023), Sep 2023, Marseille, France. . hal-04204572

HAL Id: hal-04204572

<https://hal.science/hal-04204572v1>

Submitted on 12 Sep 2023

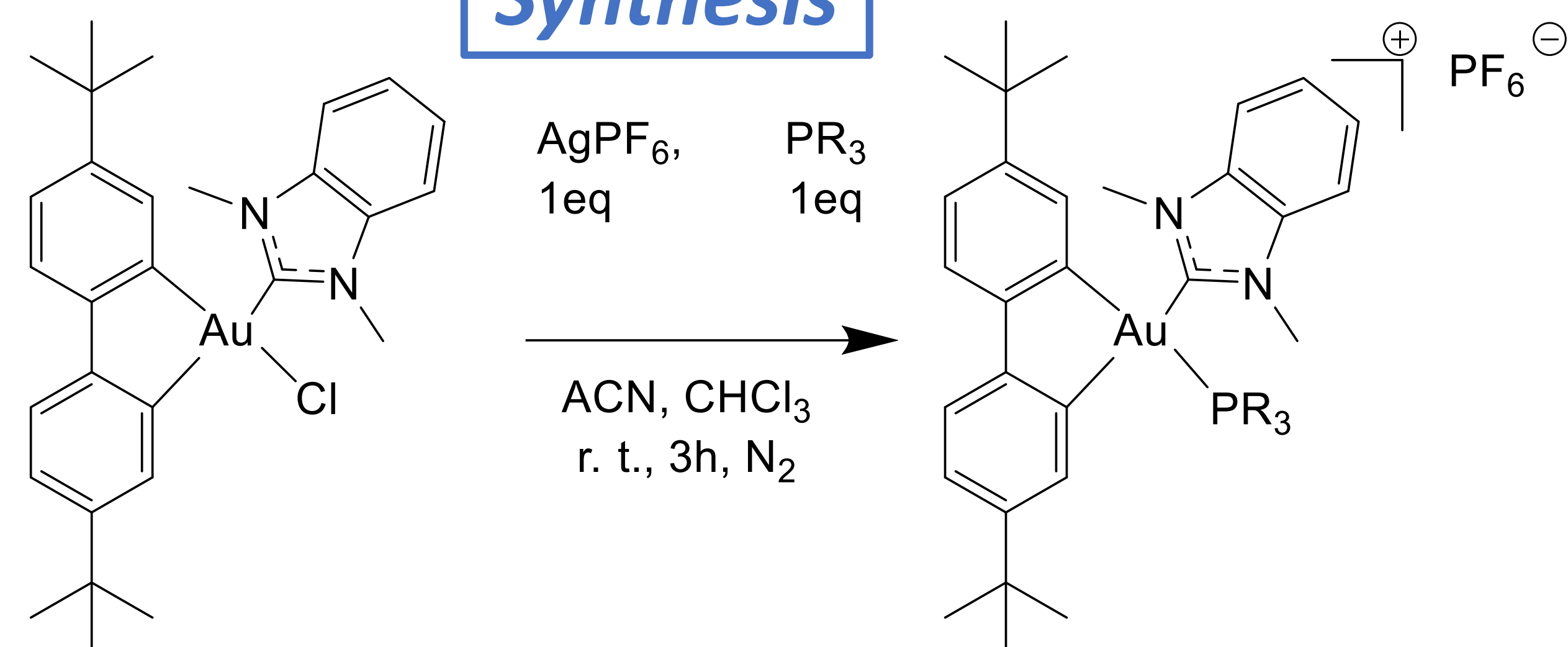
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

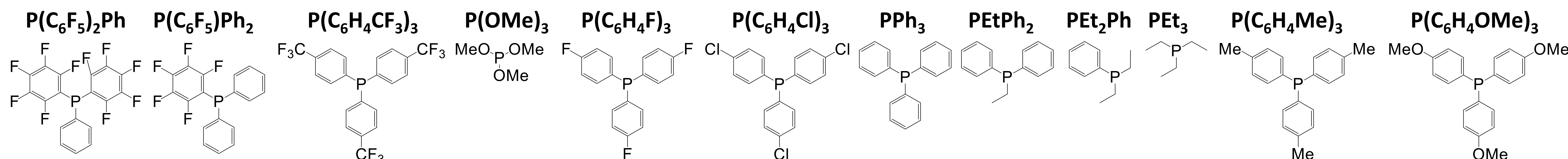
Introduction

- Phosphino-Gold based complexes are of interest as potential anticancer agents [1,2].
- The understanding of the molecular mechanism of mode of action of the complexes is limited [3].
- To improve the efficacy of these complexes and understand their mechanism of action, we need to understand the effects of ligands.
- A large family of phosphine ligands with various electronic effects have been investigated.
- The electronic effects of the ligands were assessed by measuring the bond dissociation energy of the Metal ligand bond using mass spectrometry [4].

