

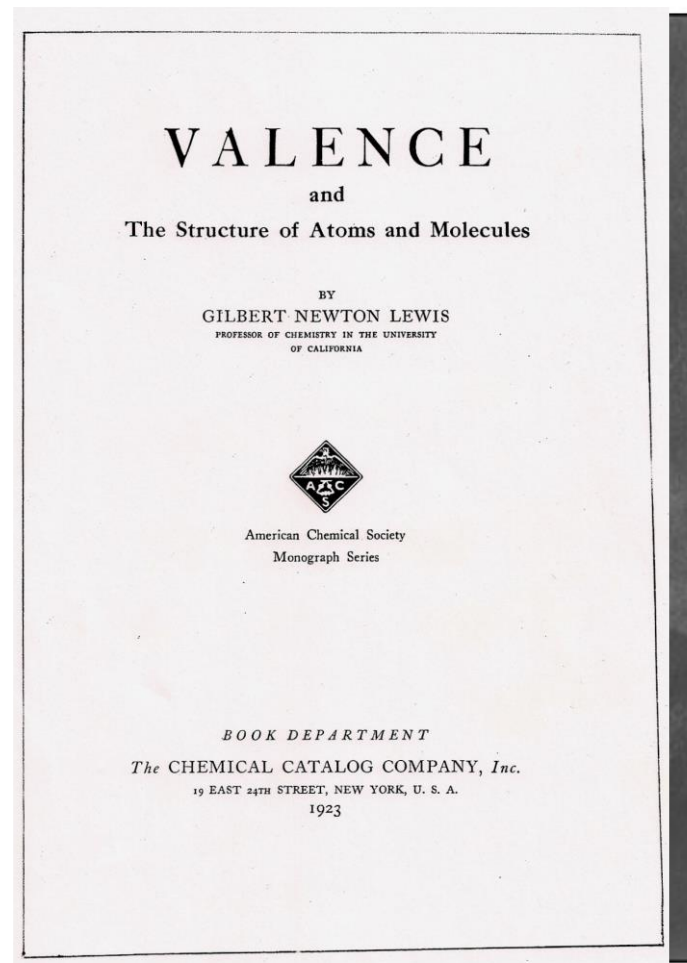
FRUSTRATED LEWIS PAIRS:

structure and synthetic applications

Gilbert Newton Lewis

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- Born: 1875
- PhD: 1899 Harvard
- Berkley Professor: 1912-1946
- *Valence and the Structure of Atoms and Molecules* – 1923
 - ▣ Shared electron-pair bond
 - ▣ Continuity of bonds/polarization
 - ▣ Inductive effect
 - ▣ Free radicals
 - ▣ Hydrogen bond
 - ▣ Limitations of the octet rule



Jensen, W. B. *The Trait  of the Third Chemical Revolution*
Lewis, G. N. *Valence and the Structure of Atoms and Molecules*, Chemical Catalogue Company; New York, 1923

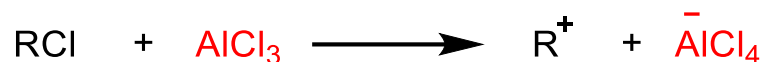
Lewis Acid / Lewis Base

3

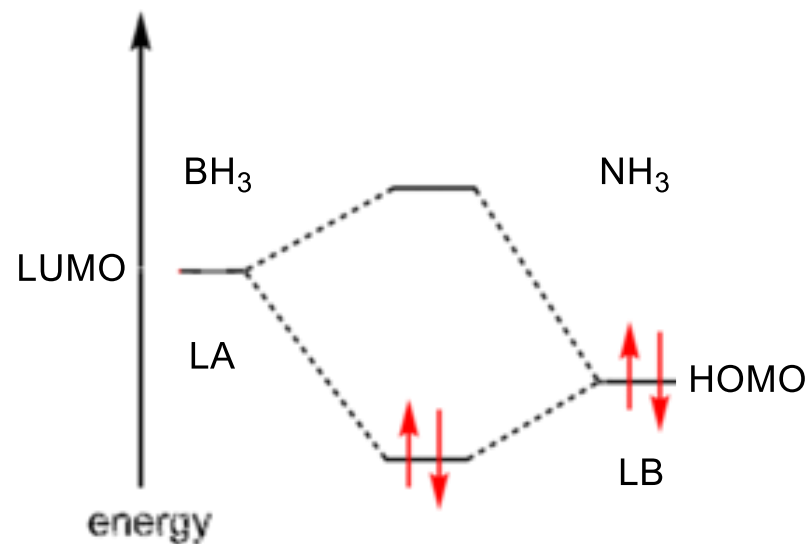
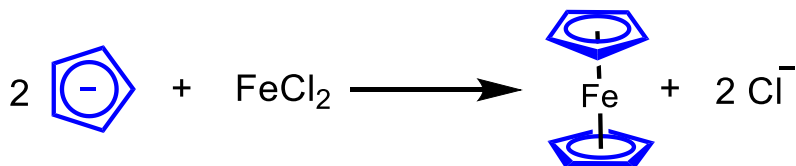
'A basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom, and ... an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms.' – **G.N. Lewis**

- Focus is on electrons, not proton
– differs from Brønsted acid/base

- LA have an unoccupied LUMO



- LB have an unoccupied HOMO



Lewis Acid / Lewis Base Adduct

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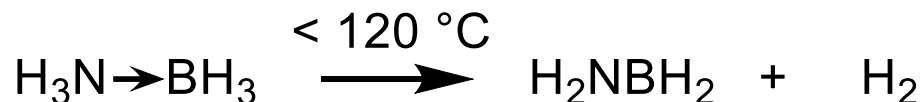
- Stable compound from mixing of LA & LB



- Held together by a dative/coordinate bond
 - ▣ Often fairly strong in nature

Lewis Base	Lewis Acid	ΔH_{rxn} (kcal/mol)
Pyridine	B(Me) ₃	-4.0
NH ₃	B(Me) ₃	-22.6
NH ₃	B(Cl) ₃	-35.9
NH ₃	B(<i>i</i> Pr) ₃	-18.3

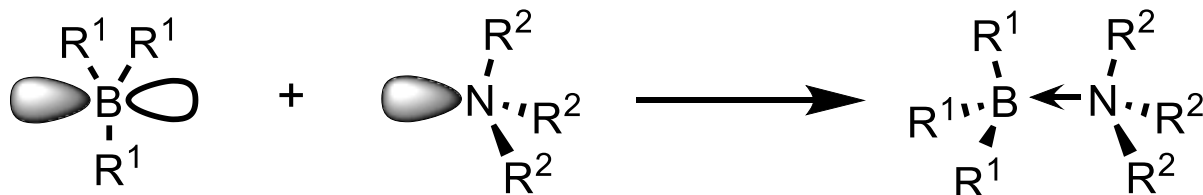
- Adducts often have distinct chemical properties



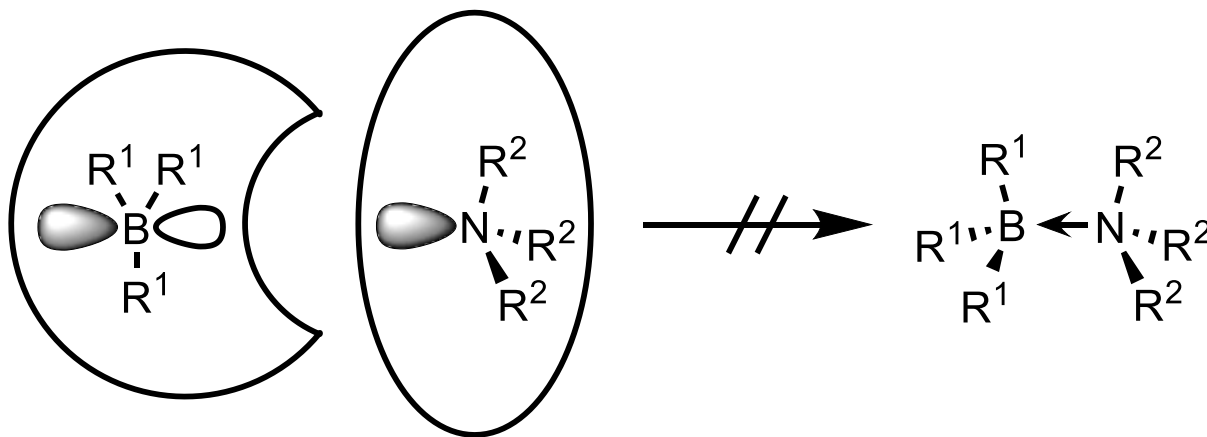
Lewis Pair Adduct – Steric Effects

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- Typical adduct formation – small R^1 and R^2



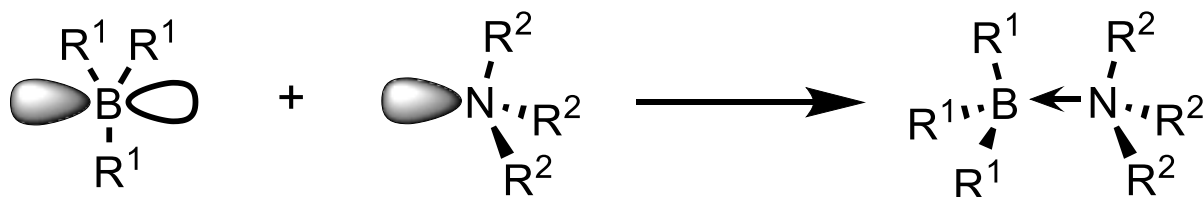
- Frustrated Lewis Pair – large R^1 and R^2



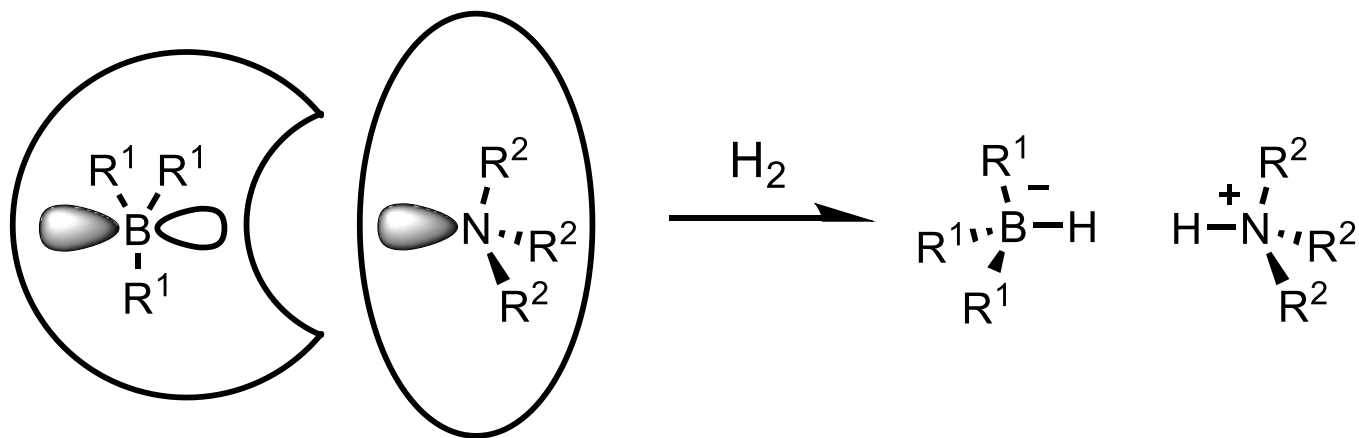
Lewis Pair Adduct – Steric Effects

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- Typical adduct formation – small R^1 and R^2



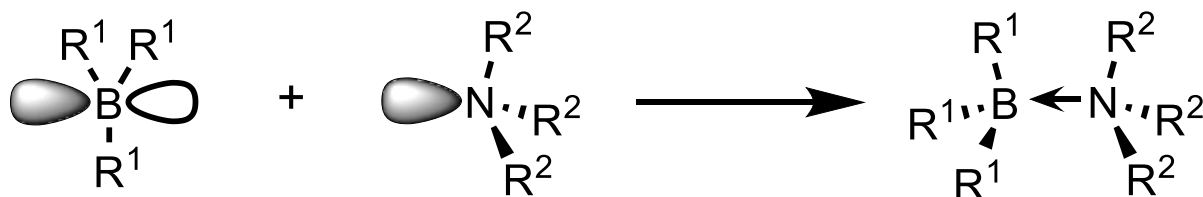
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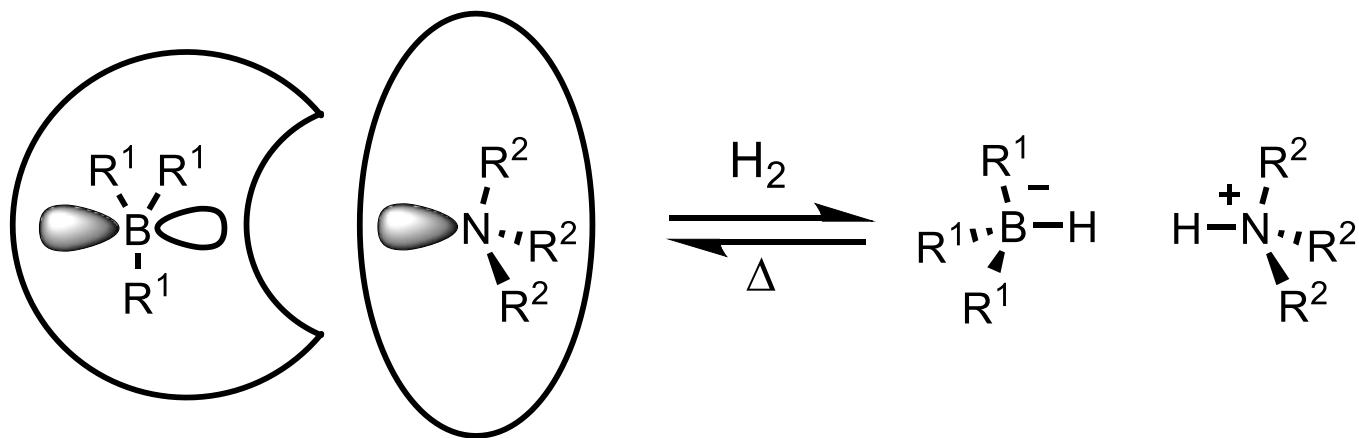
Lewis Pair Adduct – Steric Effects

7

- Typical adduct formation – small R^1 and R^2



- Frustrated Lewis Pair – large R^1 and R^2

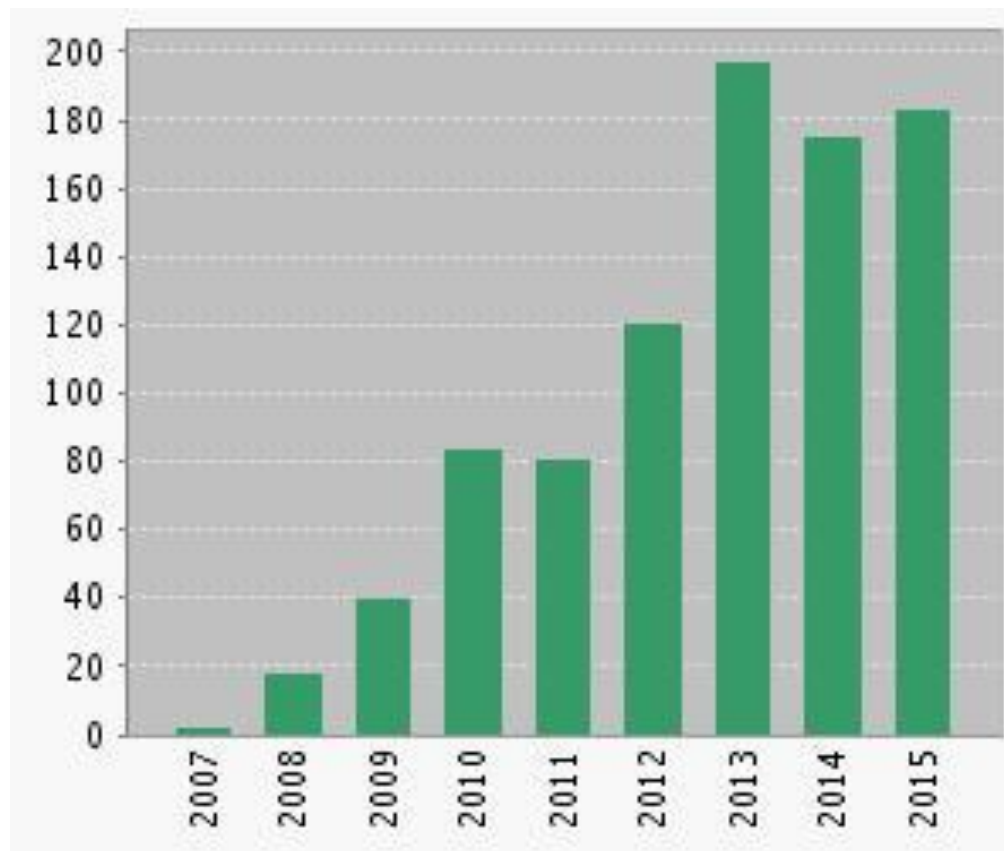


- Result: strong, unquenched Lewis acid and base coexist

Frustrated Lewis Pairs

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- Number of publications per year since 2007
- Total number of publications: 902
- Three main investigators:
 - Douglas Stephan
 - Gerhard Erker
 - Imre Pápai

