Reseach area: Synthesis, structure and applications of cationic phosphines

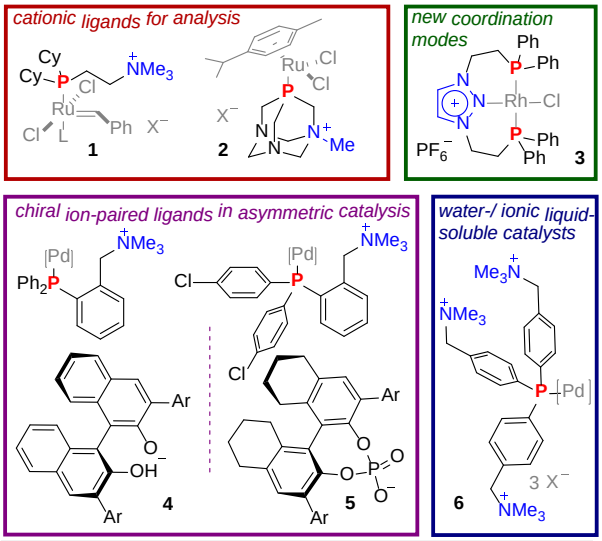


Figure 1. Phosphines with cationic groups attached to the periphery and their applications.

Introduction: The world of ligands is dominated by anionic and neutral species. This is not surprising considering that they have been designed to coordinate metals, and these very often behave as Lewis acids. Cationic ligands are exceptions and when they are used, the positive charged group is mostly located at a remote position from the donating atom. This allows the modification of the physicochemical properties of the corresponding ligands (and catalysts thereof derived) without significantly altering their donor properties. Interesting applications resulting from these ionic architectures are, among others, the identification of reaction intermediates by electrospray mass spectrometry,[1] the isolation of species characterized by new coordination modes,[2] the employment of chiral ion-paired ligands in asymmetric catalysis,[3] and the preparation of water- or ionic liquid-soluble catalysts (Figure 1).[4]

However, the renaissance that the field of cationic phosphines has experienced over the last few years more probably originates from the recognition of the beneficial effects derived from the incorporation of positive charges in close proximity to the donor position. Due to the very strong inductive effect (–I) of positively charged groups, the σ-donor ability of α-cationic phosphines is systematically reduced when compared with that of their neutral analogues. Simultaneously, the new very low lying σ*(P-C$^+$) orbital in α-cationic phosphines increases their π-acceptor character. As consequence, the global electron donation of these ligands to the metals they coordinate is quite low, and in some extreme cases even results in net donation from the metal to the ligand. Only polyhalogenated phosphines such as PF_3, $P(CF_3)_3$ or PCl_3 depict similar electronic properties, but in contrast to those the absence of easy to hydrolyze phosphorus-halogen bonds makes α-cationic phosphines much more robust against moisture, and in general, easier to handle compounds.[5]

Theoretical analysis of the donor properties in α-cationic phosphines and synthesis of the most promising candidates: Willing to investigate in a more quantitative manner these aspects, an inspection of the frontier orbitals was carried out at the B3LYP-D3/def2-TZVP level on α-cationic phosphines **7-10**, each one bearing a different charged unit directly bonded to the central P-atom. This analysis was done at the beginning of the project in cooperation with Prof. Walter Thiel from the MPI-Kohlenforschung (Mülheim an der Ruh). As expected, the introduction of the cationic groups lowers the HOMO energy in relation to Ph_3P, in all the compounds under study. This stabilization is relatively similar in all cases and the HOMO associated energies lay in a relatively narrow range between -9.05 and -9.85 eV. These numbers suggest that the magnitude of the σ-donation for phosphines **7-10** is similar in all cases and not specially influenced by the nature of the charged group (Figure 2). The nearly identical charges calculated at the P-atom for **7-10** corroborate this interpretation.[6]

Conversely, as also depicted in Figure 2, the LUMOs become gradually more localized on the cationic group and their energies diminish progressively along a much wider range, in the sequence from cyclopropenium (-4.10 eV), imidazolium (-4.37 eV), formamidinium (-5.00 eV), pyridinium (-6.07 eV) and CF_3-substituted pyridinium (-6.34 eV). Hence, it seems that the π-acceptor properties of α-cationic phosphines are more receptive to the nature of the substituent that bears the charge. In conclusion, the progressive reduction of global donor properties in cationic phosphines **7**, **8**, **9**, **10 and 10(CF_3)** can be mainly attributed to an increase of their acceptor character following the same sequence.

