Ambiphilic Molecules: From Organometallic Curiosity to Metal-Free Catalysts

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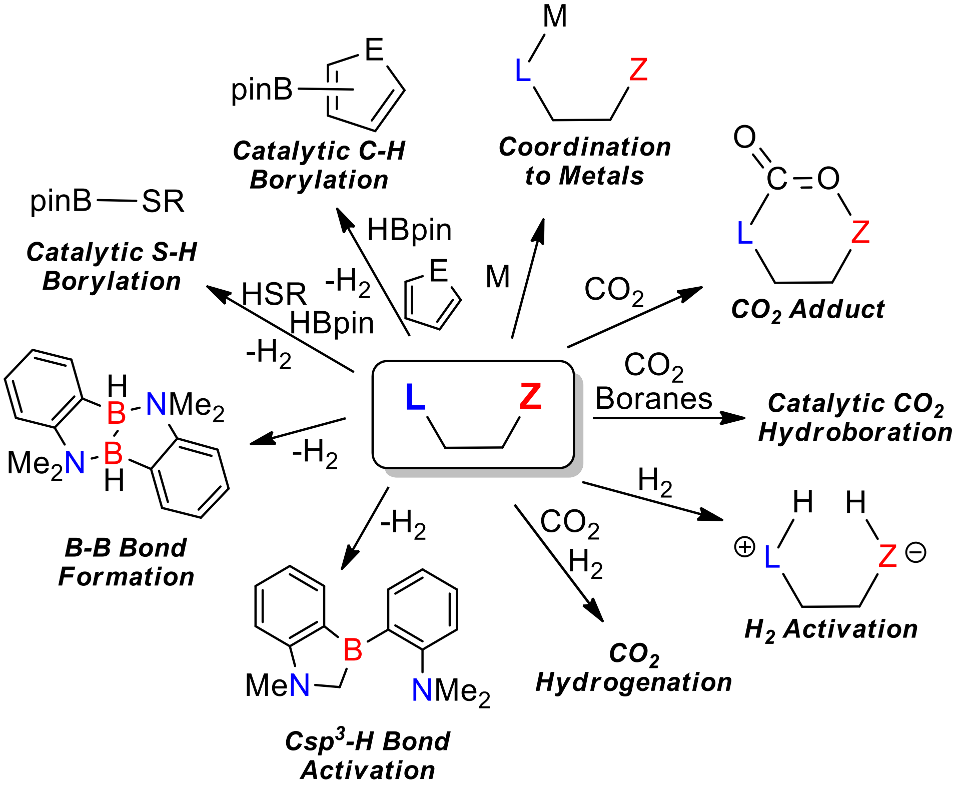
Conspectus

Ambiphilic molecules were first used as functional ligands for transition elements, which could enable intriguing organometallic transformations. In the past decade, these intramolecular Lewis pairs, first considered organometallic curiosities, have become staples in organometallic chemistry and catalysis, acting as Z ligands, activating inert molecules using the concept of frustrated Lewis pair (FLP) chemistry, and acting as metal-free catalysts. In this account, we detail our contribution to this blossoming field of research, focusing on the use of ambiphilic molecules as metal-free catalysts for CO_2 reduction and C-H borylation reactions. A major emphasis is put on the mechanistic investigations we carried out using reactivity studies and theoretical tools, which helped us steer our research from stoichiometric transformations to highly active catalytic processes. We first report the interaction of aluminum-phosphine ambiphilic molecules with carbon dioxide. Although these Lewis pairs can activate CO_2, a study of the deactivation process in presence of CO_2 and hydroboranes led us to discover that simple phosphinoborane molecules could act as active precatalysts for the hydroboration of carbon dioxide into methanol precursors. In these systems, the Lewis basic sites interact with the reducing agents rather than with the electrophilic carbon of CO_2, increasing the nucleophilicity of hydroboranes. Simultaneously, the weak Lewis acids stabilize the oxygen of the gas molecule in the transition state, leading to high reduction rates. Replacing the phosphine by an amine leads to a system enabling CO_2 hydrogenation, albeit only in stoichiometric transformations. Investigation of the protodeborylation deactivation of aminoboranes led us to develop metal-free catalysts for the C-H borylation of heteroarenes. By protecting the Lewis acid sites of these catalysts using fluoride, we were able to synthesize practical, air-

stable precatalysts allowing the convenient synthesis of heteroarylboronic esters on a multi-gram scale. Contrary to general perception of FLP chemistry, we also demonstrated that a significant increase in activity could be obtained by reducing the steric bulk around the active site. These smaller systems exist as stable dimers and are more energetically costly to dissociate into active FLPs, but the approach of the substrate and the C-H activation step are significantly favored compared to the bulkier analogues. An in-depth study of the stability and reactivity of these aminoborane molecules also allowed us to develop a metal-free catalytic S-H bond borylation system, and to report stoichiometric and spontaneous B-B bond formation and Csp^3-H bond activation processes, highlighting the importance of H_2 release as a thermodynamic driving force in these FLP transformations.

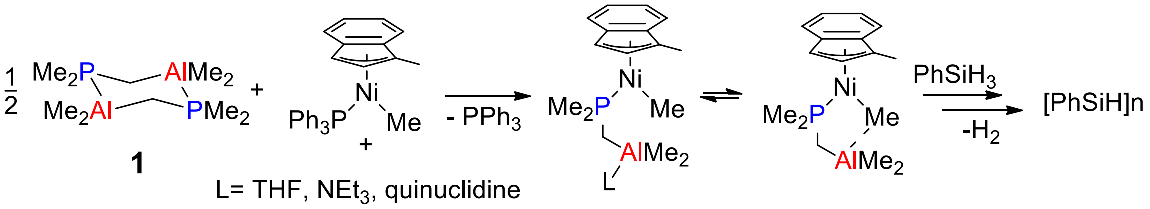


Introduction

Many modern synthetic technologies rely on catalysis, a major component behind the concept of green chemistry.[1] Decades of catalyst design have highlighted the importance of the ligand sphere in transition metal (TM) catalysis. In addition to tuning the electronic and steric properties of the catalysts, ligands can play a synergistic role in the activation and functionalization of bonds, as demonstrated numerous times in homogeneous[2] and enzymatic catalytic systems.[3] While non-innocent ligands containing multiple donor sites have been extensively studied, our initial interest stemmed from the scarcity of examples where Lewis acids are included in the ligand framework. Although few examples of ambiphilic molecules had been reported,[4] notably for their optoelectronic properties,[5] the propensity of the antagonistic Lewis moieties to neutralize each other by formation of Lewis adducts was thought to be detrimental for catalysis. Nevertheless, the last decade has clearly demonstrated the positive impact ambiphilic molecules can have on catalysis. It led to the development of Z ligands, which can stabilize unusual bonding modes and increase the activity of metal complexes.[6,7,8] Also, ambiphilic molecules can participate in bond activation processes and catalysis without transition elements, which resulted in the field of "frustrated Lewis pair (FLP)" chemistry, pioneered notably by Stephan and Erker.[9] This account will describe our contribution to this field, focusing on the exploitation of stable ambiphilic Lewis pairs as metal-free catalysts for CO_2 reduction and C-H bond functionalization.

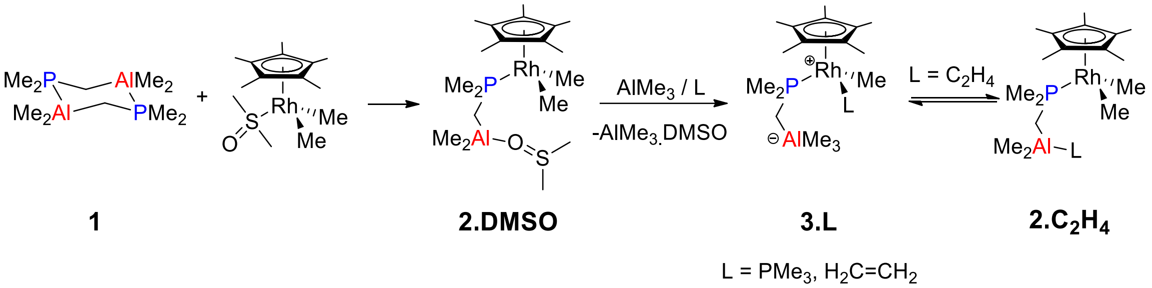
Aluminum-phosphine ambiphilic molecules: from ligand to trapping of reactive intermediates

Following the early work of Labinger,[10] we first investigated the reactivity of aluminum-phosphine molecule $(Me_2AlCH_2PMe_2)_2$ (**1**), first reported by Karsch,[11] as a ligand for transition metals. In 2004, Fontaine and Zargarian reported that **1** interacts with nickel complexes to generate a highly active catalyst for phenylsilane homologation, surpassing by several orders of magnitude the reactivity of the nickel phosphine analogues (Scheme 1).[12]