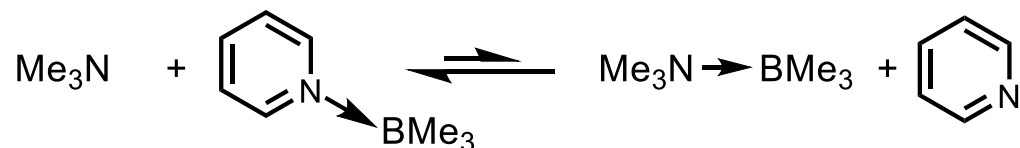
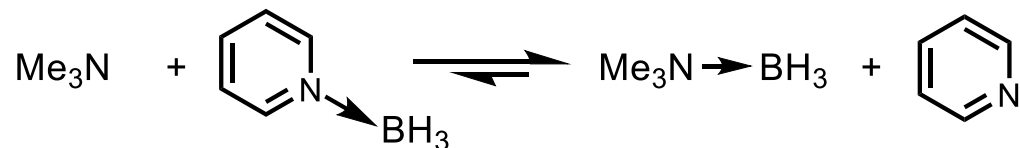
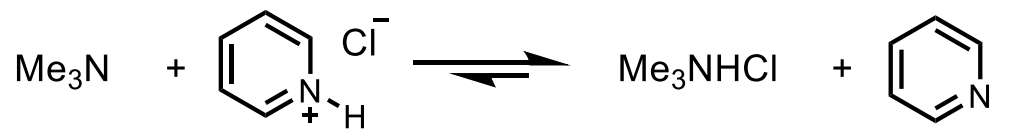


History – Early observation

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□ Brown – 1942

- Investigating the free rotation of alkane single bonds and steric effects
- B-N isoteric with C-C bond (1.54 Å to 1.58 Å)



- Indicated that pyridine is the “stronger” base anomalously

History – Early observation

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□ Brown – 1942

▣ Steric effect of similarly strengthened bases

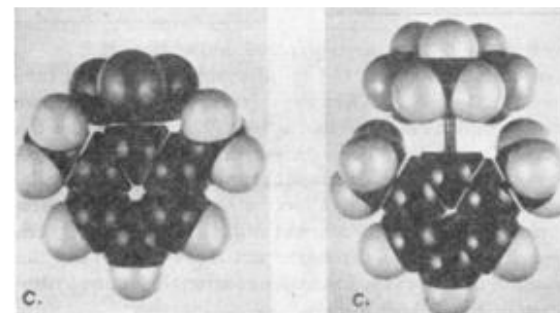
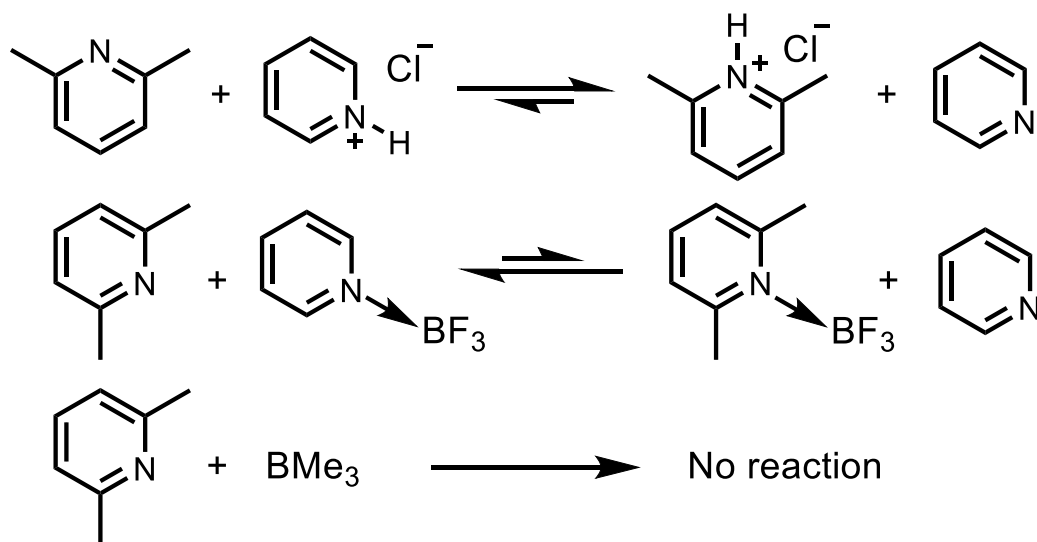


Fig. 1.—Molecular models of the coordination compounds of boron fluoride with (a) trimethylamine, (b) pyridine and (c) α, α' -lutidine.

Fig. 2.—Molecular models of the coordination compounds of trimethylboron with (a) trimethylamine, (b) pyridine and (c) α, α' -lutidine.

Lewis Base	Lewis Acid	ΔH_{rxn} (kcal/mol)
NMe ₃	BMe ₃	0.3
Pyridine	BMe ₃	-4.0
2,6-DiMePyr	BMe ₃	7.4

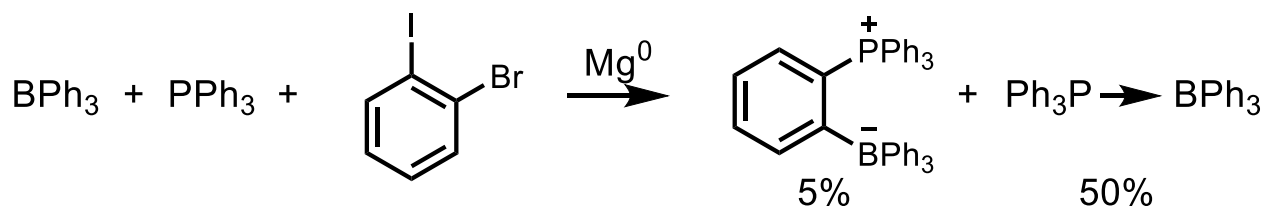
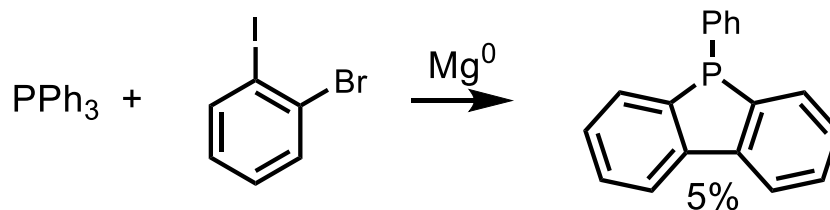
- Sterics of LA / LB reveal large impact on compound formation

History – Unexpected product formation

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□ Wittig – 1959

▣ Investigations into the reactivity of benzyne



▣ Addition of BPh_3 did not fully quench reaction

▣ Therefore, a new reactive pathway was found for LA / LB

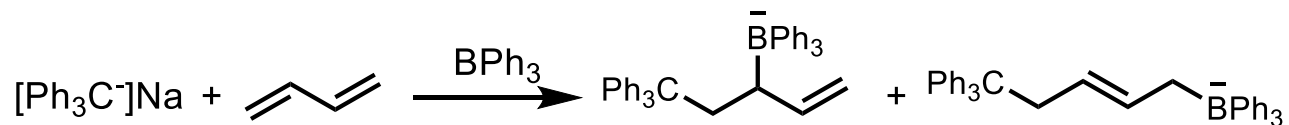
History – Alkenes and FLP

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- Tochtermann – 1966
 - ▣ Research into formation of organo-ate complexes
 - ▣ Known method for polymerization of alkenes



- ▣ Formation of stable intermediates formed when BPh_3 is added



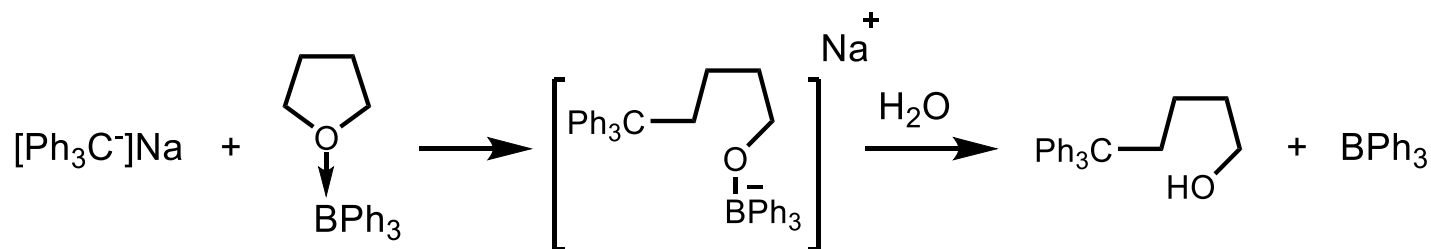
- Further evidence for non-quenching of sterically bulky LA / LB

History – Cyclic ethers and FLP

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□ Tochtermann – 1966

- Further research into the interesting activity of sterically bulky LA/ LB



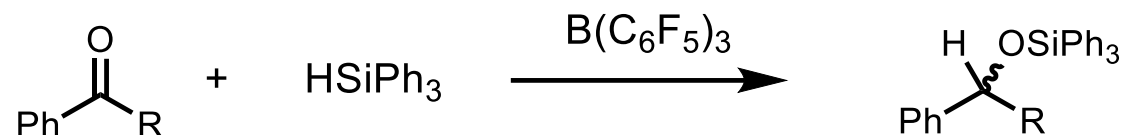
- Reveals ability of pair to attack a molecule nucleophilically and electrophilically at the same time

History – Hydrosilation of Carbonyl Compounds

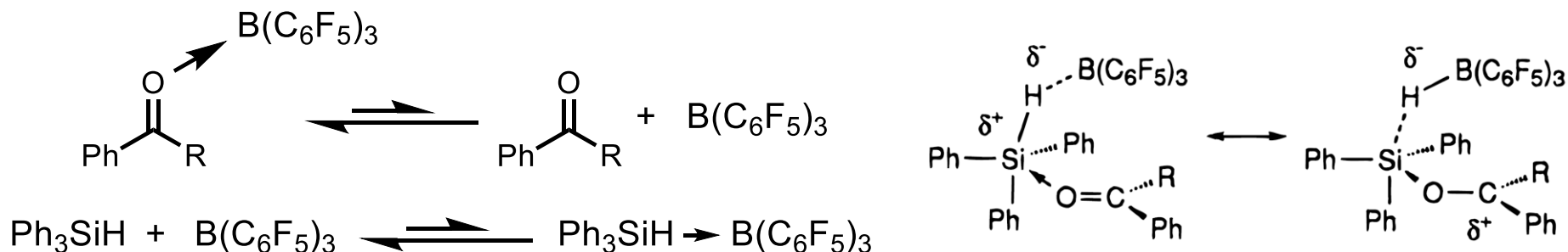
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□ Piers – 1996

- Exploring the use of $B(C_6F_5)_3$ as LA in hydrosilation reaction



- Observed a rate difference where esters > ketone > aldehyde
- Realized role of LA is not to activate the carbonyl compound



- While no significant mention is made of FLP, the activation of the Si-H bond by boron does abide by this terminology

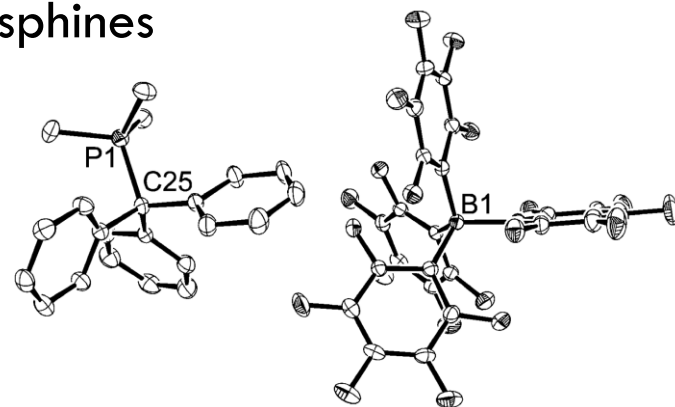
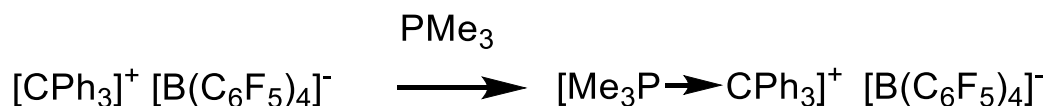
History – Effect of R-group on PR_3

16

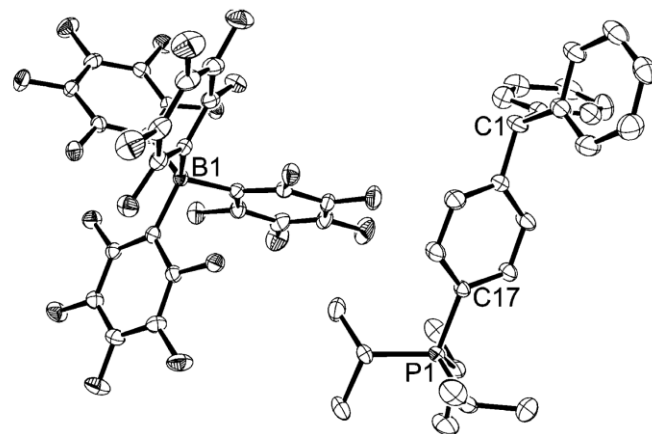
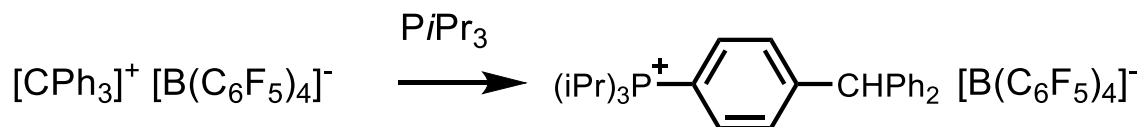
□ Stephan – 2006

▣ Investigation of trityl borate salts and phosphines

▣ Normal adduct with small phosphine



▣ New compound with larger phosphine

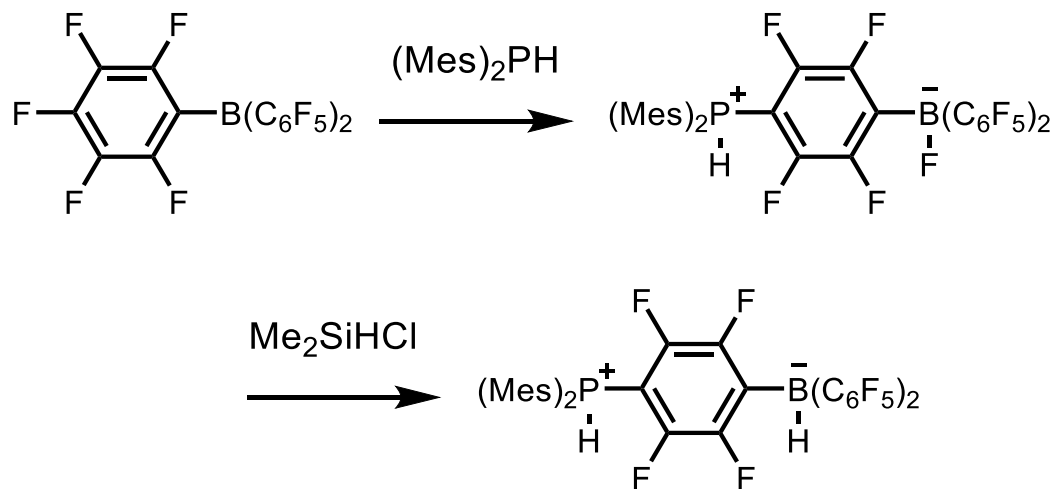


□ New reactivity the result of unquenched LA / LB

History – Splitting H₂

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- Stephan – 2006
 - ▣ Further investigations of the sterics impacts of P-B pairs
 - ▣ Synthesis of new compound containing both P and B segments

