The Synthesis of P-Stereogenic Phosphorus Compounds

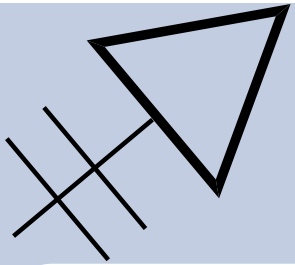
Increasing accessibility to a privileged class of ligand

Craig Seymour

Group Meeting Presentation

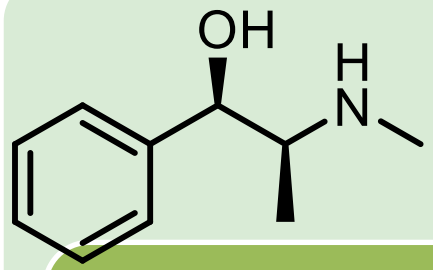
22 April 2014

Outline



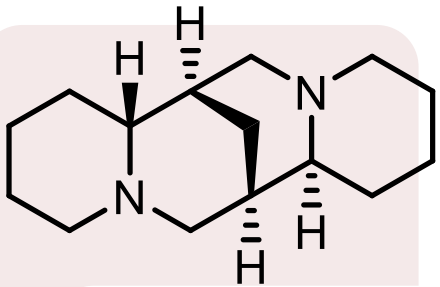
Introduction

- History
- Importance
- Phosphine Inversion



Ephedrine

- Jugé-Stephan Method
- Han Improvements



Sparteine

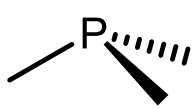
- Evans' Introduction
- Catalytic Usage

Objectives

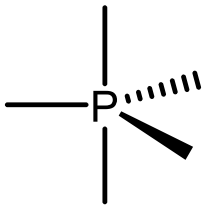
1. Demonstrate the effectiveness of an ephedrine based synthesis.
2. Demonstrate the ability of sparteine to create P-stereogenic centers that complement an ephedrine based synthesis.
3. Briefly discuss applications of P-stereogenic ligands as they relate to non-hydrogenation processes.

Nomenclature

- In the literature, a phosphorus atom bonded to three different substituents is also called “P-stereogenic”, “P-chirogenic”, or “P-chiral”. It should noted that “P-chiral” is not strictly correct because the chirality is a property of a molecule as a whole.



Phosphane
Phosphine

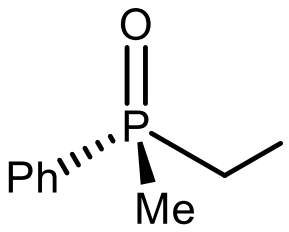


λ^5-Phosphane
Phosphorane

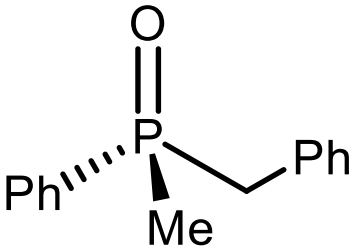
Muller, G., *et. al. Coord. Chem. Rev.* **2007**, *251*, 25.
IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book").

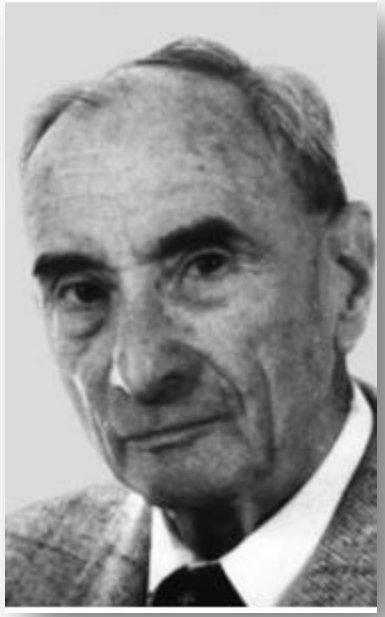
History

Meisenheimer at Berlin, 1911

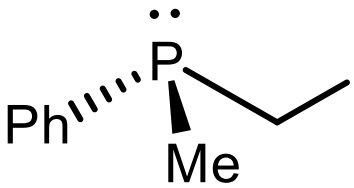


Meisenheimer at Berlin, 1926





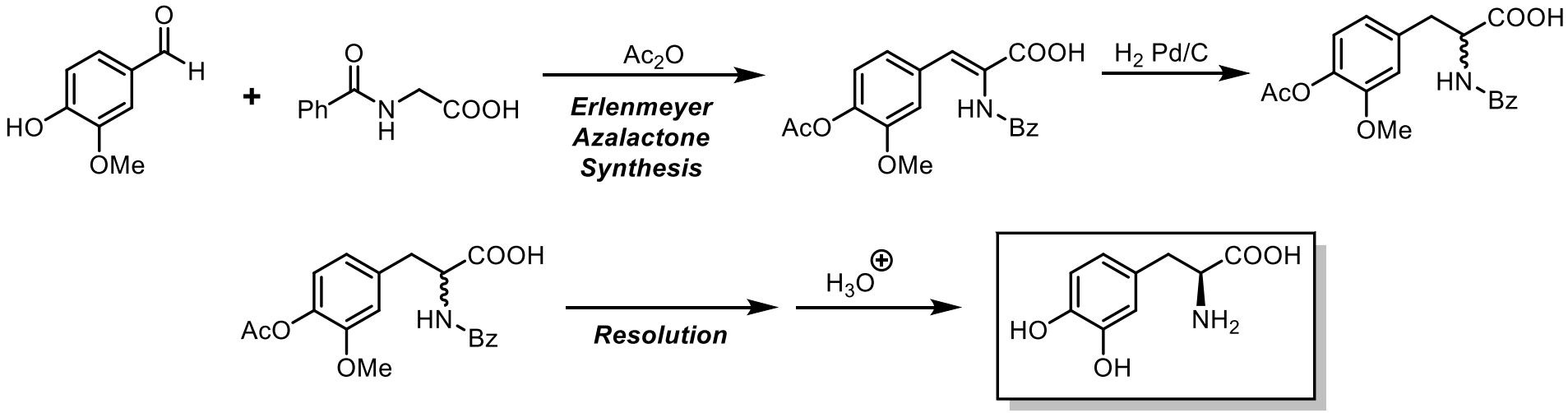
Horner at Mainz, 1961

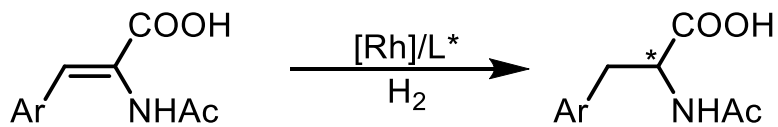


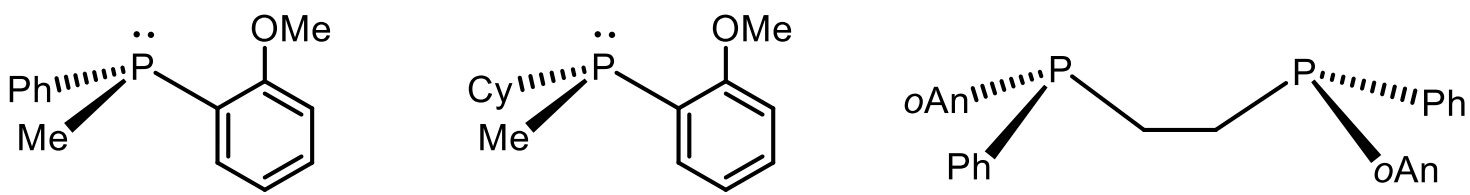
Meisenheimer, J., *et. al*. *Chem. Ber.* **1911**, *44*, 356. Meisenheimer, J., *et. al*. *Liebigs Ann. Chem.*. **1926**, 213.
Horner, L. *et. al. Tetrahedron Lett.*, **1961,** *2*, 161.

