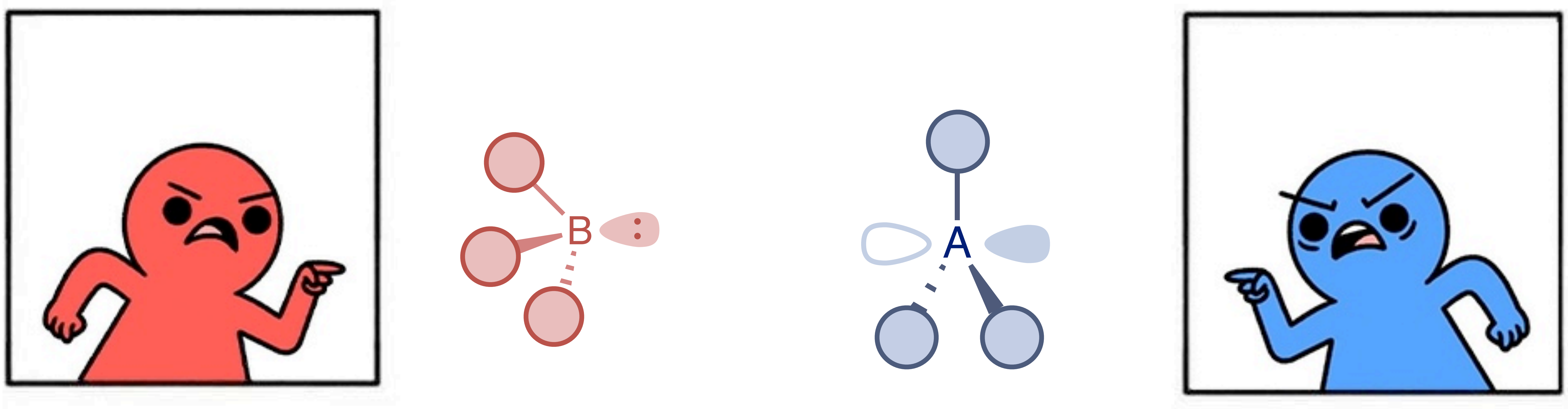
Frustrated Lewis Acid-Base Pair



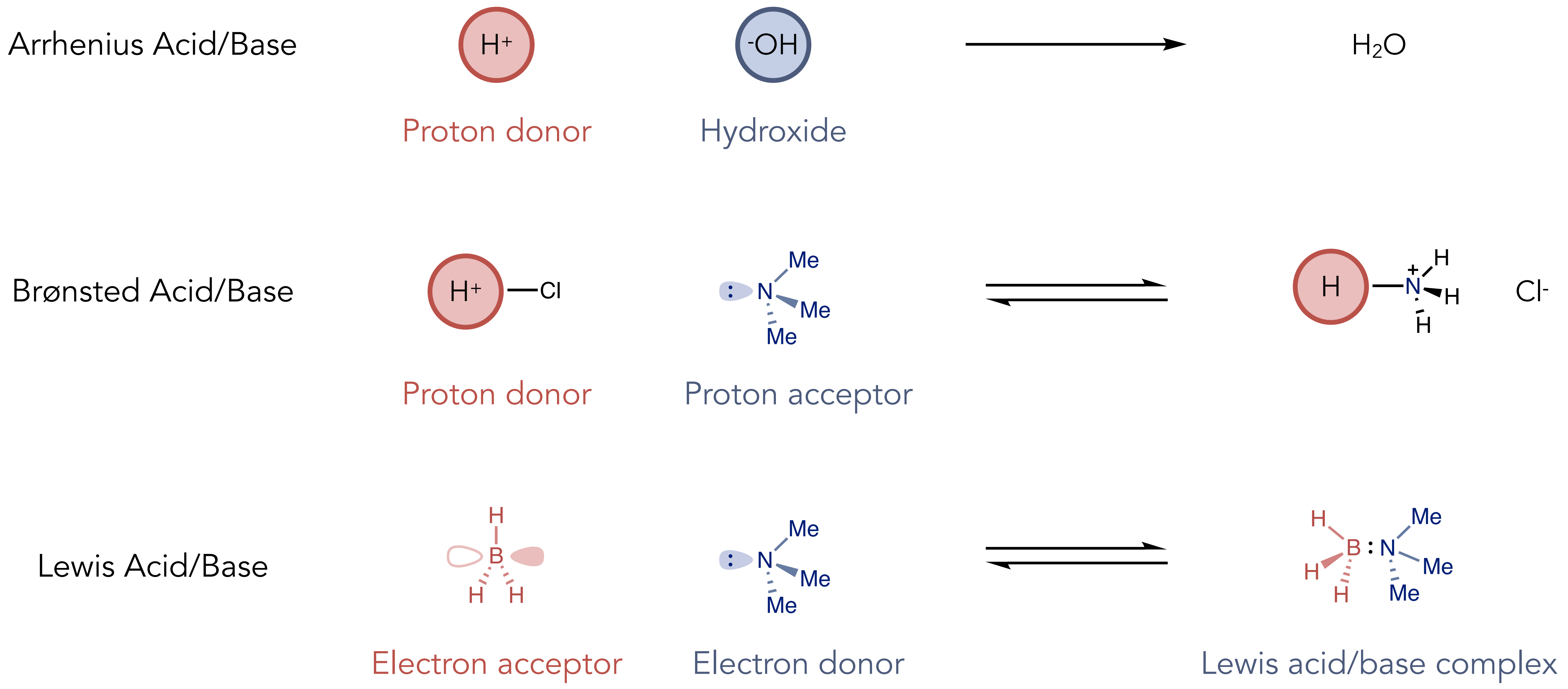
Lit Talk, MacMillan lab

Mar 12th, 2024

Alina Chen

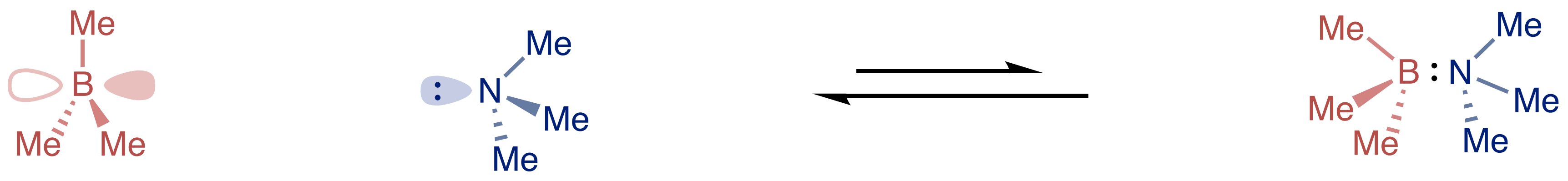
Acid-Base Chemistry in Daily Life

The Evolution of Acid & Base Definitions



Frustrated Lewis Acid-Base Pairs

Lewis Acid/Base



Electron acceptor

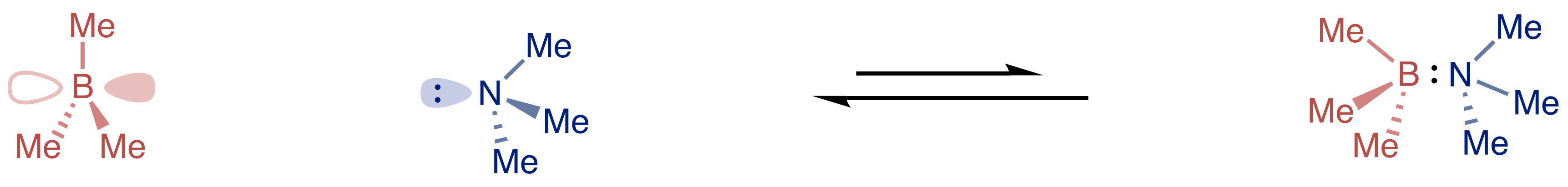
Electron donor

Lewis Acid/Base pairs that could not form stable dative bonds due to steric repulsion or orbital energy mismatch are called FLPs

Fontaine, F-G.; Stephan, D.W. *Phil. Trans. R. Soc. A* **2017**, *375*:20170004.

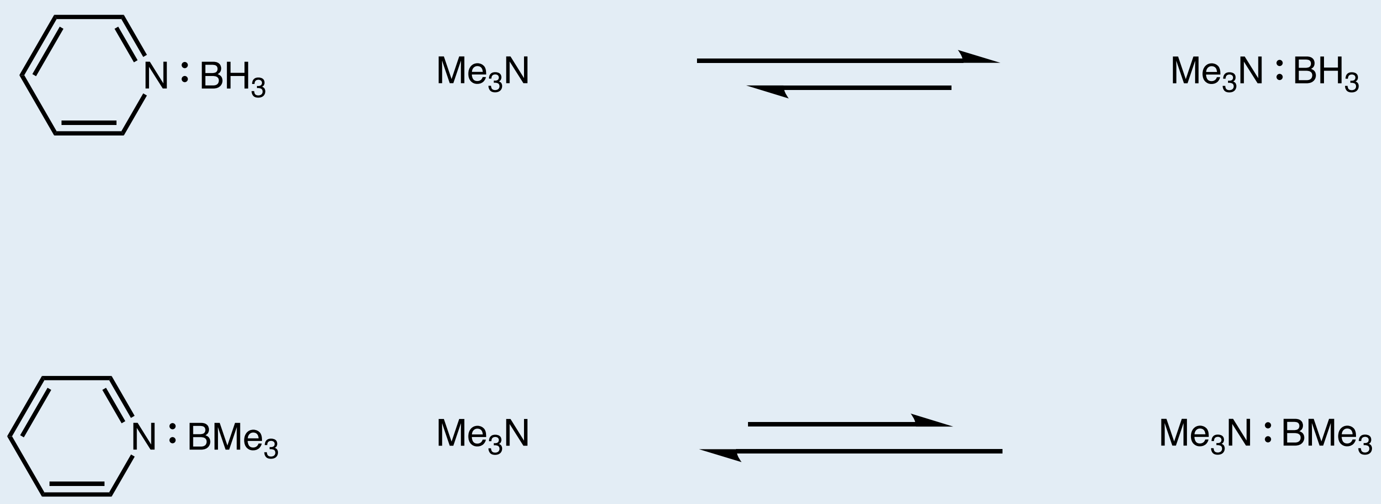
Frustrated Lewis Acid-Base Pairs

Lewis Acid/Base



Electron acceptor

Electron donor



Brown, H. C.; Schlesinger, H. I.; Cardon, S. Z. *J. Am. Chem. Soc.* **1942**, *64*, 325-329.

The Discovery & Development of Frustrated Lewis Pairs

$Me_3N:BMe_3$

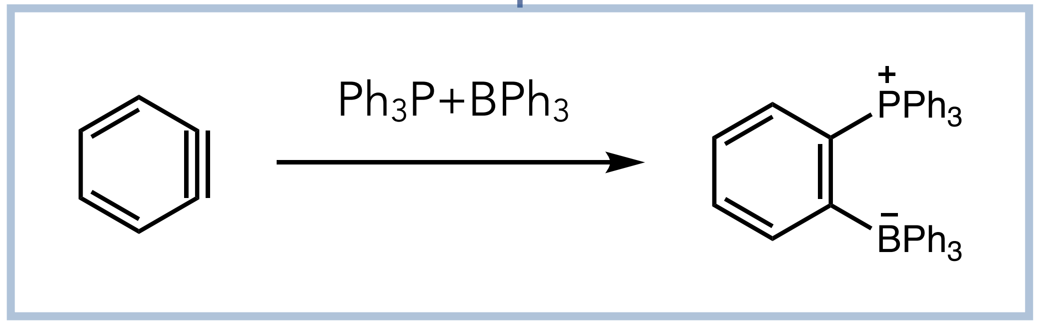
1942

Wittig, G., Benz, E. *Chem. Ber.* **1959**, *92*, 1999–2013.

The Discovery & Development of Frustrated Lewis Pairs

1942

1959



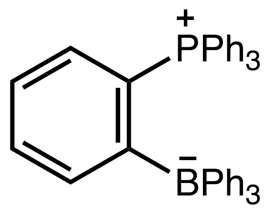
Wittig, G., Benz, E. *Chem. Ber.* **1959**, *92*, 1999–2013.

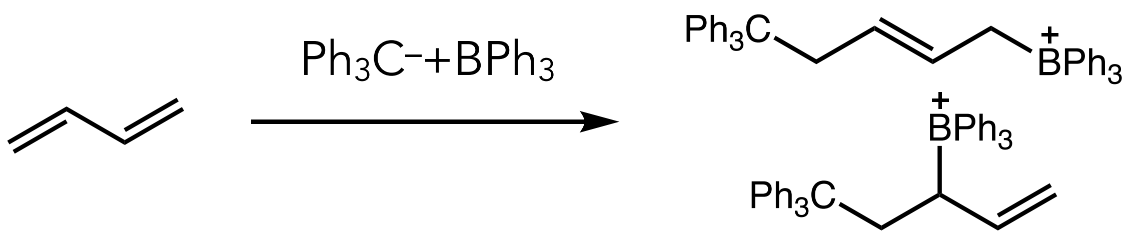
The Discovery & Development of Frustrated Lewis Pairs

$Me_3N : BMe_3$

1942

1959





1966

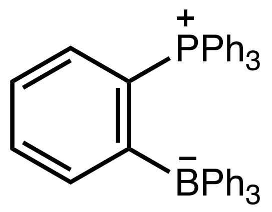
Tochtermann, W.. *Anger. Chem. Int. Ed.* **1966**, *5*, 351–371.

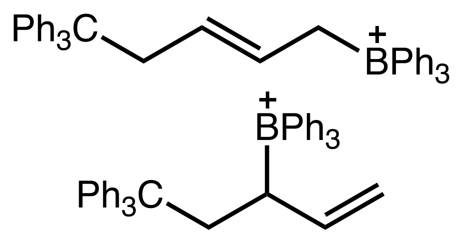
The Discovery & Development of Frustrated Lewis Pairs

$Me_3N : BMe_3$

1942

1959



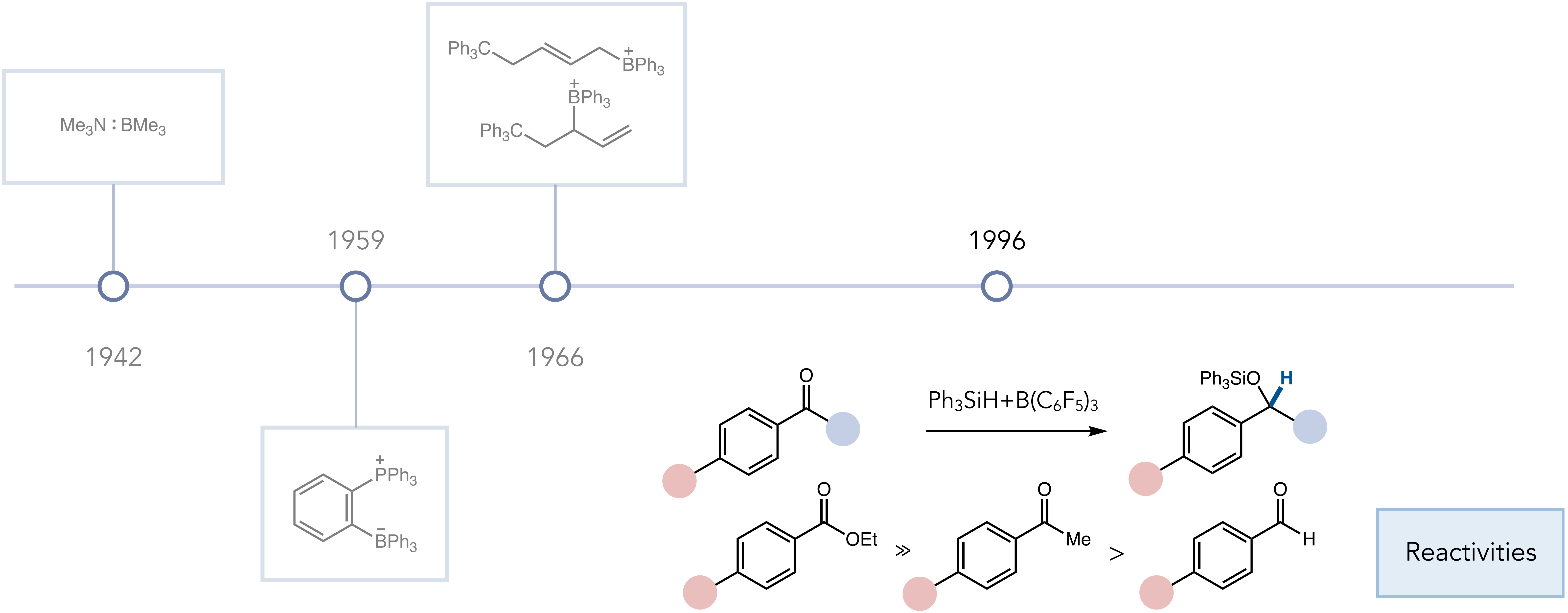


1966

"Antagonistic pair"

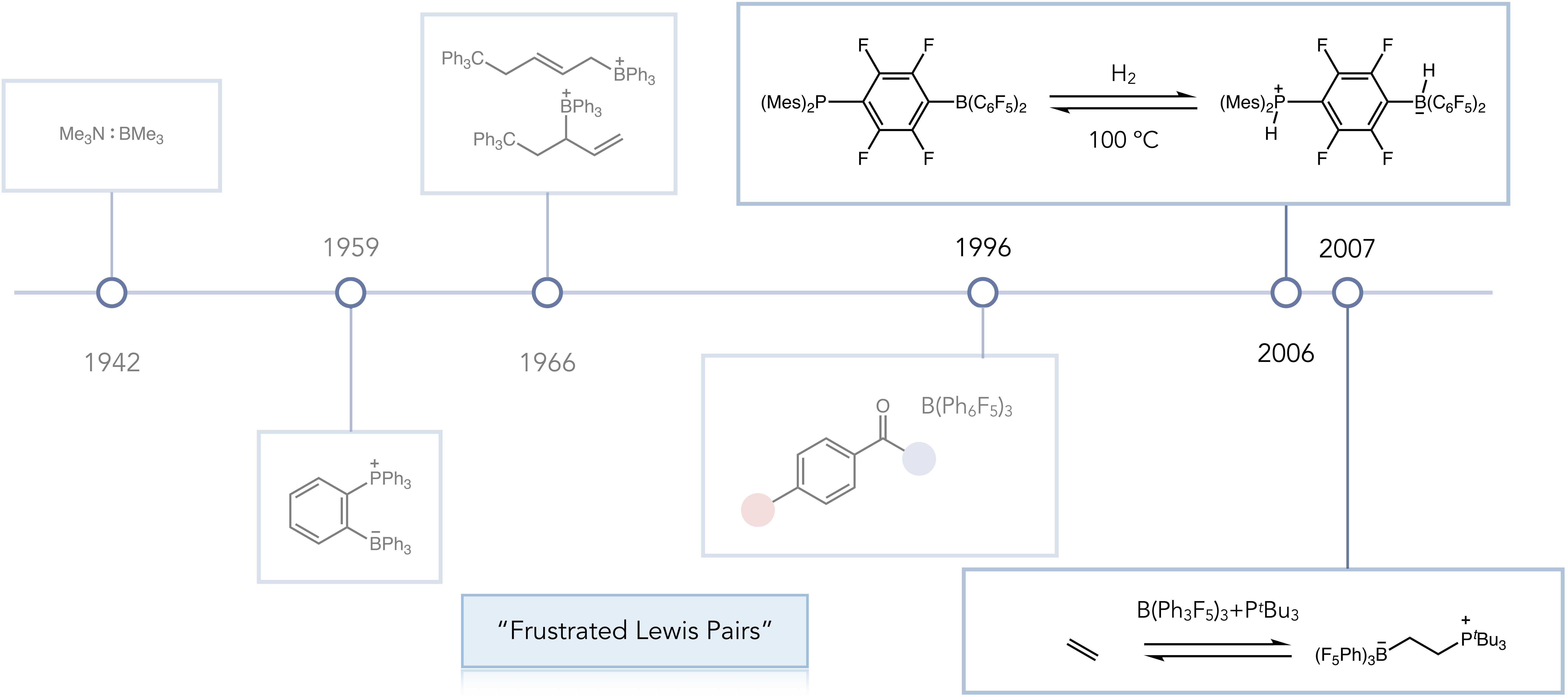
Tochtermann, W.. *Anger. Chem. Int. Ed.* **1966**, *5*, 351–371.

The Discovery & Development of Frustrated Lewis Pairs



Parks, D. J.; Piers, W. E.. *J. Am. Chem. Soc.* **1996**, *118*, 9440–9441.

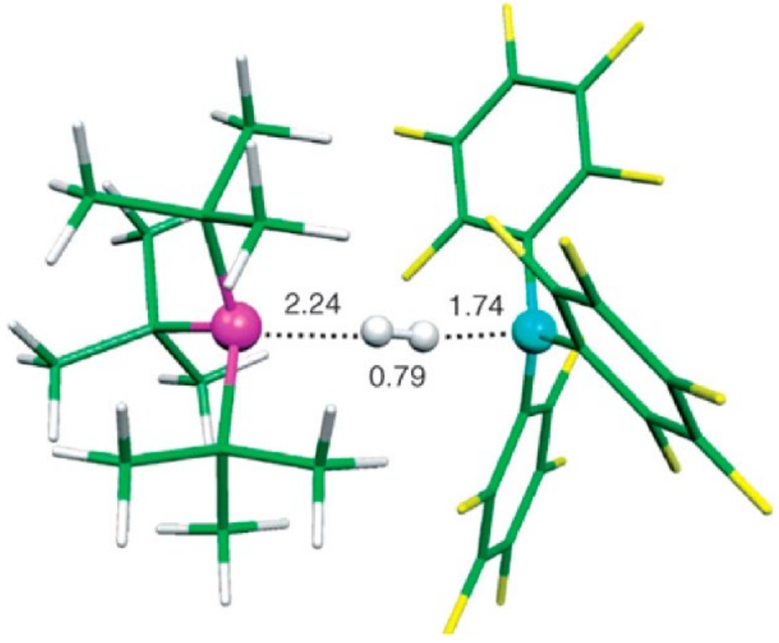
The Discovery & Development of Frustrated Lewis Pairs



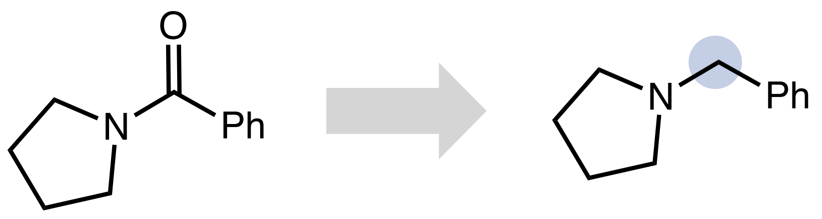
McGahill, J. S. J.; Welch, G. C.; Stephan, D. W.. *Angew. Chem. Int. Ed.* **2007**, *46*, 4968–4971.

