

Synthesis in High Temperature Water and Hydrophosphination of Carbodiimides with Phosphine Boranes

John Milligan

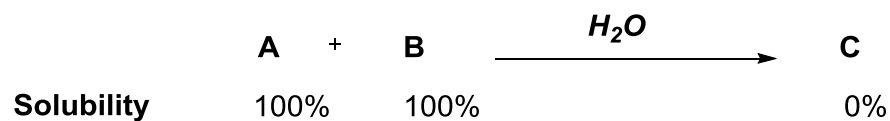
Research Topic Seminar

Wipf Group Meeting- September 13, 2014

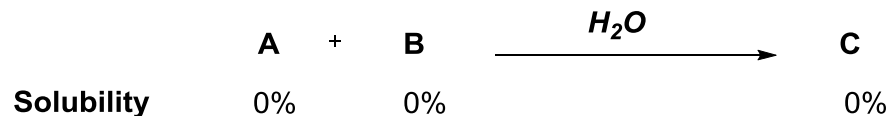
PART I: SYNTHESIS IN HIGH TEMPERATURE WATER

Water in organic synthesis

In Water

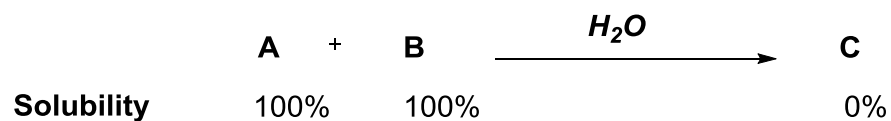


On Water

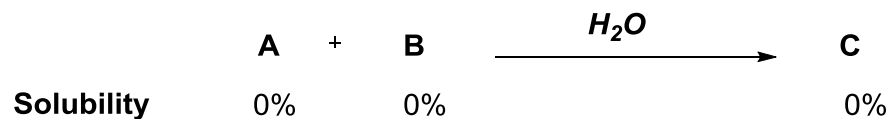


Water in organic synthesis

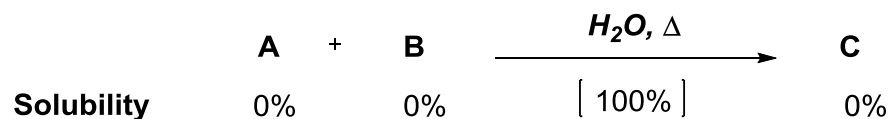
In Water



On Water

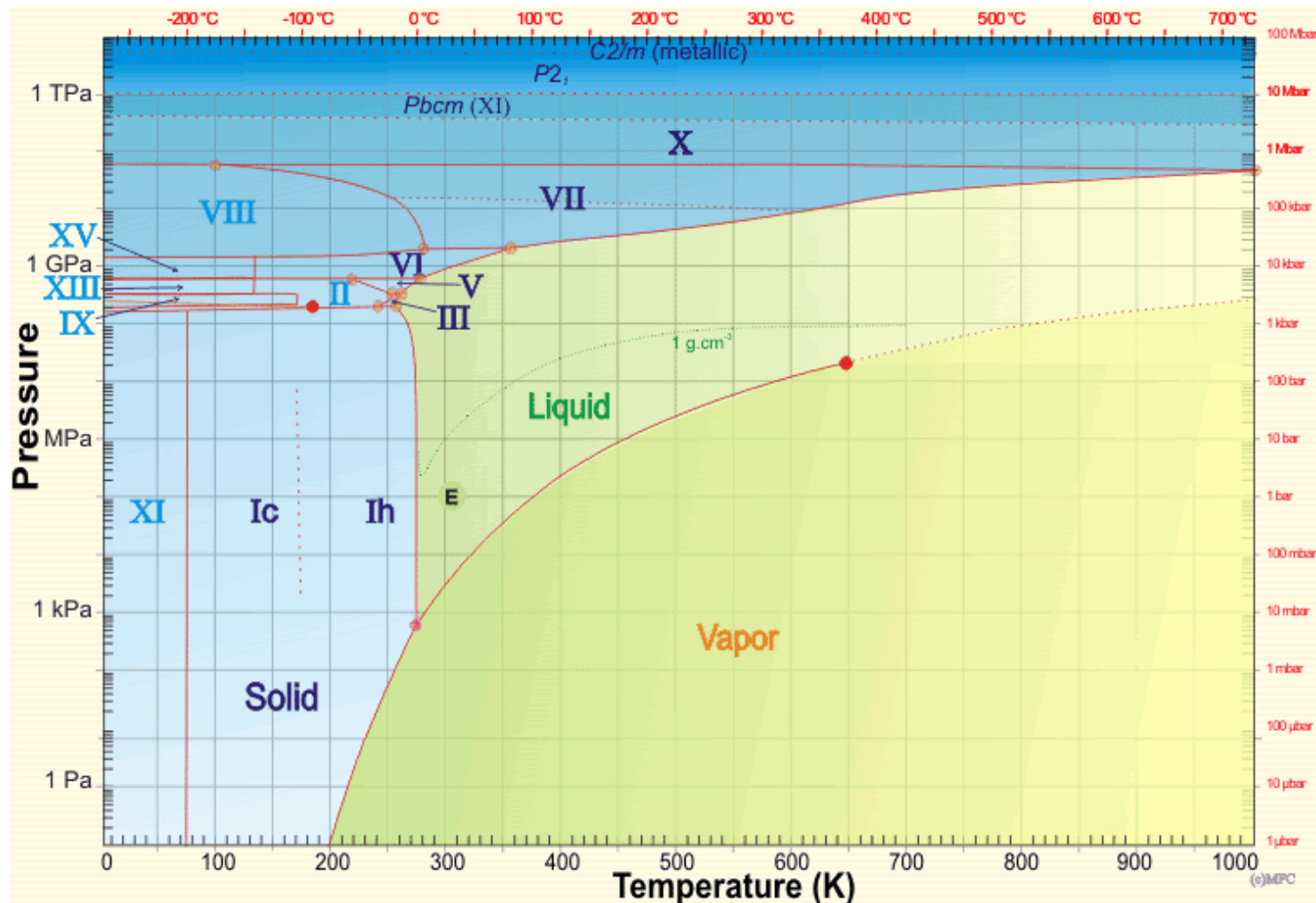


Supercritical Water (SCW)

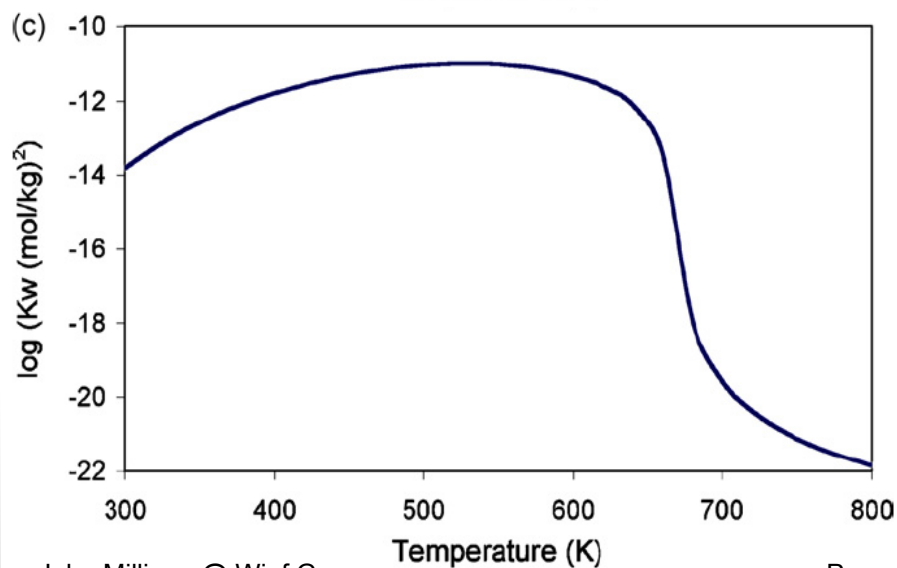
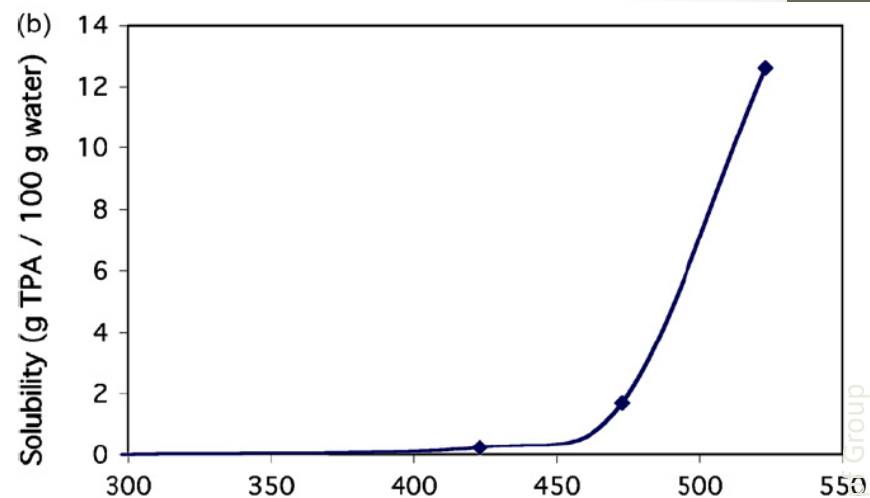
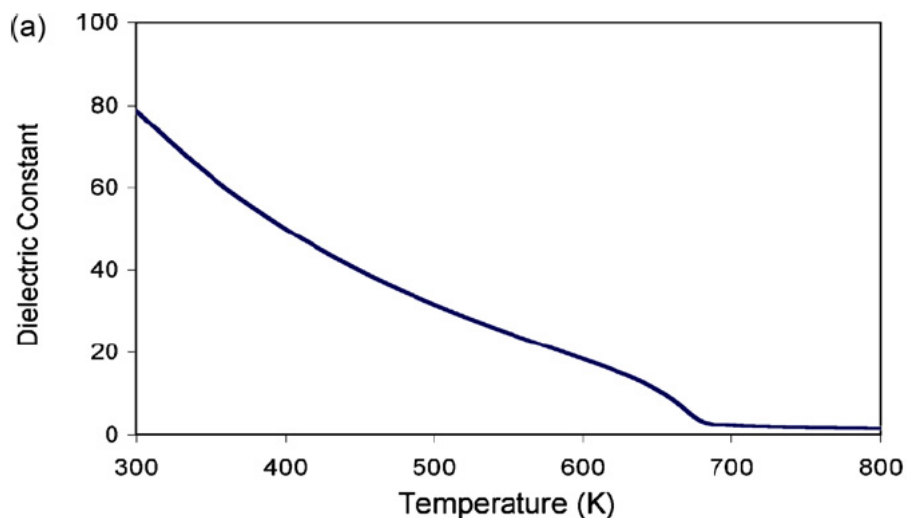


Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302.

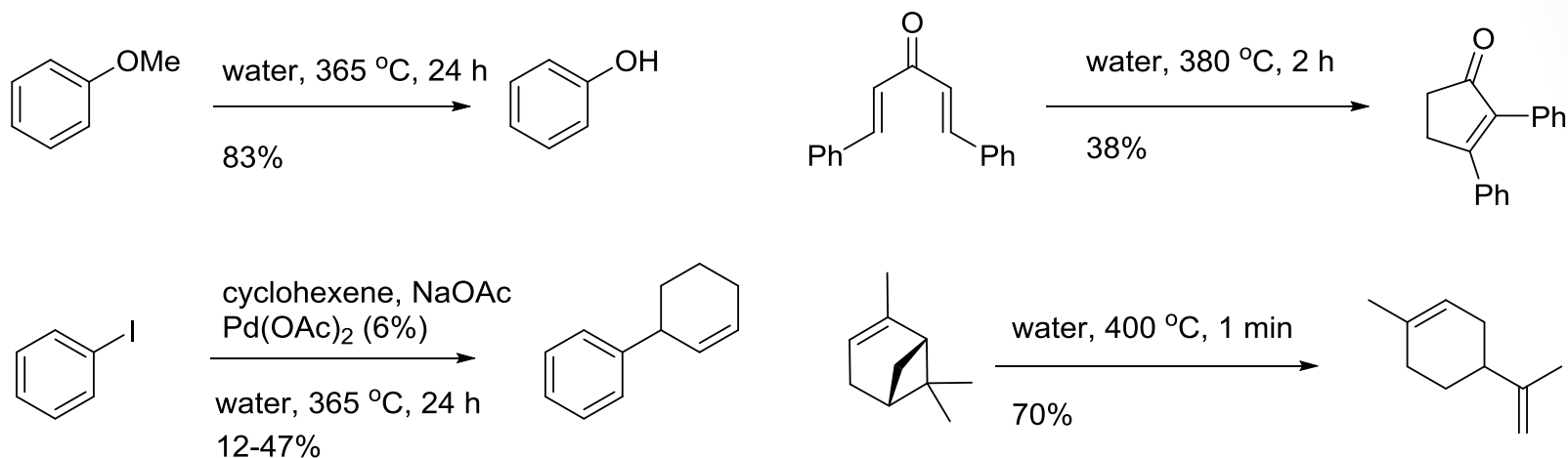
The critical point



Physical properties



Previous work in SCW



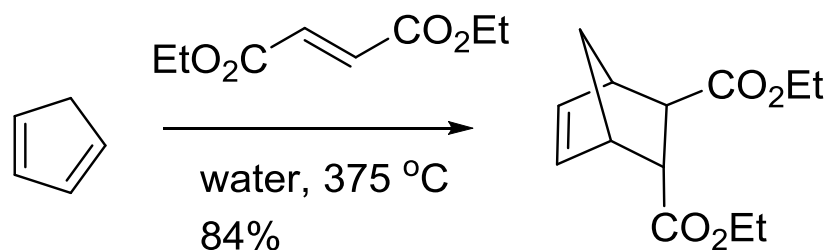
Rebacz, N. A.; Savage, P. E. *Phys. Chem. Chem. Phys.* **2013**, *15*, 3562.

Leikoski, T. et al. *Org. Process Res. Dev.* **2005**, *9*, 629-633, 9.

Kus, S. N. *Montash. Chem.* **2010**, *141*, 307-310.

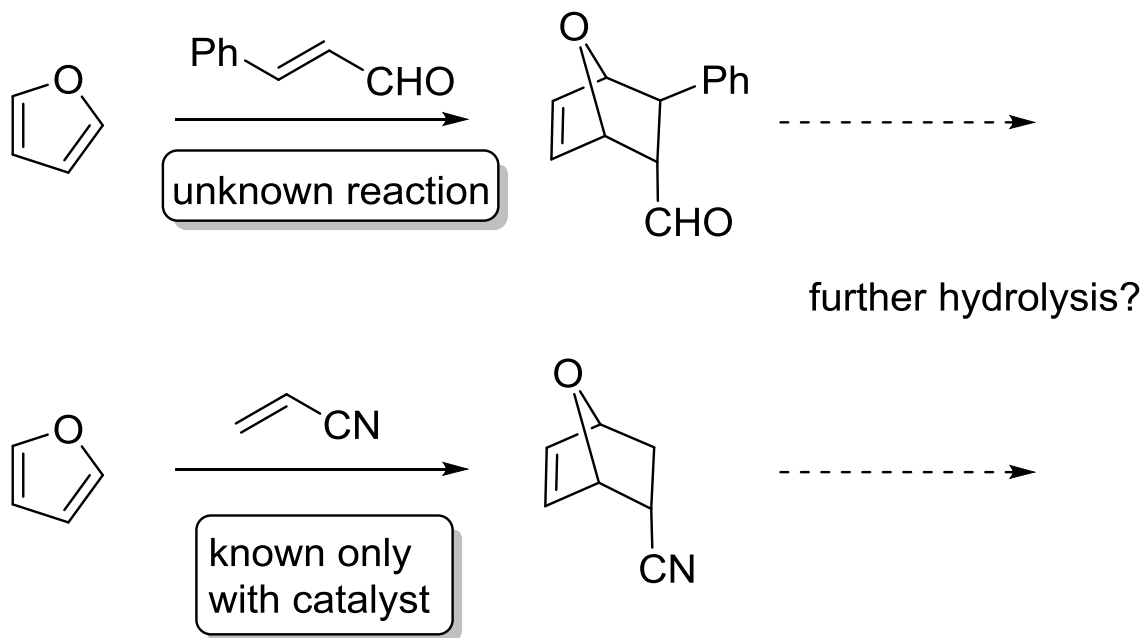
Kawahara, T. et al. *Org. Process Res. Dev.* **2013**, *17*, 1485-1491.

Diels-Alder in SCW



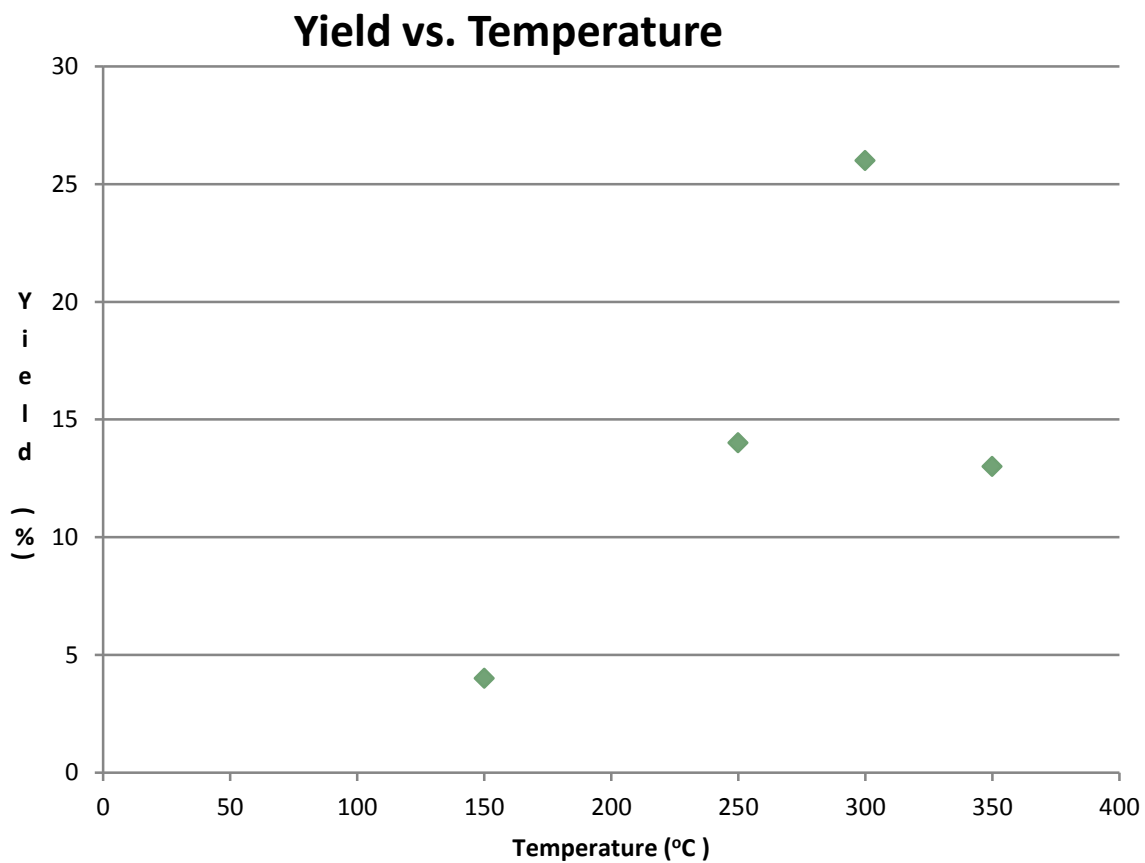
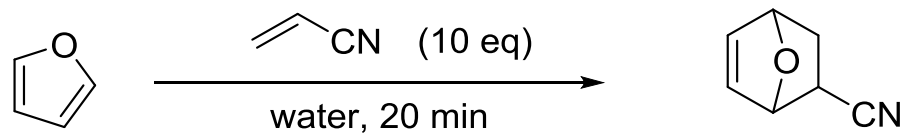
Korzenski, M. B.; Kolis, J. W. *Tetrahedron Lett.* **1997**, 38, 5611