DiPAMP

Knowles at Monsanto, 1968-77







PAMP
79: 10 er

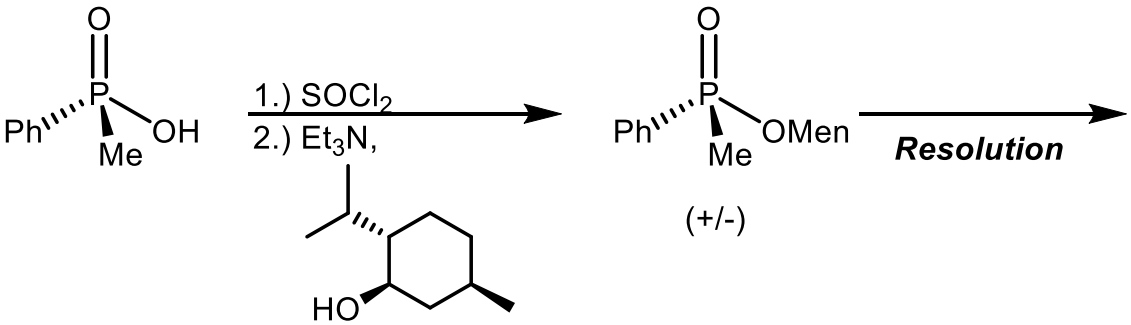
CAMP
92:8 er

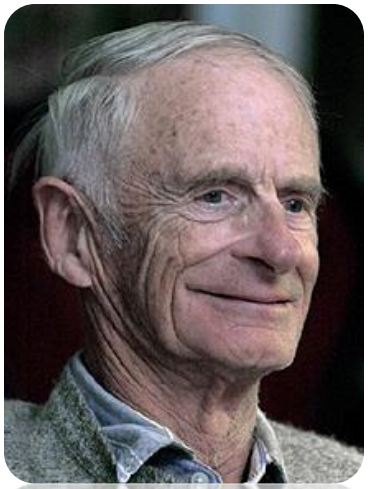
DiPAMP
98:2 er

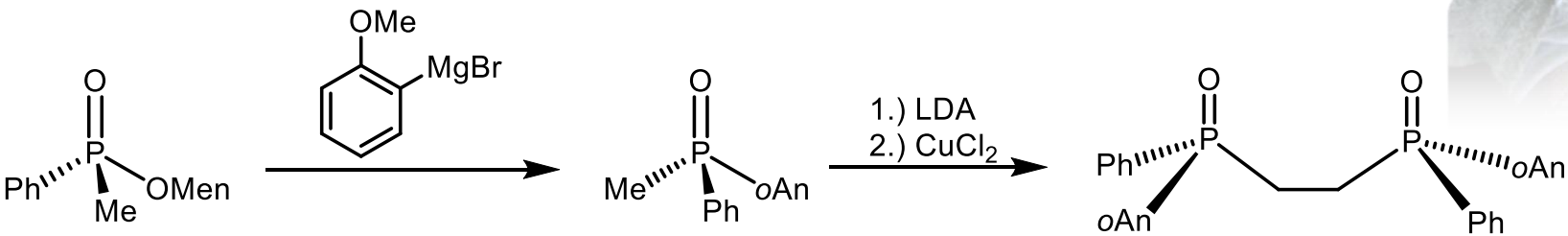
Knowles, W, *et. al. J. Am. Chem. Soc.* **1977**, *99*, 5946.

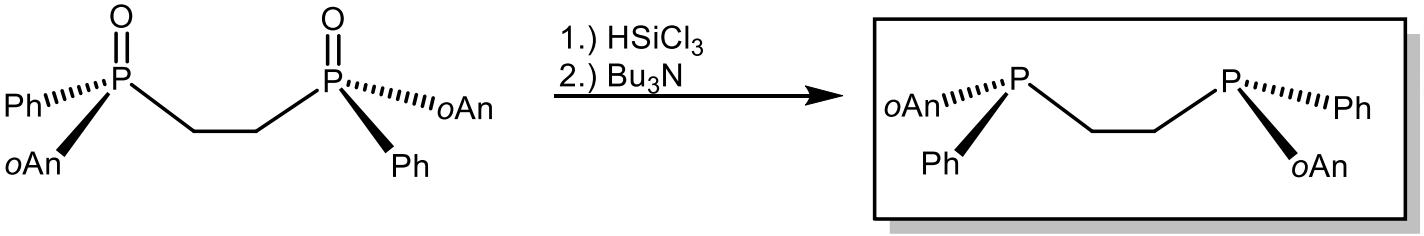
DiPAMP Synthesis

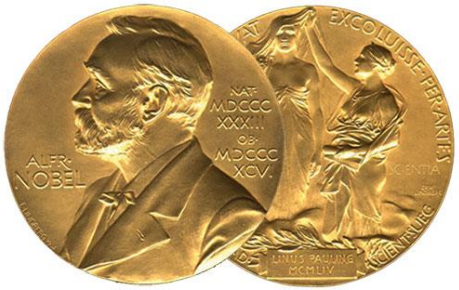
Knowles at Monsanto, 1968-77









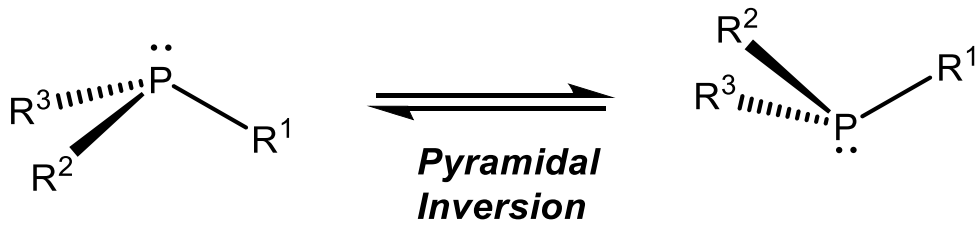


Mislow, K., *et. al. J. Am. Chem. Soc.* **1968**, *90*, 4842.

Why Were P-Stereogenic Ligands Ignored?

- "Chiraphos, BINAP, DuPhos… showed that stereogenic phosphorus atoms were not required to obtain high enantioselectivities…attention was shifted away from P-stereogenic systems, leaving them in the shadow for decades" – Arnald Grabulosa
- "Chiral phosphines bearing stereogenic phosphorus atoms are prone to racemization" – Quirmbach Börner
- "Interest in P-stereogenic compounds fell away because of the synthetic difficulties encountered" – Guillermo Muller

Configurational Stability of Phosphorus

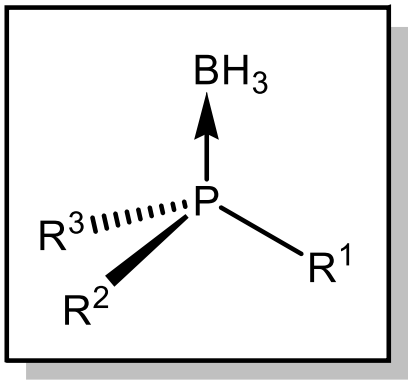


- Amines have an inversion barrier typically quoted as 7-12 kcal/mol.
- Phosphines have an inversion barrier that is much higher, 35-40 kcal/mol.
  - Steric effects increases this barrier.
  - Delocalization of the lone pair lowers this barrier.
- In practical terms an inversion barrier of approx. 29 kcal/mol has $t_{1/2}$ of 7h at 95°C

Mislow, K.; *J. Am. Chem. Soc.* **1971**, *93*, 6507.

Phosphorus Stabilizing Groups

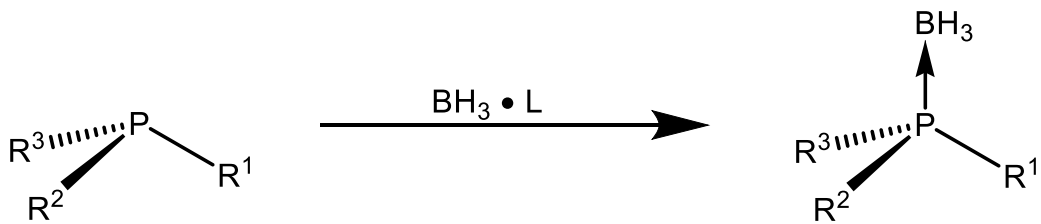
Imamoto at Chiba University, 1990



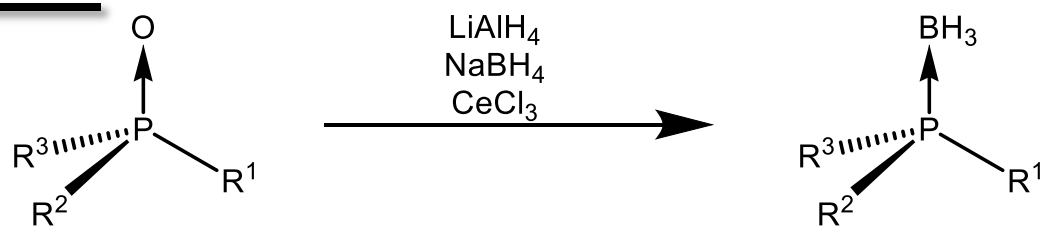
- The borane group quenches the lone pair, preventing oxidation and inversion.
  - Phosphine boranes are air-stable and usually crystalline.
- Hydrogen and methyl groups on phosphorus are activated. (Discussed in part III of the talk)
- Protection with $BH_3 \bullet THF$ or $BH_3 \bullet SMe_2$ occurs with retention of configuration.
- Easily deprotected with 2° amines or DABCO with retention of configuration.
  - Deprotection is not always required; phosphine boranes can prepare metal complexes from metal salts, e.g. $PdCl_2$ to Pd^o. (Juge, S. *et. al. J. Organomet. Chem.*, **2001**, *624*, 333.)
- Can be converted to the phosphine oxide (mCBPA), phosphine sulfide (S^8), or into a phosphonium salt (alkyl iodide).