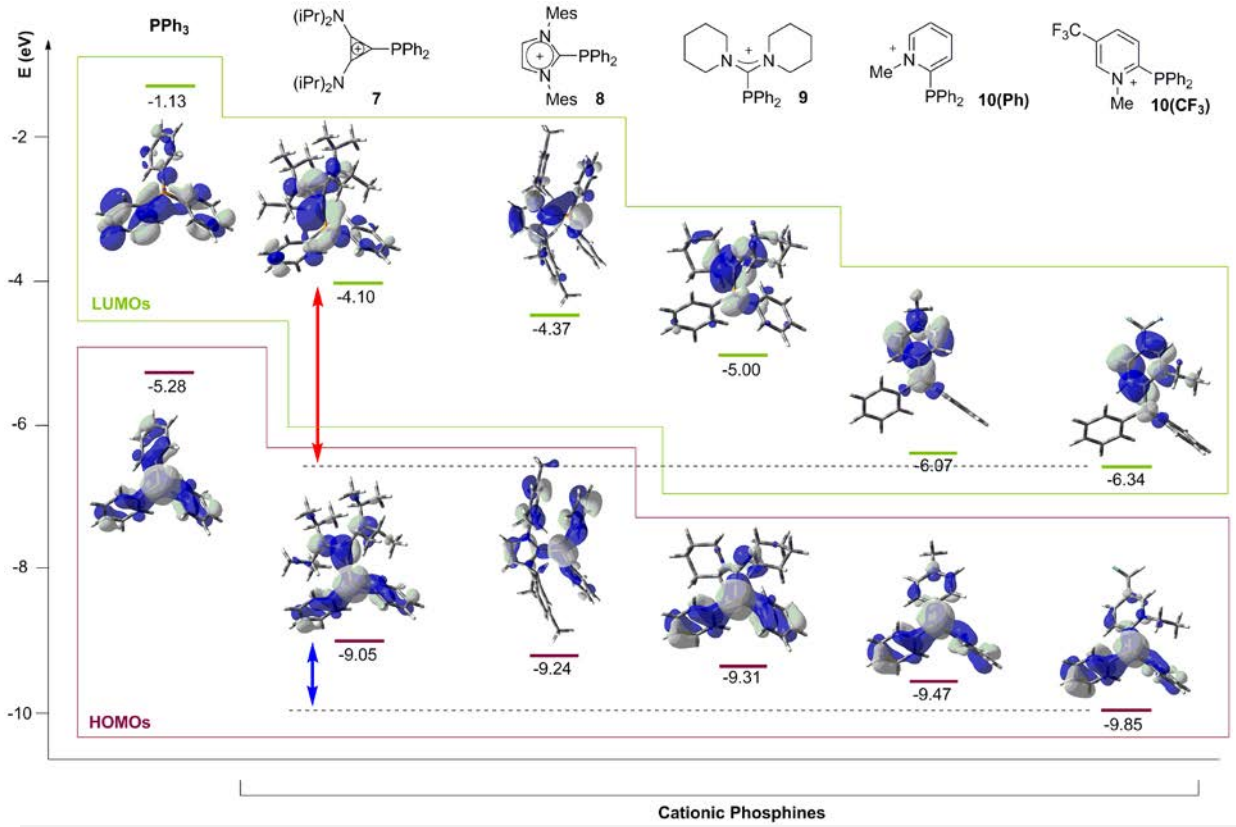


Figure 2. Frontier orbitals for cationic phosphines at the B3LYP-D3/def2-TZVP. Energies in eV.