Proposed Diels-Alder in SCW

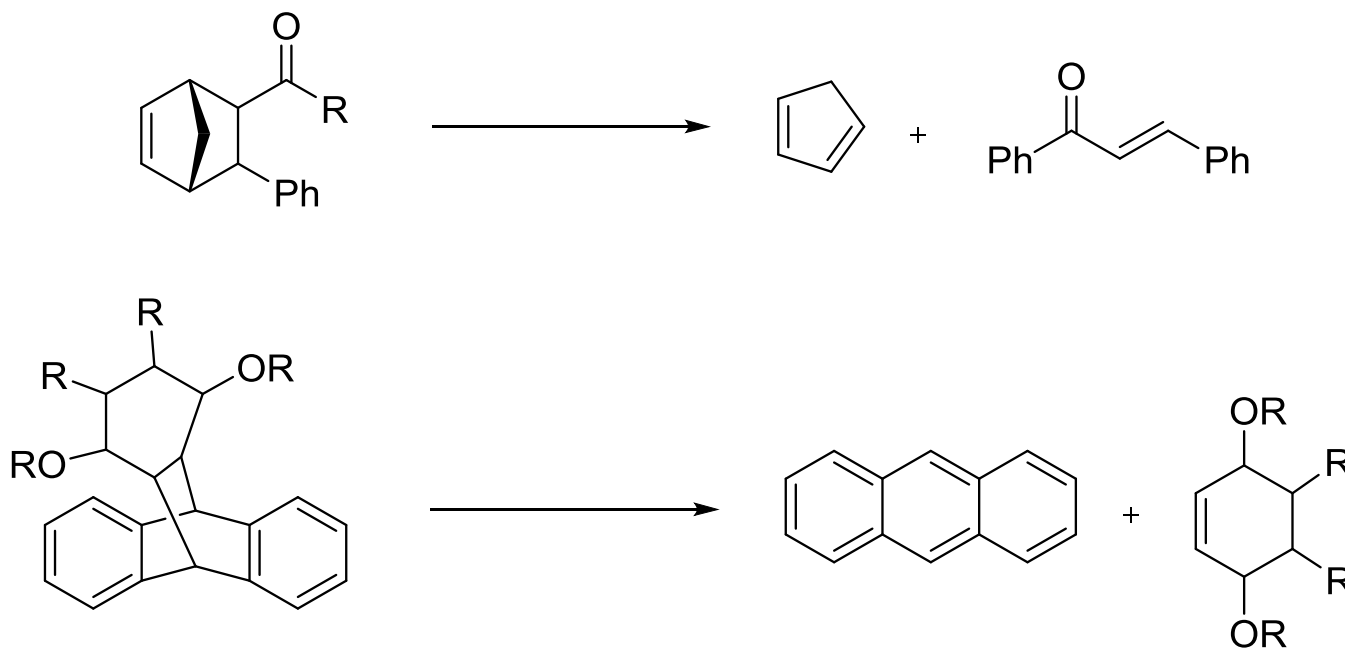


Apparatus

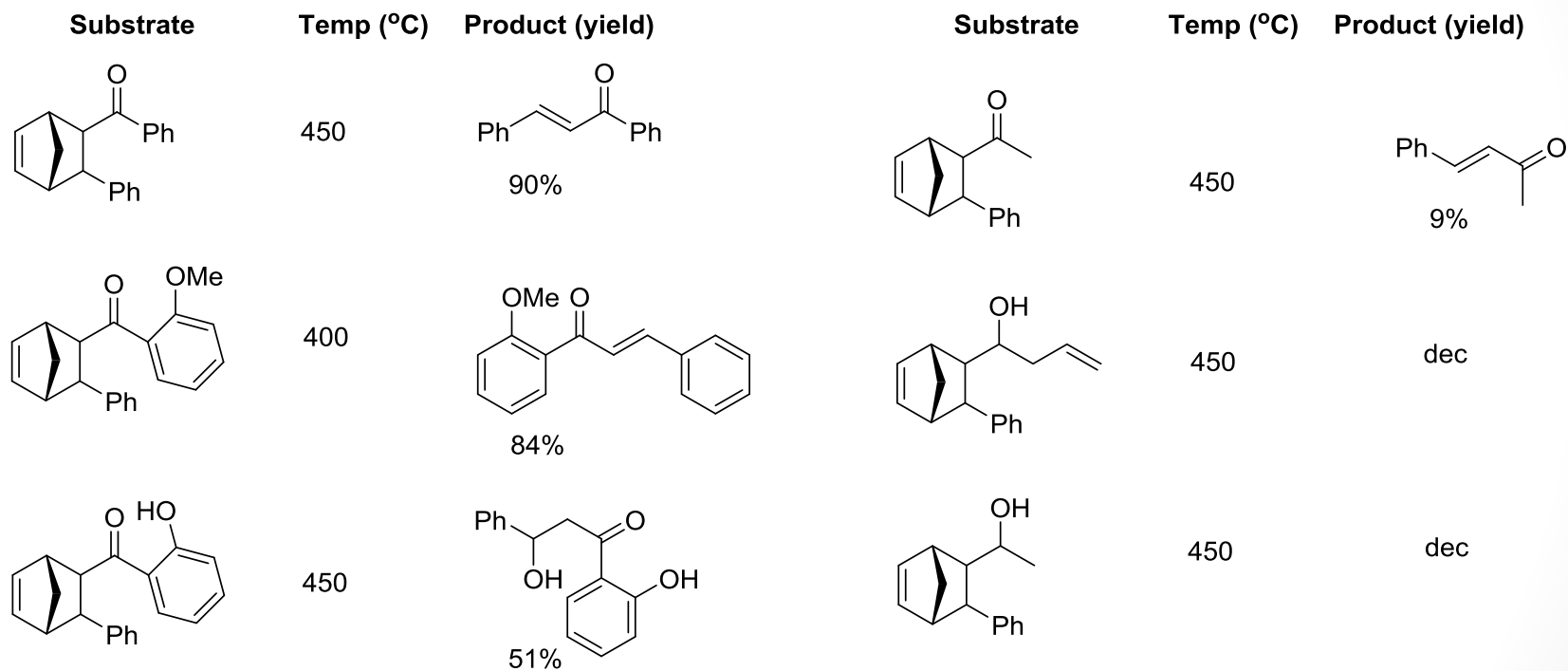


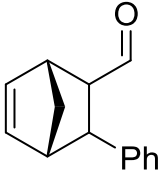
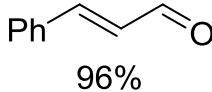
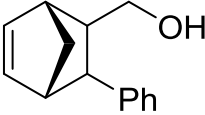
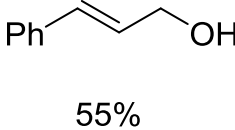
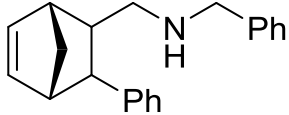
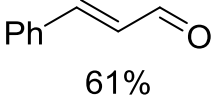
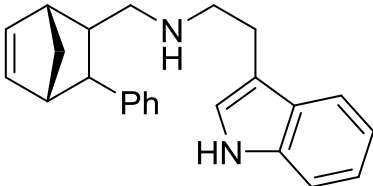
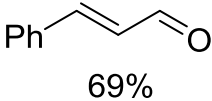


Retro-Diels-Alder

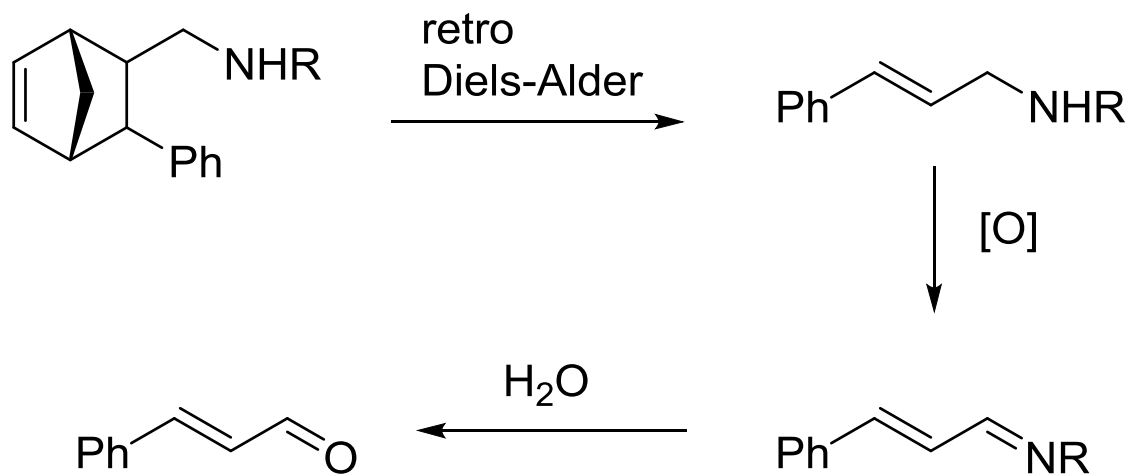


Retro-Diels-Alder

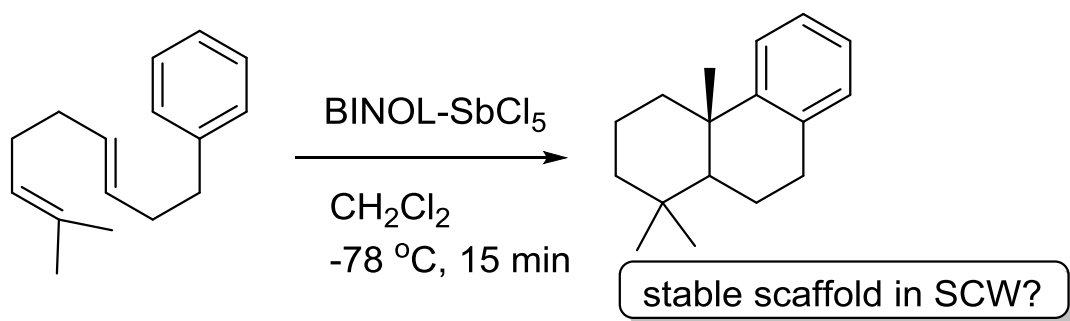


Substrate	Temp °C	Product (yield)
	450	 96%
	450	 55%
	450	 61%
	450	 69%

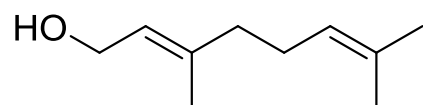
Oxidation



Biomimetic Cyclizations



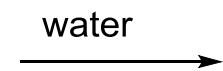
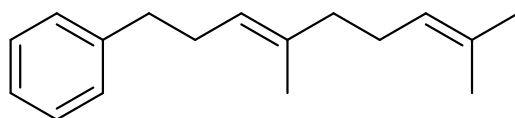
Corey, E. J. et al. *J. Am. Chem. Soc.* **2014**, 136, 642



complex mixture

400 °C

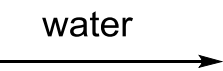
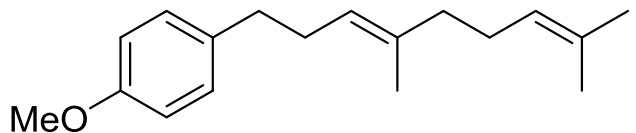
25 min



complex mixture

400 °C

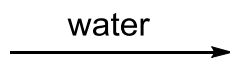
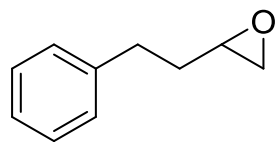
36 min



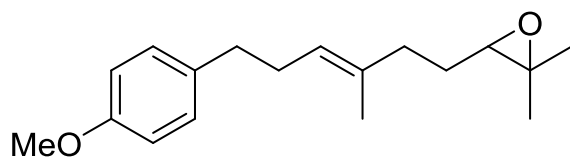
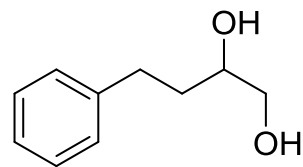
complex mixture

400 °C

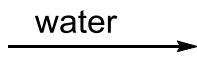
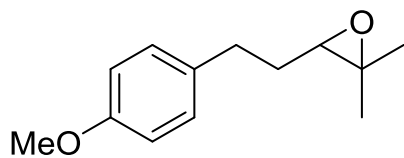
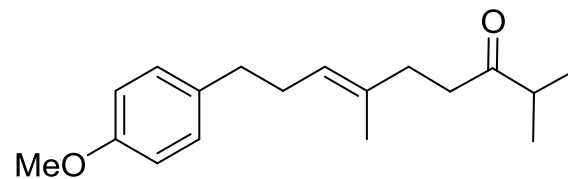
35 min



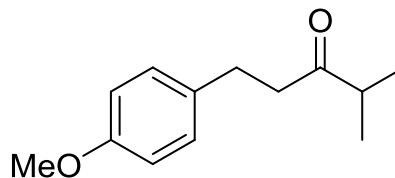
400 °C
38 min
98%



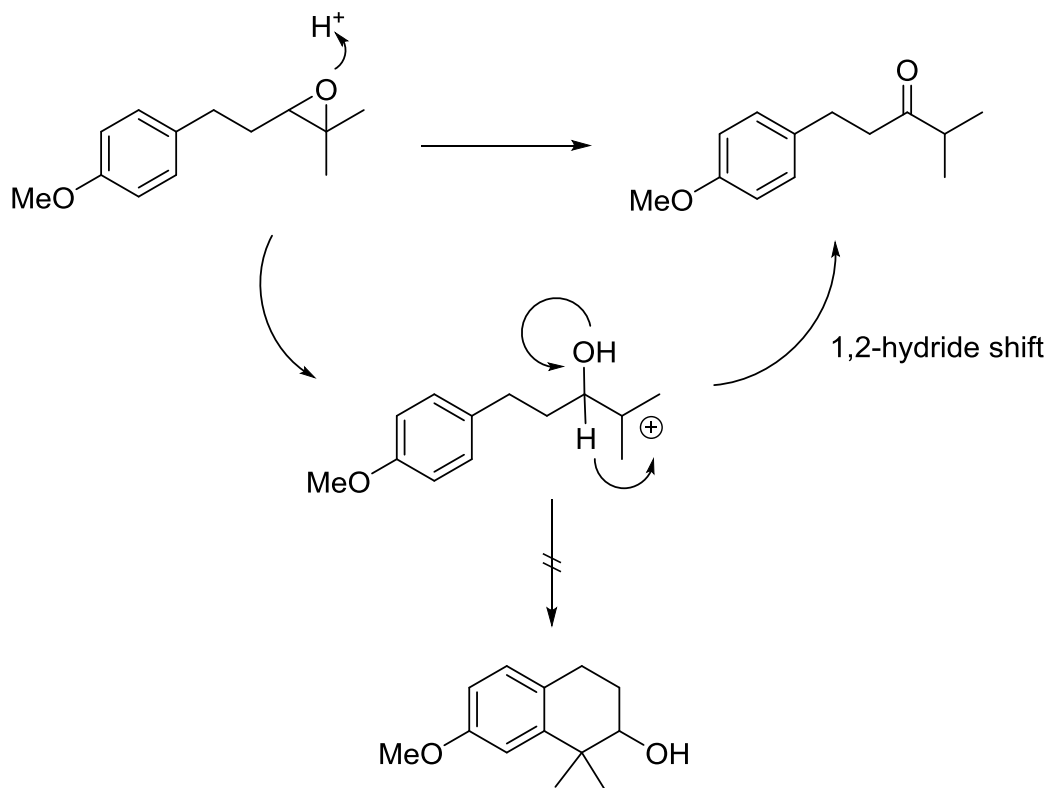
400 °C
34 min



400 °C
34 min
40%



Epoxide Rearrangement



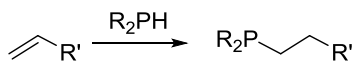
Conclusion

- Stable starting materials can be converted to stable products using the stainless steel tube
 - Retro-Diels-Alder reactions of stable substrates work well
 - Rearrangement of epoxides can be conducted
 - Labile functionality is not well tolerated
- Apparatus material is important in expanding this work to more complex molecules

PART II: HYDROPHOSPHINATION OF CARBODIIMIDES WITH PHOSPHINE BORANES

This work

Hydrophosphination

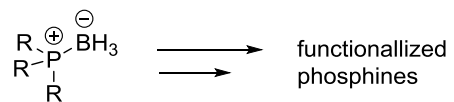


Base-mediated methods

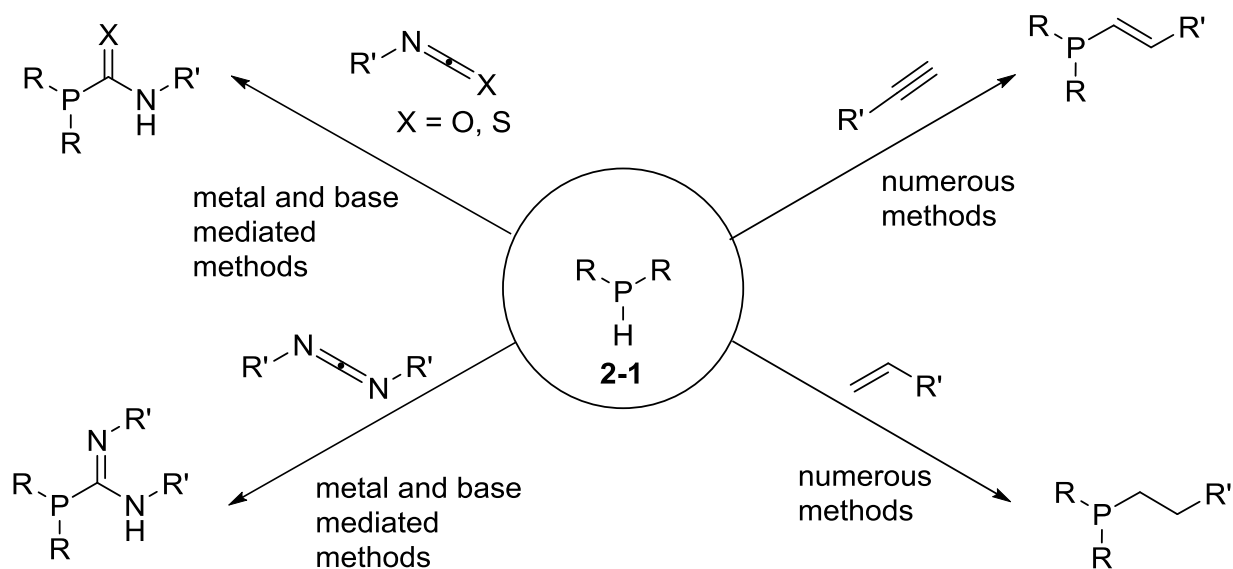
Metal catalysis

Radical Methods

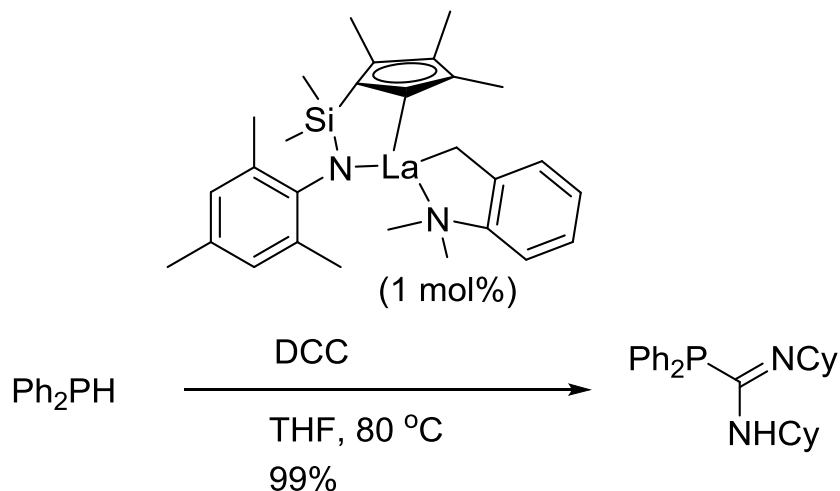
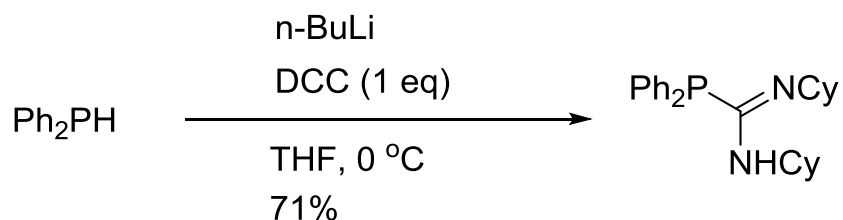
Phosphine Borane Chemistry



Hydrophosphination



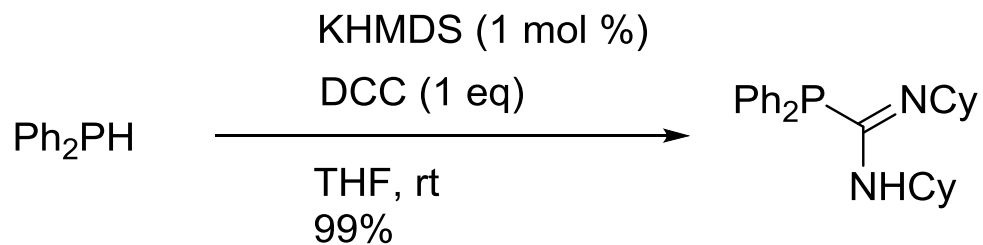
Carbodiimide Hydrophosphination



Grundy, J.; Coles, M. A.; Hitchcock, P. B. *Dalton Trans.* **2003**, 2573-2577

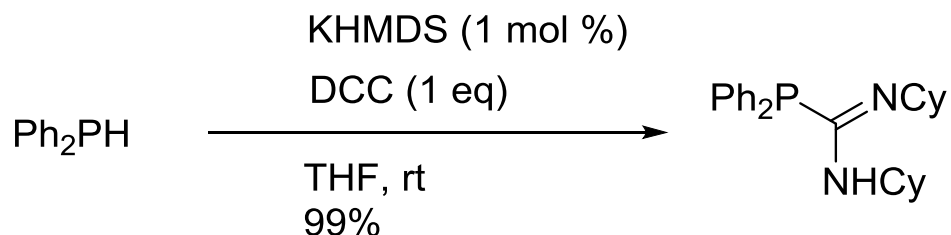
Zhang, W-X.; Nishiura, M.; Mashiko, T.; Hou, Z. *Chem. Eur. J.* **2008**, 14, 2167-2179