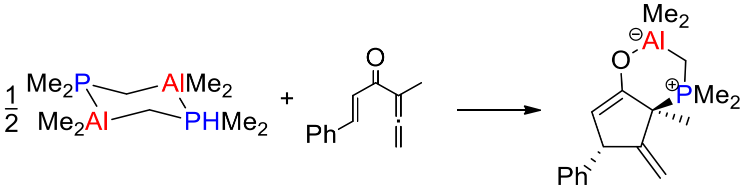
Scheme 1: Nickel catalyzed polymerization of phenylsilane using ambiphilic ligand $(Me_2AlCH_2PMe_2)_2$

We further looked at the reactivity of **1** in the presence of rhodium(III) cyclopentadienyl complexes relevant to C-H bond functionalization processes.[13,14] The coordination of the phosphine moiety of **1** to rhodium(III) precursor $Cp^*Rh(DMSO)(Me)_2$ (DMSO = dimethylsulfoxide) generated $Cp^*Rh(Me)_2(\kappa_P\text{-}Me_2PCH_2AlMe_2\bullet DMSO)$ (Scheme 2, **2.DMSO**).[15] While all attempts to remove DMSO from **2.DMSO** led to the generation of zwitterionic $Cp^*Rh(Me)(\kappa_{P,P}\text{-}Me_2PCH_2AlMe_2CH_2PMe_2)$, the addition of a Lewis base L (L = phosphine, ethylene) in the presence of $(AlMe_3)_2$ gave $Cp^*Rh^+(Me)(L)(\kappa_P\text{-}Me_2PCH_2AlMe_3^-)$ (**3.L**) and $AlMe_3.DMSO$.[15,16] Although interesting stoichiometric transformations occurred with species **3.L**, no catalytic processes could be observed since molecule **1** proved to be extremely sensitive and underwent degradation readily. Nevertheless, the ability of **1** to interact with transition elements even if it existed as a stable Lewis adduct dimer in solution led us to investigate its use in metal-free transformations.



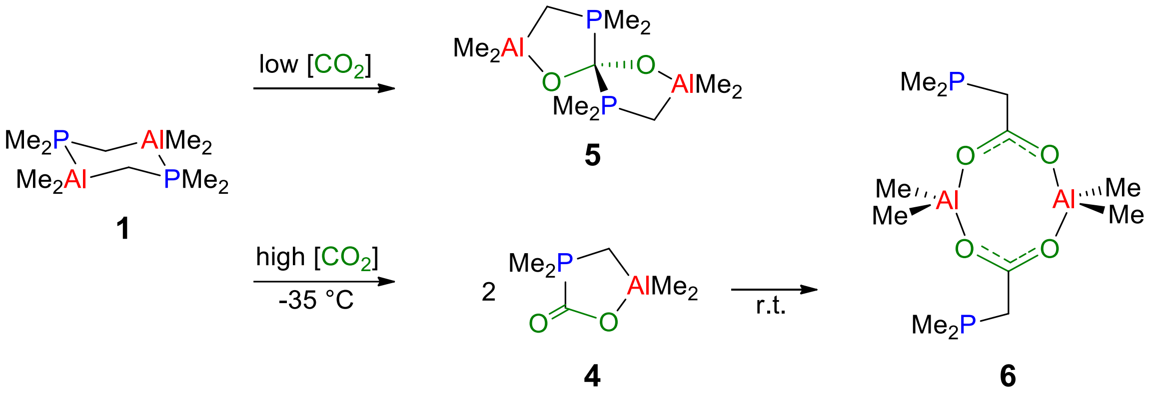
Scheme 2: Coordination chemistry of $Cp^*Rh(Me)_2(\kappa_P\text{-}Me_2PCH_2AlMe_2{\bullet}DMSO)$

Accordingly, it was possible to use **1** to trap interrupted Nazarov cyclization products when reacted with allenyl vinyl ketones (Scheme 3).[17]



Scheme 3: $(Me_2AlCH_2PMe_2)_2$ interrupted Nazarov cyclization

However, it was the reactivity of **1** with CO_2 that allowed establishment of a clear comparison with FLP chemistry.[18] As observed with bulkier FLP systems,[19] when one atmosphere of CO_2 was added to **1** at -35 °C, the phosphine and aluminum centers of the ambiphilic molecule interacted with the electrophilic carbon and the nucleophilic oxygen of CO_2, respectively, generating species **4** (Scheme 4).[18] Because of the smaller steric constraints in **1** compared to typical FLP systems, it was also possible to isolate spirocyclic compound **5**, which arises from the activation of both carbonyl bonds of carbon dioxide. Remarkably, the same products were observed spectroscopically when the reaction was carried out in the solid state under a CO_2 atmosphere, suggesting that the reactivity of an FLP is the result of an intrinsic ability of a Lewis pair rather than a phenomenon caused by the absence of Lewis pair formation. However, the irreversible insertion of CO_2 into an Al-C bond to generate product **6** proved to be a thermodynamic sinkhole.

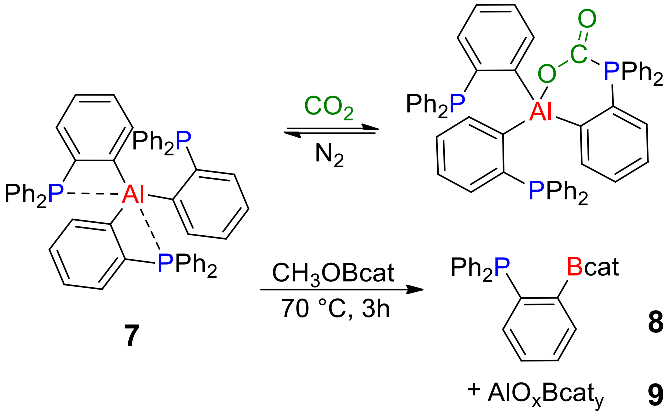


Scheme 4: Reactivity of $(Me_2AlCH_2PMe_2)_2$ with CO_2

Developing metal-free CO_2 reduction catalysts

Whereas several transition metal catalysts were reported to promote the catalytic hydrogenation, hydrosilylation, and hydroboration of carbon dioxide,[20] efficient metal-free catalytic processes were scarce prior to our contributions to the field.[19] It was known for several decades that nucleophilic hydrides could reduce CO_2[21] and N-heterocyclic carbenes were reported to catalyze the hydrosilylation of CO_2.[22] While some stoichiometric CO_2 reduction processes using FLP adducts were known,[23] the only catalytic process reported used TMP/$B(C_6F_5)_3$ to hydrosilylate CO_2 to methane.[24] We hypothesized based on TM chemistry that a metal-free catalyst should play two roles. First, it should increase the nucleophilicity of the reducing agent. Second, the catalyst should stabilize the bent form of CO_2 in the transition state (TS) without quenching the electrophilic carbon atom or forming too strong bonds with the oxygen atom. The multidentate species $Al(C_6H_4PPh_2)_3$ (**7**; Scheme 5) was a target of choice since in addition to the Al/P Lewis pair that could interact with CO_2, the additional phosphines could activate the incoming reducing agents. In addition, Bourissou demonstrated that the phenylene linker was robust,[25] which should prevent the insertion of CO_2 into the Al-C bond as observed for **1**.[18]

When monitoring a benzene-*d_6* solution of **7** under 1 atmosphere of CO_2 by $^{31}P\{^1H\}$ NMR spectroscopy, the singlet of **7** at -1.5 ppm transformed into a doublet and a triplet at -5.1 and -6.2 ppm, respectively.[26] The presence of a $^1J_{C\text{-}P}$ of 102 Hz when using $^{13}CO_2$ confirmed the coordination of carbon dioxide (Scheme 5). Dissociation of CO_2 occurs readily when the atmosphere is purged out, demonstrating the labile and weak **7**-CO_2 interaction. The rapid hydroboration of CO_2 was observed when 1000 equivalents of catecholborane (HBcat) was added to a solution of **7** under 1 atmosphere of carbon dioxide, generating $(catB)_2O$ and CH_3OBcat, which can be readily hydrolyzed to generate methanol. An initial turnover frequency (TOF) of 314 h^{-1} at 70 °C was achieved and complete conversion was possible after 72 h.[26] However, the presence of a significant induction period suggested that **7** is not the actual catalyst, which was confirmed by the isolation of $1\text{-}PPh_2\text{-}2\text{-}Bcat\text{-}C_6H_4$ (**8**) and a solid precipitate. The isolation and structural characterization of $Al(\kappa^2O,O\text{-}(MeO)_2Bcat)_3$ (**9**) from the reaction between **7** and CH_3OBcat suggests that the precipitate is composed of boron and aluminum oxide clusters.[26]



Scheme 5: Reactivity of $Al(C_6H_4PPh_2)_3$ with CO_2 and CH_3OBcat.

