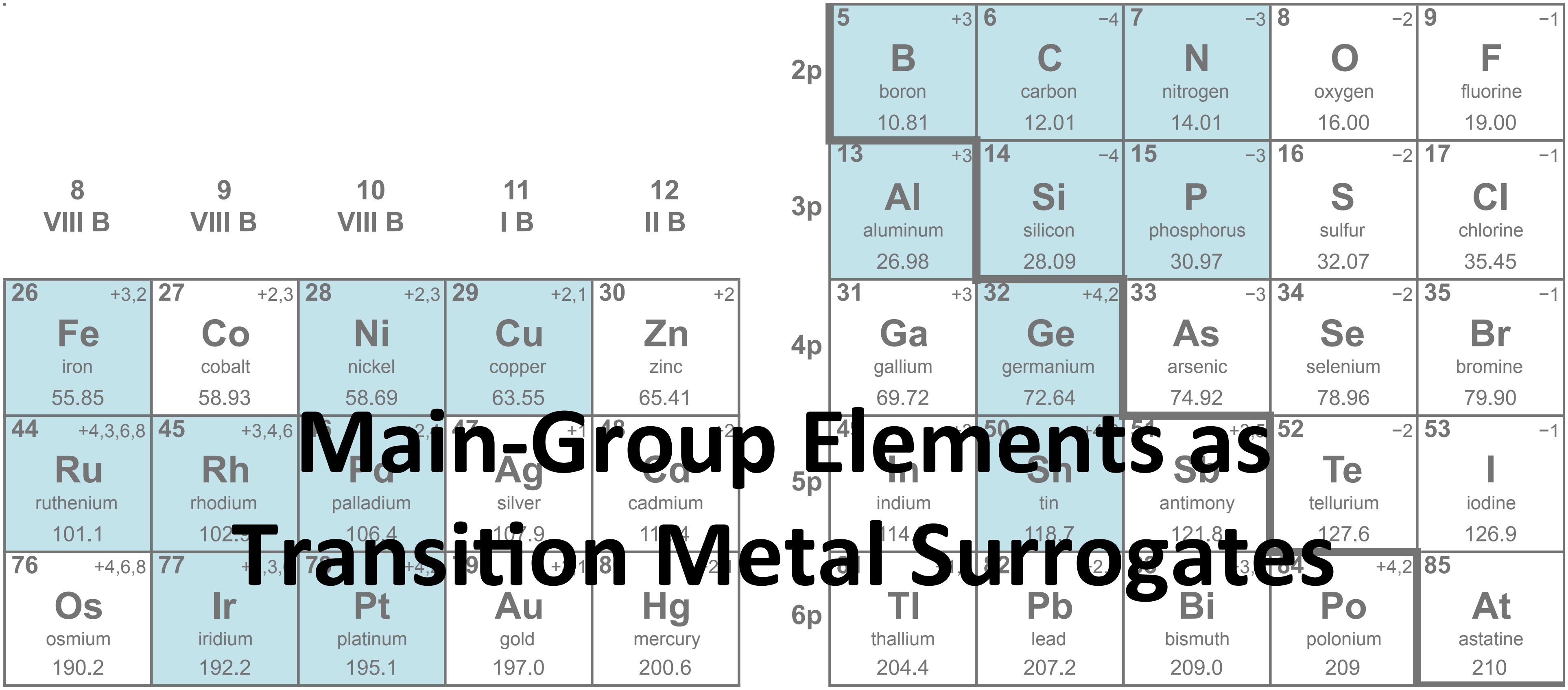
Main-Group Elements as Transition Metal Surrogates



Joshua Sacher

Frontiers of Chemistry

23 Nov 2013

Transition Metals in Synthetic Chemistry: Nobel Prizes

1912 – Catalytic Hydrogenation (Ni) – Sabatier

1918 – Ammonia Synthesis (Os, Fe) – Haber

1963 – Polymers (Ti, V) – Ziegler/Natta

2001 – Chiral Hydrogenation (Rh, Ru) – Knowles/Noyori; Chiral Oxidation (Os) – Sharpless

2005 – Metathesis (Ru, Mo, W) – Chauvin/Grubbs/Schrock

2010 – Cross Coupling (Pd) – Heck/Negishi/Suzuki

Transition Metals: Pros and Cons

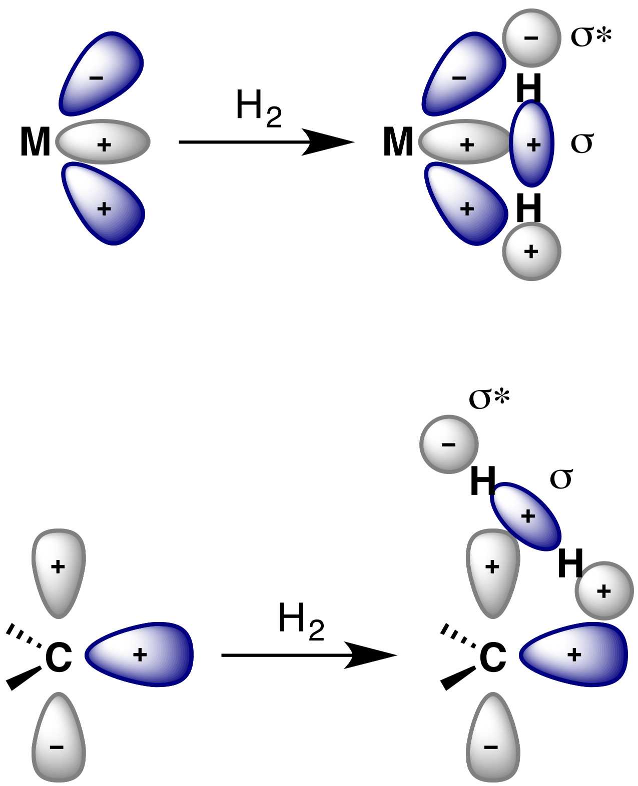
Pros	Cons
New transformations	Cost
Reactivity	Sensitivity/Instability
Tunability	Screening
Selectivity	Toxicity

Emerging solutions via 1st row transition metals

Catalytic Hydrogenation

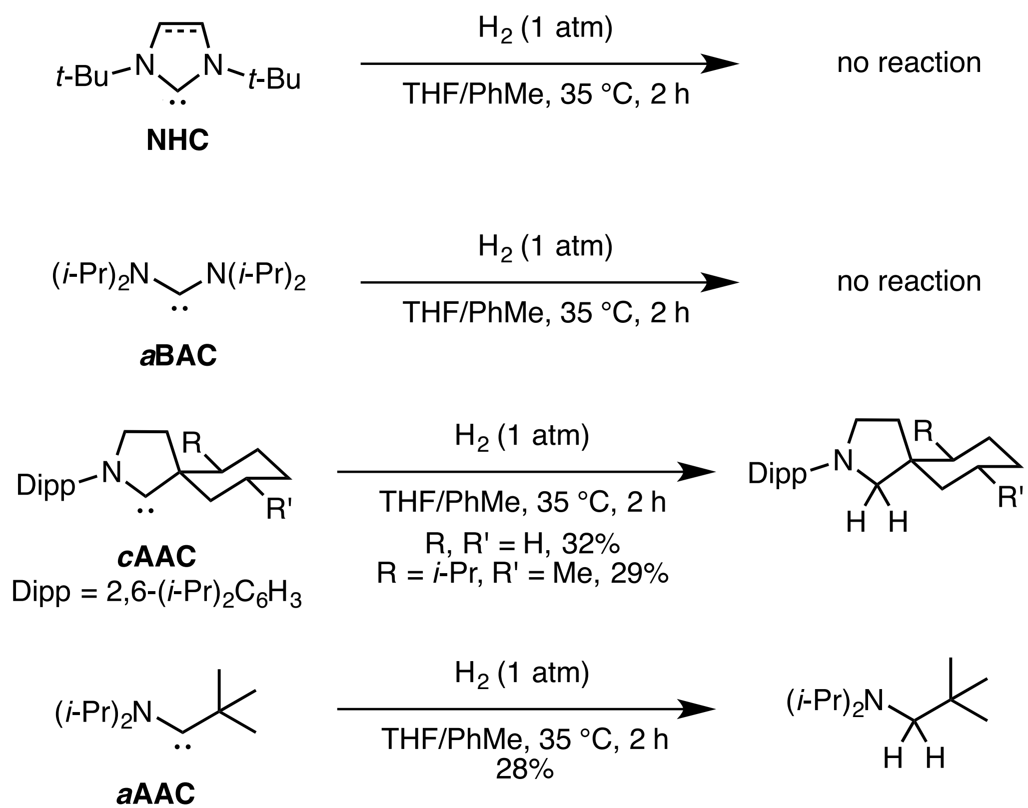
- Industrial processes
  - Food industry
  - Hydrocarbons (Fischer-Tropsch, hydrocracking, etc.)
  - Production of alcohols and amines
- Fine Chemicals
- Catalysts
  - Fe, Co, **Ni**, Ru, Rh, **Pd**, Ir, **Pt**
  - Solid supported often preferred (purification)

Carbenes as TM equivalents



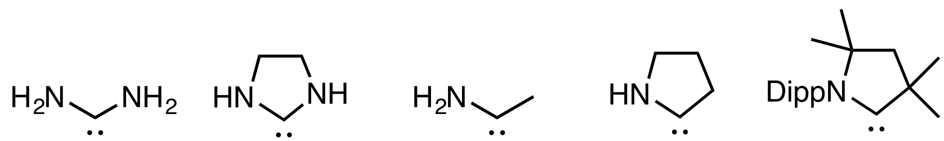
Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science*, **2007**, *316*, 439.