Note that the introduction of two or even three positively charged groups is also possible. In these cases the global donor porperties of the resulting ligands is reduced even more. **After this analysis, monocationic pyridinium phosphines of general formula 10 and dicationic bis(cyclopropenium)phosphines 11 were chosen as the most promising ligands.** The general synthetic route to both compounds is depicted in Figure 3 together with their X-ray structures.[7]

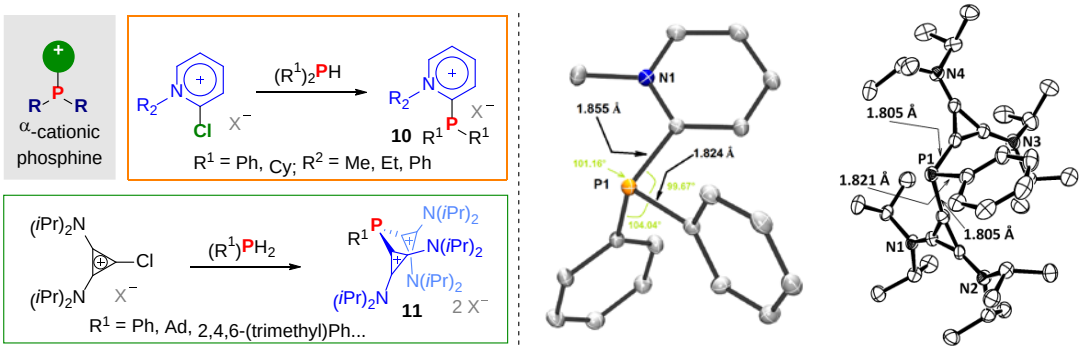
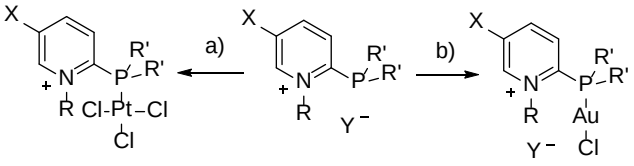


Figure 3. Synthesis and structure of mono- and dicationic phosphines **10** and **11**.

Catalyst design and synthetic applications of α-pyridiniophosphines: Encouraged by this analysis and once the synthesis of the ligands was optimized, we decided to test the potential of pyridiniophosphines in catalysis. With this idea in mind, we prepared a set of Pt(II) and Au(I) complexes **12-18** by reaction of K_2PtCl_4 or $(Me_2S)AuCl$ with solutions of the corresponding ligands (Scheme 3). In addition, crystals of **12** and **15** were obtained and their structure determined by X-ray diffraction confirming the expected connectivity.



12; X = H; R = Me; R' = Ph
13; X = CF_3; R = Me; R' = Ph

14; X = H; Y = BF_4; R = Me; R' = Ph
15; X = H; Y = BF_4; R = Ph; R' = Ph
16; X = F; Y = BF_4; R = Me; R' = Ph
17; X = CF_3; Y = BF_4; R = Me; R' = Ph
18; X = CF_3; Y = SbF_6; R = Et;
R' = 3,5-di(CF_3)Ph

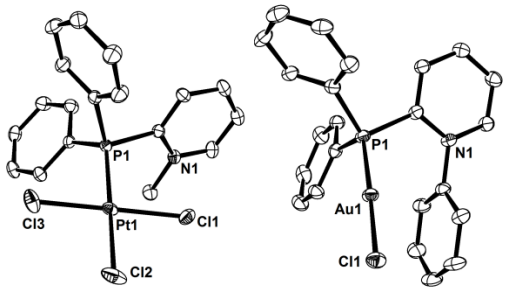
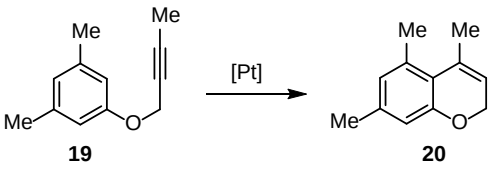


Figure 4. Synthesis of Pt- and Au-complexes and crystal structure of **12** and **15.**

To compare the catalytic performance of complexes **12** and **13** with standard Pt catalysts, the hydroarylation of propargyl aryl ether **19** to chromene **20** was chosen as first model reaction because the proposed mechanism for this transformation suggests that a platinum catalyst with enhanced cationic character should facilitate the whole process.[8] In fact, increased reaction rates were observed when $(C_6F_5)_3P$ was employed as ancillary ligand or if higher oxidized Pt species such as $PtCl_4$ were used as catalysts. Figure 5 also shows the conversion versus time plot for precatalysts **12** and **13** under otherwise identical conditions (2 mol% Pt, 80°C). Their vastly superior performances, that clearly surpass the other catalytic mixtures, beautifully demonstrate the exquisite ability of pyridiniophosphine ligands to increase the π-acidity of Pt centres.