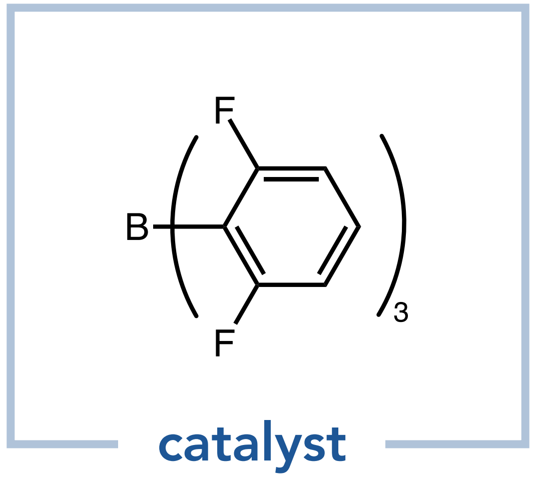
The Discovery & Development of Frustrated Lewis Pairs

Mechanism & Proof of Concept

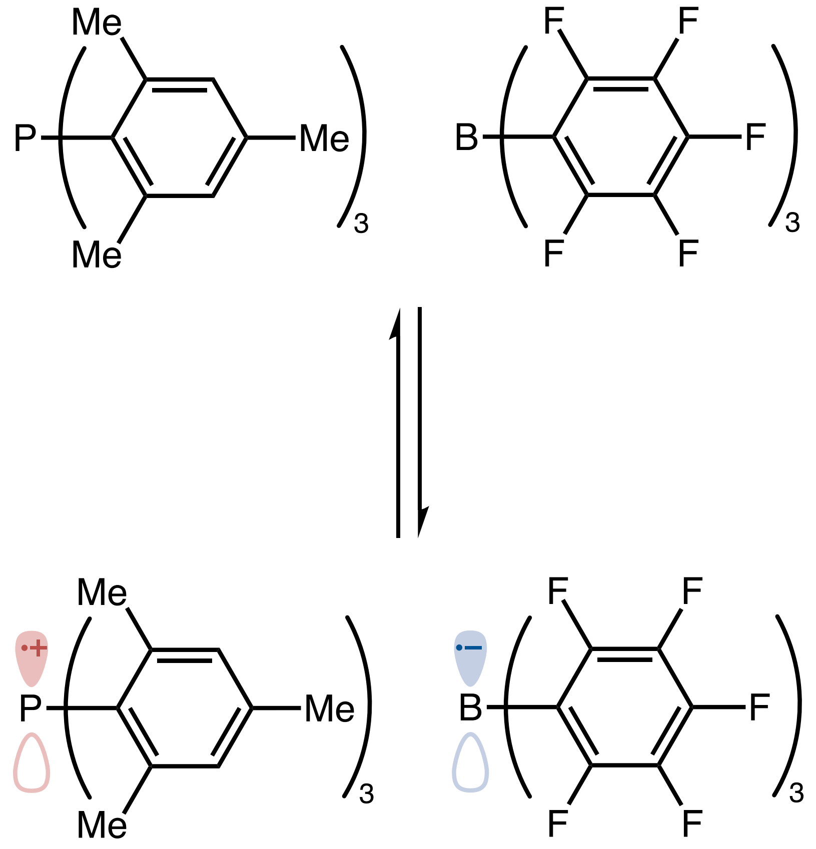


Application in Organic Reactions



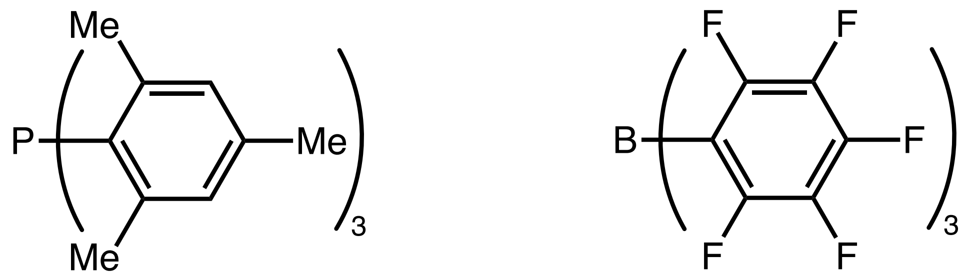


Redefining FLP & FRP



Insight Into FLP Adducts

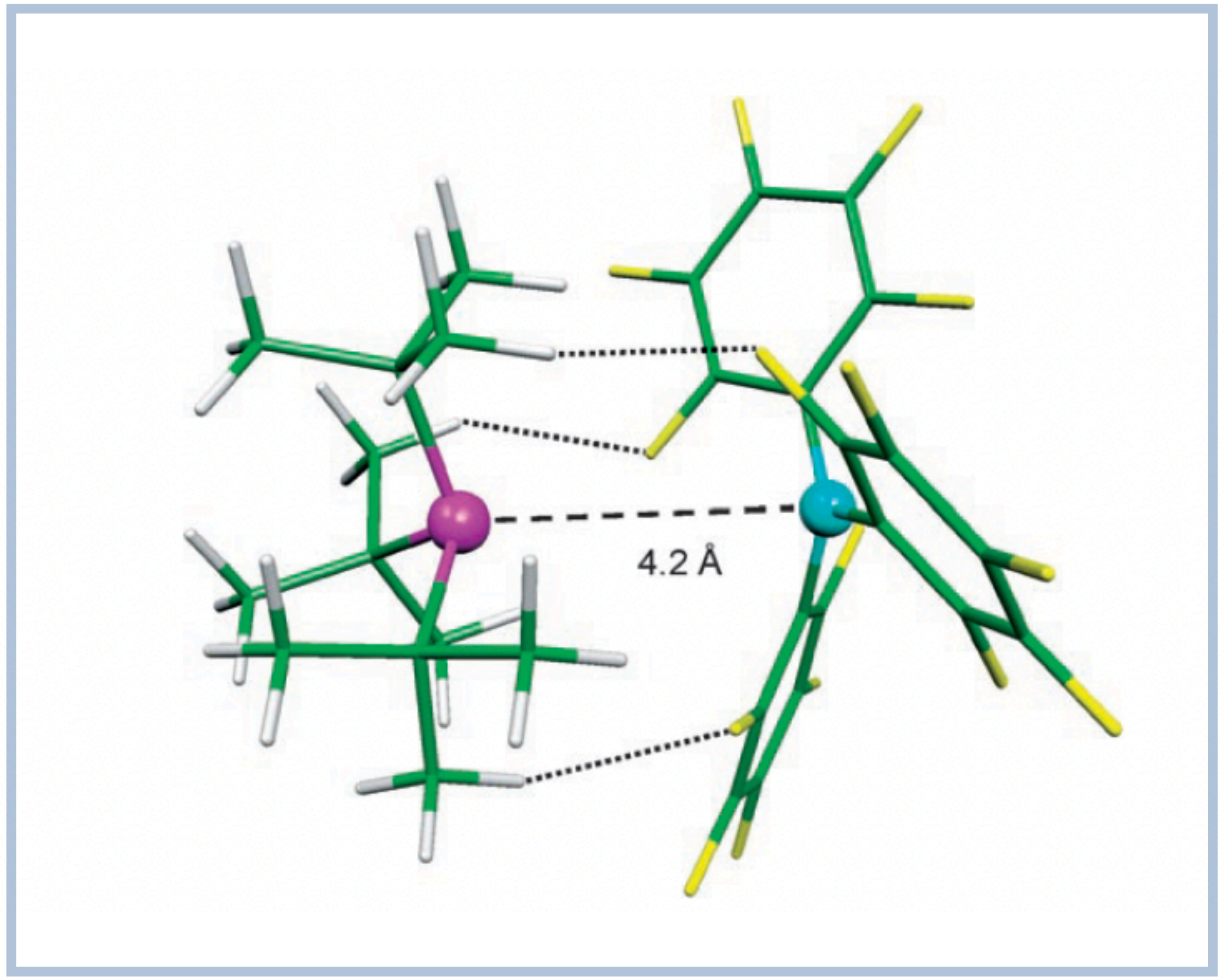
Lewis Acid/Base pairs that could not form stable dative bonds due to steric repulsion or orbital energy mismatch are called FLPs

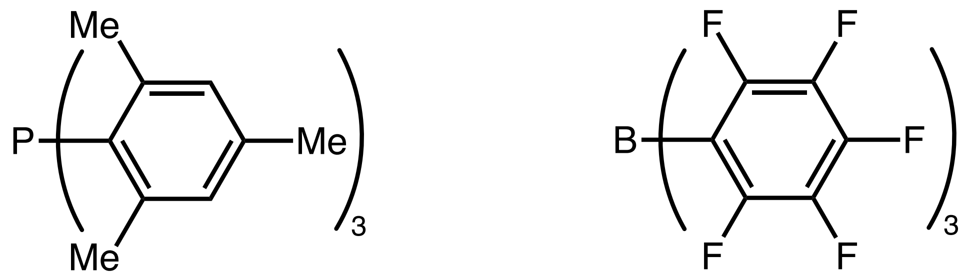


No detection of Lewis Acid/Base pairs by NMR at 25 °C or -50 °C

Welch, G. C.; Stephan, D. W.. *J. Am. Chem. Soc.* **2007**, *129*, 7, 1880–1881.

Insight Into FLP Adducts





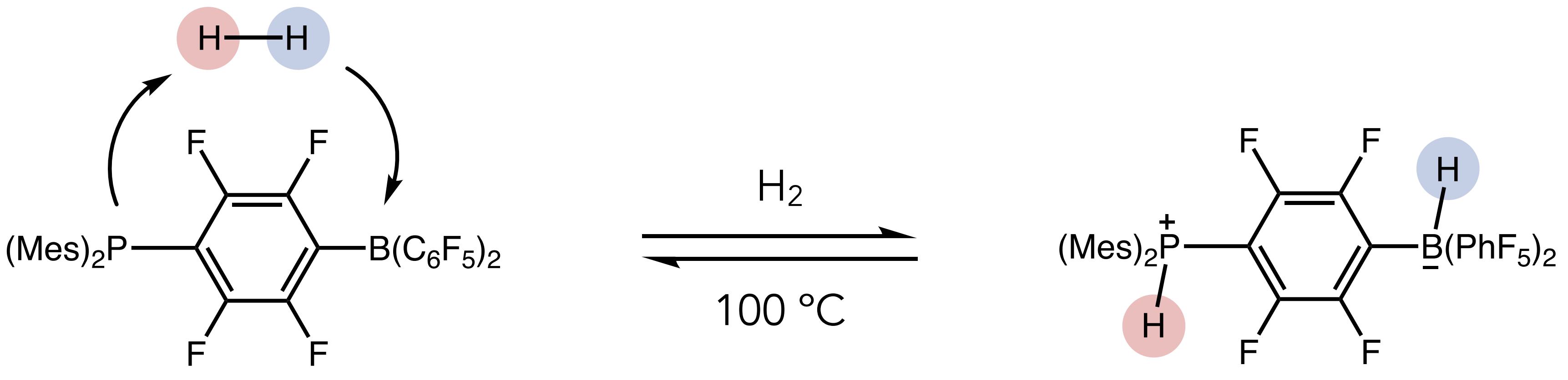
No detection of Lewis Acid/Base pairs by NMR at 25 °C or -50 °C

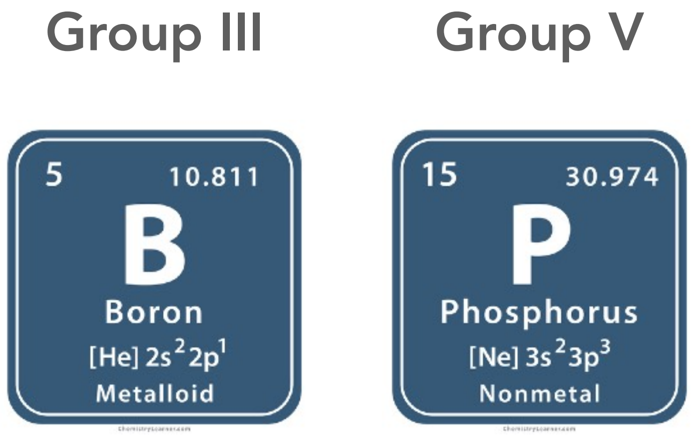
Van der Waals’ interactions

ΔE = -11.5 kacal/mol

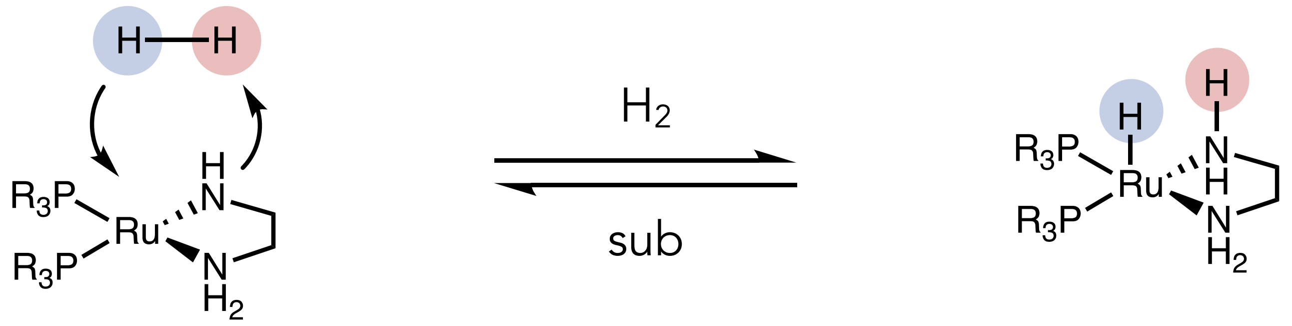
Welch, G. C.; Stephan, D. W.. *J. Am. Chem. Soc.* **2007**, *129*, 7, 1880–1881.
Rokob, T. A.; Hamza, A.; Stirling, A.; Soos, T.; Papai, I. *Angew. Chem.* **2008**, 120, 2469-2472.

FLP: Enzyme Mimetic

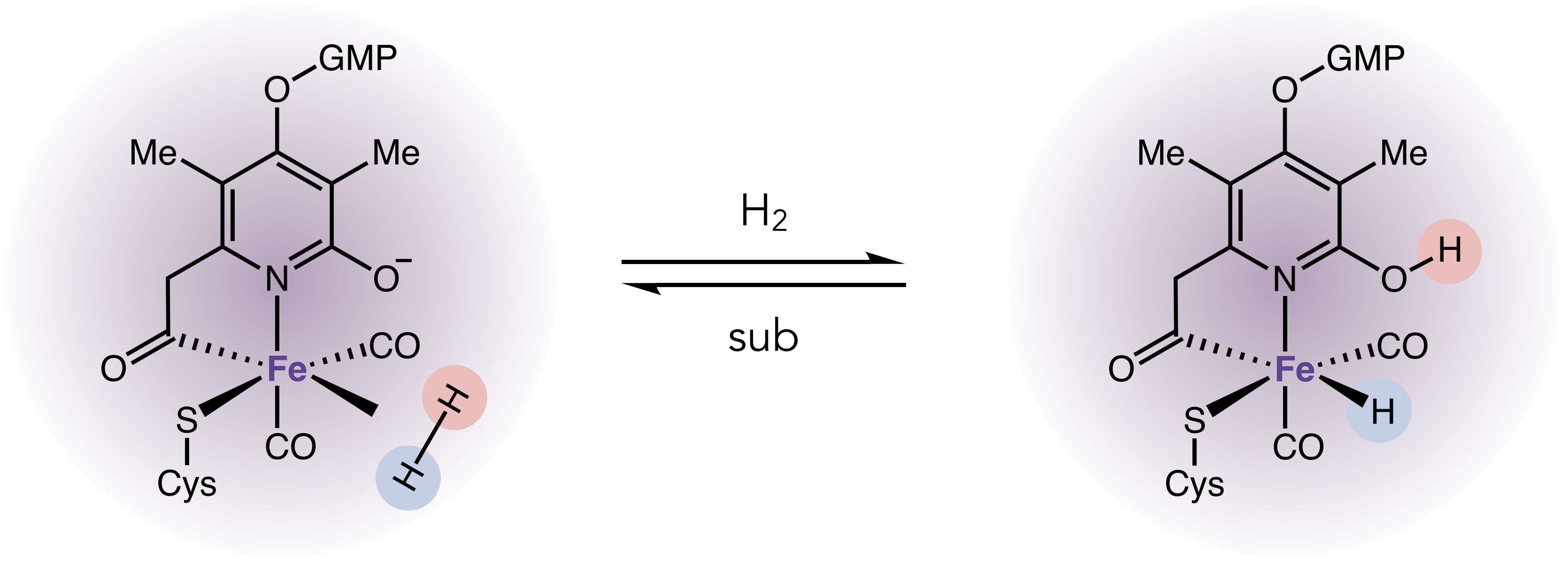




Transition Metal Catalysis

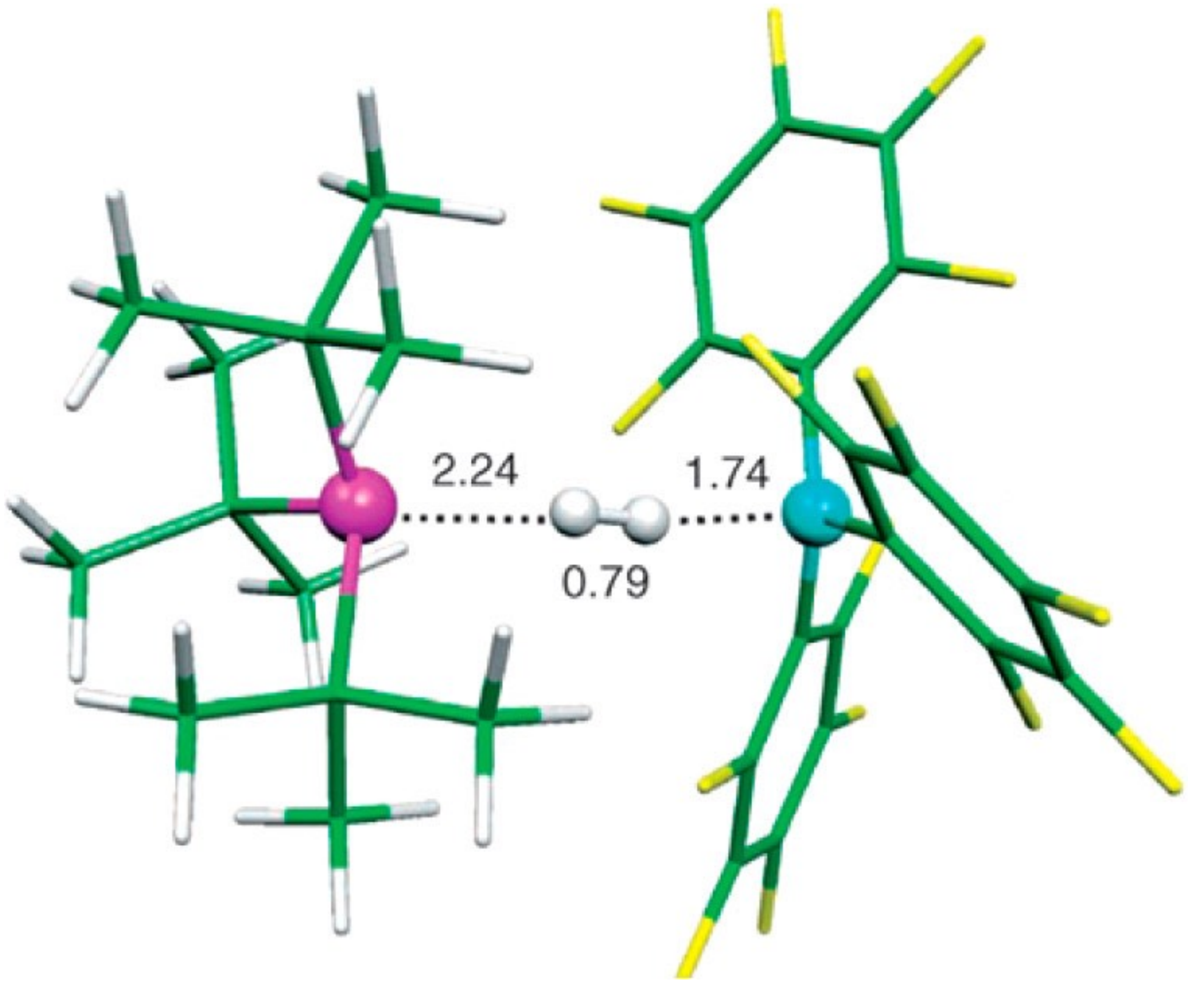


Enzymatic Catalysis



Sang, C.; Lai, Z.; Huang, G.; Pan, H. *Chem. Eur. J.* **2022**, *28*, e202201499.
Fontaine, F-G.; Stephan, D.W. *Phil. Trans. R. Soc. A* **2017**, *375*:20170004.

Mechanistic Studies For H_2 Splitting

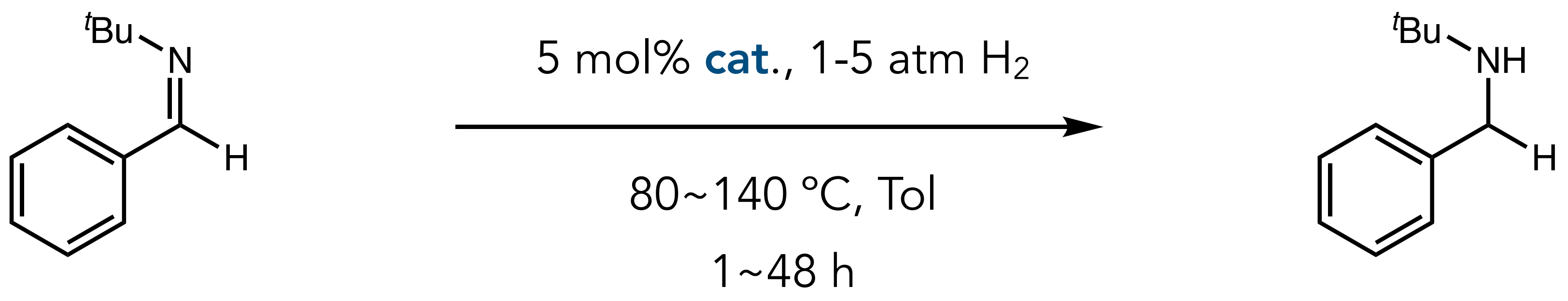


ΔG_{TS} = 10 kcal/mol*

Van der Waals' interactions matained

Rokob, T. A.; Hamza, A.; Stirling, A.; Soos, T.; Papai, I. *Angew. Chem*. **2008**, 120, 2469-2472.

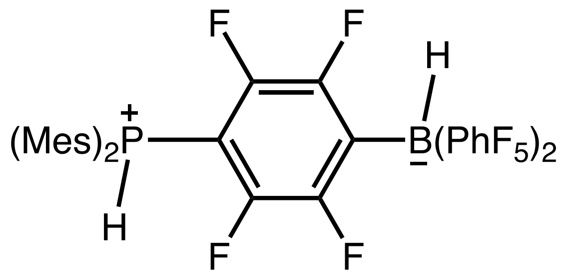
Hydrogenation of Imines With FLP



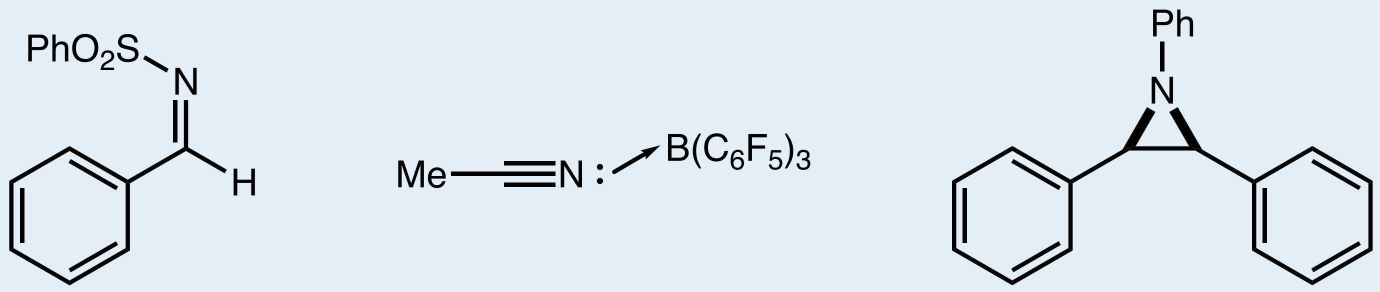
Imines

Amines

57~99%



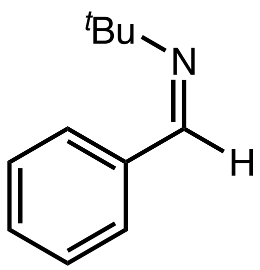
catalyst



10 examples

Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007,** *46*(42):8050-3.

