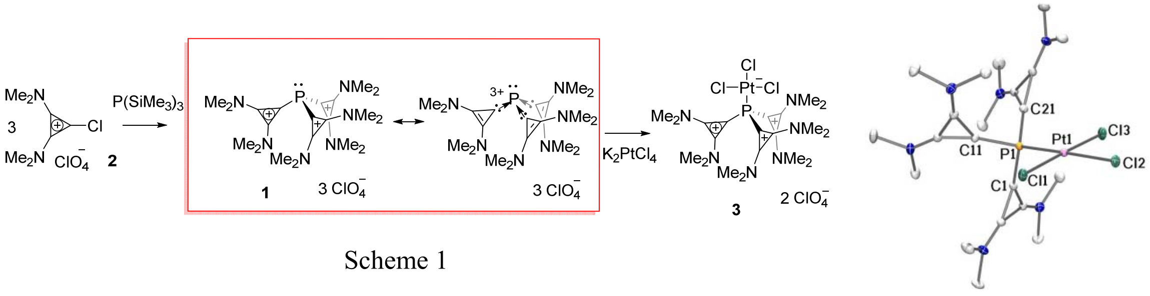
2.4.5 Research Area “Cationic Ligands: Synthesis and Applications of Extreme π-Acid Catalysts” (M. Alcarazo)

Involved: J. Petuškova, J. Carreras, E. González, L. Gu, Á. Kozma, P. Linowski, G. Mehler, H. Tinnermann, C. Wille, T. Deden, A. Gimeno, P. Gualco, A. Zanardi

Objective: The goal of this project is the synthesis of extreme π-acceptor phosphines through the introduction of positively charged homo- or heteroaromatic substituents directly attached to the phosphorus atom. By exploiting this property, new Au and Pt catalysts have been developed that display a dramatically enhanced capacity to activate π-systems.

π-Acid catalysis, mainly with Au(I) and Pt(II) based species, has emerged in the last decade as one of the most efficient tools for the promotion of rearrangements in unsaturated organic substrates, which provide an exquisite entry to the synthesis of intricate skeletons that may be otherwise difficult to prepare. The generally accepted mechanism that governs most of these transformations involves three main steps: (i) coordination of the π-acid metal to the alkyne or allene moiety present in the starting material, (ii) nucleophilic intra- or intermolecular attack to the activated substrate forming a vinyl-metal species, and (iii) protodemetallation of the vinyl intermediate with concomitant regeneration of the active catalyst. It seems reasonable to expect that the first two of these steps may be accelerated by strong π-acceptor ancillary ligands, which should increase the Lewis acidity of the metal center they coordinate. In striking contrast, potent σ-donating ligands will weaken the M-C bond in the vinyl intermediates by their *trans*- influence and thus facilitate the protodemetallation step. Hence, the selection of the most appropriate ligand for a particular transformation can only be done based on an in-depth understanding of the nature of the rate-determining step.

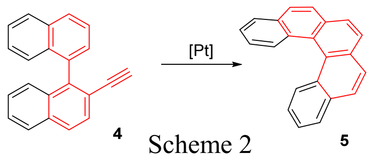
Very recently, we reported the synthesis of the first ever isolated carbene-stabilized P_1-centered trication $[L_3P]^{3+}$ (L = 2,3-dialkylaminocyclopropenium) **1** by reaction of the 1-chloro-2,3-(dimethylamino) cyclopropenium salt **2** and $P(SiMe_3)_3$ (Scheme 1). Despite the three positive charges on the groups directly attached to the P atom, this compound can still serve as a ligand for π-acidic metals such as Pt. Thus, when **1** is treated with K_2PtCl_4 in acetonitrile, the bench stable complex **3** is formed. More interestingly, charge decomposition analysis of the metal-ligand interaction in **3** gave the surprising result that the total L→M σ-donation (0.31 *e*) is lower than the M→L π-back donation (0.43 *e*) into the very low-lying LUMO of **1**, which must hence be regarded as the main interaction in **3**. This unconventional situation in which the P-ligand removes net electron density from the metal suggests that compound **1** increases the natural π-acidity of Pt(II) centers. It should thus accelerate known reactions, or even permit new ones, in which either the coordination of the substrate or the nucleophilic attack to the activated substrate are the rate-determining steps.