Substoichiometric base

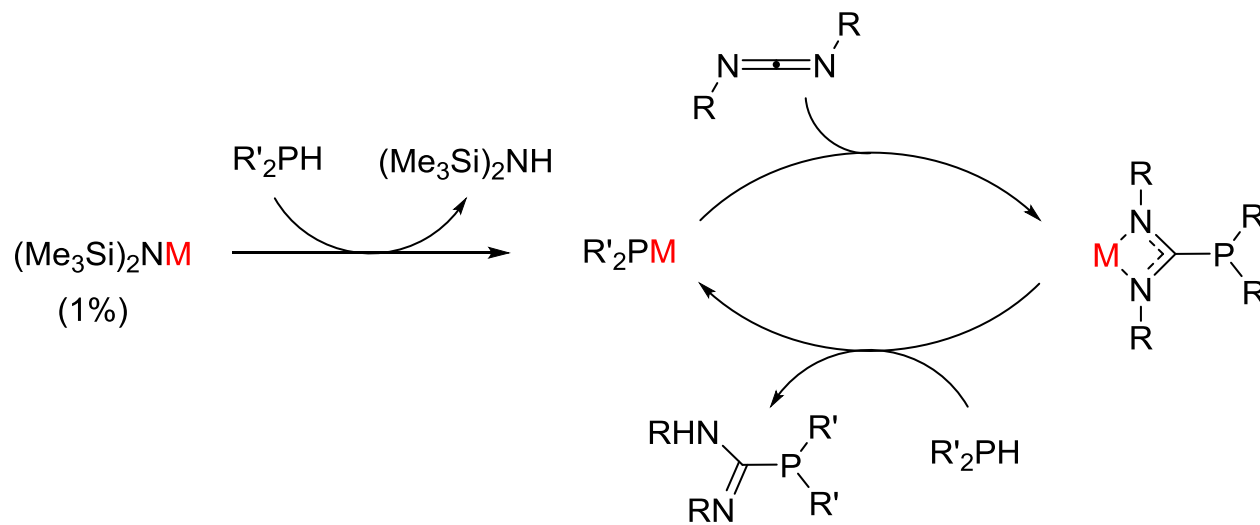


Zhang, W-X., Nishiura, M.; Hou, Z. *Chem Commun.* **2006**, 3812-3814

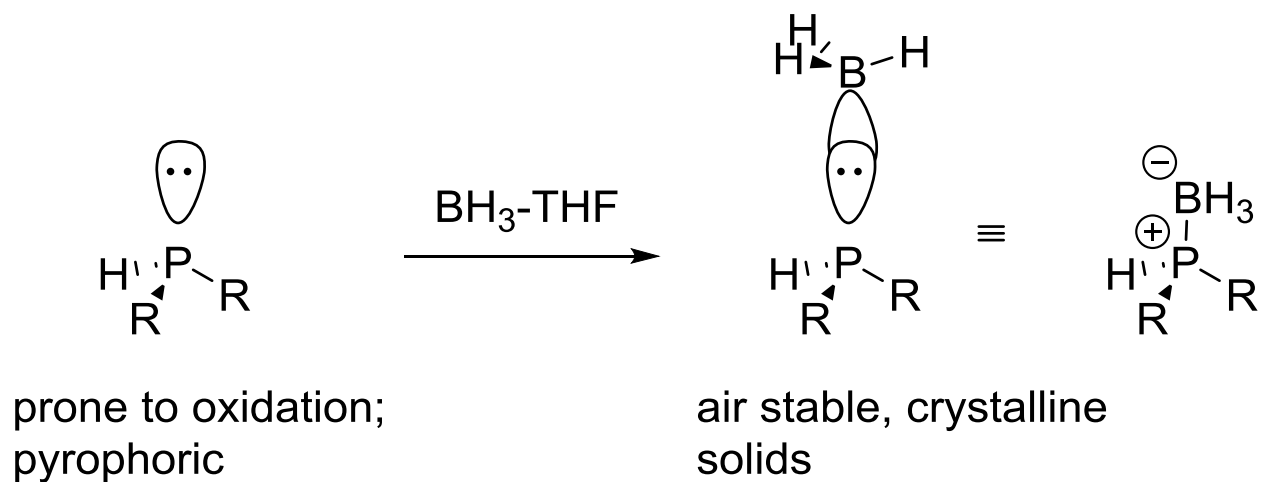
Substoichiometric base



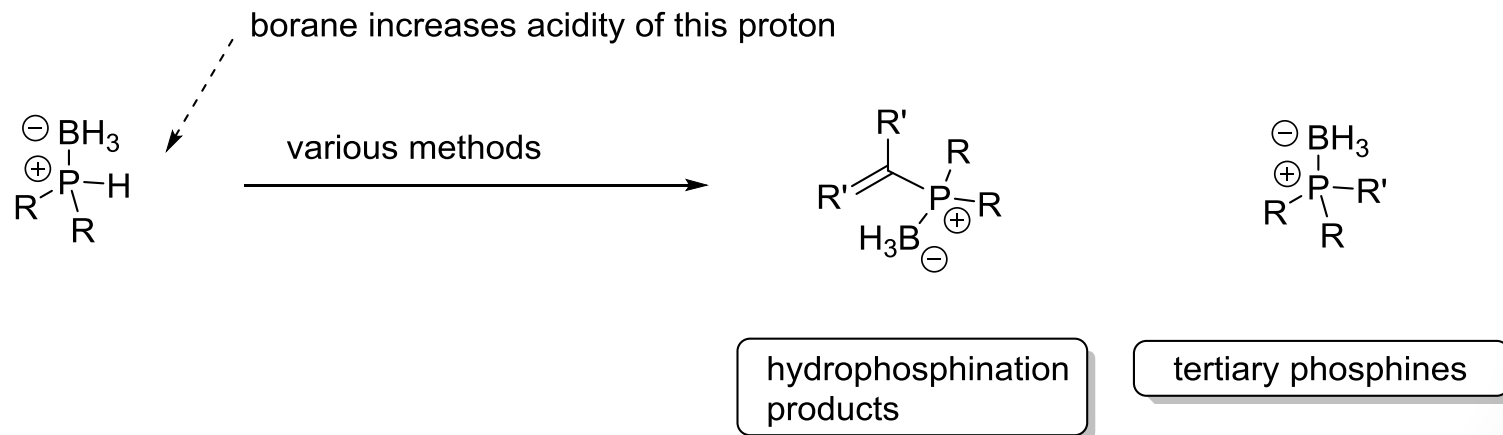
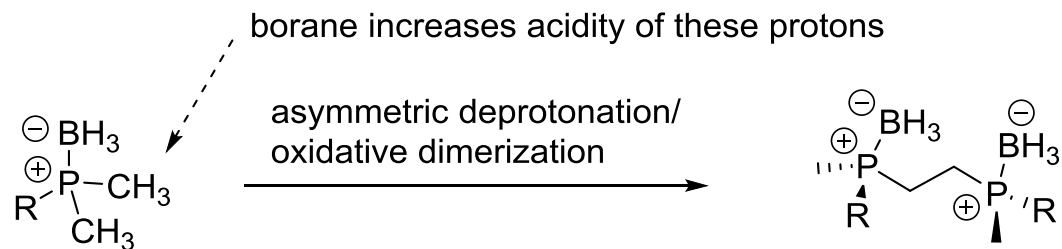
Zhang, W-X., Nishiura, M.; Hou, Z. *Chem Commun.* **2006**, 3812-3814



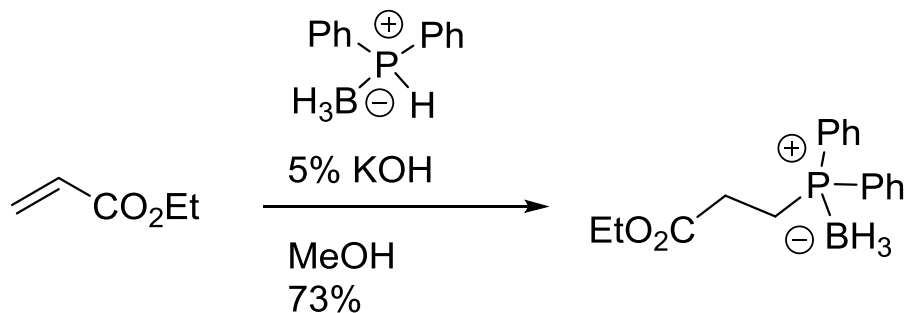
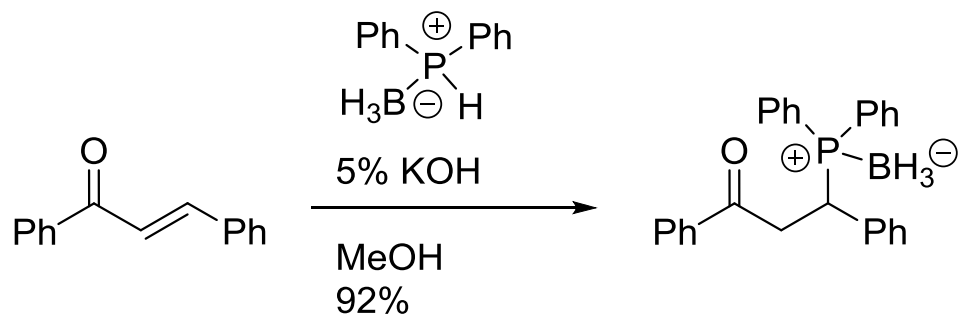
Phosphine Boranes



Phosphine Boranes

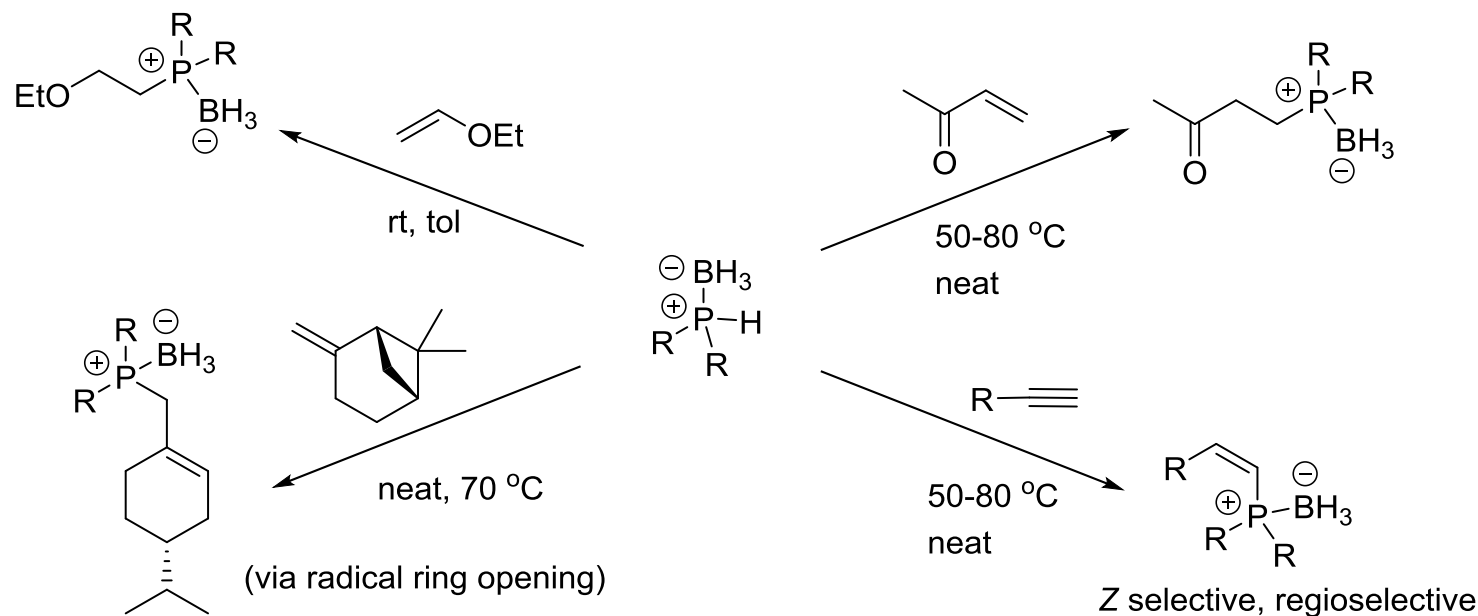


Hydrophosphinations



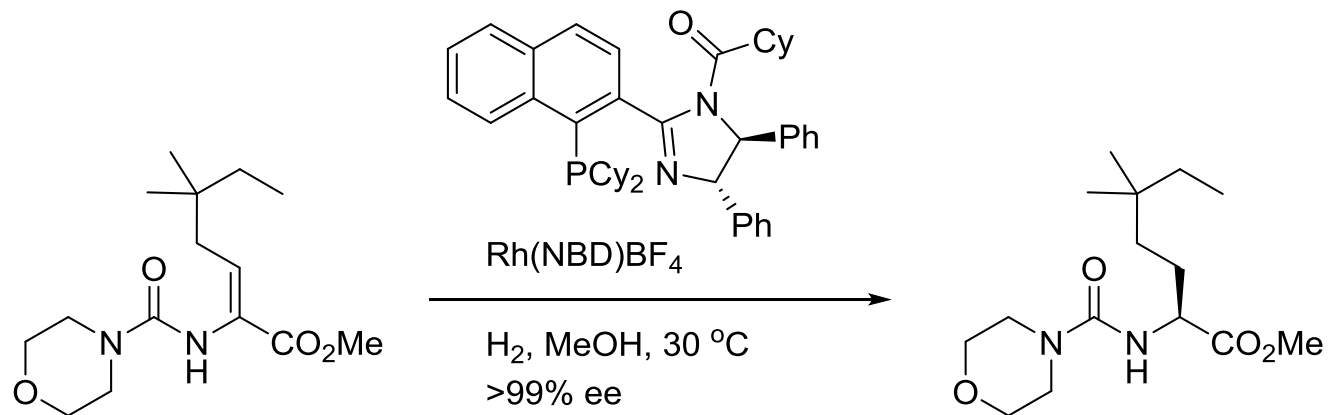
Imamoto, T et al. *J. Am. Chem. Soc.* **1990**, *112*, 5244

Neat hydrophosphinations



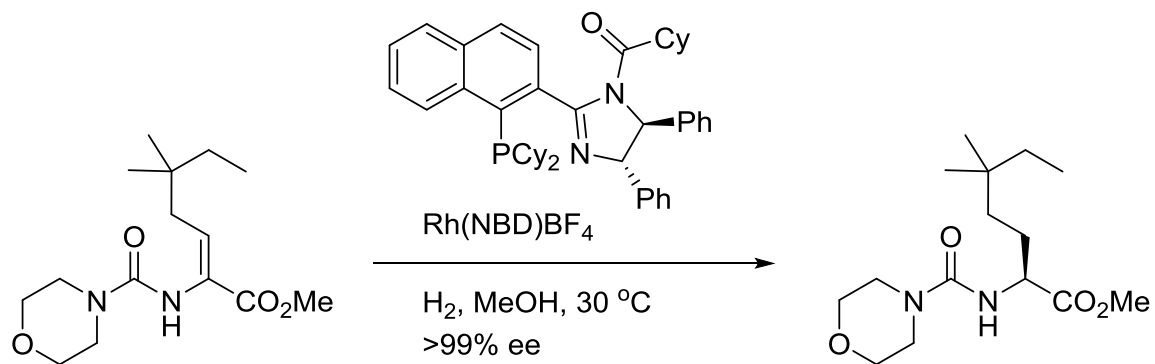
Gaumont, A.-C. et al: *Synlett* **2005**, No. 12, 1881-1884.
J. Org. Chem. **2003**, 68, 7016-7022.
Chem. Commun. **2006**, 3249-3251.
Synthesis **2008**, No. 19, 3121-3125.

BIPI ligands

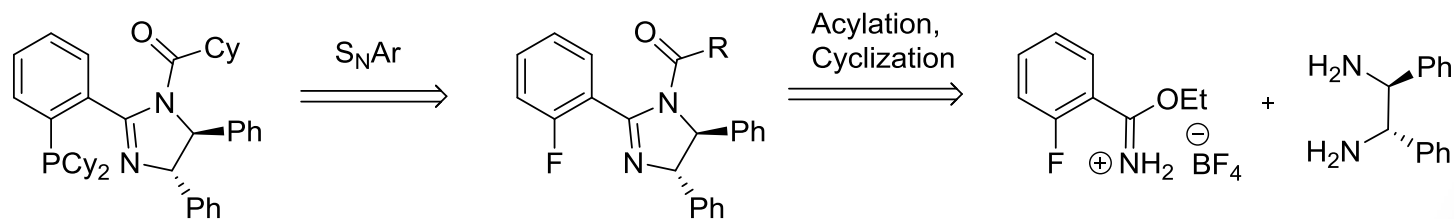


Busacca, C. A. et al. *Org. Lett.* **2008**, *10*, 341-344

BIPI Ligands

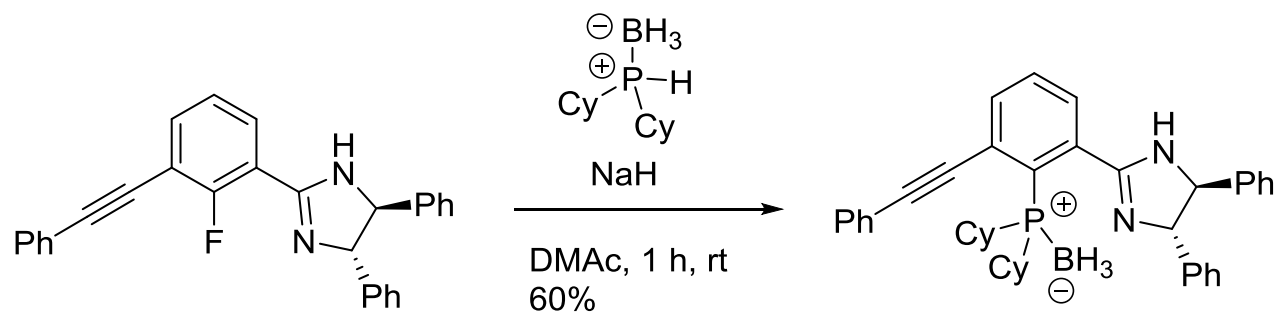


Busacca, C. A. et al. *Org. Lett.* **2008**, *10*, 341-344

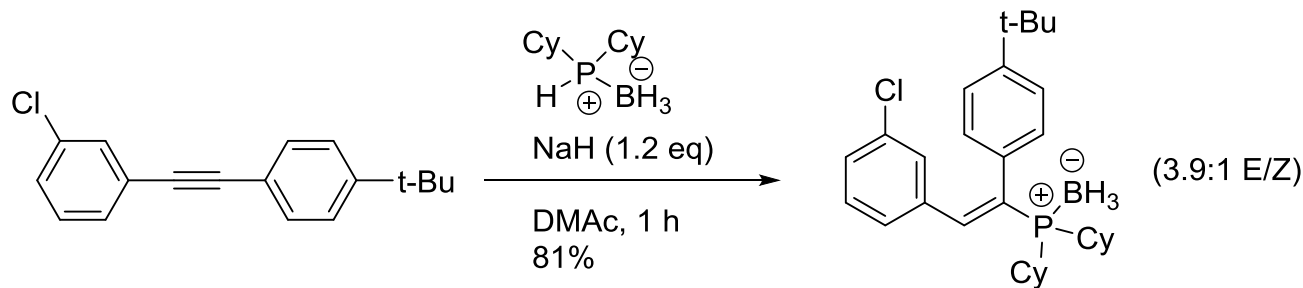
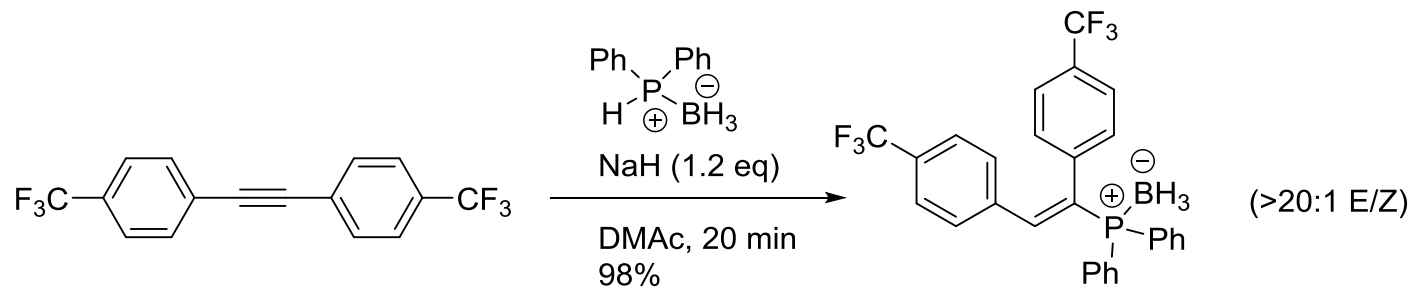
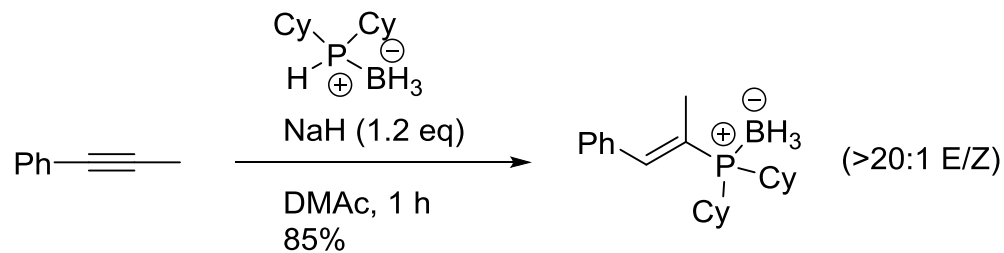


Busacca, C. A. et al. *Org. Lett.* **2003**, *5*, 595-598

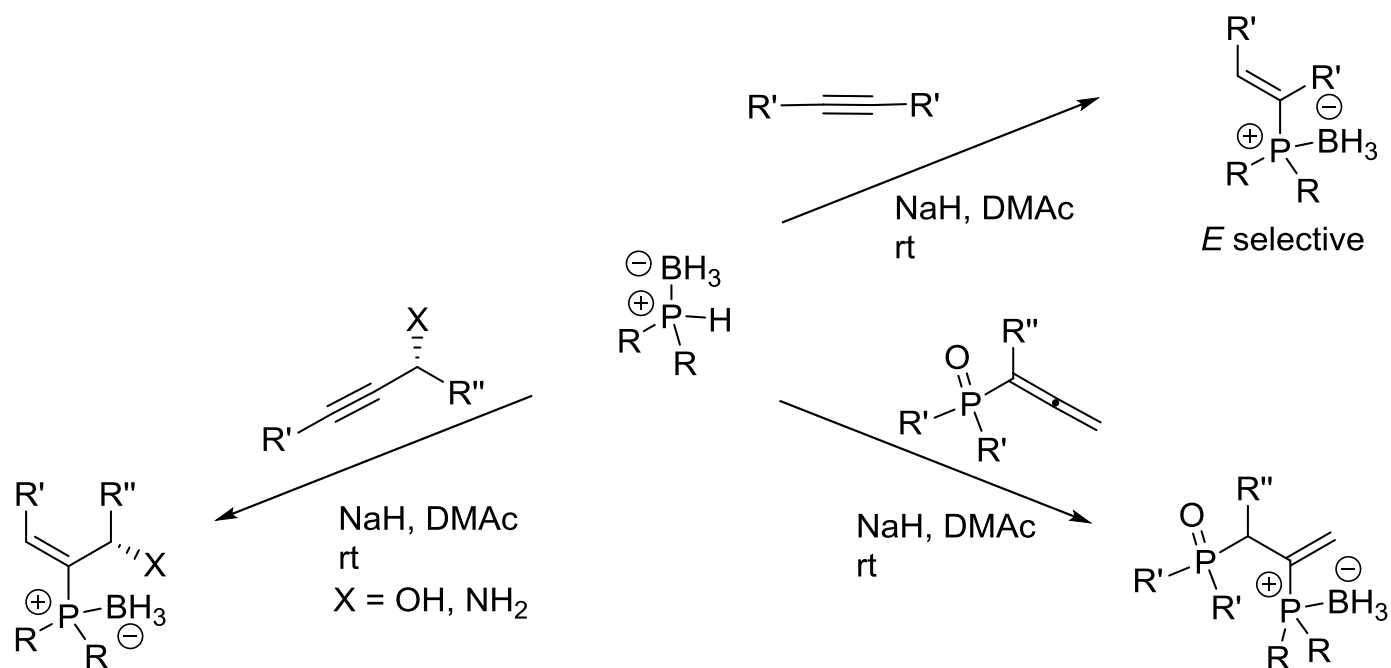
Hydrophosphination Discovery



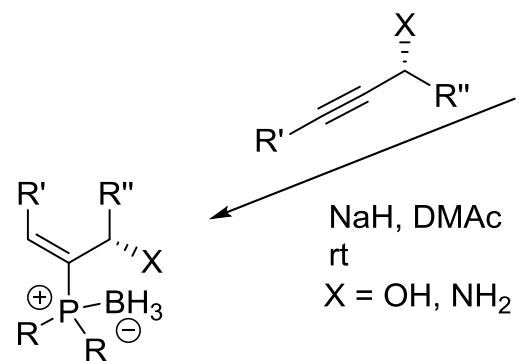
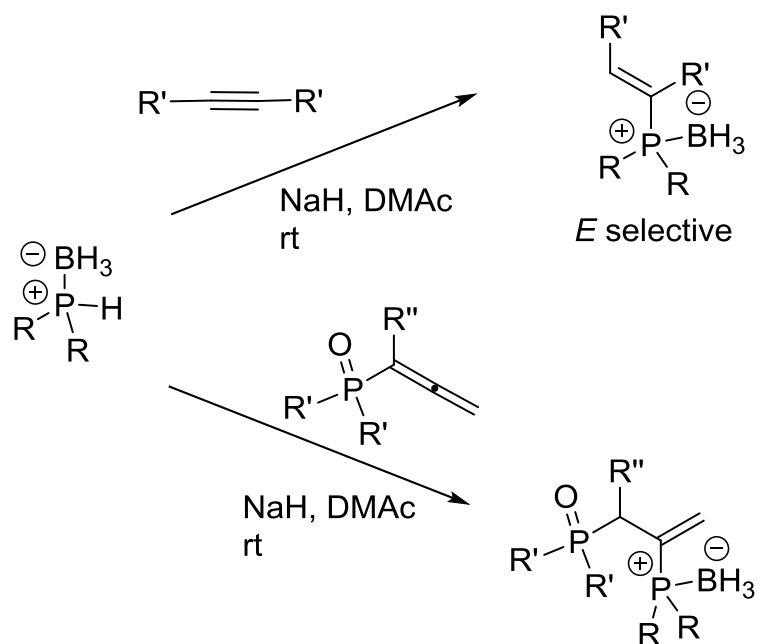
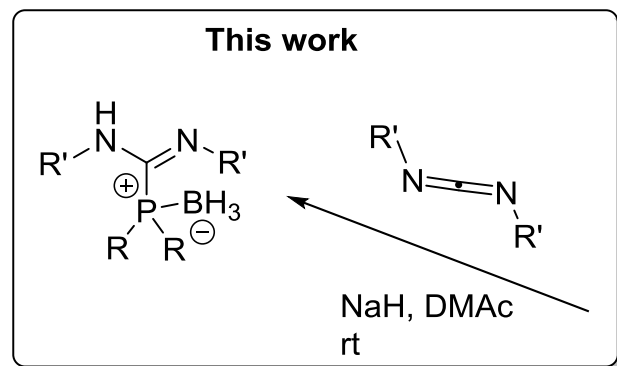
Alkyne Hydrophosphination