19 **20**

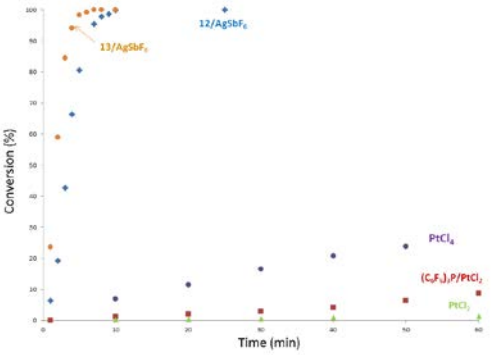


Figure 5. Ligand effect on the Pt-catalyzed hydroarylation of propargyl aryl ether **19** to chromene **20**.

Interestingly, other synthetically useful and mechanistically more complex Pt(II)-promoted transformations also responded to the strong π-acceptor properties of ligands **12**-**19**. Specifically, the cycloisomerization of enyne **21** to cyclobutene **22** was chosen as additional model because this process is known to be accelerated when performed under CO atmosphere (1 atm).[9] Hence, the study of this reaction allows a direct comparison between pyridiniophosphines and the archetypical π-acceptor ligand. Figure 6 shows the kinetic profiles compiled for a set of different catalytic systems under otherwise identical conditions (2 mol% Pt, 80°C). It can be appreciated that CO performed better in terms of reactivity than any the other π-acceptor ligands tested: $(PhO)_3P$ and $(C_6F_5)_3P$. However, the activity exhibited by catalysts **12** and **13** has no rival, and cyclobutene **22** could be obtained in excellent yields after only few minutes.

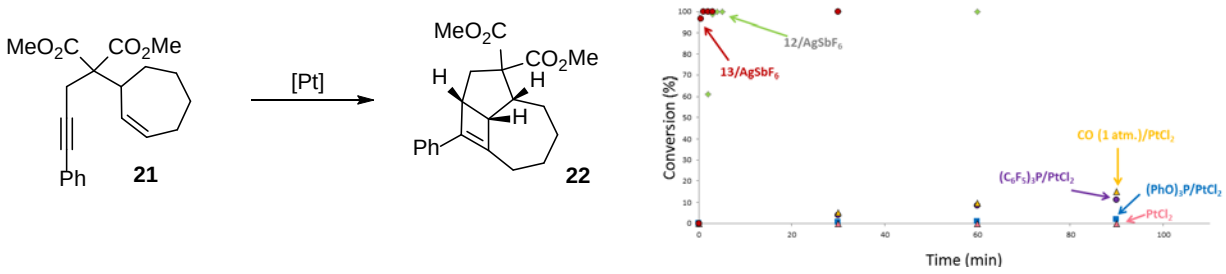


Figure 6: Ligand effect on the Pt-catalyzed cycloisomerization of enyne **21** to cyclobutene **22**. Reagents and conditions: Pt precatalysts 2 mol%, $AgSbF_6$ 2 mol%, $(CH_2)_2Cl_2$, 80 °C.

Synthetic applications of bis(cyclopropenio)phosphines: The examples already described show how the use of α-pyridinio phosphines can be really beneficial in π-acid catalysis. However, there are transformations that are reluctant to happen even with catalysts derived from these phosphines. An illustrative example along these lines is the Au-catalyzed cycloisomerization of 2-ethynyl-1,1'-biphenyls bearing substituents on positions 6 and 6' into twisted phenanthrenes (Figure 7).

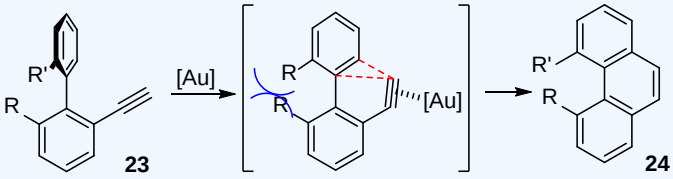


Figure 7. Cycloisomerization of sterically hindered biphenyls.