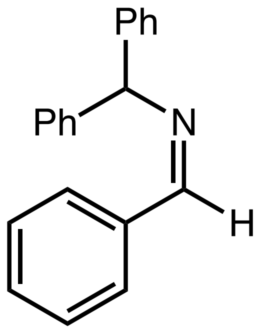
Mechanistic Insights into Hydrogenation of Imines



80 °C, 1 h

98% yield

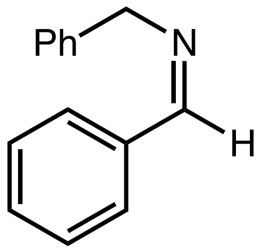
>



140 °C, 1 h

88% yield

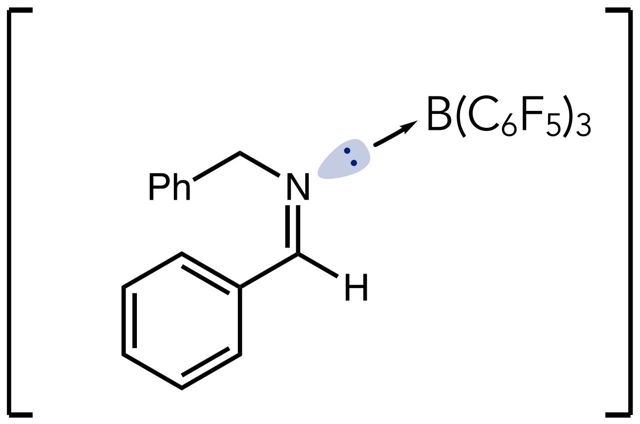
≫



120 °C, 48 h

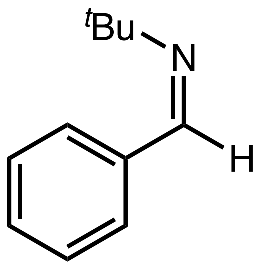
5% yield

Decreasing sterics



120 °C, 46 h

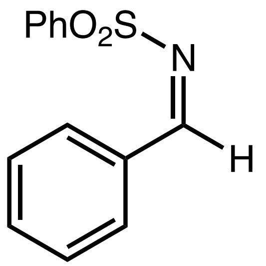
57% yield



80 °C, 1 h

98% yield

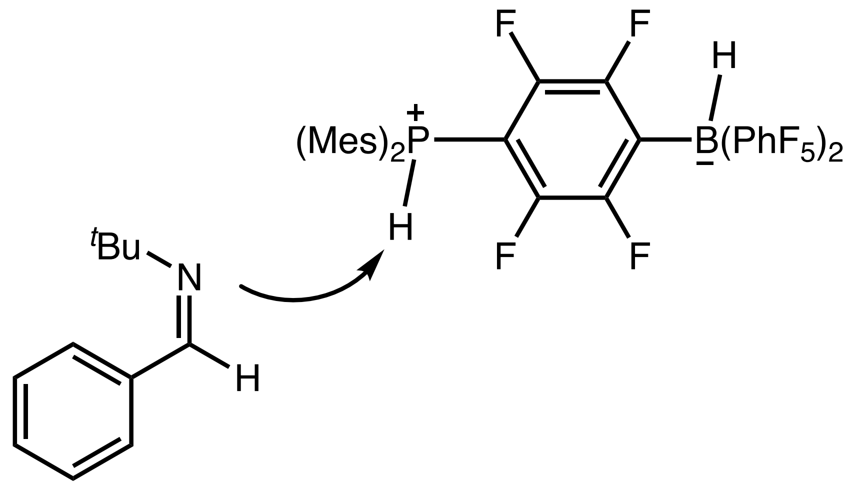
>



120 °C, 16 h

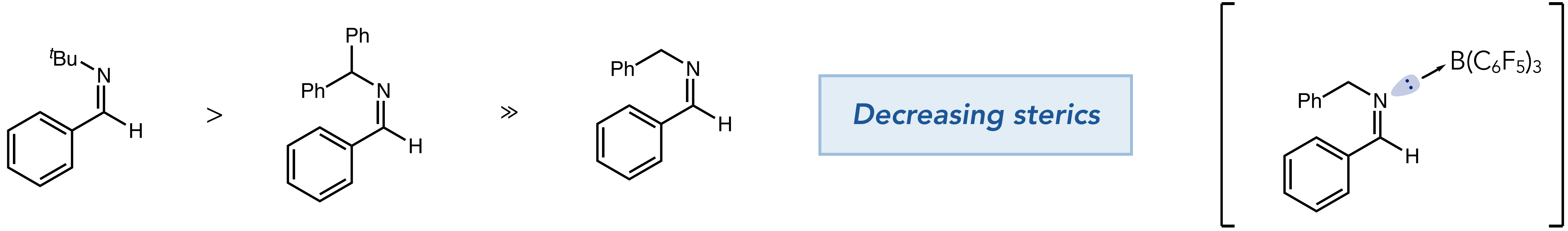
87% yield

Decreasing basicity



Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007,** *46*(42):8050-3.

Mechanistic Insights into Hydrogenation of Imines



80 °C, 1 h — *98% yield*

140 °C, 1 h — *88% yield*

120 °C, 48 h — *5% yield*

120 °C, 46 h — *57% yield*

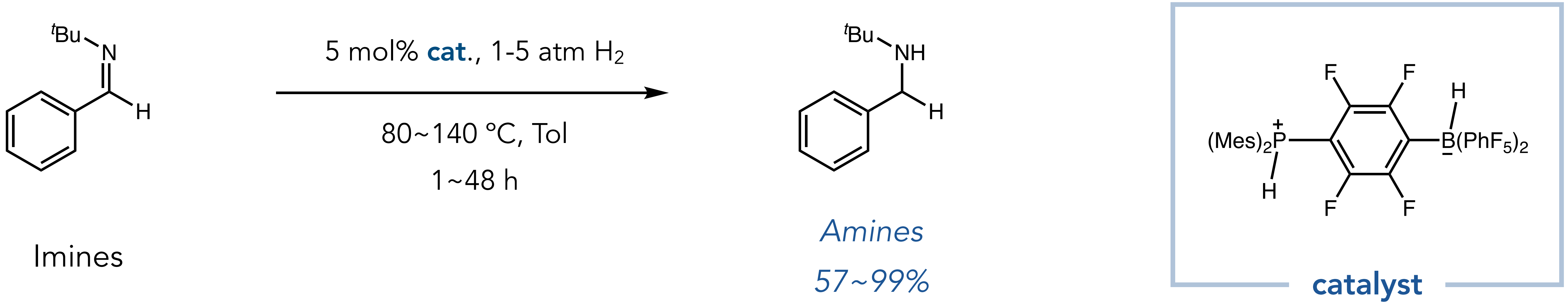
No reaction after 24 h at 120 °C

80 °C, 1 h — *98% yield*

120 °C, 16 h — *87% yield*

Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007,** *46*(42):8050-3.

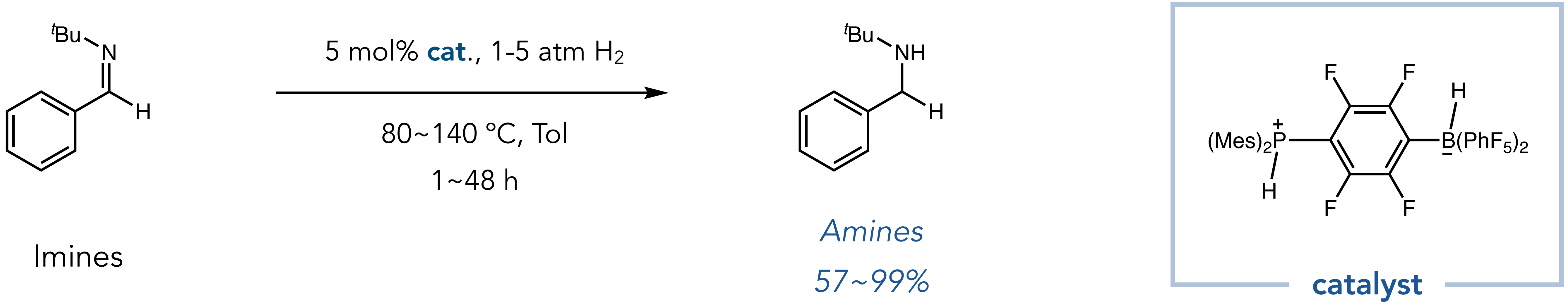
Mechanistic Insights into Hydrogenation of Imines

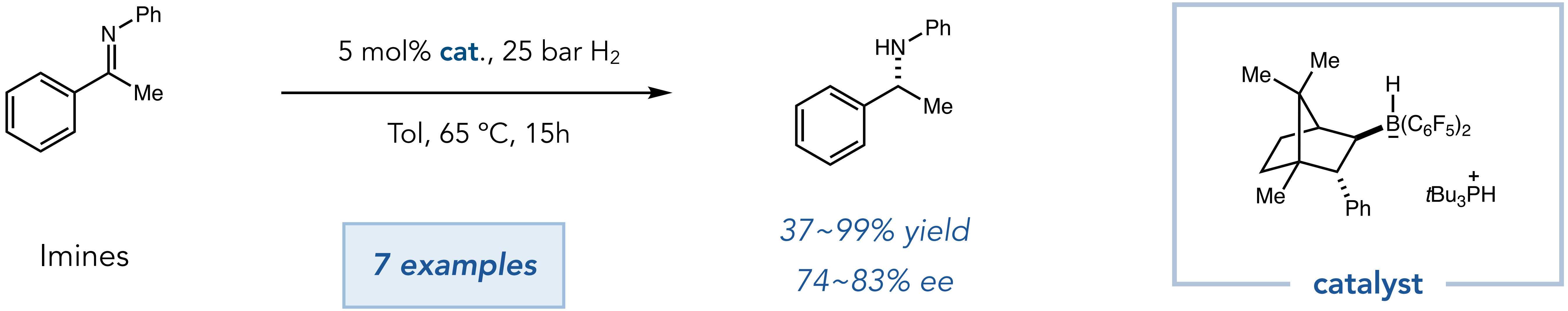


Favors more sterically encumbered, basic imines

Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007,** *46*(42):8050-3.

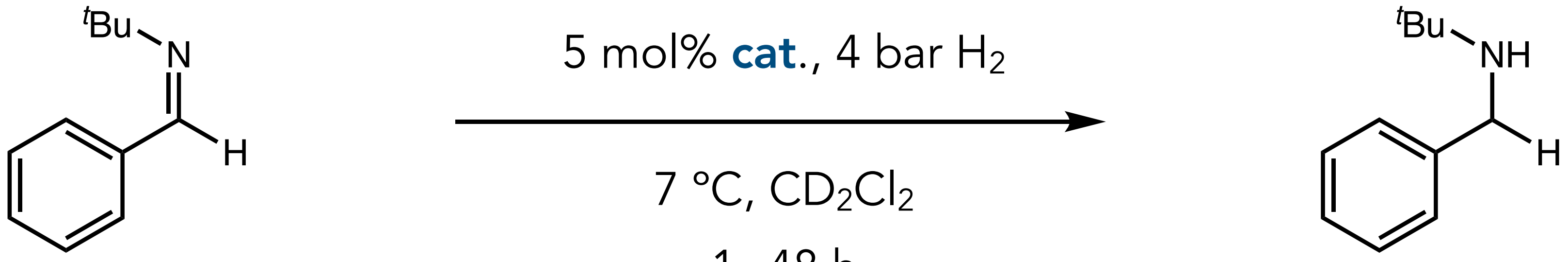
Hydrogenation of Imines With FLP





Chen, D.; Wang, Y.; Klankermayer, J. *Angew. Chem. Int. Ed.* **2010,** *49*, 9475-9478.
Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007,** *46*(42):8050-3.

SAR Studies: An Effort to Broaden the Scope

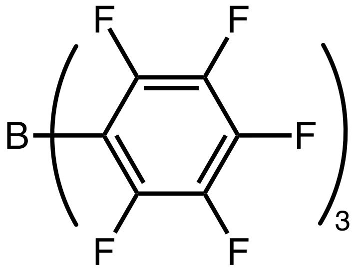


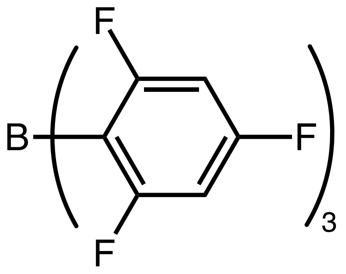
Imines

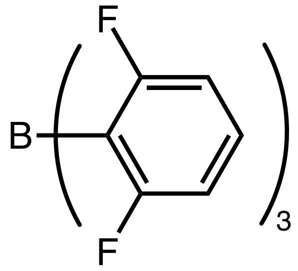
Amines

Problem: Strong LA has low functional group tolerance for basic moieties

Decreasing electrophilicity



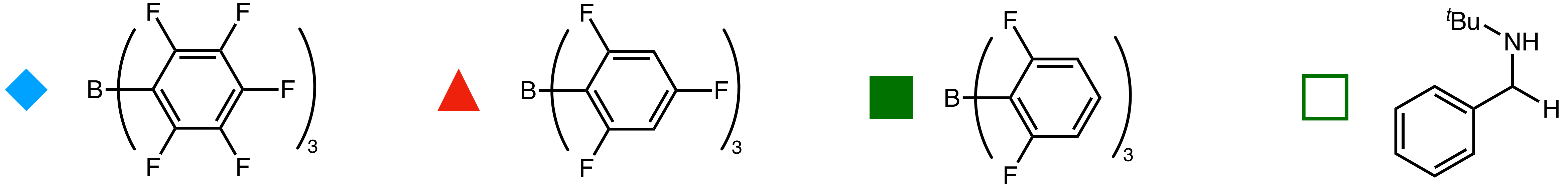




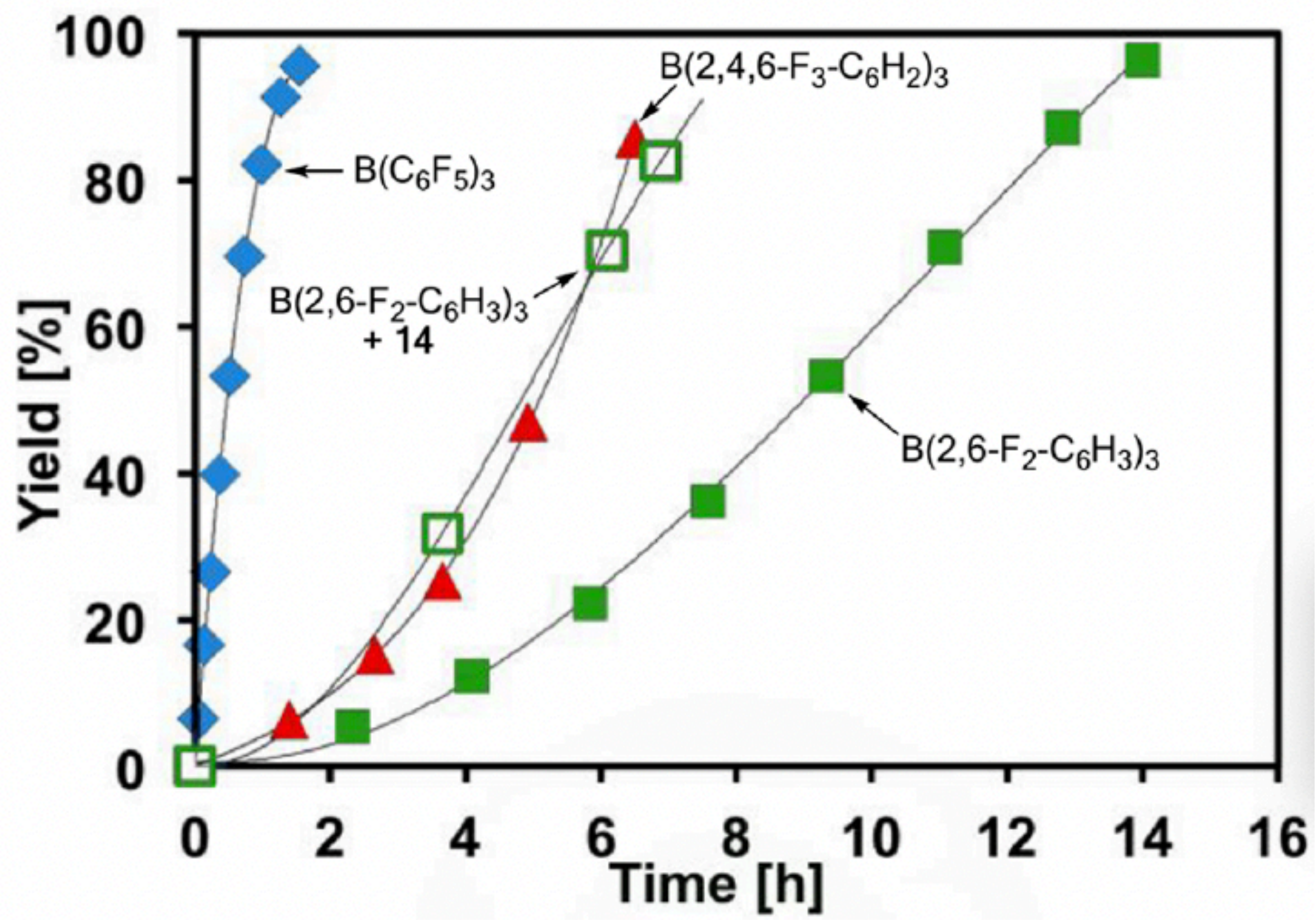
Global electrophilicity Index ω:	1.408	0.961	0.833

Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

The Role of Product As A Lewis Base



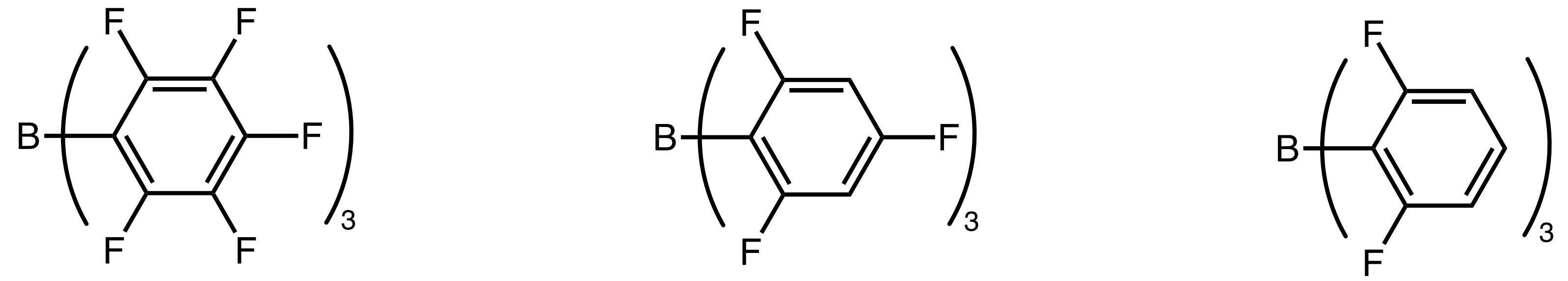
Global electrophilicity Index ω: 1.408 | 0.961 | 0.833 | + 5mol%



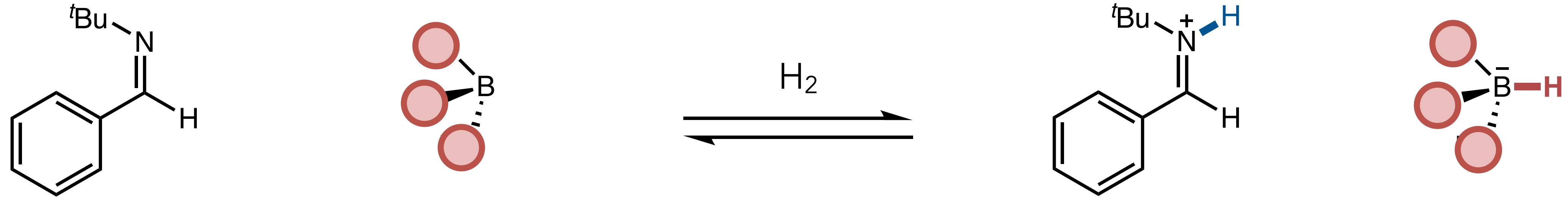
- *No bases is needed*
- *The more acidic the LA, the faster the reaction*
- *The reaction is auto induced catalytic*
- *With additional cat. LB, sluggish reactions can be improved*

Paradies, J. *Acc. Chem. Res.* **2023,** *56,* 821-834.

Relative Rate of SM and Pdt As A LB

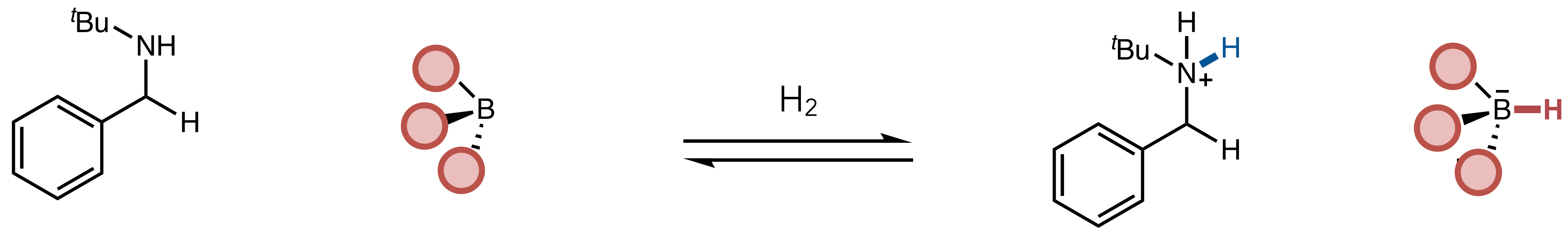


k1



SM as a LB

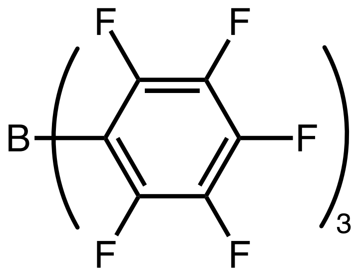
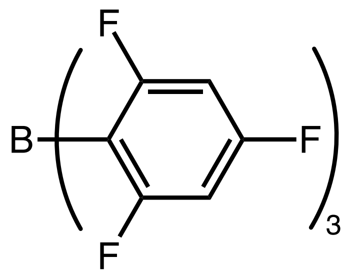
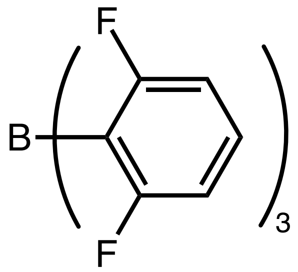
k2

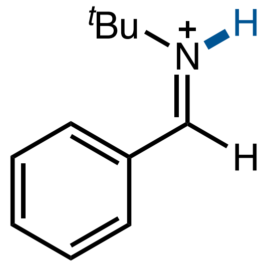
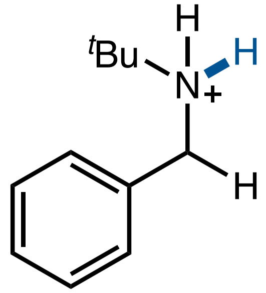


pdt as a LB

Paradies, J. *Acc. Chem. Res.* **2023,** *56,* 821-834.

