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

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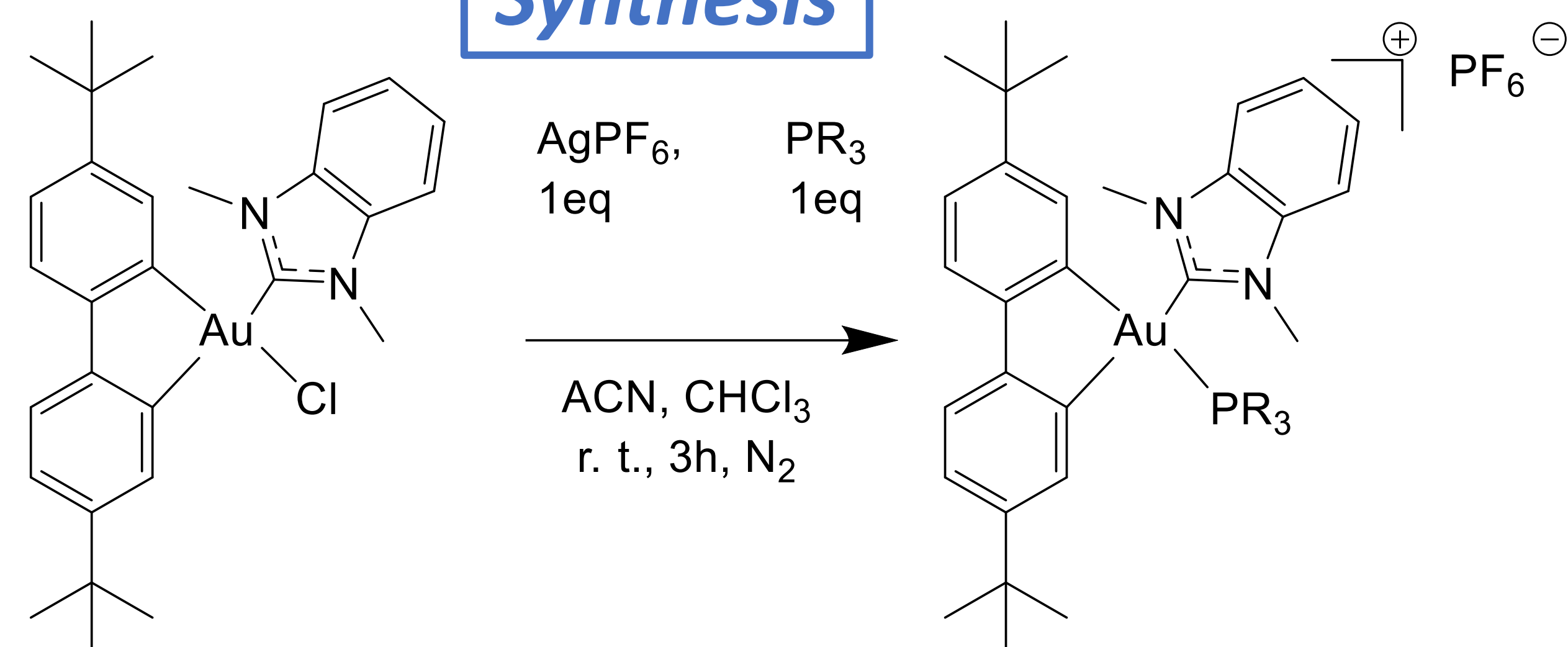
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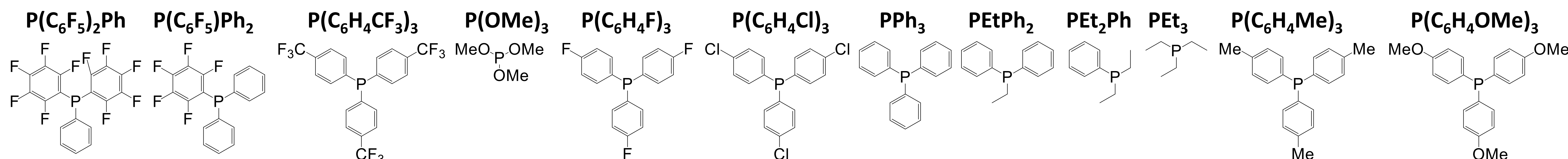
Introduction

- 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].