While **9** was inactive towards CO_2 hydroboration, 1-PPh_2-2-Bcat-C_6H_4 (**8**) proved to be exceptionally potent for the hydroboration of CO_2.[27] When 100 equivalents of HBcat were added to a solution of **8** under one atmosphere of CO_2 at 70 °C, over 86% conversion to CH_3OBcat was observed after 36 min (TOF of 143 h^{-1}). One novel feature of this system is the possibility of using BH_3 adducts as reducing agents. In presence of 1000 equivalents of $BH_3{\bullet}SMe_2$ at 70 °C under 2 atmospheres of CO_2, turn-over numbers (TON) over 2,950 and TOF of 853 h^{-1} were observed after 4 and 2 h, respectively. At the time of publication, this was the fastest system ever reported for CO_2 hydroboration. Interestingly, once reaction is over by depletion of either CO_2 or $BH_3{\bullet}SMe_2$, catalysis can be reinitiated without losing significant activity by adding more reagent, suggesting a robust and living system. The reaction still operates at 20 °C, with TON and TOF values of 34 and 17 h^{-1} after 2 h, but NMR monitoring showed that an induction period was still present.

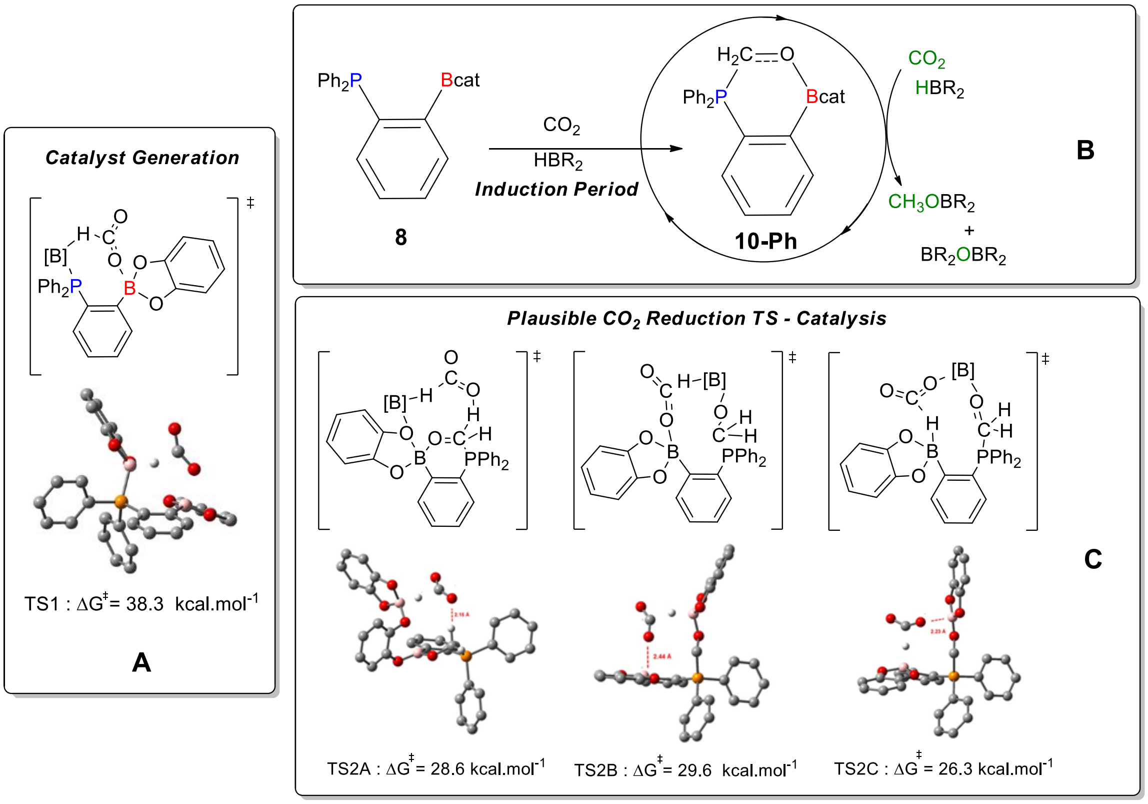
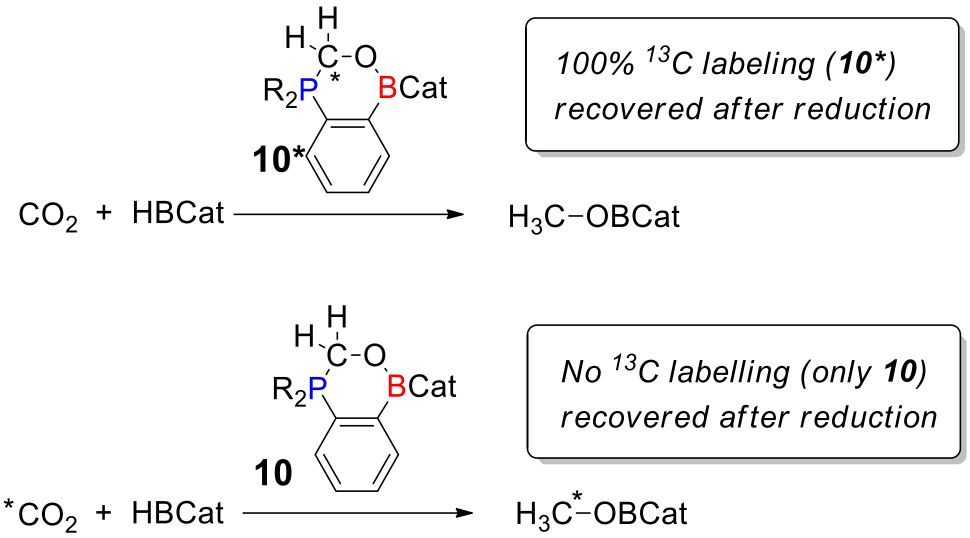


Figure 1: Proposed catalyst and transition states in the phosphinoborane catalyzed CO_2 hydroboration. Mechanism (B) and transition state for the CO_2 reduction process by complex **8** (A) and **10** (C).

The mechanistic investigation, carried out with the help of Bourissou and Maron, allowed us to propose the mechanism illustrated in Figure 1.[28,29] As evidenced by the absence of observable reactivity between **8** and CO_2, the typical FLP adduct of CO_2 is endothermic by about 7 kcal.mol^{-1} and does not play a significant role in the catalytic process. Using density functional theory (DFT), the TS for the direct reduction of the FLP-CO_2 adduct was located at 55.7 kcal.mol^{-1} and is thus inaccessible.[28] The coordination of a Lewis base to the electrophilic carbon of CO_2, which is a typical feature of FLP coordination to CO_2, makes the electrophilic attack of the reducing agent on the carbon challenging, a requirement for catalysis. A more plausible TS for this reduction process, lower by 17 kcal.mol^{-1} and illustrated in Figure 1A, involves the Lewis base of **8** interacting with HBpin, while the weak Lewis acid interacts with one oxygen atom of CO_2.[28] Although the overall energy is too high to justify the catalytic rate observed at 70 °C, we propose that the generation of the active catalyst is promoted by this transformation. Once the reduction of CO_2 with hydroborane HBR_2 has taken place to generate the borylformate $HC(O)OBR_2$, no catalysis is required to generate formaldehyde and CH_3OBR_2, the intermediate and final product of this catalytic reduction, respectively. However, the catalyst free route is significantly slower than the catalyzed system, suggesting that **8** is taking part in some, and possibly in all, reduction steps.[28]

Testing a variety of ambiphilic 1-PR_2-2-BR'_2-C_6H_4 demonstrated that the phosphine had only a minor impact on the activity of the system.[29] We also observed that mixing 1-PR_2-2-Bpin-C_6H_4 (pin = pinacol) derivatives with HBcat led to the redistribution of the alkoxide moieties to generate species **8**. Yet, with all ambiphilic systems the formaldehyde adducts are constantly present once catalysis starts. The independent synthesis and characterization of formaldehyde adducts 1-PPh_2-2-Bcat-C_6H_4•H_2CO **10-Ph** and 1-P*i*Pr_2-2-Bcat-C_6H_4•H_2CO **10-iPr** was carried out to examine their catalytic activity in the BH_3 reduction of CO_2 (Figure 1B).[29] With **10-iPr**, we observed the evolution of $B(OMe)_3$ with a TOF of 228 h^{-1} at ambient temperature without any induction period, in contrast to the system catalyzed by **8**, suggesting that the formaldehyde adducts are catalytically active. This hypothesis was confirmed using isotopic labelling experiments where no ^{13}C was incorporated in the formaldehyde adduct under an atmosphere of $^{13}CO_2$, the same way no