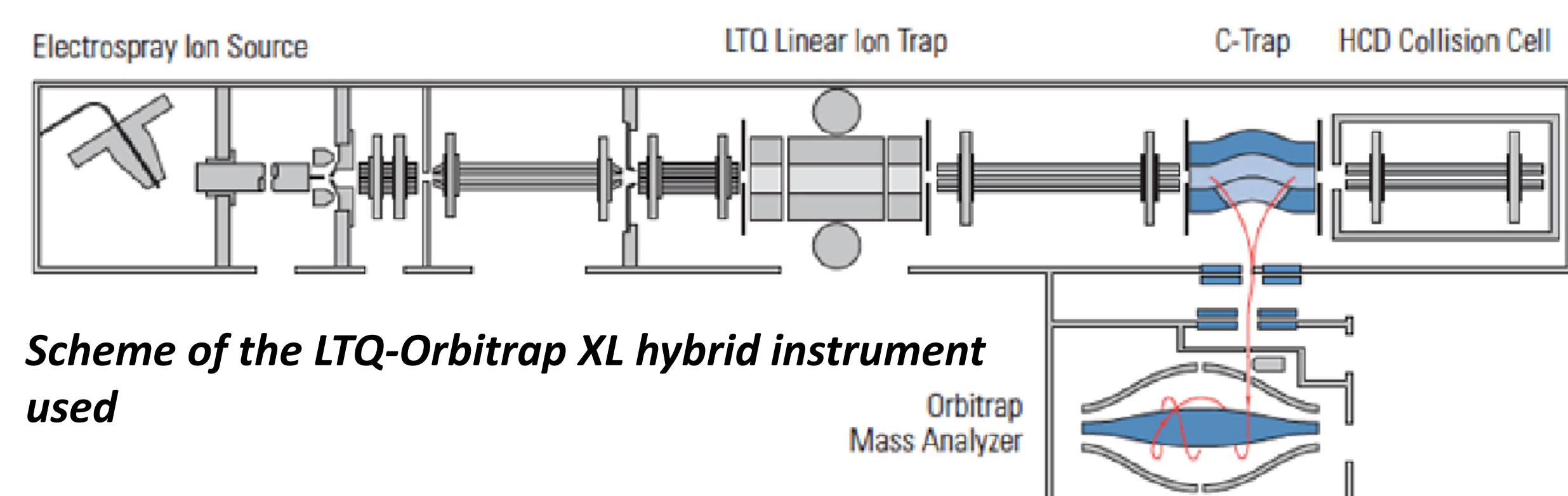
Synthesis



Reaction of formation of the gold(III) complexes



Structures of the