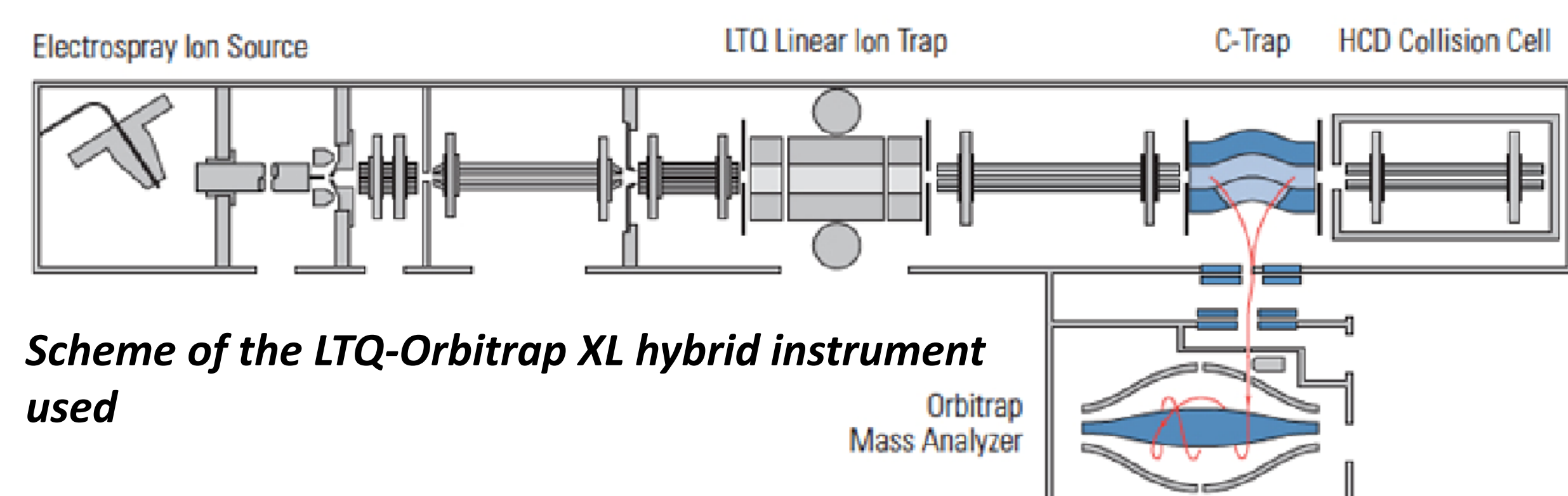
Synthesis



Reaction of formation of the gold(III) complexes



Structures of the