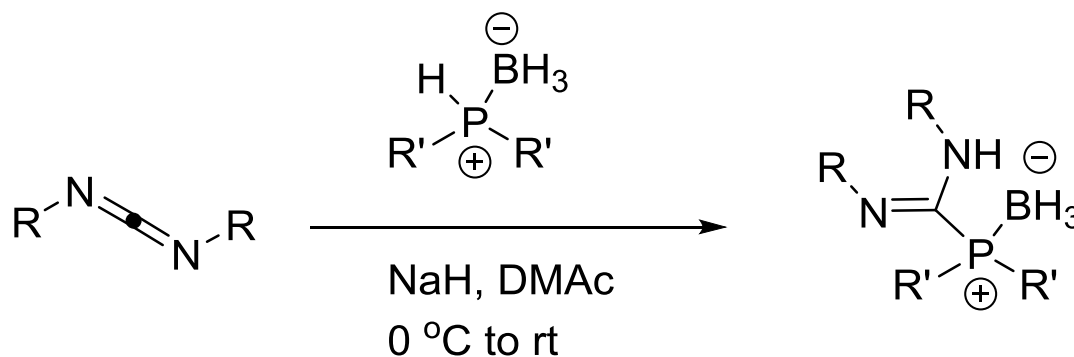
Busacca's hydrophosphination



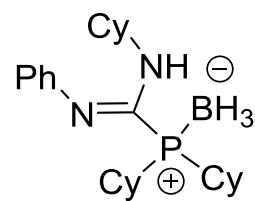
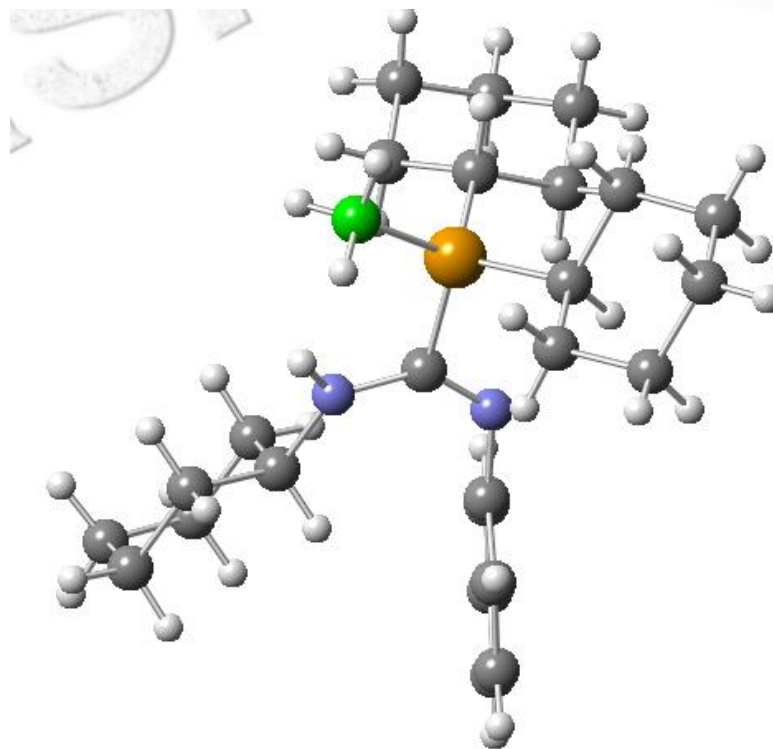
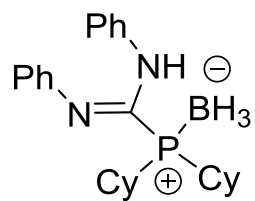
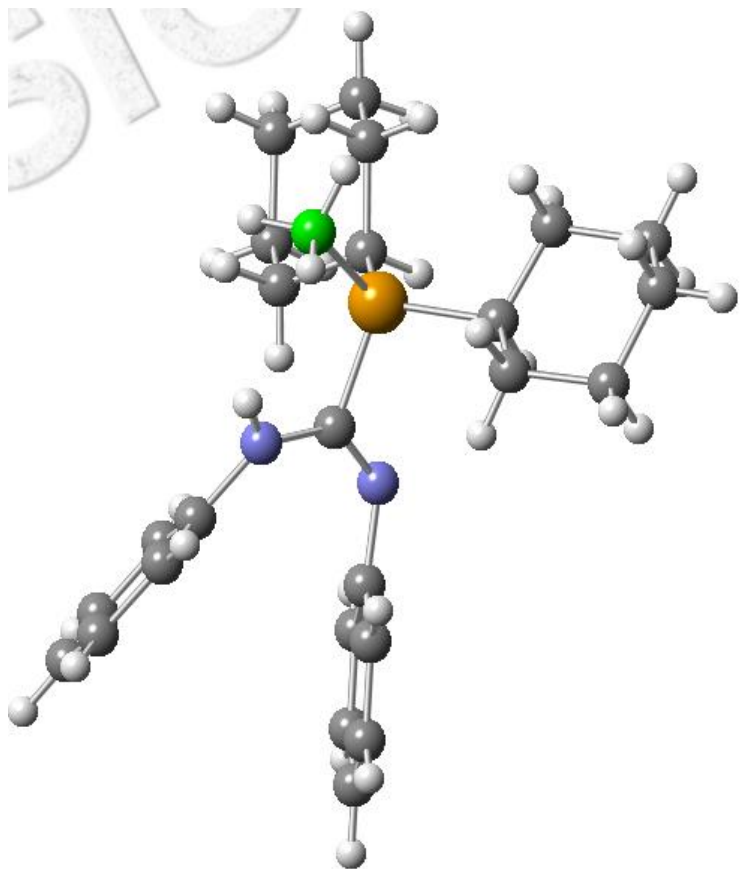
Busacca's hydrophosphination



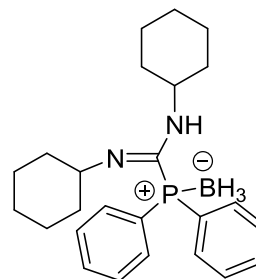
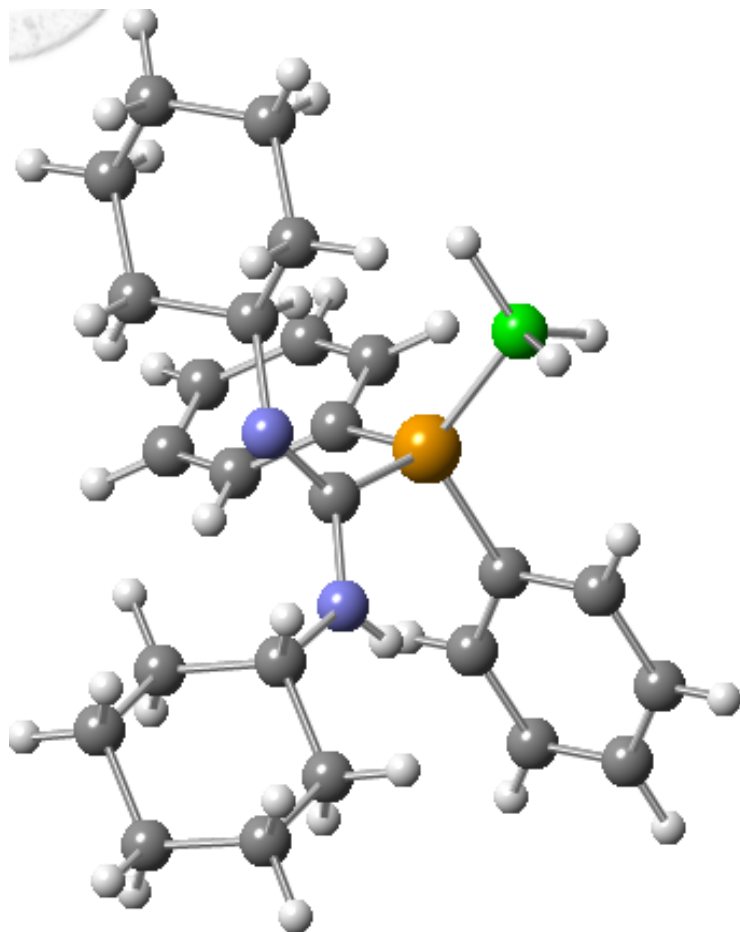
Preliminary results



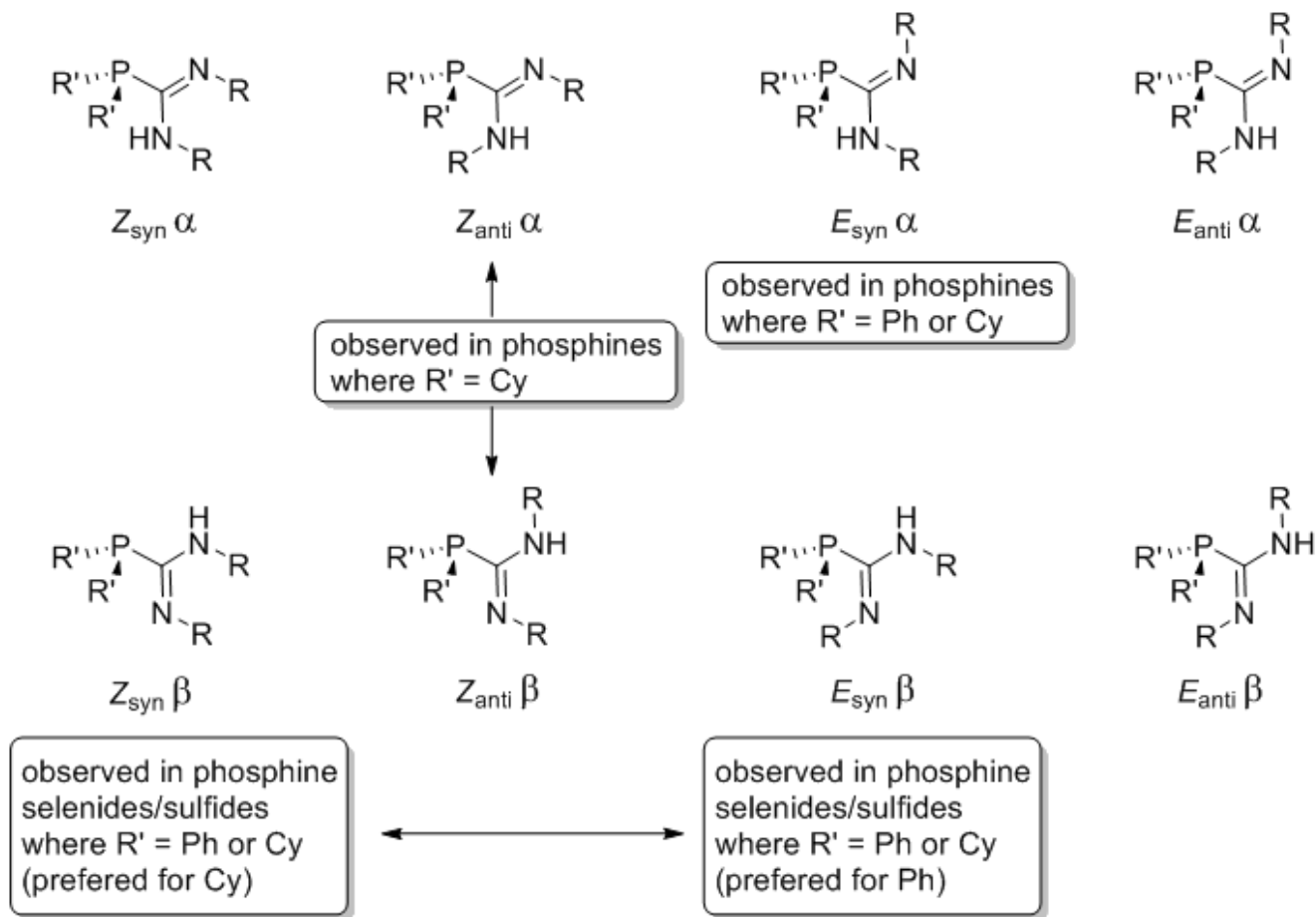
<u>R</u>	<u>R'</u>	<u>yield</u>
Cy	Cy	71%
Cy	t-Bu	58%
Ph	Cy	69%
Ph	t-Bu	77%
Cy/Ph	Cy	63%
Cy/Ph	t-Bu	58%



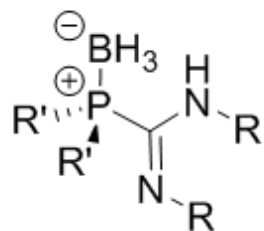
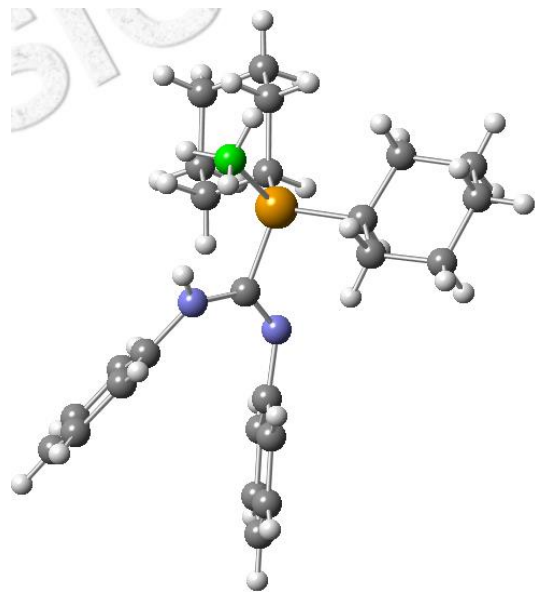
- Only one phosphaguanidine borane prior to this work:



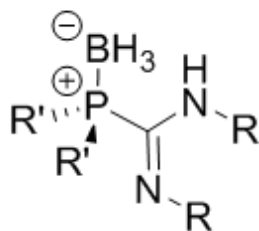
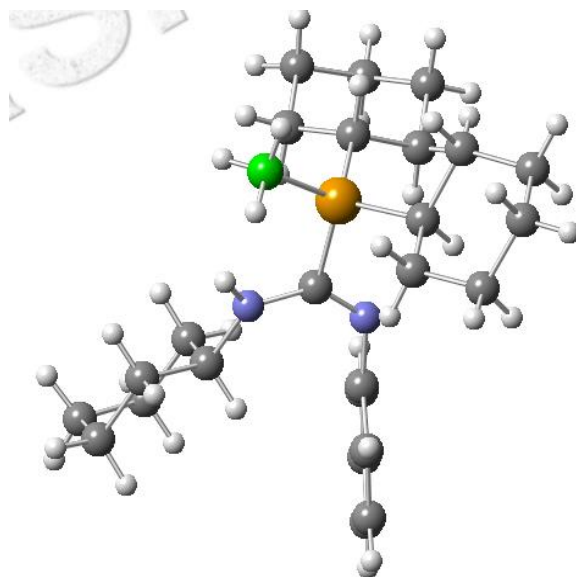
Nomenclature System



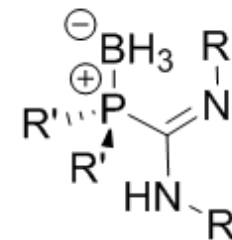
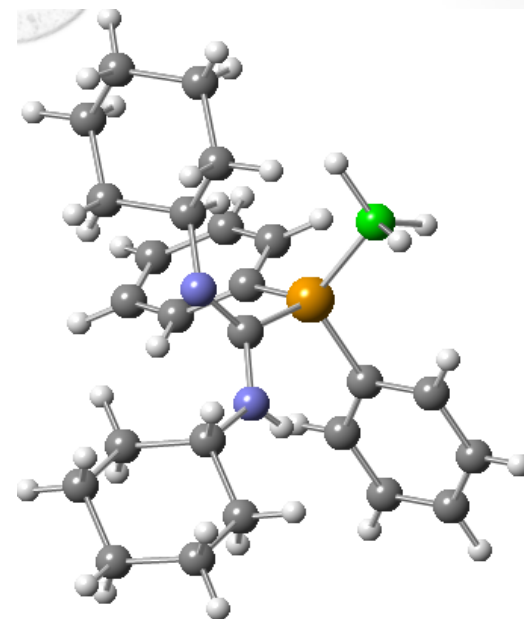
Comparison



$Z_{\text{syn}} \beta$

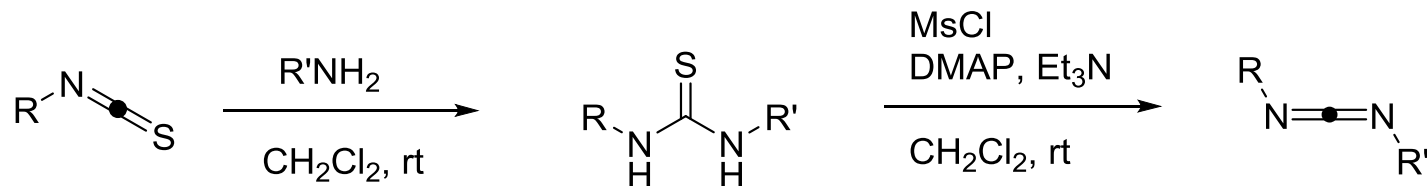


$Z_{\text{syn}} \beta$



$E_{\text{syn}} \text{ pseudo-}\alpha$

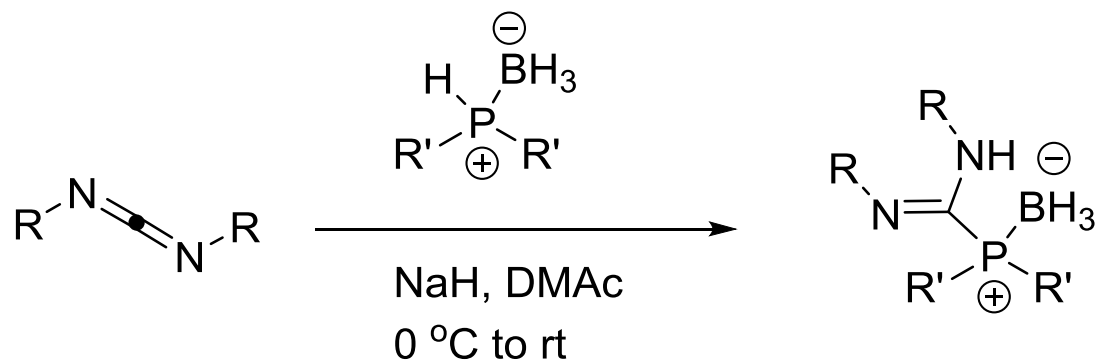
Carbodiimide preparation



<u>R</u>	<u>R'</u>	<u>yield</u>
(3,5-CF ₃)-Ph	Cy	74%
Ph	(4-OMe)-Ph	76%
(2-OMe)-Ph	Cy	82%

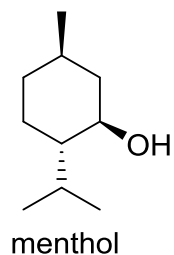
<u>R</u>	<u>R'</u>	<u>yield</u>
(3,5-CF ₃)-Ph	Cy	82%
Ph	(4-OMe)-Ph	87%
(2-OMe)-Ph	Cy	72%
Ph	Cy	81%

Results



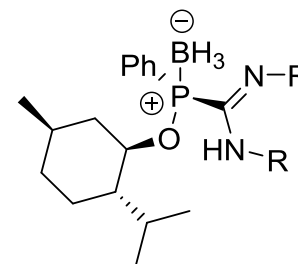
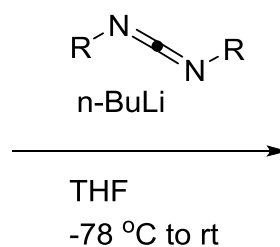
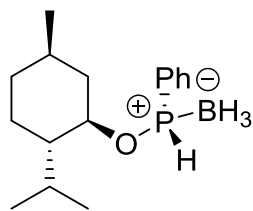
<u>entry</u>	<u>R</u>	<u>R</u>	<u>R'</u>	<u>yield</u>
1	(3,5-CF ₃)-Ph	Cy	Cy	55%
2	Ph	(4-OMe)-Ph	t-Bu	78%
3	(2-OMe)-Ph	Cy	Cy	58%
5	Ph	Ph	Tol	35%
6	Ph	(4-OMe)-Ph	3,5-Me-4-OMe Ph	13%
7	Cy	Cy	Tol	<10 %
8	TMS	TMS	Cy or t-Bu	RSM