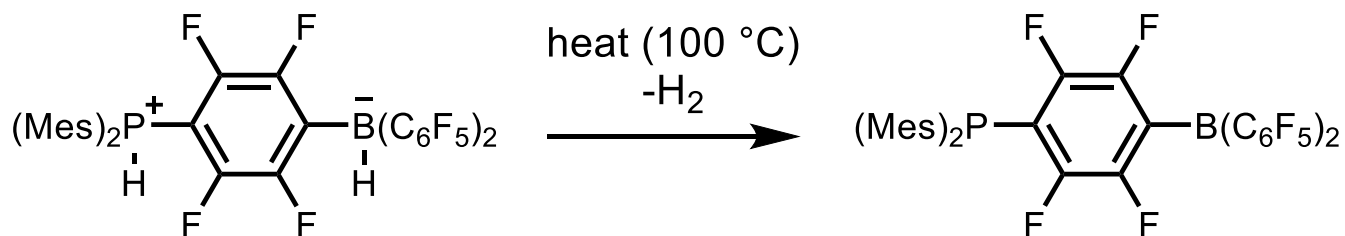


- ▣ Air- and moisture-stable white solid
- ▣ Phosphorus is unable to coordinate to the boron, thus undergoing aromatic substitution instead

History – Splitting H₂

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- Stephan – 2006
 - When heated, compound liberated H₂

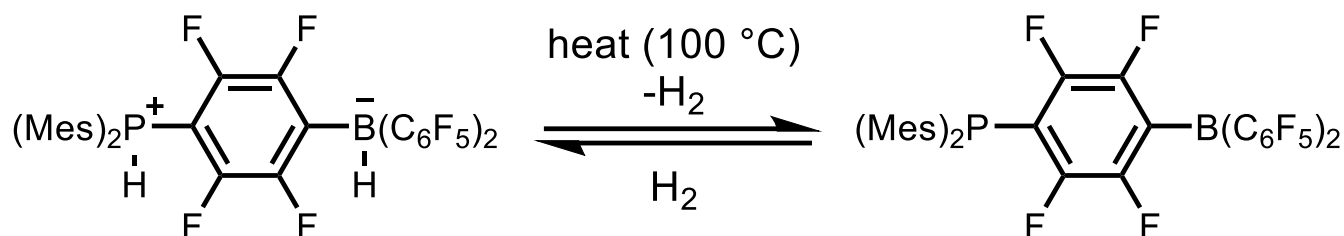


- Monitoring by ^{19}F reveal para-F shift from -164 to -143 ppm – consistent with change from four- to three-coordinate boron
- Furthermore, the disappearance of P-H and B-H resonances observed

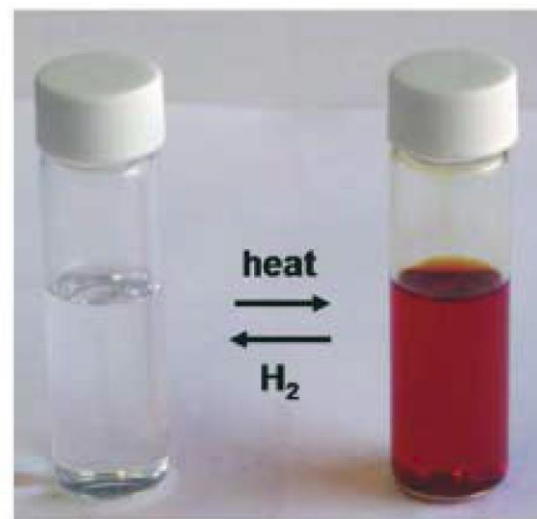
History – Splitting H₂

19

- Stephan – 2006
 - ▣ Hydrogen release is reversible!

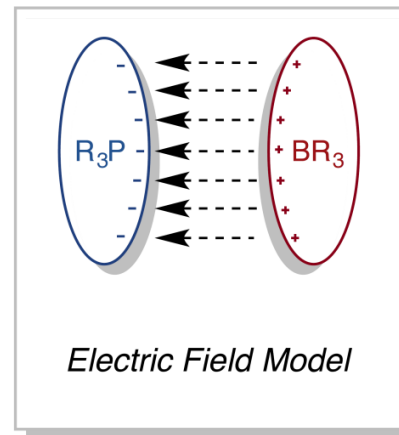
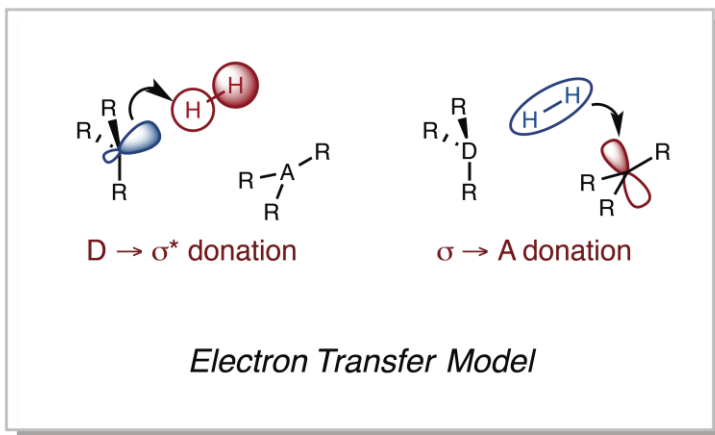


- ▣ Accompanied by a color change
 - ▣ @ 25 °C – less than 5 min
 - ▣ Could occur as low as - 25 °C
- Small molecule activation in the absence of transition metal!



Mechanistic Models

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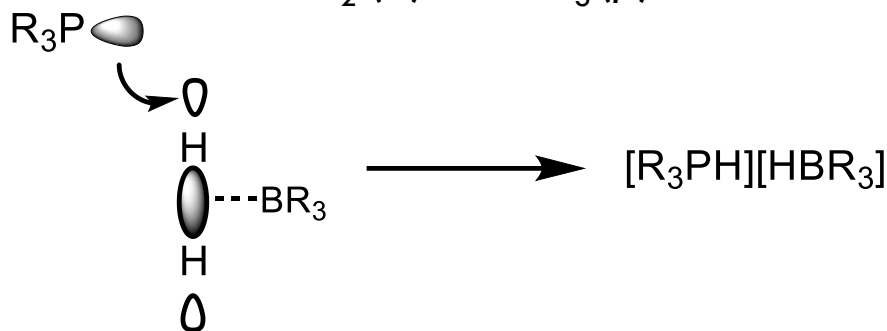


Starting Hypothesis for Mechanism

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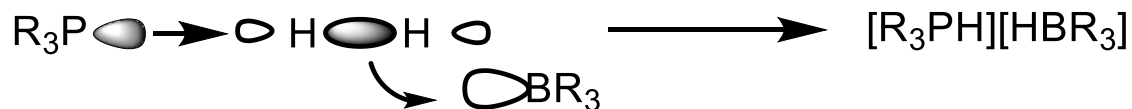
- Two prevailing possibilities for action of FLP on hydrogen

- Side-on interaction of H_2 (σ) with BR_3 (p)



- However, in reactions with $B(C_6F_5)_3$ and H_2 (4 atm) no adduct visible by 1H NMR

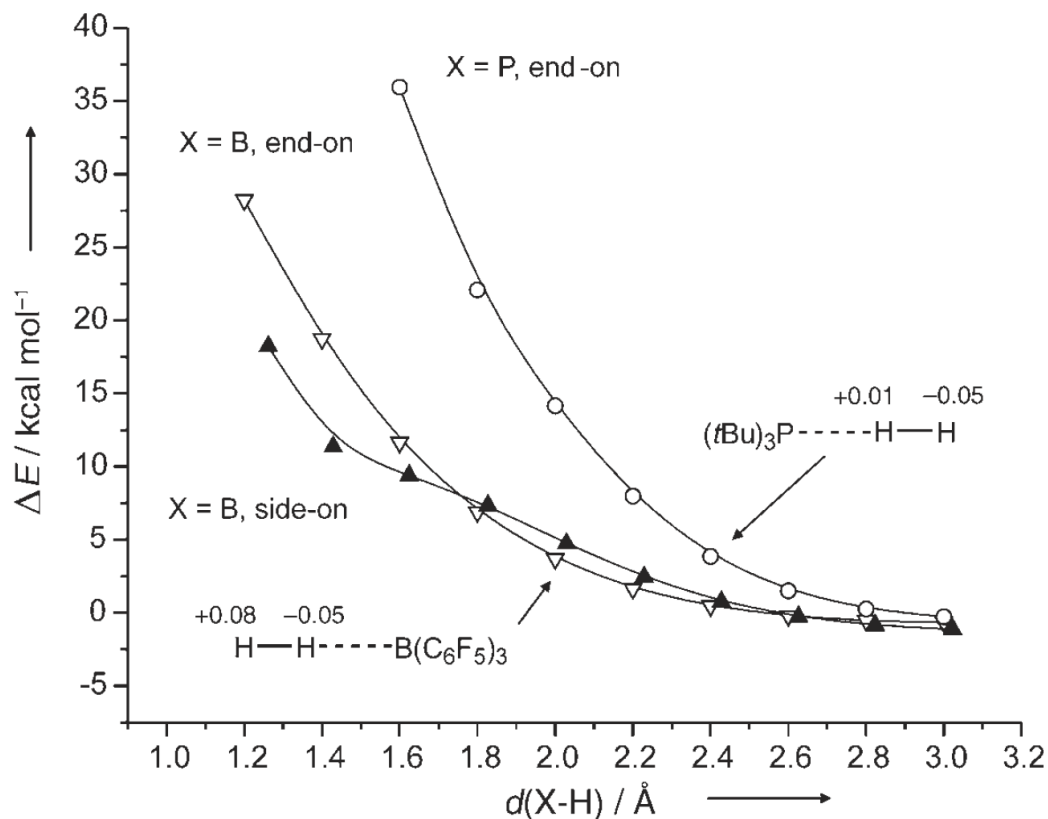
- Alternatively, end-on-base interaction of R_3P (LP) with H_2 (σ^*)



ET Model – Initial calculations

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- First attempt: compute the theorized mechanisms

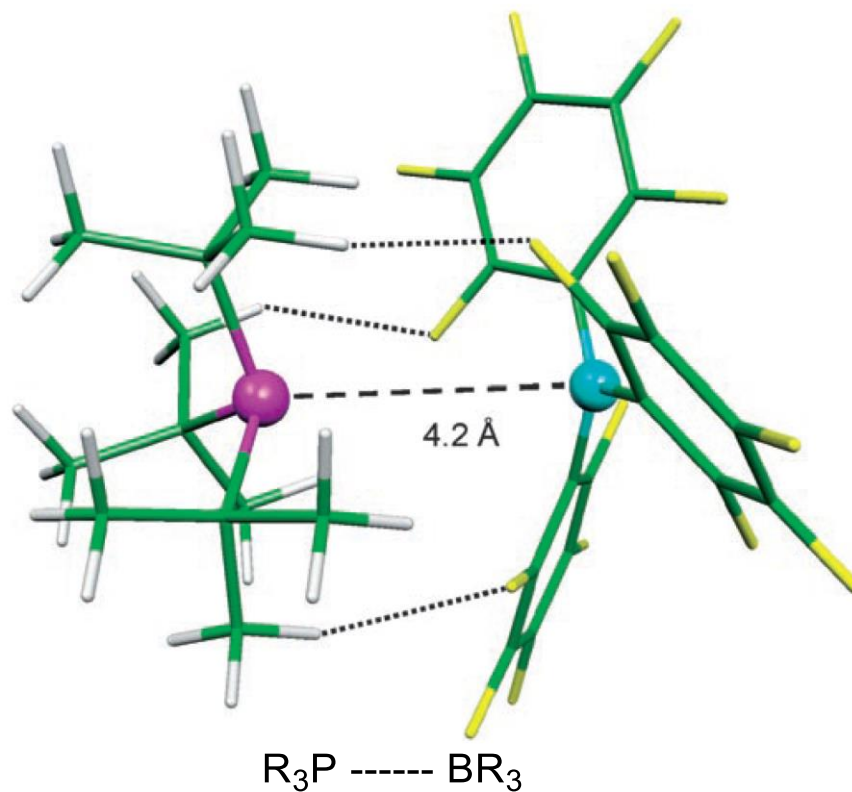
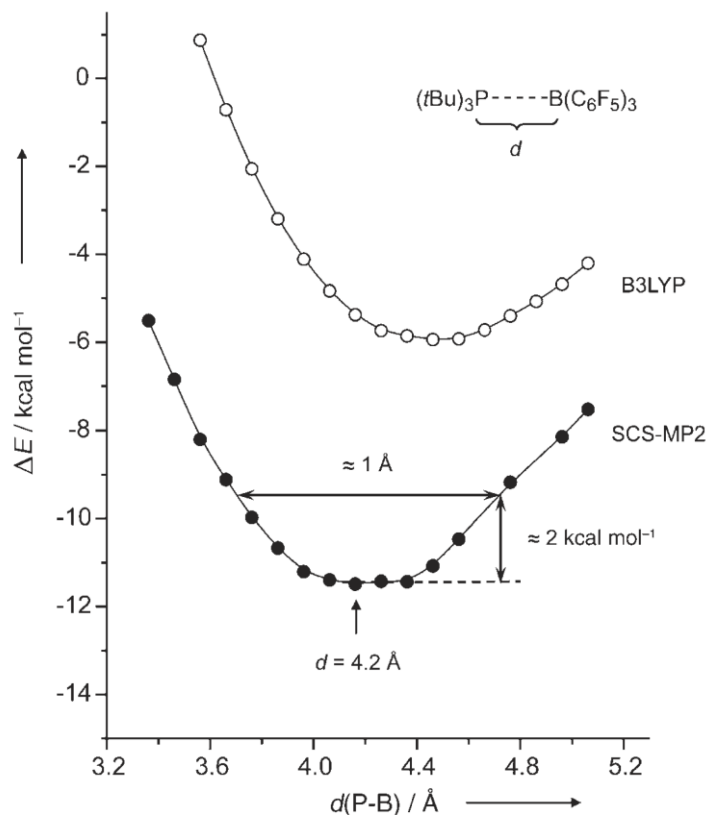


- Each possibility eliminated due to Pauli repulsion

ET Model – Secondary interactions

23

□ Searching for a pre-organization of LA and LB

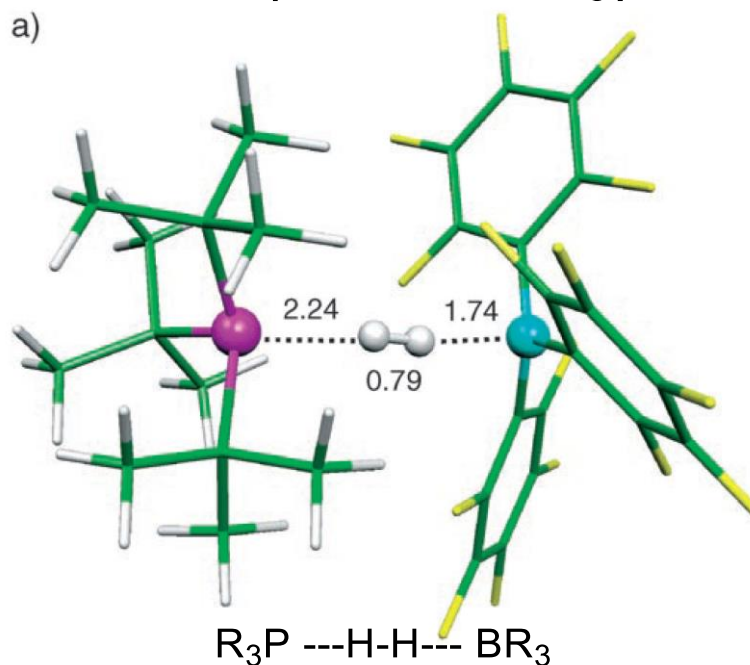


- Flat energy minimum may allow for flexibility in bond lengths
- Association also aids in making a bimolecular process