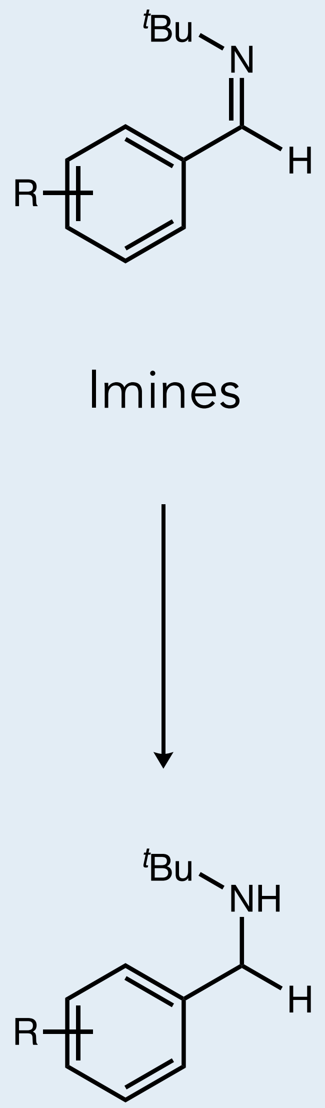
Relative Rate of SM and Pdt As A LB

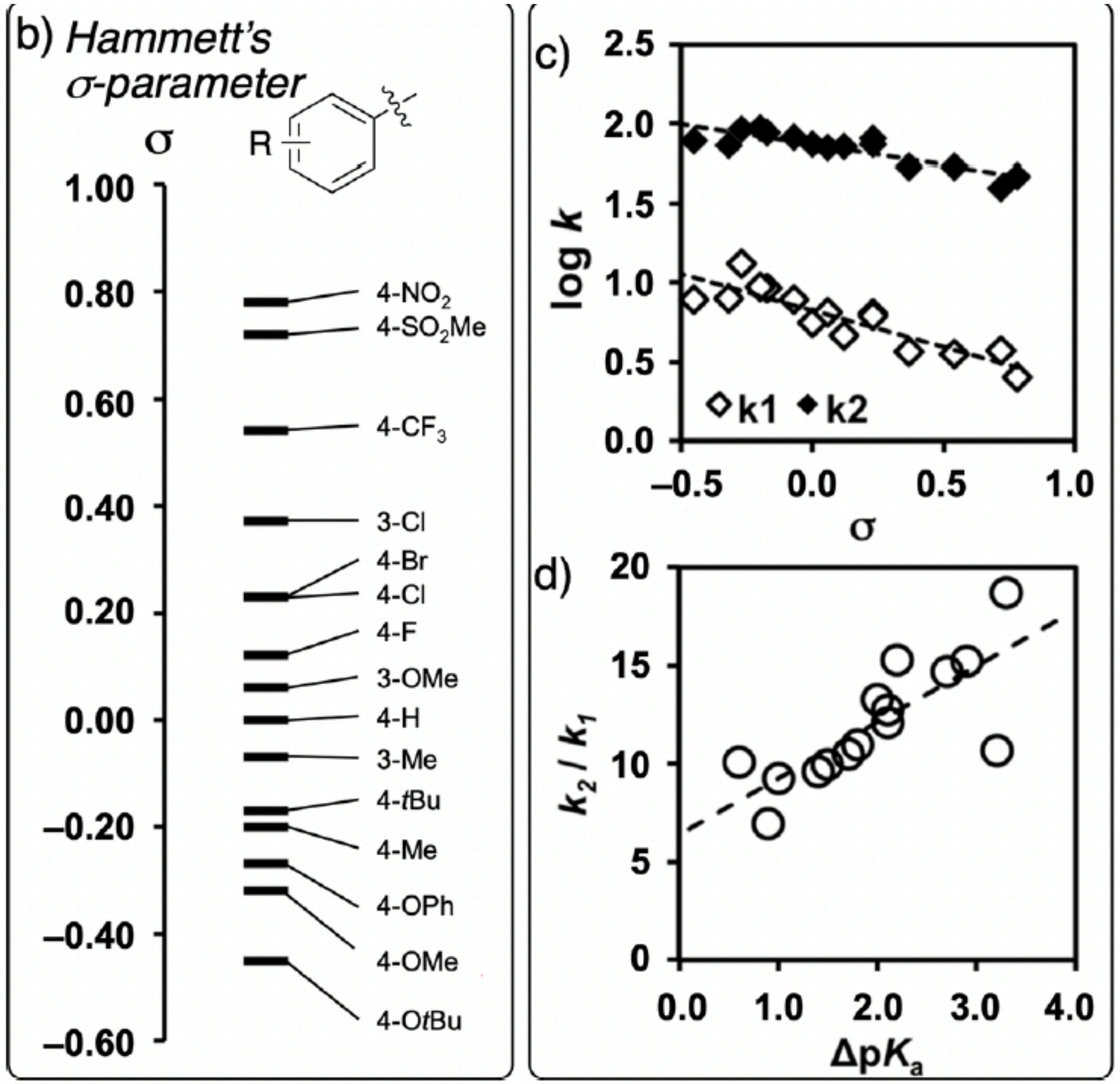




k1	ΔG* (kacal/mol) = 21.4±13.9	ΔG* (kacal/mol) = 24.1±3.5	ΔG* (kacal/mol) = 24.5±4.0	
k2	ΔG* (kacal/mol) = 20.1±23.7	ΔG* (kacal/mol) = 22.5±2.5	ΔG* (kacal/mol) = 22.7±2.3	

Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

The Role of Product As A Lewis Base

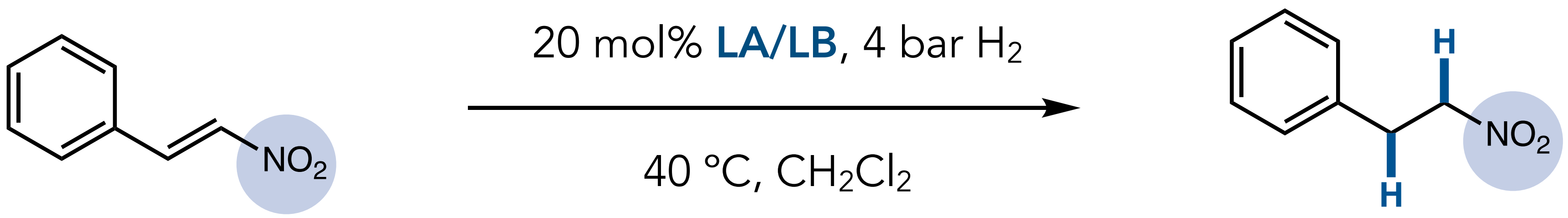




- *Electron rich substrates reacts faster*
- *Higher pKa of product favors k_2*

Paradies, J. *Acc. Chem. Res.* **2023,** *56,* 821-834.

Hydrogenation of Nitroalkenes

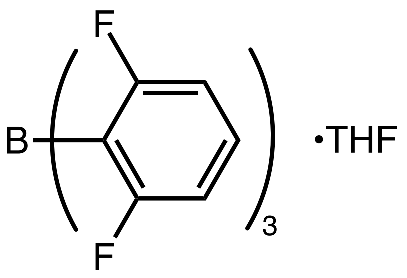


Nitroalkenes

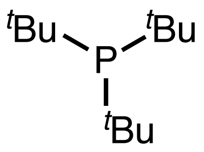
Hydrogenated pdt

Contains coordinating basic moieties

Needs weaker LA



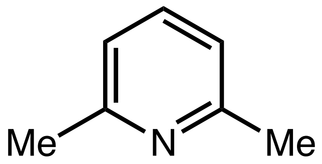
LA



No pdt

P–H bond too strong

Slow proton transfer

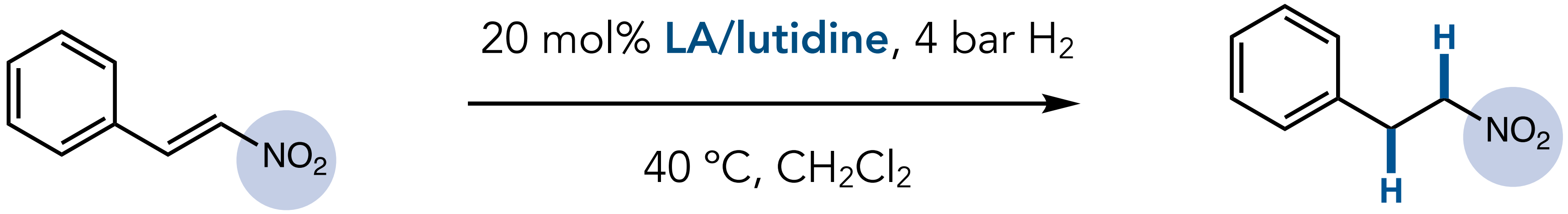


>95% yield

LB

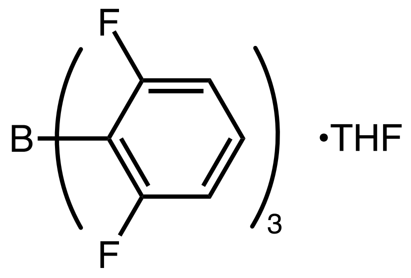
Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Hydrogenation of Nitroalkenes

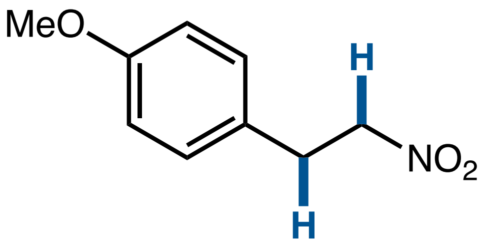


Nitroalkenes

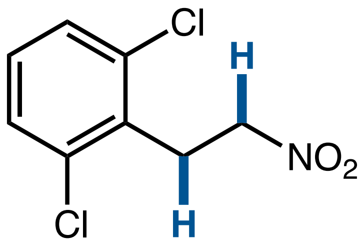
Hydrogenated pdt



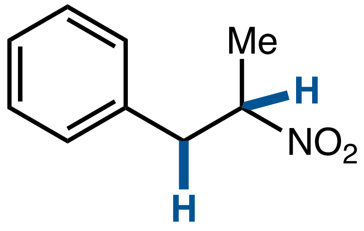
LA



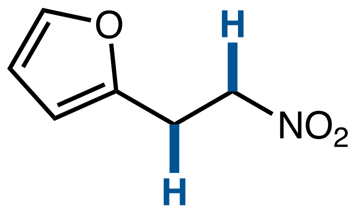
>95% yield



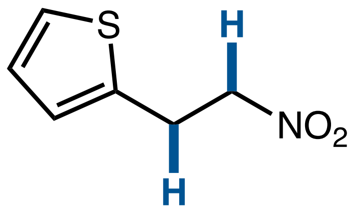
95% yield



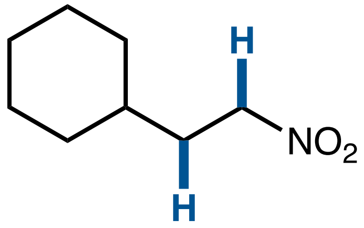
94% yield



89% yield



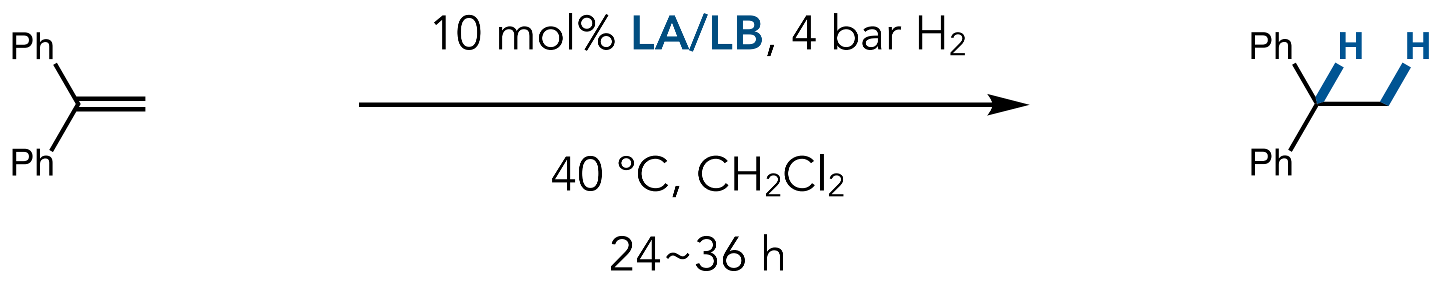
94% yield



>95% yield

Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Hydrogenation of Unactivated Olefins

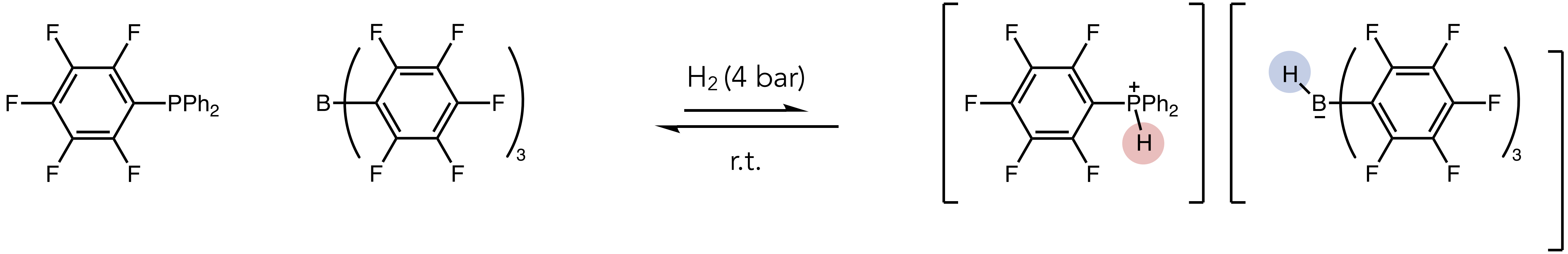


Unactivated olefin

Hydrogenated pdt

Low electrophilicity, low basicity

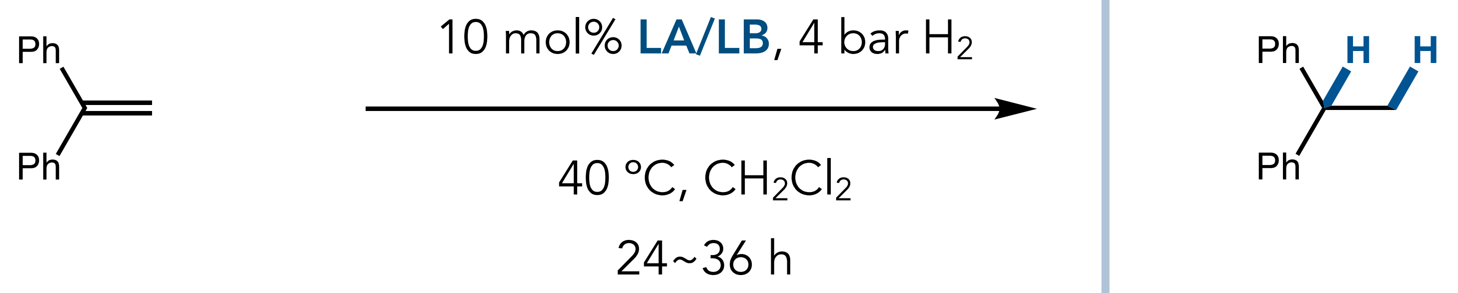
Strong LA, weak LB



Undetected by NMR at r.t.

Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Hydrogenation of Unactivated Olefins

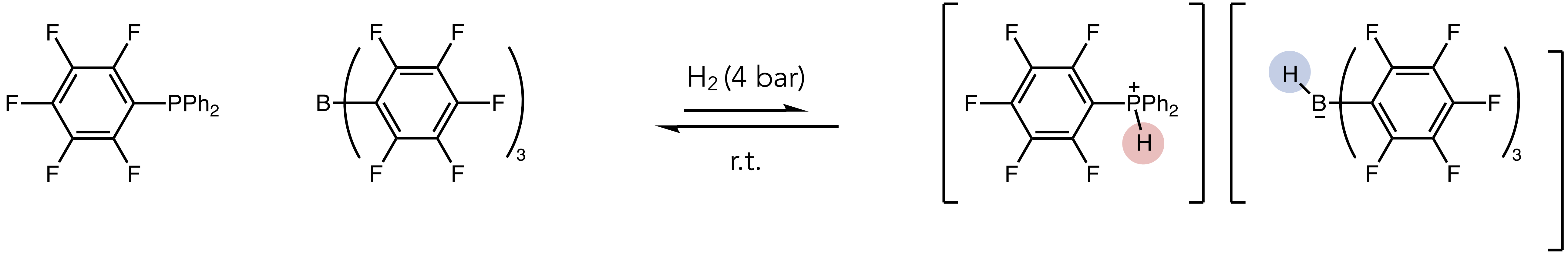


Unactivated olefin

quant.

Low electrophilicity, low basicity

Strong LA, weak LB

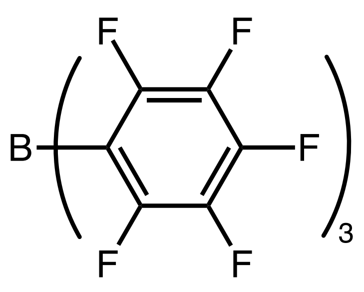


Undetected by NMR at r.t.

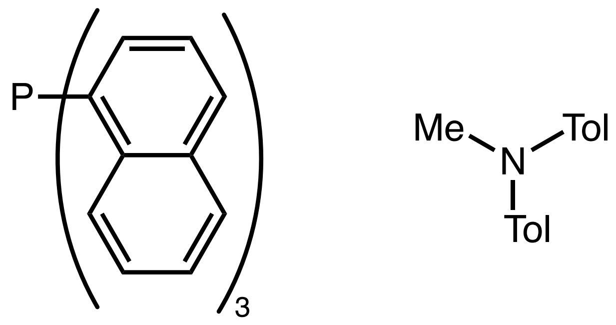
FLP reactivity can be driven by Le Chatlier's Principle

Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

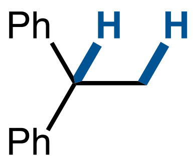
Hydrogenation of Unactivated Olefins



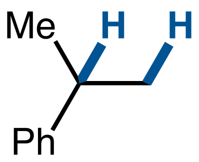
LA



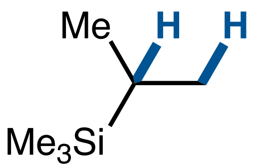
LB



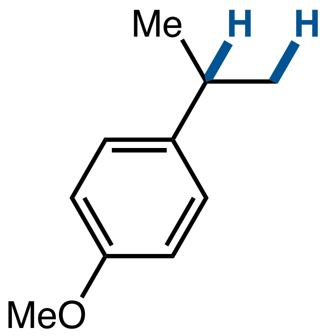
95% yield



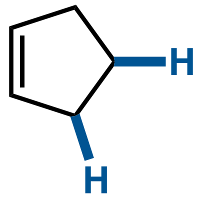
96% yield



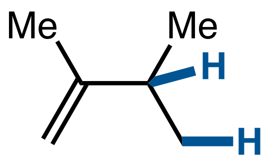
95% yield



99% yield



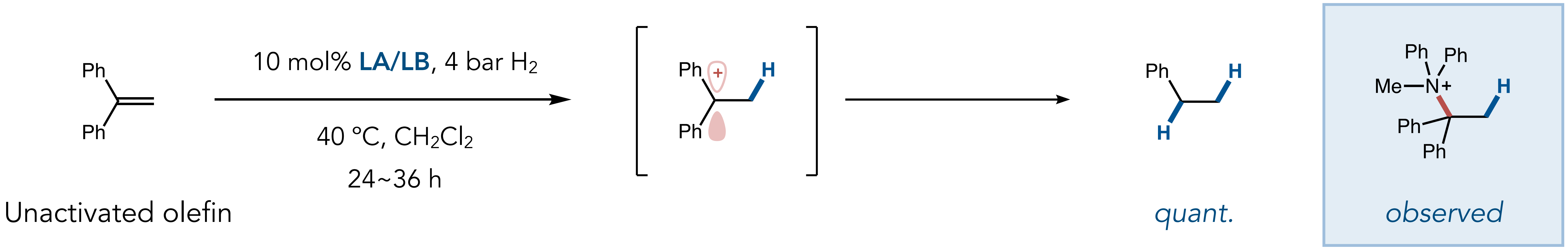
99% yield



99% yield

Paradies, J. *Acc. Chem. Res.* **2023,** *56,* 821-834.

Hydrogenation of Unactivated Olefins



- *For less activated olefins, protonation step is rate limiting*

Weaker LB is needed

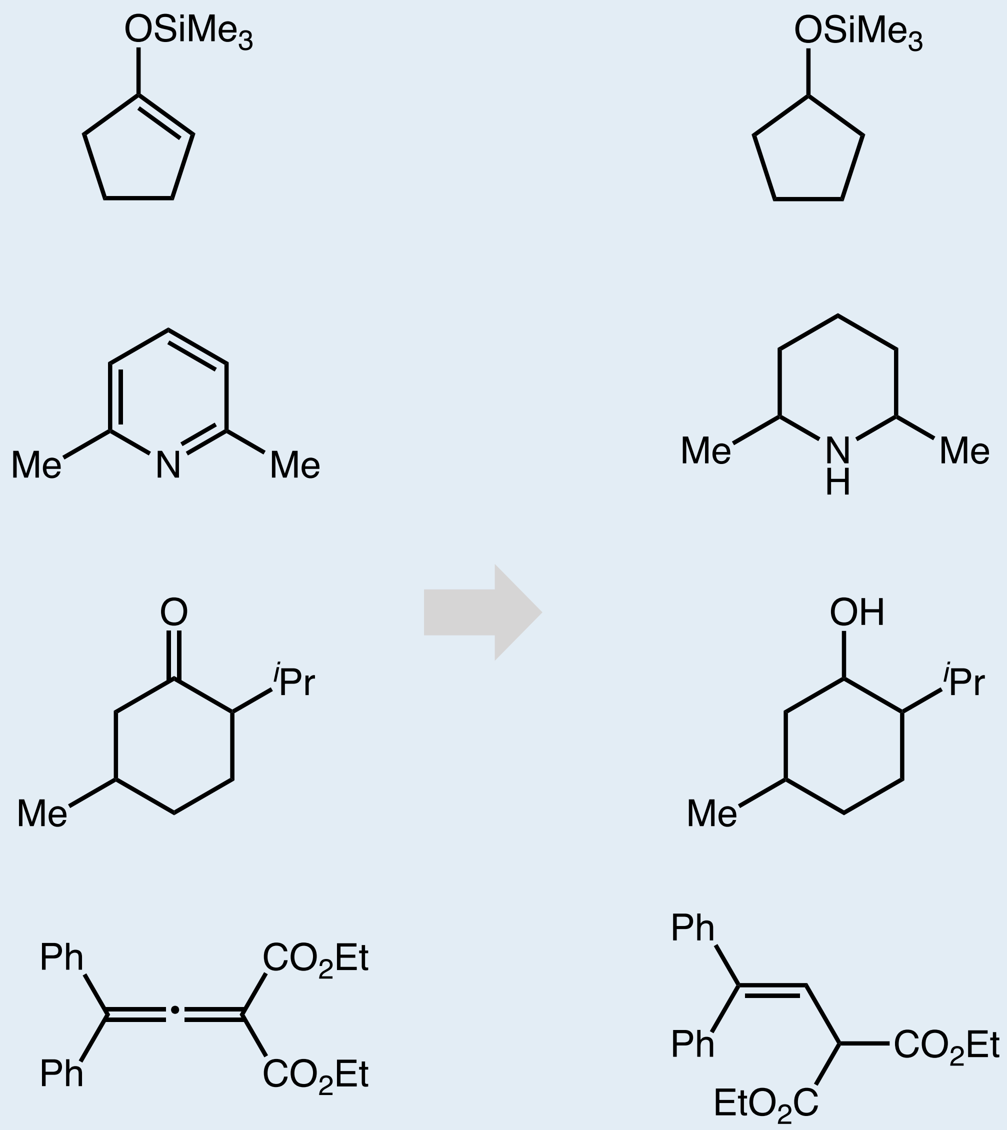
- *For slightly more activated olefins, H_2 splitting is rate limiting*