^{13}C leaching was observed under $^{12}CO_2$ when using ^{13}C-labelled catalysts 1-PPh_2-2-Bcat-C_6H_4•$H_2{}^{13}CO$ and 1-P*i*Pr_2-2-Bcat-C_6H_4•$H_2{}^{13}CO$ (Figure 2).[29]



*100% ^{13}C labeling (**10***) recovered after reduction*

*No ^{13}C labelling (only **10**) recovered after reduction*

Figure 2: Isotopic labeling catalytic experiment using **10**

To explain the reduction process using **10**, three different TS with ΔG‡ between 26.3 and 29.6 kcal.mol^{-1} were modeled by DFT. As can be observed in Figure 1C, one B-O bond in the zwitterionic structure of **10** can dissociate and interact with the incoming reducing agent, increasing the nucleophilicity of the hydride. Simultaneously, a weak interaction occurs either with the empty orbital on boron or via hydrogen bonding with the methylene moiety of bound formaldehyde. The electron-withdrawing effect of the phosphonium moiety gives an increased Lewis acidic character to this hydrogen atom. One can find similarity with iridium pincer catalysts for CO_2 hydrogenation reported by Hazari and co-workers,[30] suggesting that for outer sphere transformations, main group catalysts can replace transition metals.

Although the hydrogenation reaction is the main driving force behind FLP chemistry, the metal-free hydrogenation of carbon dioxide is particularly challenging. The reduction process involves the generation of water and formic acid, which are detrimental to the stability of several group XIII Lewis acids (Figure 3). To our knowledge, $B(C_6F_5)_3$ and tetramethylpiperidine is the only FLP able to generate methanol from H_2 and CO_2 in substoichiometric amounts.[23b]

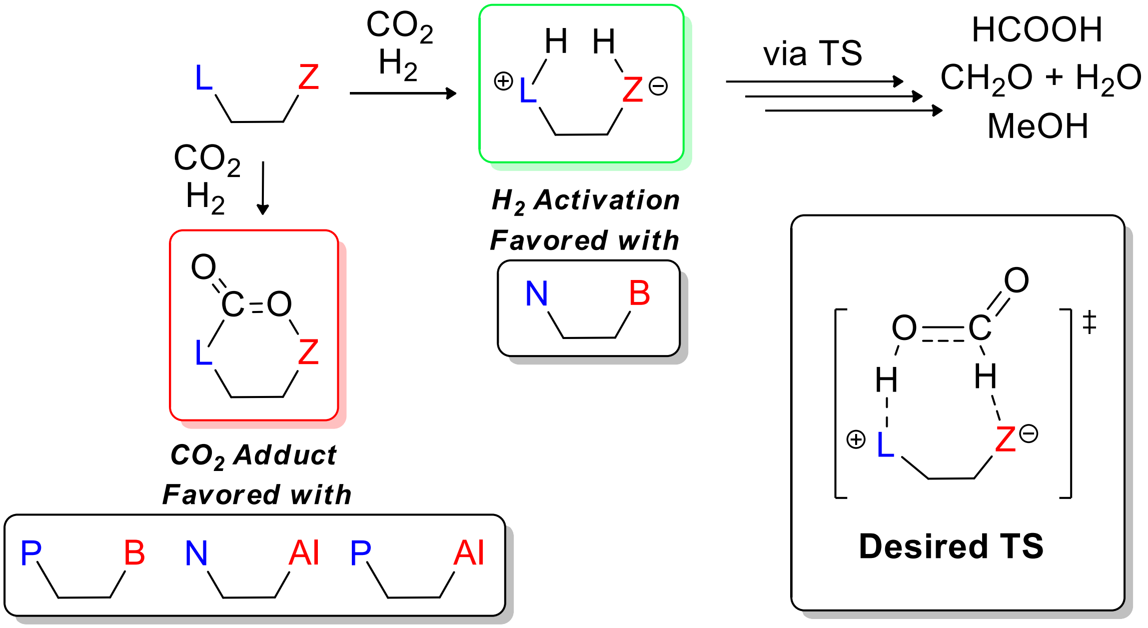


Figure 3: Plausible pathway for the catalytic hydrogenation of CO_2

Figure 3 illustrates a possible way to catalyze the hydrogenation of CO_2. An effective catalyst should split hydrogen preferably over binding CO_2, and transfer simultaneously both the proton and the hydride to CO_2 to generate formic acid. A quick DFT investigation indicated that a N/B FLP should favor such a process over the P/B, N/Al and P/Al Lewis pairs, which preferably bind carbon dioxide over activating H_2.[31]

Following a collaborative effort with Douglas Stephan, we demonstrated such a concept using ambiphilic molecules 1-NMe_2-2-$B(Ar)_2$-C_6H_4 (Ar = 2,4,6-$Me_3C_6H_2$ (**11-Mes**); 2,4,6-$Me_3C_6H_2$ (**11-Mes'**)).[32] Although there was no direct observation of H_2-activation products, we observed the release of Ar-H species along with the formation of the formyl, acetal, and methoxide 1-NMe$_2$-2-B(R)$_2$-C_6H_4 (R = HCOO; OCH_2O and CH_3O) species. Computational details support the fact that H_2 cleavage is accessible using **11** to generate zwitterionic species 1-(H)N$^+$Me$_2$-2-(H)B$^-$(Ar)$_2$-C_6H_4, with **11-Mes'** being more active because of reduced steric congestion. However, the intramolecular protodeborylation reaction occurs preferentially over the hydride transfer to CO_2, generating in turn 1-NMe$_2$-2-B(Ar)(H)-C_6H_4 and 1-NMe$_2$-2-B(H)$_2$-C_6H_4. H_2 splitting with 1-NMe$_2$-2-B(Ar)(H)-C_6H_4 was computed to be easy, which can in turn react with CO_2 with a barrier of 24.4 kcal.mol^{-1} to generate the observed CO_2 reduced species. One fascinating feature is the concerted transfer of both the proton and the hydride on CO_2 by a Noyori-type TS (Figure 4), as previously proposed by Musgrave and co-workers.[33]

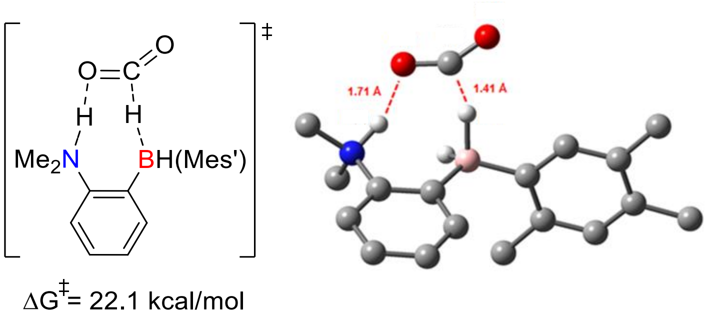
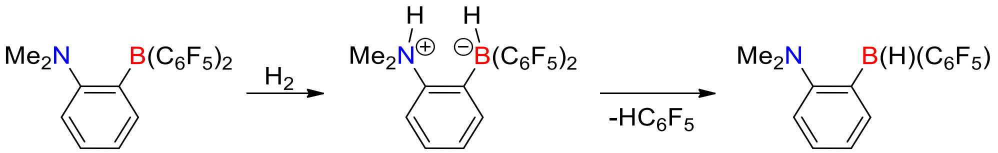
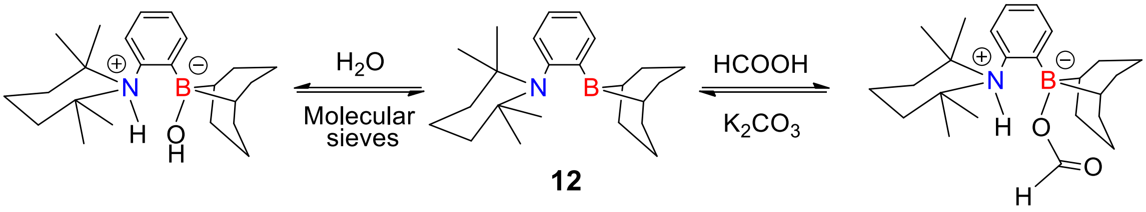


Figure 4: Proposed transition state for the aminoborane CO_2 hydrogenation



Scheme 6: The protodeborylation reaction

The protodeborylation reaction (Scheme 6) is detrimental when hydrogenating carbon dioxide using ambiphilic amino-borane catalysts.[34] However, more robust ambiphilic frameworks could prevent such side-reaction and promote the catalytic hydrogenation reaction. We were able to synthesize ambiphilic molecule 1-TMP-2-BBN-C_6H_4 (TMP = 2,2,6,6-tetramethylpiperidinyl; BBN = borabicyclo[3.3.1]nonane, **12**) containing endocyclic amine and borane moieties.[35] Interestingly, this molecule is stable in presence of a moderate excess of water and formic acid (Scheme 7). Even if **12** binds these reduction side-products, the reversibility of these processes suggests that catalysis might be accessible. Unfortunately, no evidence of hydrogen activation was observed and further optimization is still required.