ET Model – Transition State

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- Transition state located on the potential energy surface

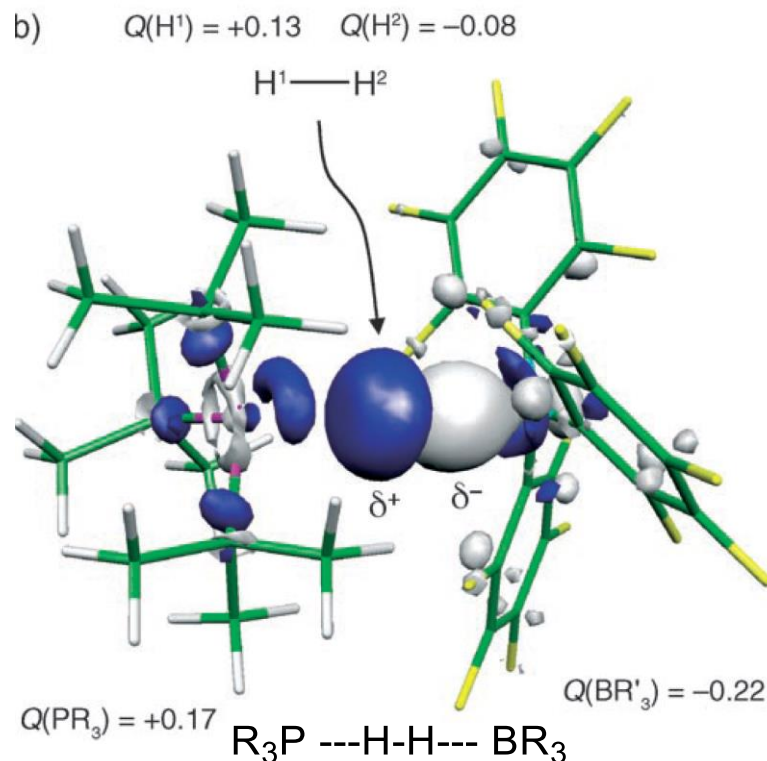


- Located ~ 10 kcal/mol above LB-LA pair
- Nearly linear P-H-H-B axis forming
- H_2 bond already lengthening (0.74 \AA to 0.79 \AA) \rightarrow Early TS

ET Model – Electron density map

25

- Investigation of polarization in transition state

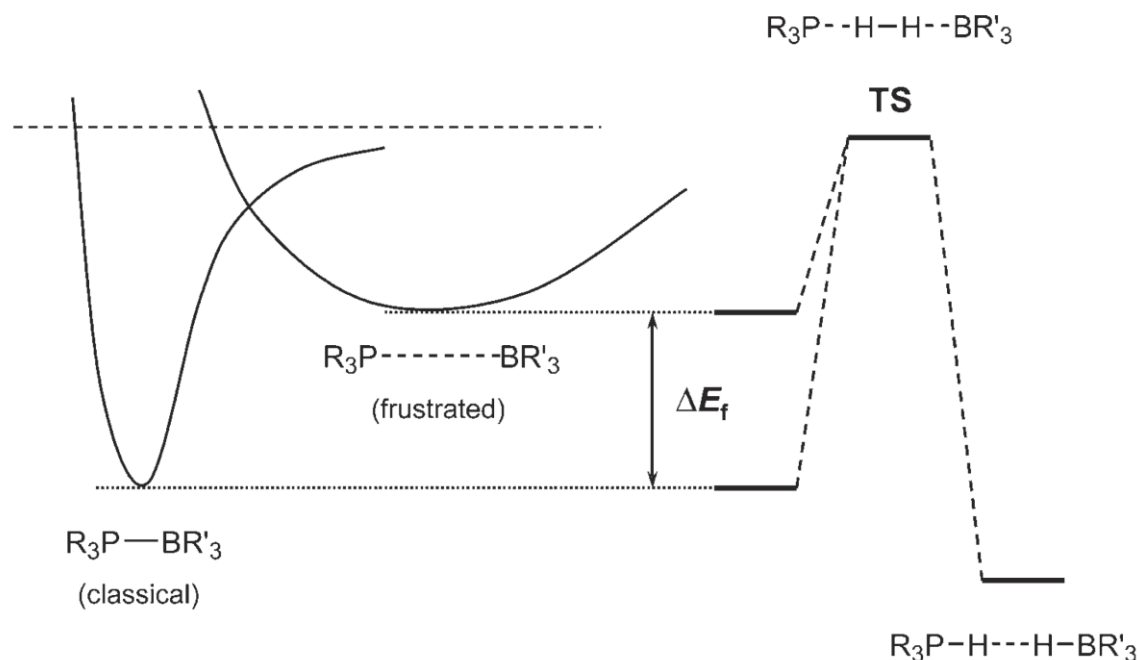


- Significant H₂ polarization
- Theorized to be a simultaneous ET: H₂ (σ) → BR₃ (p) / R₃P (LP) → H₂ (σ*)

ET Model – Energy diagram

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- Based upon the observed calculations

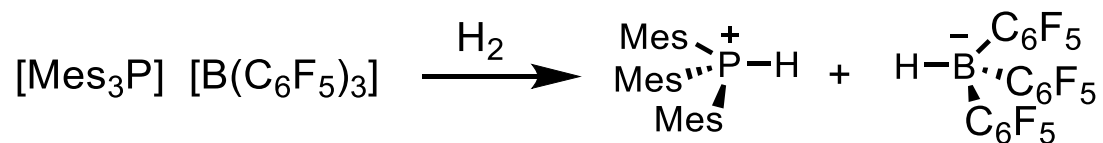


- Non-bonding interactions raise energy of frustrated complex
- Activation barrier is decreased and overall exothermicity increased
- Product further stabilized by non-bonding interactions

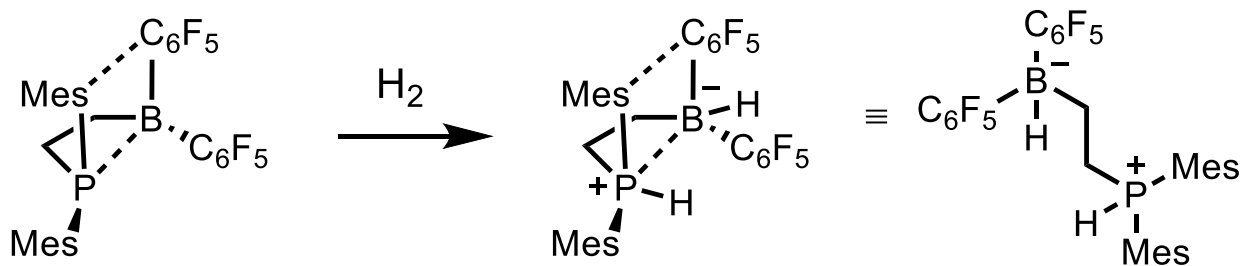
Alternative Model

27

- Intermolecular FLP can adopt any required orientation



- Intramolecular FLP have a pre-arranged orientation to each other

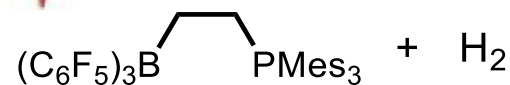
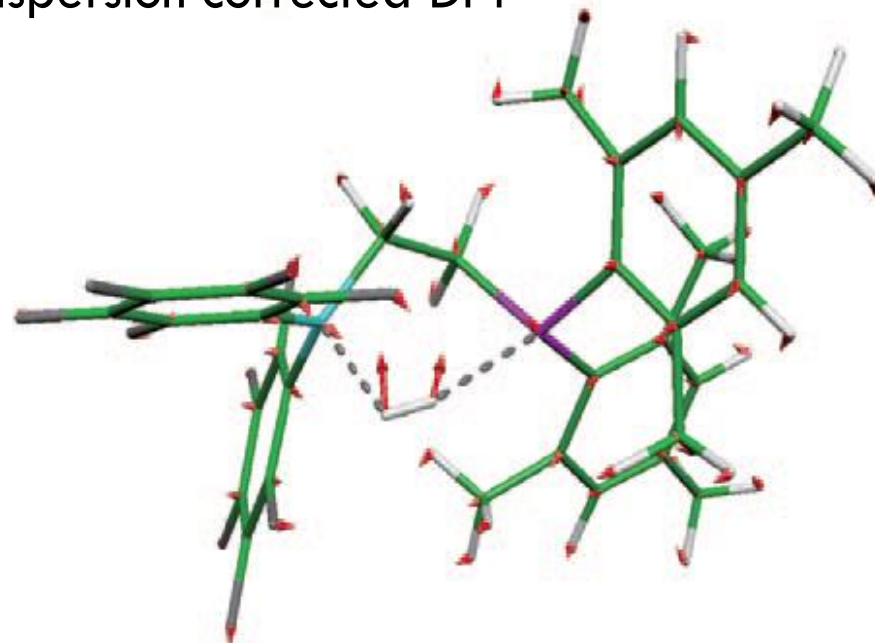
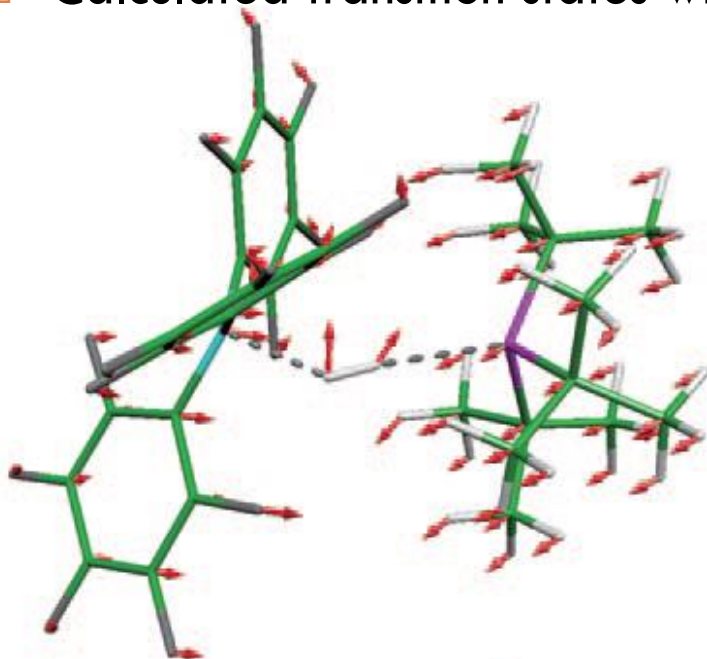


- Some intramolecular FLP cannot adopt linear arrangement as shown previously

Alternative Model – Non-linear TS

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- Calculated transition states with a dispersion corrected DFT

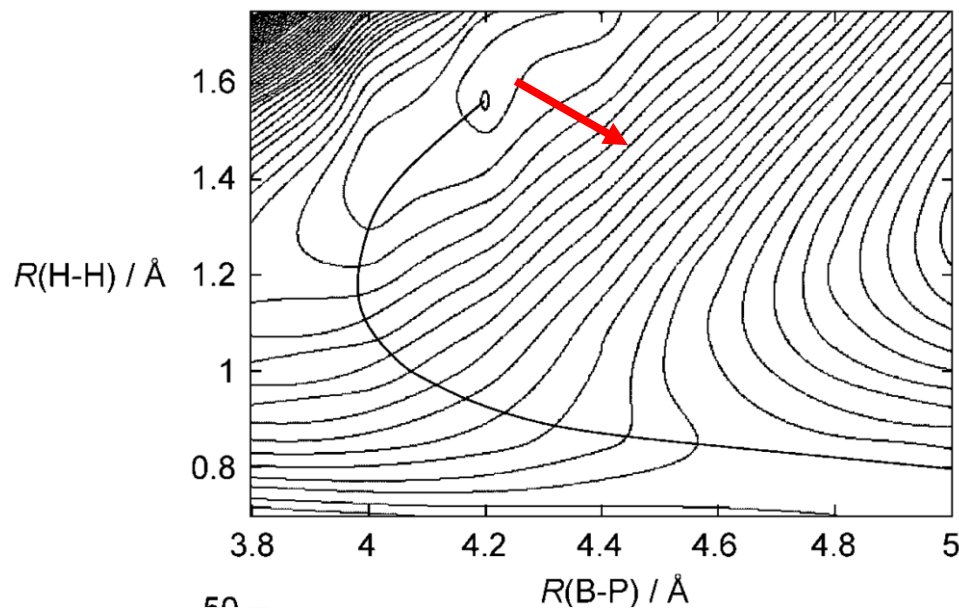


- The B-H-H-P bond is non-linear and lies away from the B-P axis
- H₂ bond shows similar lengthening (0.74 Å to 0.79/0.80 Å)
- Believed to show barrierless reaction, once inside the EF pocket

Alternative Model – PE surface

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- 2-D potential energy surface for: $t\text{Bu}_3\text{P} + \text{B}(\text{C}_6\text{F}_5)_3$ system

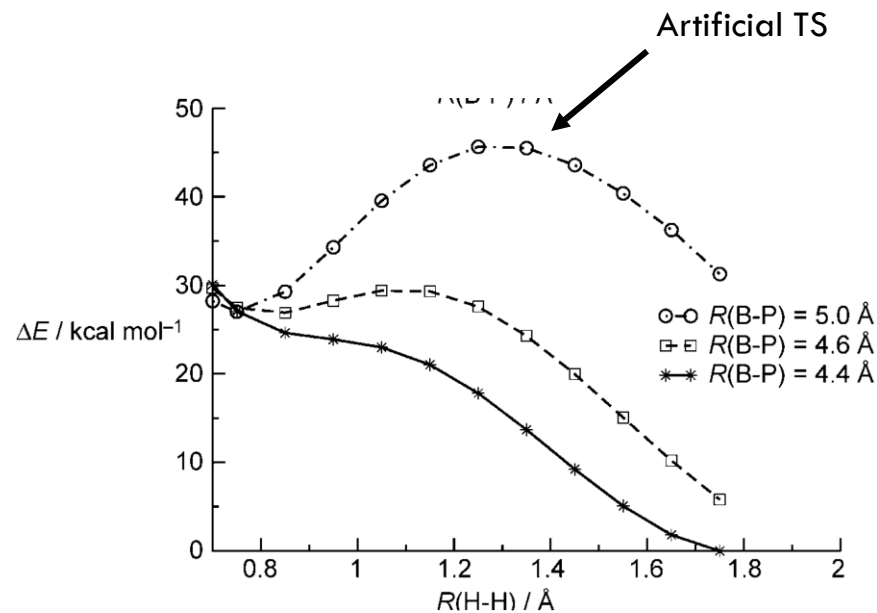
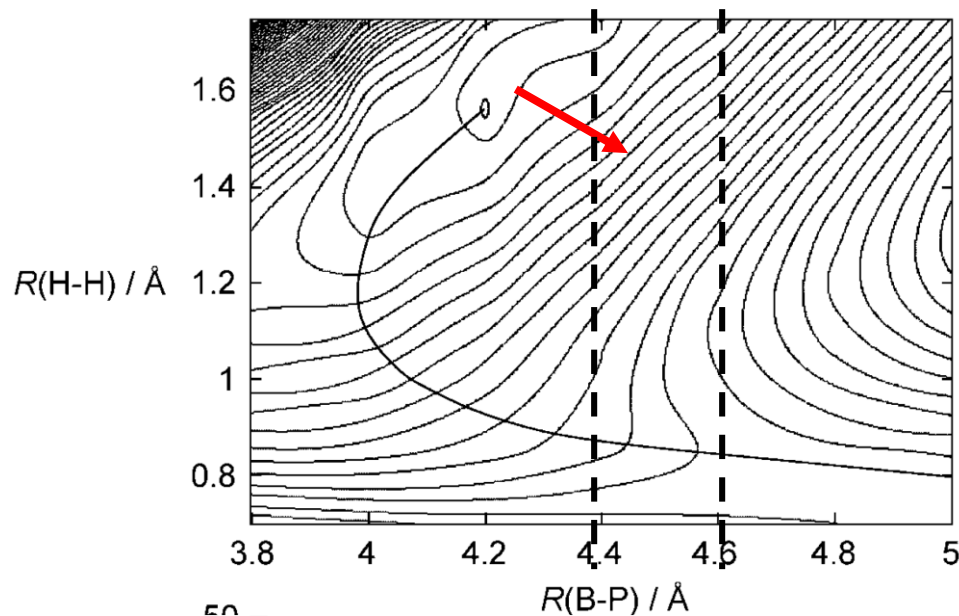