various substituents studied



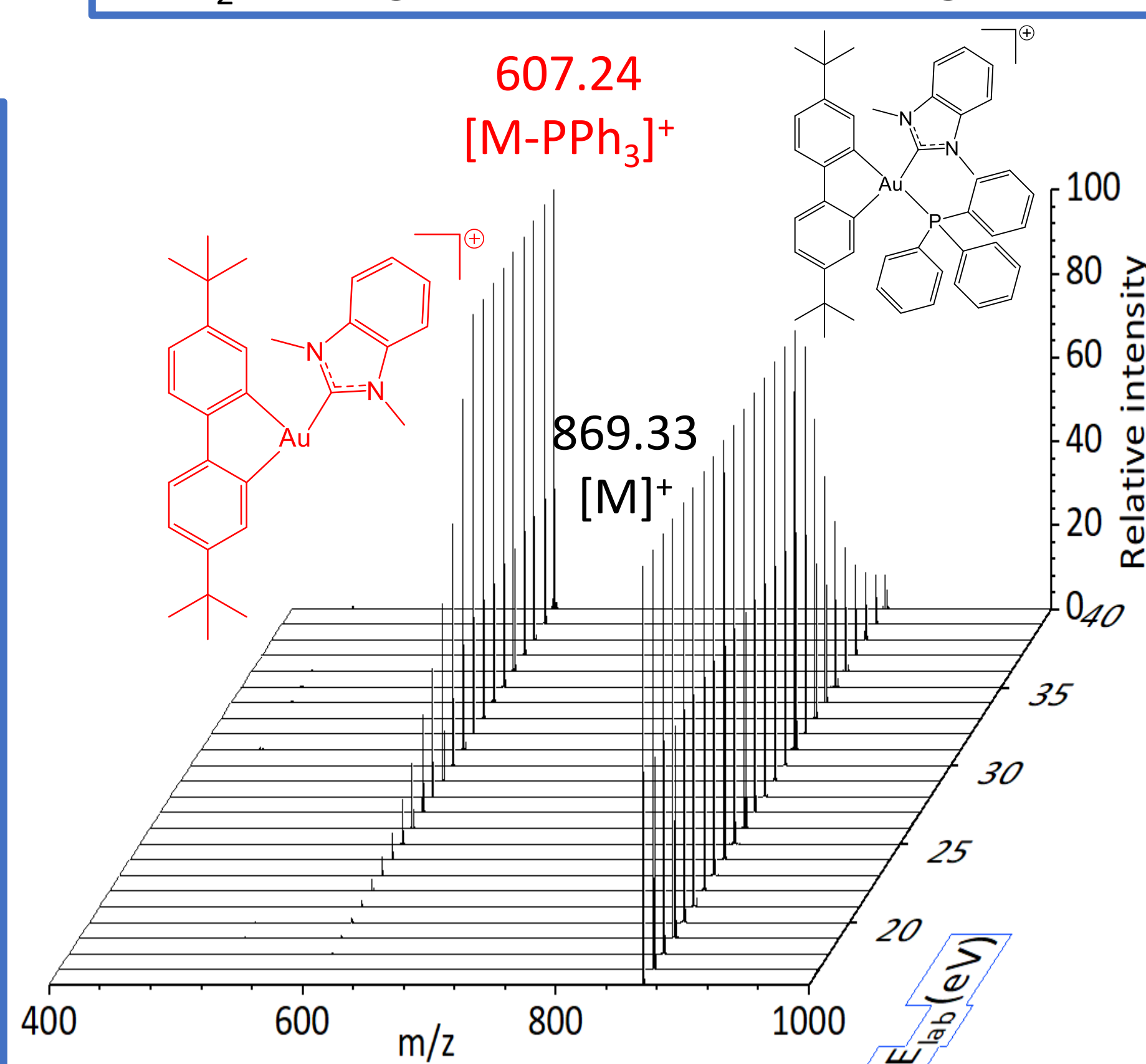
Scheme of the LTQ-Orbitrap XL hybrid instrument used