Scheme 1

In a preliminary screening of plausible applications for these ligands, we chose the Pt-catalyzed 6-*endo*-dig cyclization of 2-ethinyl-1,1'-binaphtalene **4** into pentahelicene **5**, as model reaction for two main reasons (Scheme 2).

(a) The interest in polycyclic homo- and heteroarenes has been refueled during the last years due to their unique optoelectronic properties and their potential applications in organic electronic devices. The chosen cyclisation is a very attractive entry for the preparation of these carbon-rich materials. Moreover, this reaction can be also used to prepare highly substituted phenanthrene moieties that are present in the structure of natural products. Therefore, expeditious syntheses to these compounds may be envisaged.



Scheme 2

(b) Due to the relatively weak nucleophile that is employed (an aromatic ring), the nucleophilic attack is expected to be the rate-determining step for this reaction. Hence, the use of strong π-acceptor ancillary ligands such as **1** should facilitate this transformation.

Accordingly, we chose for our studies on ligand effects a series of phosphanes such as PPh_3, $P(OPh)_3$, $P(C_6F_5)_3$ and precatalyst **3** in combination with a silver salt. As expected, both $P(OPh)_3$ and $P(C_6F_5)_3$ performed better than PPh_3 in terms of reactivity (Figure 1).

Interestingly, our ligand **1** produces a much faster reaction, clearly surpassing any of the classical π-acceptor ligands. In fact, complete conversion of the model substrate to pentahelicene **5** was achieved in less than 20 minutes under the newly developed reaction conditions.

Furthermore, the compatibility of our catalytic system with several functional groups is outstanding. Up to now, our experiments indicate that biaryl substrates containing ethers, free or silylated alcohols, esters, halogen substituents, silyl- and trifluoromethyl groups, thiophenes, and furanes are well tolerated (for representative examples see Scheme 3). Moreover, all products were obtained in few minutes with very good to excellent yields.

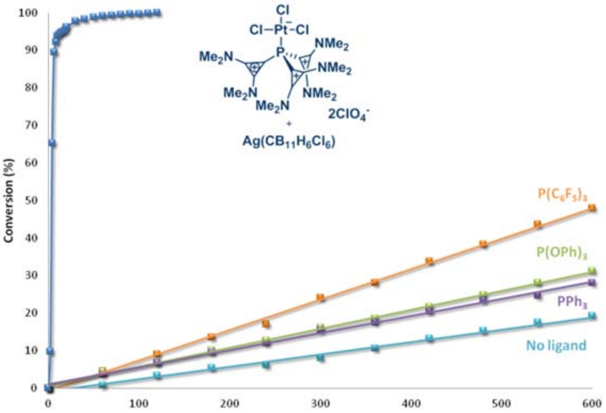
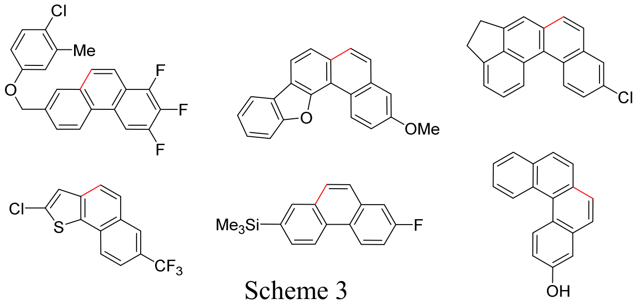


Figure 1



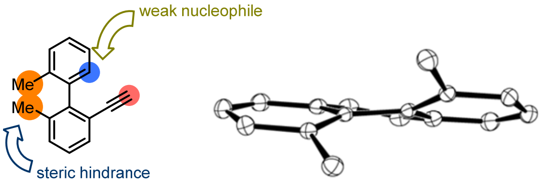
Scheme 3

However, despite of the remarkable activity depicted by **3**, there are still three main aspects regarding this catalyst that deserve further optimization:

a) Catalyst stability needs to be enhanced. With catalysts **3**, no reaction progress is observed after reaction times of about one hour, presumably due to catalysts decomposition.