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

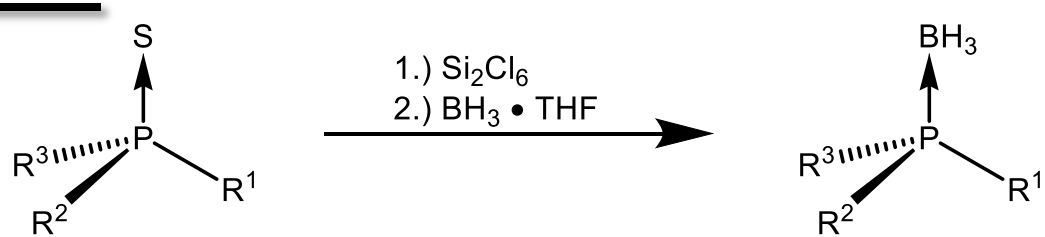
Phosphorus Stabilizing Groups



Imamoto at Chiba University, 1985



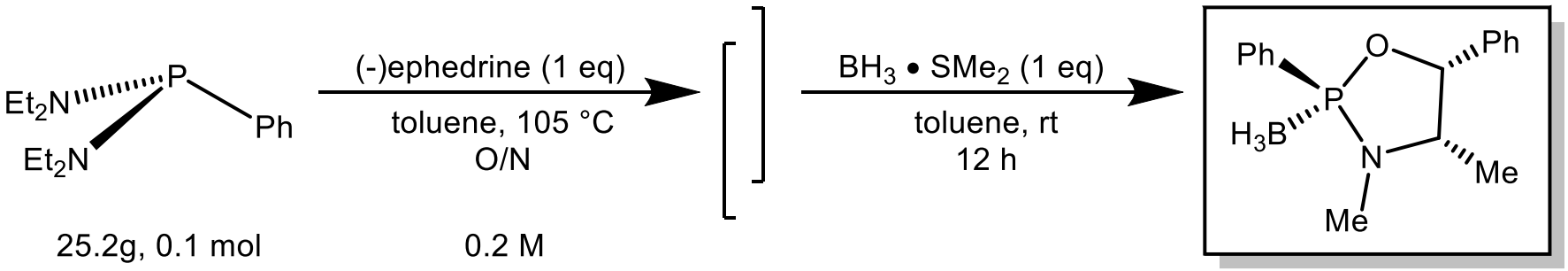
Corey at Harvard, 1993



Imamoto, T, *et. al. Chem. Lett.* **1985**, *14*, 1491.
Corey, E. J., *et. al. J. Am. Chem. Soc.* **1993**, *115*, 11000.

Jugé-Stephan Method

Jugé at CNRS, 1989 & 1990



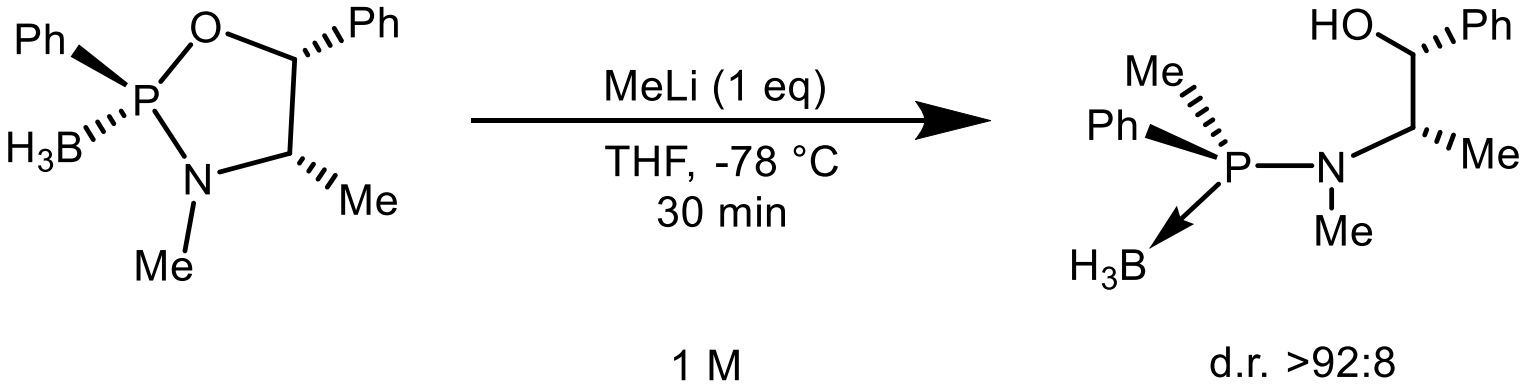
ozazaphopholidine **1**

- The P-O and P-N bonds in **1** have differentiated bond strengths ergo, they have differentiated reactivity toward nucleophiles.
- Intermediates in this process can be purified and/or recrystallized.

Jugé, S., *et. al. Tetrahedron Lett.* **1989**, *30*, 2783.
Jugé, S., *et. al. Tetrahedron Lett.* **1990**, *31*, 6357.

Alkyl or Aryl Lithium Cleavage of The P-O Bond

Jugé at CNRS, 1989 & 1990



1 M

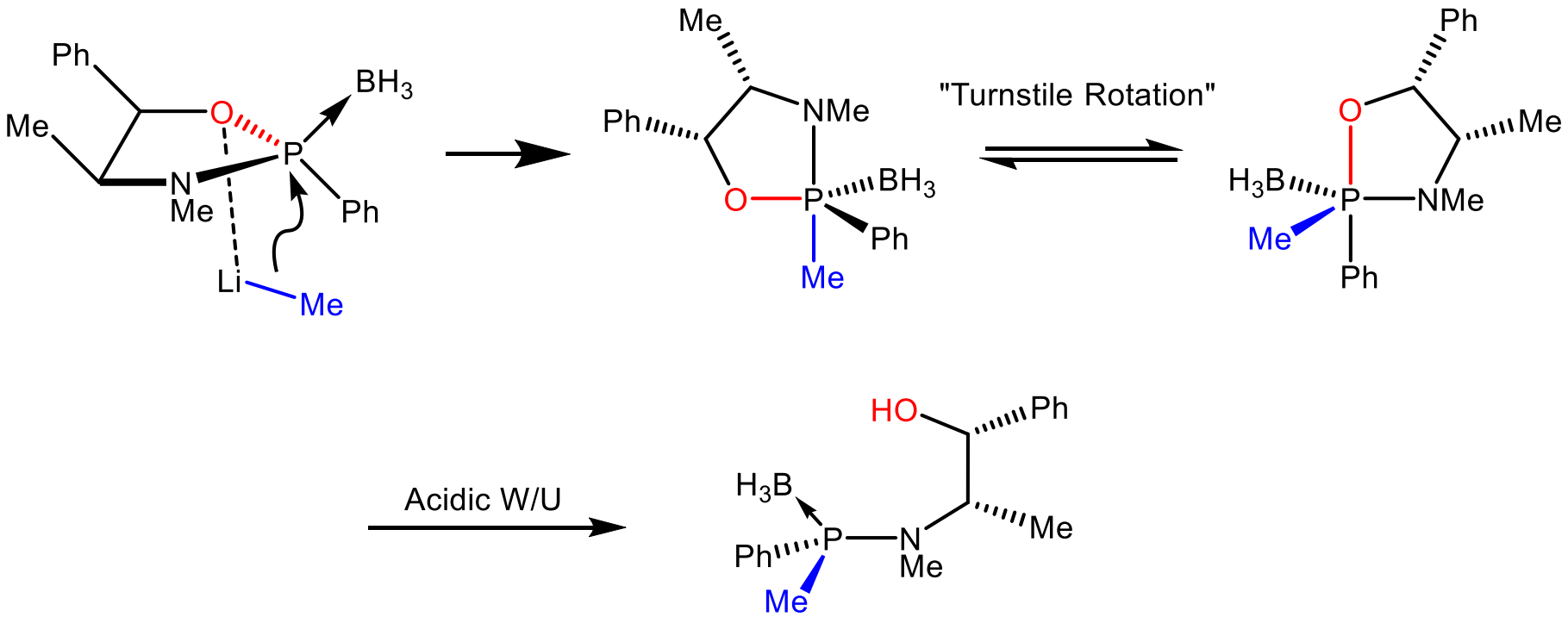
d.r. >92:8

- In general, both alkyl and aryl substituents will produce good yields and diastereoselectivities. Bulky Li nucleophiles remain a challenge for this method.
- Many aminophosphines are obtained optically pure after purification.

Jugé, S., *et. al. Tetrahedron Lett.* **1990**, *31*, 6357.