Experimental setup

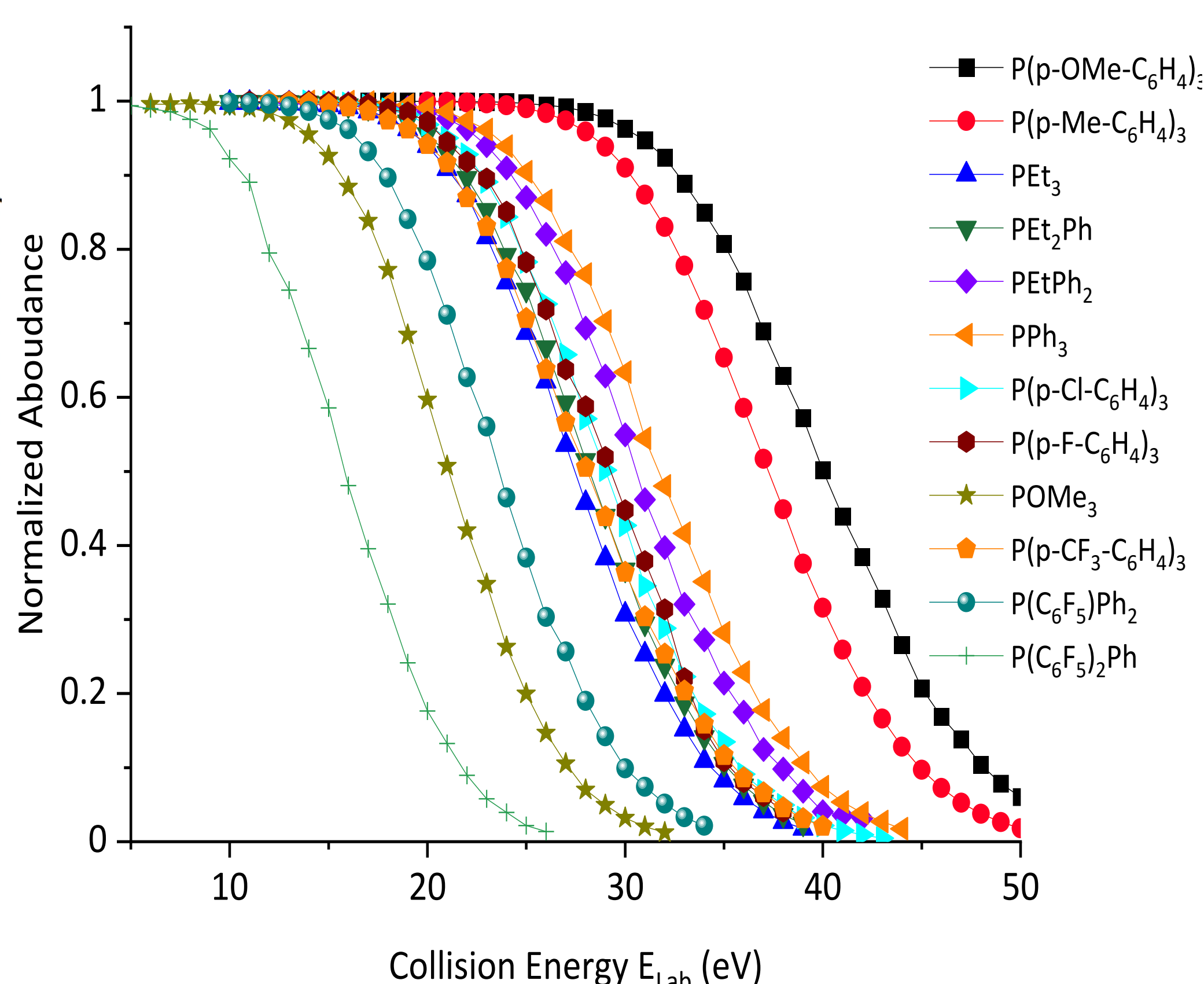
- Ions are formed by an electrospray source and analyzed in a LTQ-Orbitrap XL hybrid instrument (ThermoFisher Corporation, San Jose, USA).
- Precursor ions are isolated in the Linear Ion Trap and accelerated into a collision cell containing N₂ leading to the formation of fragments.

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].