Carbene Activation of H_2



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

Amino-Alkyl vs. Bis-Amine

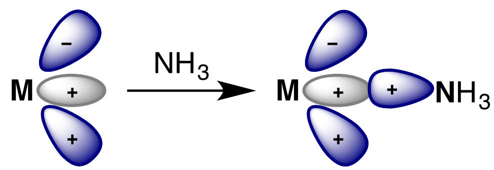


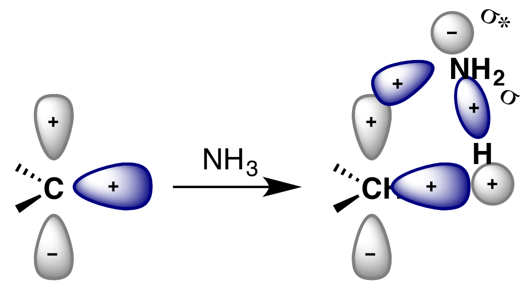
ΔE(**H_2**) (kJ/mol)	-121	-106	-212	-189	-180
ΔE(**H_2**)‡ (kJ/mol)	148	150	93	99	108
ΔE(**NH_3**) (kJ/mol)	-71	-73	-162	-139	--
ΔE(**NH_3**)‡ (kJ/mol)	141	138	87	95	--

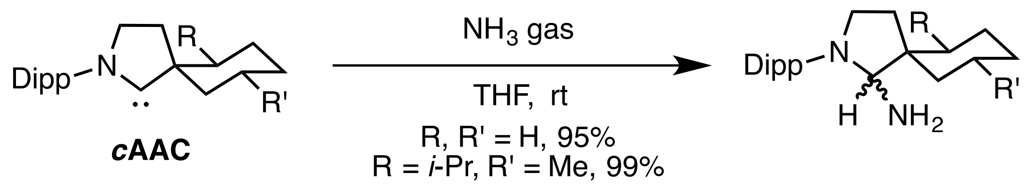
BDE:
H_2 = 436 kJ/mol
NH_3 = 460 kJ/mol

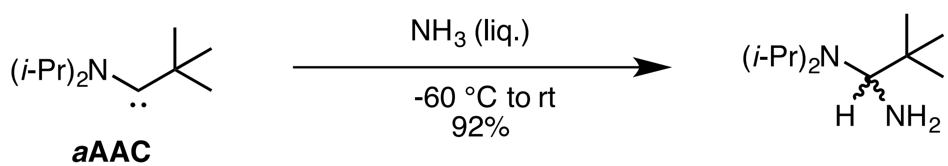
Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science*, **2007**, *316*, 439

Better than Metals: Ammonia



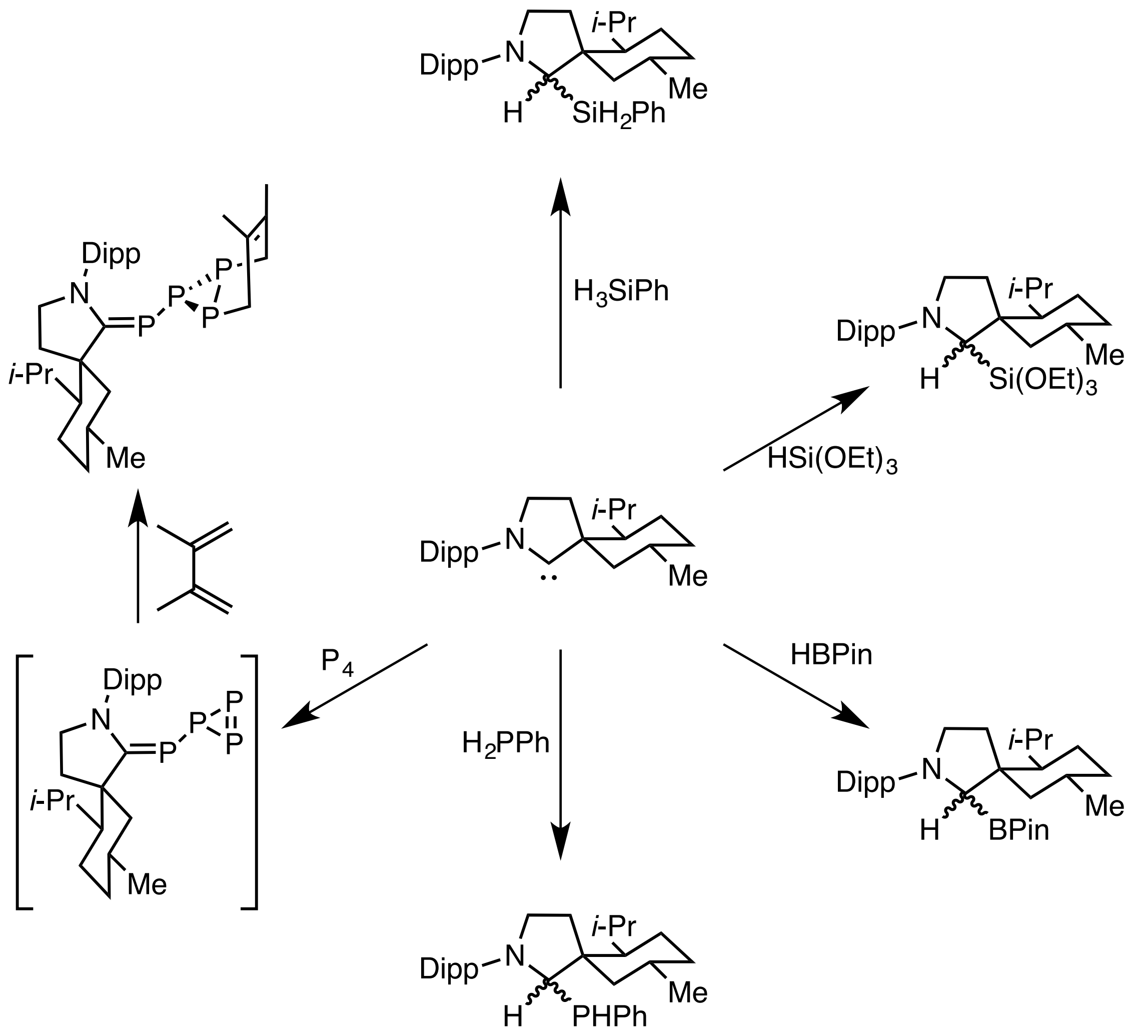






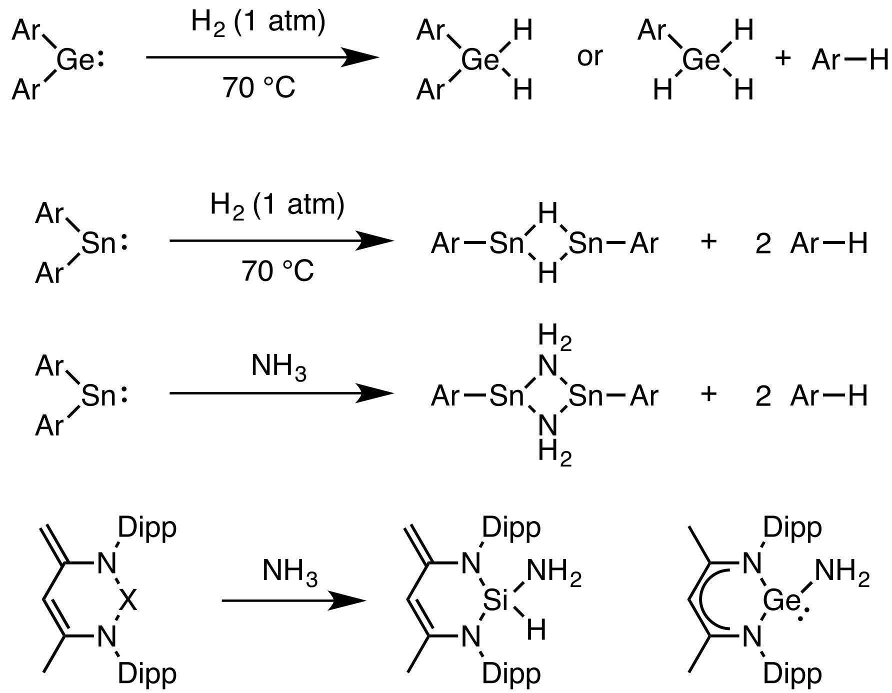
Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science*, **2007**, *316*, 439

Metal-Like Interactions



Frey, G. D.; Masuda, J. D.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 9444
Masuda, J. D.l Schoeller, W. W.; Donnadieu, B.; Bertrand, G. **2007**, *46*, 7052

Reactions of Heavier Analogs



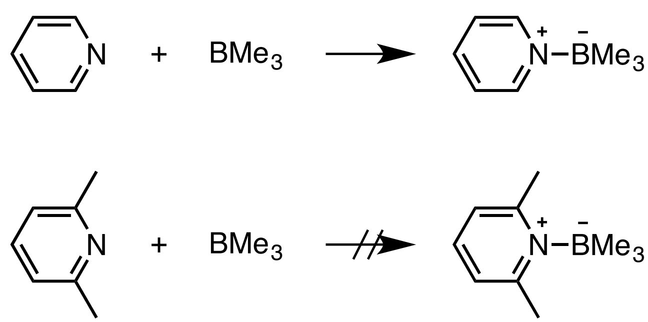
Martin, D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2011**, *2*, 389
Power, P. P. *Nature* **2010**, *463*, 171

Carbene Summary

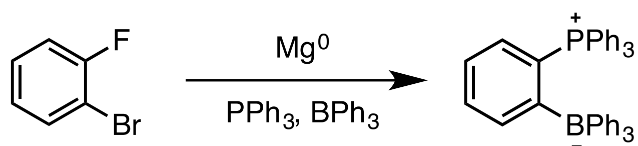
- Orbitals similar to TMs
- Inserts into wide variety of bonds
- Irreversible addition
- Limited application to further transformations

Frustrated Lewis Pairs

Brown, 1942:

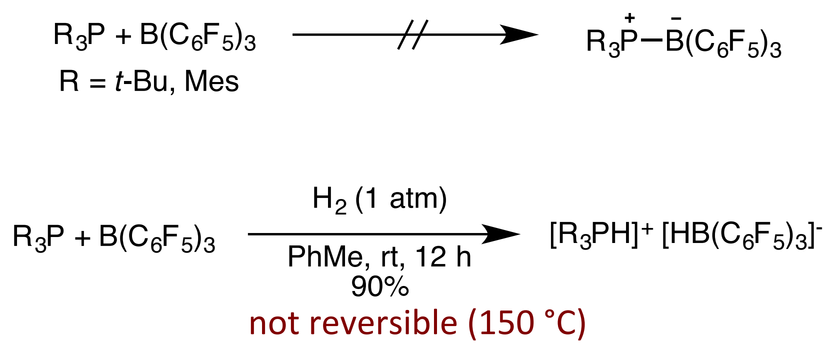


Wittig, 1959:

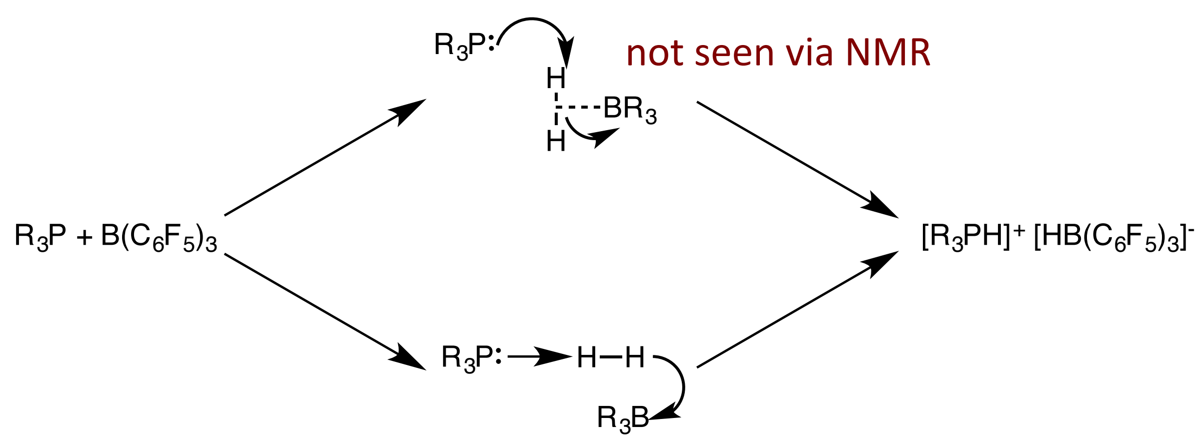


Brown, H. C.; Schlesinger, H. I.; Cardon, S. Z. *J. Am. Chem. Soc.* **1942**, *64*, 325
Wittig, G.; Benz, E. *Chem. Ber.* **1959**, *92*, 1999

H_2 Activation by FLPs

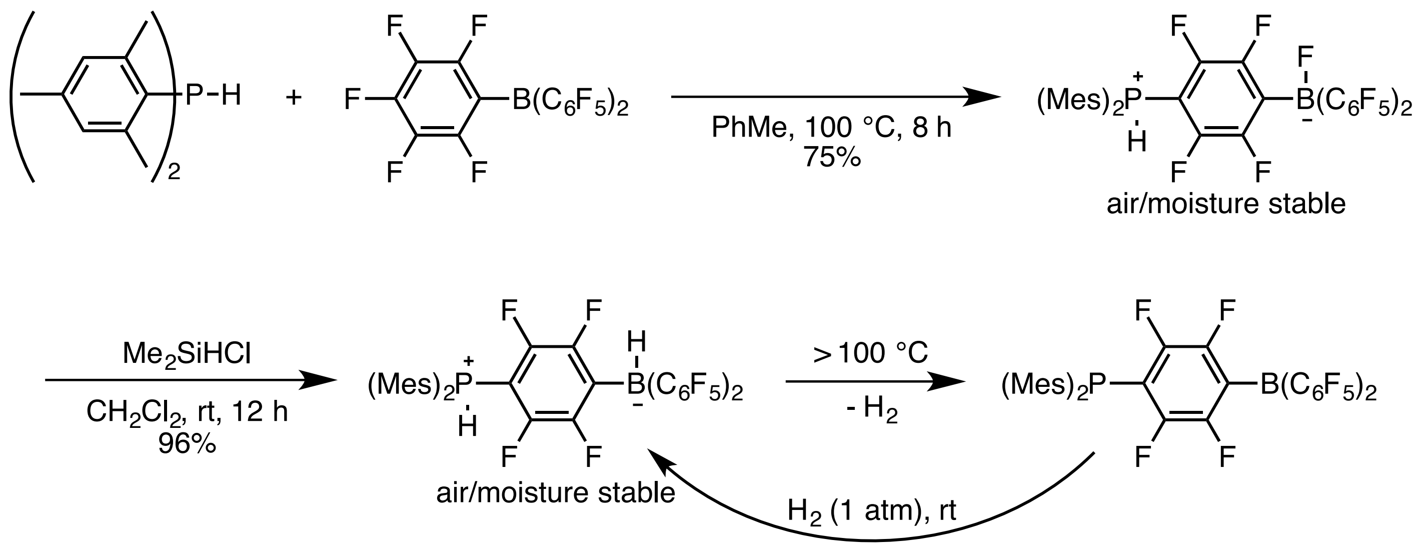


Mechanism:



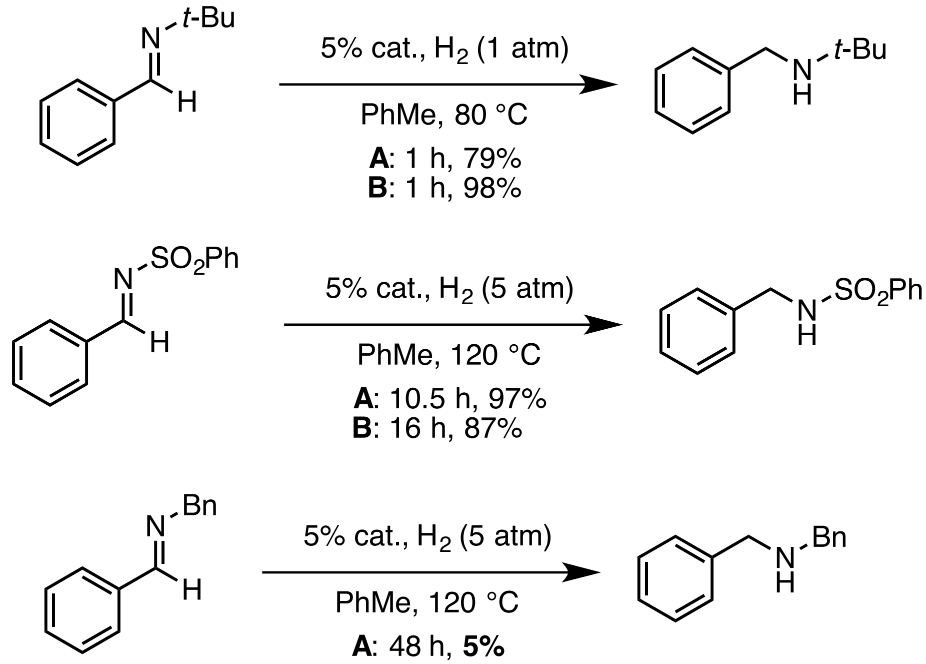
Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2007**, *129*, 1880

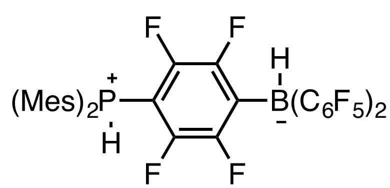
Reversible Metal-Free H_2 Activation



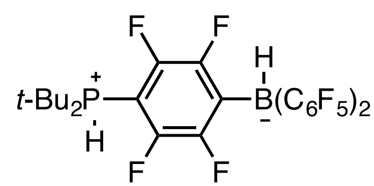
Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science*, **2006**, *314*, 1124