Retention In The P-O Cleavage Step

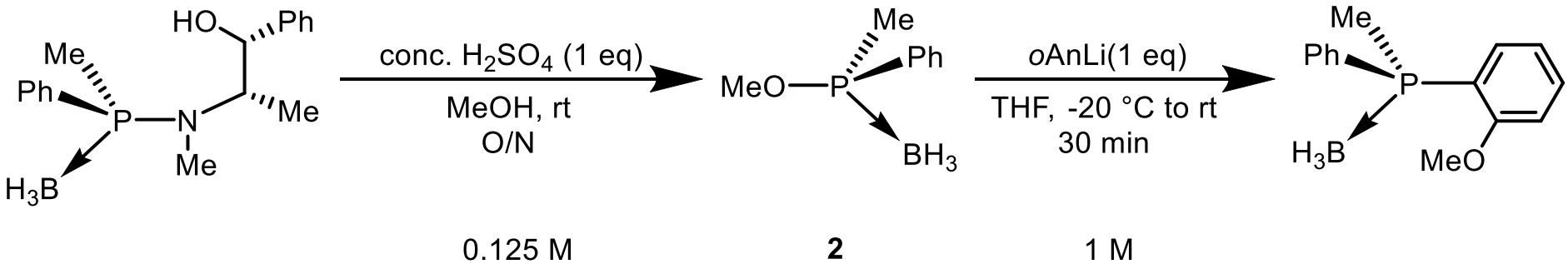
Jugé at CNRS, 1993



Jugé, S., *et. al. J. Chem. Soc., Chem Commun.* **1993**, *6*, 531.

P-N Bond Cleavage by Acidolysis

Jugé at CNRS, 1989 & 1990

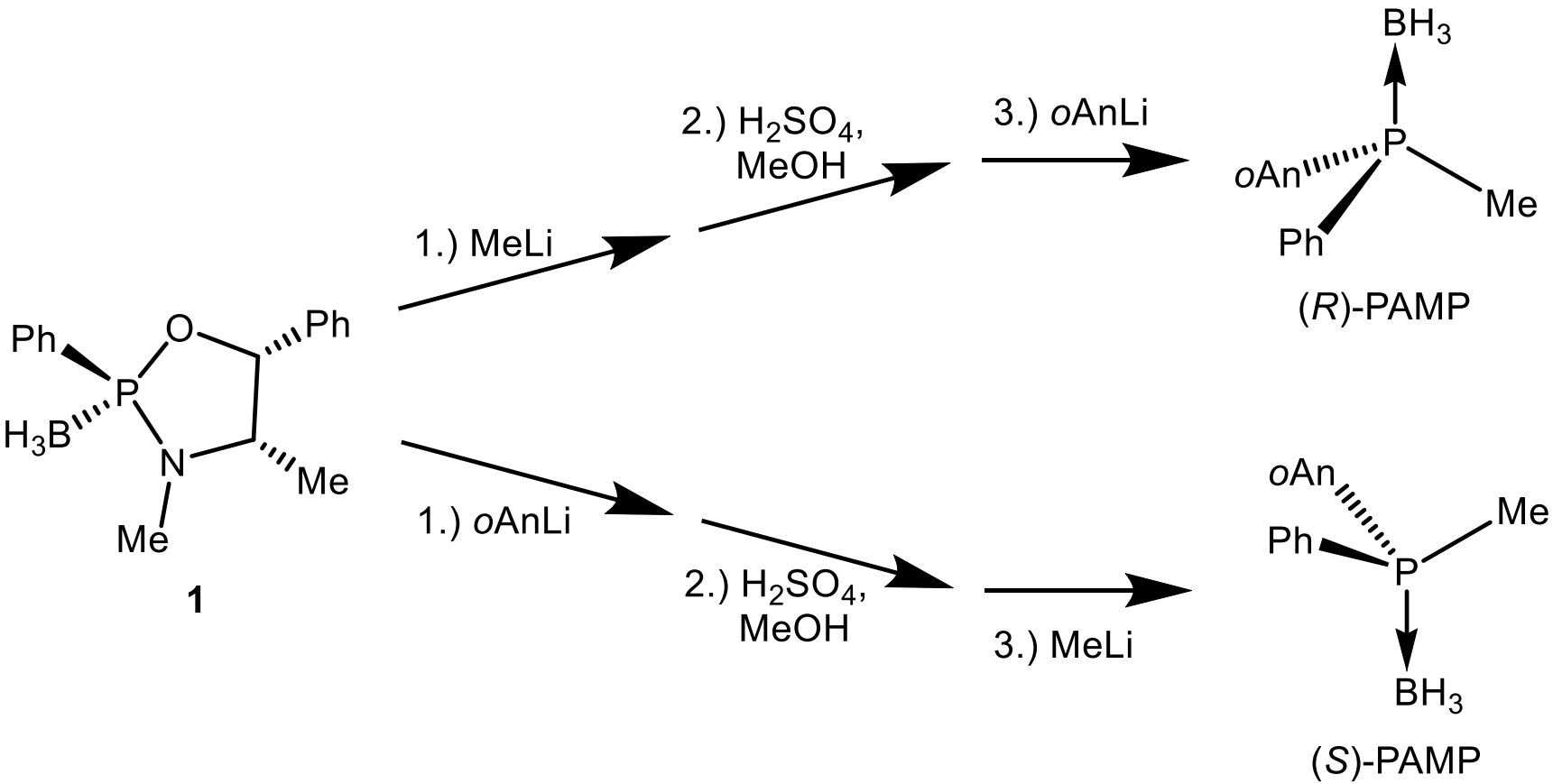


- S_N2@P substitution with an inversion of configuration forming a phosphinite.
- Does not proceed if bulky groups were introduced in the first P-O cleavage step.
- Typically, phosphinite **2** is treated as an intermediate. Followed by a *second* P-O cleavage step with inversion.
- Ephedrine is released with the formation of **2.**

Jugé, S., *et. al. Tetrahedron Lett.* **1989**, *30*, 2783.
Jugé, S., *et. al. Tetrahedron Lett.* **1990**, *31*, 6357.

Stereodivergent Phosphine Synthesis

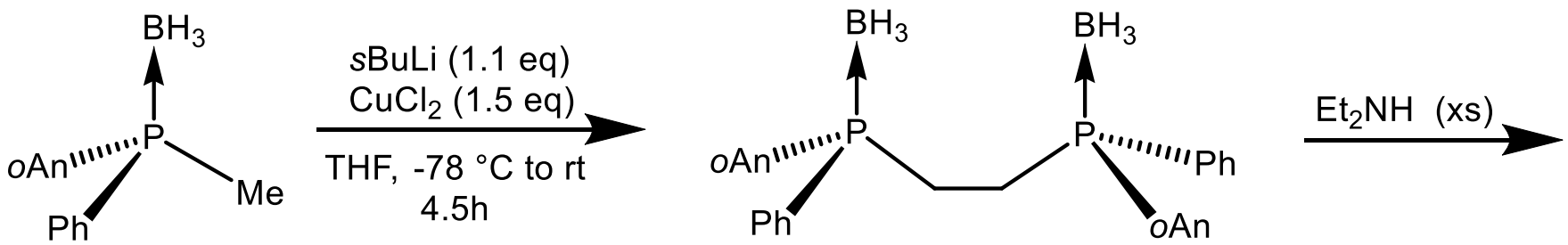
Jugé at CNRS, 1990



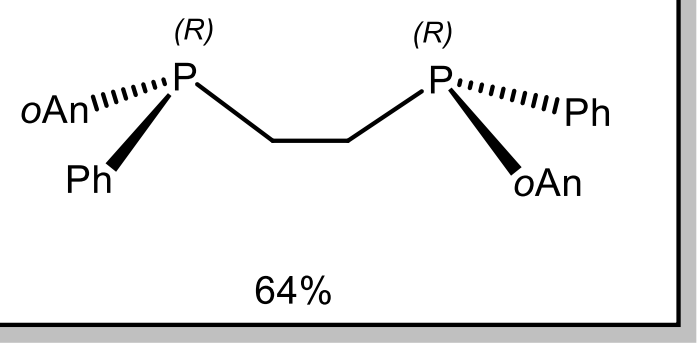
Jugé, S., *et. al. Tetrahedron Lett.* **1990**, *31*, 6357.