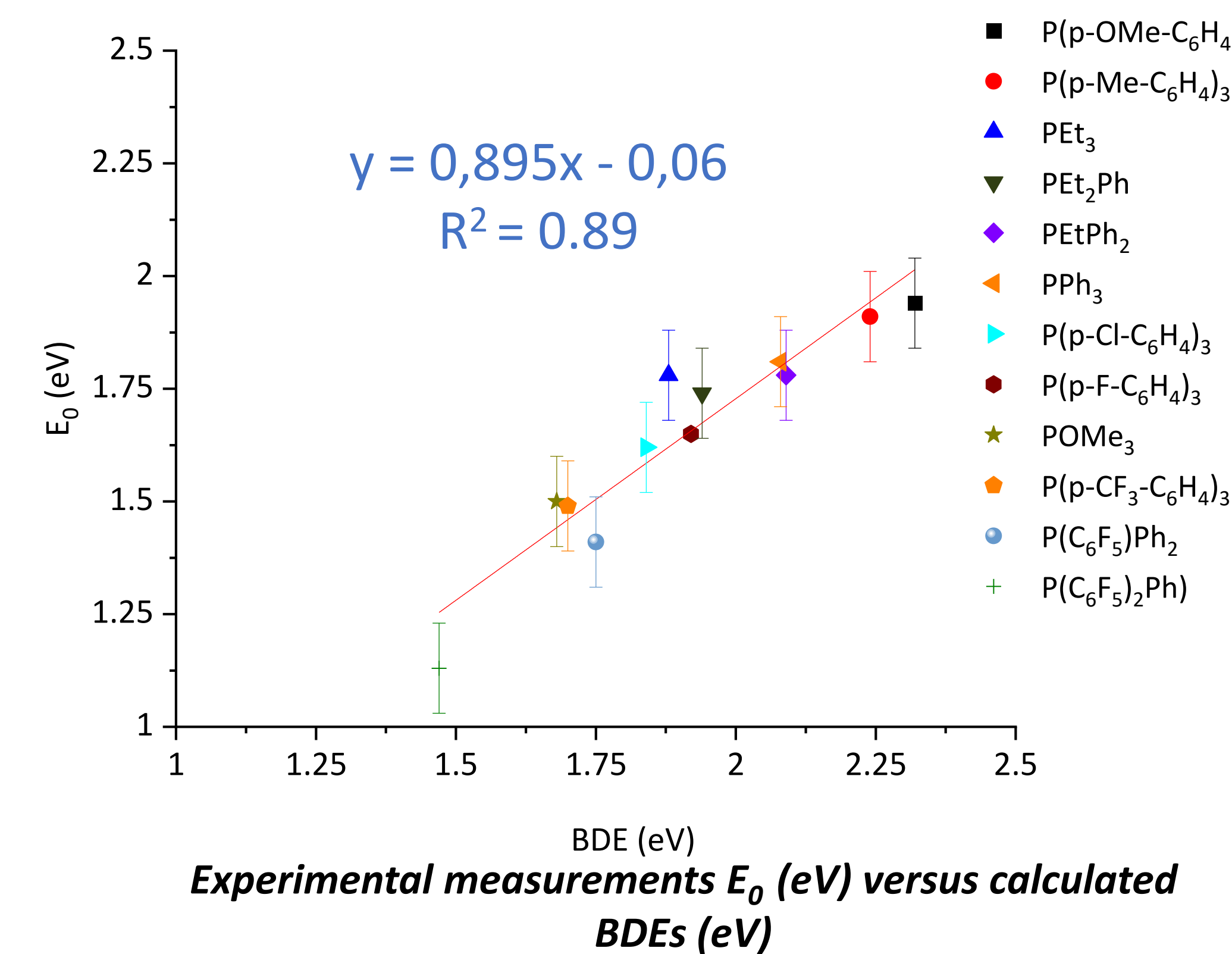


HCD fragmentation spectrum of $[(C^A C)Au(NHC)(PPh_3)]^+$