FLP-Catalyzed Hydrogenation





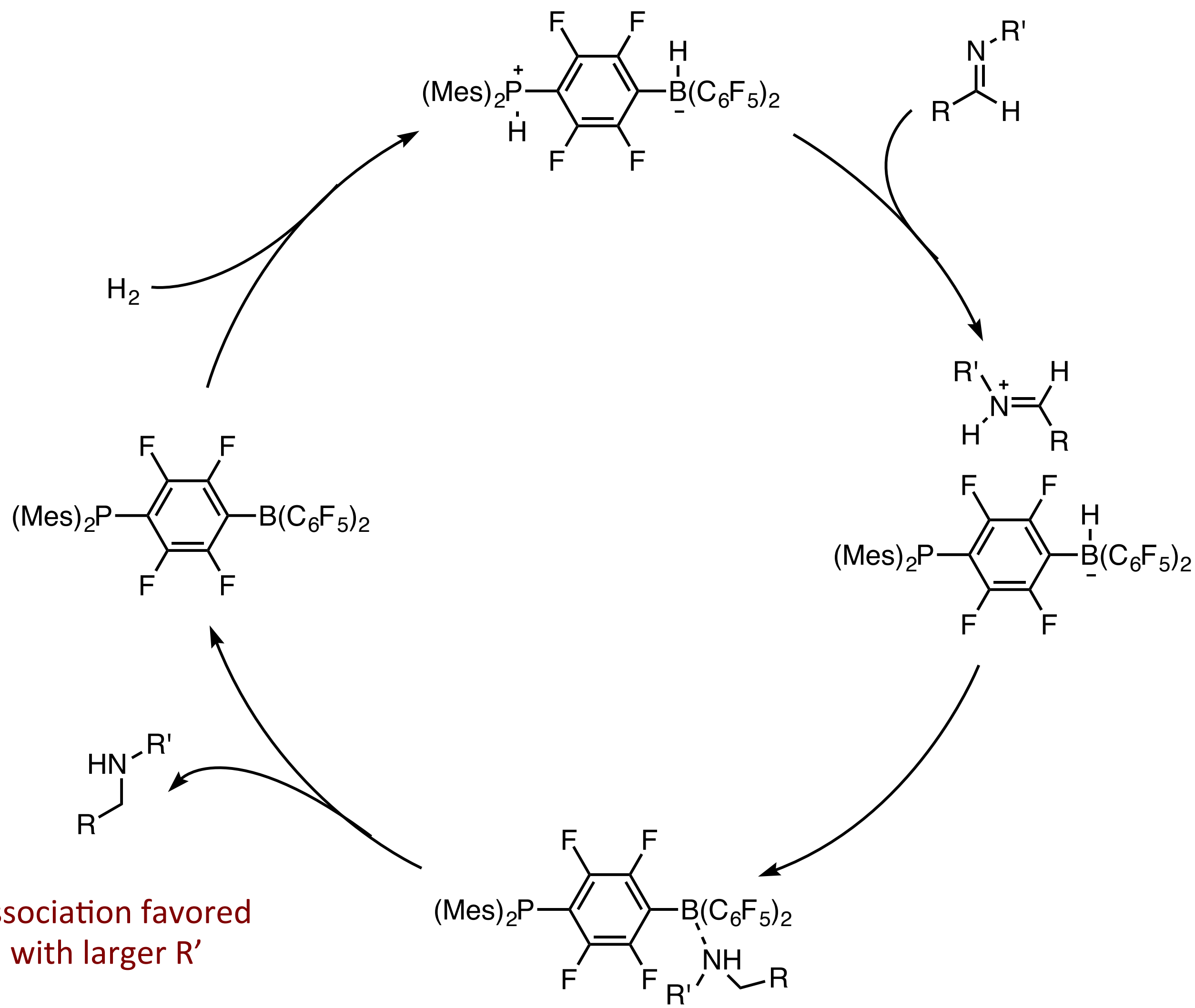
A



B

Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007**, 8050

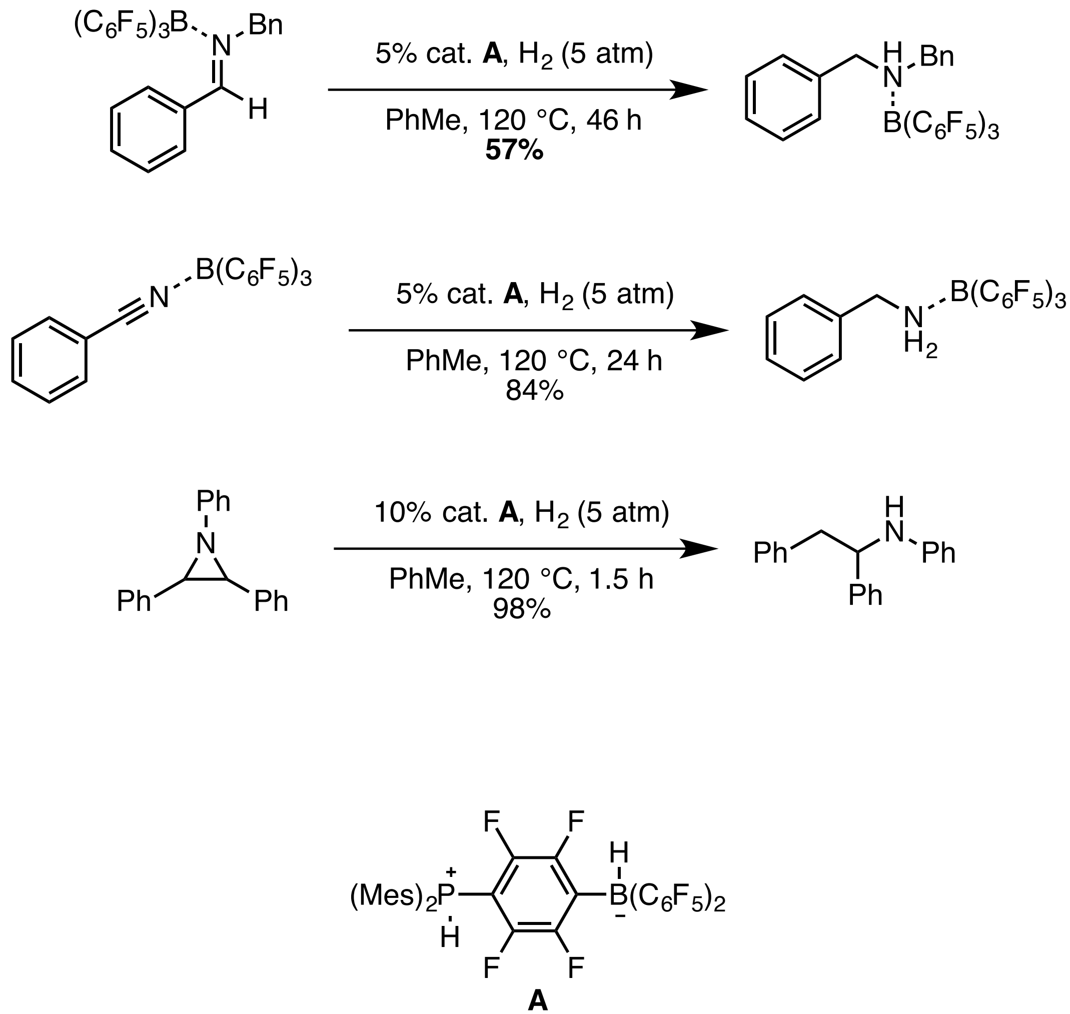
FLP Catalytic Cycle



dissociation favored
with larger R'

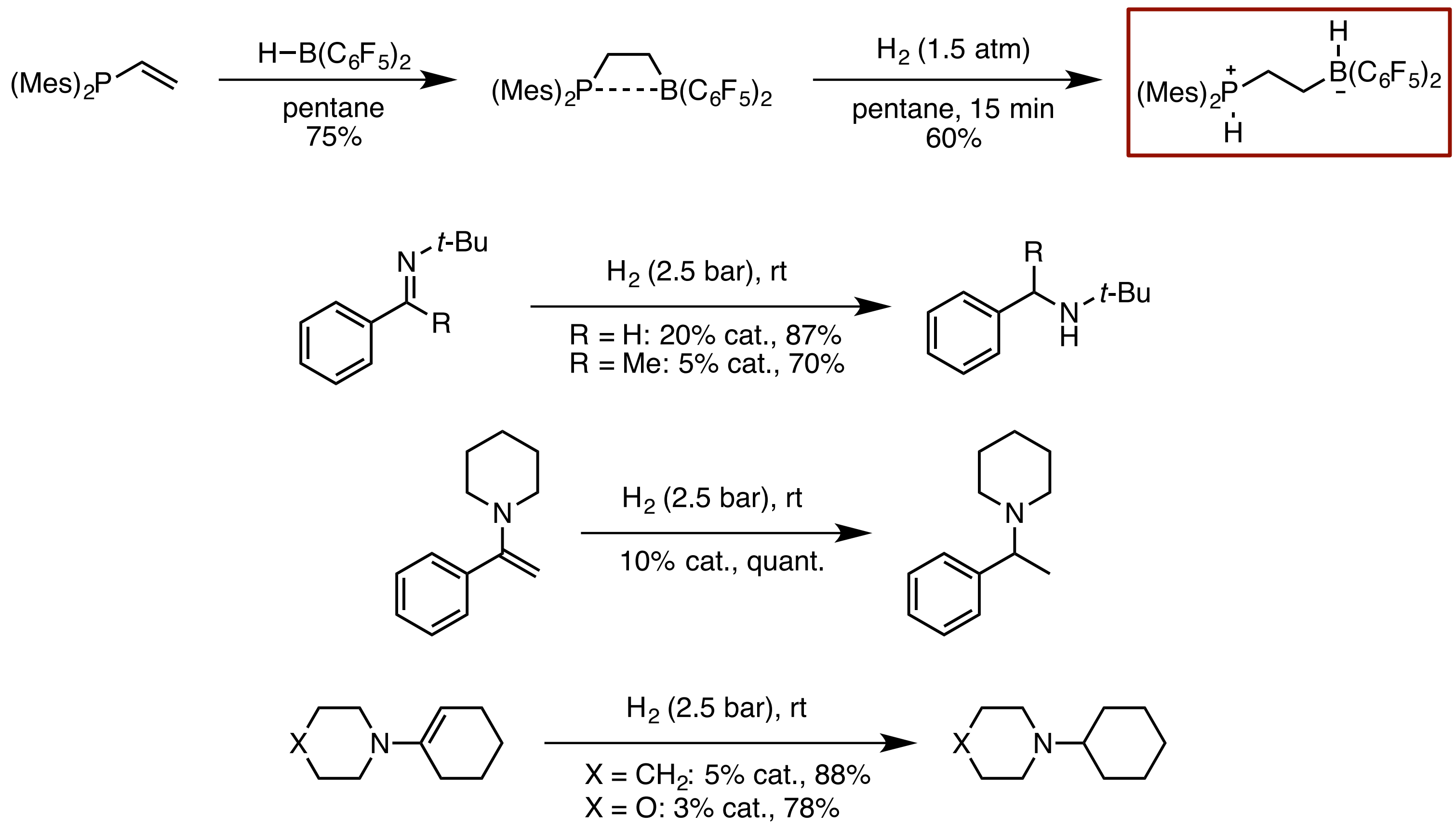
Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007**, 8050

Improving the Substrate Scope



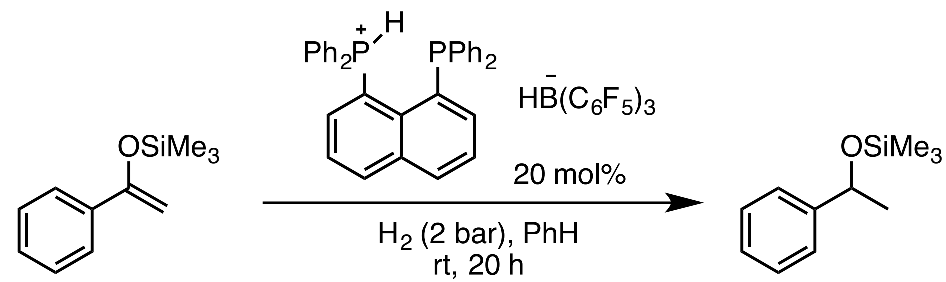
Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007**, 8050

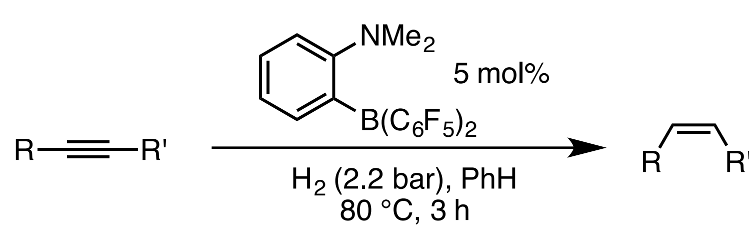
Room Temp FLP Hydrogenation



Spies, P.; Erker, G.; Kehr, G.; Bergander, K.; Fröhlich, R.; Grimme, S.; Stephan, D. W. *Chem. Commun.* **2007**, 5072
Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 7543