Phosphinite Borane



PhPCl₂, pyridine
Toluene, rt

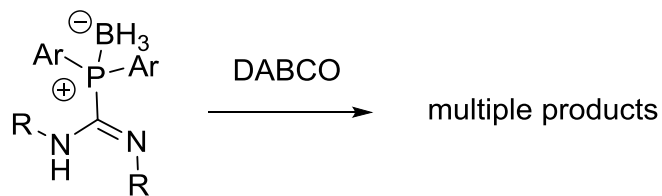
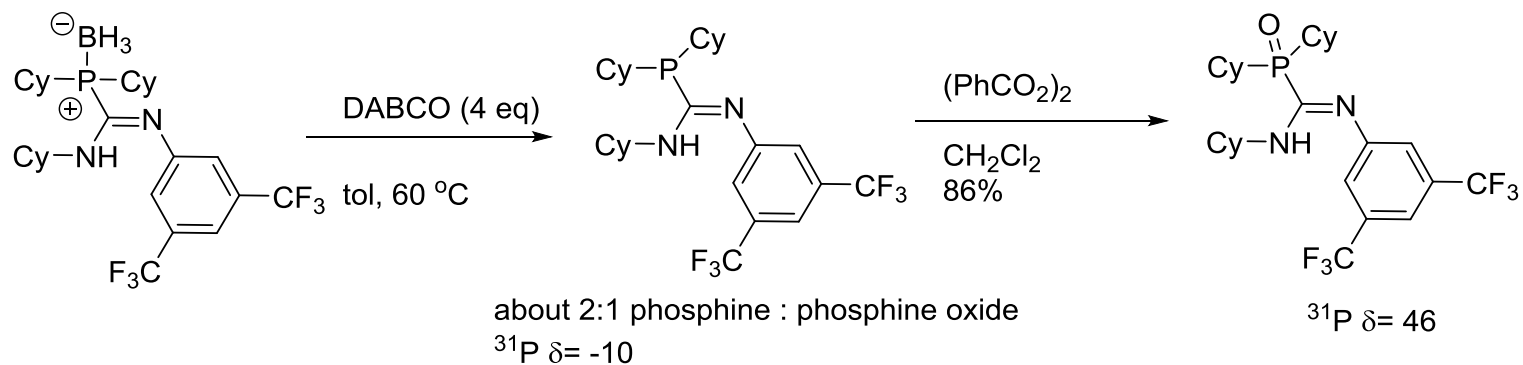
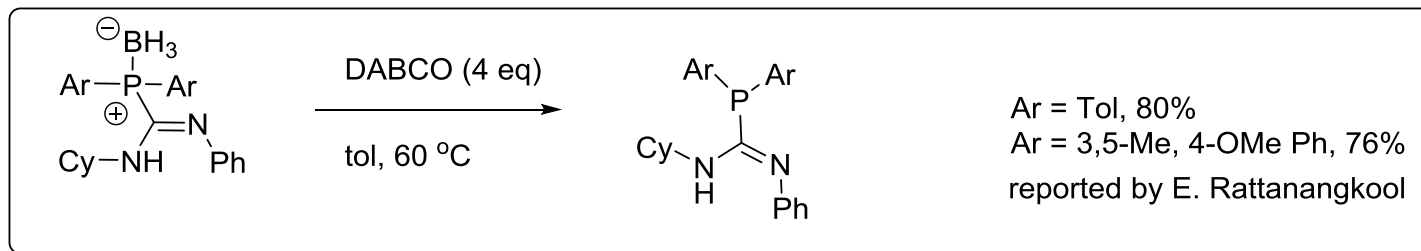
then BH₃/THF, LAH
THF, 0 to rt
8% (pure diastereomer)
+ 5% with a 3.3:1 dr



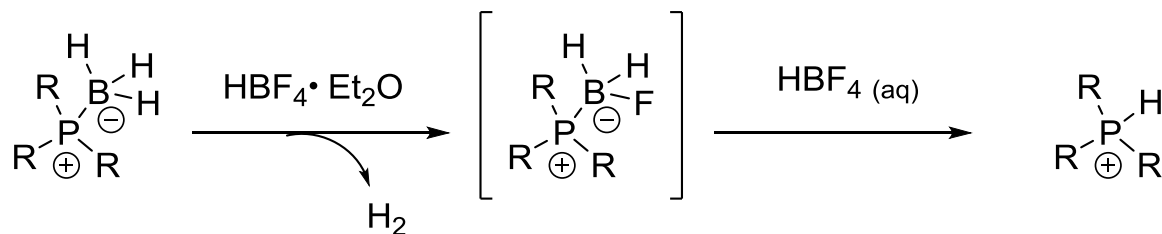
<u>R</u>	<u>yield</u>
(R-phenyl)ethyl	52%
Ph, 4-OMe Ph	38%
Cy	20%

→ reported by C. Buscca

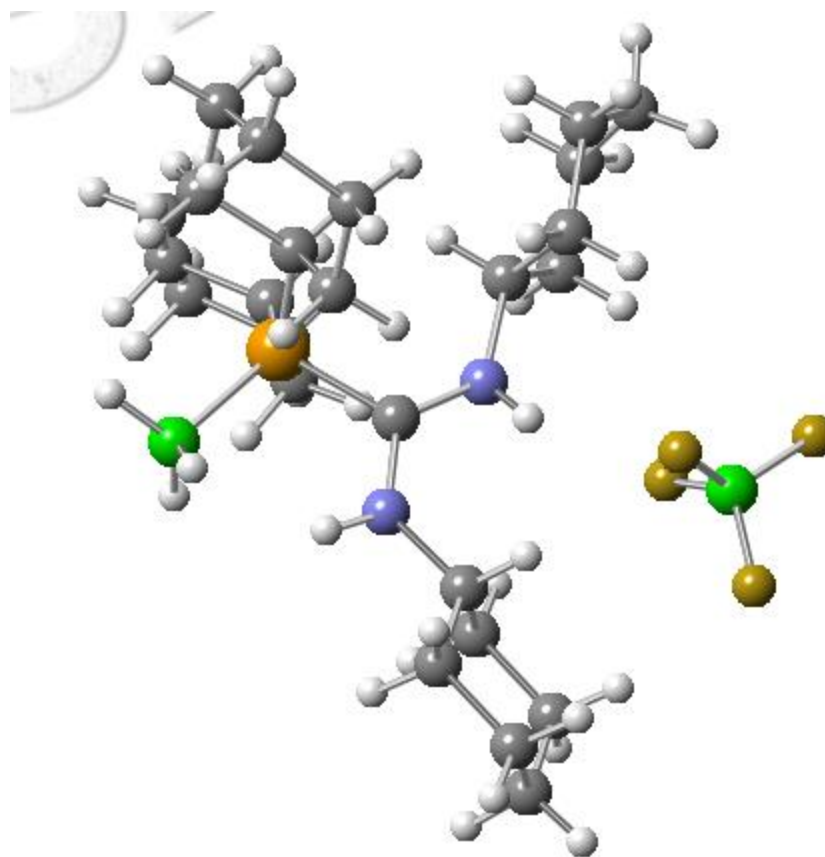
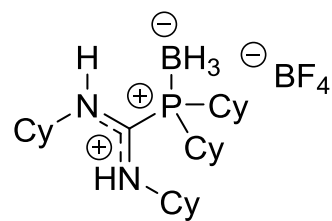
Deprotections



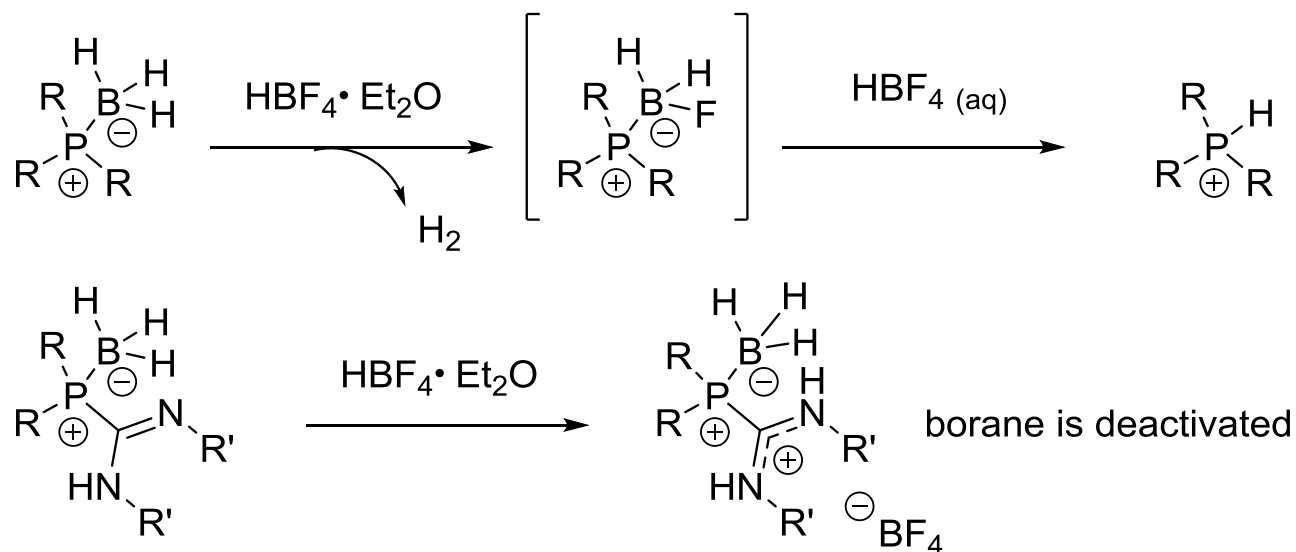
Air-stable HBF_4 salts



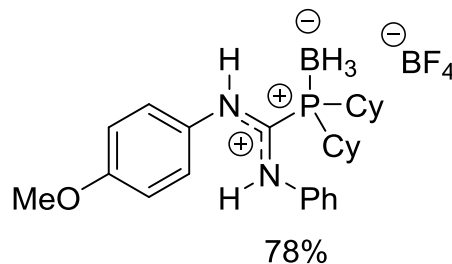
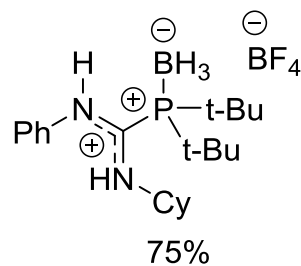
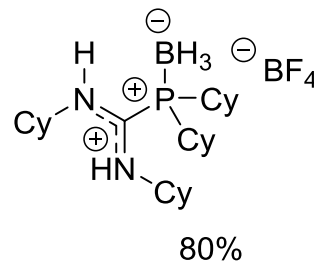
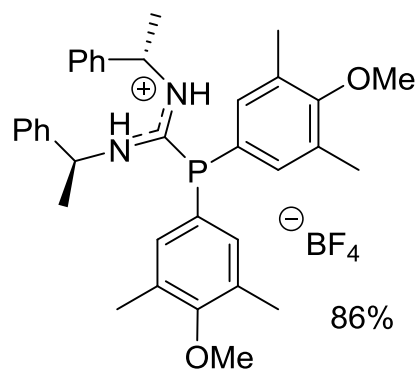
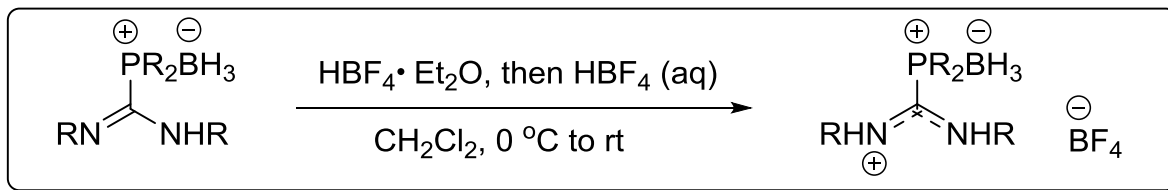
Product



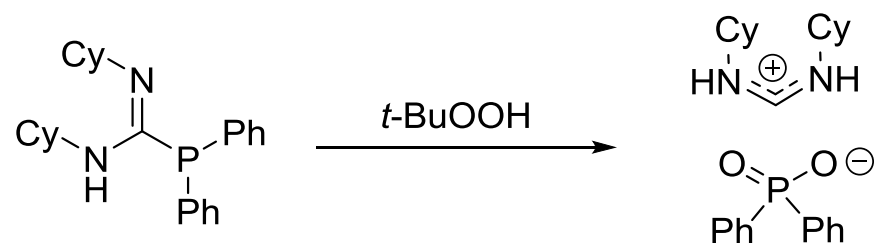
Divergent result



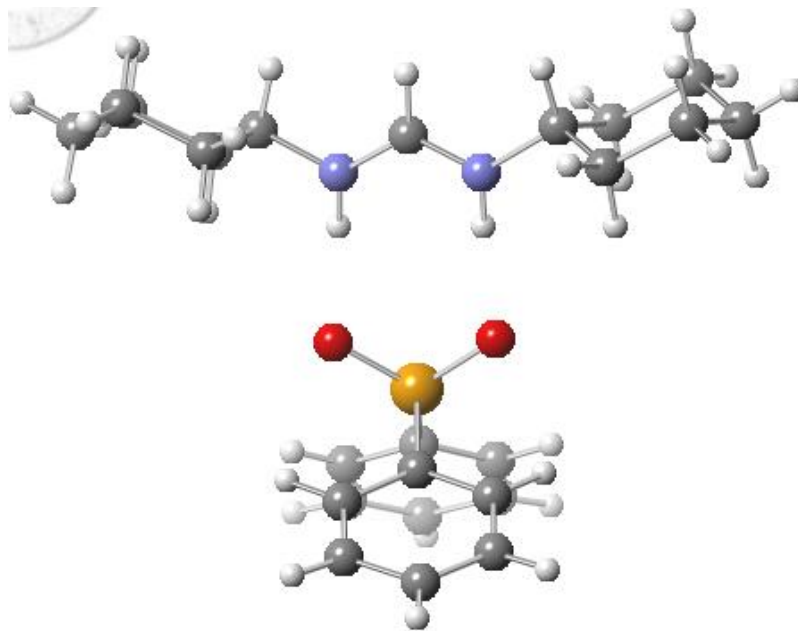
Guanidinium Salts



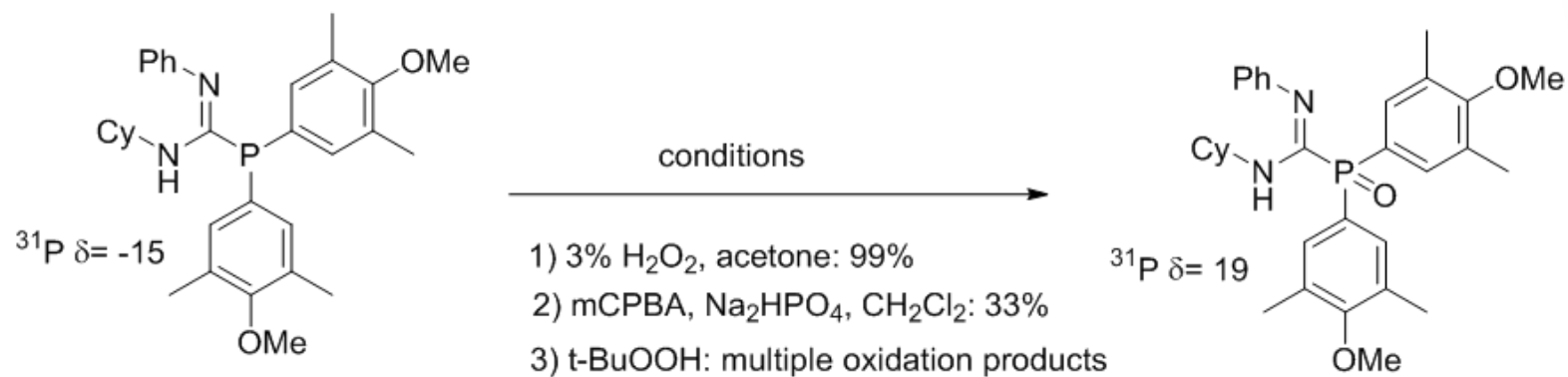
Feasible Oxidation?



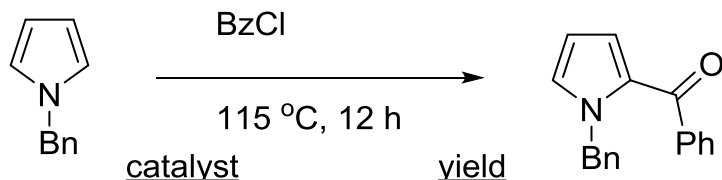
Mansfield, N. E.; Coles, M. P.; Hitchcock, P. B. *Polyhedron*, **2012**, 9-13.



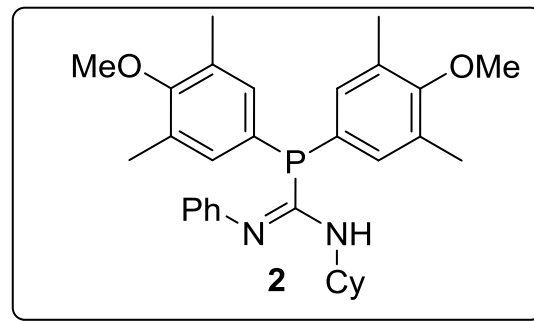
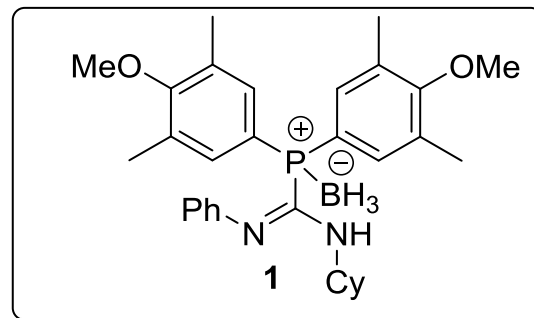
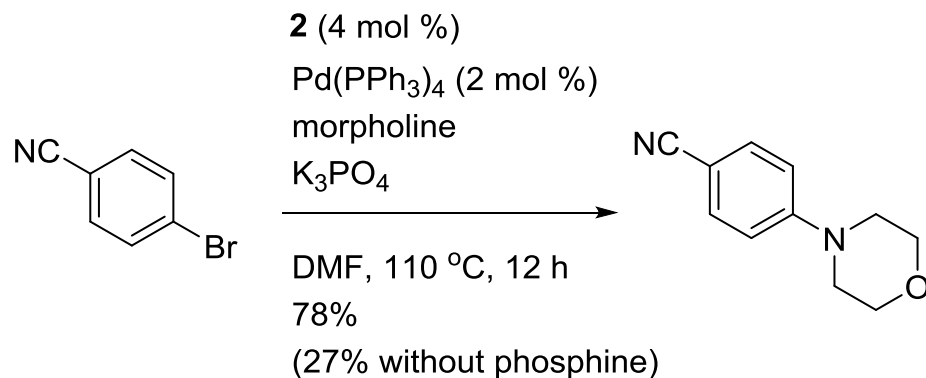
Oxidation Studies



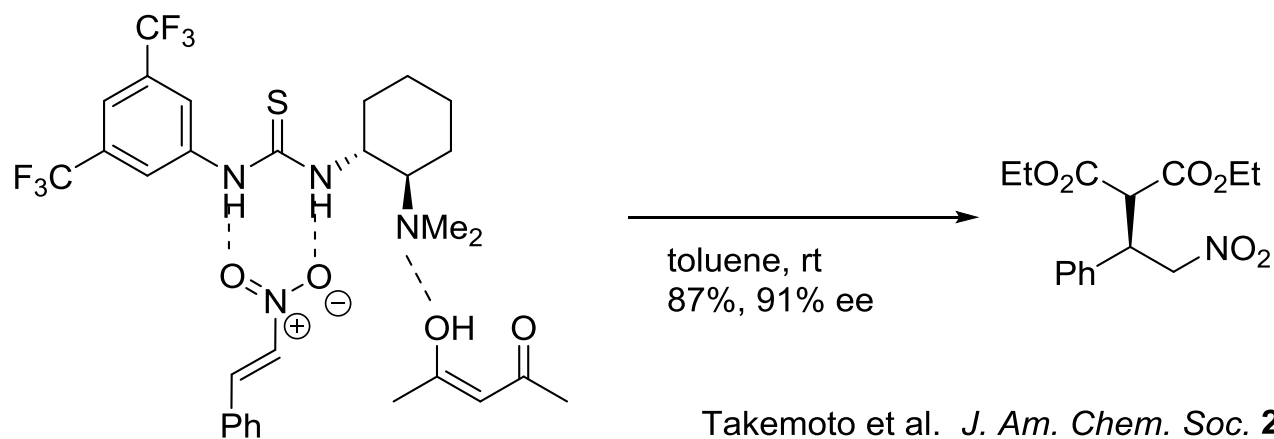
Catalytic applications

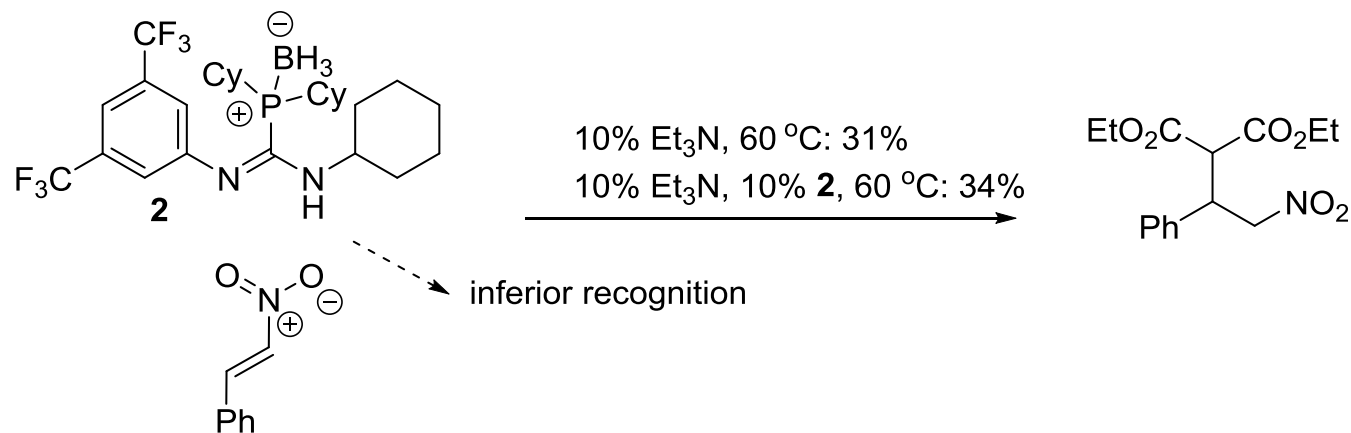
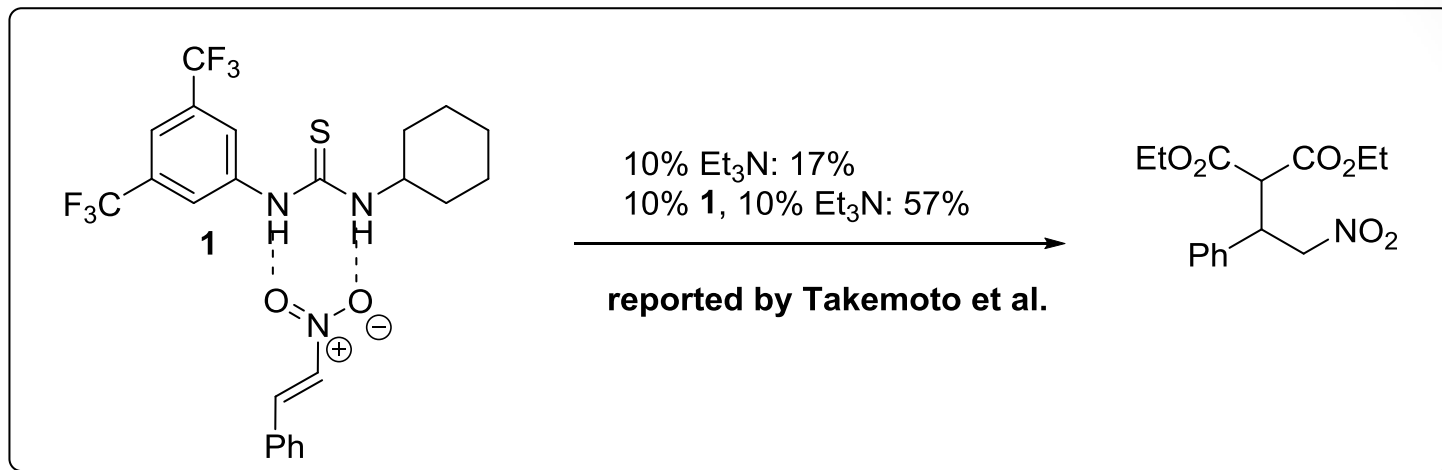


<u>catalyst</u>	<u>yield</u>
none	42%
PPh ₃ (15 mol %)	47%
1 (15 mol %)	56%
2 (15 mol %)	76%

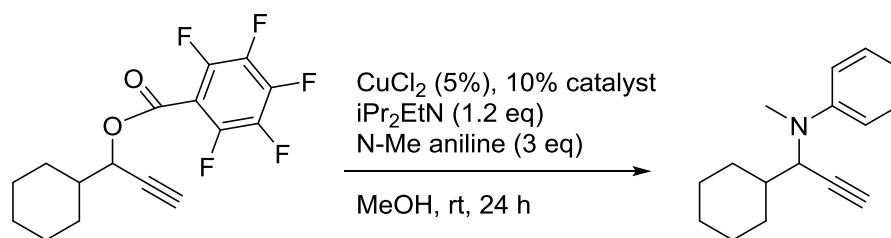


A Thiourea mimic?