Oxidative Coupling

Mislow at Princeton, 1973



0.3 M 85% 0.1 M



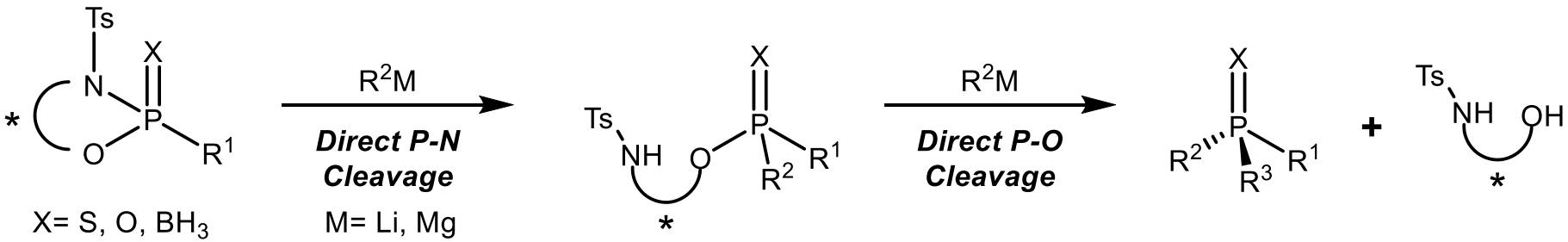
64%

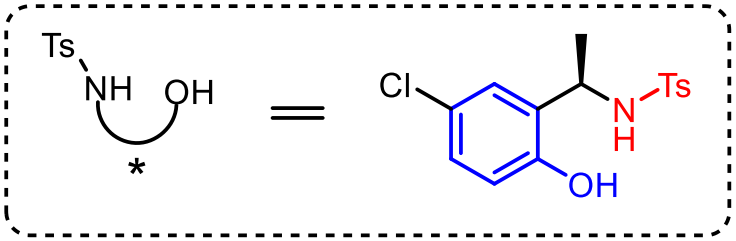
Conditions Reproduced From: Imamoto, T.; *J. Am. Chem. Soc.* **1990**, *112*, 5244.

Mislow, K.; *J. Am. Chem. Soc.* **1973**, *95*, 5839.

What About The Addition of Bulky Groups?

Han at Boehringer ingelheim, 2013

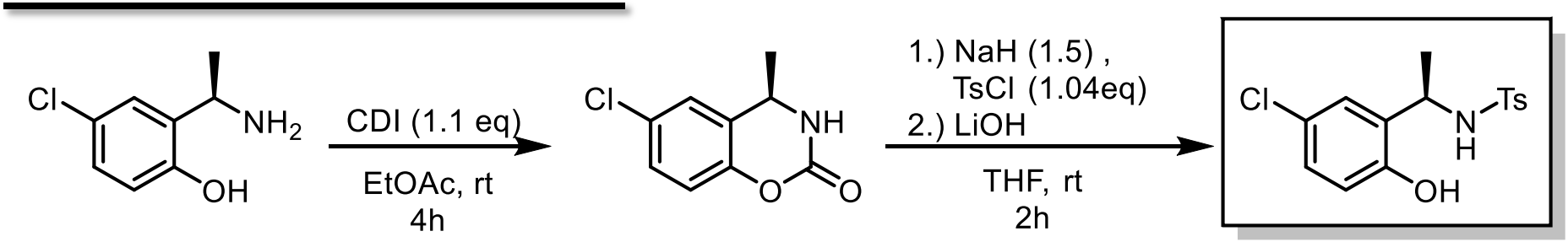




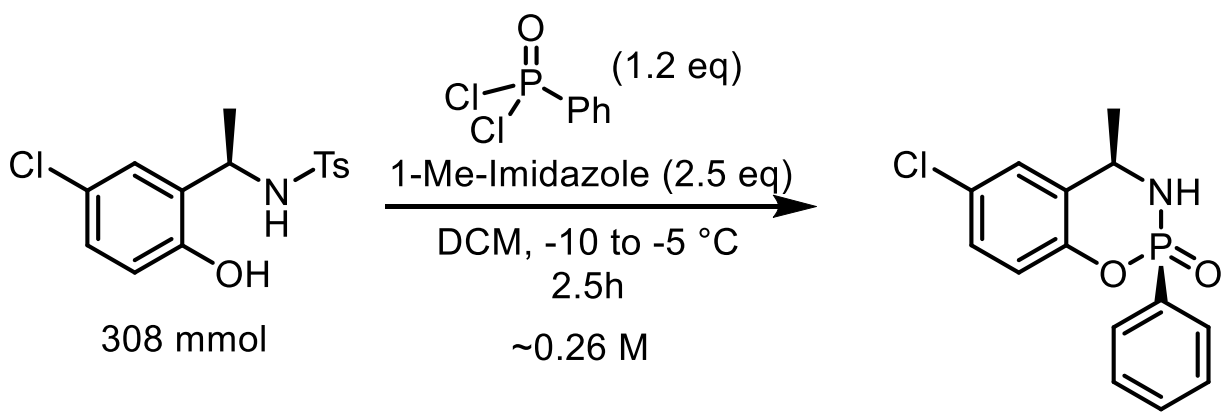
Han, Z.S., *et. al. J. Am. Chem. Soc.* **2013**, *135*, 2474.

What About The Addition of Bulky Groups?

Han at Boehringer ingelheim, 2013



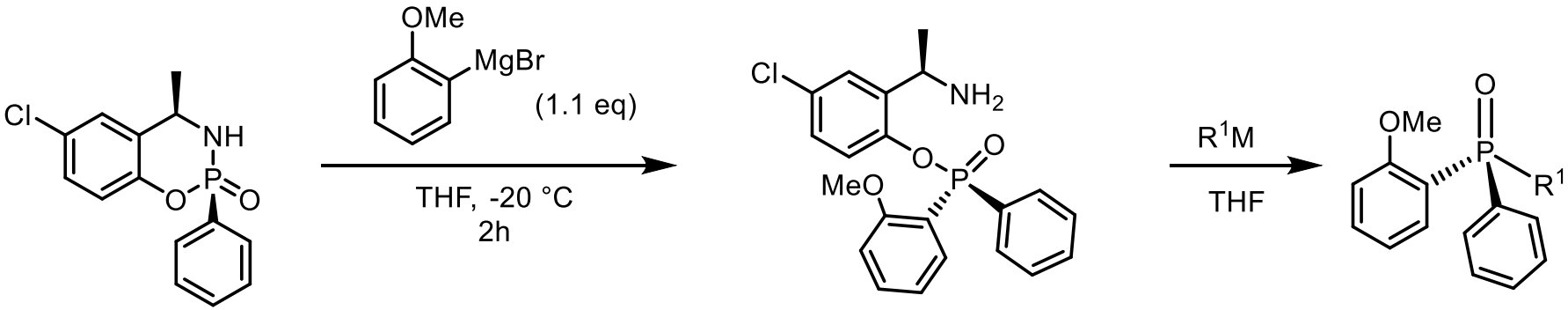
1.16 mmol ~0.7 M 97% yield ~0.55 M 94% yield



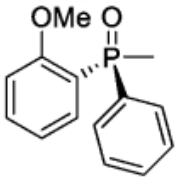
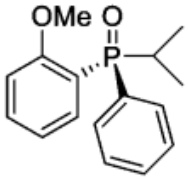
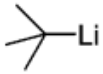
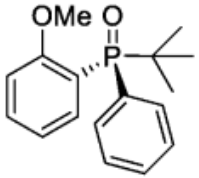
308 mmol ~0.26 M

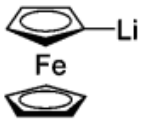
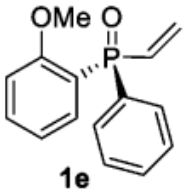
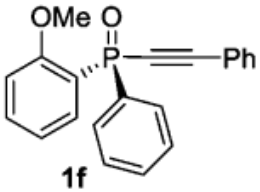
85% yield > 99.5:0.5 dr

Han, Z.S., *et. al. J. Am. Chem. Soc.* **2013**, *135*, 2474.



8.9 mmol ~0.22 M 91% yield > 99.5:0.5 dr

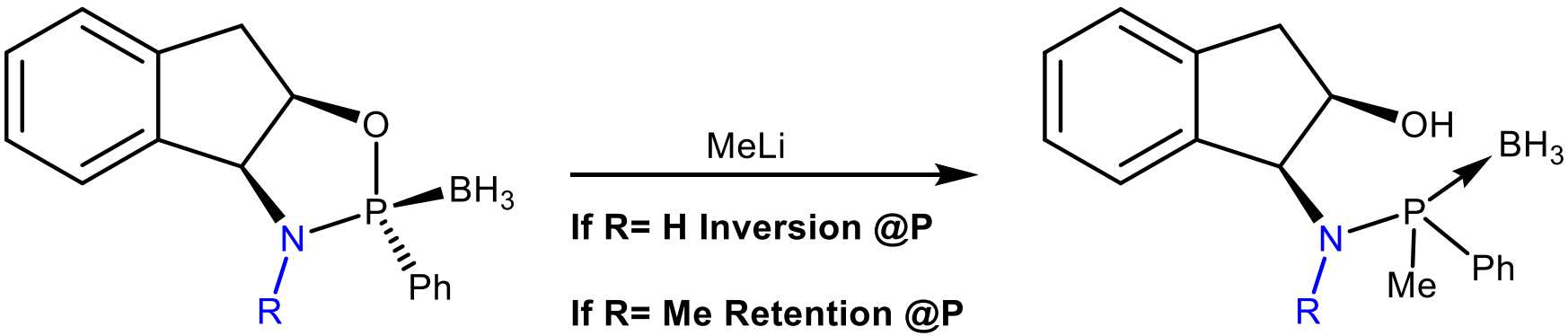
Entry	R^1M	Product	Yield (%)	er
1	MeMgBr		91	>99.5:0.5
2			63	>99.5:0.5
3			84	98.2:1.8

Entry	R^1M	Product	Yield (%)	er
4		 **1d**	82	99.6:0.4
5		 **1e**	70	>99.5:0.5
6		 **1f**	62	95:5

Han, Z.S., *et. al. J. Am. Chem. Soc.* **2013**, *135*, 2474.