various substituents studied



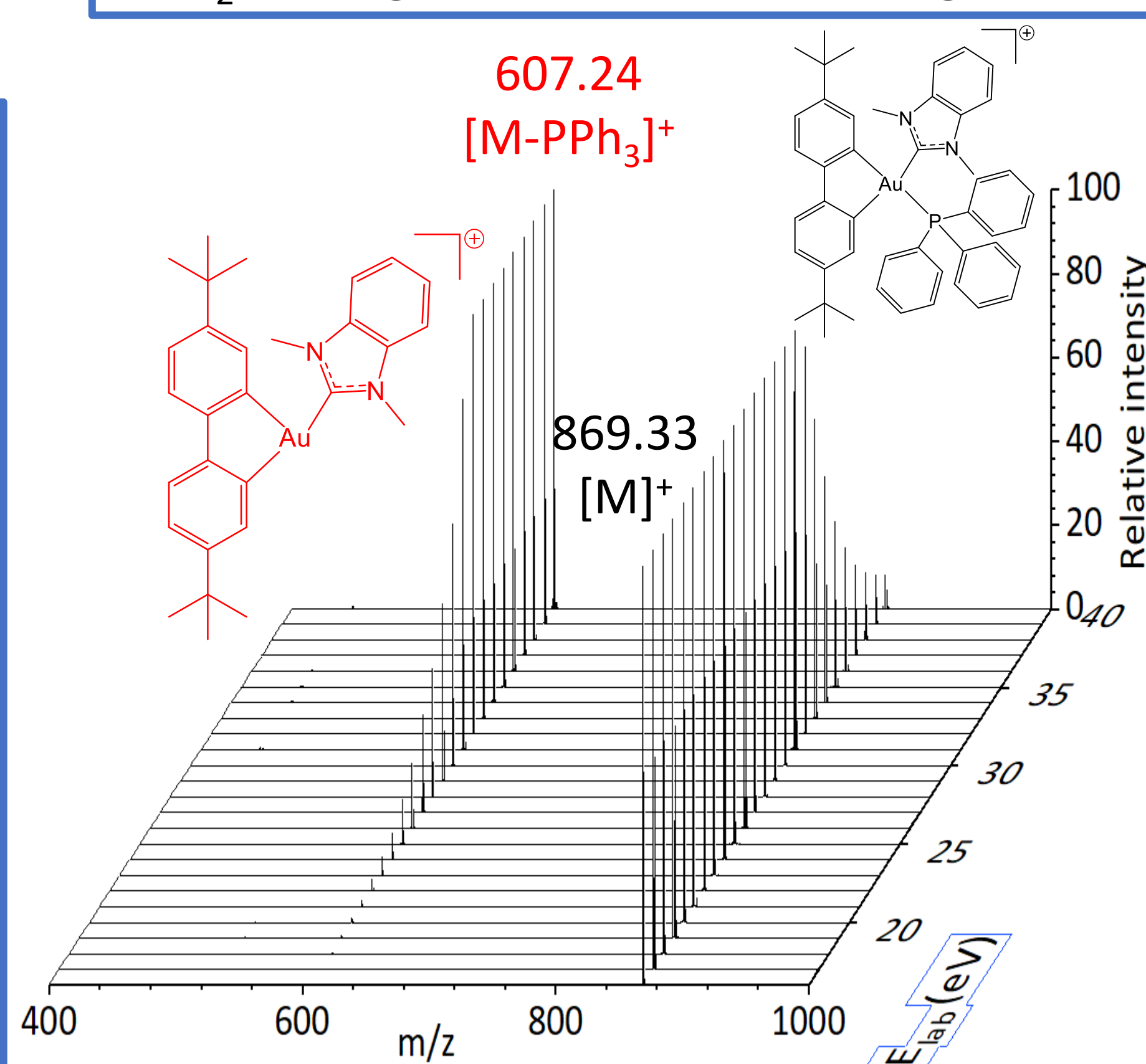
Scheme of the LTQ-Orbitrap XL hybrid instrument used