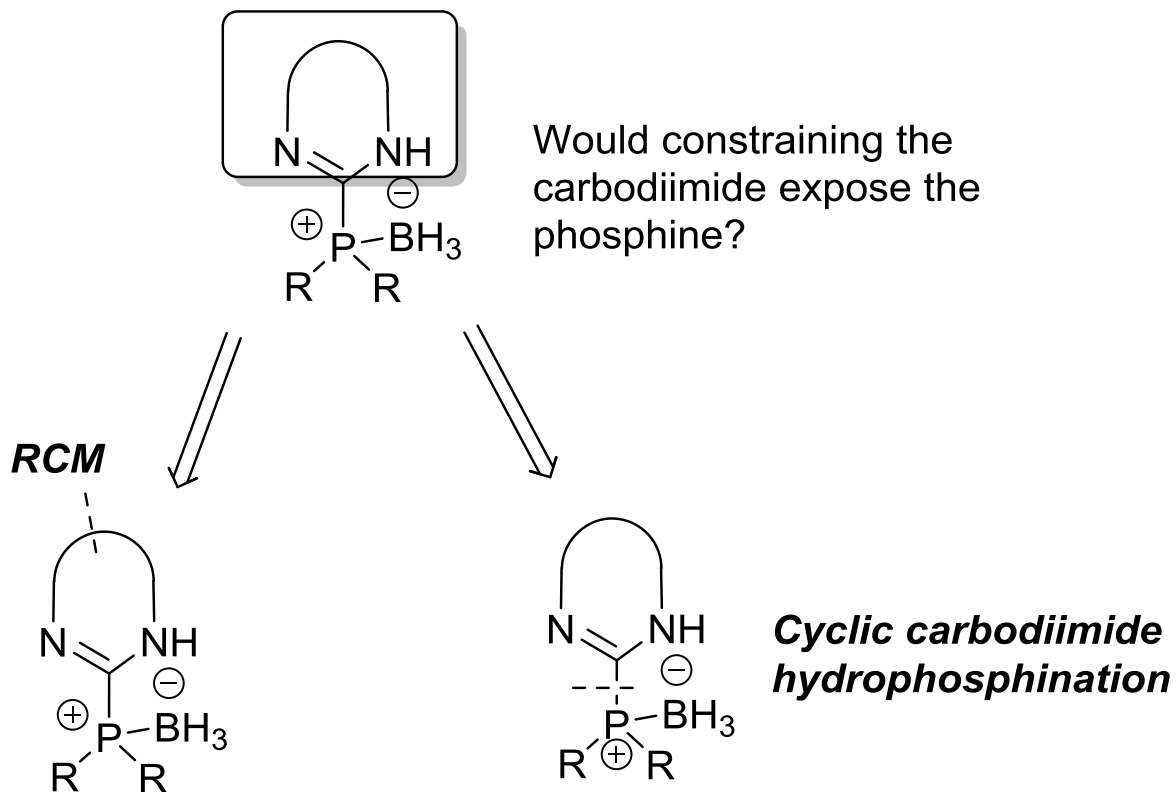


Attempted asymmetric propargylation

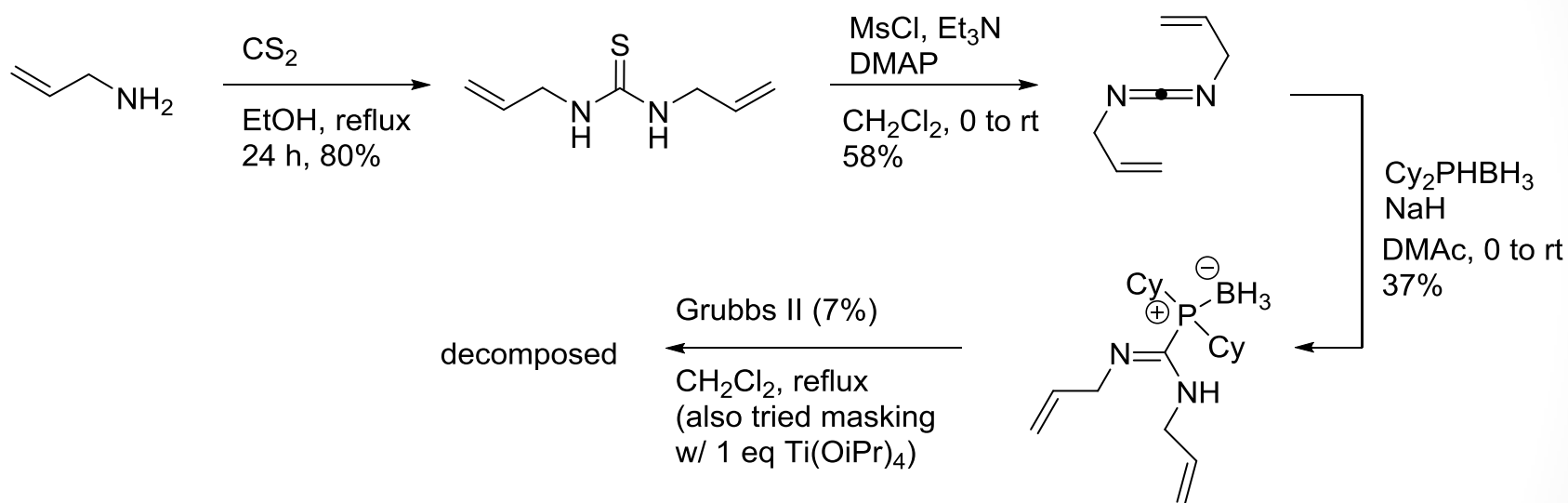


Phosphine	Yield	Chiral HPLC result
PPh_3 (CuOTf used)	89%	
	49%	no ee
	40%	no ee

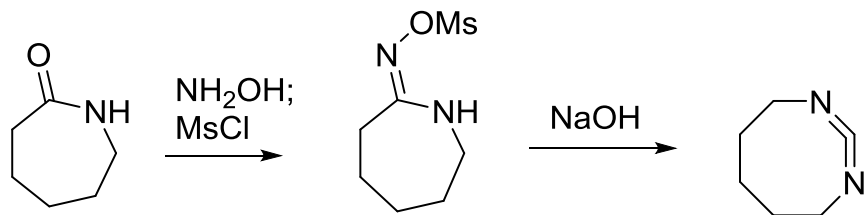
New strategy



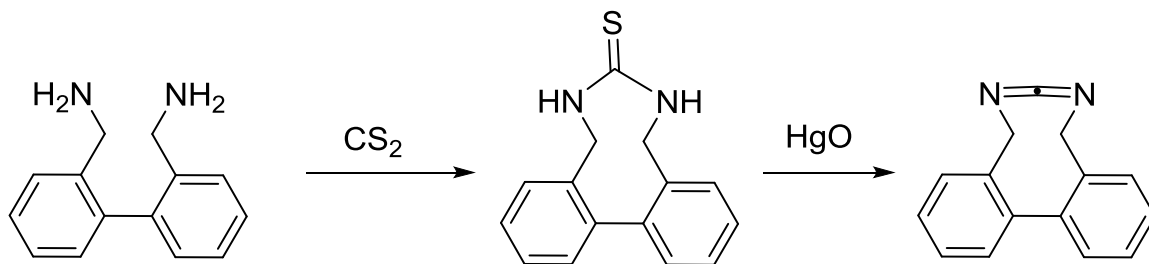
Metathesis approach



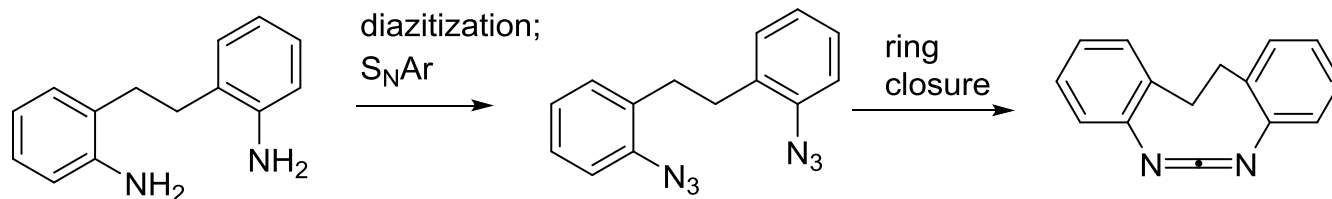
Cyclic carbodiimides



Richter, R.; Tucker, B., Ulrich, H. *J. Org. Chem.* **1982**, *48*, 1694-1700

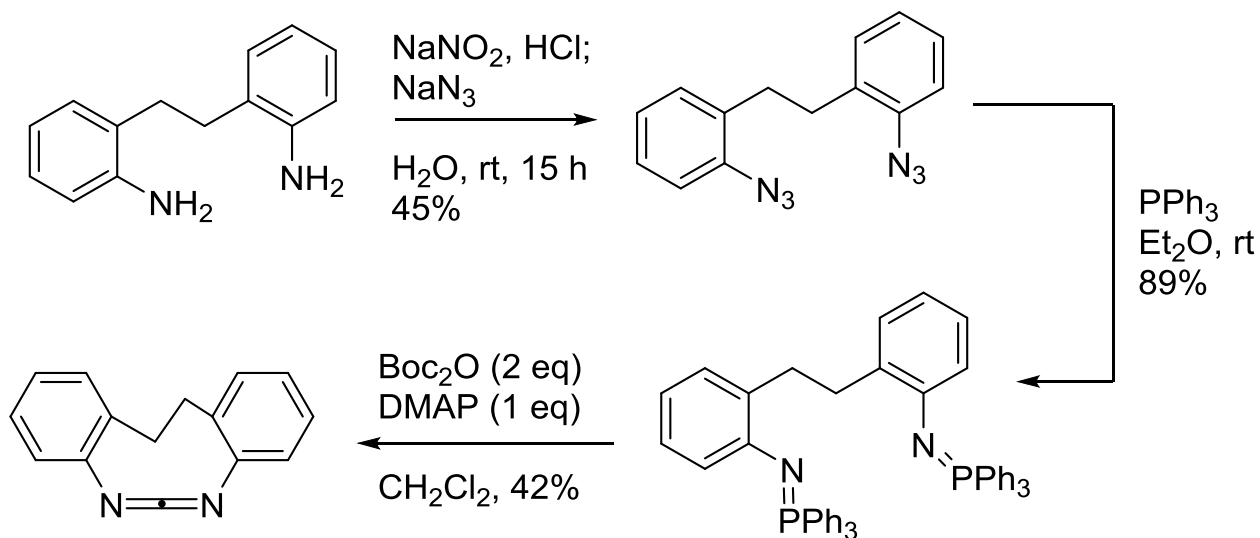


Hiatt, R. R.; Shaio, M-J.; Georges, F. *J. Org. Chem.* **1979**, *44*, 3265-3266



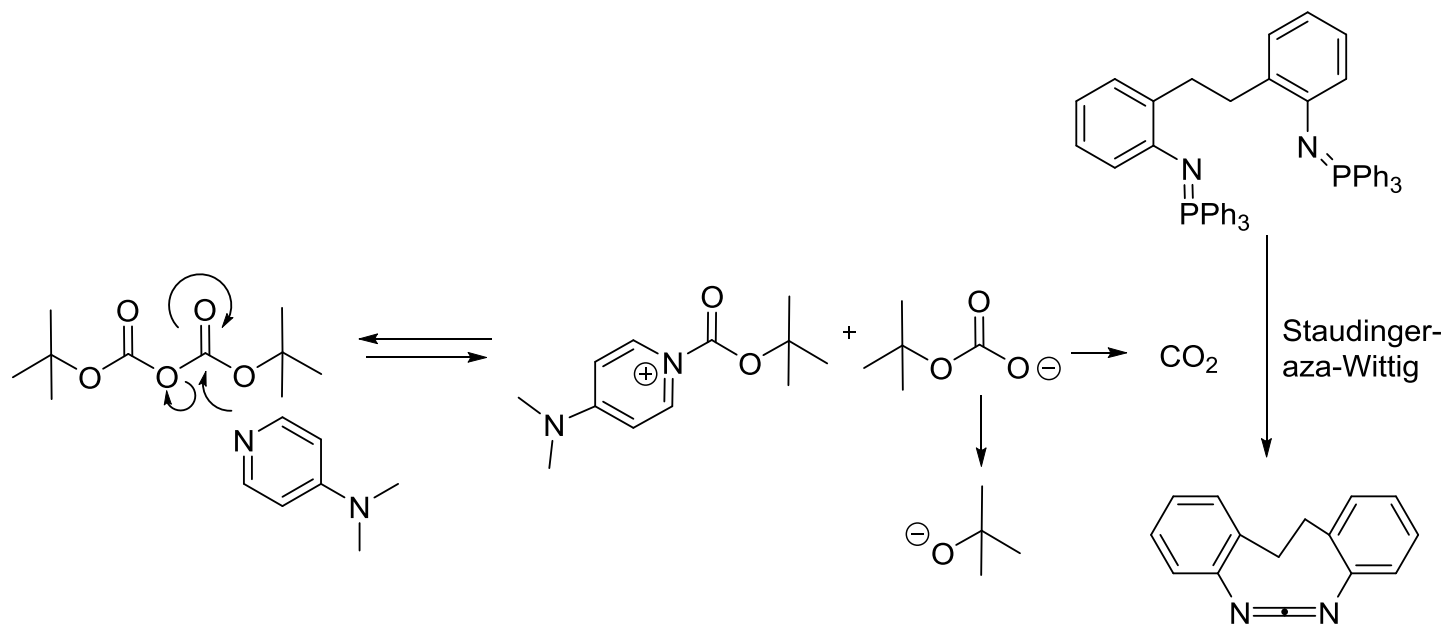
Molina, P.; Alajarin, M.; Sanchez-Andrada, P. *J. Org. Chem.* **1994**, *59*, 7306

Cyclic carbodiimide



- Inexpensive materials
- One column chromatography
- >1 g prepared

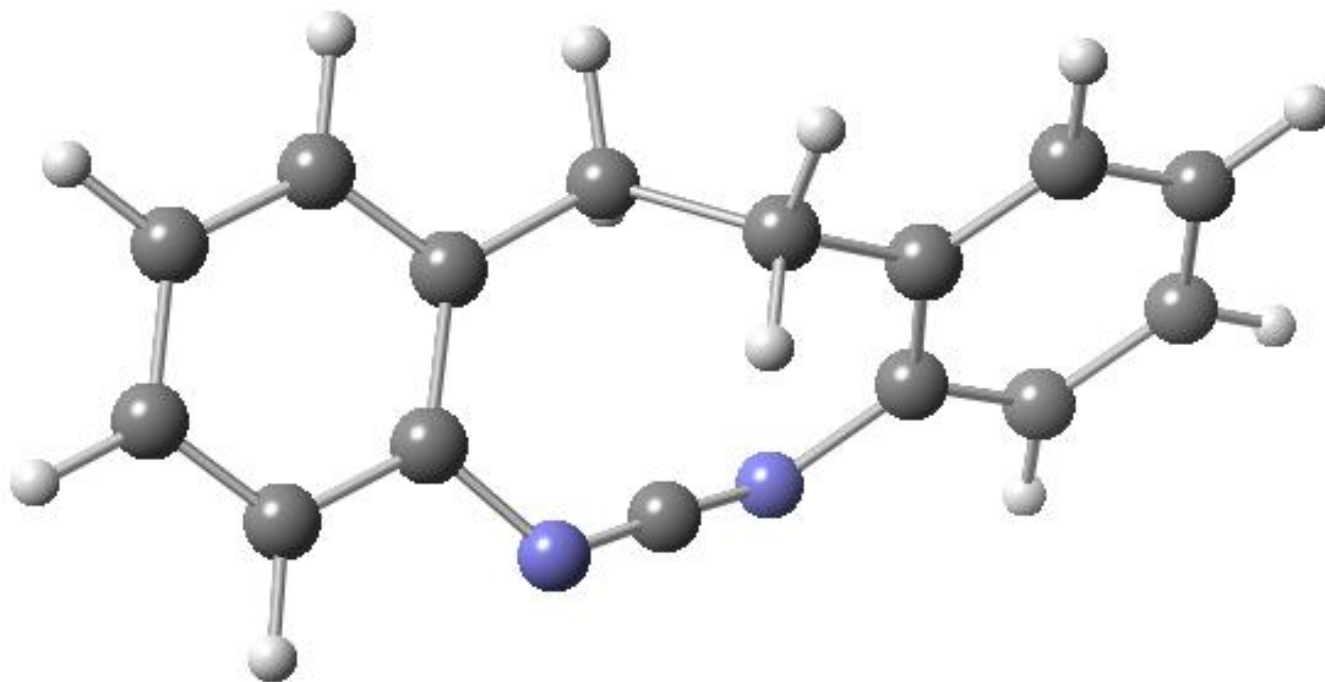
In situ CO₂



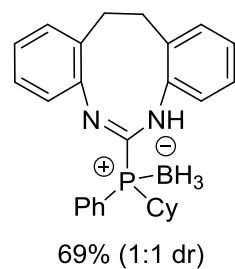
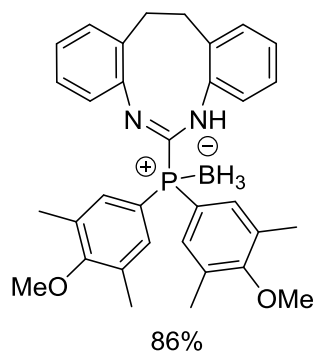
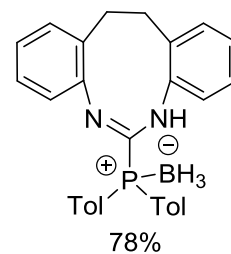
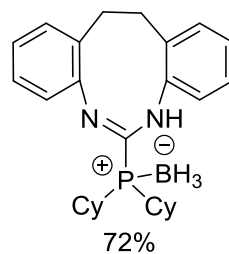
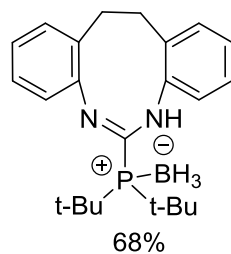
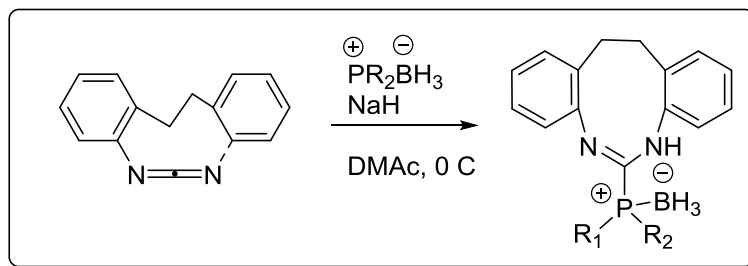
Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368-6380

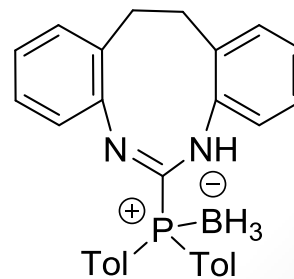
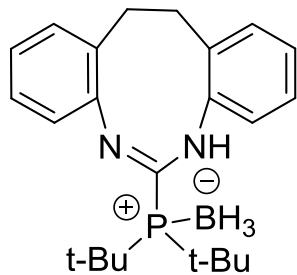
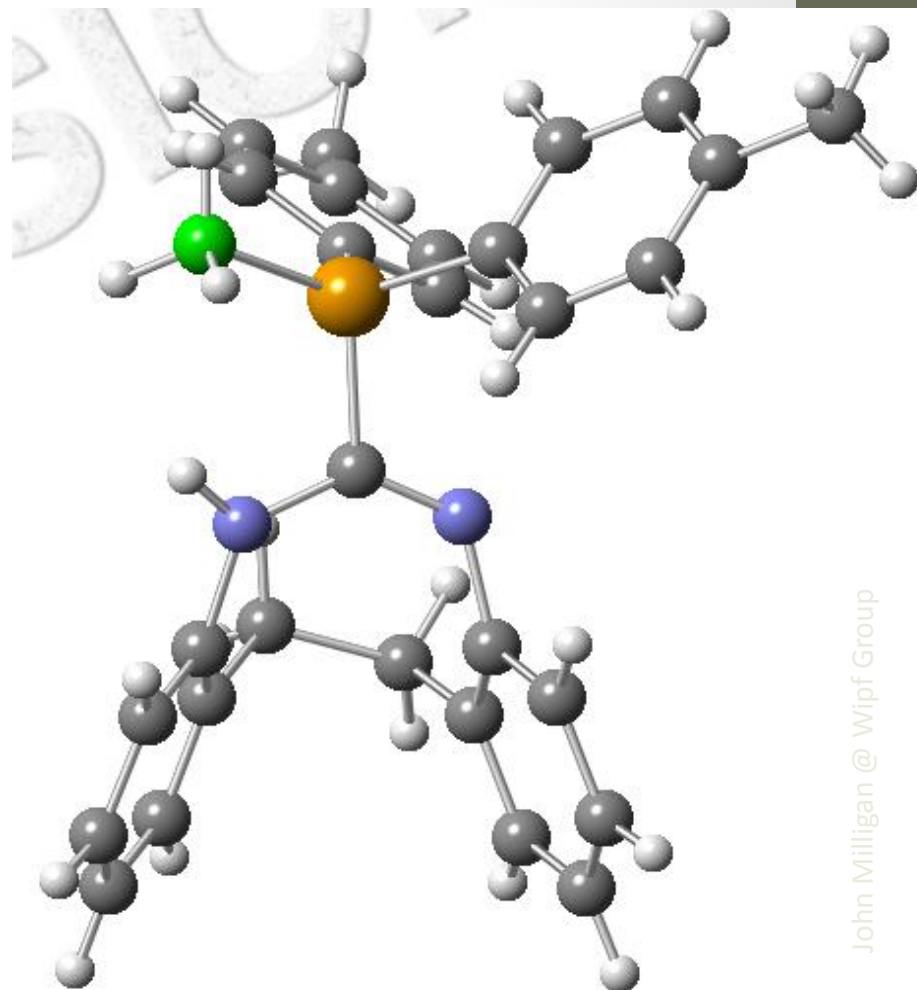
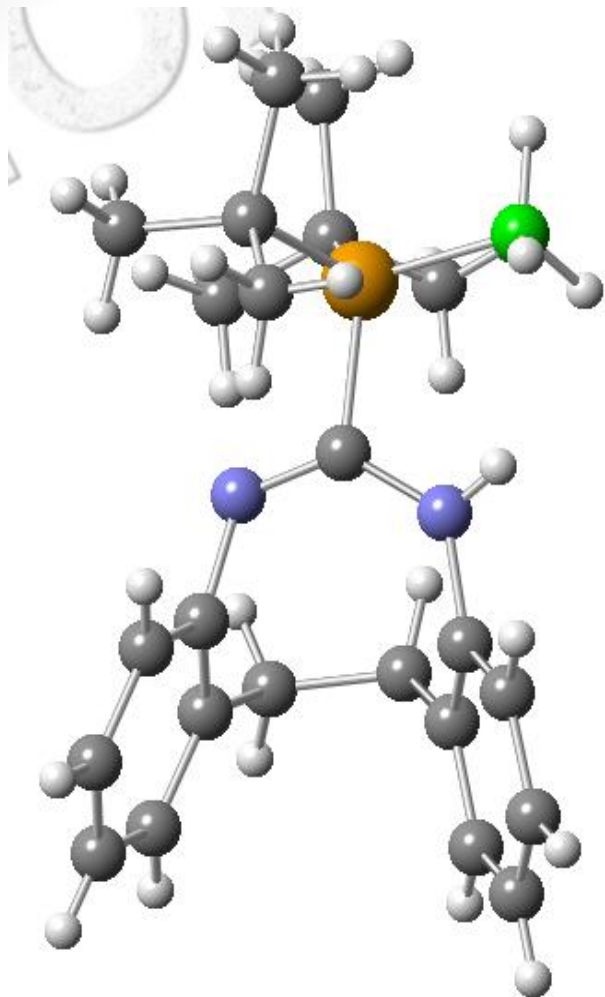
Conformation