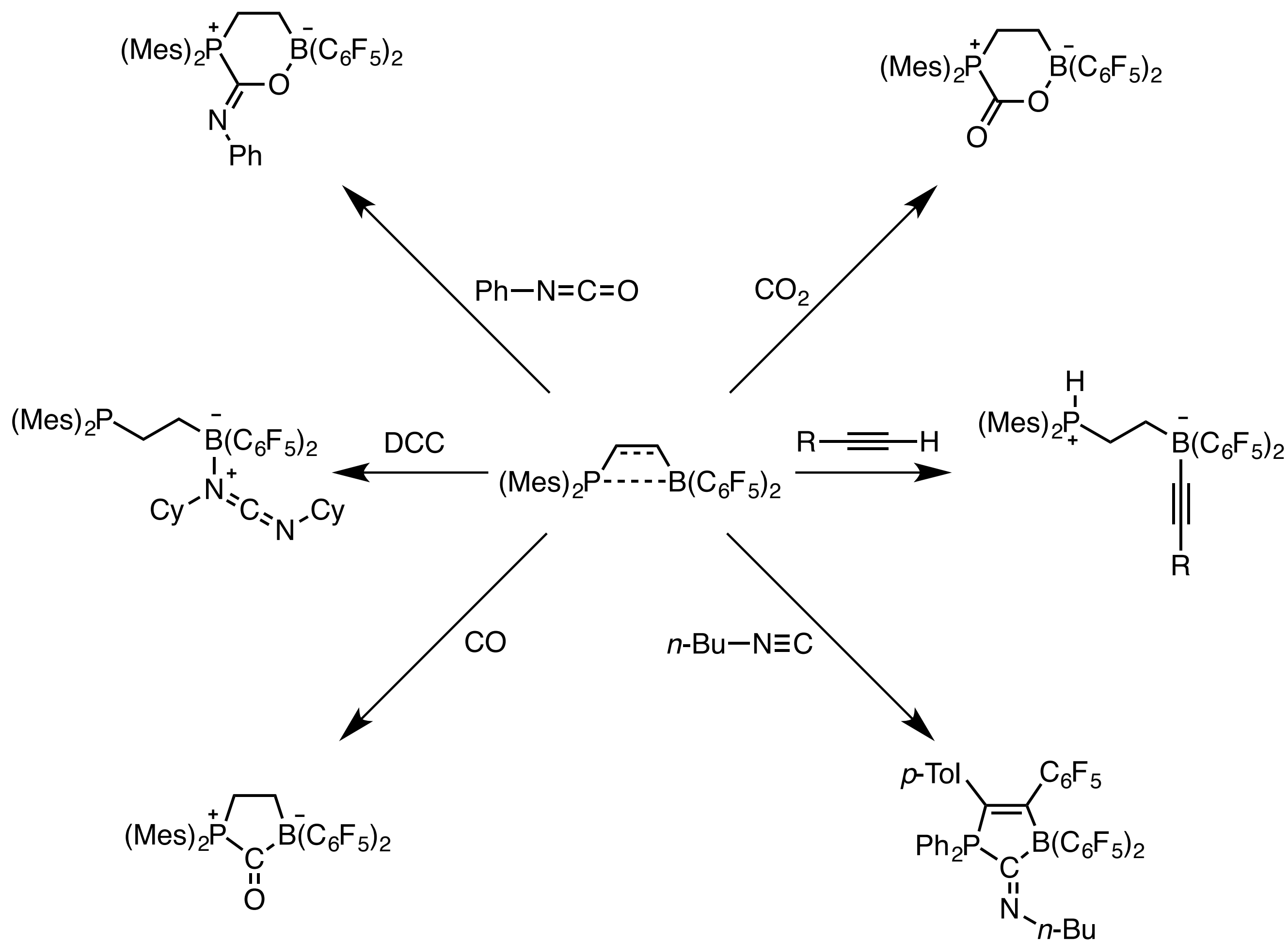
Growing Hydrogenation Scope





Wang, H.; Fröhlich, R.; Kehr, G.; Erker, G. *Chem. Commun.* **2008**, 5966
Chernichenko, K.; Madarász, Á.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. *Nat. Chem.* **2013**, *5*, 718

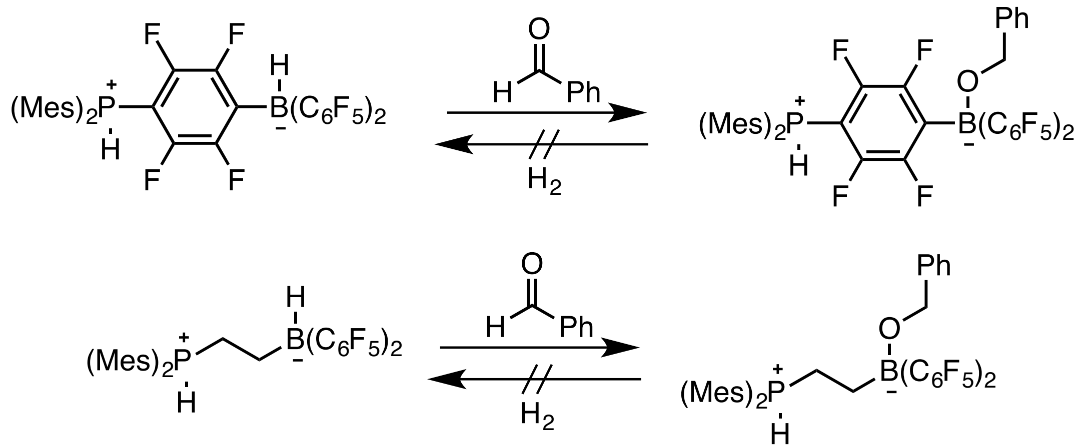
FLP Activation of Other Systems



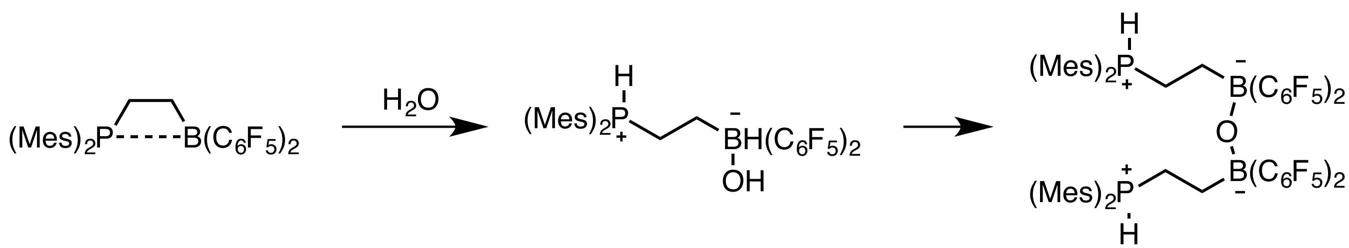
Review: Stephan, D. W.; Erker, G. *Agew. Chem. Int. Ed.* **2010**, *49*, 46
R-NC: *Chem. Sci.* **2013**, *4*, 2657; **CO**: *J. Am. Chem. Soc.* ASAP DOI: 10.1021/ja408815k

Limitations of FLPs

Oxygen-containing substrates:



Water sensitivity:



References

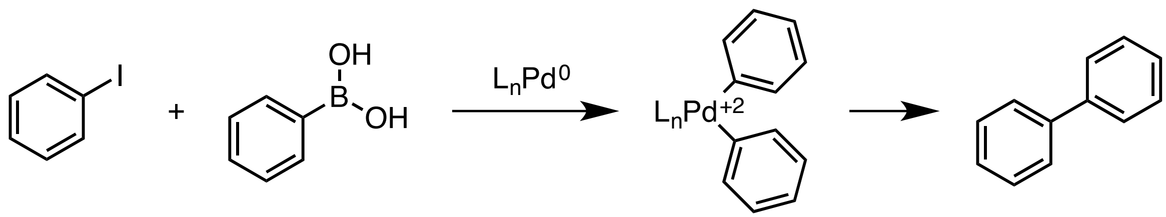
FLP Summary

- Activate H_2 under mild conditions
- Reversible reactions possible
- Application to catalytic hydrogenation
- Limited Scope to date, but expanding
- Great potential for further transformations

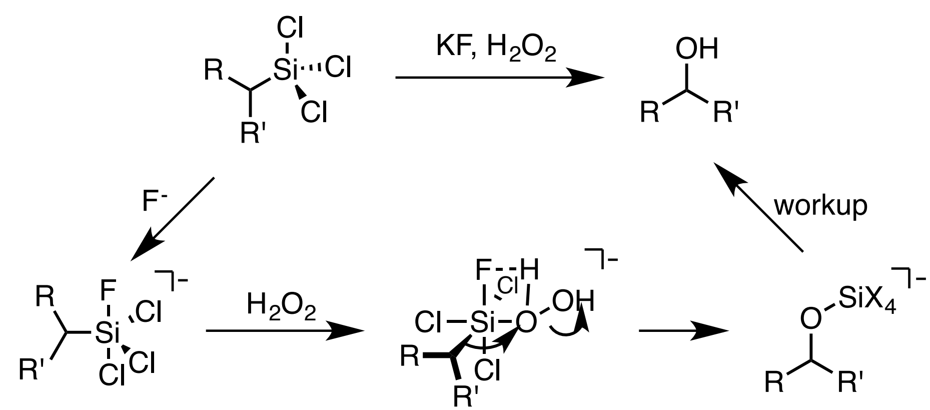
Stephan, D. W. *Dalton Trans.* **2009**, 3129
Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 46
Stephan, D. W. *Org. Biomol. Chem.* **2012**, *10*, 5740

Ligand Coupling

Reductive elimination with metals

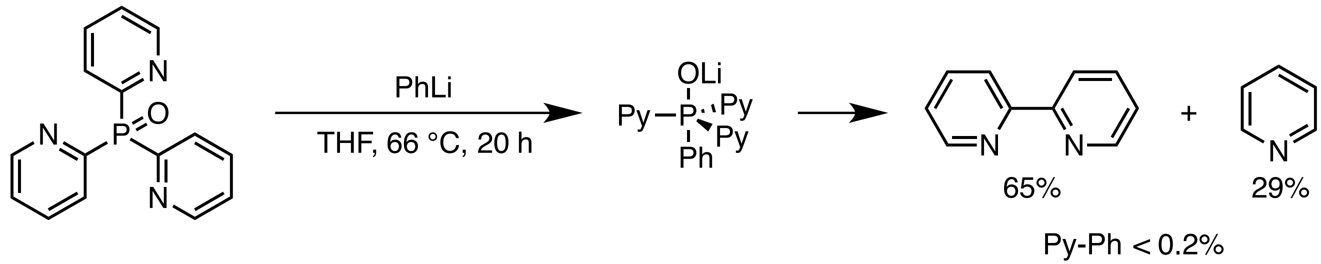


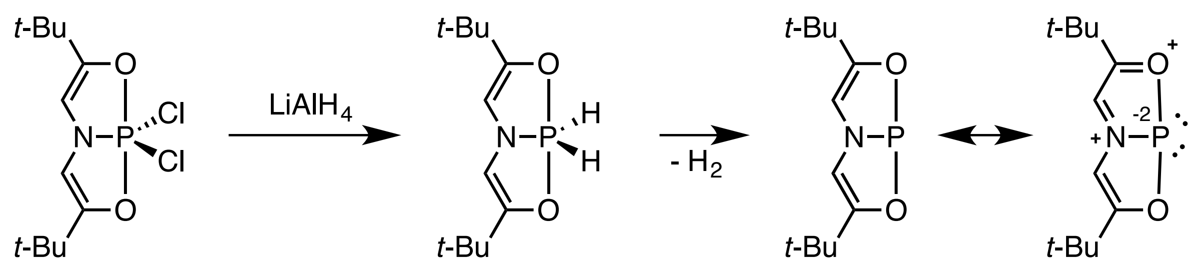
Non-metal “reductive elimination”