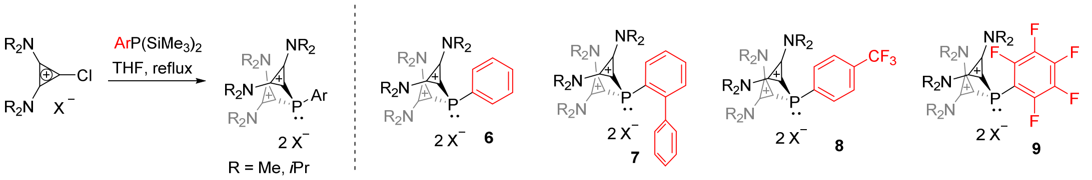
b) Catalyst activity needs to be improved. Although much faster, with the newly developed catalytic system a catalyst loading of 5 mol% and high temperatures (80 °C) are still necessary. In addition no reaction is observed if bulky substituents are located at the *ortho*- positions of the biaryl starting material (See Scheme 4). The employment of a more π-acidic Au(I)-based catalysts instead of a Pt(II)-derived one might be beneficial at this point.

c) Improvement of the substrate tolerance to heteroaromatic rings such as pyridines is desirable.



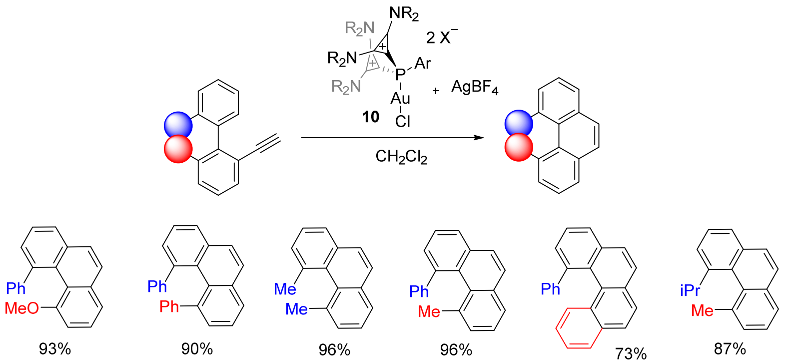
Scheme 4

As already mentioned, Au(I) based catalysts should be more active than Pt(II)-based ones due to the stronger Lewis acidity of Au(I) centers. Unfortunately, all attempts to coordinate gold to ligand **1** were unsuccessful. In contrast, dicationic ligands were found to be more appropriate in Au chemistry because: (i) their Au-derived complexes are much more stable than those derived from tricationic ligands and (ii) their reactivity is comparable. Thus, we planned to synthesize a set of dicationic ligands bearing several R substituents on the phosphorus with different steric demands and electronic nature (Ph, biphenyl, C_6F_5-, *p*-$CF_3C_6H_4$…). Up to now, compounds **6** and **7** and the Au(I) complexes thereof derived have been prepared (Scheme 5).

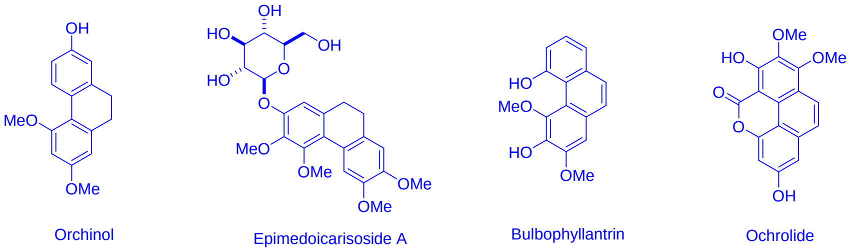


Scheme 5

To evaluate the range of application of these new Au catalysts, we focused on those substrates that were reluctant to react when the Pt-based complex **3** was employed as precatalyst; namely those with substituents in the *ortho*- positions of the biphenyl skeleton or those with electron withdrawing groups attached to the ring that has to accomplish the nucleophilic attack. Some of the substrates that could be prepared employing the new Au(I) catalysts **10** are depicted in Scheme 6.