Experimental setup

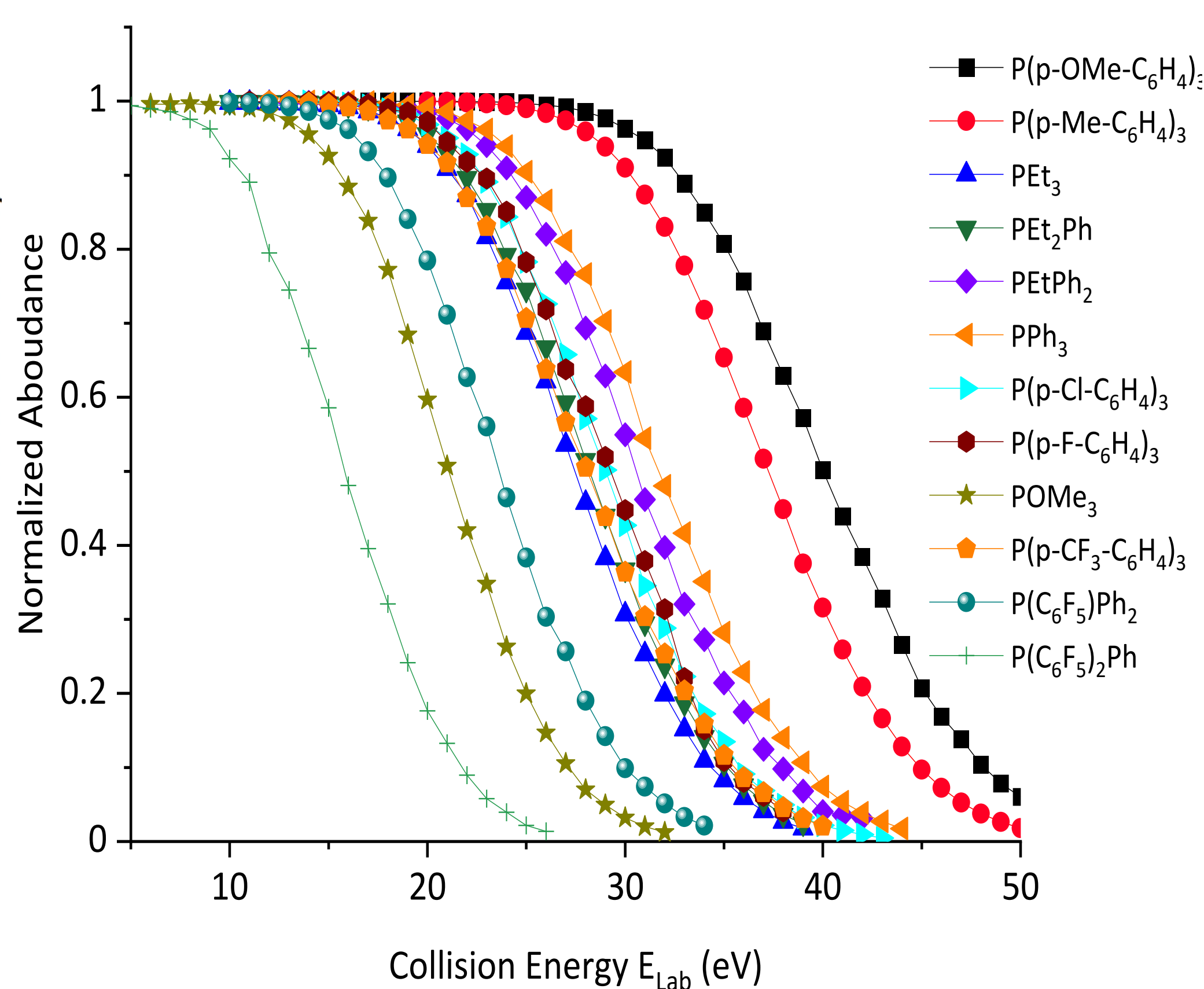
- Ions are formed by an electrospray source and analyzed in a LTQ-Orbitrap XL hybrid instrument (ThermoFisher Corporation, San Jose, USA).
- Precursor ions are isolated in the Linear Ion Trap and accelerated into a collision cell containing N₂ leading to the formation of fragments.

Kinetic modelling and theoretical calculations

- Determination of the Survival Yield (SY) of the precursor ion: $SY = \frac{I_{(P^+)}}{I_{(P^+)} + \sum I_{(F^+)}}$, $I_{(P^+)}$ the abundance of the precursor ion, $\sum I_{(F^+)}$ the sum of abundances of fragment ions.
- Kinetic treatment based on the RRKM theory [5] with the *MassKinetics* software [6] to obtain the difference between the dissociation barrier and that of the precursor ion (E_0).
- Theoretical values of Bond Dissociation Energies (BDEs) obtained using the Density Functional Theory M06/def2-TZVP with the GAUSSIAN 16 software) [7].