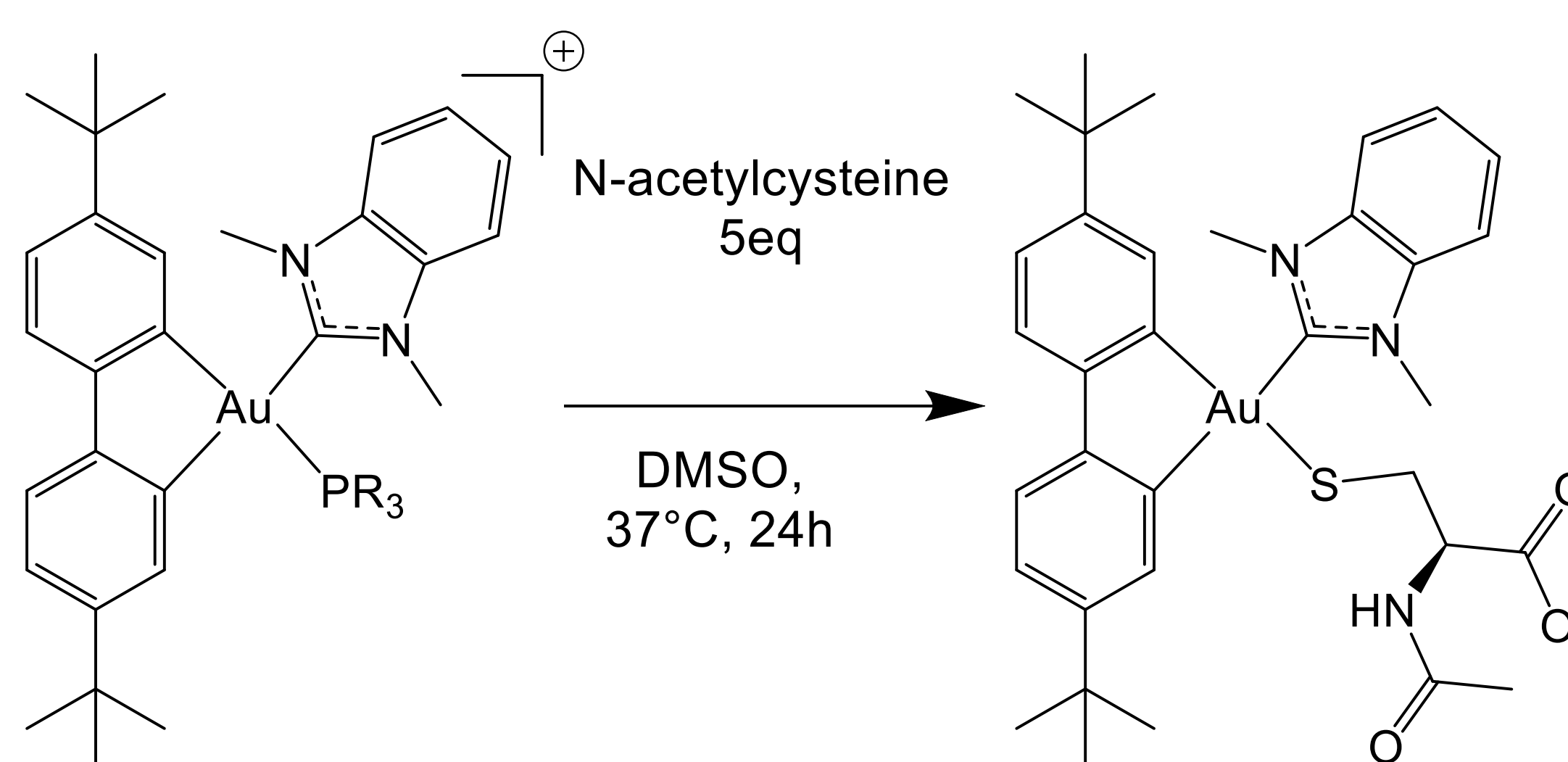


Survival yield of the complexes as a function of the collision energy