- Bold line indicates “low energy” pathway \rightarrow no transition state observed

EF Model – Potential energy surface

30

- 2-D potential energy surface for: $t\text{Bu}_3\text{P} + \text{B}(\text{C}_6\text{F}_5)_3$ system

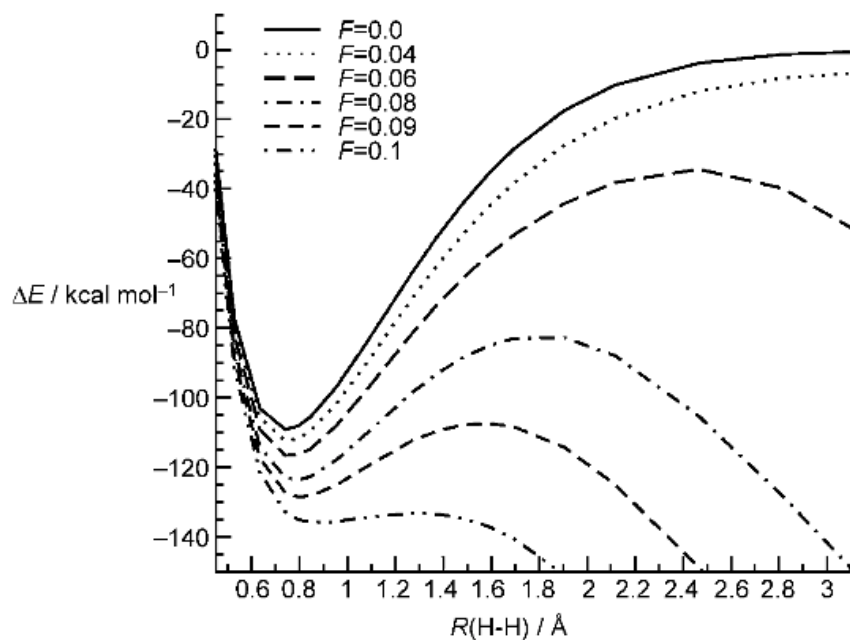
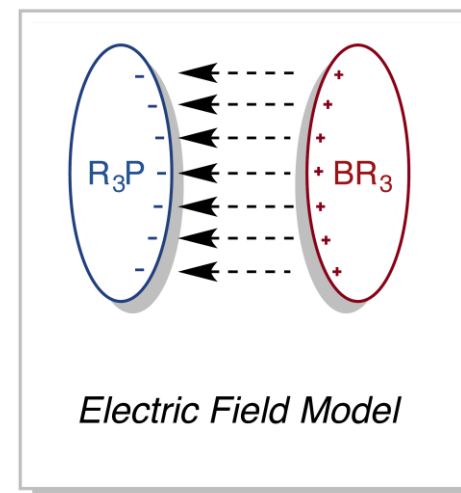


- Bold line indicates "low energy" pathway \rightarrow no transition state observed
- Transition state from previous study said to be an "artifact" of the calculation model used, giving larger B-P distances than accurate

EF Model – Overview

31

- Ignores the molecularity of the FLP
- Instead visualized as an electric field
- Interior of FLP cavity generates electric field which can polarize H₂ bond, enabling splitting

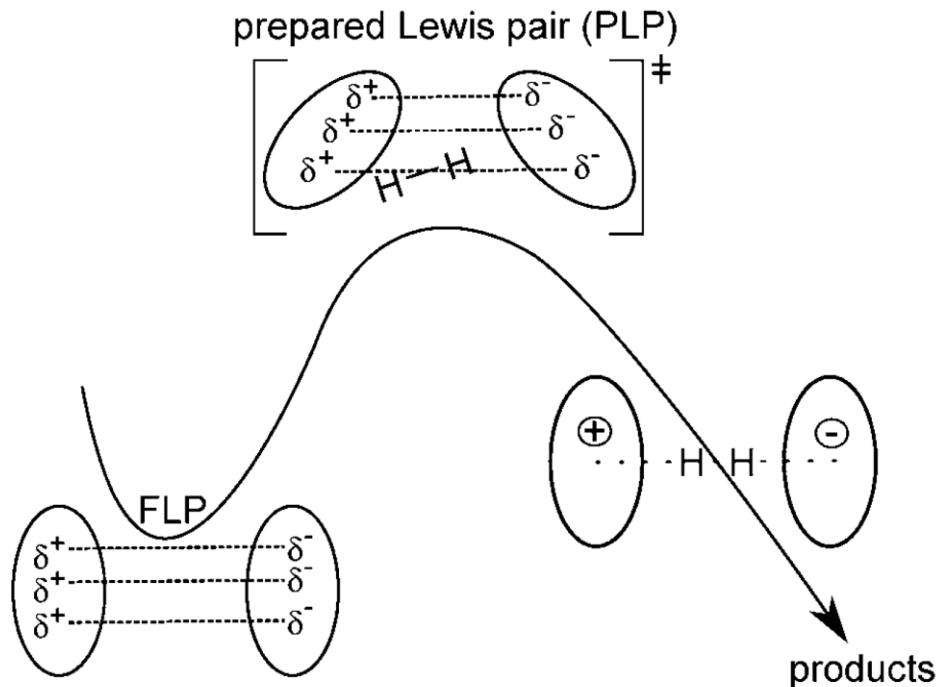


F = EF strength (1 au = 5.14×10^{11} Vm⁻¹)

- $F = 0.05-0.06$ au, maximum observed
 - ▣ FLP H-H values $\sim 0.04-0.06$ au
- Ideal value ~ 0.09 au = low barrier
- At ~ 0.1 au \rightarrow virtually no barrier
- Reason for similar activity in FLP, despite differing arrangements

EF Model – Mechanism

32

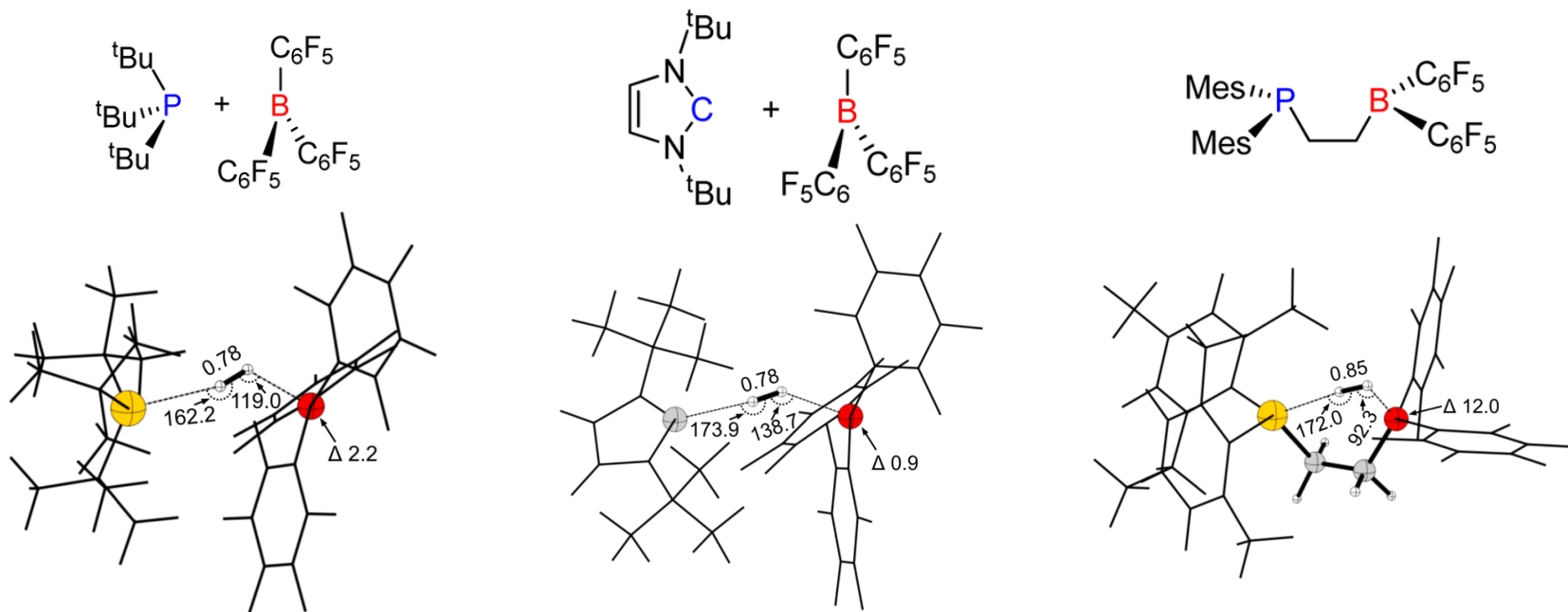


- ❑ Non-directional electric field allows for flexible FLP
- ❑ Only energy required is for H₂ to enter the pocket
- ❑ Once in cavity, splitting is barrierless
- ❑ Based purely on electronics – applicable across FLP classes

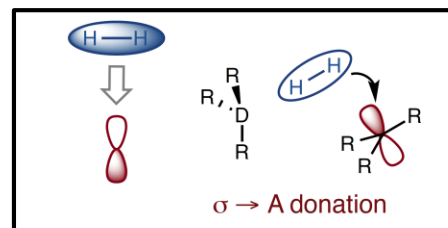
Rebuttal to EF Model

33

Reconfiguring the TS for several FLP

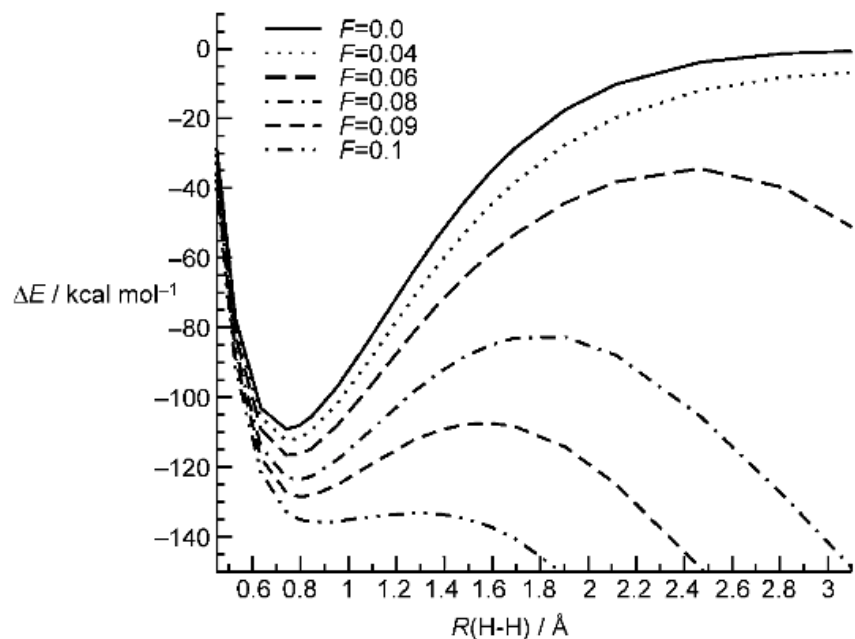


Clear linear P-H-H observed with $\sim 90^\circ$ H-H-B observed



Rebuttal to EF Model – Field Strength

34



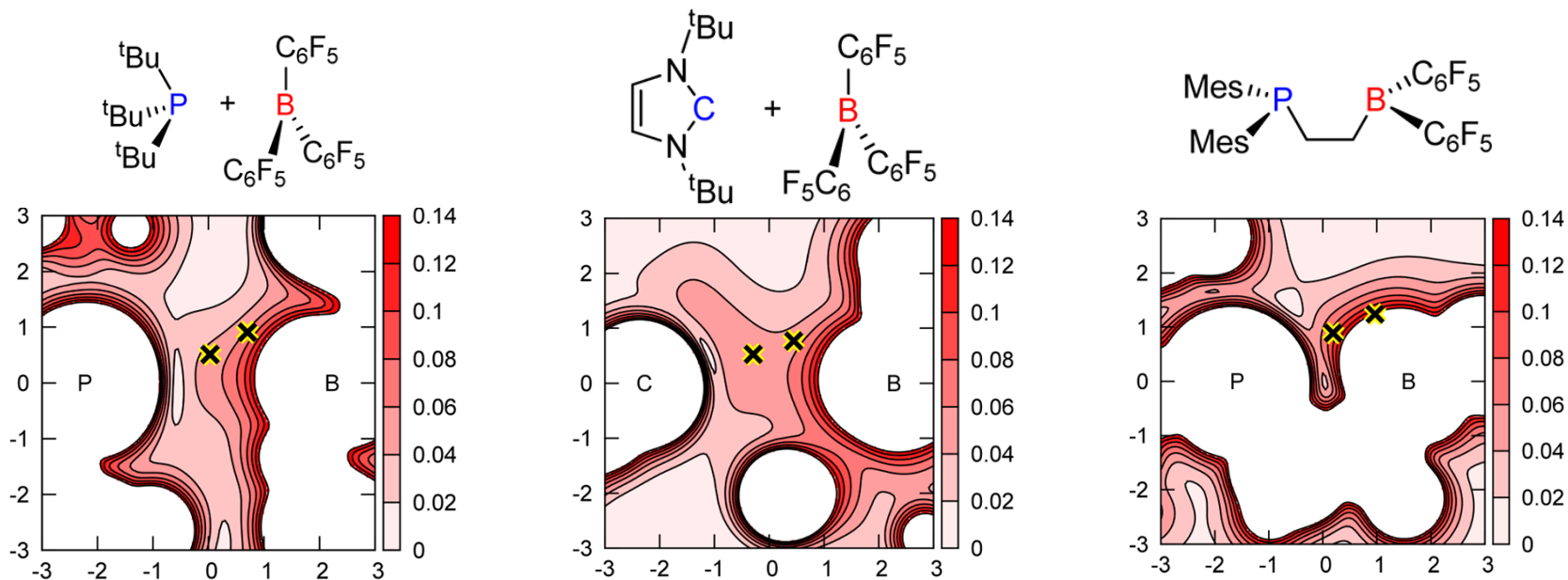
$F = \text{EF strength (1 au} = 5.14 \times 10^{11} \text{ Vm}^{-1}\text{)}$

- Reported field values for FLP are ~ 0.06 au $\rightarrow 75$ kcal/mol!
- Above 0.09 au, activation energies are reasonable $\rightarrow < 20$ kcal/mol
- Only above 0.1 au is it barrierless

Rebuttal to EF Model – Field Strength

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Electric field diagrams for select FLP