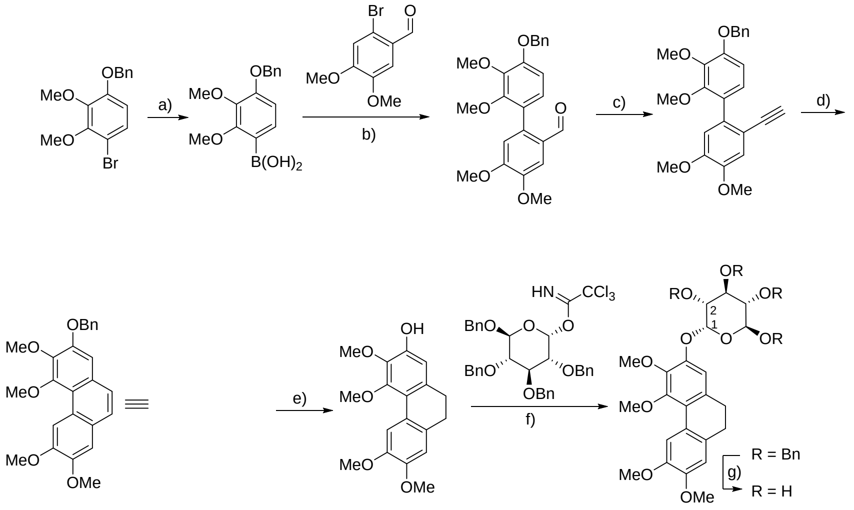
Scheme 6



Scheme 7

In addition, our synthetic program has already benefitted from these novel tools and natural products such as Orchinol, Ochrolide, Bulbophyllantrin and Epimedoicarisoside A have been prepared using our Pt and Au catalysts for the key hydroarylation step (Scheme 7). As representative example, Scheme 8 depicts the synthesis of Epimedoicarisoside A, a compound with potential application in the treatment of cardiovascular and cerebrovascular diseases such as myocardial infection or cerebral thrombosis.

Future directions: Many transformations might benefit from the use of extremely π-acceptor ligands. At the moment we are focused on the application of our ligands in Rh and Pd-catalyzed processes. The synthesis of cationic phosphines containing other –onium substituents different than cyclopropenium is also being investigated.



Scheme 8 a) *n*BuLi, -78 °C, $B(OMe)_3$, H^+, (59%); b) $Pd(PPh_3)_4$ (2 mol%), µwave oven, 120 °C, 25 min (98%); c) Ohira-Bestmann reagent, (3 eq.), K_2CO_3, MeOH, RT, 48 h (83%); d) **10** (2 mol%), $Cl(CH_2)_2Cl$, 80 °C, 3 h, (92%); e) H_2 (30 bar), Pd/C (20%), MeOH, RT, 48 h, (82%); f) $BF_3{\cdot}OEt$ (1 eq.), CH_2Cl_2, -20 °C, 2 h, (93%); g) H_2 (1 bar), Pd/C (10%), MeOH: AcOEt (2:1), 24 h, RT, (75%).

2.4.6 Research Area "Synthesis and Applications of Simultaneous σ- and π-Donor Ligands: C-M Dative Double Bonds" (M. Alcarazo)

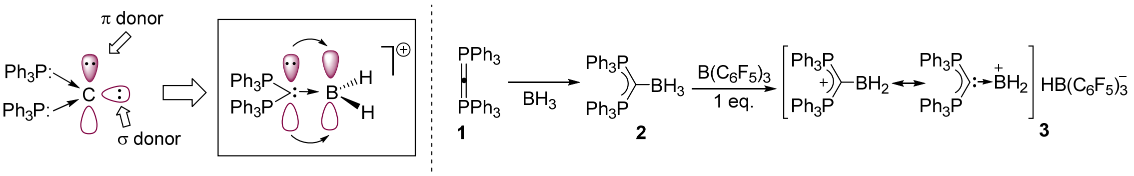
Involved: B. Inés, S. Kahn, R. Azhakar, S. Holle, F. Martín

Objective: The goal was to study new coordination modes of carbon(0) compounds.

In this area, our research has been strongly inspired by the theoretical work of Frenking about the nature of carbodiphosphorane **1** (Scheme 1). His studies revealed that in compound **1** and analogues the central carbon atom retains its four valence electrons that are thus all available for coordination. In fact, carbodiphosphoranes are known to react with two Lewis acids such as AuCl affording diaurated derivatives. However, their ability to donate their four electrons to the same electrophile in a simultaneous σ- and π-donation had not been described.