Mader, M. M.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 1970
Akiba, K. Y. *Chemistry of Hypervalent Compounds*. Wiley VCH: New York, 1999

Ligand Coupling @ Phosphorus

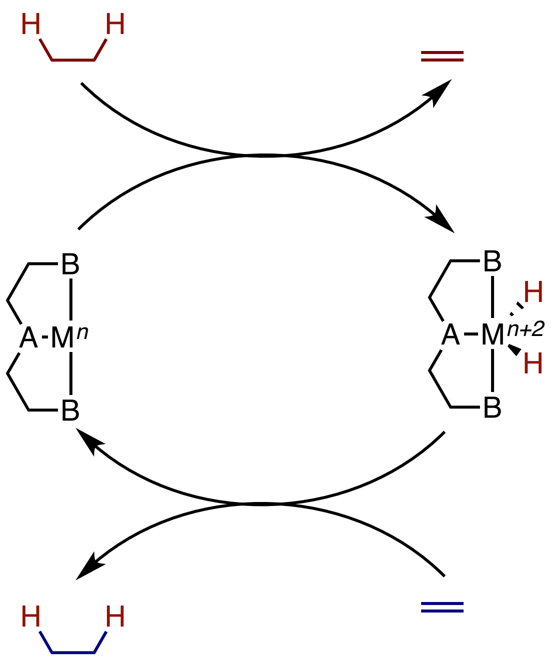


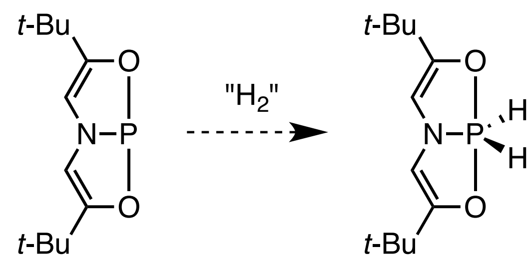


"ADPO•H_2 can be prepared from the reduction of ADPO•Cl_2 with $LiAlH_4$. However, it is unstable and slowly decomposes with reductive elimination to give ADPO."

Uchida, Y.; Onoue, K.; Tada, N.; Nagao, F. *Tetrahedron Lett.* **1989**, *30*, 567
Arduengo, A. J., III; Stewart, C. A. *Chem. Rev.* **1994**, *94*, 1215

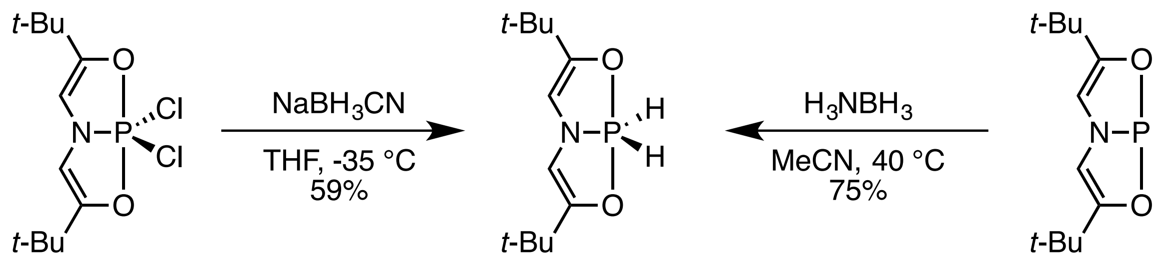
P-based "Oxidative Addition?"

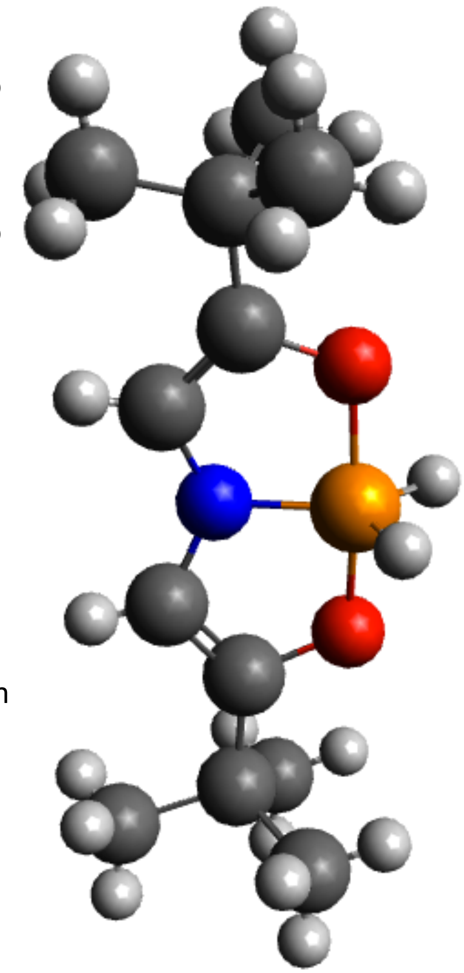




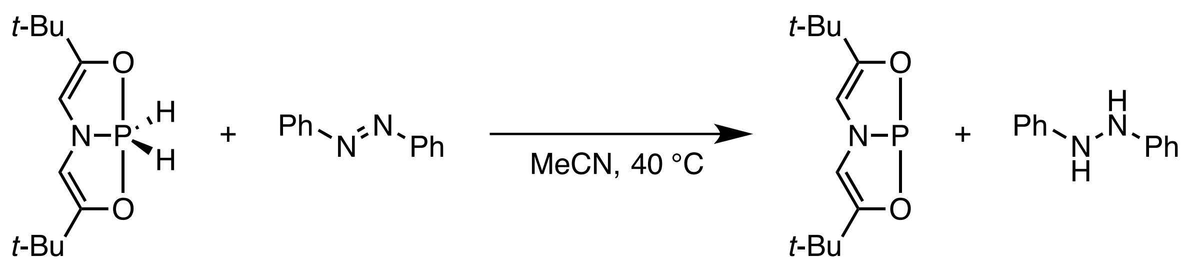
Dunn, N. L.; Ha, M.; Radosevich, A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330

Preparation and Test Reaction



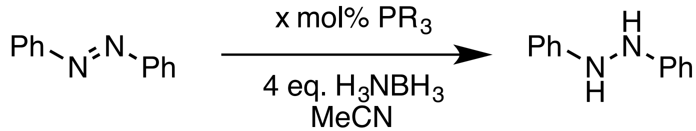


Stoichiometric reduction:

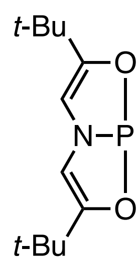


Dunn, N. L.; Ha, M.; Radosevich, A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330

Catalytic Transfer Hydrogenation



Entry	PR_3	mol %	Time (h)	T (°C)	Yield
1	none	--	24	80	< 5%
2	**A**	10	24	40	80%
3	**A**	10	48	40	94%
4	**B**	10	24	40	63%
5	**B**	10	48	40	81%
6	PPh_3	100	24	80	< 5%
7	$P(OMe)_3$	100	24	80	< 5%
8	$P(NMe_2)_3$	100	24	80	24%



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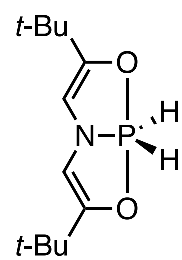
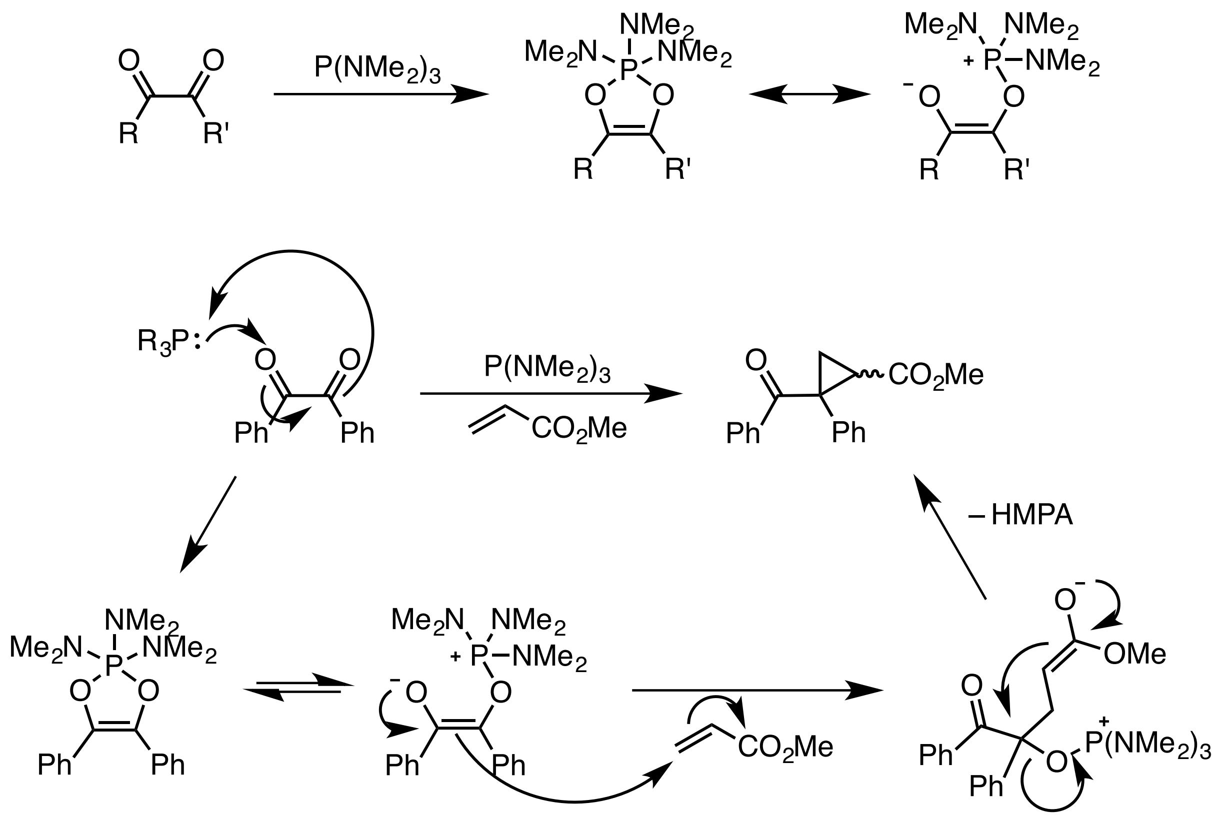