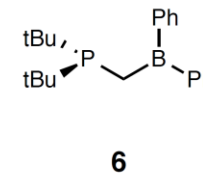
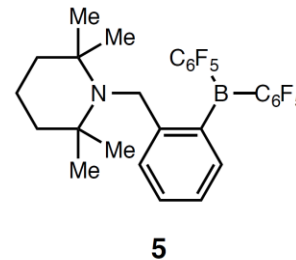
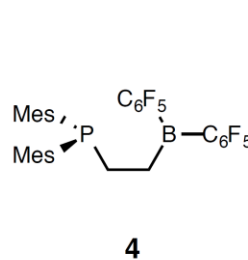
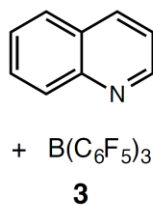
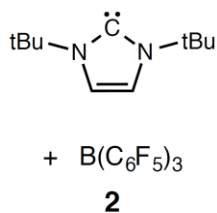
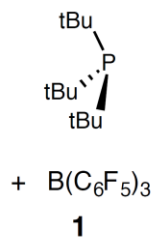
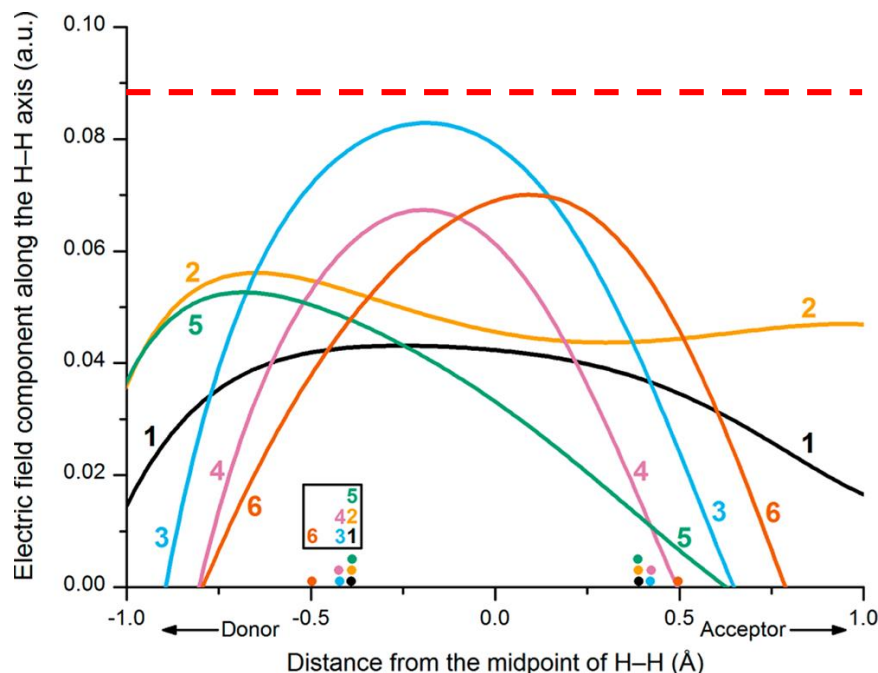


- Electric field is not homogeneous within the cavity
- Required energies are not always near H-H bond

Rebuttal to EF Model – Field Strength

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- Cross section of electric field strength across the H-H bond



- None of the FLP reach the necessary au value

Other considerations

37

- Pápai – 2012
 - Performed molecular dynamics simulation FLP in explicit solvent molecules
 - In toluene, ~2% of the B & P molecules are involved in association
 - Considering reactive encounters, relative concentration is only 0.5%
 - Still need to consider H₂ diffusion, lifetime of complexes
- Macchioni – 2013
 - NMR studies on approach orientations of FLP
 - Discovered only a 1 kcal/mol difference in approach energies for facing each other or in other directions for phosphine/boron FLP
 - No shift in peaks observed by ¹H NMR, but significant number of H/F NOEs were
 - Association instead the result of dispersion forces
- Grimme – 2015
 - Validated the ¹H NMR studies using more precise DFT calculations
 - Obtained values similar to the experimental ones

Pápai, I.; et al *Dalton Trans*, **2012**, 41, 9023

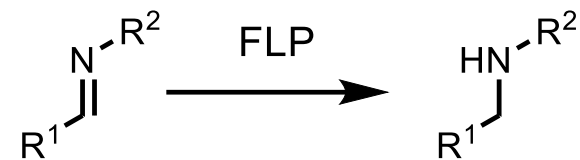
Macchioni, A.; et al *JACS*, **2013**, 136, 112

Grimme, S.; et al *Isr. J. Chem.* **2015**, 55, 235

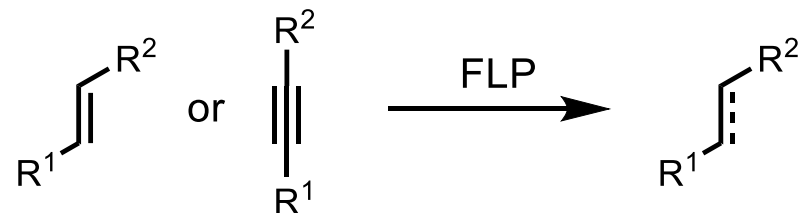
Synthetic Advances

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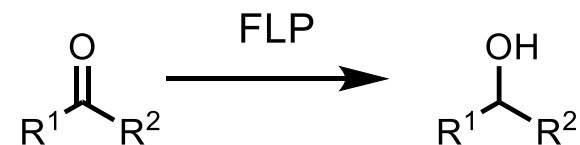
- Reduction of imines



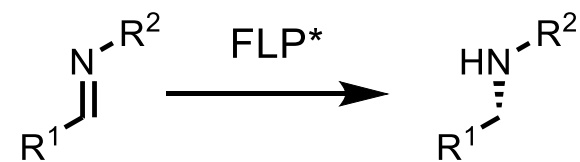
- Hydrogenation of alkene/alkyne



- Reduction of carbonyl compounds



- Chiral FLP

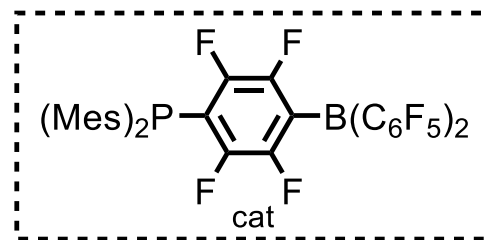
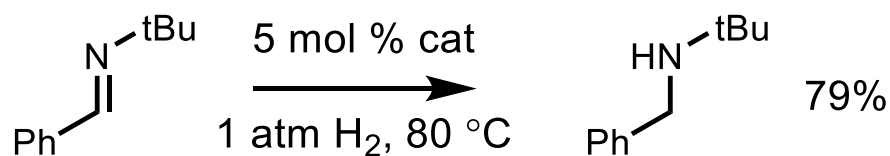


Applications – Catalytic Hydrogenation

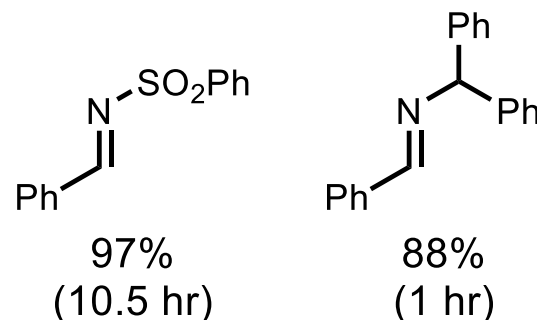
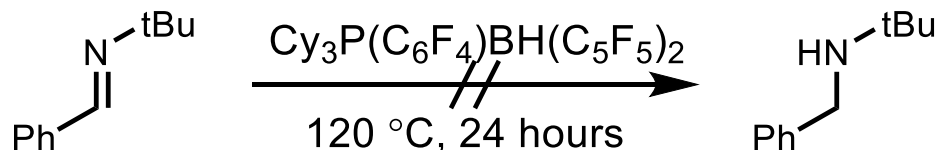
39

□ Stephan – 2007

- ▣ Using substoichiometric amount of cat, efficient reductions observed



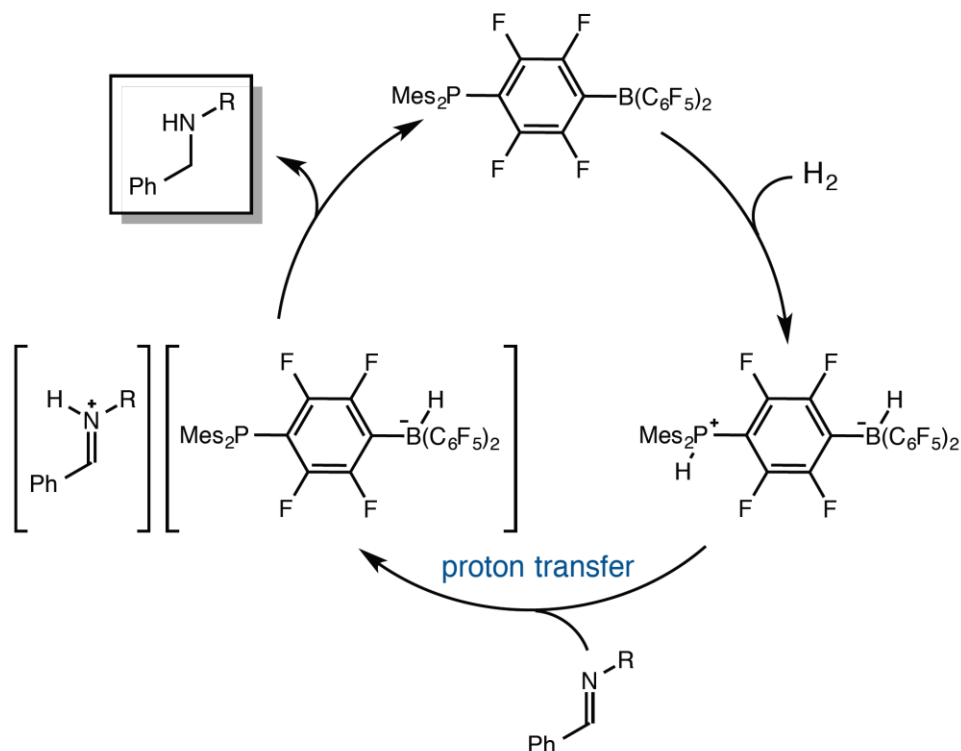
- ▣ Effect of electronics on reactivity suggests a protonation mechanism



Applications – Protonation-based mechanism

40

- Stephan – 2007
 - Based on increased rates with electron rich amines

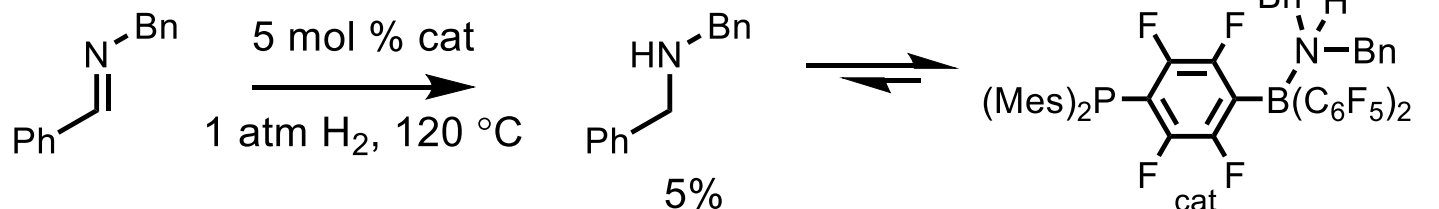


Applications – Catalytic Hydrogenation

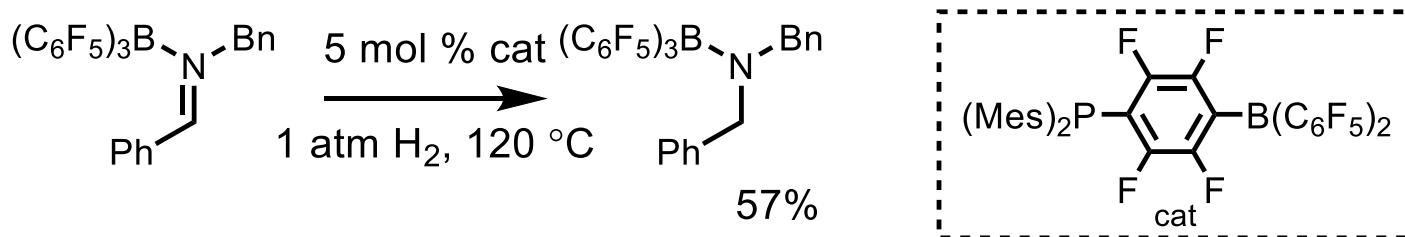
41

□ Stephan – 2007

- Requirement for sterically demanding imine



- Formation of adduct shuts down catalytic activity

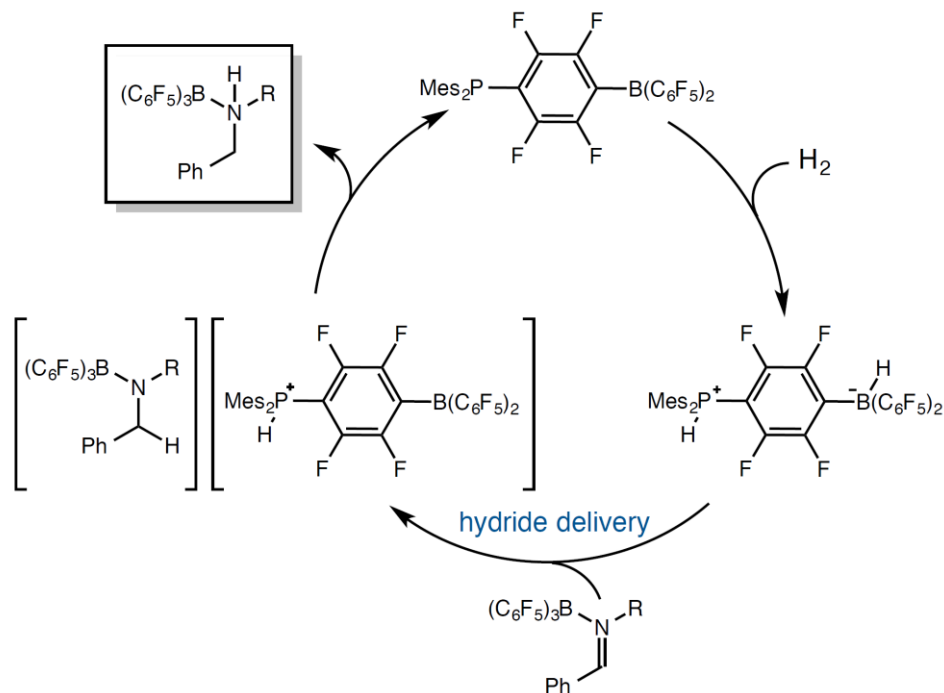


- Use of protected imine re-enables catalytic activity

Applications – Protonation-based mechanism

42

- Stephan – 2007
 - With protected-imine, hydride delivery likely occurs first

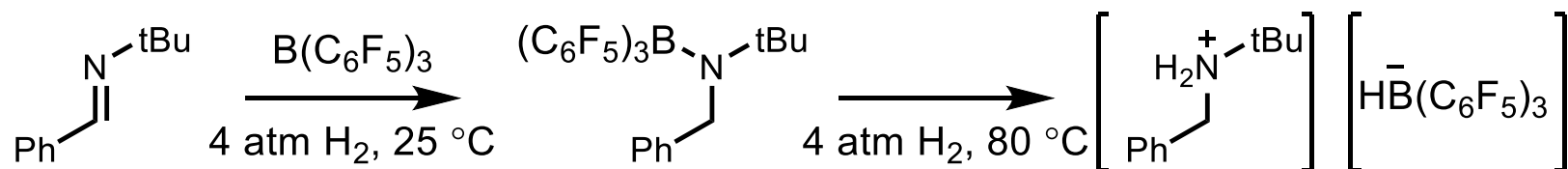


Applications – Use of only boron-LA

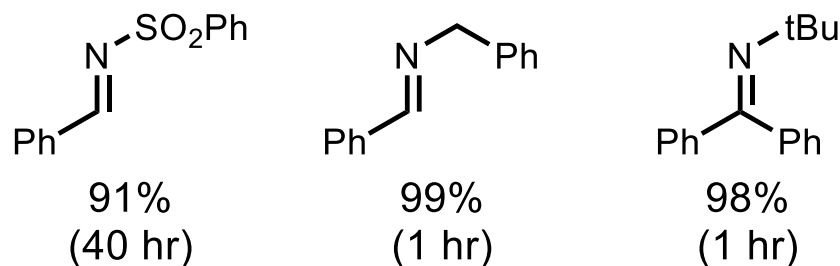
43

□ Stephan – 2008

□ Reaction of imine with $B(C_6F_5)_3$



- Formation of zwitterion suggests reversible FLP formation possible
- B-H - - - H-N close contact of 1.87 Å → like a proton-hydride bond
- Employed in several imines