In this regard, we envisaged that the use carbodiphosphoranes may provide sufficient stabilization to attenuate the reactivity and allow the isolation of dihydrido borenium cations $[L \rightarrow BH_2]^+$ (L = carbodiphosphorane), a series of compounds that cannot be isolated when classical σ-donating ligands are employed.

Hence, we allowed carbodiphosphorane **1** to react with borane dimethylsulfide complex and isolated adduct **2** as a bright yellow solid in quantitative yield (Scheme 1). Upon treatment of a solution of **2** with one equivalent of $B(C_6F_5)_3$ the color smoothly vanishes. The ^{11}B-NMR spectrum indicated the generation of the borohydride anion $HB(C_6F_5)_3^-$ (δ = -24.0 ppm; $^1J(^1H,^{11}B)$ = 92 Hz) while complete consumption of $B(C_6F_5)_3$ was confirmed by ^{19}F-NMR. Additionally, the original ^{11}B-NMR resonance of **2** (δ = -22.7 ppm; $^1J(^1H,^{11}B)$ = 84 Hz) disappeared and a new broad signal (δ = 56.6 ppm) emerged. These data suggested the formation of the dihydrido borenium borohydride **3**, an interpretation that was validated by X-ray crystallographic analysis (Figure 1).



Scheme 1. Synthesis of a dihydridoborenium cation.

In an attempt to clarify the electronic nature of **3**, density functional calculations at the B3LYP/6-31G* level were performed. Inspection of the frontier orbitals reveals that the highest occupied molecular orbital (HOMO) is the C-B π-bonding orbital that is strongly polarized toward the C atom (see Figure 1). Energy decomposition analysis also indicates that σ-donation contributes about twice as much as π-donation to the stability of the C=B bond. Presently, our efforts are directed to the application of the borenium cations in fluorine-free frustrated Lewis pair chemistry as their Lewis acidity has been proved to be very similar to the one depicted by $B(C_6F_5)_3$.

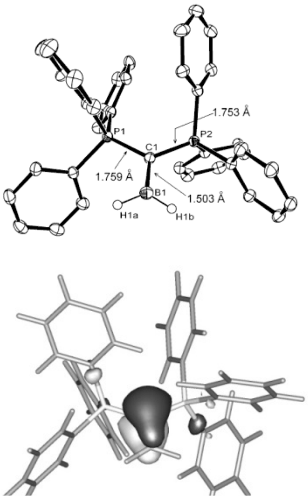
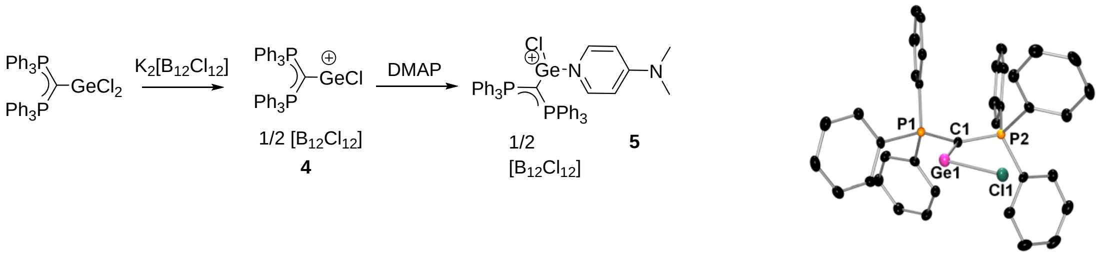
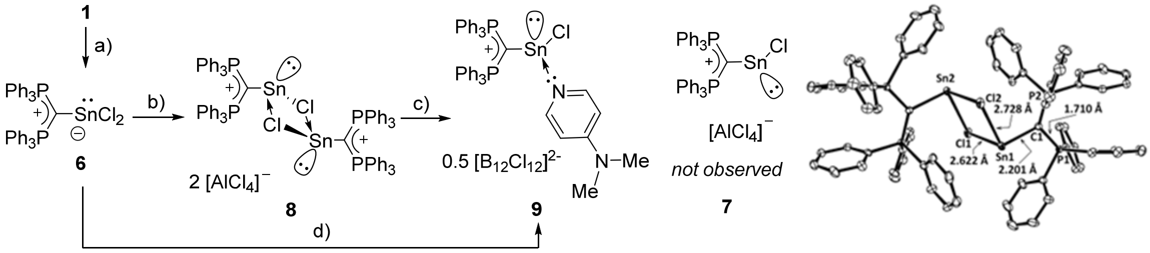


Figure 1. X-ray structure (up) and HOMO(down) of compound **3**.