Scheme 7: Reactivity of 1-TMP-2-BBN-C_6H_4 toward water and formic acid

Catalytic Activation and Functionalization of C-H bonds

Repo, Papai and co-workers reported the *cis*-hydrogenation of alkynes using an ambiphilic FLP catalyst.[34] According to the proposed mechanism (Figure 5A), species 1-NR_2-2-B(H)(Ar)-C_6H_4 can insert alkynes to generate intermediate 1-NR_2-2-B(R')(Ar)-C_6H_4, which in turn can activate dihydrogen to generate the zwitterionic species 1-$(H)^+NR_2$-2-$(H)^-$B(R')(Ar)-C_6H_4. The release of the corresponding alkene is possible by protodeborylation, regenerating the boron hydride catalyst. The transition state proposed for the R'-H formation step is similar to the one proposed by Gorelsky and Fagnou to explain the activity of pivalate palladium complexes in the direct arylation (Figure 5B).[36]

Therefore, we hypothesized that upon optimization of the amine and of the borane, the activation of C-H bonds, the reverse of the protodeborylation reaction, might be possible.

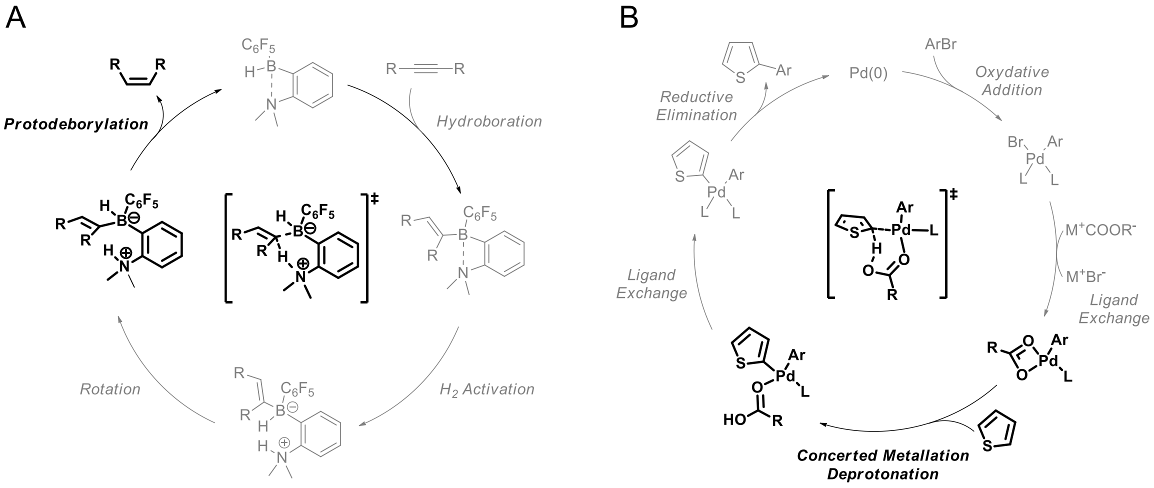
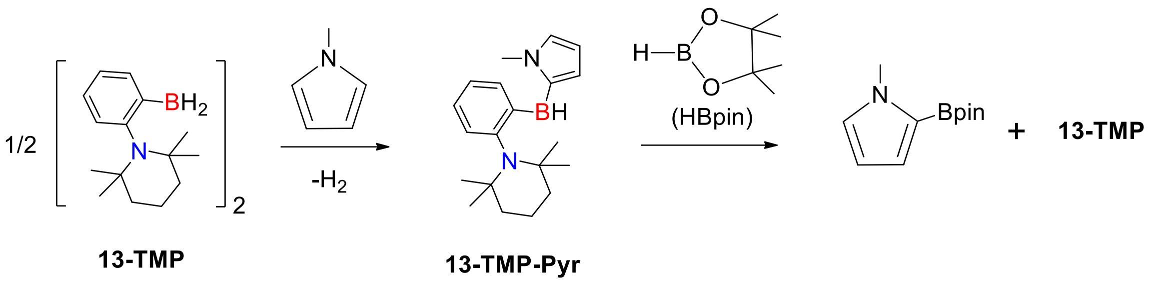


Figure 5: Comparison between FLP promoted protodeborylation (A)[34] and concerted metalation deprotonation (B).[36]

According to DFT investigation, species (1-TMP-2-BH_2-C_6H_4)$_2$ (**13-TMP**)[37] was a promising candidate. As expected, **13-TMP** can activate a C-H bond of 1-methylpyrolle when heated at 80 °C for 5 hours to form 1-TMP-2-B(H)(C_5H_6N)-C_6H_4 (**13-TMP-Pyr**; Scheme 8).[38] Interestingly, the addition of HBpin to a solution of **13-TMP-Pyr** generates rapidly 1-Me-2-Bpin-pyrolle, regenerating **13-TMP** in the process. The addition of a catalytic amount (5 mol%) of **13-TMP** to a mixture of HBpin and N-, S- or O-containing heterocycles resulted in the complete borylation of the aromatic molecules, which were isolated in excellent yields. A practical aspect of this metal-free catalytic system compared to transition metal-catalyzed systems[39] is the ease of purification since the catalyst is easily scrubbed using a small silica plug. Unfortunately, because of the reactive –BH_2 moiety on the catalyst, this system is intolerant to protic functional groups and unsaturated substrates that can undergo hydroboration.[38]



Scheme 8: C-H activation of a pyrrole by ambiphilic aminoborane

The mechanism of the transformation is illustrated in Figure 6. Once the active FLP is generated, a C-H activation step generates a zwitterionic intermediate **13-TMP-Zwi**. According to DFT modelling of the TS, the electrophilic boron interacts with the most nucleophilic carbon atom of the heterocycle, while the amine deprotonates the substrate. The kinetic isotope effect (KIE) of 1.8 observed for the stoichiometric C-H activation step using 1-Me-pyrolle-d_4 is similar to the one observed for the catalytic process, suggesting that the latter transformation is rate determining.[38] This KIE value is similar to the one reported for the direct arylation reaction.[36] Once species **13-TMP-Zwi** is generated, liberation of H_2 occurs readily to generate **13-TMP-Ar**. The final step involves σ-bond metathesis between the arylated ambiphilic intermediate and HBpin, yielding the borylated heterocycle and **13-TMP**.[38] The catalytic transformation only operates using heteroarenes, although Repo reported ambiphilic systems promoting the stoichiometric C-H activation of arenes.[40]

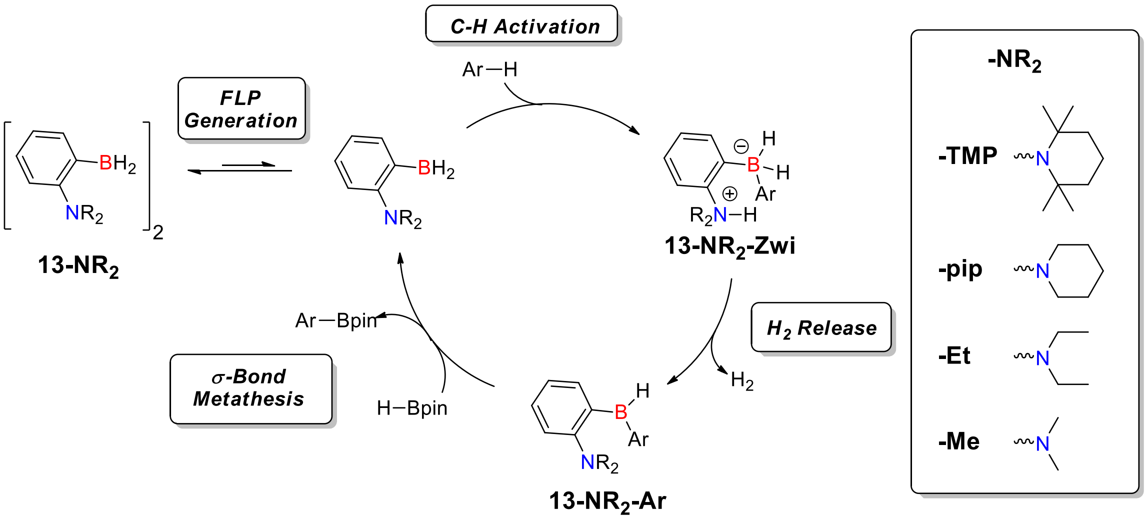


Figure 6: Mechanism of the FLP-catalyzed borylation of heteroarenes.