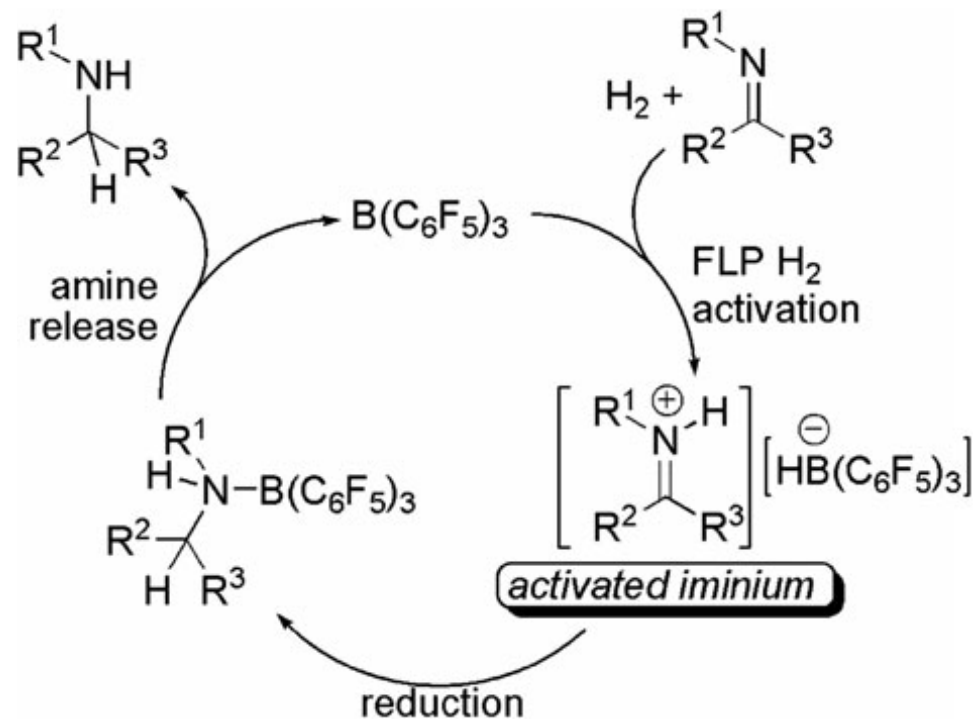


- Effect of electronics again reveals protonation mechanism

Applications – Use of only boron-LA

44

- Stephan – 2008
 - ▣ Reaction of imine with $B(C_6F_5)_3$

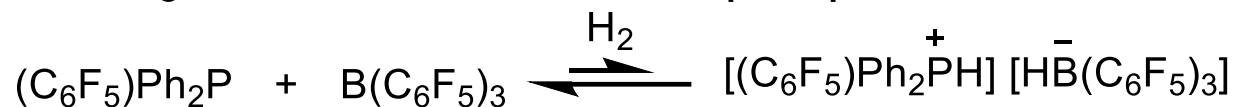


Applications – Hydrogenation of alkenes

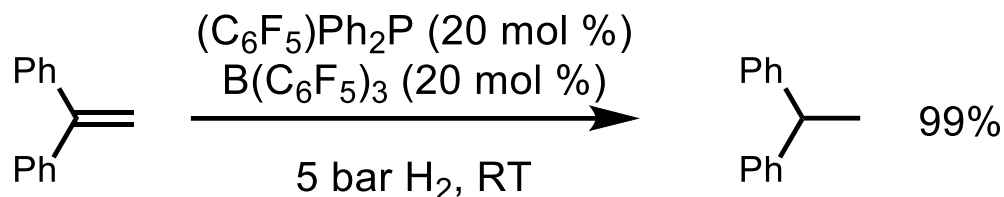
45

□ Grimme – 2012

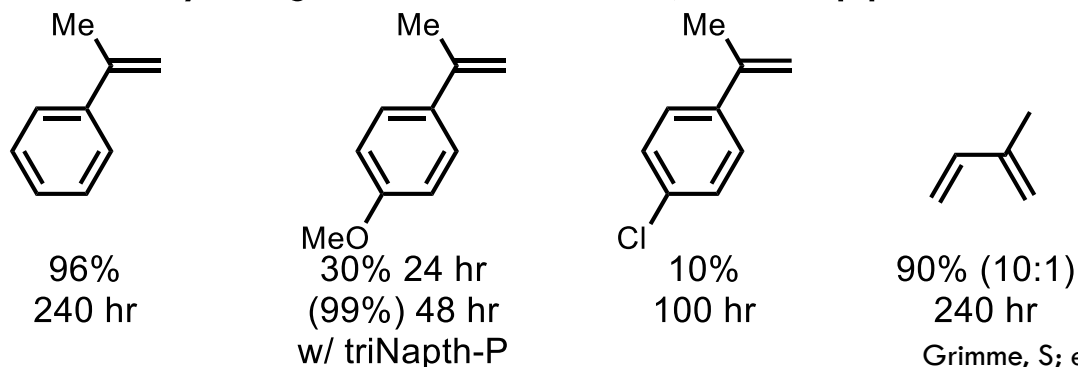
- Investigation into a more acidic phosphorus cation



- Lowered the activation of hydrogen to a -60 °C to -80 °C range
- Would allow for greater ease in protonating alkenes – more acidic



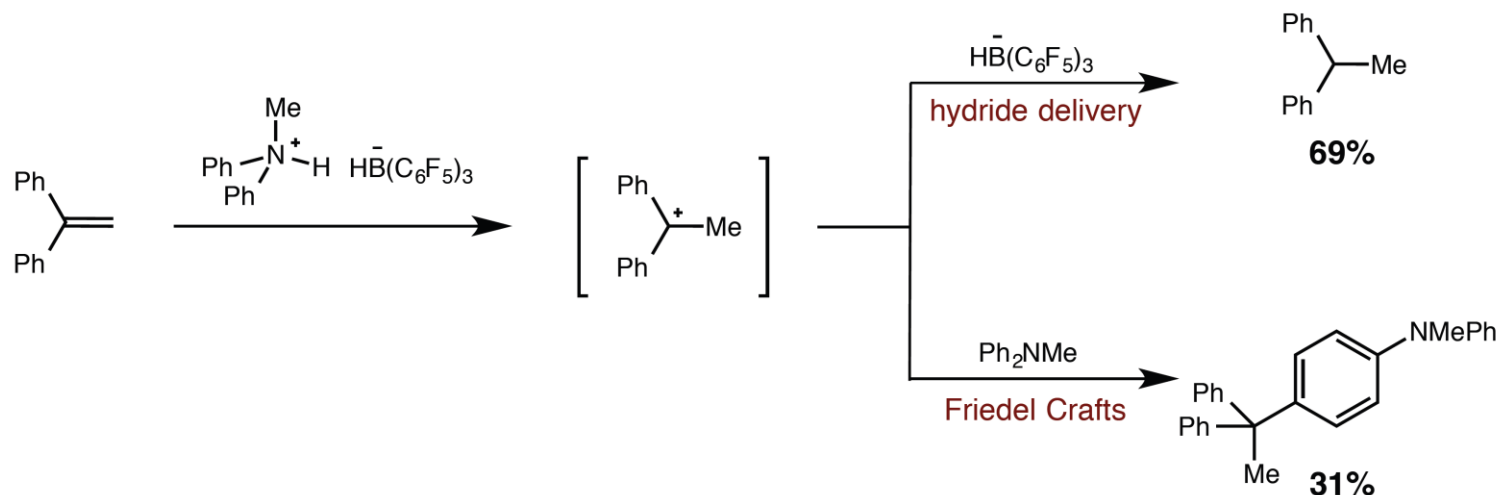
- Very efficient hydrogenation reaction, also applicable to other alkenes



Applications – Hydrogenation of alkenes

46

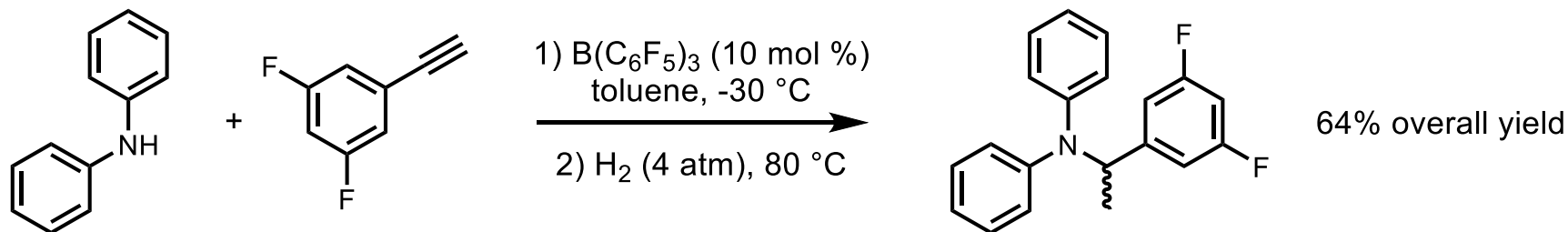
- Grimme – 2012
 - Trapping experiment with aryl amine



- Strong support for protonation, followed by hydride delivery
- Important to note – RT activity of FLP not a requirement for ability of FLP to split H₂

Group Problem: Amine synthesis

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Objective:

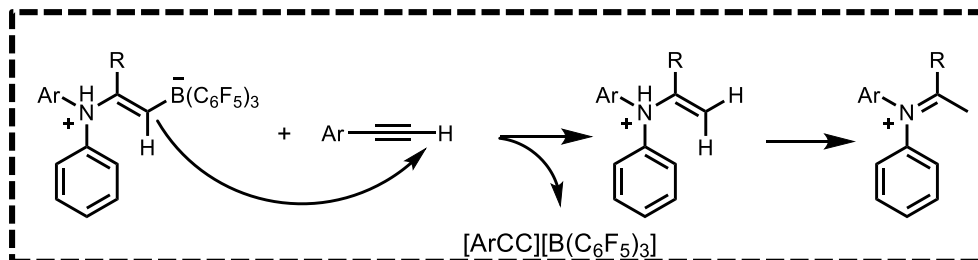
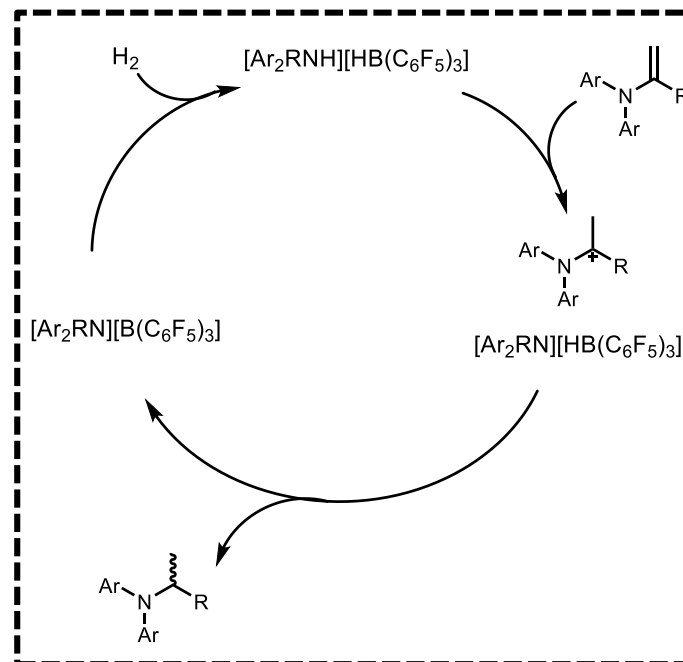
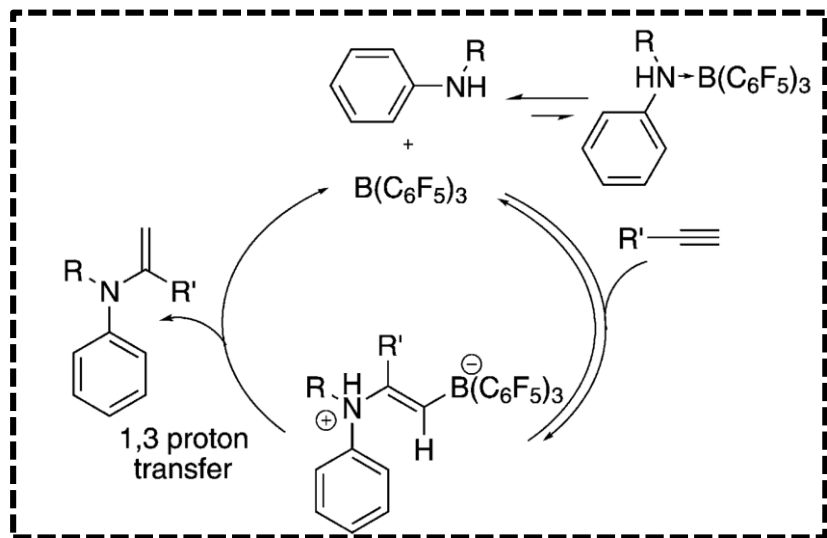
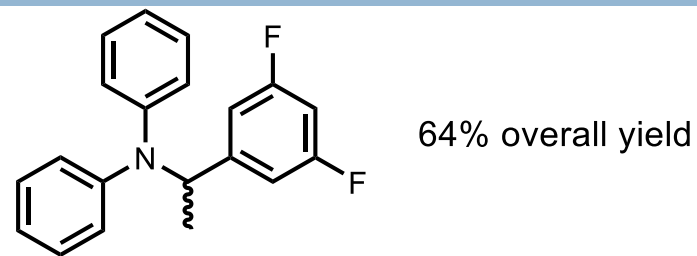
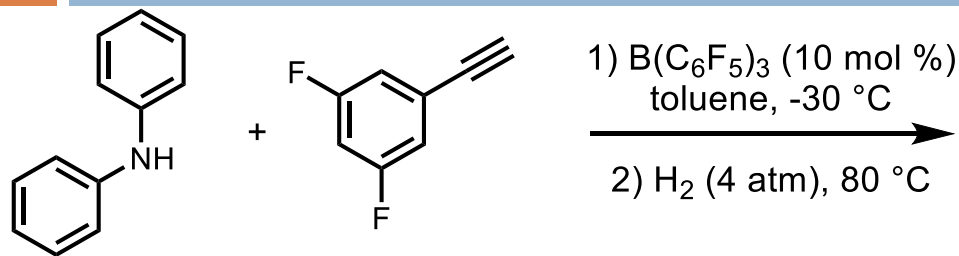
- 1) Identify the intermediate (isolateable) after the 1st step
- 2) Write a catalytic cycle for the generation of this intermediate
- 3) Write a 2nd catalytic cycle for the generation of amine product
- Bonus) The reaction requires the slow addition of alkyne – rationalize this

Extra info:

- Intermediate ^1H NMR has singlets at 5.25 and 4.90 ppm
- Intermediate $[\text{M}+\text{H}]^+$ 308.13