The employment of **1** as both σ- and π- acceptor ligand is expected to facilitate the isolation of low coordinated p-block cations such as Si(IV)$^{+2}$ or Ge(II)$^{+2}$. Our strategy, that is already producing some positive results, is depicted in Scheme 2. In broad lines it relies on the coordination of carbodiphosphorane **1** to a germanium or silicon chloride and subsequent abstraction of the chloride anions, a task that should be facilitated by the extra π-electrons of the ancillary ligand. Up to now we have been able to synthesize compound **4** which already depicts a σ- and a π-dative bonds between the central carbon atom and the GeCl moiety. Reaction with dimethylamino pyridine affords adduct **5** where the π interaction is not existing anymore. Currently, we are trying to remove the chloride moiety from **5**. In case of success, the first dicoordinated Ge(II) dication will be isolated. The same strategy is being applied for the preparation of Si(IV) dications.



Scheme 2. Proposed synthesis of Ge(II) dications and structure of 4.



Scheme 3. a) **1**, $GeCl_2$·dioxane, DCM, RT, quant.; b) **6**, $AlCl_3$, CH_2Cl_2, 67%; c) **8**, DMAP, CH_2Cl_2, $K_2[B_{12}Cl_{12}]$ (0.5 eq.); d) **6**, DMAP, CH_2Cl_2, $K_2[B_{12}Cl_{12}]$ (0.5 eq.), 53%.

Finally, the extension of this chemistry to Sn(II) was also attempted. Reaction of **1** with $SnCl_2$ afforded the very insoluble and air-sensitive adduct **6** that was subsequently treated with $AlCl_3$. In sharp contrast to the Ge analogue previously described, abstraction of a chloride anion from **6** did not yield the expected cation **7** but its dimer **8** (Scheme 3). The steric hindrances around Ge and Sn in 4 and in a hypothetical complex 7 (see calculated structure, Figure 2) are basically identical. Therefore, the isolation of **8** indicates that the plausible stabilization provided by a π(C-Sn) bond in **7** is so feeble that it is overridden by formation of chloride bridges between the Sn atoms.