Accessing FLP systems from dimeric ambiphilic molecules

Crystallographic studies confirm the dimeric nature of ambiphilic molecule **13-TMP**, which exhibits two 3-center-2-electron interactions.[37] When replacing the bulky TMP moiety by smaller amines, such as in 1-NR$_2$-2-BH$_2$-C$_6$H$_4$ (NR$_2$ = NMe$_2$ (**13-Me**); NEt$_3$ (**13-Et**); piperidinyl (**13-pip**)), new dimeric species are observed where one B-H bond is activated by the B/N FLP pair of another molecule, forming a six-membered ring (*H-bridged dimer*; Figure 7).[41]

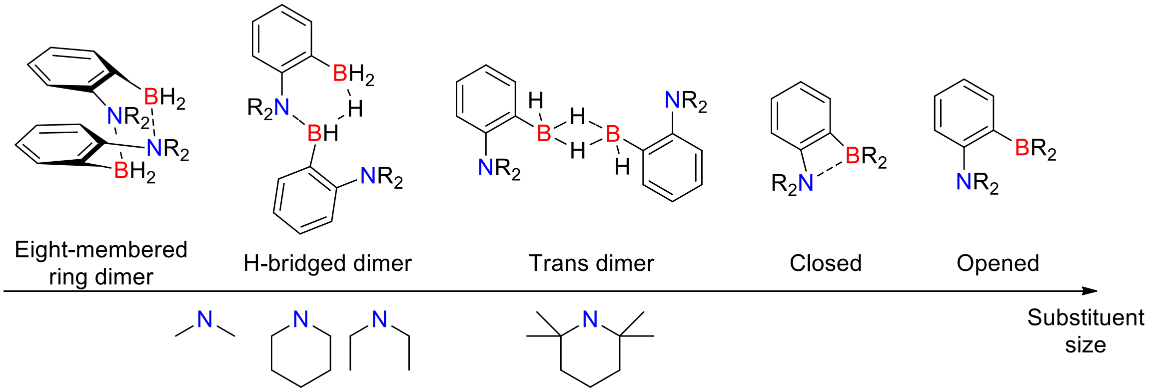
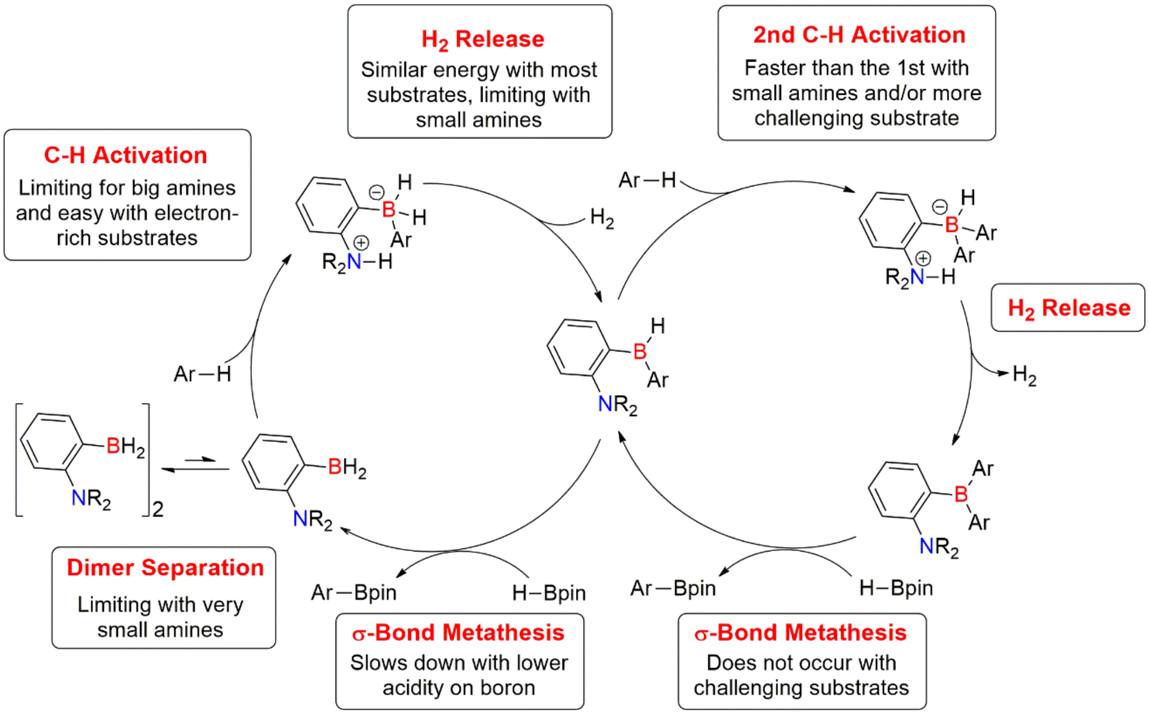


Figure 7: Reported dimeric structures of aminoboranes.

Dissociation of these dimers is required to generate the active FLP intermediates that do the C-H activation step. A computational study suggests that the dissociation of species **13-NR$_2$** is endergonic, with the bulkiest analogue, **13-TMP**, accessing the FLP state preferably ($\Delta G^{\ddagger}$ = 7.1 kcal mol^{-1}) compared to the ambiphilic molecules with smaller amines ($\Delta G^{\ddagger}$ = 9.6 – 10.7 kcal mol^{-1}).[41] It is noteworthy that the monomeric form with an intramolecular B-N interaction (*closed*) is, in all cases, more favorable than the FLP (*opened*). In addition to being thermodynamically more stable than with smaller analogues, the *opened* form of **13-TMP** is also more accessible kinetically. Whereas dissociation of **13-TMP** was speculated to require 11-14 kcal mol^{-1},[37] spin saturation transfer NMR experiments gives a $\Delta G^{\ddagger}$ of 20.5 ± 3.1 kcal mol^{-1} for the dissociation of **13-pip**.[40] Notwithstanding these observations, the borylation of 1-Me-pyrrole is actually 15 times faster when catalyzed by **13-pip** rather than by **13-TMP**.[41]

As mentioned above, the C-H activation step with 1-Me-pyrrole is rate determining with catalyst **13-TMP** according to KIE experiments.[38] As expected, we observed a dependence on pyrrole concentration when monitoring by ^{11}B NMR the disappearance of species **13-TMP** over time during the C-H activation process.[41] Interestingly, the C-H activation step was shown to be independent of pyrrole concentration with **13-pip**, suggesting that this step is no longer rate determining. The DFT model demonstrated that the barrier for the C-H activation for **13-pip** is lower by about 6 kcal mol^{-1} compared to **13-TMP** and the dimer dissociation ($\Delta G^{\ddagger}$ = 20.7 kcal mol^{-1}) and H_2 loss ($\Delta G^{\ddagger}$ = 23.5 kcal mol^{-1}) are now rate limiting. The energy required to extrude H_2 from **13-NR$_2$-Zwi** (Figure 6) is between 12 and 17 kcal mol^{-1}, with little influence from the nature of the amine. We can assume that smaller steric hindrance disfavors dissociation to generate the active FLP, but makes the access of incoming substrates to the FLP active center easier. Therefore, the right balance in steric hindrance is required, as demonstrated by the poor catalytic activity of **13-Me**, which does not generate the FLP readily.[41] The conclusions of our mechanistic study of the C-H borylation with aminoborane catalysts are summarized in Figure 8.