Group Problem

Bickelhaupt at Amsterdam, 2013

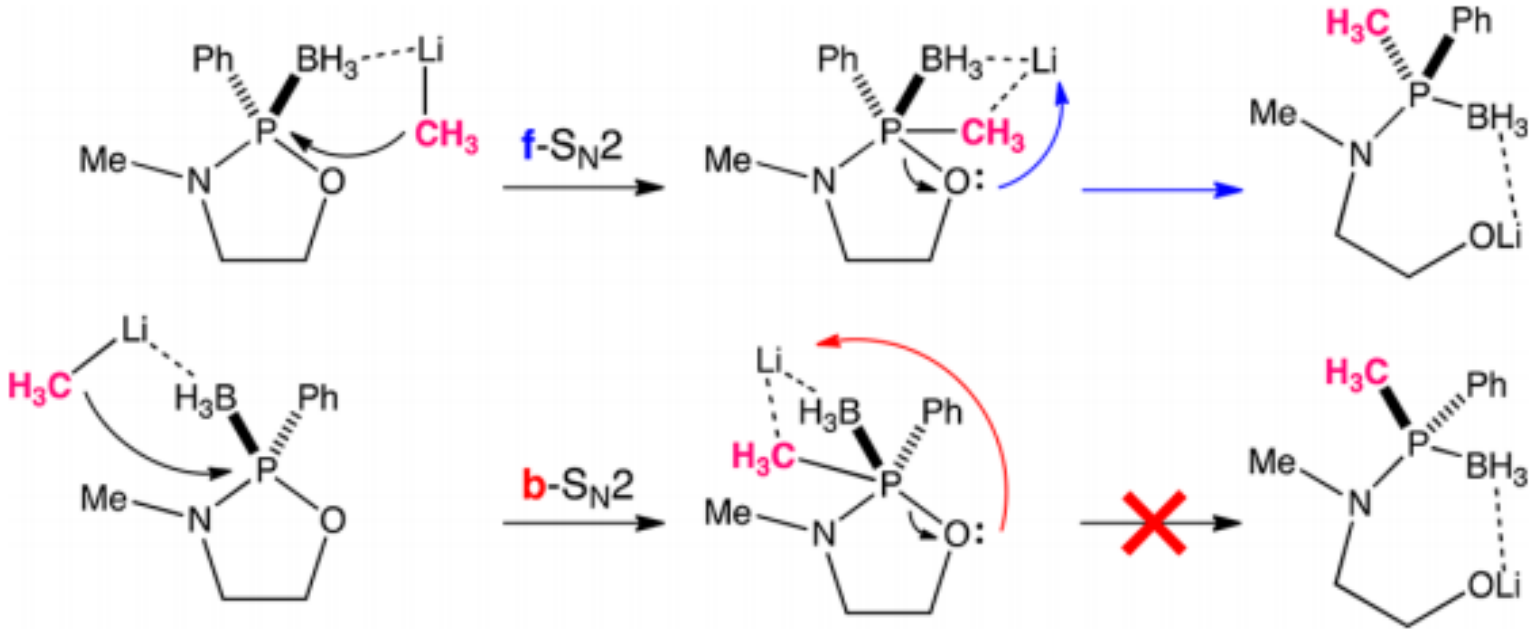


Propose a mechanism that accounts for the experimental observations.

Bickelhaupt. *et. al. J. Am. Chem. Soc.* **2013**, 135, 4483.

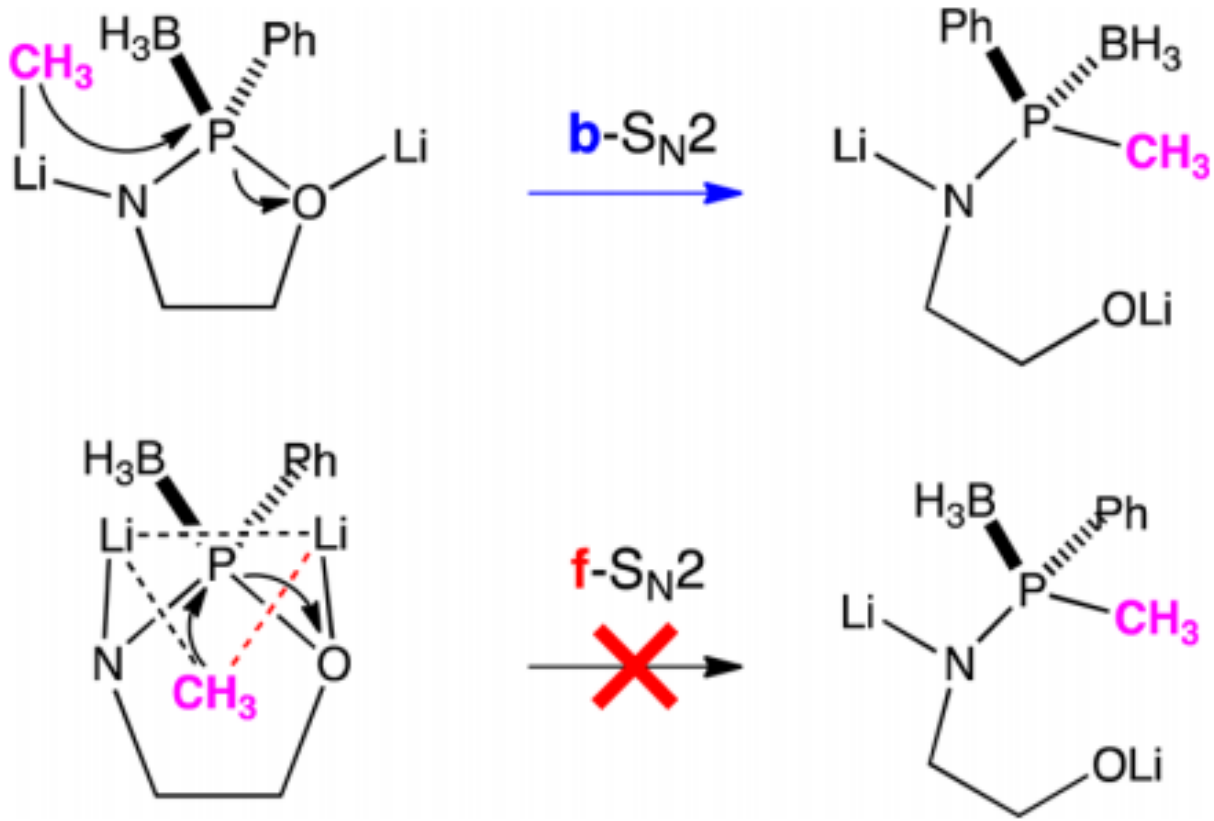
Group Problem

Scheme 6. Computed Backside and Frontside S_N2@P Pathways of MeLi + MePh



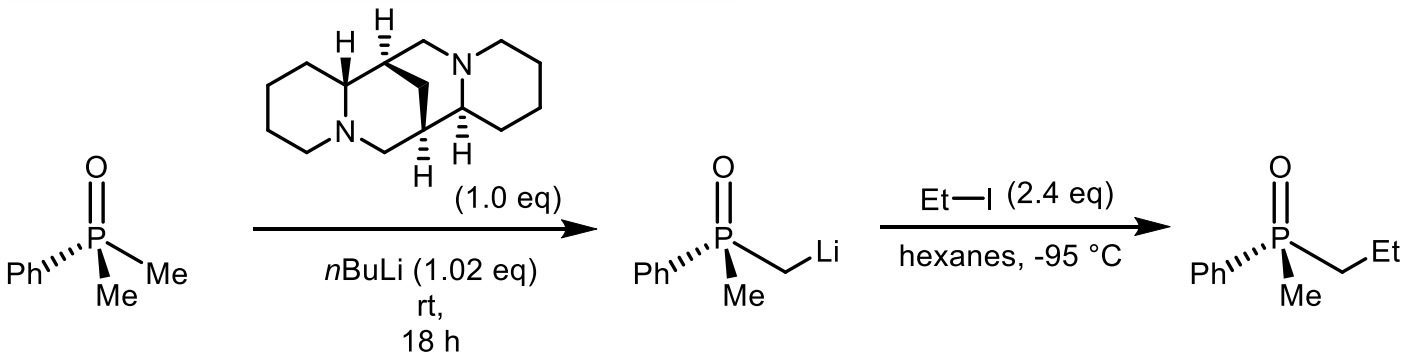
Group Problem

Scheme 8. Computed Backside and Frontside S_N2@P Pathways of MeLi + HPh, Starting from Reactant Complex after Lithiation