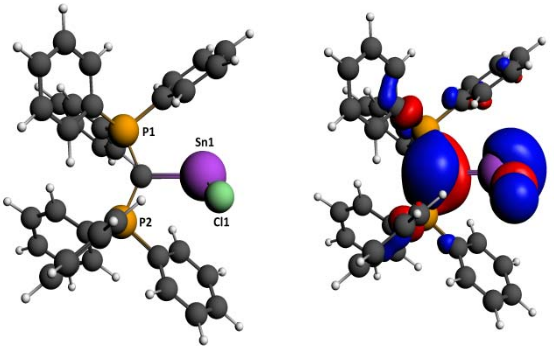


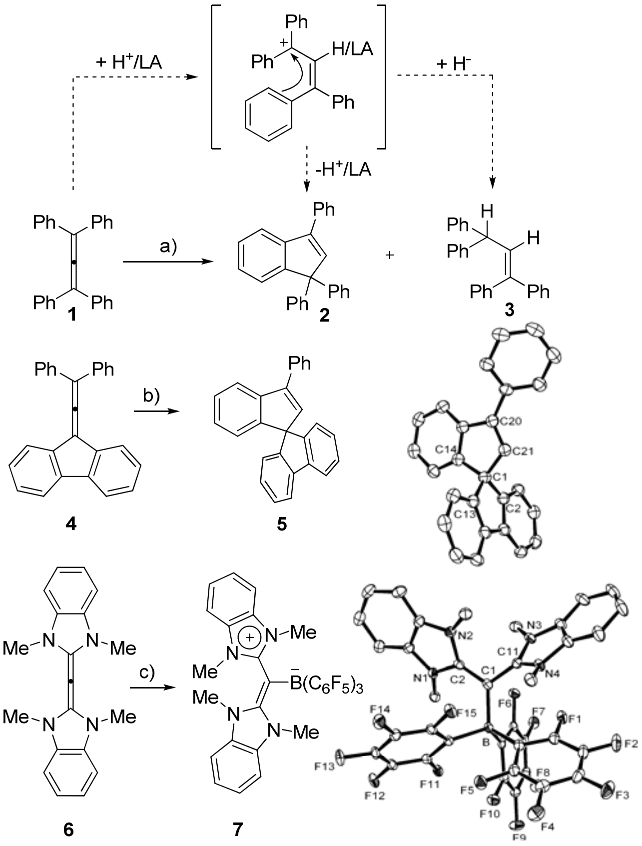
Figure 2. Calculated gas-phase structure of cation **8** (left) and plot of its HOMO (right) at BP86/6-31G* level [LANL2DZ for Sn].

2.4.7 Research Area "Metal-free Hydrogenations" (M. Alcarazo)

Involved: B. Inés, S. Holle, I. Abdellah, J. Nicasio, D. Palomas, S. Steinberg

Objective: The main objective was to expand the scope of frustrated Lewis pair chemistry to the reduction of electron poor allenes and alkenes.

Since its discovery, the chemistry of frustrated Lewis pairs (FLP) has flourished, showing exquisite reactivities towards the activation of small molecules. Thus, it has been reported in recent years that bonds such as C-O, C-H, B-H, S-S, C-C or Si-H can be activated by using this elegant concept. In spite of this, their arguably most remarkable application is still the heterolytic cleavage of H_2, and the subsequent development of metal free catalytic hydrogenations of a number or organic polar substrates such as imines, enamines, nitrogenated heterocycles or silyl enol ethers employing H_2 rather than Hantzsch esters. Surprisingly, despite these achievements, the FLP-promoted catalytic hydrogenation of electron poor unsaturated systems is still underdeveloped. In an attempt to address this limitation, we focused our efforts towards the catalytic reduction of allenes, expecting that the higher reactivity derived from their two adjacent double bonds, could make them appropriate substrates for a preliminary screen of conditions.

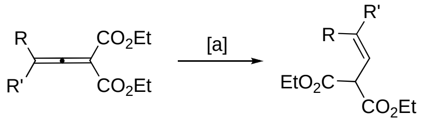


Scheme 1 Reactivity of allenes towards frustrated Lewis pairs. a) $B(C_6F_5)_3/Ph_2NMe$ (15 mol%), toluene, 80 °C, 3 days, **2** (63%), **3** (22%) or $B(C_6F_5)_3/PhNMe_2$ (15 mol%), toluene, 80 °C, 3 days, **2** (0%), **3** (96%); b) $B(C_6F_5)_3$ (15 mol%), toluene, RT, **5** (97%); c) $B(C_6F_5)_3$, toluene, RT, **7** (78%).

Thus, tetraphenylallene **1** was exposed to mixtures of $PhNMe_2$ or Ph_2NMe /$B(C_6F_5)_3$ (15 mol%) and H_2 (60 bar). Interestingly, consumption of **1** was observed and two new products **2** and **3** could be isolated from the reaction mixtures after column chromatography

(Scheme 1). While the formation of alkene **3** proves that reduction of allenes is possible by FLP chemistry, the detection of **2** suggests the existence of a competing reaction pathway. Hence, it can be envisaged that **1** is first protonated at the central carbon followed by hydride transfer to the transient cation produces **3**. Alternatively, intramolecular Friedel-Crafts alkylation affords **2**. In addition, it cannot be excluded that the undesired transformation of **1** into **2** may be directly promoted by $B(C_6F_5)_3$ without the participation of any proton since: (i) allene **4** cleanly cycloisomerizes into **5** solely in the presence of catalytic amounts of $B(C_6F_5)_3$ and (ii) the allene-borane complex **7** is obtained when the more electron rich allene **6** is employed as a substrate. These studies indicate that the hydrogenation takes probably place following a reaction pathway that starts with a Michael-type hydride addition to the allene followed by protonation.