In these substrates, the difficulties to afford the desired 6-endo-dig cyclisation with traditional catalysts derived from the notable torsion imposed by the unfavorable steric interactions between the internal substituents (in positions 6 and 6'), which impedes the approach of the aromatic ring to the activated alkyne and the concomitant cyclization.

Having identified this step as the rate limiting one, we hypothesized that a stronger activation of the alkyne moiety by a more acidic metal center might overcome this limitation. This change should provide an earlier transition state for this step and therefore, the steric factors should be less determining. If this statement is correct, an even stronger π-acceptor ancillary ligand might transform this very low yielding reaction into an useful route for the synthesis of 4,5-disustituted phenanthrenes and derivatives.[10]

After intensive screening we found that the most suitable pre-catalyst to carry out this transformation was Au complex **25**, an air stable solid prepared by reaction of the dicationic phosphine **11** with $AuCl(Me_2S)$ (Figure 8a)**.** Optimization of the reaction conditions using different catalyst loadings, solvents of different polarity, and various silver salts for precatalyst activation, allowed the identification of optimal conditions, under which the model 2-ethynyl-2,6'-dimethylbiphenyl **23** was transformed into the desired 4,5-dimethylphenanthrene **24** with excellent yields and surprisingly short reactions times. The significance of this result is better highlighted in Figure 8b where the kinetic profiles for the archetypical Au catalysts: Ph_3PAuCl (red dots) and $(PhO)_3PAuCl$ (green dots) are compared with that of **25**, under identical experimental conditions. The relative initial rate constants k_{rel} of the reaction promoted by **25** versus Ph_3PAuCl or $(PhO)_3PAuCl$ are 492.5 and 21.7 respectively. Moreover, the scope of the cycloisomerization was demonstrated to be quite general in terms of size and types of functional groups that could be introduced on the structure of the final phenanthrene. This allowed us **to explore the utility of our protocol for the synthesis of a number of biologically active, naturally occurring polyoxygenated phenanthrenes of twisted geometry** and derivatives. Some examples of the products prepared are Coeloginin **26** [11], Epimedoicarisoside A **27** [12], and Calanquinone C **28** [13] (Figure 8c).

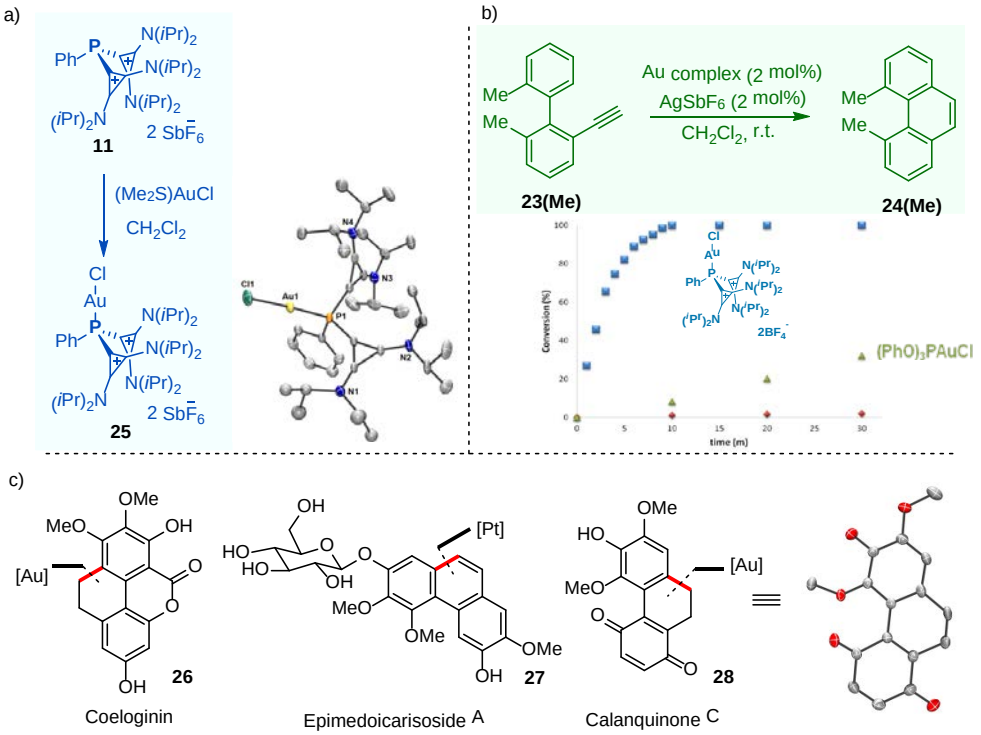


Figure 8. (a) Synthesis and structure of catalyst **25** in the solid state; (b) ligand effect of the Au(I)-catalysed cyclization of 2-ethynyl biphenyls into phenanthrenes; (c) synthesis of selected naturally occurring phenanthrenes and related structures.