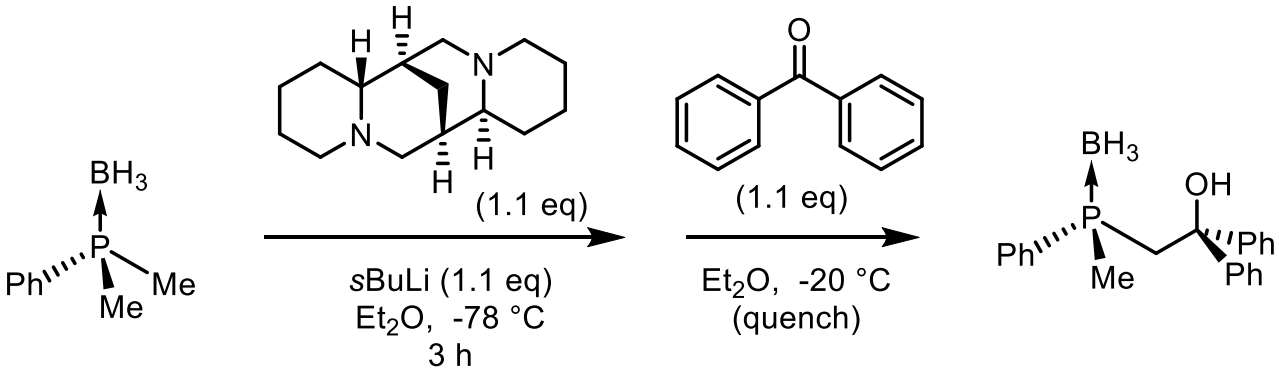
What about Bulky Groups Further Away?

White at University of Western Australia, 1989



5.2 mmol | 57% yield | 0.62 M | 57:43 er

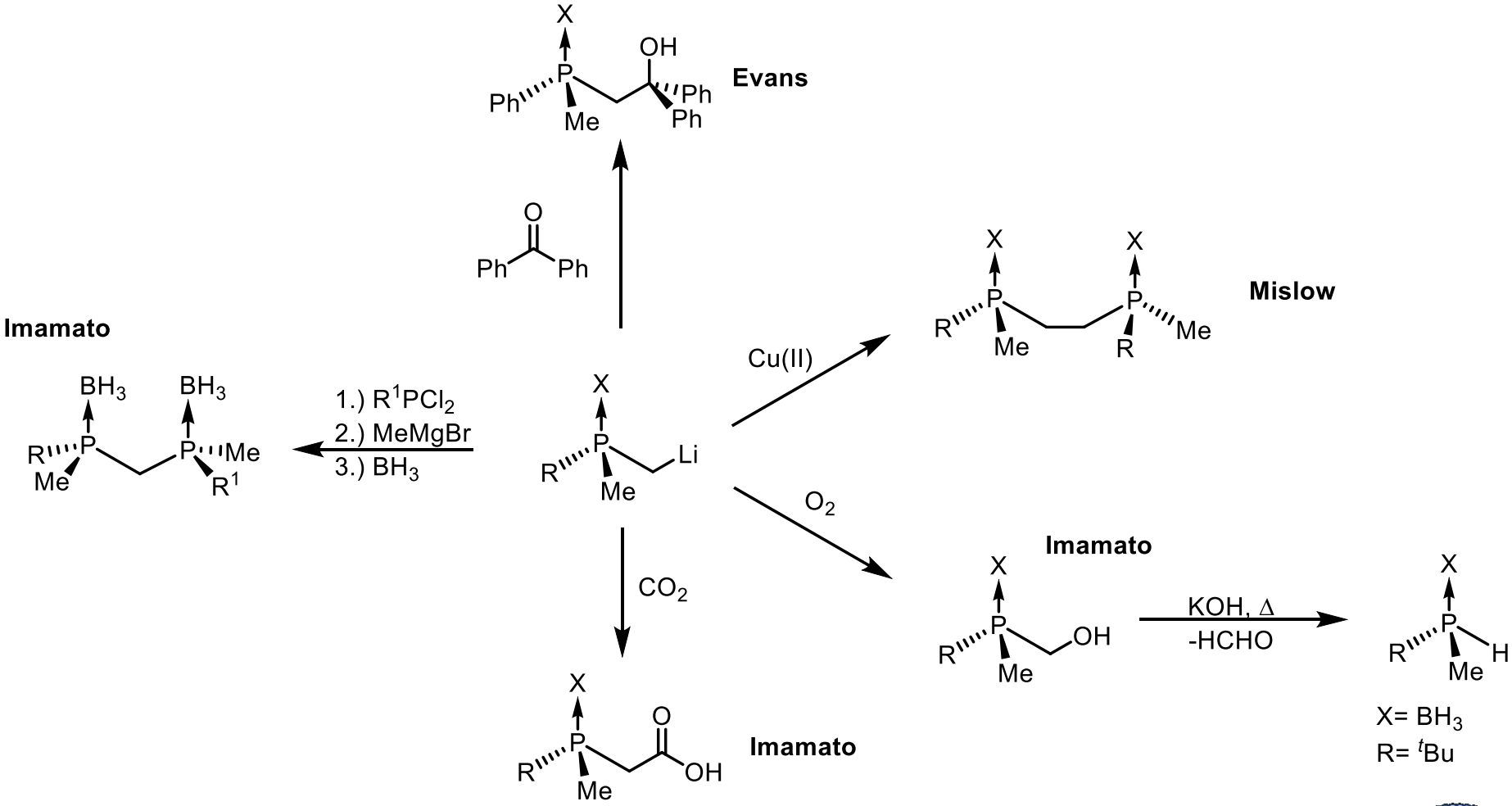
Evans at Harvard, 1995



1 mmol | 0.13 M | 88% yield 90:10 er

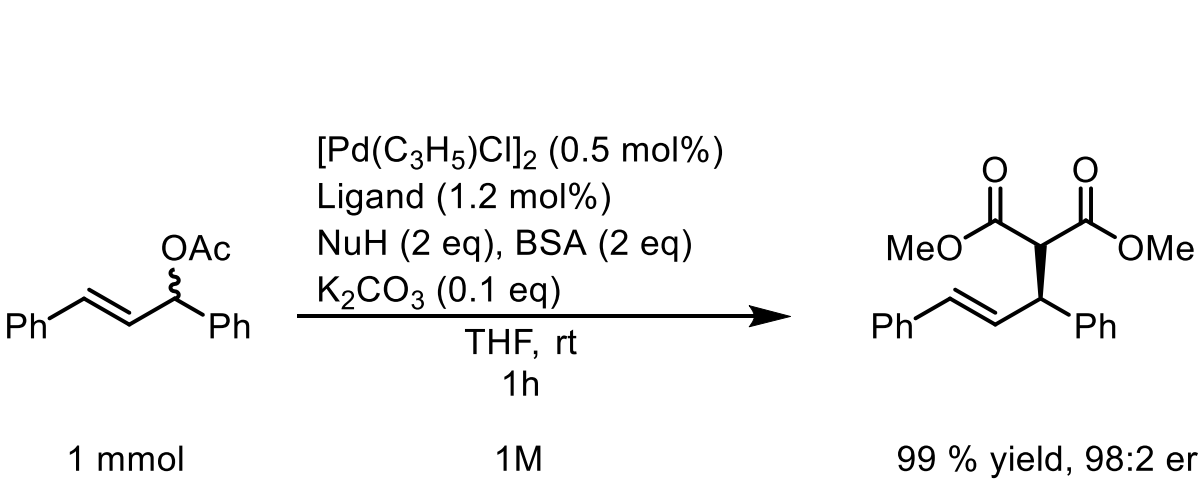
White, A.H., *et. al. J. Chem. Soc., Dalton Trans*. **1989**, *1*, 105.
Evans, D.A., *et. al. J. Am. Chem. Soc.* **1995**, *117*, 9075

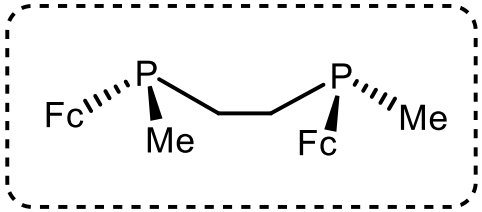
Versatility of Enantioselective Deprotonation