Next, an electron deficient allene **8** unable to interact with the borane through the central carbon atom was chosen as new model substrate. In this case, hydrogenation (80 °C, 60 bar) gave the reduced product in very good yield and no traces of cyclised products were detected. Interestingly, despite the formation of ester-$B(C_6F_5)_3$ complexes is known, this process is probably reversible under the studied conditions and does not seem to affect the desired hydrogenation. Screening of different bases revealed that DABCO is most suitable for this transformation. With this optimized catalytic mixture in hand we were committed to explore the scope of this methodology. To this end, a representative set of diaryl substituted allenes **8**-**12** containing substituents of different electronic nature was synthesized and submitted to the optimized conditions (Table 1).



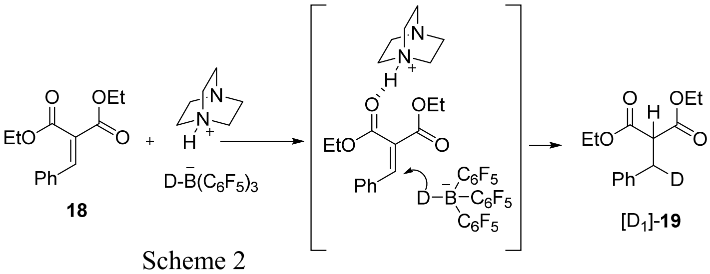
Entry	Allene	Product	Yield (%)[b]
1	**8**; R, R' = Ph	**13**	75
2	**9**; R, R' = *p*-(Me)Ph	**14**	65
3	**10**; R, R' = *p*-(F)Ph	**15**	94
4	**11**; R , R'= *p*-(OMe)Ph	**16**	68
5	**12**; R-R' = 3,5-di(F)-9-fluorene	**17**	43[c]

Table 1. [a] Reaction conditions: Toluene, 80 °C, 3 days; H_2 60 bar and DABCO/$B(C_6F_5)_3$ (15 mol%); [b] isolated yields; [c] the low yields are probably due to dimerization of the allene at the working conditions.

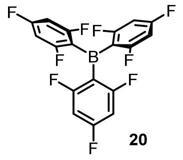
In view of this reactivity, we decided to study whether the additional activation provided by the two double bonds of the allene moiety was necessary to accomplish the desired hydrogenations or if a structurally simpler alkylidene malonate or other electron poor alkenes could also undergo the same transformation.

With this idea in mind, we first carried out a series of experiments to gain some evidence about the operating mechanism. Interestingly, the equimolar reaction of alkylidene malonate **18** with [HDABCO][DB(C_6F_5)$_3$] afforded the hydrogenated product [D_1]-**19** that bears the deuterium label exclusively in the β-position. This clearly indicates that the hydride from the borohydride anion is transferred at the electrophilic position of the substrate (Scheme 1). No reaction was detected when the reduction was attempted with K[HB(C_6F_5)$_3$] followed by quenching with DABCO·HCl, demonstrating that the [HDABCO]$^+$ cation plays an active role during the hydrogenation process. Thus, we rationalized that in this transformation the [HDABCO]$^+$ moiety should activate the substrate, presumably through the formation of a hydrogen bond, followed by nucleophilic attack of the hydride (Scheme 2).

The fact that an activation of the alkylidene malonate is necessary to carry out the desired reduction suggests that for these substrates, hydride transfer from the borohydride moiety is the rate determining step. Hence, the employment of boranes depicting weaker Lewis acidity than B(C_6F_5)$_3$ should facilitate this elemental process. However, weak Lewis acids are not the most adequate ones to promote H_2 cleavage that is necessary for the reduction to take place. Therefore, a compromise situation regarding the Lewis acidity of the borane partner had to be found in order to optimize this transformation in terms of reaction conditions and substrate scope. In our hands, borane **20** exhibits optimum properties (Scheme 3). With this compound we were able to extend this metal-free hydrogenation to alkylidene malonates, nitroalkenes and vinyl sulfones.



Scheme 2



Scheme 3