H_2 Release
Similar energy with most substrates, limiting with small amines

2nd C-H Activation
Faster than the 1st with small amines and/or more challenging substrate

C-H Activation
Limiting for big amines and easy with electron-rich substrates

H_2 Release

Dimer Separation
Limiting with very small amines

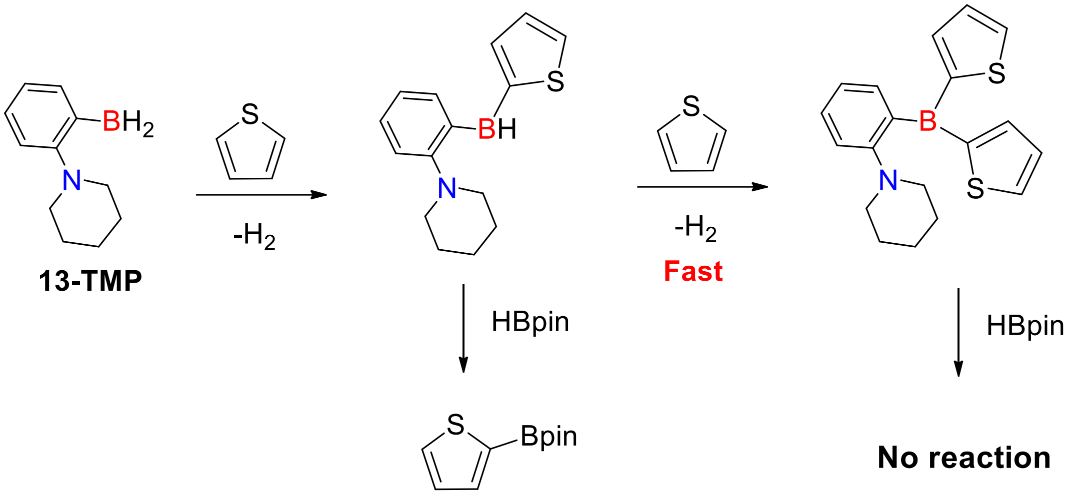
σ-Bond Metathesis
Slows down with lower acidity on boron

σ-Bond Metathesis
Does not occur with challenging substrates

Figure 8: Mechanistic conclusions concerning the FLP catalyzed borylation of heteroarenes.

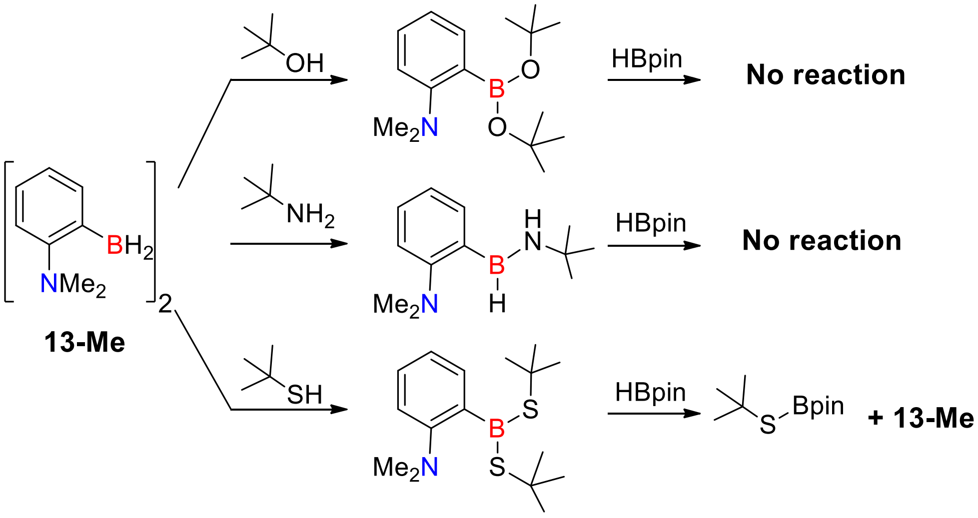
σ-Bond metathesis with ambiphilic molecules

Since both **13-NR$_2$-Ar** and HBpin have empty p_z orbitals on boron, σ-bond metathesis can take place and generate the thermodynamically favored borylated heterocycles. As initially demonstrated by Repo by the isolation of species 1-TMP-2-B(thiophenyl)$_2$-C$_6$H$_4$,[40] the absence of catalytic activity for the borylation of pristine thiophene with **13-NR$_2$** does not stem from the absence of C-H activation. We observed with **13-pip** that the first C-H bond activation of thiophene occurs readily and some 2-Bpin-thiophene is generated under catalytic conditions, but the intermediate species 1-pip-2-B(H)(thiophenyl)-C_6H_4 undergoes another C-H activation more readily than σ-bond metathesis (Scheme 9). The resulting complex, 1-pip-2-B(thiophenyl)$_2$-C_6H_4, does not undergo metathesis.



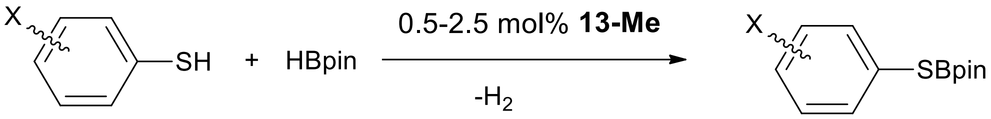
Scheme 9: Reaction of **13-pip** with thiophene.

We also demonstrated that species **13-Me** reacts with *tert*-butanol, *tert*-butylamine and *tert*-butylthiol to generate the corresponding B-O, B-N, and B-S containing species (Scheme 10).[42] Interestingly, whereas two equivalents of the alcohol and thiol were reacted with the starting material, only one equivalent of the amine did. We demonstrated by DFT that the energy required to activate a second N-H bond was too high as the activation product has a strong π overlap between the boron and the nitrogen, which significantly reduces the Lewis acidity on boron. Such a result not only explains the inhibition of C-H borylation reactions with alcohols and secondary amines, but also demonstrates how filling the p_z orbital on boron prevents metathesis. Indeed, both B-N and B-O containing species do not undergo metathesis with HBpin, in contrast to the B-S containing species.[42]



Scheme 10: Reactivity of **13-Me** with alcohols, amines and thiols.

13-Me is a highly active catalyst for the metal-free borylation of thiols. Thioboranes are useful reagents for the catalyst-free Michael addition to α,β-unsaturated carbonyls, which can generate a large array of sulfur containing bioactive molecules.[43] The borylation of thiophenol was possible using loadings as low than 0.5 mol% (complete conversion after 2 h at 80 °C) and at ambient temperature (complete conversion after 24 h with 2.5 mol% of **13-Me**). Using a catalyst loading of 2.5 mol% at 60 °C, most 2-, 3-, or 4-substituted thiophenols (F, Cl, Br, Me, OMe) tested gave complete conversion under 4 hours (Scheme 11). As demonstrated by Bertrand, the catalyst-free transformation is possible but is significantly slower (31% conversion after 48 h at 80 °C).[44] The catalytic system we developed tolerates aliphatic and benzyl thiols even if longer reaction times and/or catalyst loadings are often required. The borylation of selenophenol is also possible, albeit being less reactive than its sulfur counterpart.[42] Interestingly, a DFT investigation of the mechanism allowed us to observe that both the mono- and bis-thiolated ambiphilic molecules are active towards σ-bond metathesis, suggesting that the thiolate group does not affect significantly the acidity of the boron center (Figure 8).[45]

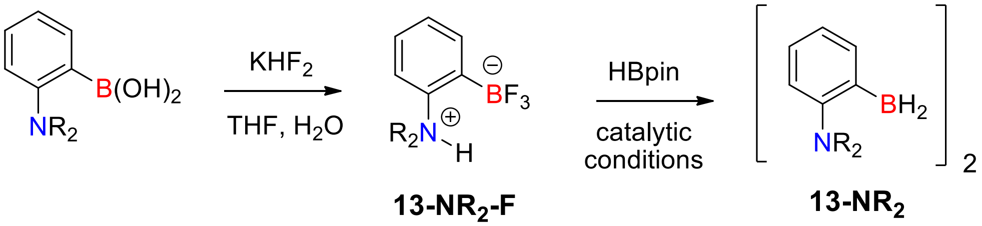


Scheme 11: Catalytic borylation of thiols

Towards practical and bench-stable metal-free catalysts

As for most hydroboranes, catalysts **13-NR$_2$** are sensitive towards moisture and require handling under air- and moisture-free conditions, thus limiting their convenient use. On the other hand, fluoroborate salts are resistant to air and moisture,[46] while remaining active reagents in Suzuki-Miyaura coupling reactions.[47] Inspired by these precedents, we investigated the reactivity of fluoride ambiphilic molecules as bench-stable precatalysts for C-H borylation reactions.

The synthesis of the fluoride-protected species **13-NR$_2$-F** is conveniently carried out from the boronic acid precursors using KHF_2 as a fluorinating agent (Scheme 12).[41,48] We observed by NMR spectroscopy that the addition of HBpin to species **13-NR$_2$-F** generates hydridoborane catalysts **13-NR$_2$.** Under catalytic conditions, both **13-NR$_2$** and **13-NR$_2$-F** give similar product distribution and yield, even if the latter product is handled under ambient conditions. Careful monitoring of the reaction evolution showed an induction period, which can be associated with the deprotection step. Even if the borylation reaction can be carried out in a large range of solvents, catalysis was observed to be significantly more rapid under solvent-free conditions. For example, whereas 60% conversion was observed for the borylation of 1-Me-pyrrole after 4 hours using 5 mol% of **13-TMP-F** in chloroform, over 97% conversion was observed after 2 hours under neat conditions.