B

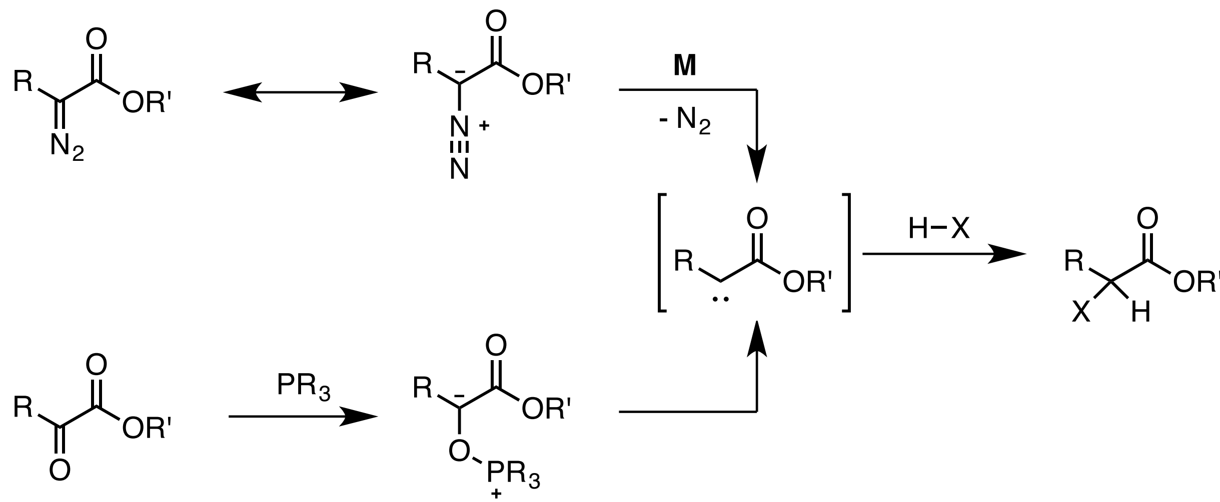
Dunn, N. L.; Ha, M.; Radosevich, A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330

Other Metal-Like Reactions



Osman, F. H.; El-Samahy, F. A. *Chem. Rev.* **2002**, *102*, 629
Fauduet, H.; Burgada, R. *Synthesis*, **1980**, 642

Metal-Free Carbene Equivalents

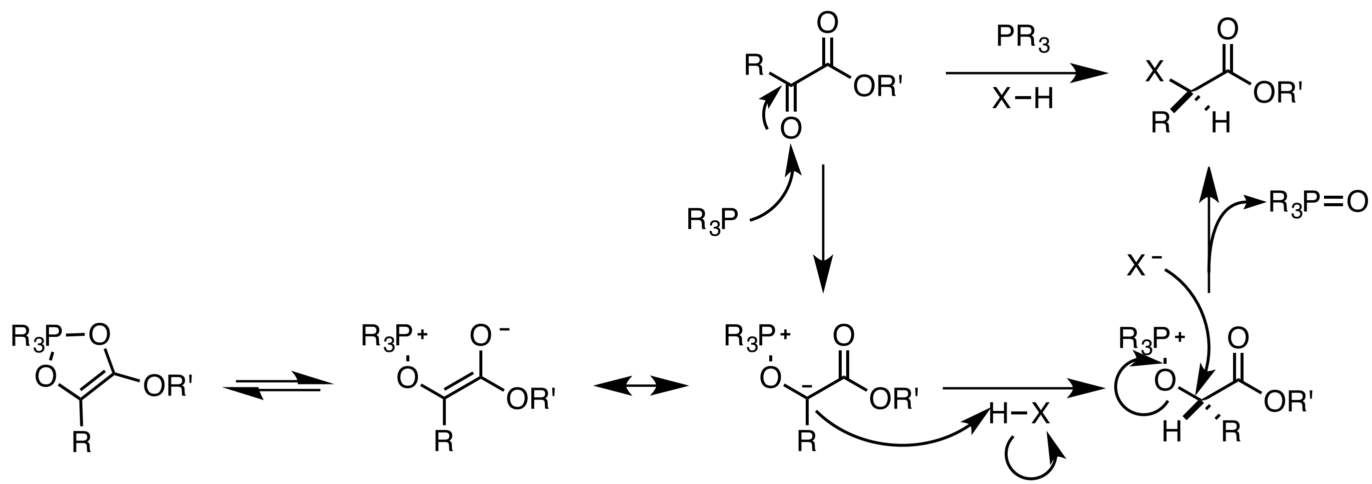


Pitfalls of diazo compounds:

- Hazardous
- N_2 on scale
- TM catalysts
- Extra synthetic steps

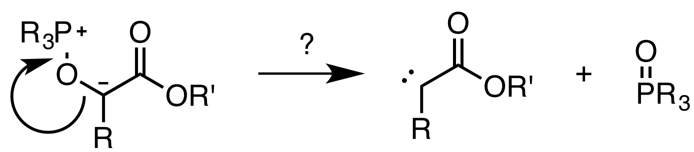
Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

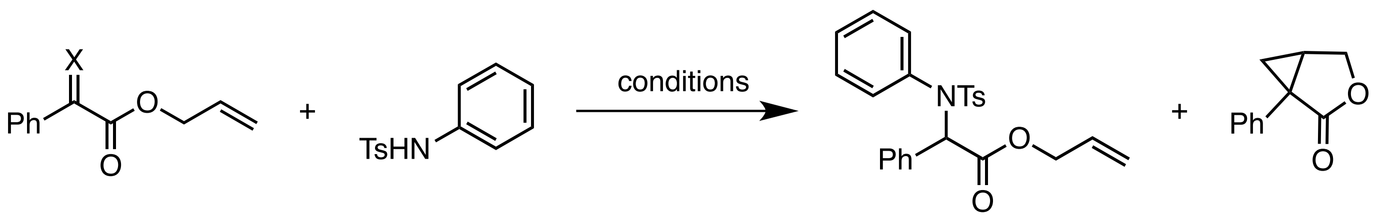
Mechanistic Hypothesis



Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

Possible Carbene Intermediate

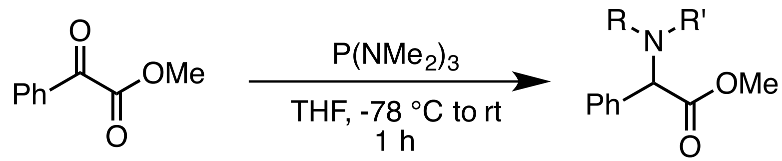




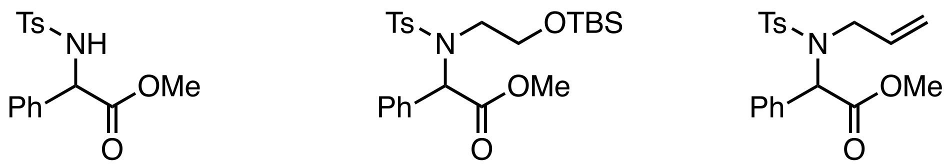
X = O, $P(NMe_2)_3$, THF, -78 °C to rt	82%	0%
X = N_2. $Rh_2(OAc)_4$, CH_2Cl_2, rt	0%	64%

Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

Reductive N–H "Insertion"