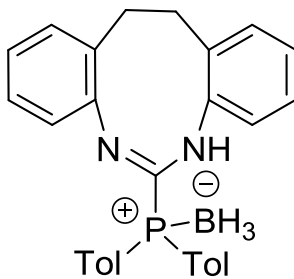
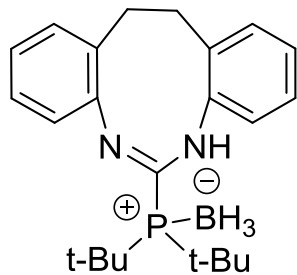
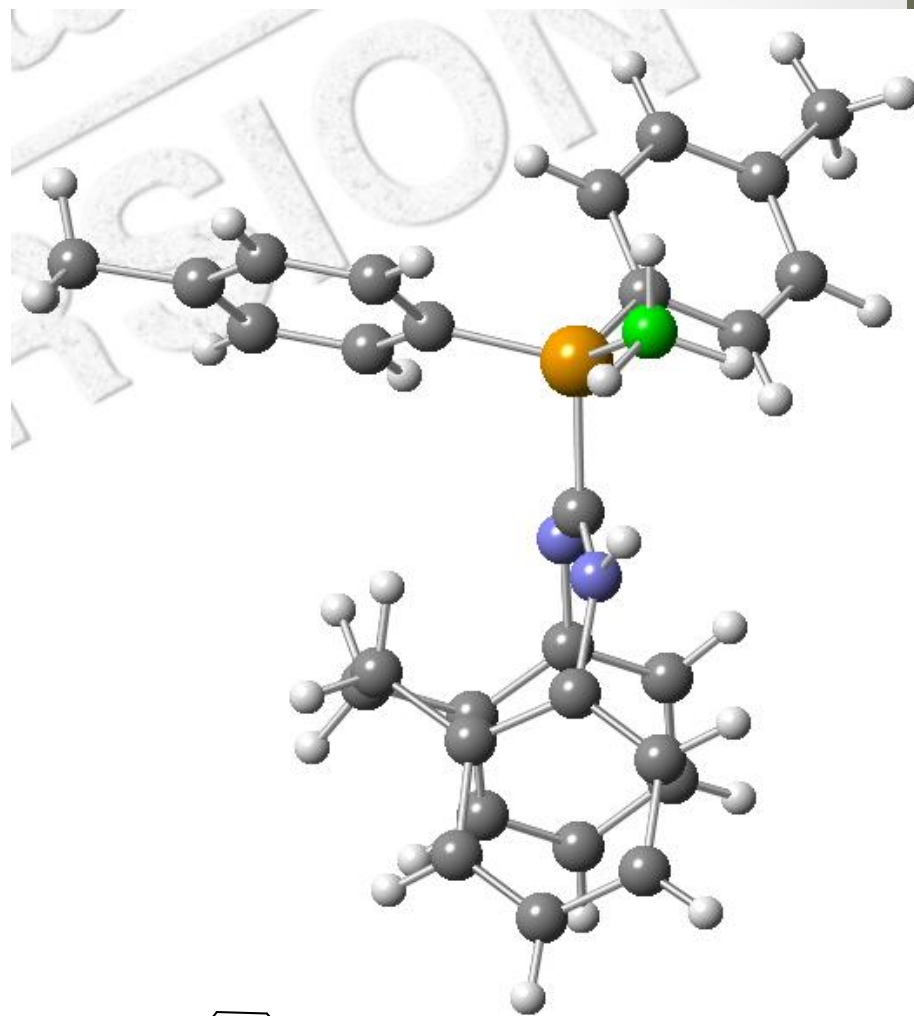
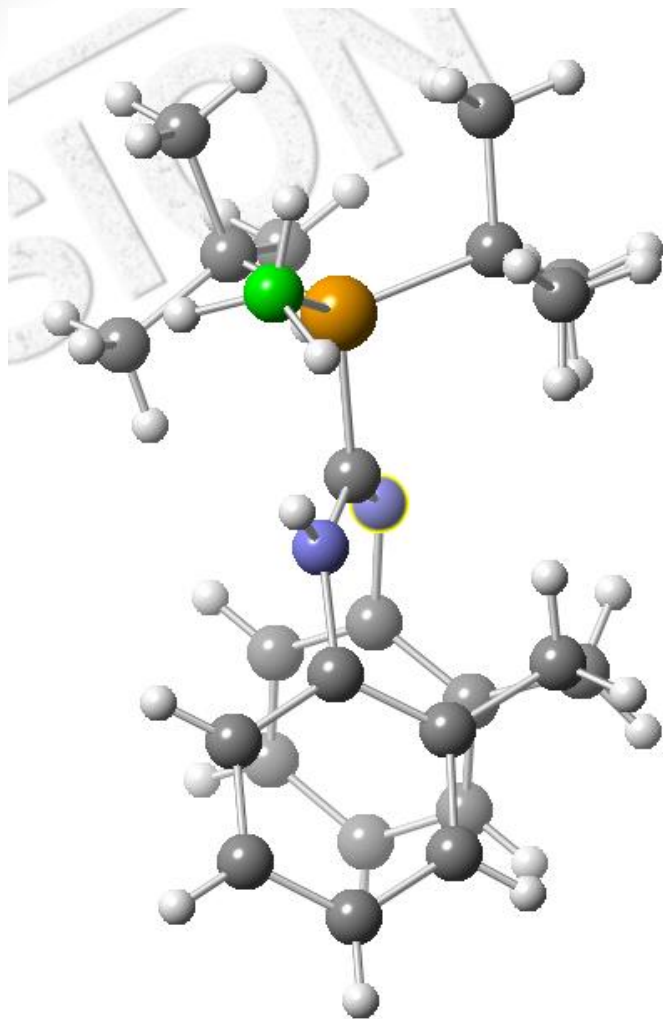
- Equilibrating axially chiral enantiomers
- C-N=C=N-C dihedral angle: 68°

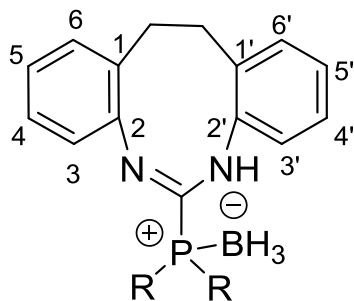


Hydrophosphination



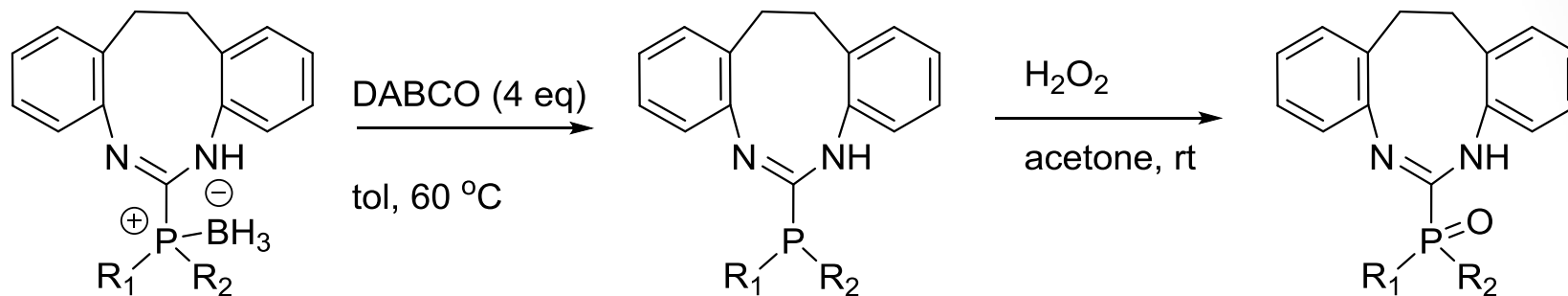






	R = t-Bu	R = Tol
ethylene bridge H-C-C-H dihedral angle	17°	24°
B-P-C-N dihedral angle	5°	21°
NH-B distance	2.50 Å	2.53 Å
C1-C1' distance (minimum)	2.80 Å	2.83 Å
C4-C4' distance (maximum)	5.15 Å	5.33 Å
CX-CX' average distance	3.98 Å	4.07 Å

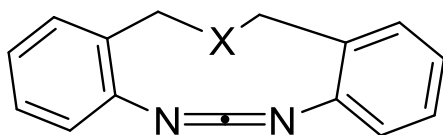
Deprotection



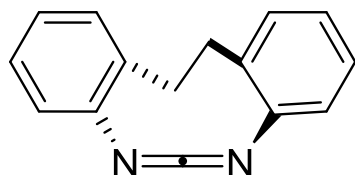
R₁=R₂ = Tol, 86%
R₁=R₂ = 3,5-dimethyl-4-methoxyphenyl, 65%
R₁= Ph, R₂ = Cy, 94%

R₁=R₂ = Tol, 86%
R₁=R₂ = 3,5-dimethyl-4-methoxyphenyl, 91%

An improved carbodiimide?

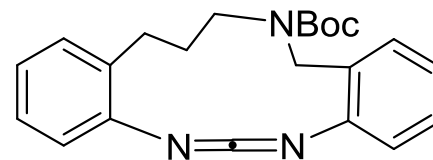
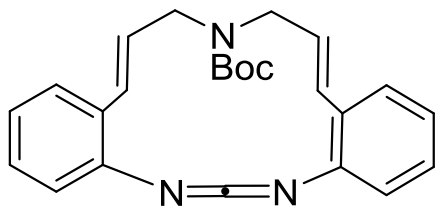
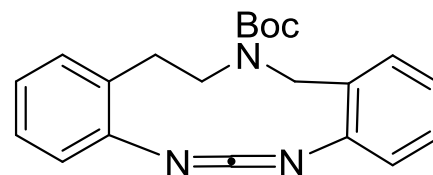
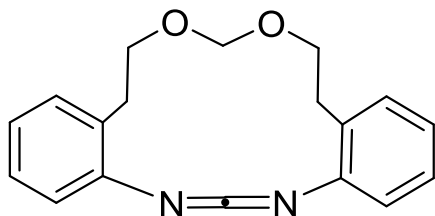


Can heteroatoms provide additional binding motifs?



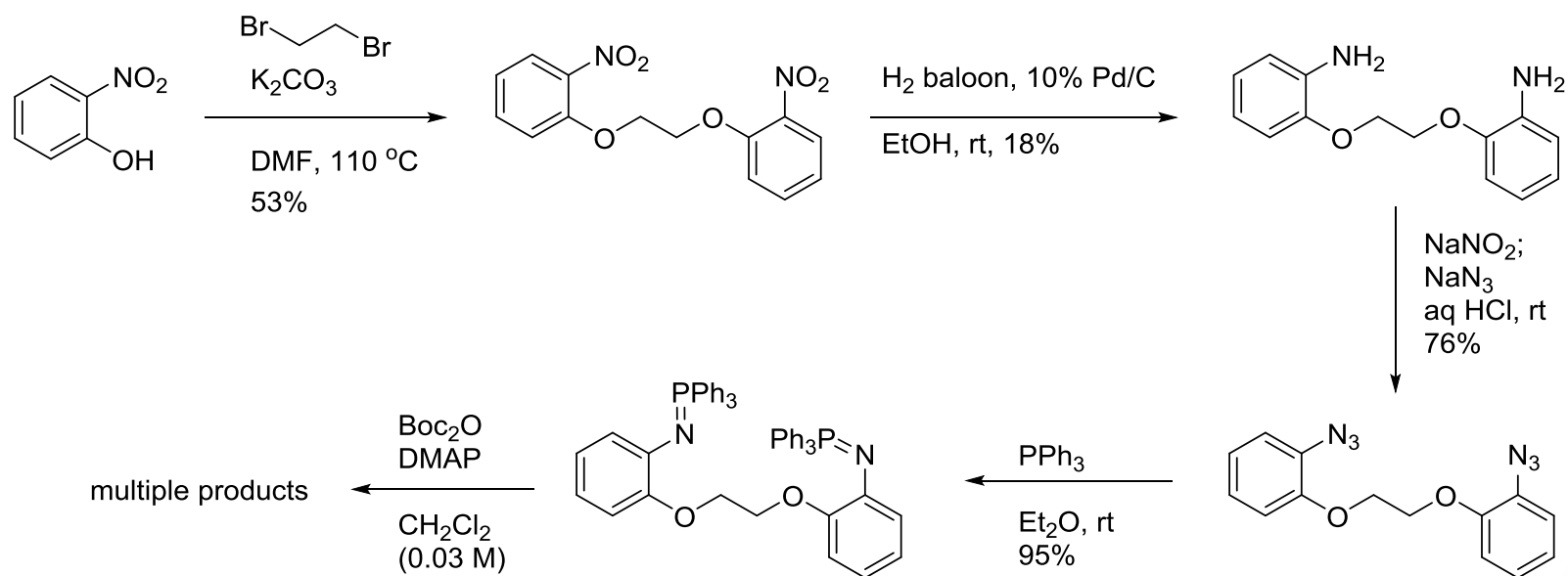
Can axial chirality be enforced?

Successful tethers

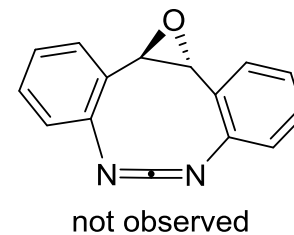
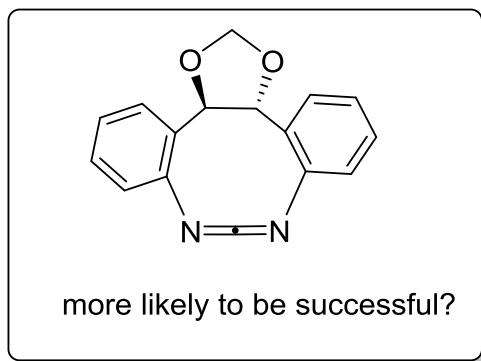
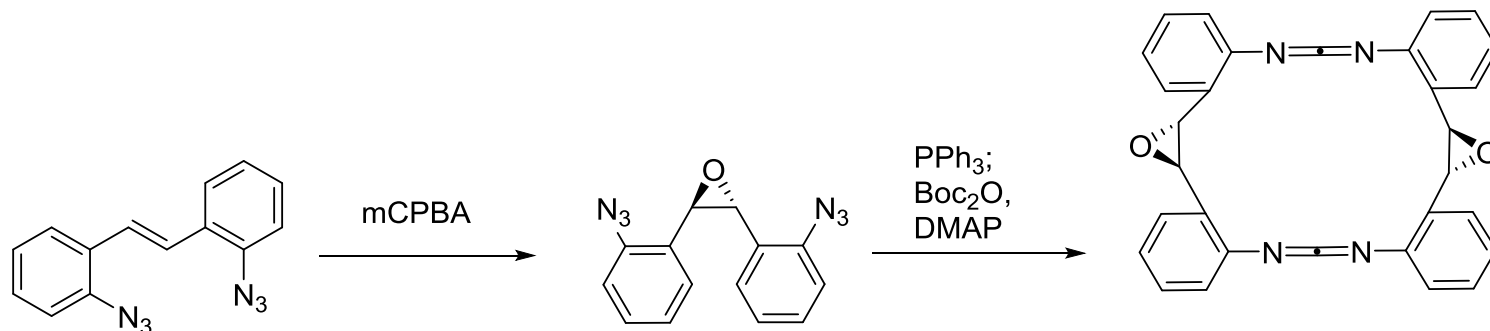


Molina, P. et al. *J. Org. Chem.* **1996**, *61*, 4289-4299.

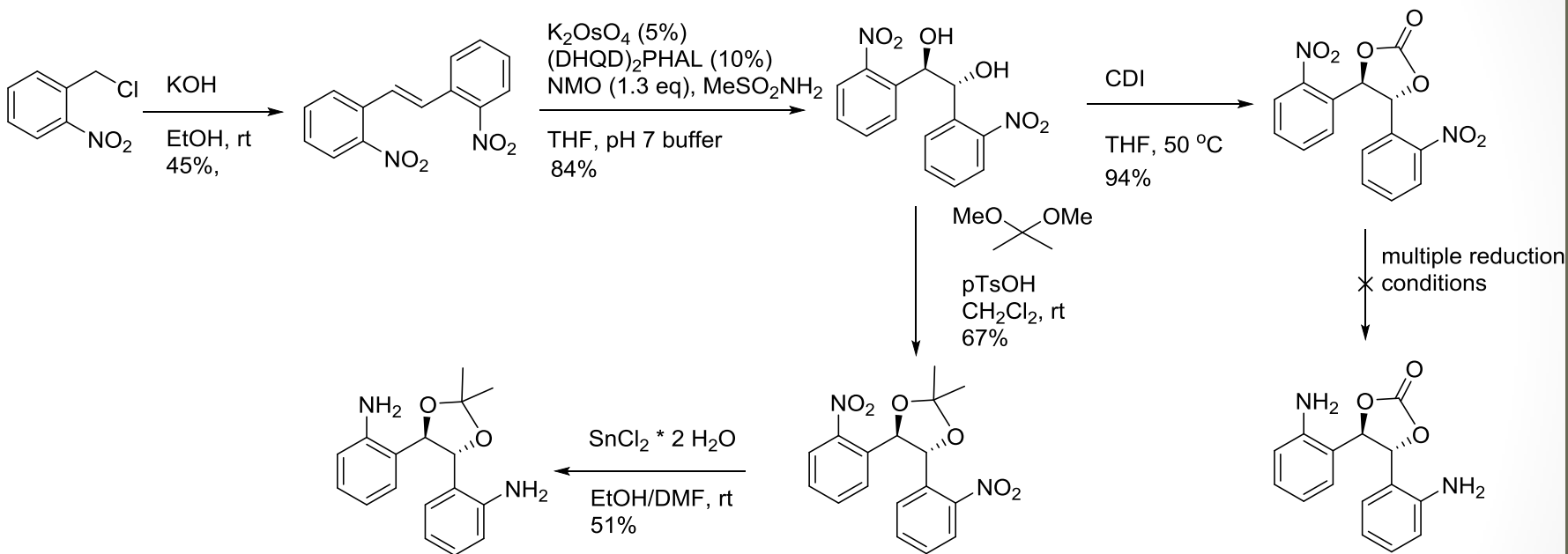
Glycol-based tether



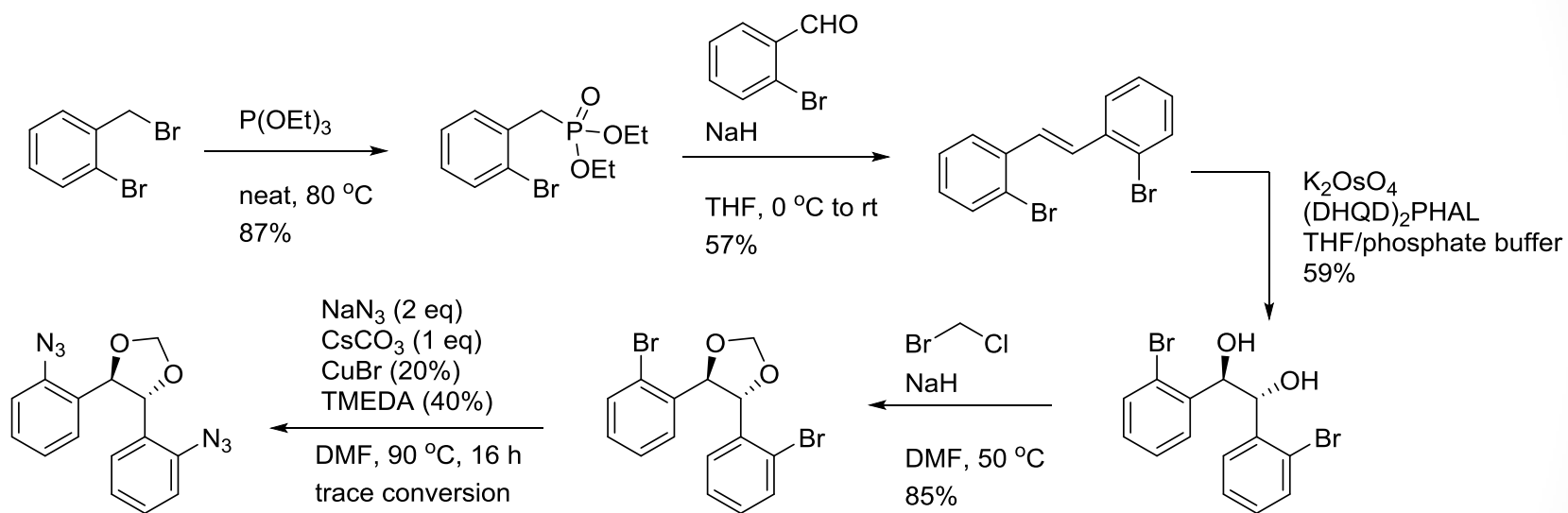
A chiral constraint?