Scheme 12: Synthesis of fluoride-protected ambiphilic catalysts

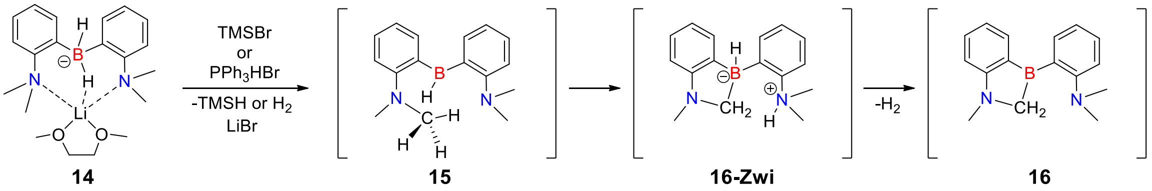
Release of dihydrogen as a driving force in metal-free processes

Because of its importance in the metal-free hydrogenation reaction, many studies have focused on the mechanism of H_2 activation by FLPs.[49] The following examples demonstrate the importance of H_2 release, the micro-reverse reaction of H_2 activation, as a driving force for bond activation processes.

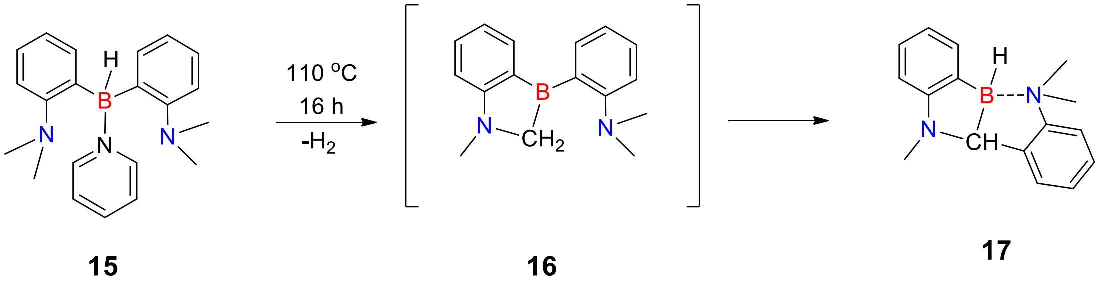
Although several C_{sp}-H and C_{sp2}-H bond functionalization systems have been reported, the functionalization of C_{sp3}-H bonds is more challenging.[50] The unavailability of the frontier orbitals in saturated hydrocarbons prevents efficient interaction with the active site of the catalysts. Nevertheless, it was proposed by computational chemists that endocyclic aminoboranes could activate methane, although the molecules modeled are synthetically inaccessible.[51] Following these inspiring results, DFT simulations on molecules 1-NR_2-2-BH(Ar)-C_6H_4, where a functional group on Ar was positioned for intramolecular C_{sp3}-H bond activation, were done to probe whether a B/N Lewis pair could promote such bond cleavage.[52] Even if the activation of the methyl group C-H bond in $–CH_2CH_3$ and $–OCH_3$

is too demanding to occur under thermal conditions, the functional group –$N(CH_3)_2$ was promising with a barrier of 25.5 kcal.mol^{-1}.

The borohydride molecule **15** was synthesized by removing LiH from the hydridoborate salt **14** using TMSBr or PPh_3HBr (Scheme 13). As expected, **15** is quite reactive and readily generates molecule **16** by losing H_2, confirming that the desired C_{sp3}-H bond activation took place. The zwitterionic intermediate **16-Zwi** is unstable, being 5.6 kcal.mol^{-1} higher in energy than the borohydride precursor, and the release of hydrogen is the driving force for the C-H activation process. Although the borohydride precursor **15** could not be observed, it was possible to stabilize the ambiphilic molecule by adding either pyridine or triphenylphosphine, generating the Lewis adducts. When the reaction was carried out from the pyridine adduct, we observed that species **17** was formed when the solution was heated at 110 °C for 16 h. DFT calculations support the idea that species **16** can undergo an hydride abstraction of the B-N bridging methylene, generating the iminium intermediate prior to forming fluorescent heterocycle **17** after a 1,2-aryl shift (Scheme 14).

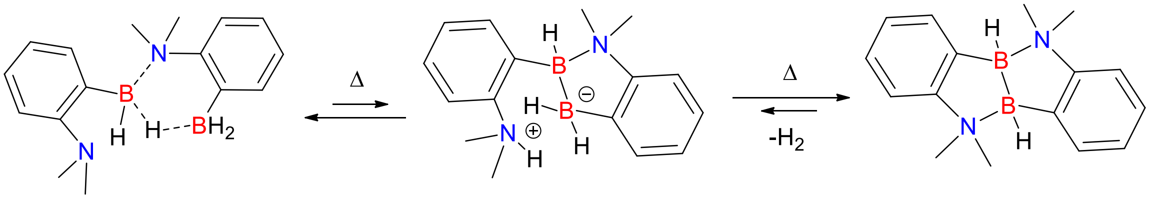


Scheme 13: Intramolecular Csp^3-H bond activation from ambiphilic molecule **15**,



Scheme 14: Rearrangement of molecule **16**

As mentioned above, ambiphilic aminoboranes with smaller amines exhibit a structure in which a B-H bond of one molecule is interacting with the B/N Lewis pair of another. Whereas the dissociation of the Lewis adducts is thermally accessible with most molecules, 1-NMe_2-2-BH_2-C_6H_4 (**13-Me**) was shown to lose hydrogen upon mild heating, generating diborane product **18** (Scheme 15).[53] This transformation is highly unusual since diboranes are usually generated under reducing conditions, or by dehydrogenative coupling using transition metal catalysts.[54] Kinetic monitoring of this transformation confirmed a first-order transformation with $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of 3.8±0.1 kcal mol^{-1} and 0.02±0.01 cal mol^{-1} K, respectively, suggesting an intramolecular process. It was also observed that the reaction was significantly slower under 3-4 atmospheres of H_2, in line with a reversible process. A KIE of 2.0 ±0.4 was observed when 1-NMe_2-2-BD_2-C_6H_4 (**13-Me-D_2**) was used instead of **13-Me**. **13-Me-D_2** was generated by exposing **13-Me** to a D_2 atmosphere, confirming the FLP activity of smaller ambiphilic aminoboranes towards H_2 activation.[53]



13-Me **18-Zwi** **18**

Scheme 15: Spontaneous generation of diborane **18**

The DFT modeling of this transformation suggests that the FLP component of **13-Me** is essential to this transformation, since the intramolecular positioning of the amine allows deprotonation of the hydride at the same time as the boron atom is reduced. As expected, zwitterionic intermediate **18-Zwi** with the B-B bond is high in energy (about 20 kcal mol^{-1}), but the release of H_2 drives the formation of species **18**. Although the deprotonation of a hydride is unexpected, it was later reported by Wagner that strong Lewis bases can promote the intermolecular reduction of borohydrides.[55]

Conclusion

Since our report on the catalytic activity of $(Me_2AlCH_2PMe_2)_2$ in the nickel-catalyzed silane polymerization, which to our knowledge is the first example of the use of a group XIII ambiphilic ligand in catalysis, ambiphilic molecules went from main group curiosity to predominant players in catalytic processes. Every year, numerous reports highlight how Z-type ligands can be used to promote unusual and highly practical catalytic transformations with metal complexes. However, ambiphilic molecules really shine as exceptional catalysts in metal-free FLP transformations. Whereas most researchers have focused on FLP hydrogenation reactions, our group demonstrated that FLPs are highly active molecules for novel bond formation reactions, such as in the hydroboration of carbon dioxide or in the C-H bond functionalization of heteroarenes. More importantly, we were able to gain valuable insight on the *modus operandi* of FLP molecules, highlighting how some Lewis adducts without steric hindrance can also access transformations that are typical of frustrated Lewis pairs. With this knowledge in hand, we hope to extend the number of catalytic that can be catalyzed by these simple, yet versatile, main group molecules.

Biographical Information

Frédéric-Georges Fontaine received his Ph.D. from Université de Montréal in 2002 under the supervision of Davit Zargarian where he worked on the nickel-catalyzed polymerisation of phenylsilane. He then joined the group of T. Don Tilley at the University of California Berkeley as an NSERC postdoctoral fellow. In 2004, he started as an assistant professor at Université Laval, where he became a full professor in 2013.

Étienne Rochette received his B.Sc. from Université Laval in 2014 and he is currently pursuing his Ph.D. under the supervision of Prof. Fontaine as an NSERC and Vanier scholar.

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