Stronger LB is needed

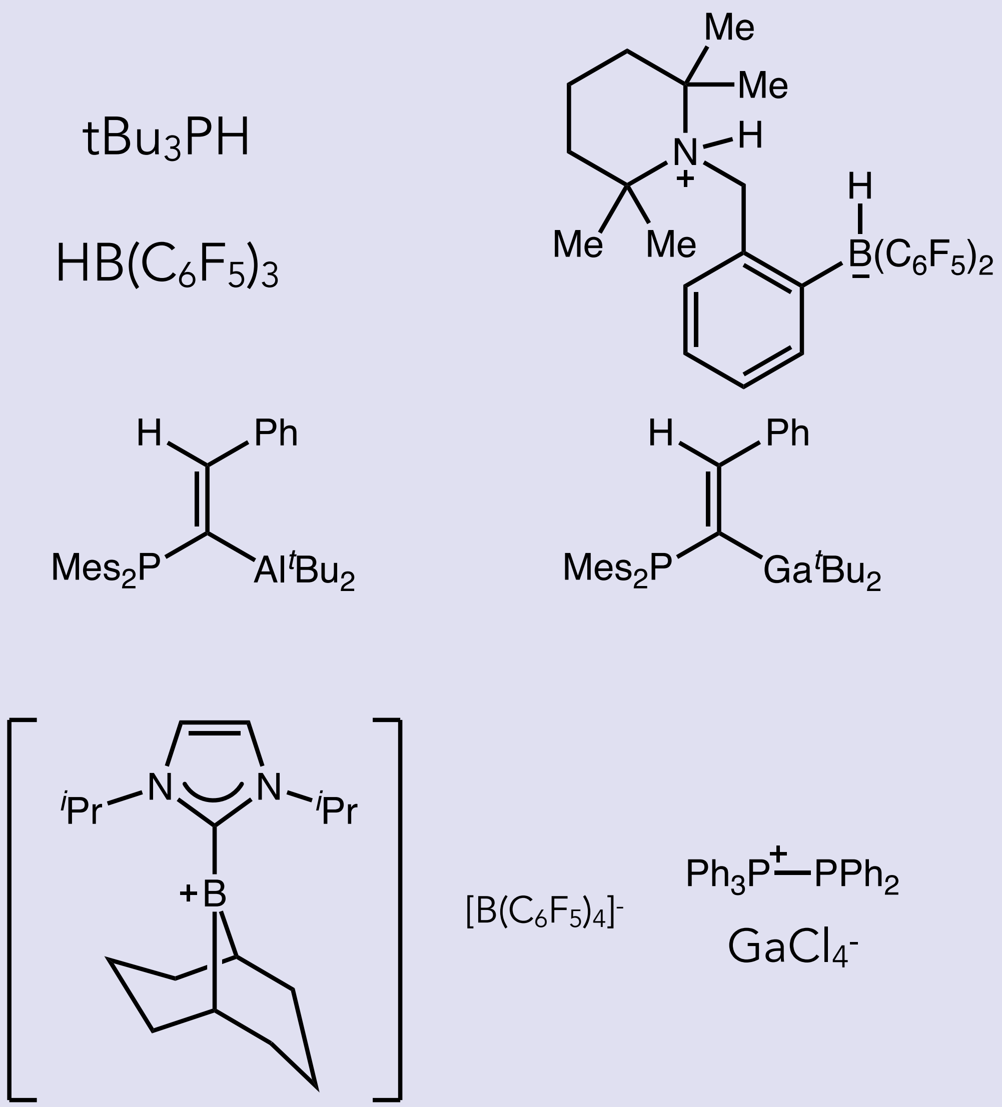
Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Exploring Substrate Scope With Different FLPs

Reduction of Various substrates

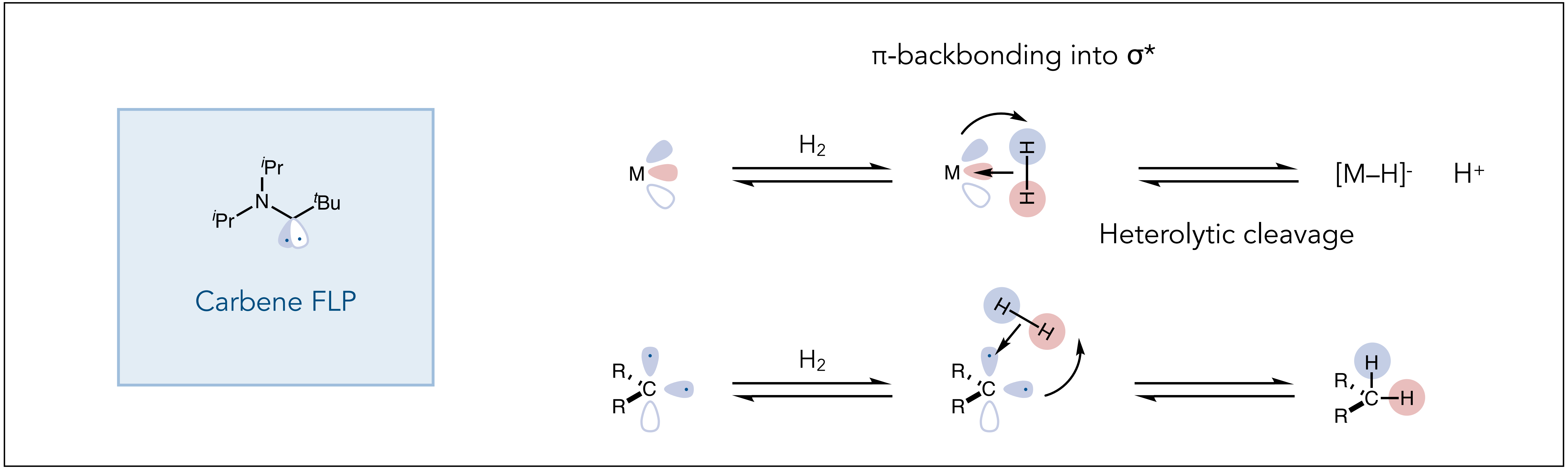


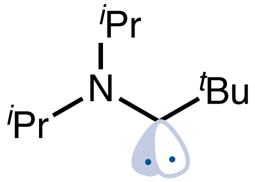
Diversifying FLPs



Stephan, D. W. *Acc Chem Res.* **2015,** *48*(2):306-16.

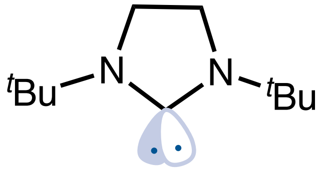
Uncommon FLPs: Singlet Carbenes





$-(E_S - E_T) = 33.3$ kcal/mol

$\Delta E(H_2)^* = 22.1$ kcal/mol

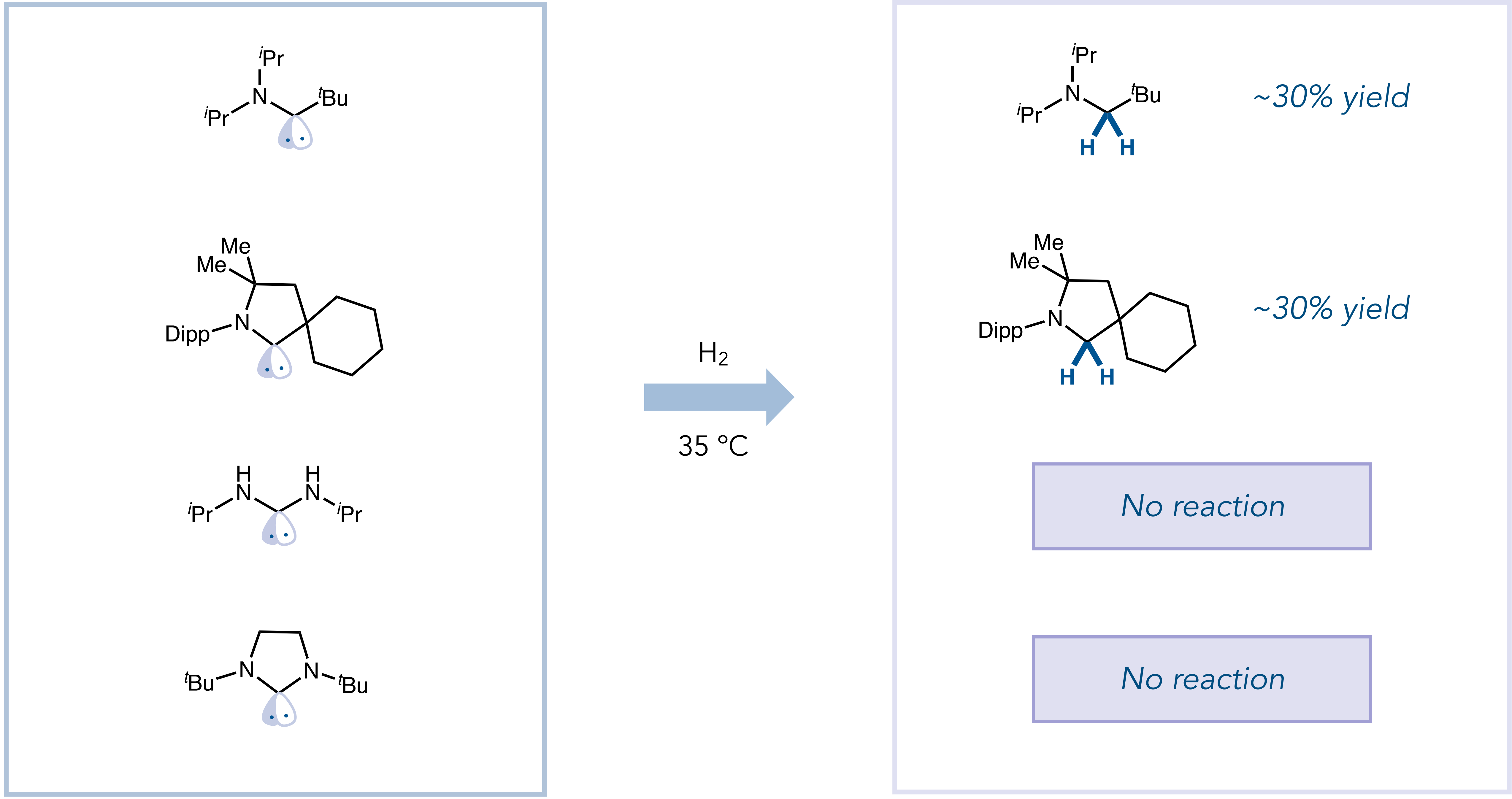


$-(E_S - E_T) = 68.1$ kcal/mol

$\Delta E(H_2)^* = 35.9$ kcal/mol

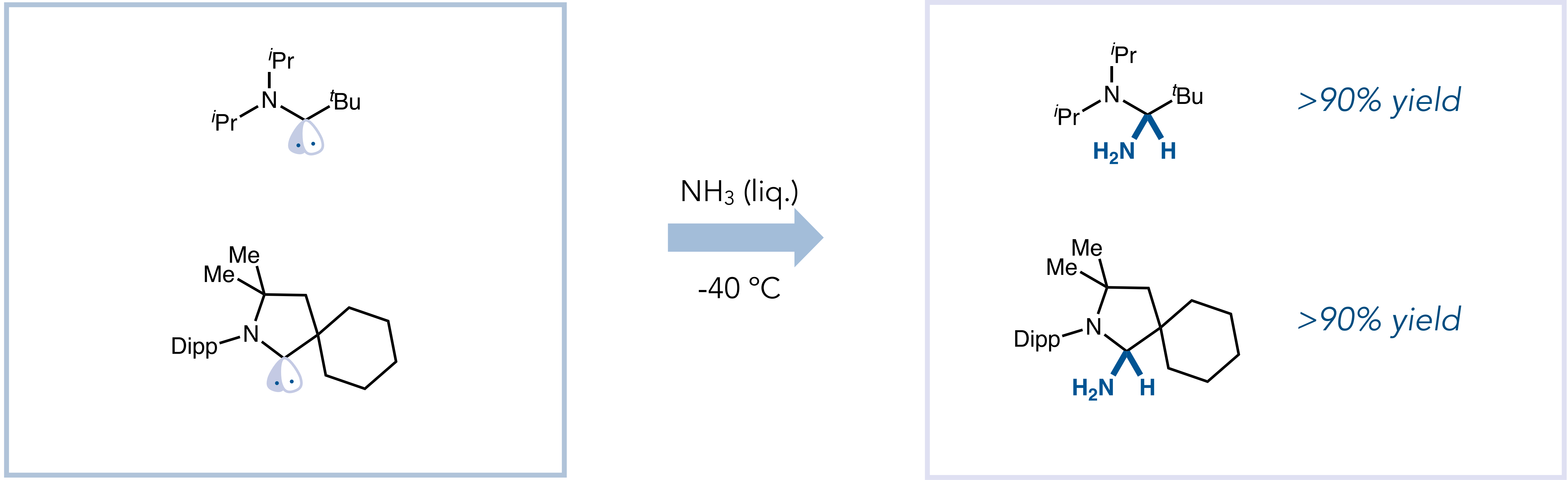
Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007,** *316*,439-441.

Uncommon FLPs: Singlet Carbenes



Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007,** *316*,439-441.

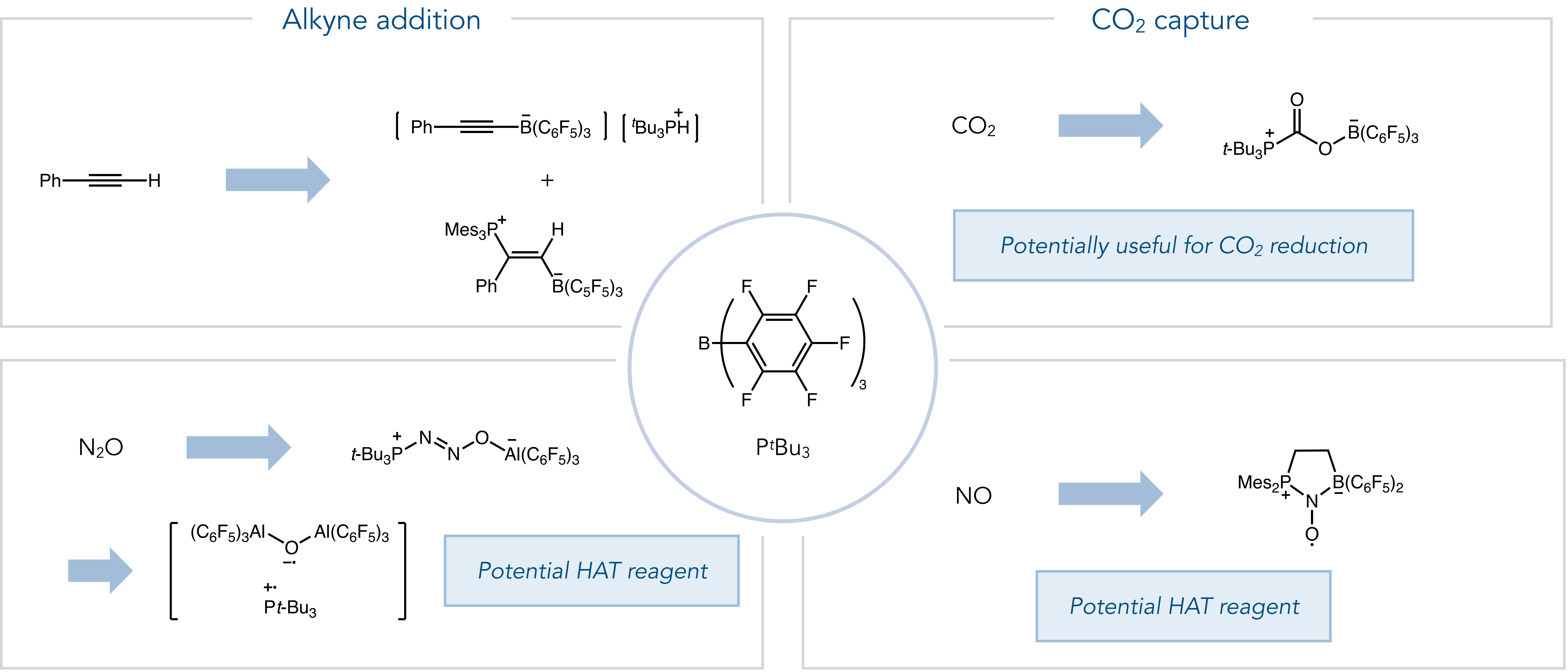
Uncommon FLPs: Singlet Carbenes



Unique reactivity couldn't achieve using transition metal catalysis

Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007,** *316*,439-441.

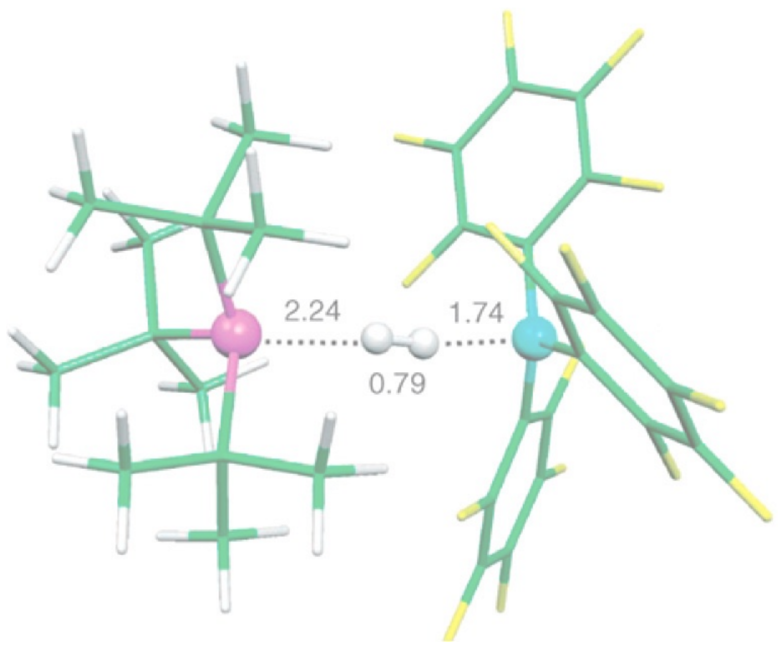
Exploring FPL Reactivities



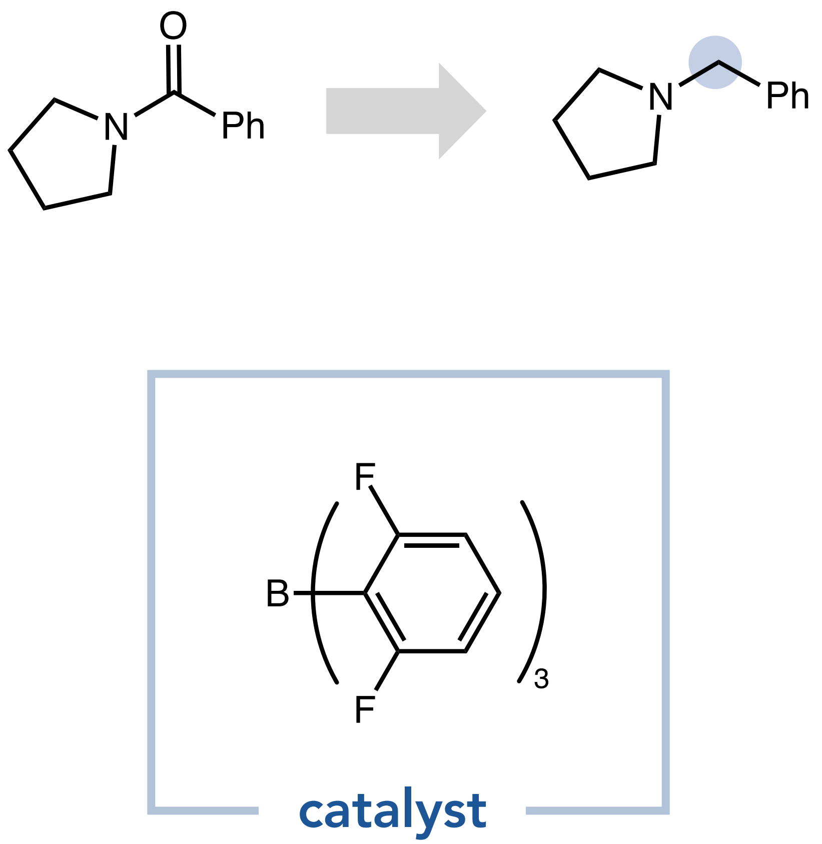
Stephan, D. W. *J. Am. Chem. Soc.* **2015,** *137, 10018*-10032.