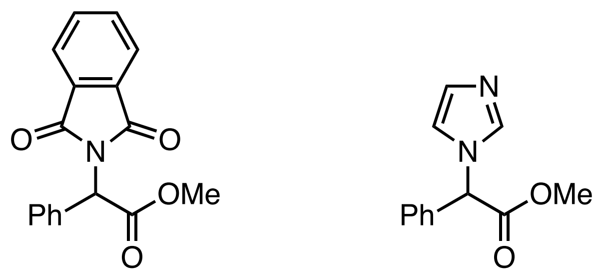


Sulfonamides



70% 85% 85%

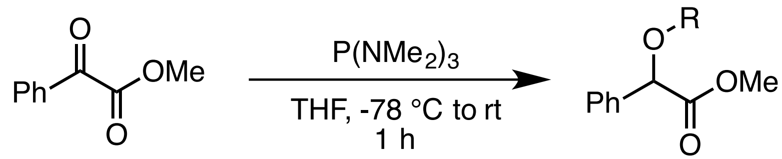
Heterocycles



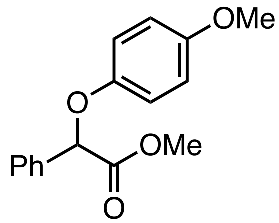
83% 81%

Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

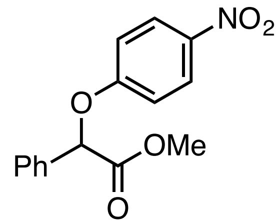
O–H Addition



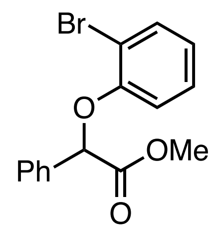
Phenols



91%

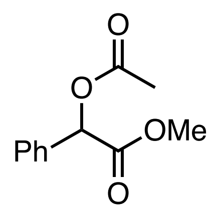


60%

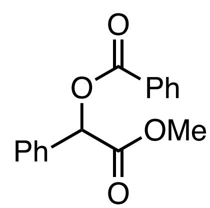


99%

Acids

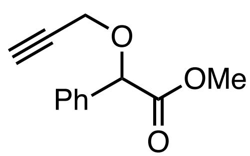


63%

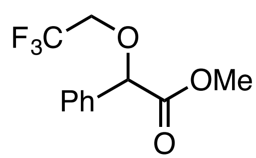


89%

Aliphatics



60%



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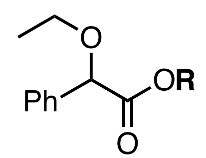
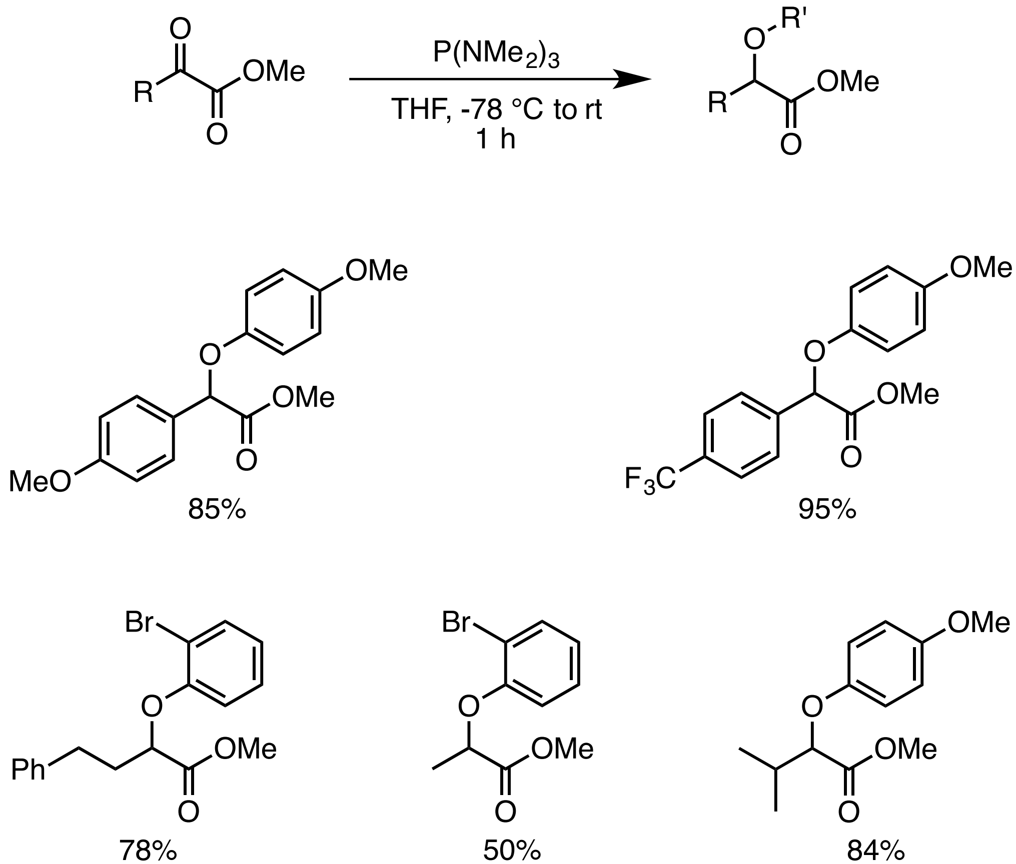


R = OMe, < 5%
EtOH solv. R = OEt, 57%

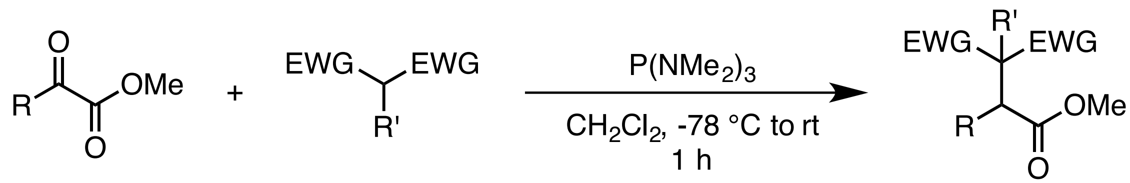
Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

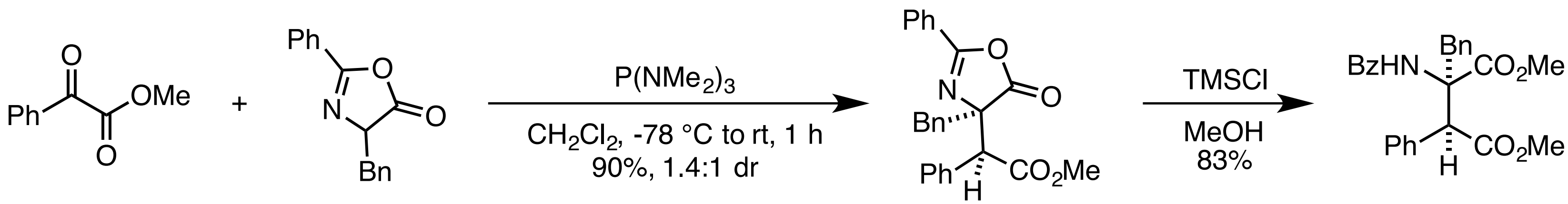
α-Ketoester Substrates

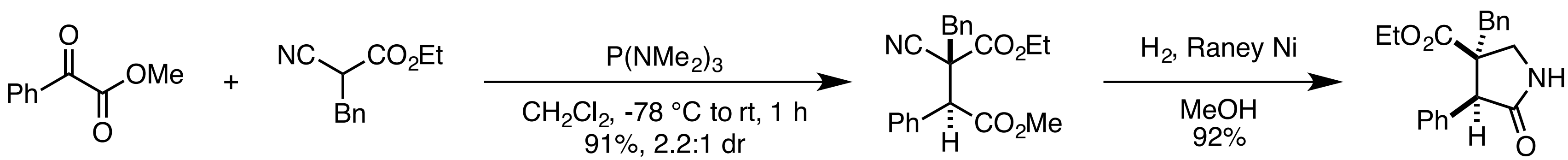


Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

C_{sp^3}–C_{sp^3} Bond Formation

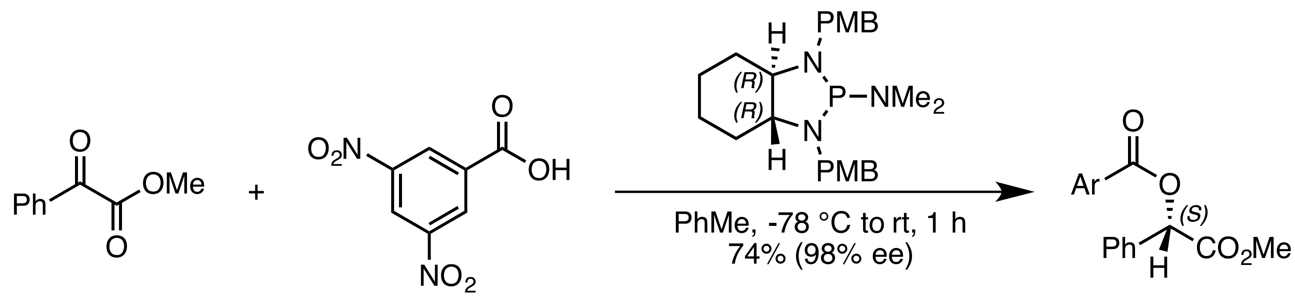






Zhao, W.; Fink, D. M.; Labutta, C. A.; Radosevich, A. T. *Org. Lett.* **2013**, *15*, 3090

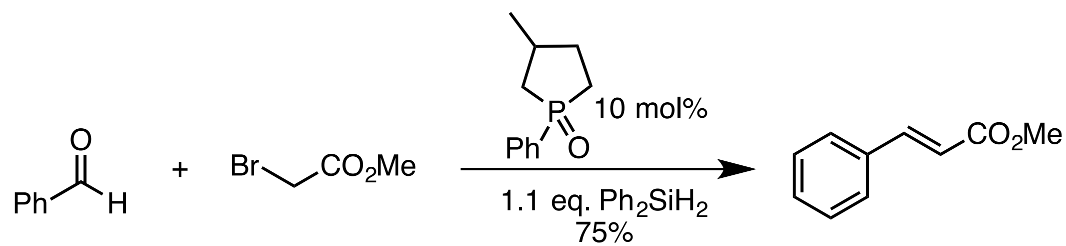
Enantioselective X–H Addition



Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605

Toward a Catalytic Variant?

Catalytic Wittig



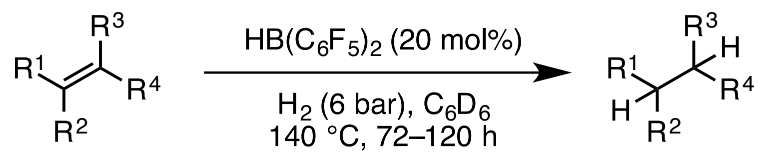
No practical reduction of HMPA to HMPT is known

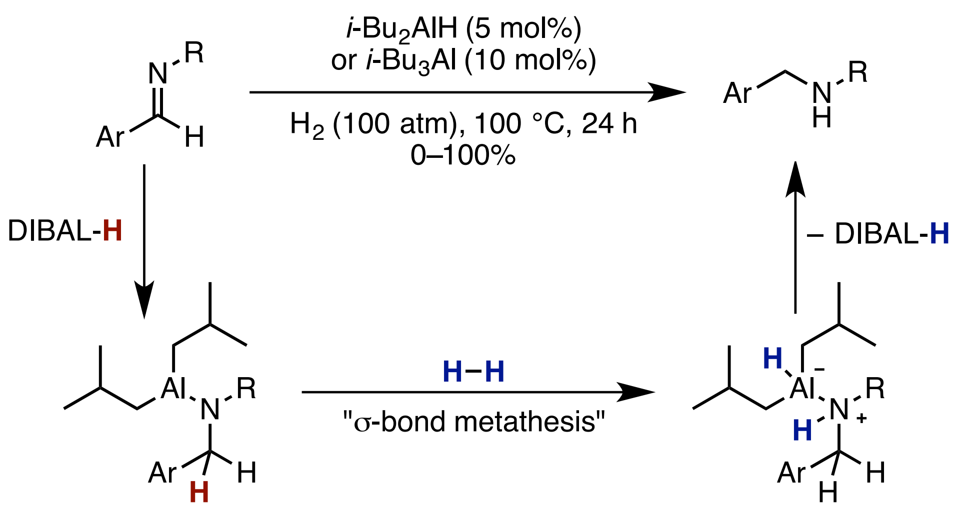
O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836

Phosphine Summary

- Metal-free transfer hydrogenation
  - Easy to prepare, use
  - Air/moisture sensitive
  - Very limited reaction scope
- Metal-free carbene equivalents
  - Easily accessible SM
  - Reasonably broad substrate scope
  - Generally good yields
  - Asymmetric reaction possible
  - Stoichiometric HMPT/HMPA
  - Need other source of chirality

σ-Bond Metathesis





Wang, Y.; Chen, W.; Lu, Z.; Li, Z. H.; Wang, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7496
Hatnean, J. A.; Thomson, J. W.; Chase, P. A.; Stephan, D. W. *Chem. Commun.* ASAP DOI: 10.1039/C3CC47889K

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