Group Problem: Answer

48

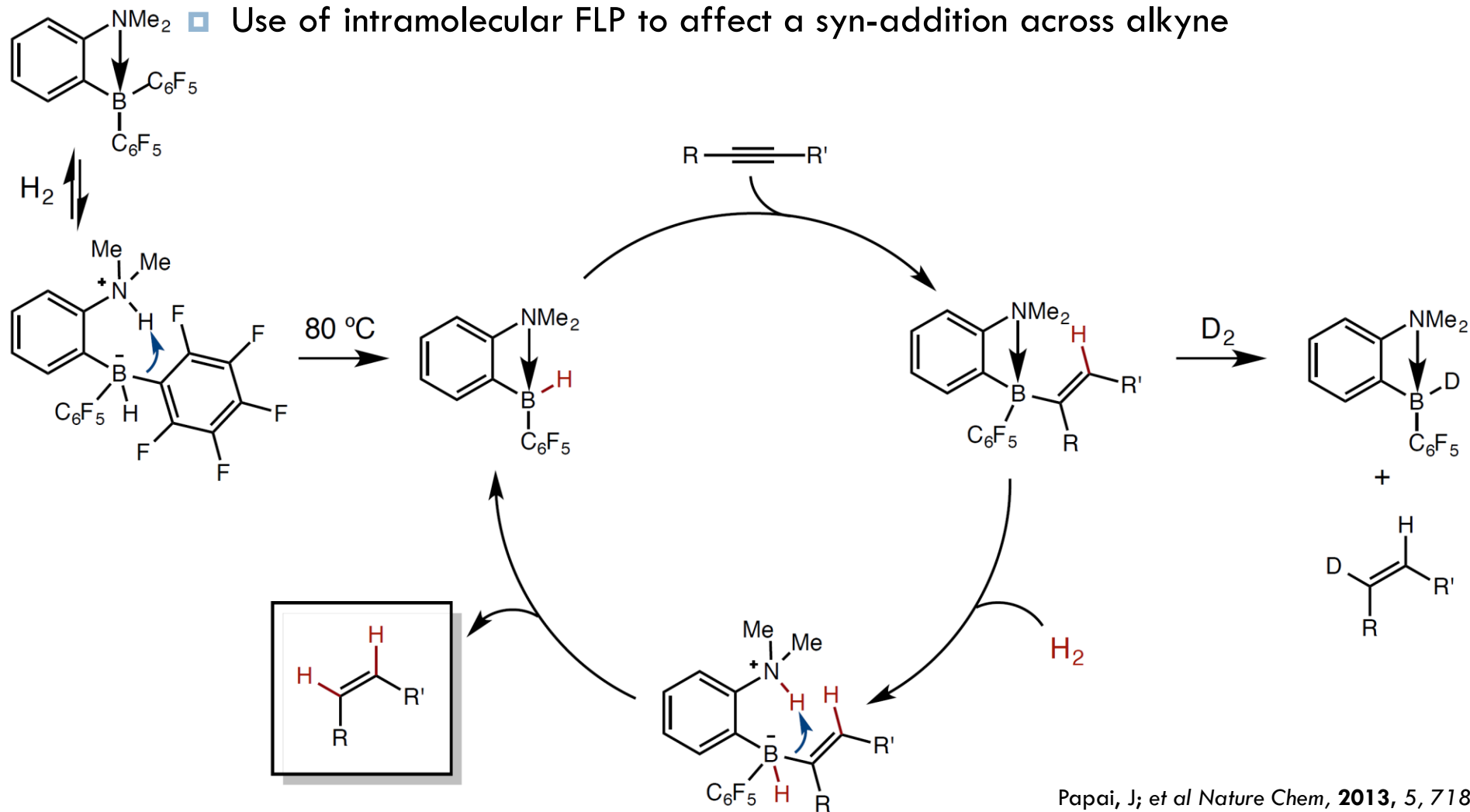


Applications – Syn-hydrogenation of alkynes

49

□ Papai – 2013

□ Use of intramolecular FLP to affect a syn-addition across alkyne

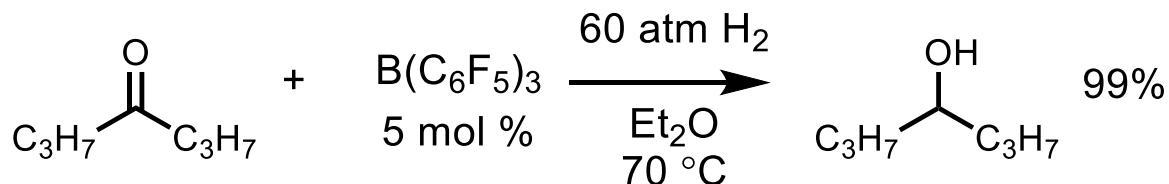
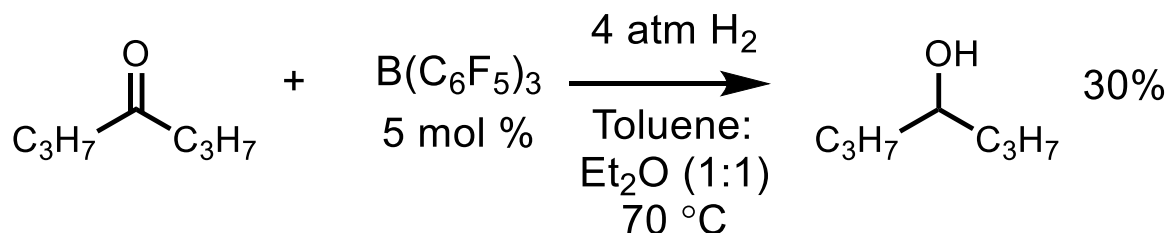
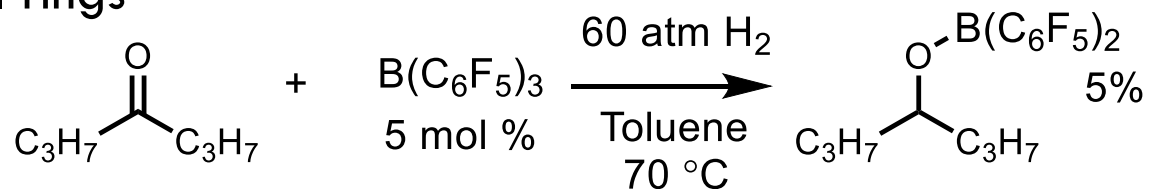


Applications – Reduction of carbonyls

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□ Stephan – 2014

- Use of a moderate strength LA avoids previous B-C cleavage of the aryl rings

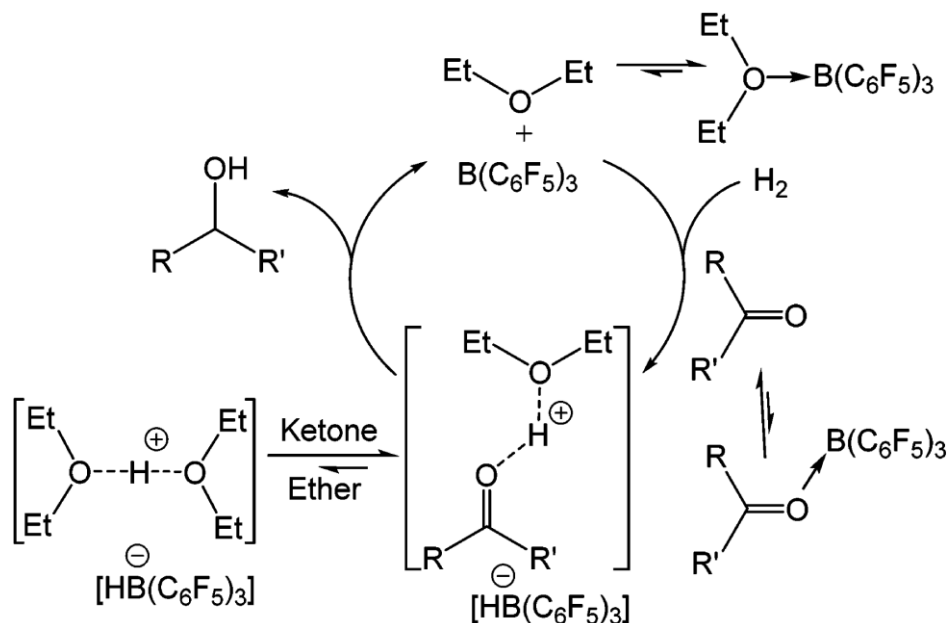
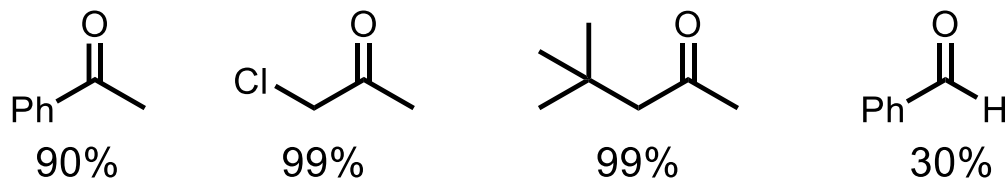


Applications – Reduction of carbonyls

51

□ Stephan – 2014

- Highly effective for various ketone and even benzaldehyde



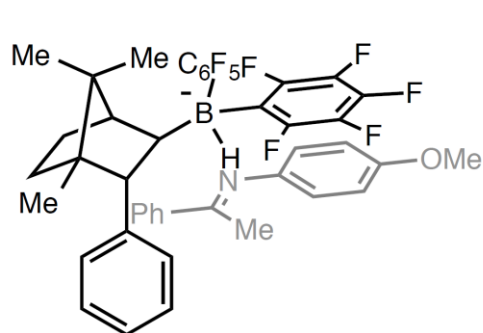
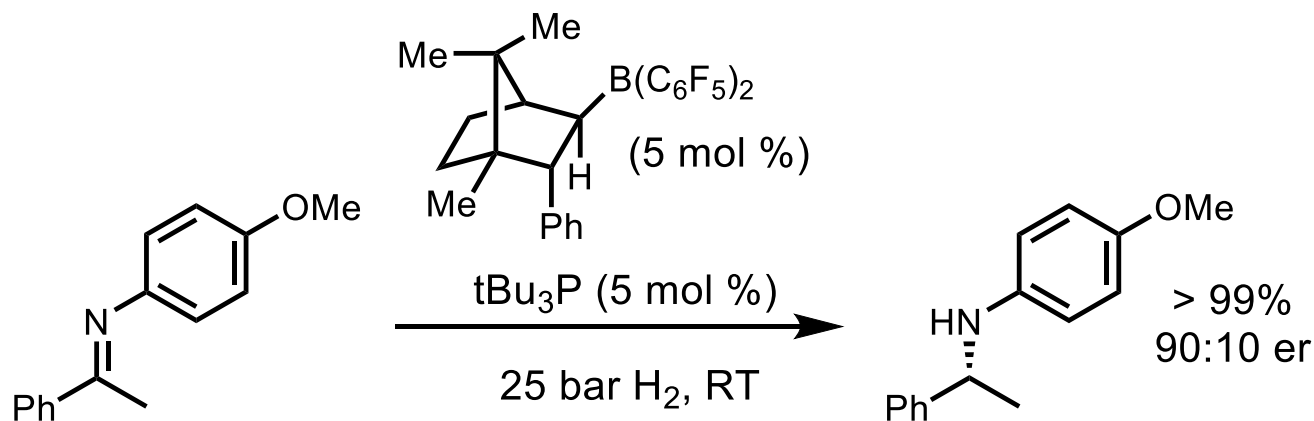
- Critical use of Et₂O to modulate acidity of the proton and activate carbonyl towards hydride addition

Applications – Asymmetric Hydrogenation

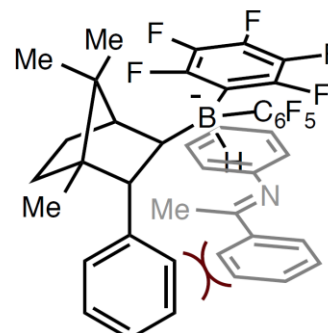
52

□ Klankermayer – 2010

- ▣ Use of chiral boron LA to induce an asymmetric imine reduction



favored approach



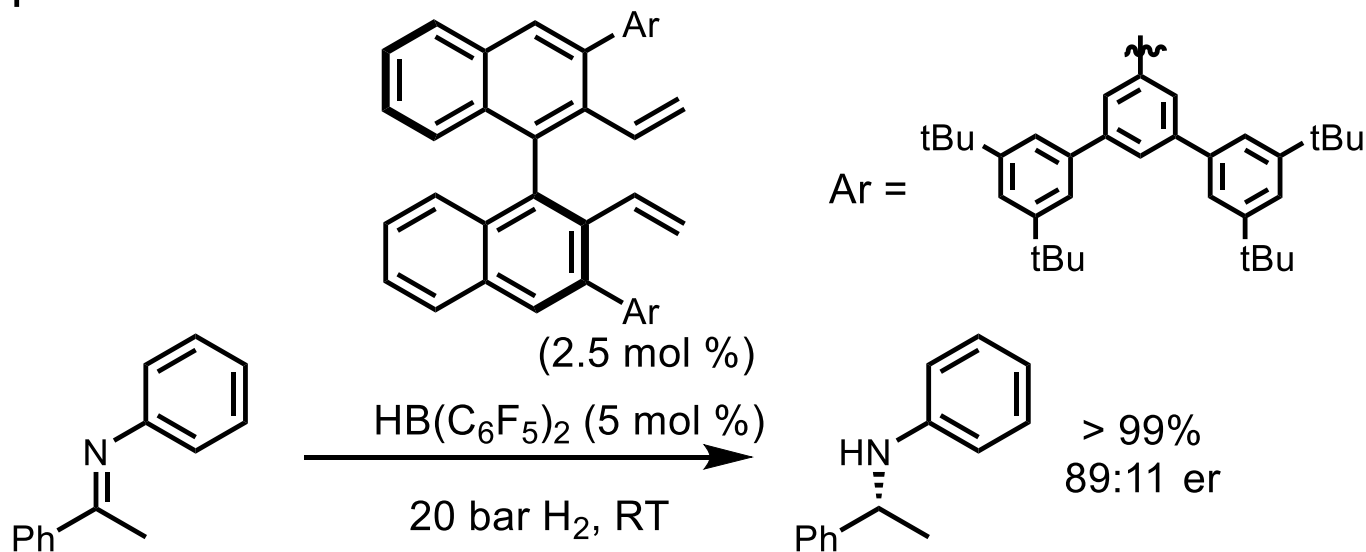
disfavored approach

Applications – Asymmetric Hydrogenation

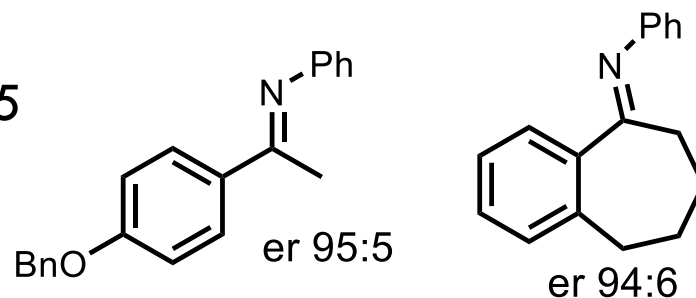
53

□ Du – 2013

- Application of chiral dienes for in situ formation of chiral boron LA



- Able to achieve er's up to 95:5



Conclusion

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- Frustrated Lewis Pairs are a new, but rapidly growing field
 - ▣ Not covered in this talk, but has application in small molecule (CO , CO_2 , N_2O , SO_2 capture) and reduction
- Complementary reactions to TM based methods
 - ▣ Without the side effects of using TM
- Substrate scope steadily increasing
- Asymmetric methods exist, but have room for improvement in selectivity and substrates
- Wide variety of types of FLP possible – allowing for dialing into a specific need or application

References

- Lewis, G. N. *Valence and the Structure of Atoms and Molecules*, Chemical Catalogue Company; New York, 1923
- Manners, I, *et al. Chem. Rev.* **2010**, *110*, 4079
- Brown, H. C.; Schlesinger, H. I. *JACS*, **1942**, *64*, 325-329.
- Wittig, G; Benz, E. *Chem. Ber.* **1959**, *92*, 1999-2013
- Tochtermann, W. *ACIE*, **1966**, *5*, 351-371
- Stephan, D. W., *et al. Inorg. Chim. Acta* **2006**, 3066
- Stephan, D. W., *et al. Science*, **2006**, *314*, 1124-1126
- Stephan, D. W., *et al. JACS*, **2007**, *129*, 1880
- Pápai, I.; *et al ACIE*, **2008**, *120*, 2469-2472
- Erker, G. *ACIE*, **2010**, *49*, 1402-1405
- Pápai, I.; *et al JACS*, **2013**, *135*, 4425-4437.
- Pápai, I.; *et al Dalton Trans*, **2012**, *41*, 9023
- Macchioni, A.; *et al JACS*, **2013**, *136*, 112
- Grimme, S.; *et al Isr. J. Chem.* **2015**, *55*, 235
- Stephan, D. W., *et al. ACIE*, **2007**, *46*, 8050-8053
- Stephan, D. W., *et al Chem. Comm.*, **2008**, 1701
- Grimme, S; *et al ACIEE*, **2012**, *51*, 10164
- Mahdi, T.; Stephan, D. W. *ACIEE*, **2013**, *52*, 12418
- Papai, J; *et al Nature Chem*, **2013**, *5*, 718
- Stephan, D. W.; *et al JACS*, **2014**, *136*, 15809
- Klankermayer, J; *et al ACIEE*, **2010**, *49*, 9475
- Du, H; *et al JACS*, **2013**, *135*, 6810