The Discovery & Development of Frustrated Lewis Pairs

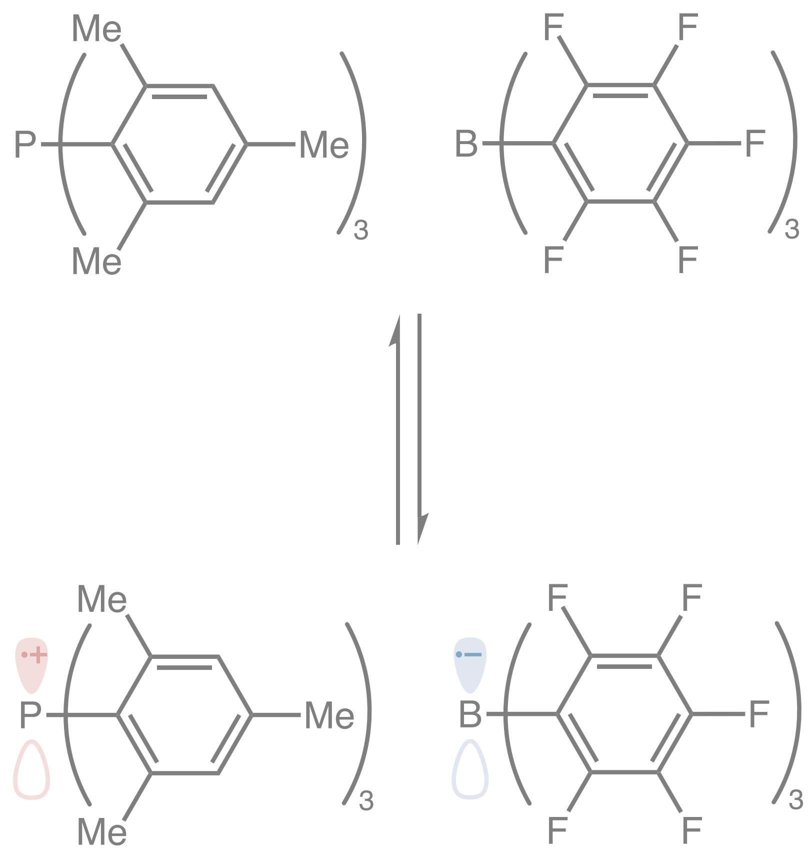
Mechanism & proof of Concept



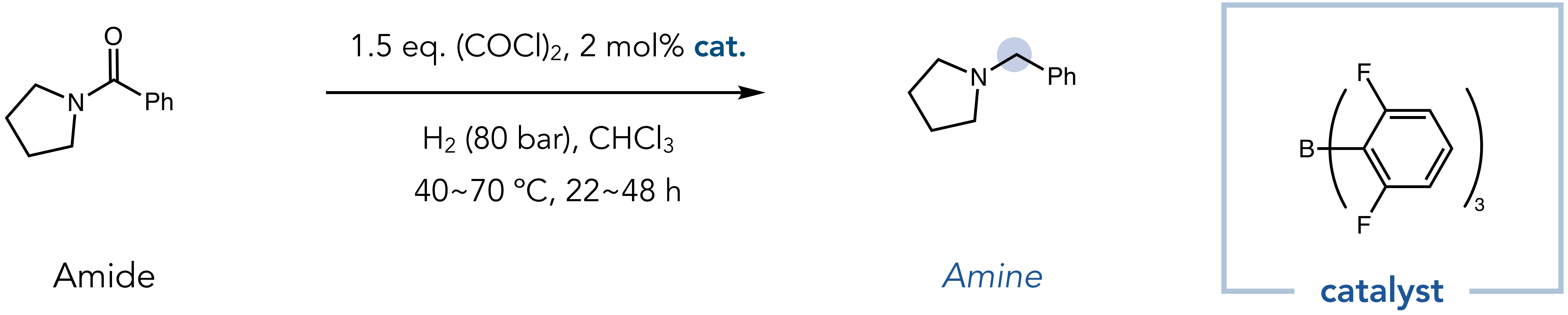
Application in Organic Reactions

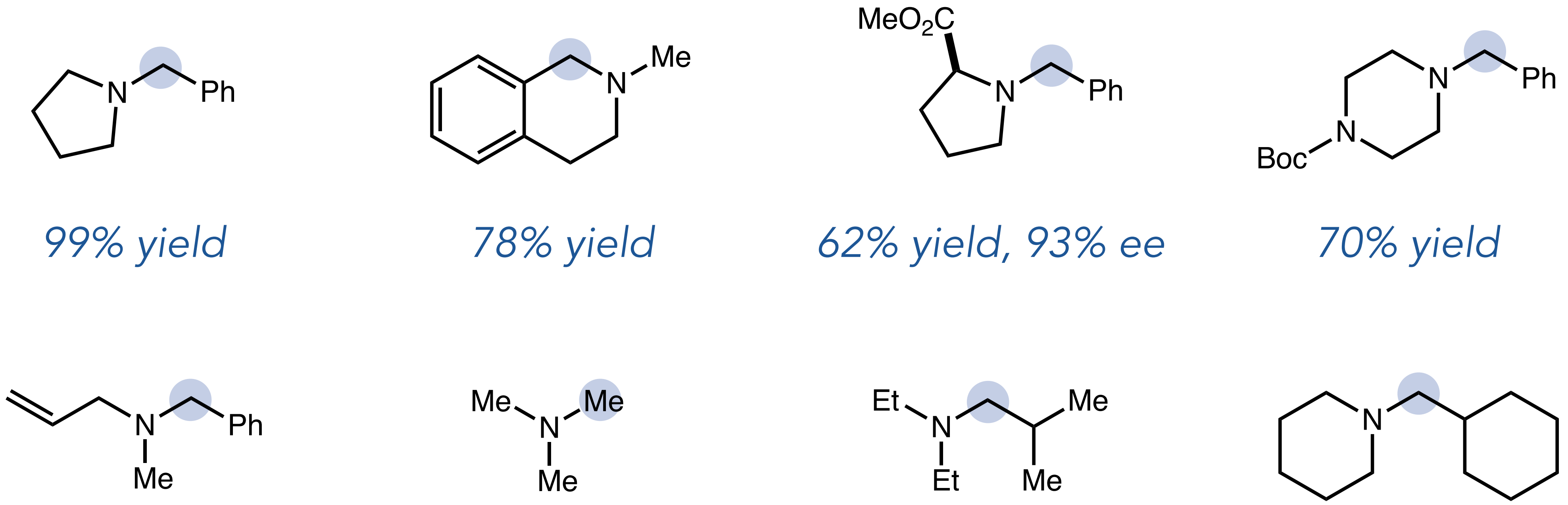


Redefining FLP & FRP



Amide Reduction With FLPs



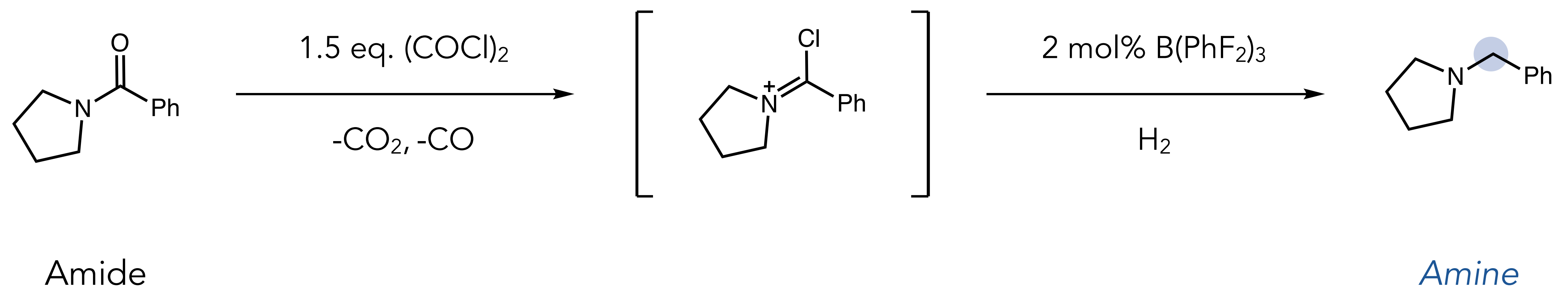


99% yield | 78% yield | 62% yield, 93% ee | 70% yield | 96% yield

87% yield | 94% yield | 76% yield | 82% yield

Sitte, N. A.; Bursch, M.; Grimme, S.; Paradies, J. *J. Am. Chem. Soc.* **2019,** *141*, 159-162.

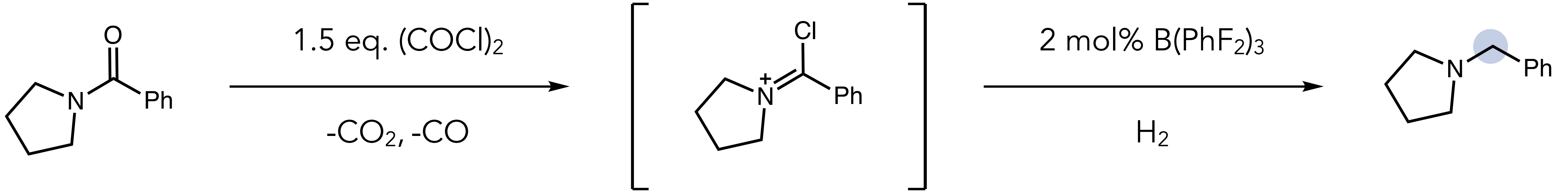
Amide Reduction With FLPs



What's serving the Lewis base?

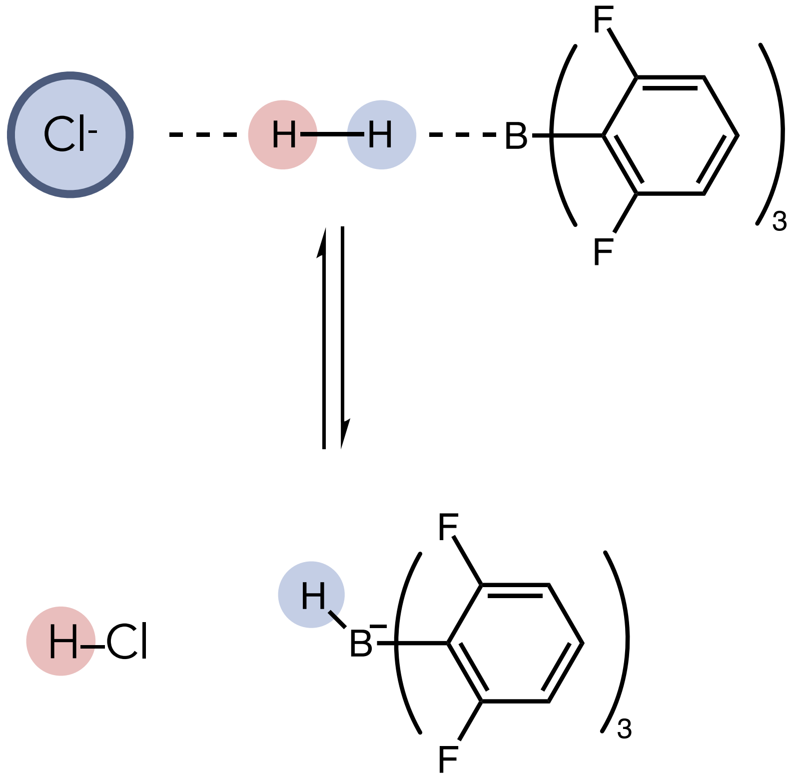
Sitte, N. A.; Bursch, M.; Grimme, S.; Paradies, J. *J. Am. Chem. Soc.* **2019,** *141*, 159-162.

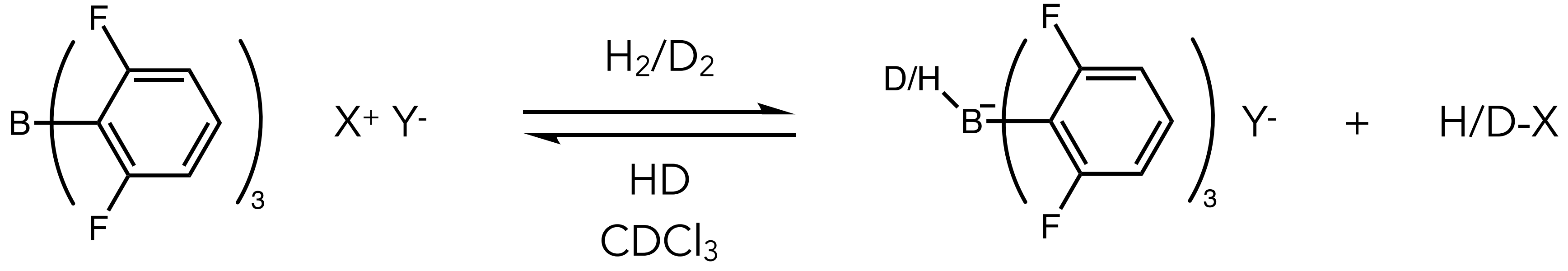
Chlorine Anion As A Lewis Base



Amide

Amine





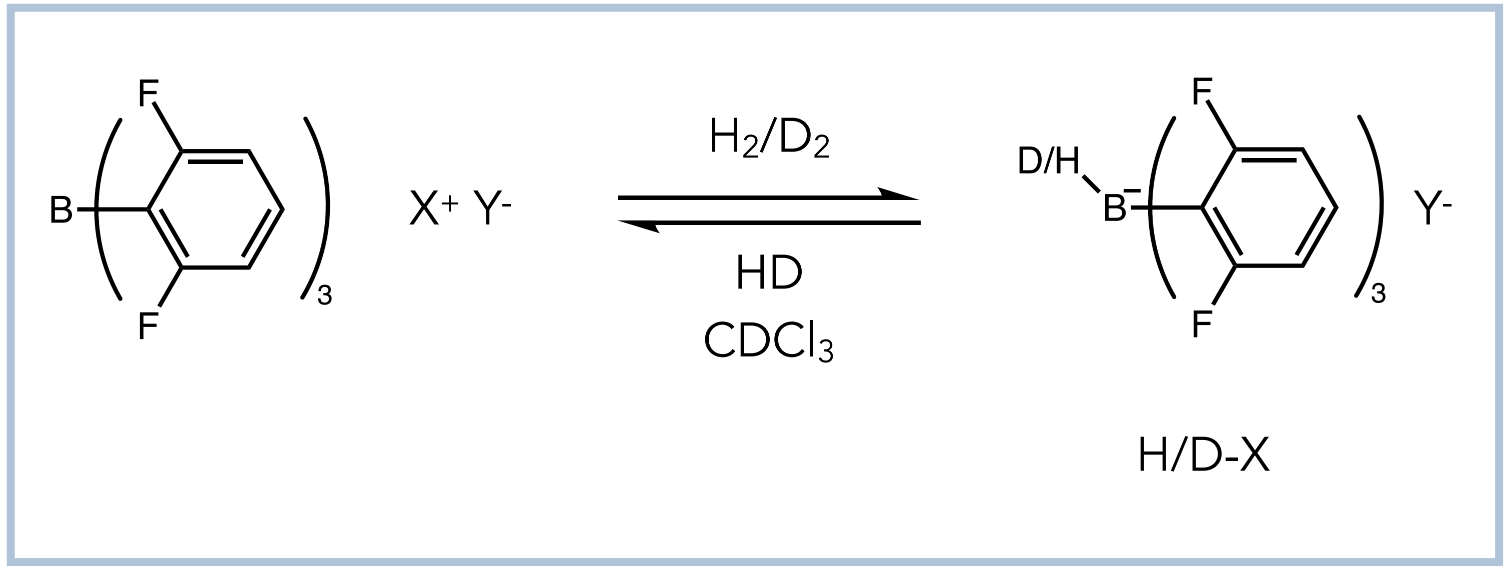
X=Cl, Y=PPh4, NBu4

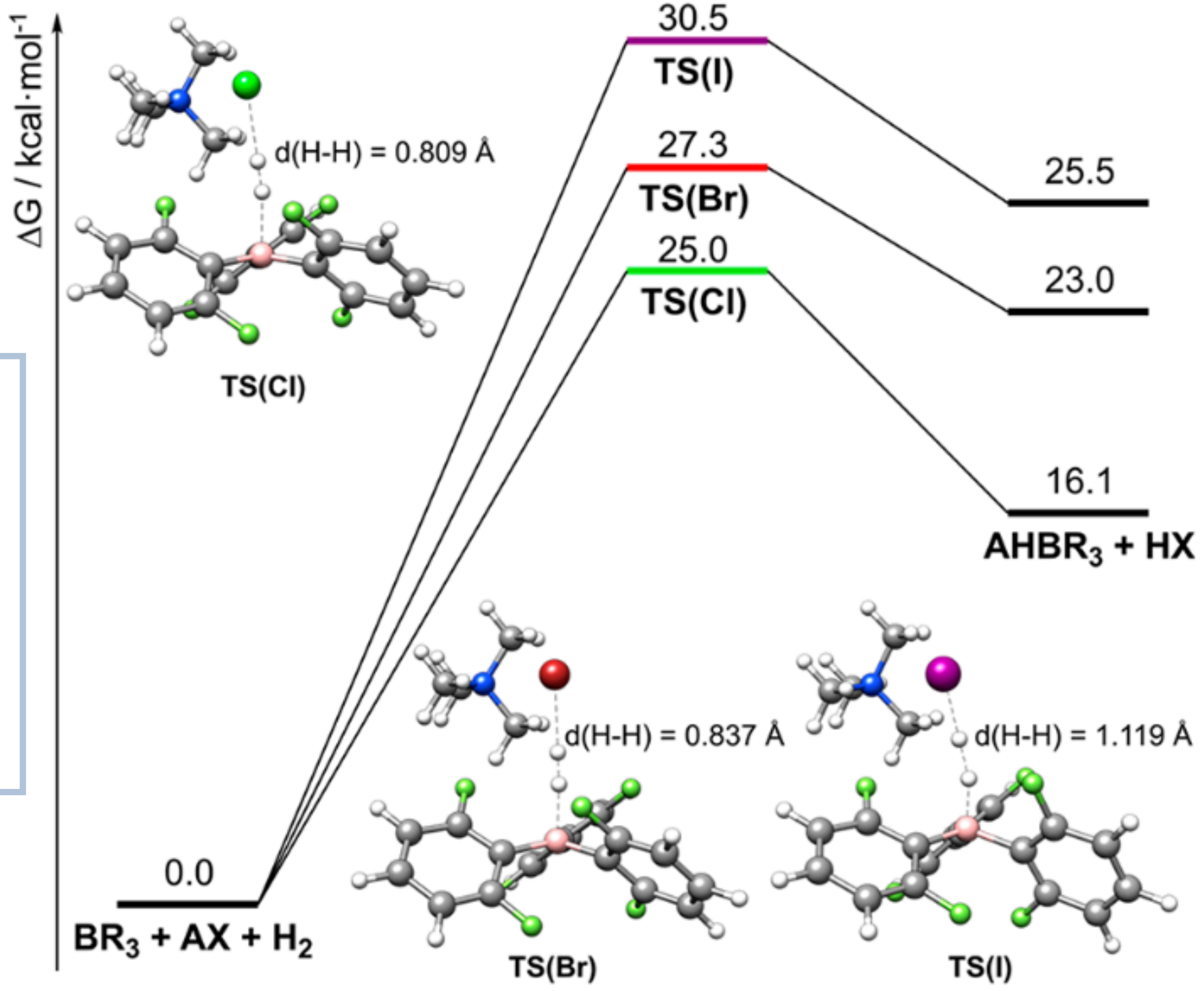
X=Cl, Br, I, Y=BMIM

Deuterium incorporation in HD were all bserved

Sitte, N. A.; Bursch, M.; Grimme, S.; Paradies, J. *J. Am. Chem. Soc.* **2019,** *141*, 159-162.

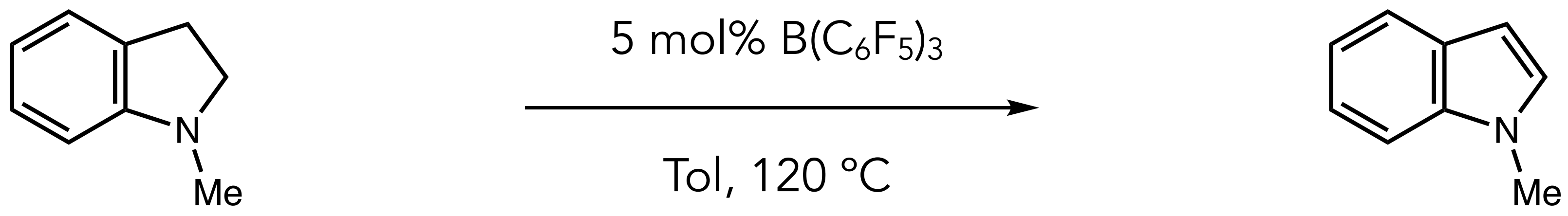
Chlorine Anion As A Lewis Base





Sitte, N. A.; Bursch, M.; Grimme, S.; Paradies, J. *J. Am. Chem. Soc.* **2019,** *141*, 159-162.

Dehydrogenation With FLPs

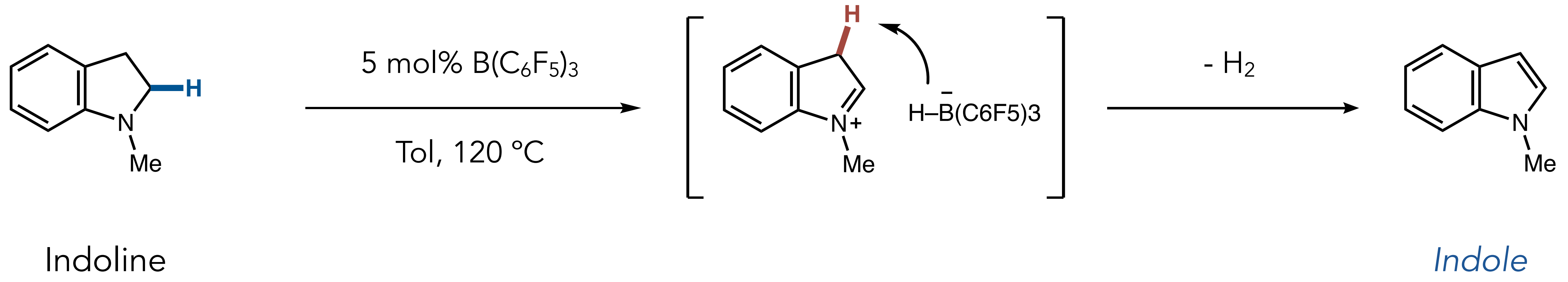


Indoline

Indole

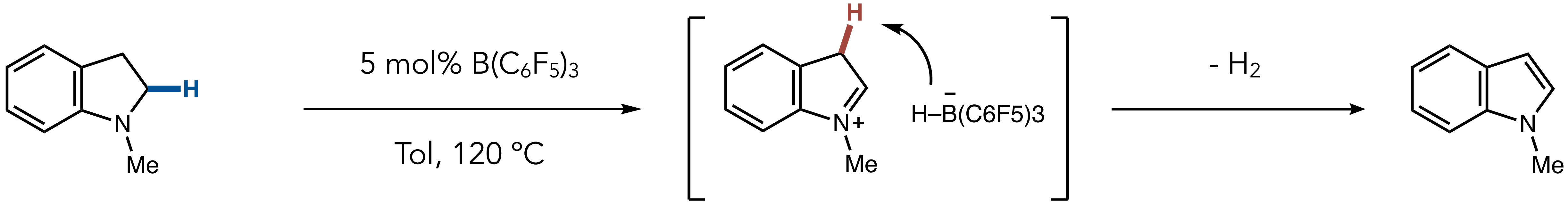
Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Dehydrogenation With FLPs



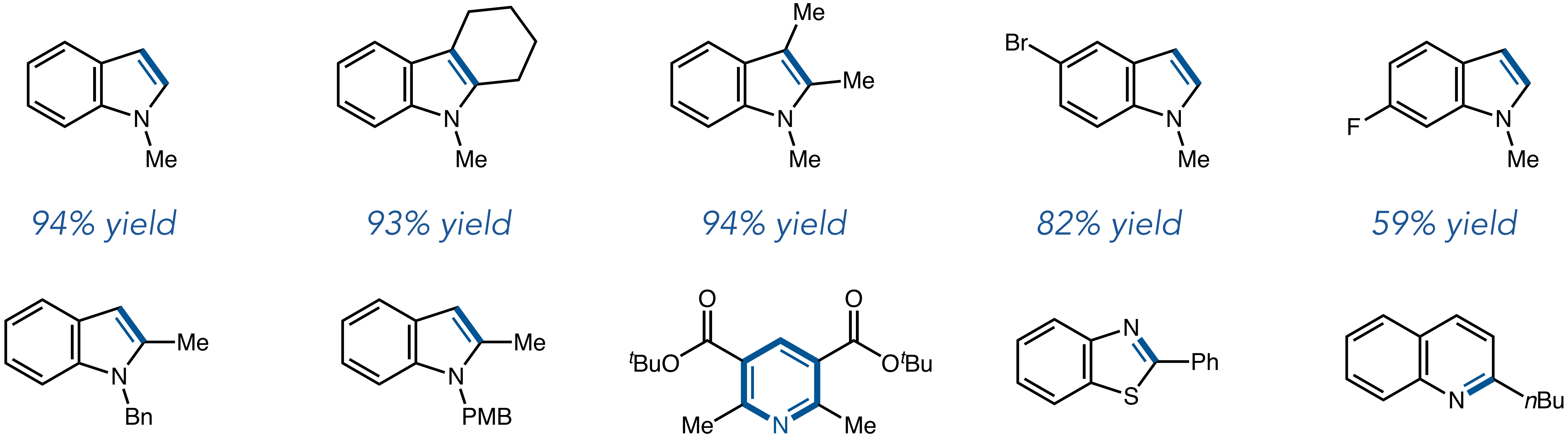
Paradies, J. *Acc. Chem. Res.* **2023,** *56*, 821-834.