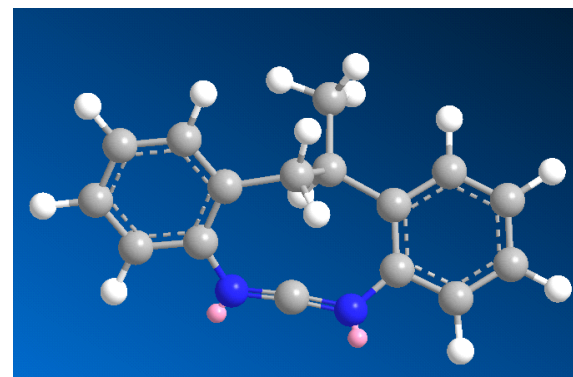
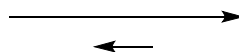
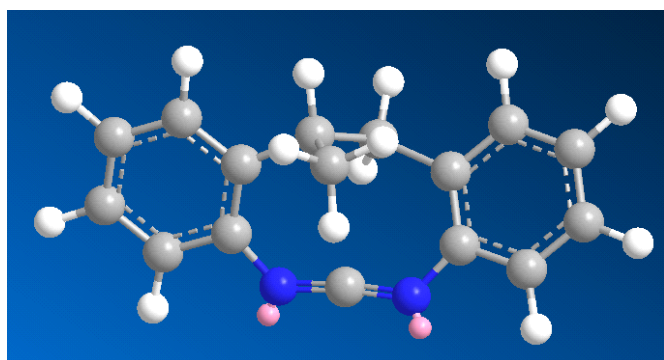
Chiral acetal



Chiral acetal

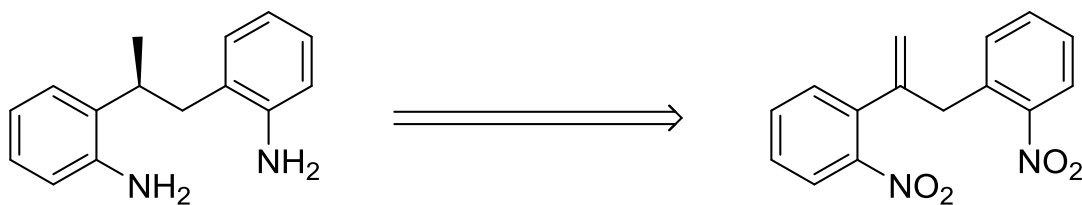


Alternative: A chiral methyl

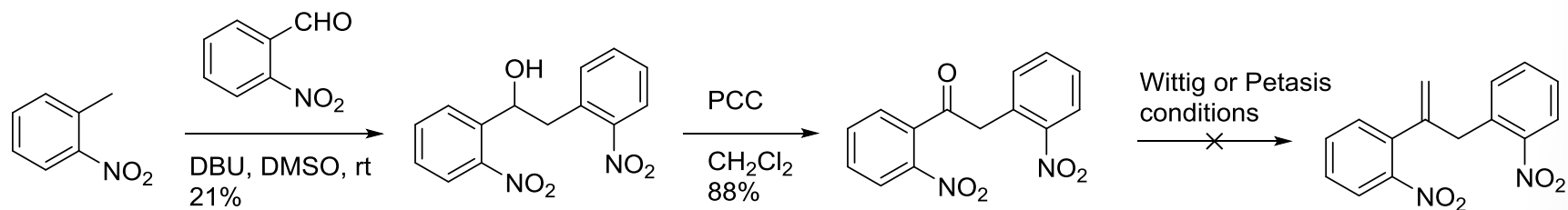
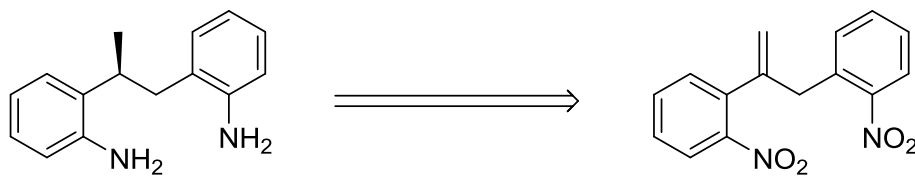


Molina, P. et al. *J. Org. Chem.* **1996**, *61*, 4289-4299.

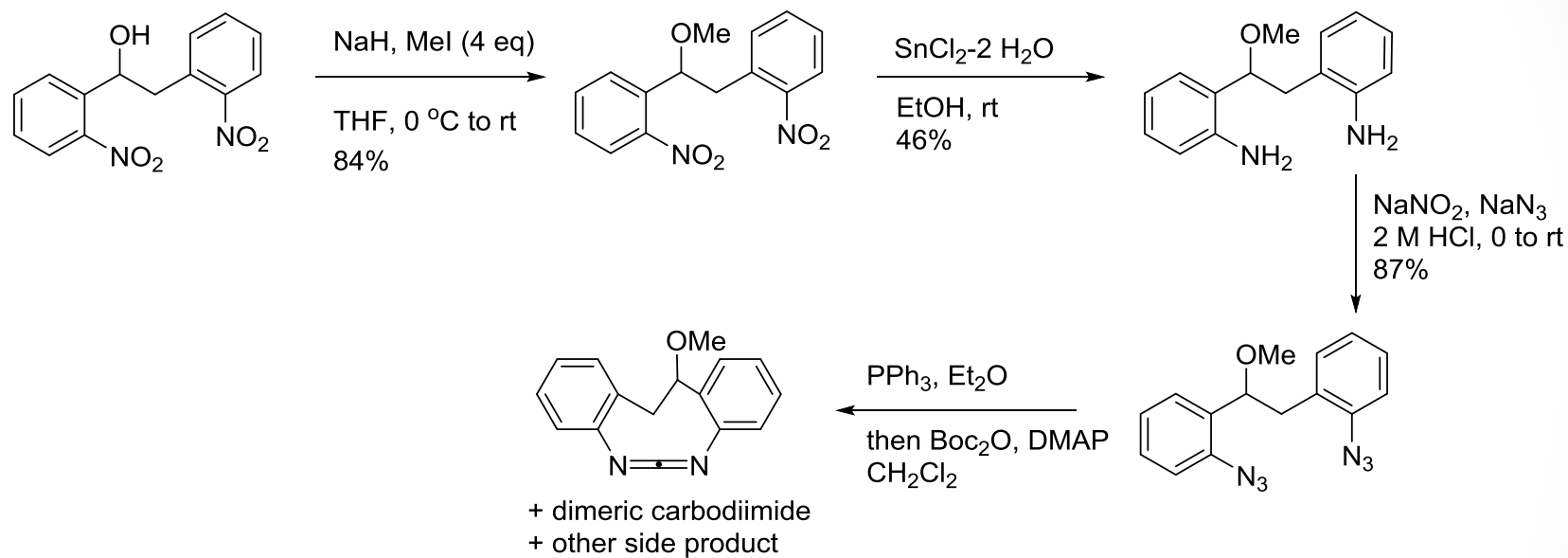
A chiral methyl



A chiral methyl



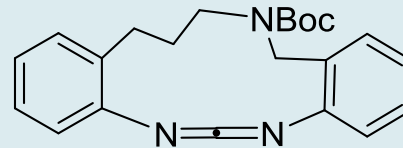
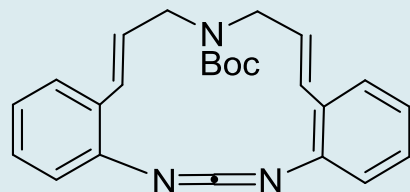
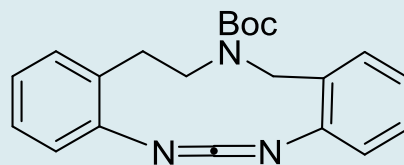
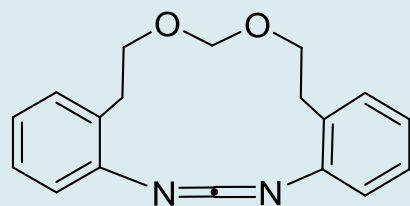
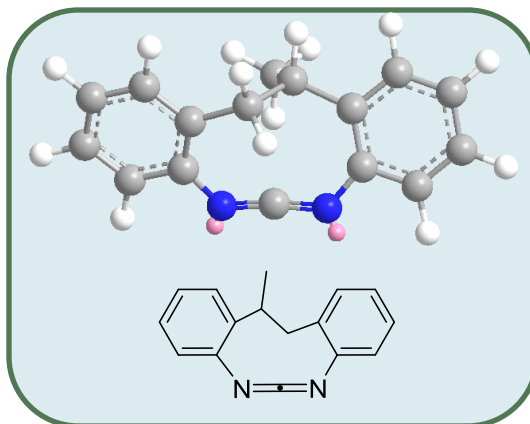
Alternate approach



Isolated by Molina

Isolated as dimer in
low yield by JAM

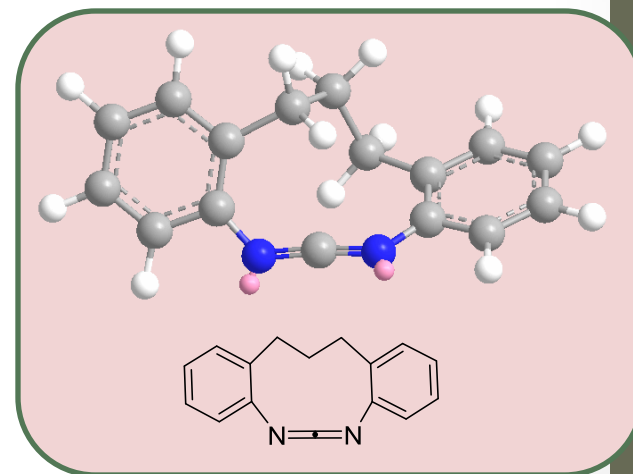
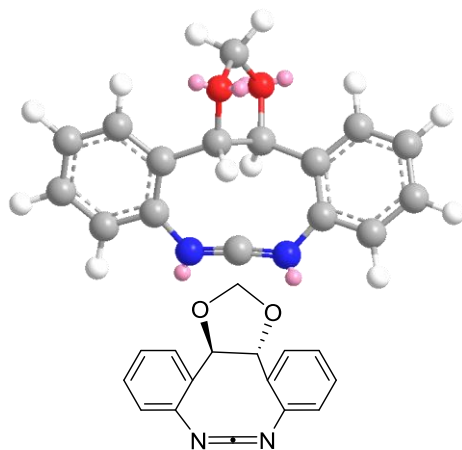
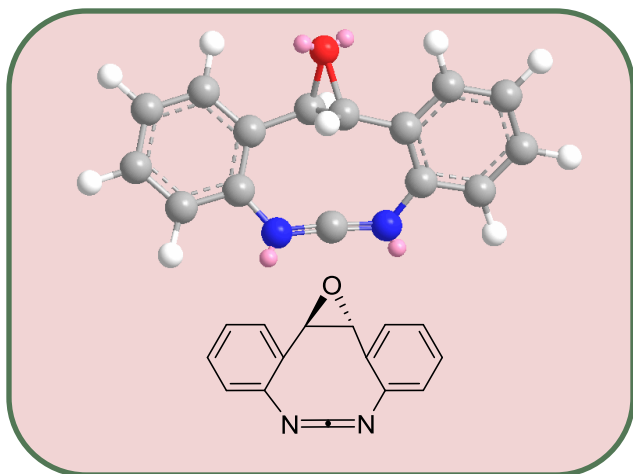
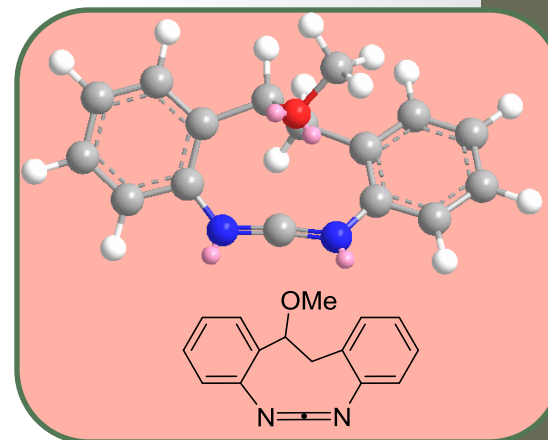
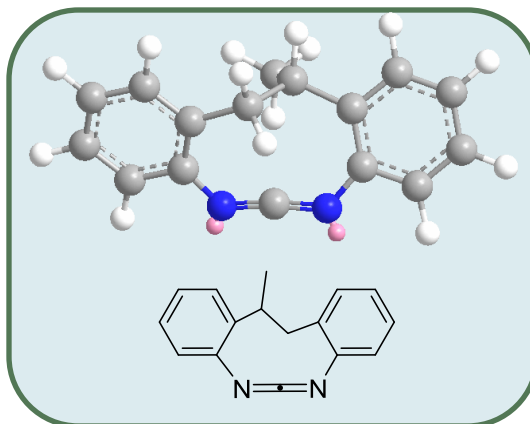
Isolated as dimer in
low yield by Molina



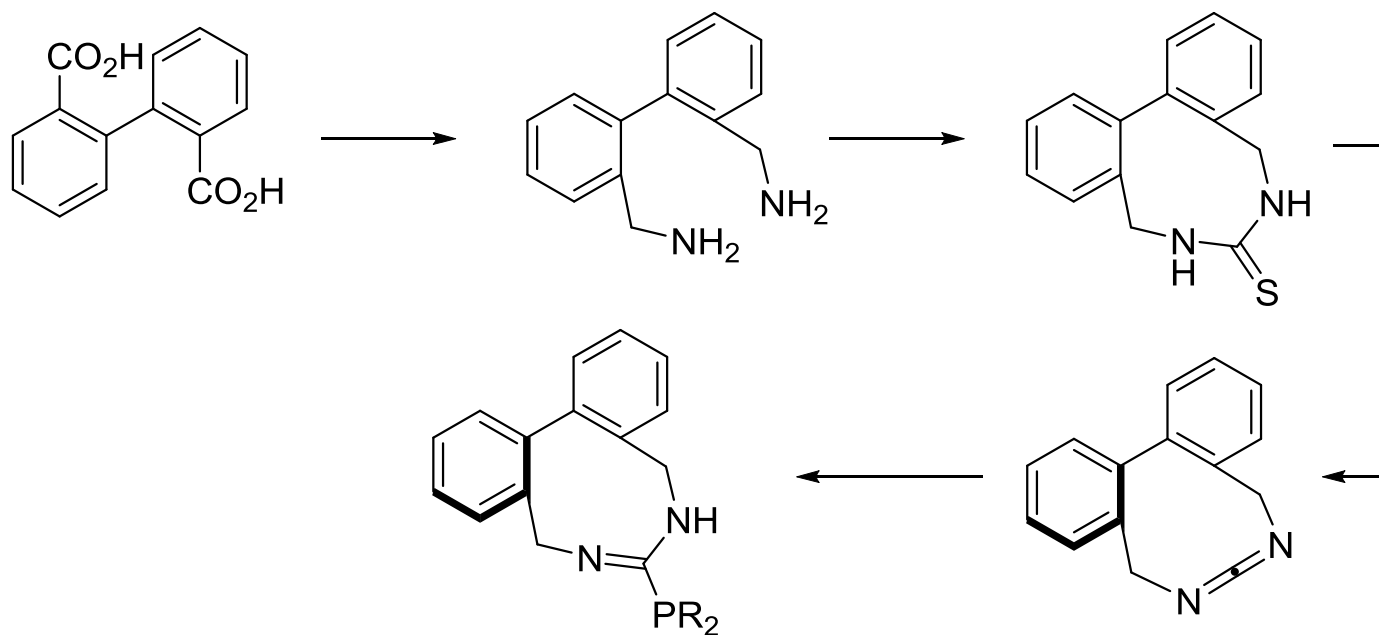
Isolated by Molina

Isolated as dimer in low yield by JAM

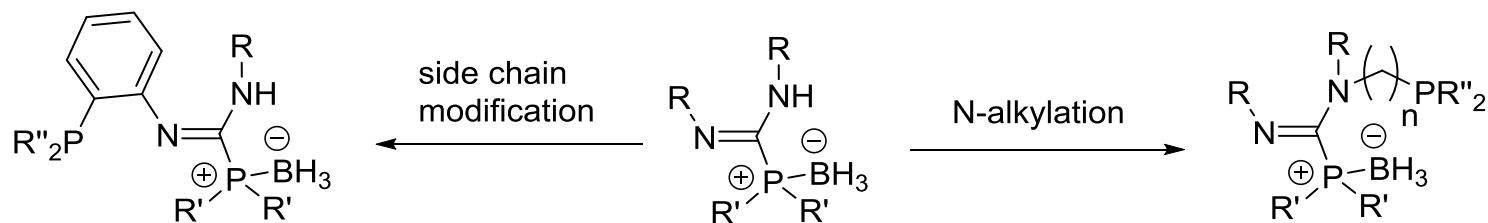
Isolated as dimer in low yield by Molina



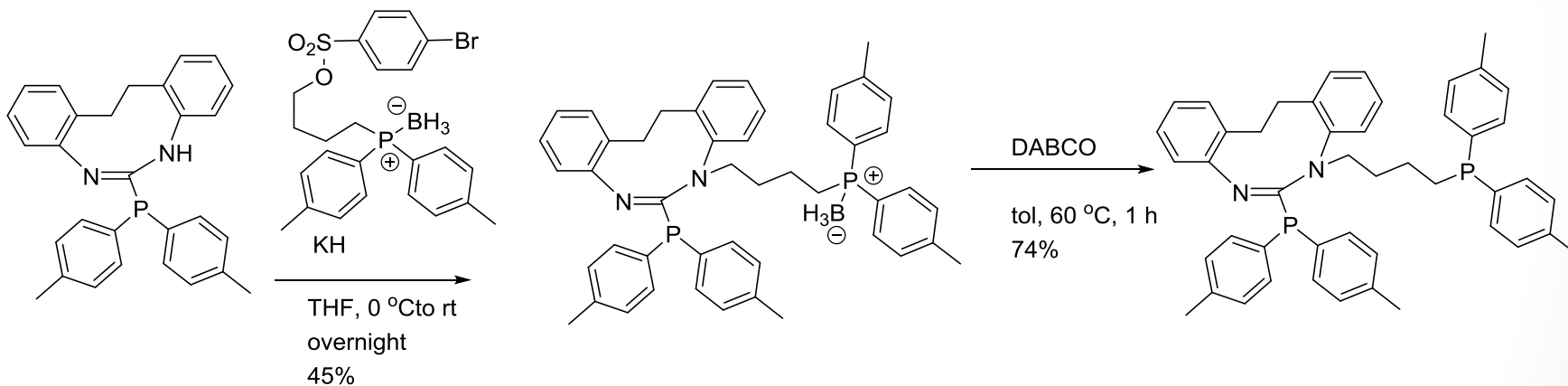
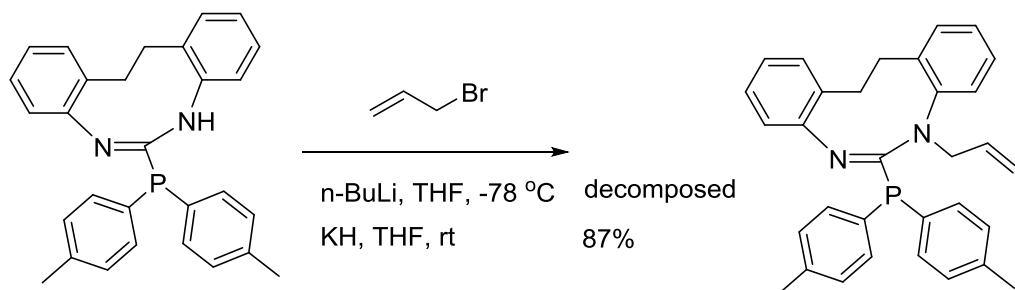
An alternative cyclic system?



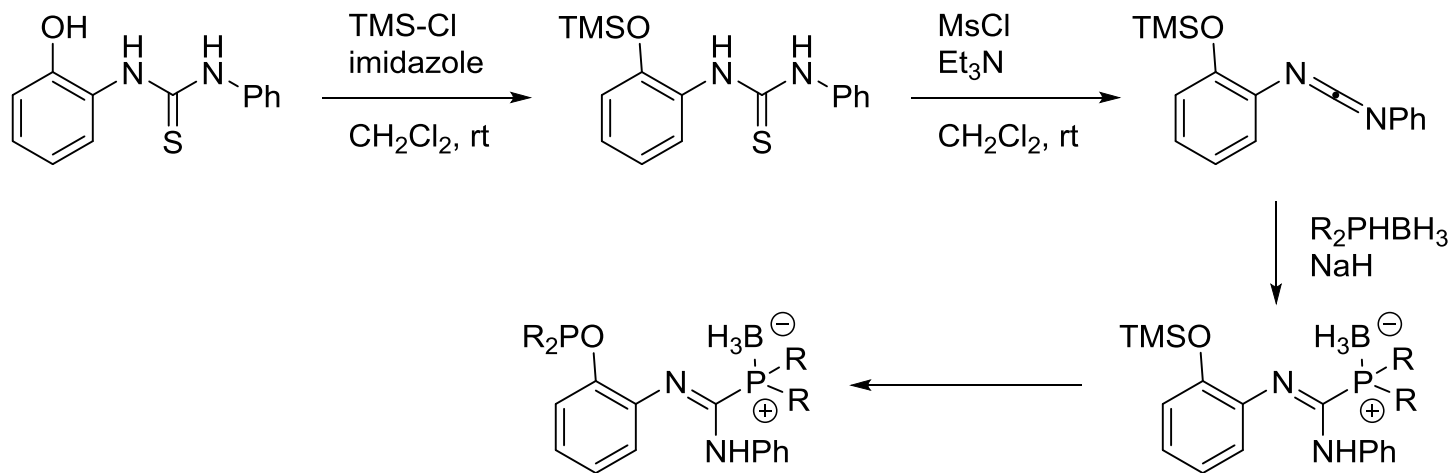
Toward Bidentate phosphines



Tethering



Side Chain Modification



Conclusion

- The scope of Busacca's hydrophosphination was further explored
 - The reaction is tolerant of a variety of carbodiimides
 - Aryl phosphine boranes are not as effective as alkyl derivatives
- Acidic deboronations of phosphaguanidine boranes afford guanidinium borane salts, not deboronated products
- A cyclic carbodiimide was prepared, and underwent facile hydrophosphination with this method
 - Modifications of the cyclic core have proven difficult to date
- Future directions include developing catalytic systems, preparing chiral phosphaguanidines, and crystallizing transition metal complexes

Acknowledgements



- Dr. Carl Busacca
- Dr. Chris Senanayake
- Cyrus Ramavarapu
- Others



- Dr. Wipf
- Wipf group past and present
- Eakkaphon “Onie” Rattanangkool
- Dr. Steve Geib
- Dr. Bhaskar Godugu
- A&S Graduate Fellowship