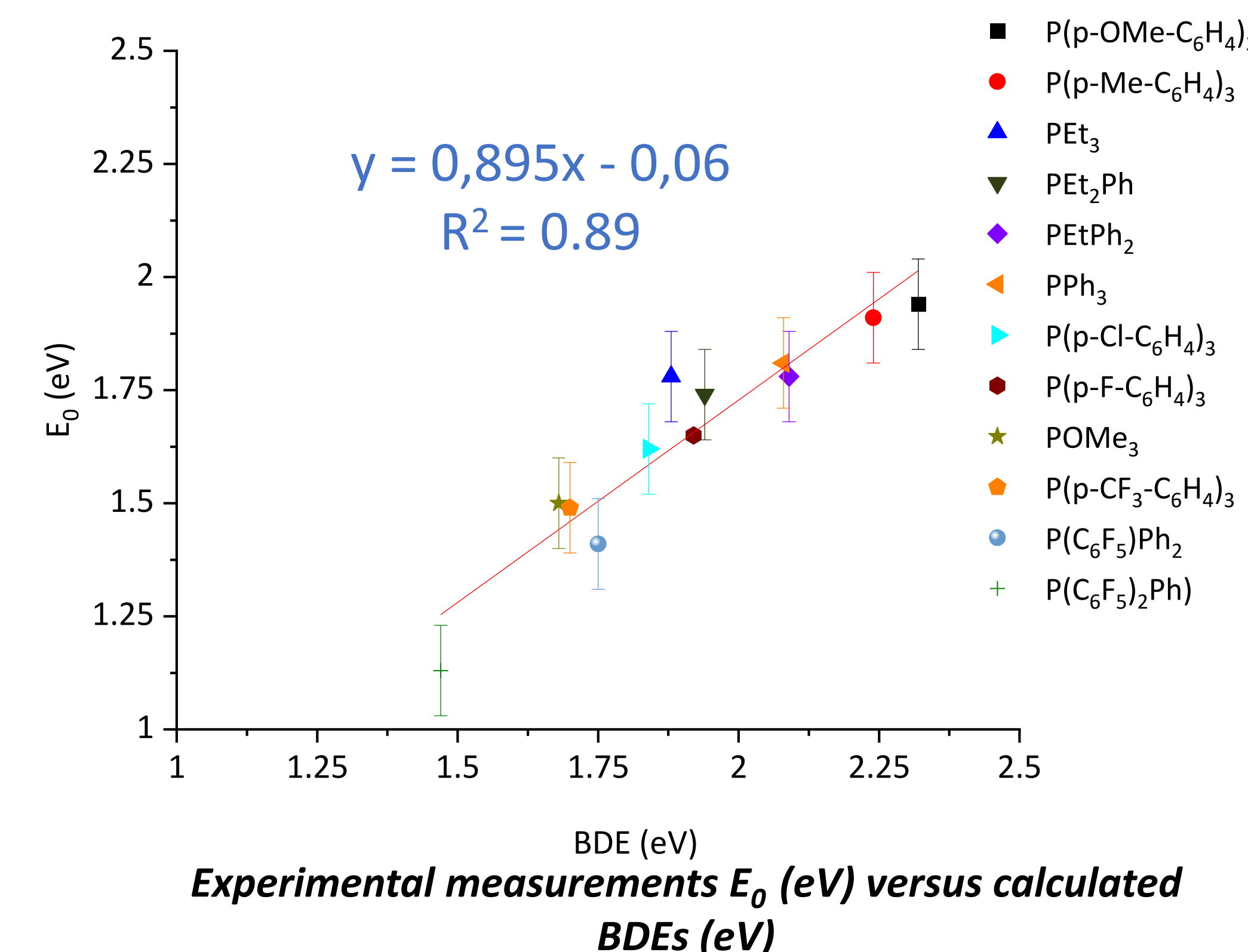


HCD fragmentation spectrum of $[(C^A C)Au(NHC)(PPh_3)]^+$

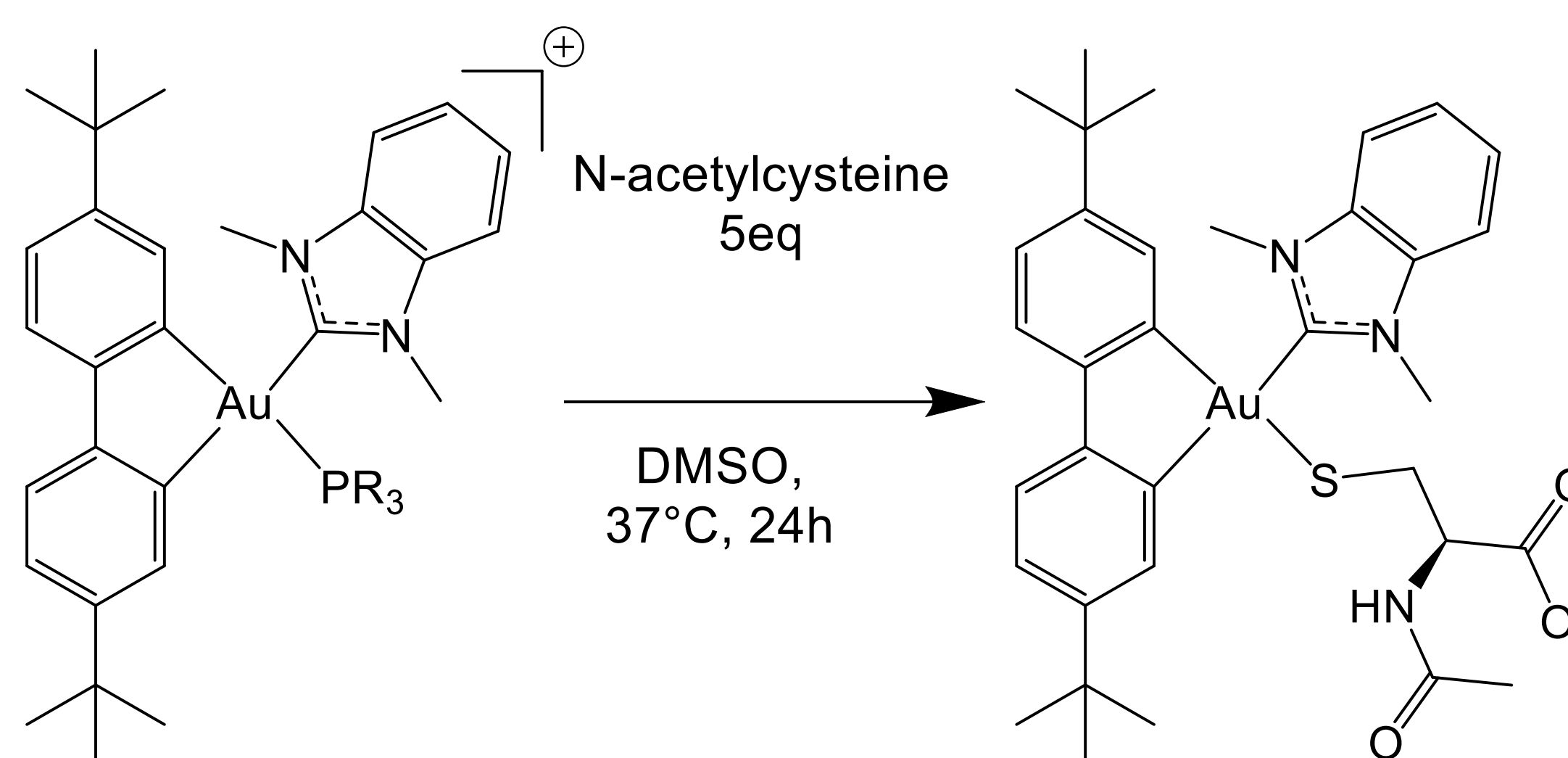


Survival yield of the complexes as a function of the collision energy

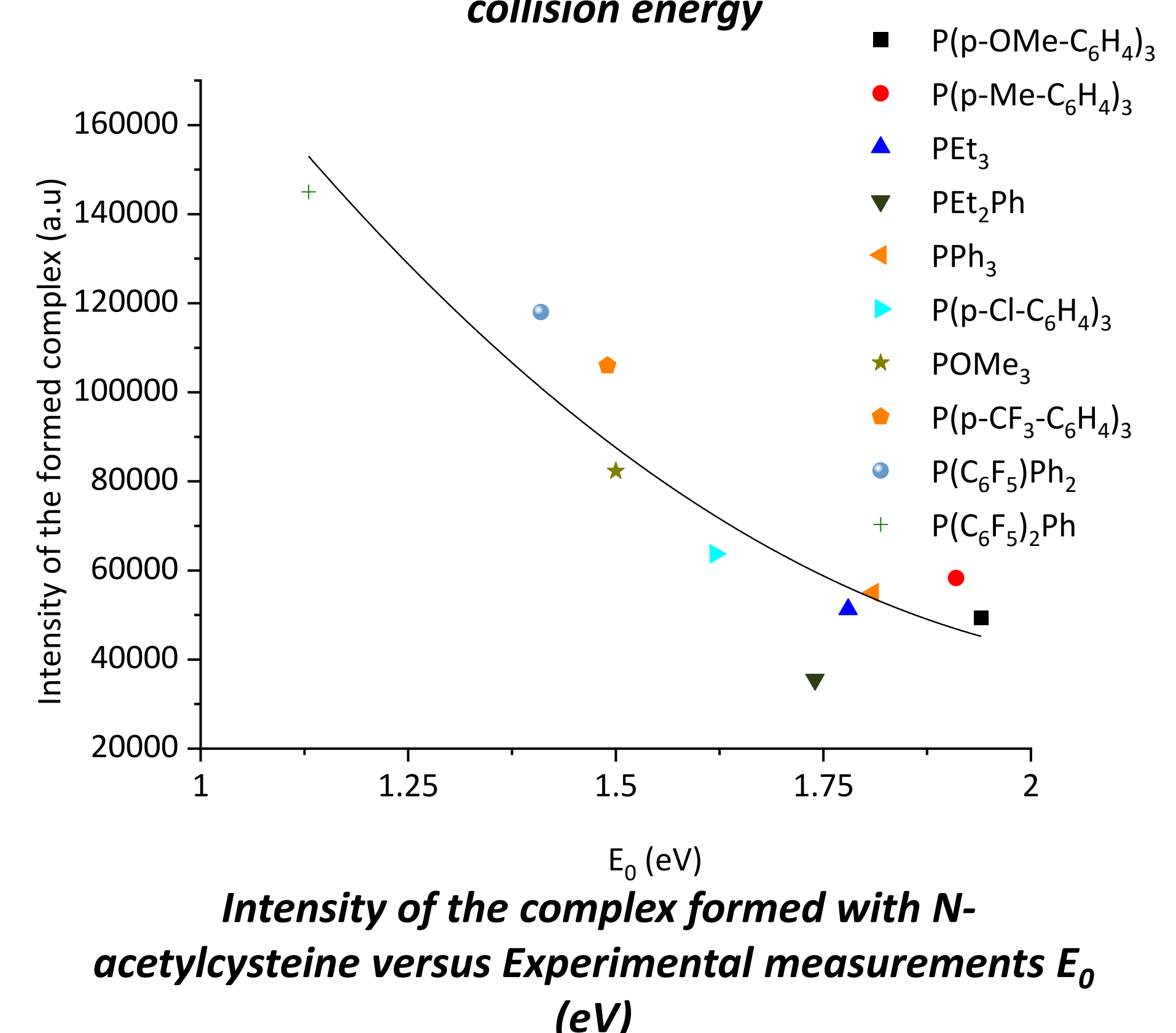
Results



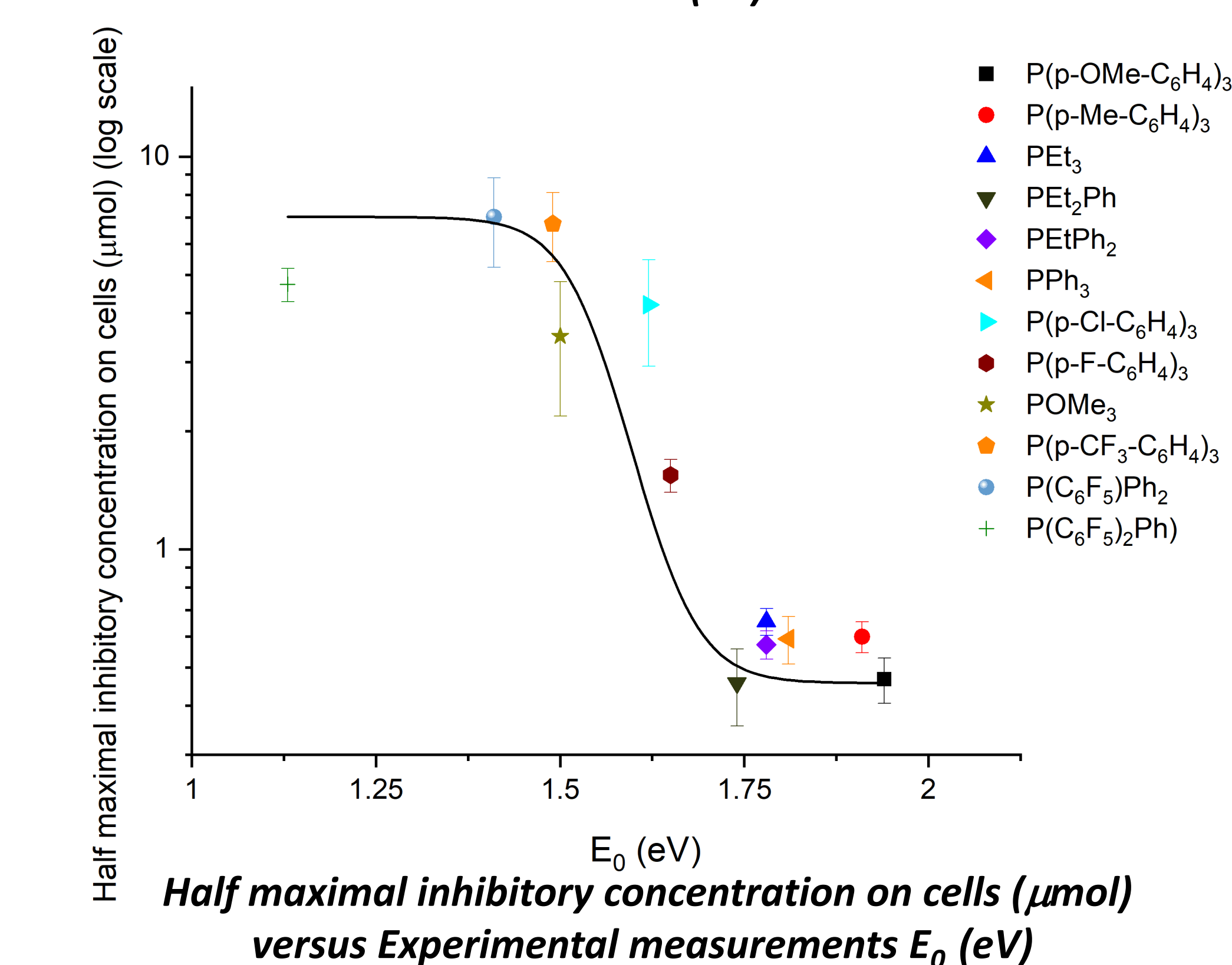
Experimental measurements E_0 (eV) versus calculated BDEs (eV)



Incubation protocol to test the reactivity of the complex toward N-acetylcysteine