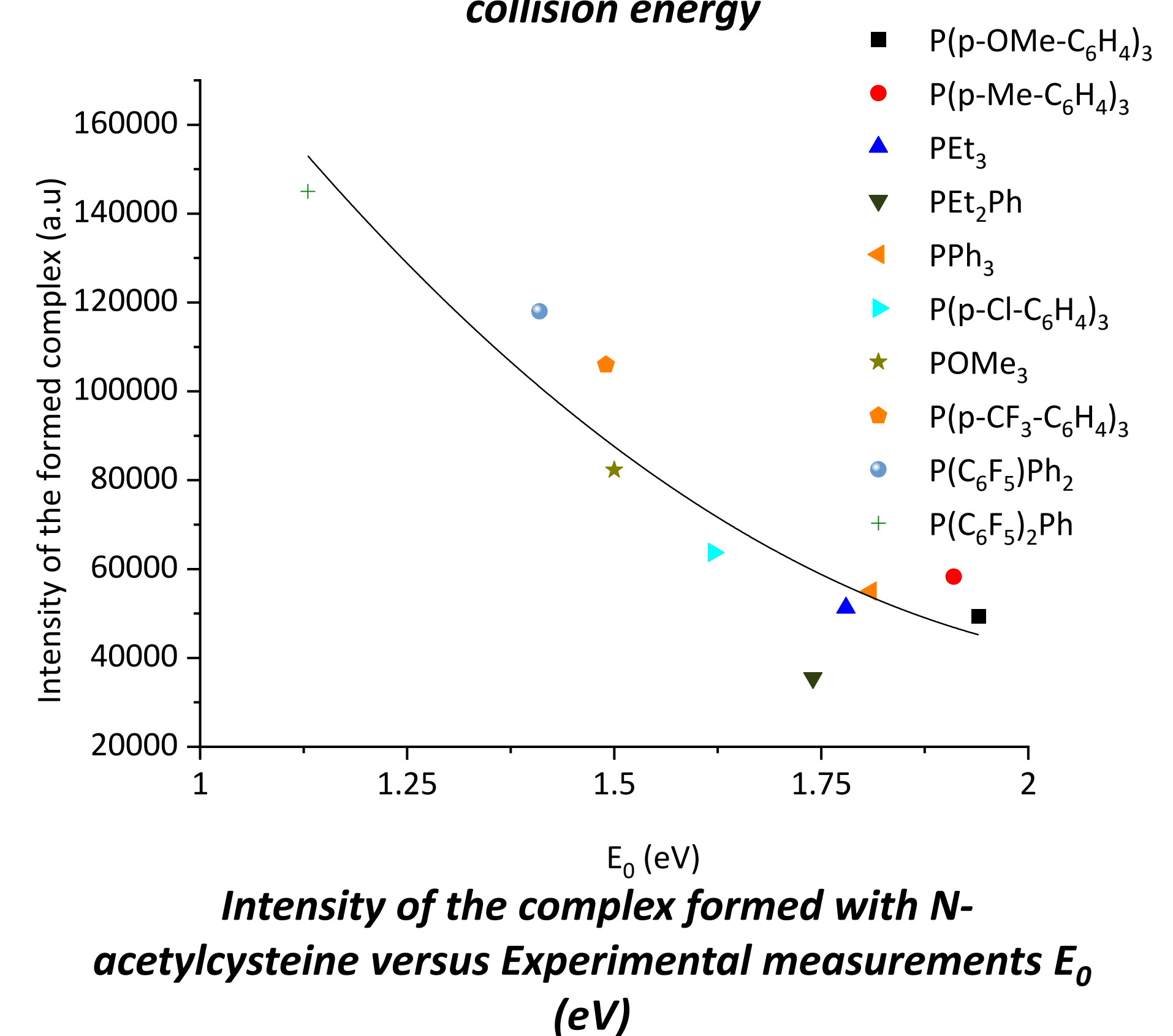
Results



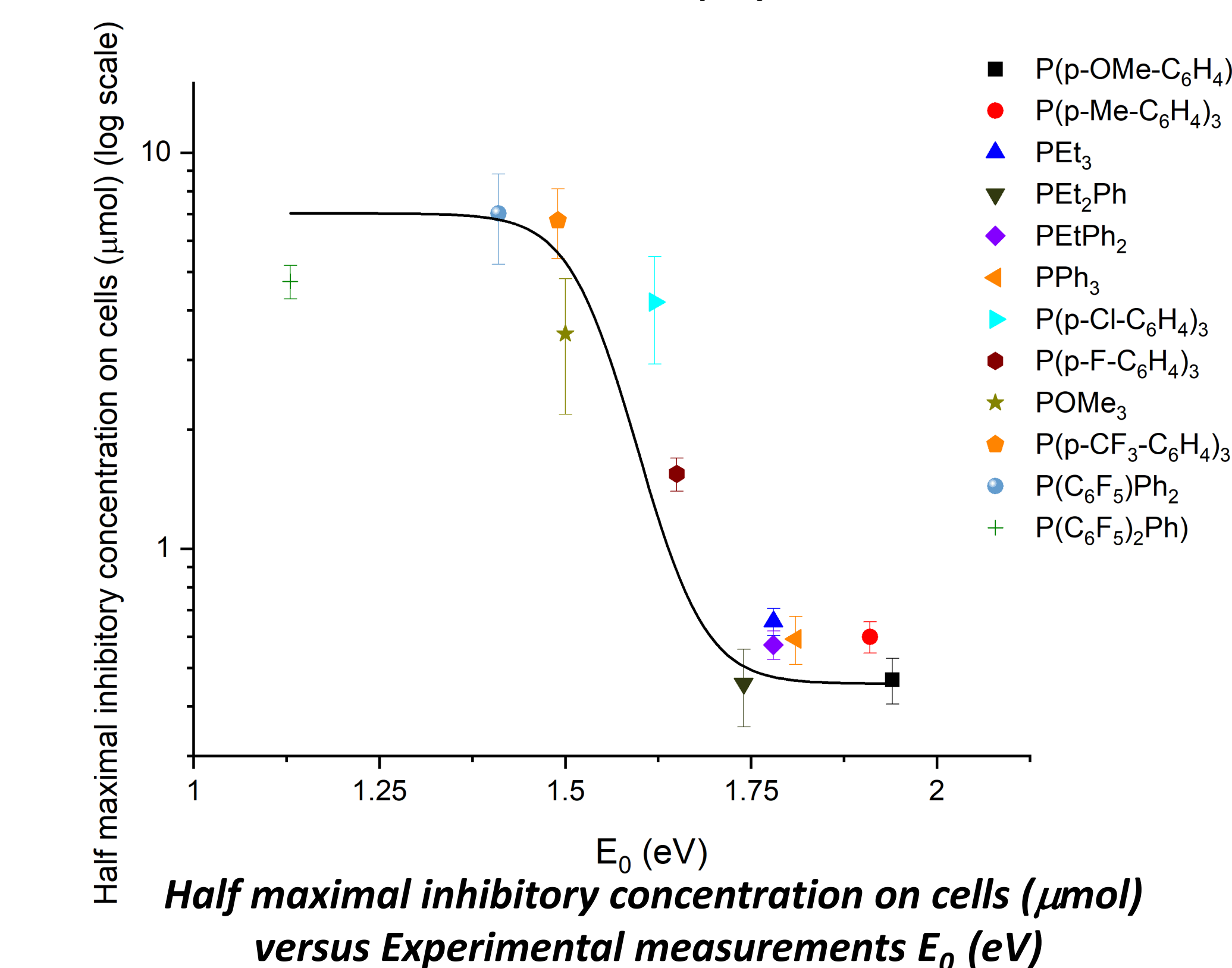
Experimental measurements E_0 (eV) versus calculated BDEs (eV)



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**.