Dehydrogenation With FLPs



Indoline

Indole

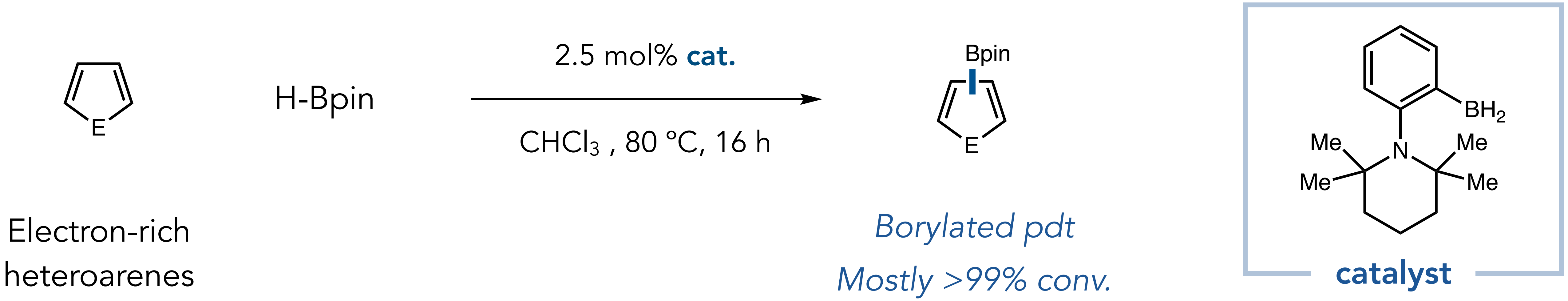


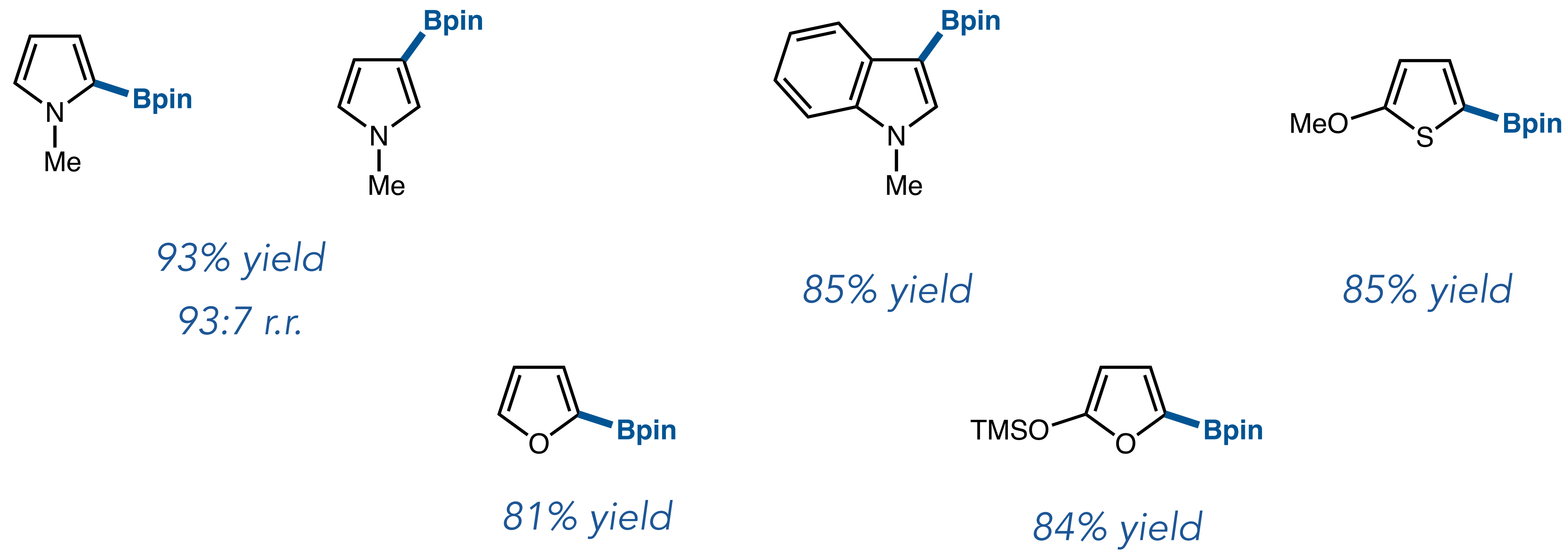
94% yield *93% yield* *94% yield* *82% yield* *59% yield*

86% yield *51% yield* *50% yield* *48% yield* *93% yield*

Paradies, J. *Acc. Chem. Res.* **2023,** *56,* 821-834.

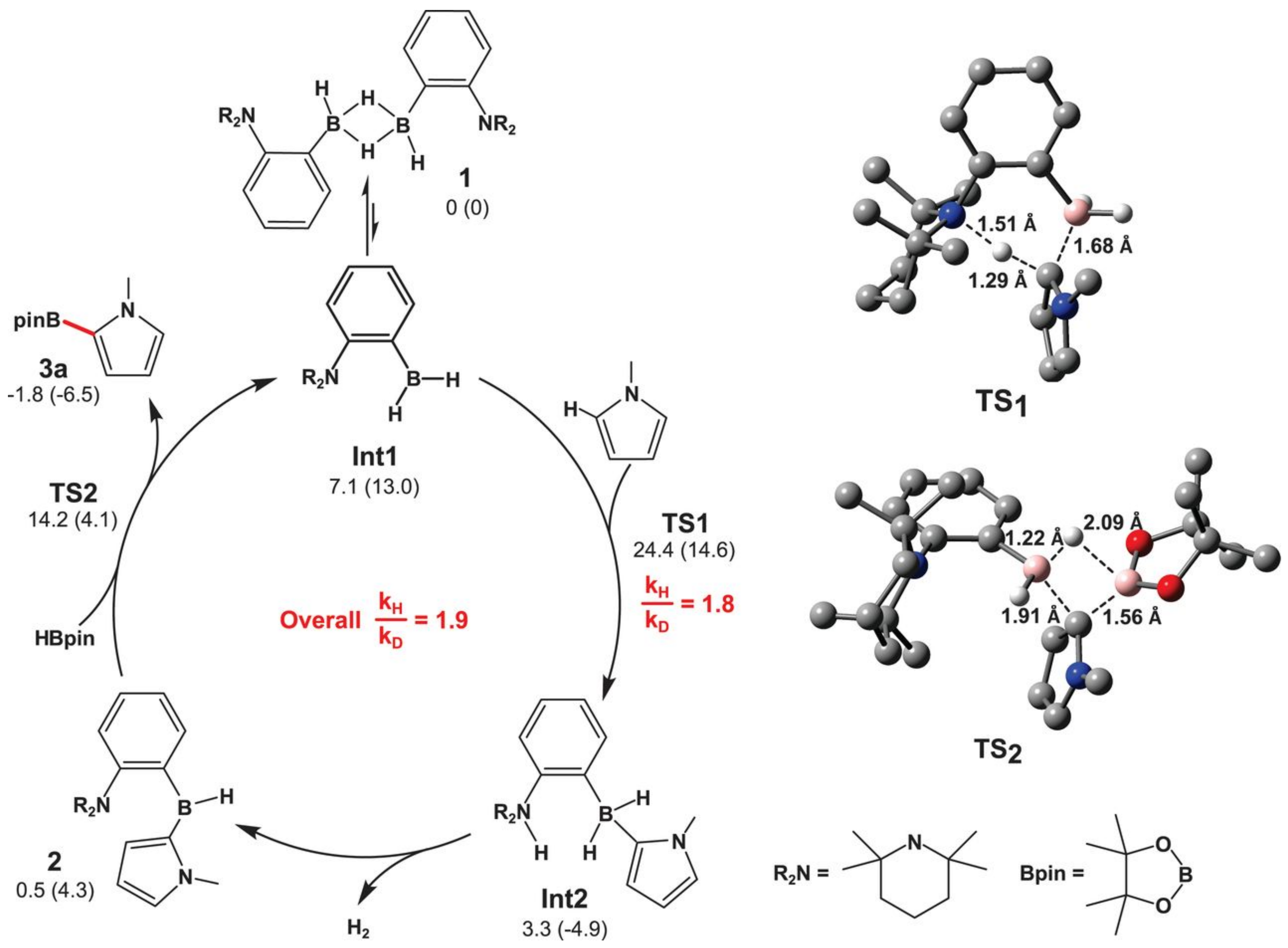
Borylation of Electron-Rich Heteroarenes





Legare, M-A.; Courtemanche, M-A.; Rochette, E.; Fontaine, R-G. *Science* **2015,** *349*, 6247, *513*-516.

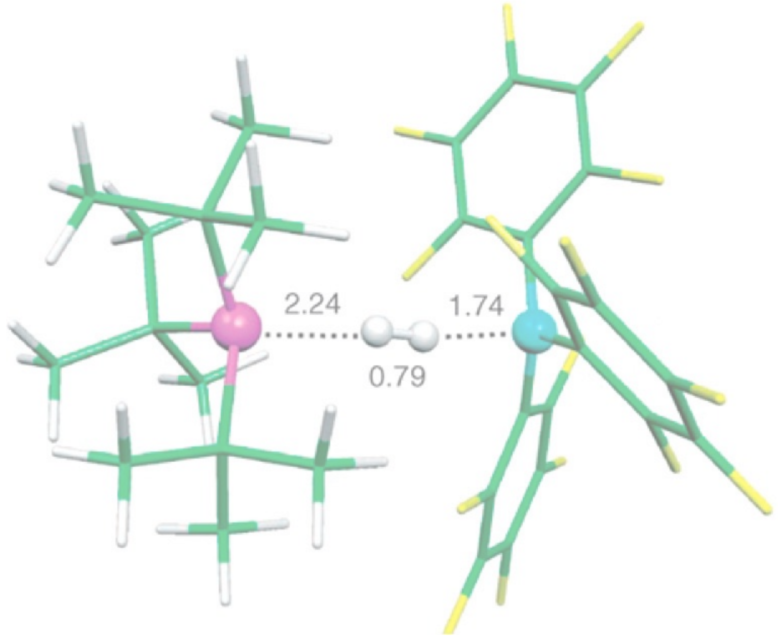
Borylation of Electron-Rich Heteroarenes



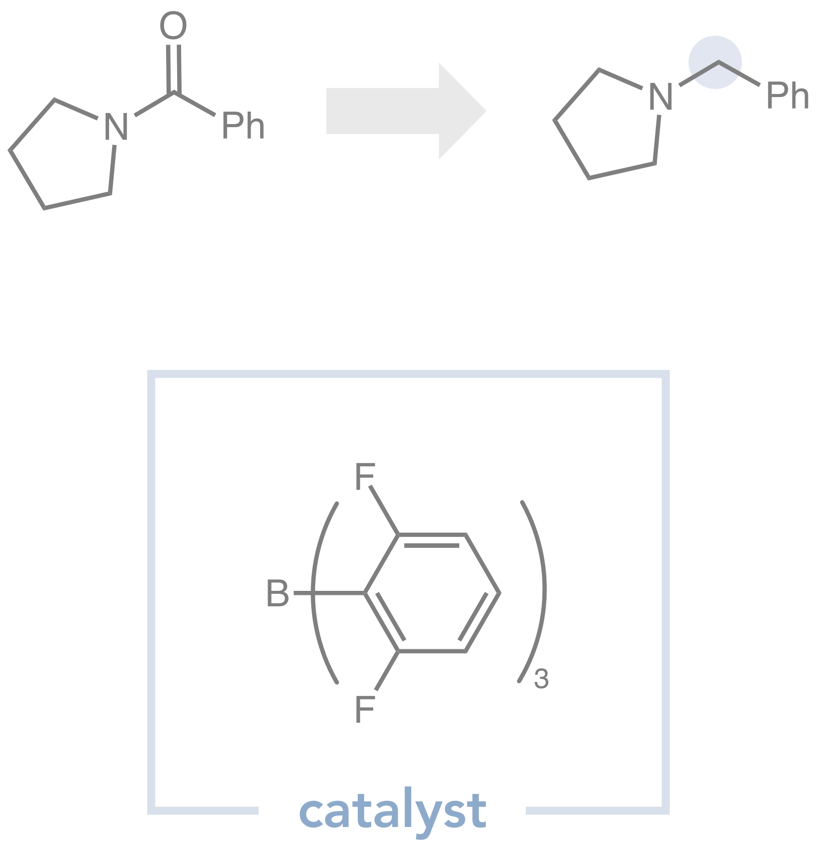
Legare, M-A.; Courtemanche, M-A.; Rochette, E.; Fontaine, R-G. *Science* **2015,** *349*, 6247, *513*-516.

The Discovery & Development of Frustrated Lewis Pairs

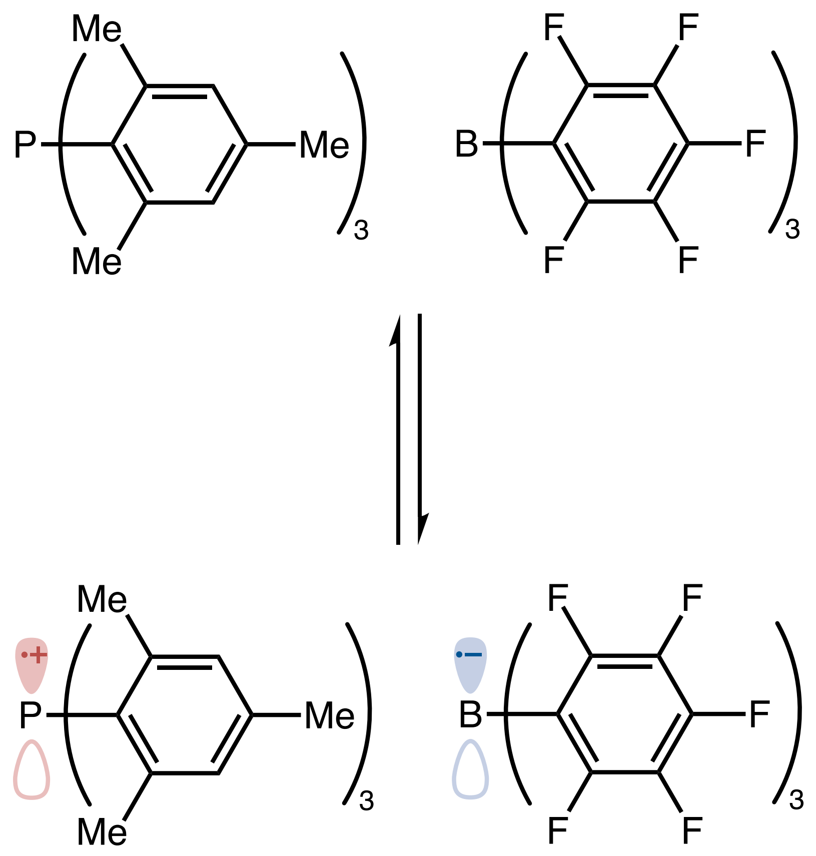
Mechanism & proof of Concept



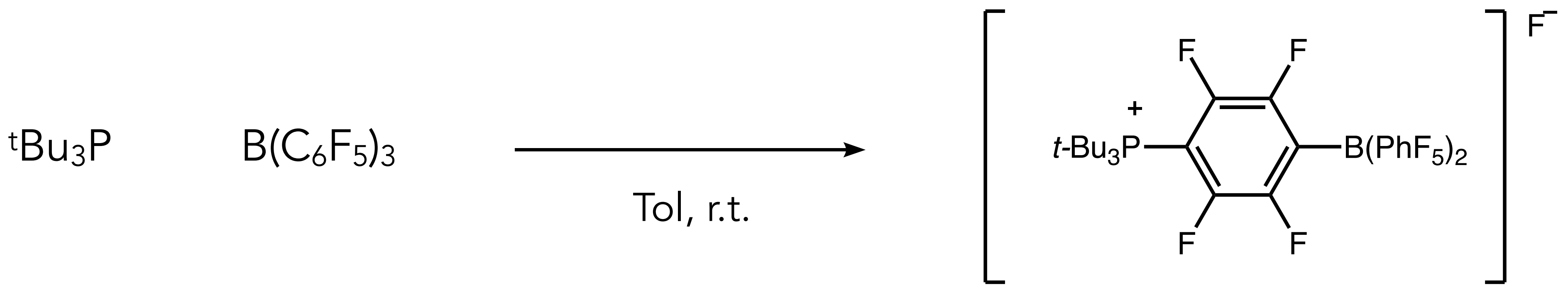
Application in Organic Reactions



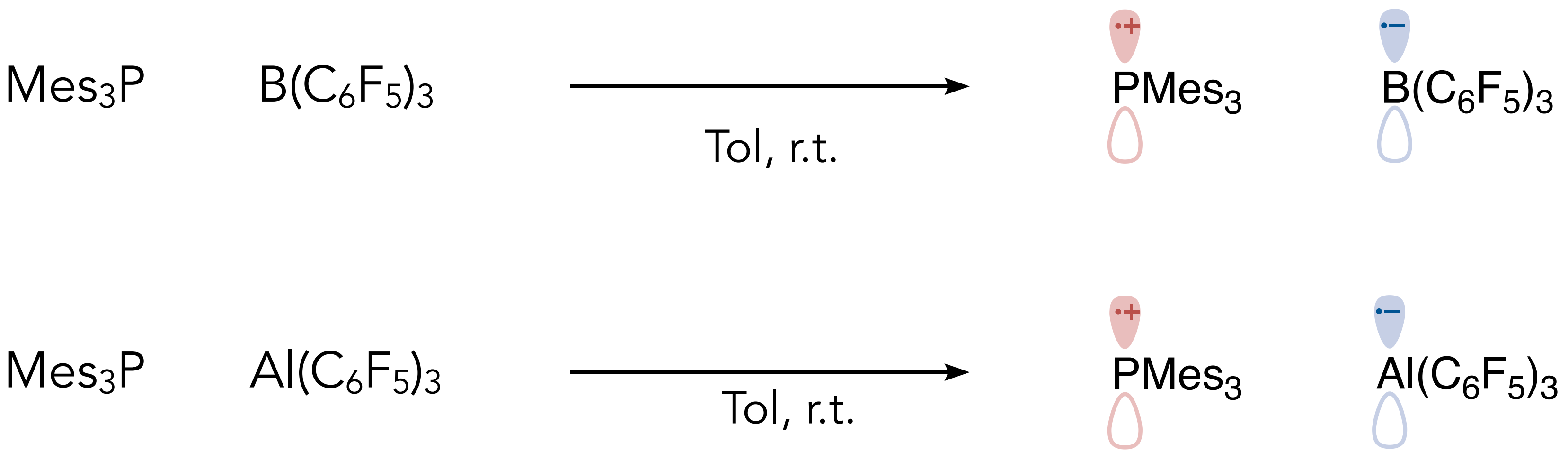
Redefining FLP & FRP



Radical Generation From FLP



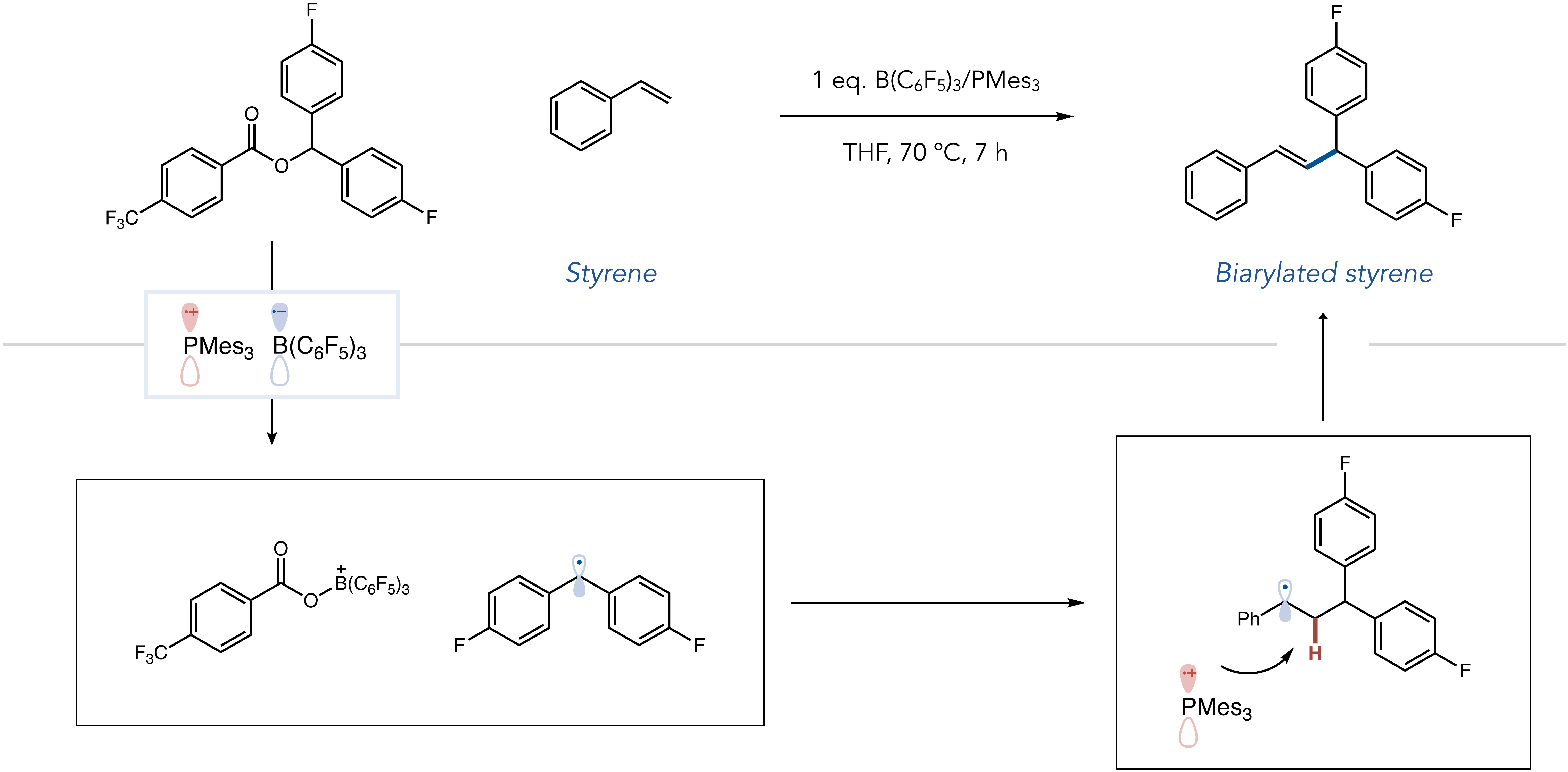
Only zwitterionic adduct formed



Radical formation observed by EPR

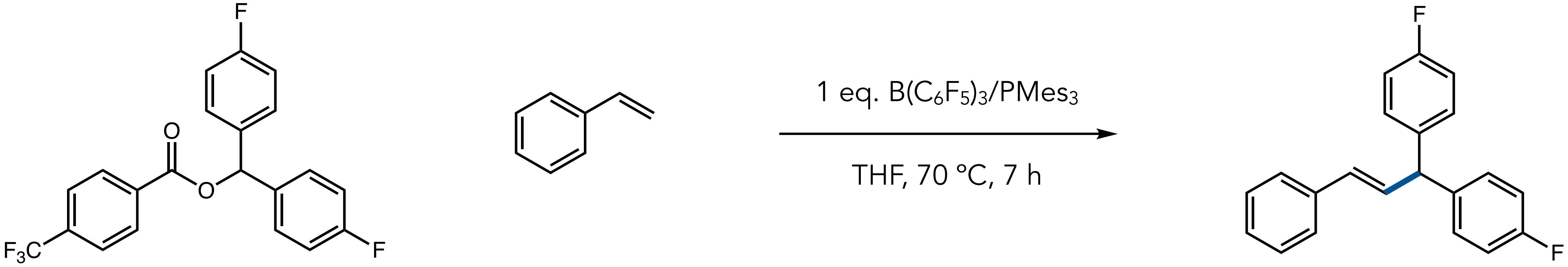
Liu, L.; Cao, L. L.; Shao, Y.; Menard, G.; Stephan D. W. *Chem* **2017**, *3*, 259-267.