Beyong π-acid catalysis: A priori any catalytic cycle whose global rate is controlled by an elementary step that increases the electron density at the metal center might also benefit from the reduction of the energetic span supplied by strong π-acceptor ligands. In this regard, we subsequently selected catalytic processes characterized by challenging reductive eliminations from Pd(II) centers as starting points for a new investigation. Although none of the model transformations tested could be performed in a catalytic fashion, the isolation of the Pd-containing species originating from catalyst decomposition during these attempts was possible (Compounds **29** and **30**; Figure 9). We postulate that upon formation of the Pd(0)-cationic ligand complex, intensive back donation from Pd(0) to the low lying σ*(P-C^{+}) orbital induces its oxidative insertion into this bond and the formation of a Pd(II)-NHC complex, which is inactive. Alternative Pd(0) sources and cationic ligands provide similar core structures, although with different flanking ligands.[14] **The formation of undesired 29, 30 and related**

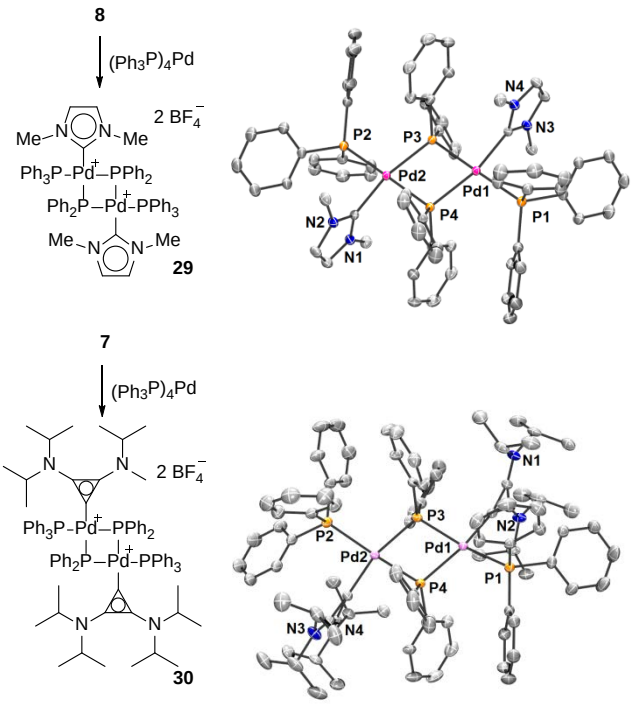


Figure 9. Synthesis and structure of **29** and **30** in the solid state.

species upon reaction of cationic phosphines with electron rich metal species demarcates one of the current frontiers of α-cationic phosphines as ancillary ligands.

Conclusions and future perspectives:

Over the past several years and thanks to the research project AL 1348/5-1, we have demonstrated that α-cationic phosphines of different structures can be easily synthesized and effectively employed as ancillary ligands. Due to their strong acceptor properties, these ligands efficiently accept electron density from the metal centers they coordinate and, for this reason, they facilitate catalytic cycles requiring strong Lewis acidity at the metal center during the rate determining step. This has been efficiently exploited in our group in the framework of Au(I) and Pt(II)-catalysis. α-Cationic arsines have also been prepared; they have found to depict even enhanced acceptor properties than these of their lighter analogues.

We anticipate that the intensive acceleration effects observed in π-acid catalysis by the use of α-cationic phosphines might have tremendous implications in the area of asymmetric catalysis, where catalysts able to work at lower temperatures are usually required to obtain good enantiomeric excess. The profitable employment of α-cationic phosphines beyond π-acid catalysis is another challenge still remaining in this area. We look forward to addressing both of these in the near future.

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