Intensity of the complex formed with N-acetylcysteine versus experimental measurements E_0 (eV)



Half maximal inhibitory concentration on cells (μmol) versus experimental measurements E_0 (eV)

Conclusion and Perspectives

- A series of 12 $[(C^A C)Au(NHC)(PR_3)]^+$ complexes were synthesised, isolated and characterized.
- Experimental and theoretical values of bond dissociation energies of the M-L bond were obtained and correlated well. They confirm the expected trends of the ligand donating effects: the richest phosphines are able to donate more to the metal and thus render the Au-L bond stronger.
- There is a correlation between complex stability and median inhibitory concentration.
- The Reactivity of a complex is not necessarily linked to its toxicity.
- Develop a quantitative method for measuring reactivity by mass spectrometry.
- Measure lipophilicity and cellular uptake of complexes.

References: 1-Kim, J. H.; Reeder, E.; Parkin, S.; Awuah, S. G., *Sci. Rep.* **2019**, 9 (1),2- Srinivasa Reddy, T.; Privér, S. H.; Rao, V. V.; Mirzadeh, N.; Bhargava, S. K., *Dalton Trans.*, **2018**, 47 (43), 15312–15323, 3-Yeo, C.; Ooi, K.; Tiekink, E., *Molecules*, **2018**, 23 (6), 1410., 4-Bourehil, L., et al., *Inorg. Chem.*, **2023**, 62 (33), 13304-13314, 5-Marcus, R.A., *J. Chem. Phys.*, **1952**, 20(3): p. 359-364, 6-Drahos, L. and K. Vékey R.A., *JMS*, **2001**, 36(3): p. 237-263, 7- Frisch, M.J., et al., *Gaussian 16 Rev. C.01*, **2016**.