Borylation of Styrenes Using FRP



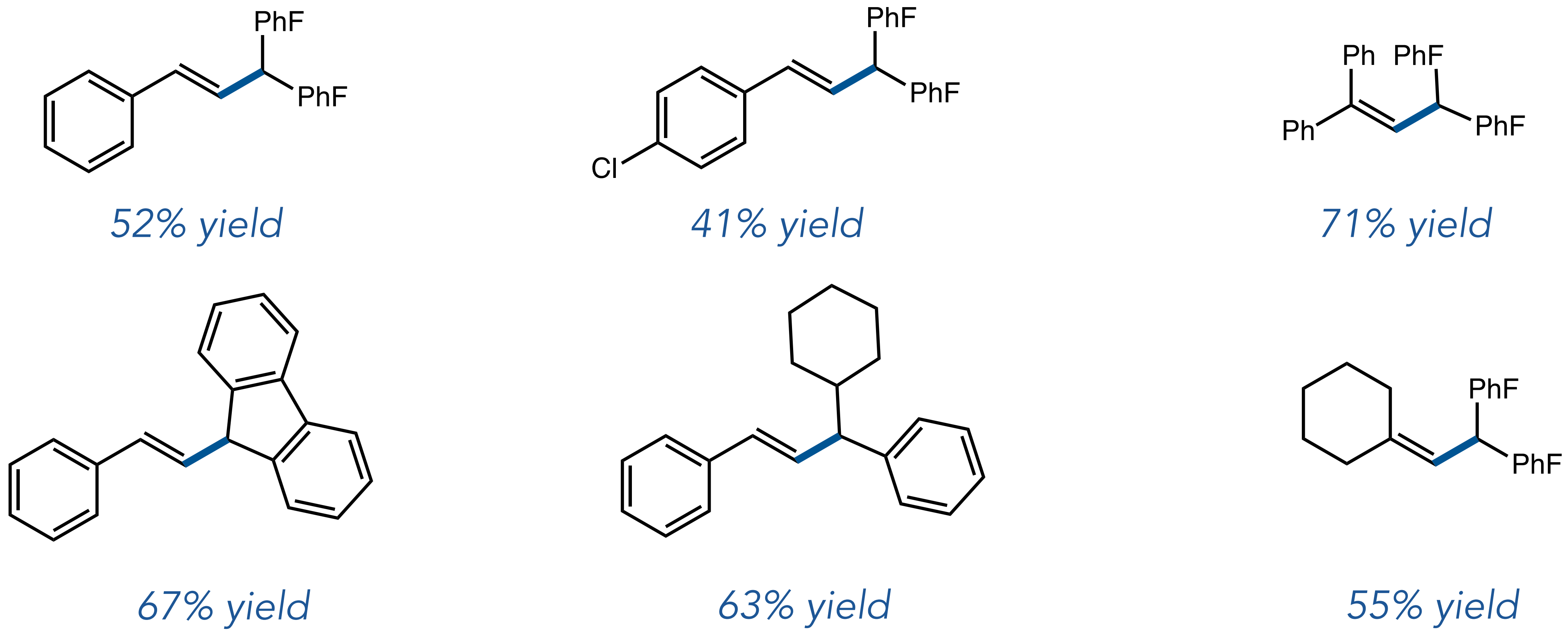
Soltani, Y.; et al. *Cell Rep. Phys. Sci.* **2020,** *1*, 100016.

Borylation of Styrenes Using FRP



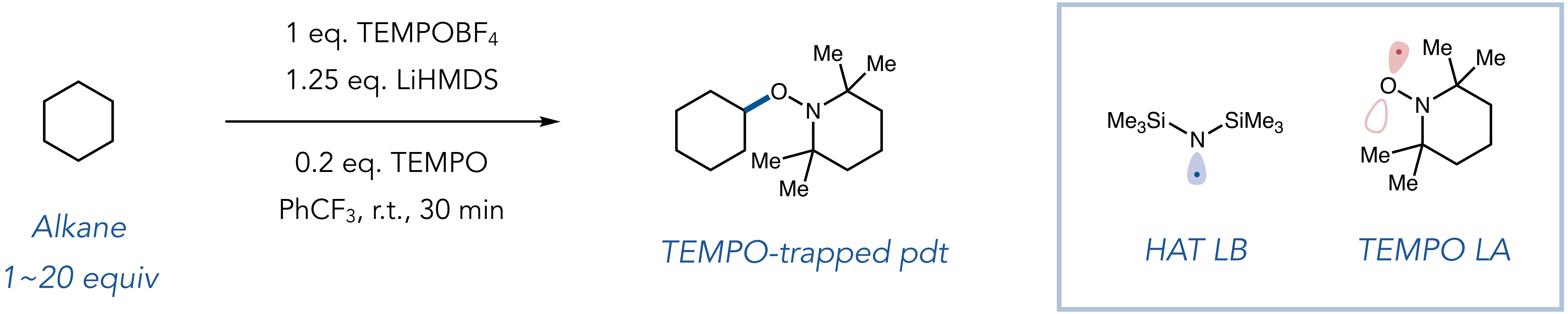
Styrene

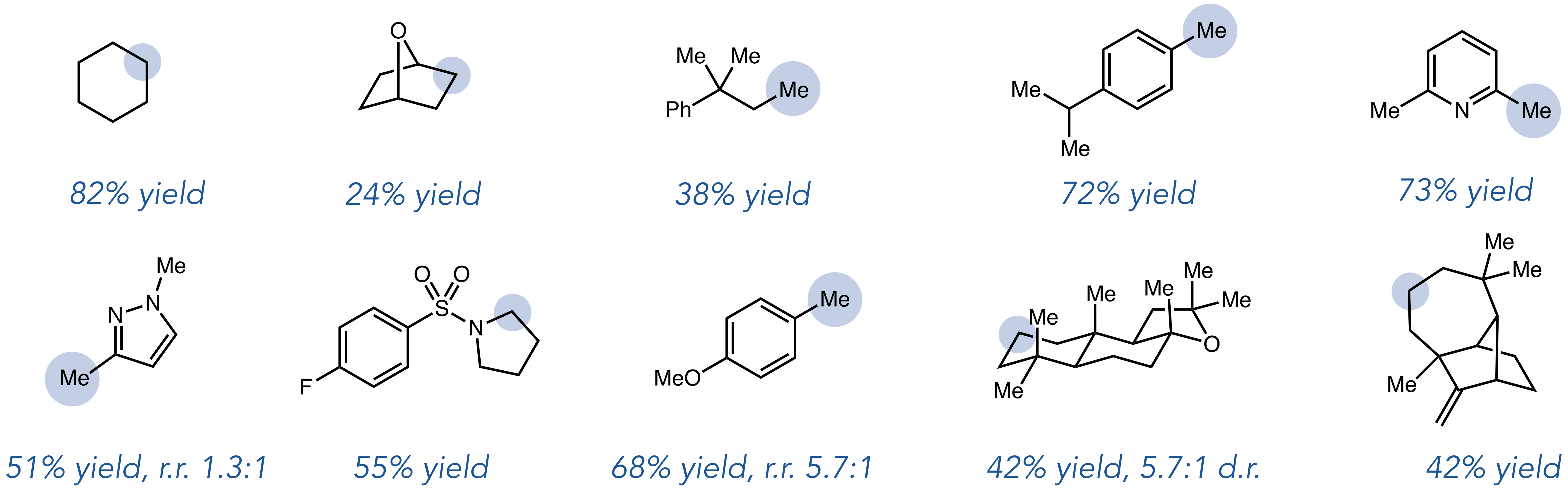
Biarylated styrene



Soltani, Y.; et al. *Cell Rep. Phys. Sci.* **2020,** *1*, 100016.

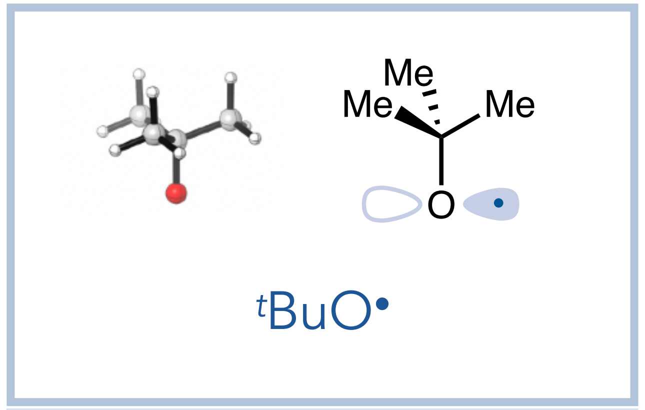
C–H Activation Using FRP

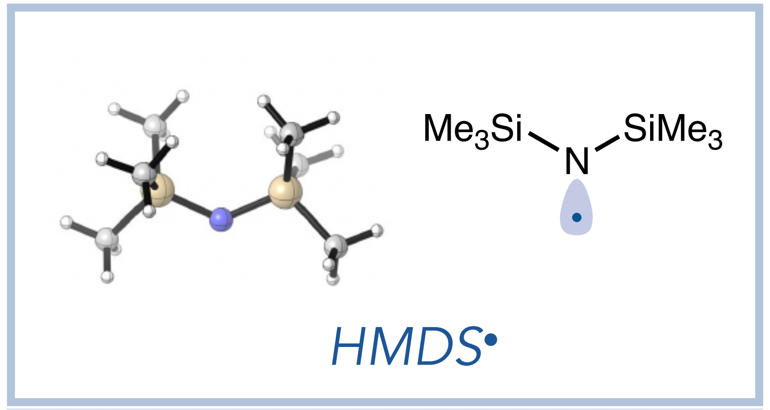


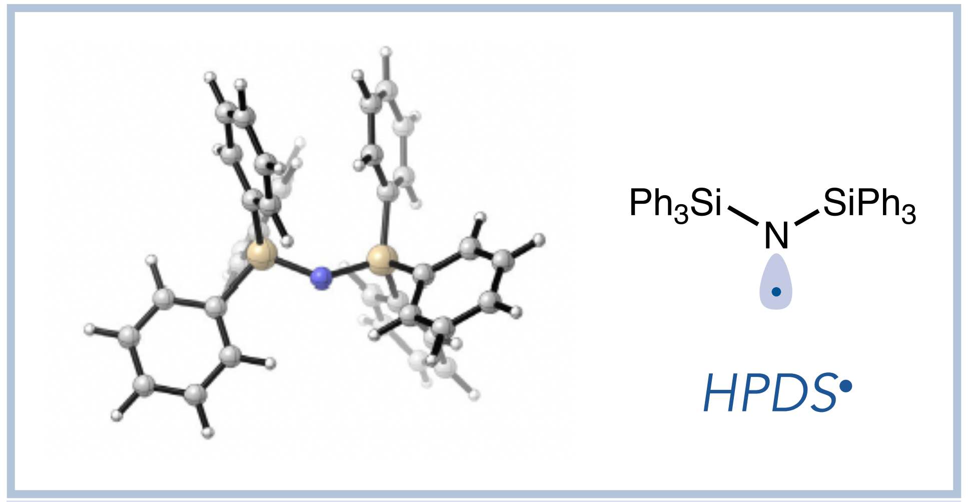


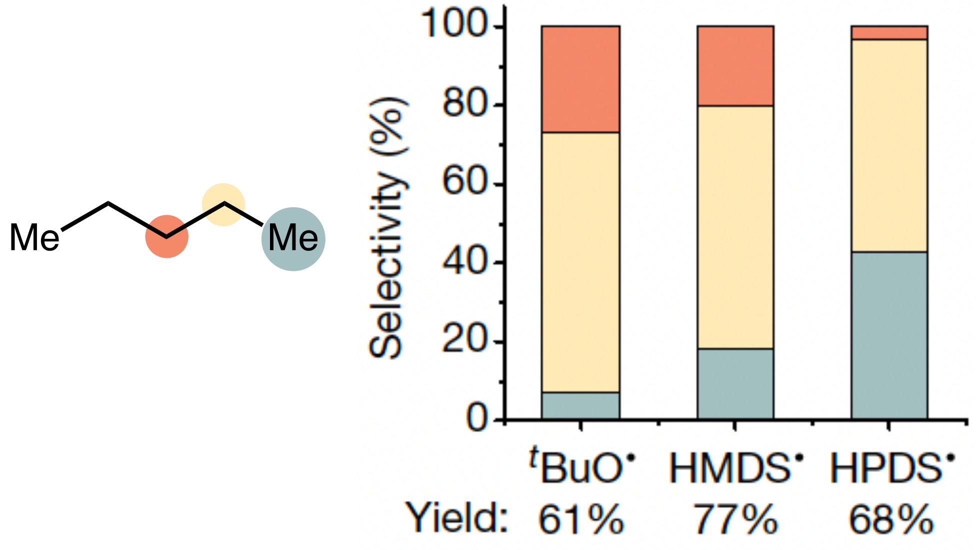
Lu, Z.; Ju, M.; Wang, Y.; Meinhardt, J. M.; Martinez-Alvarado, J. I.; Villemure, E.; Terrett, J. A.; Ling, S. *Nature* **2023,** 619, 514.

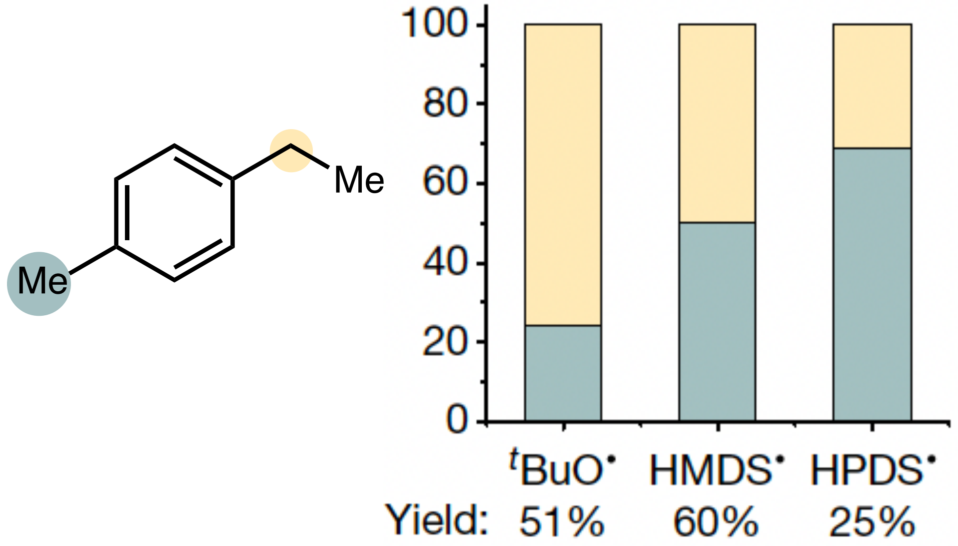
Probing C–H Selectivity

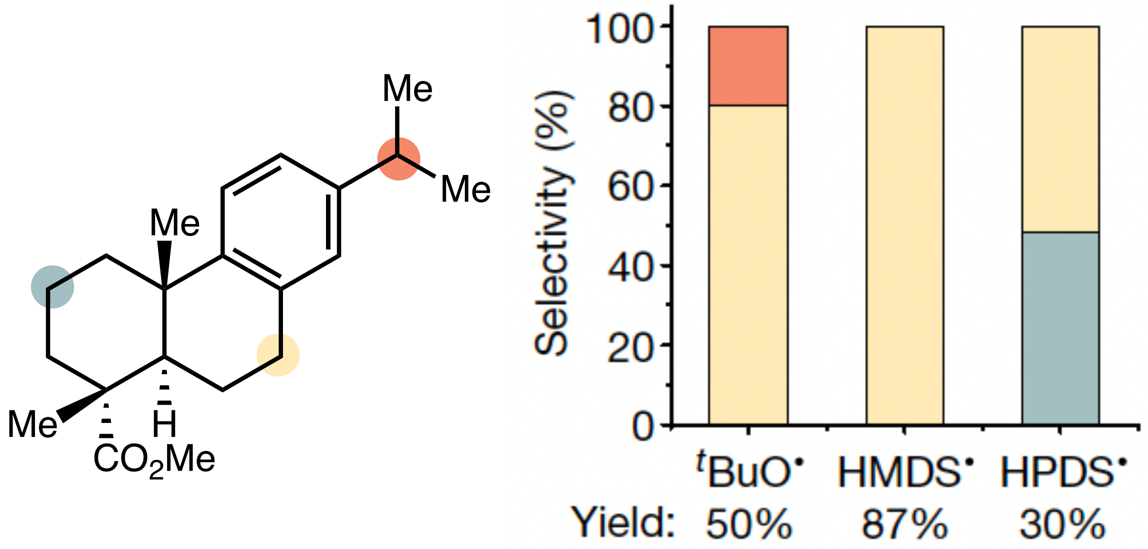












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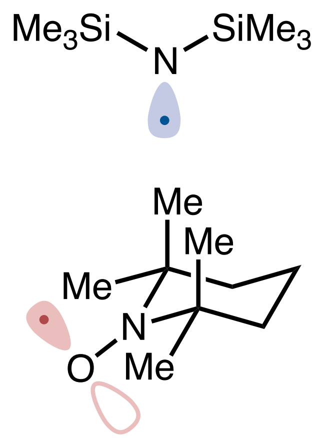
Redefining FRP



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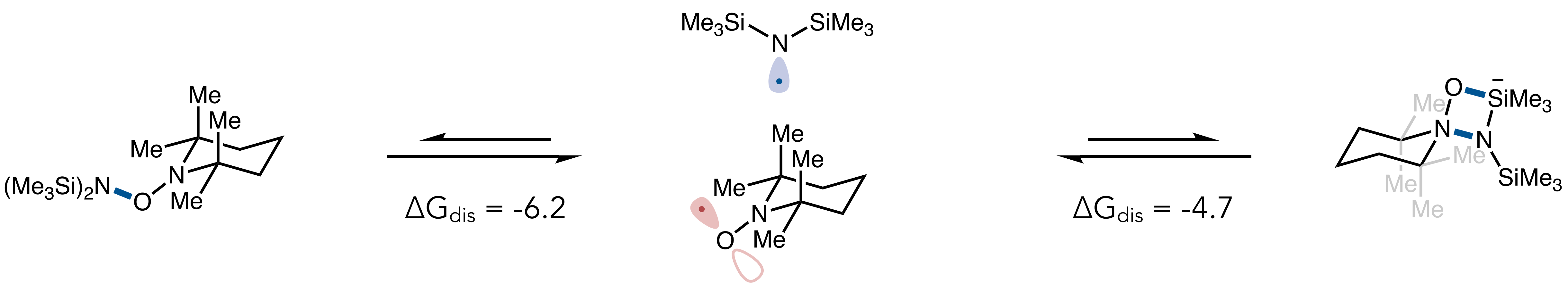
Redefining FRP



"One difference between well-known frustrated Lewis pairs (FLPs) and the relatively new 'FRPs', is that the Lewis pairs must have a tendency to associate through polar effects [although a full bond cannot be made], so that they likely travel together as a real pair, whereas the pairs of radicals formed here would diffuse freely… If 'FRP' is retained as a title, future developments would see molecular oxygen called a frustrated gas? and TEMPO as a frustrated reagent??"

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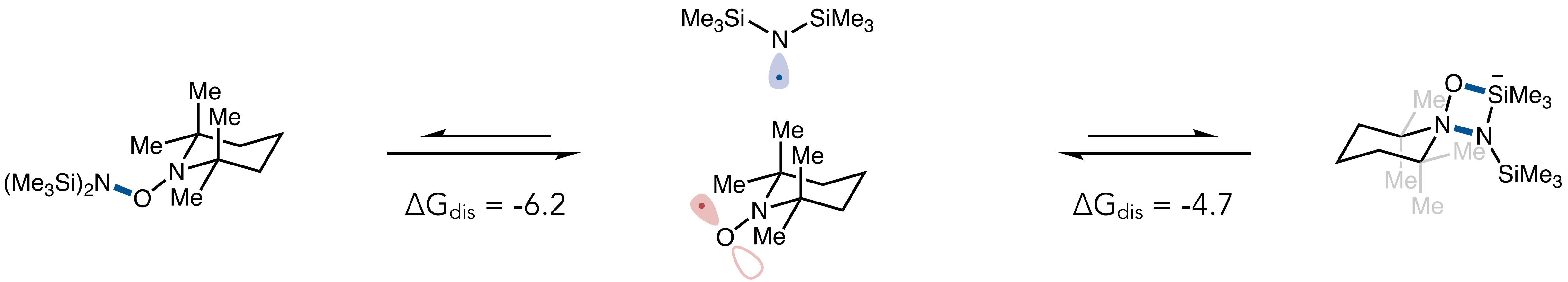
Redefining FRP



"… the disilylaminyl and tert-butoxyl radical in our FRPs are transient species generated from closed-shell ground state $HMDS^{-}$ and $tBuO^{-}$. In addition, as described above and similarly to FLPs, the two radicals in an FRP in our case display orthogonal properties and reactivities, and can synergistically achieve desired bond activation. If there is a system where two molecules of O_2 or two molecules of TEMPO• could act in synergy to react with a reaction substrate, then they would also be referred to as FRPs in that context per our definition. "

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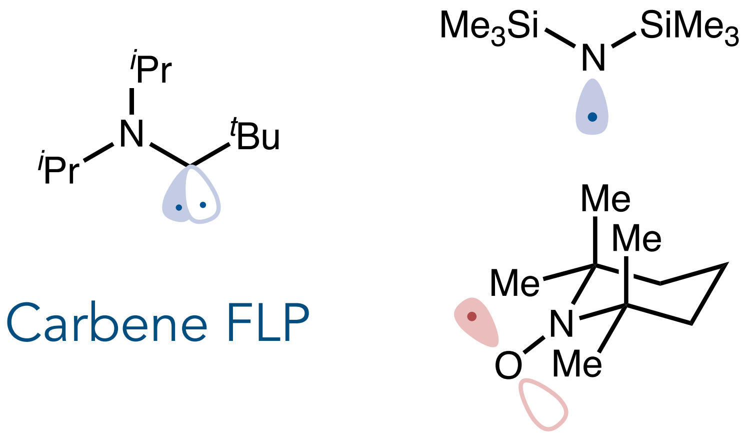
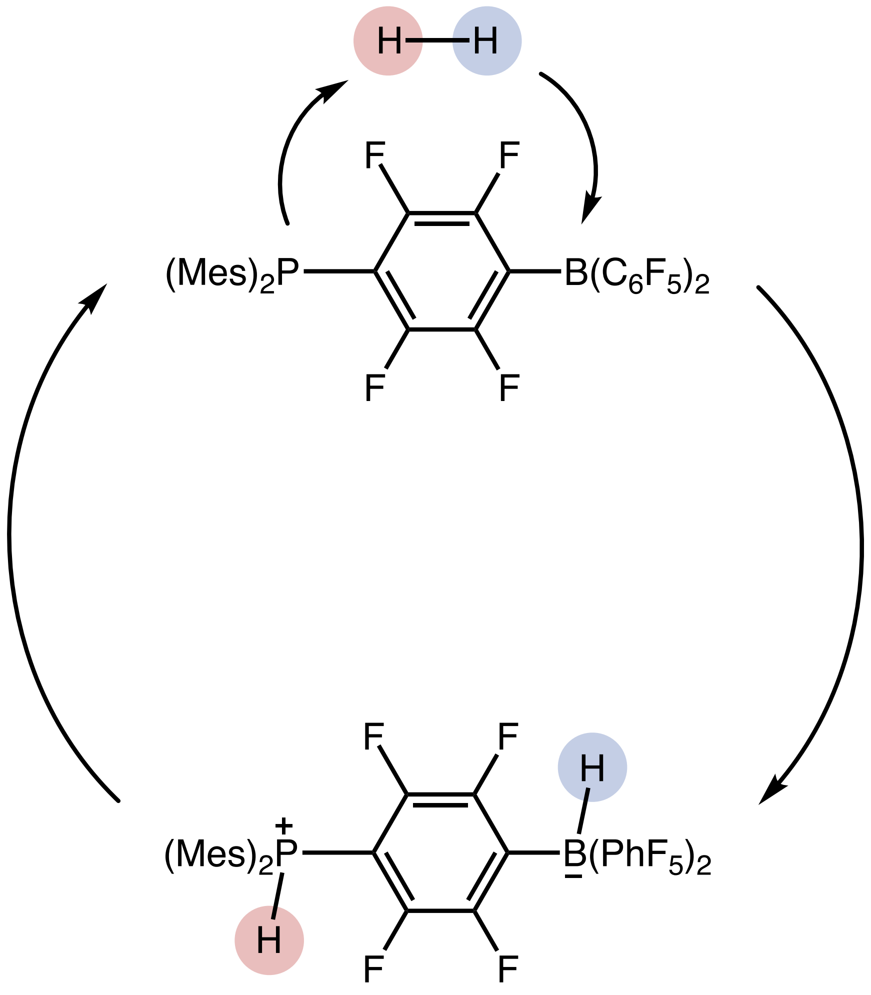
Future Directions



Carbene FLP



- Exploring different FLP & FRP complexes
- Functional group tolerance
- Catalytic turnover rate
- Air/moisture sensitivity

Questions?