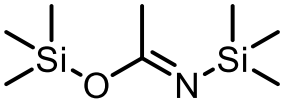
Allylic Substitutions

Imamoto at Chiba University, 2003

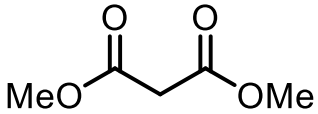




BSA =

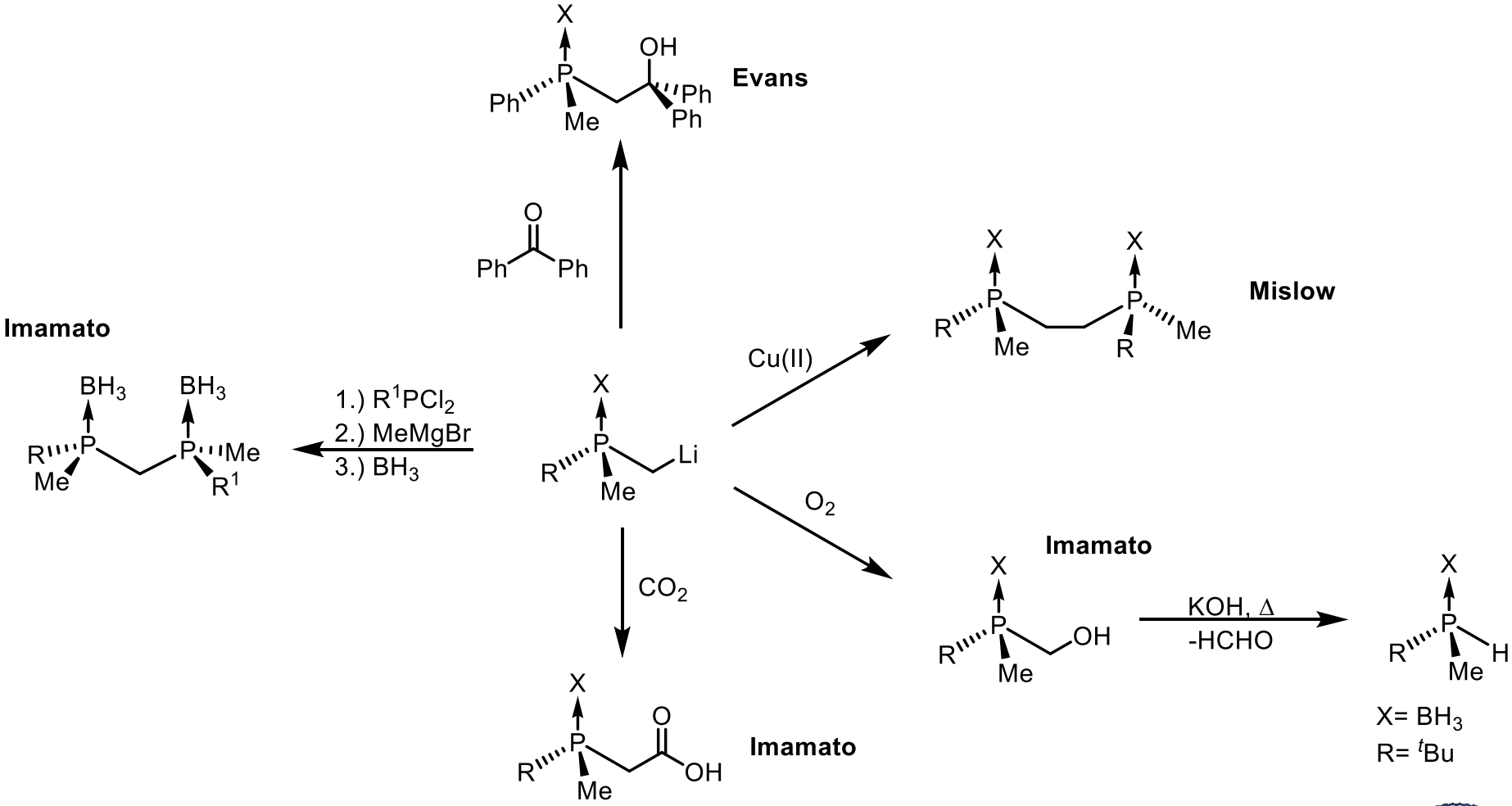


Nu-H =



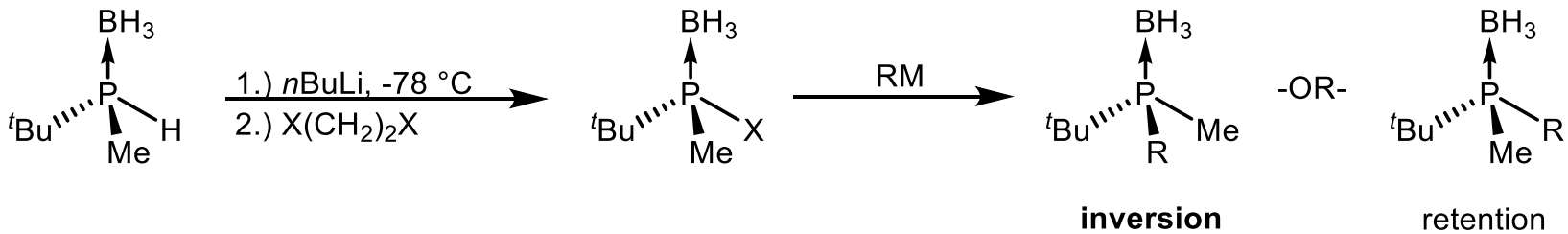
Imamoto, T. *et. al. Tetrahedron Asymmetry.* **2003**, *14*, 2171

Versatility of Enantioselective Deprotonation



Halophosphanylboranes

Imamoto at Chiba University, 2007

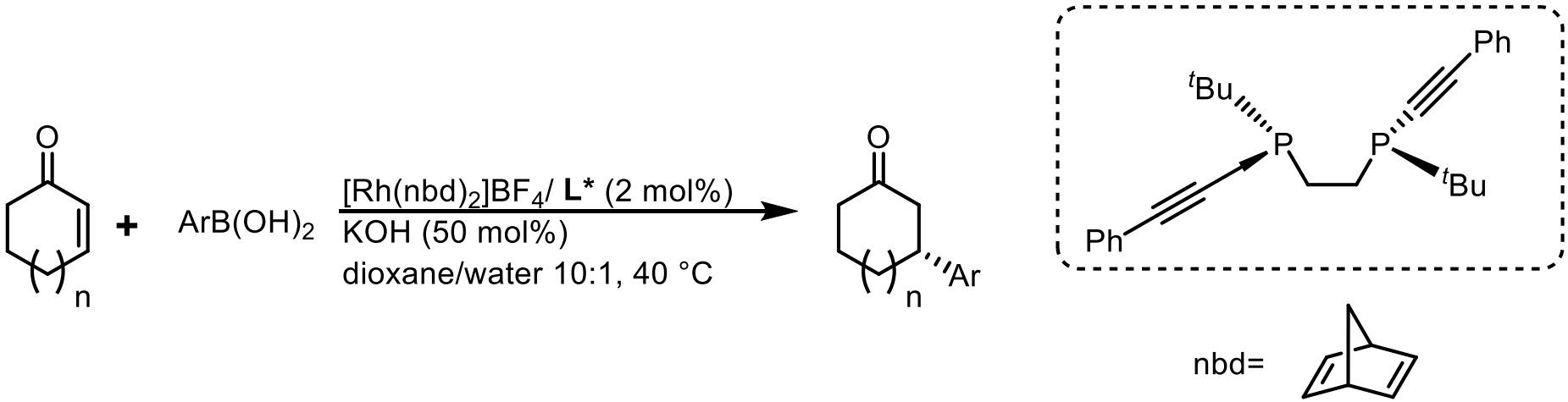


Entry	X	RM	Yield (%)	ee (%)
1	Br	PhCCLi	83	97 (inv.)
2	I	PhCCLi	12	32 (inv.)
3	Br	*t*-BuCCLi	82	98 (inv.)
4	Br	TMSCCLi	81	99 (inv.)
5	Br	$(i\text{-Pr})_3$SiCCLi	86	98 (inv.)
6	Br	PhMgBr	28	83 (inv.)
7	I	PhMgBr	0[a]	–
8	Br	*o*-AnMgBr	68	93 (inv.)
9	Br	BuLi	63	91 (ret.)
10	I	BuLi	79	89 (ret.)
11	Br	BnMgCl	94	96 (ret.)
12	I	BnMgCl	92	93 (ret.)

Imamoto, T. *et. al. J. Org. Chem.* **2000**, *65*, 4185
Imamoto, T, *et. al. Angew. Chem Int. Ed.* **2007**, *46*, 8636.

Application of Alkynyl Ligands

Imamoto at Chiba University, 2007

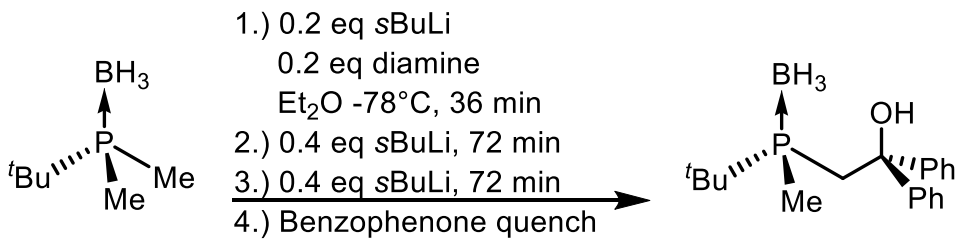


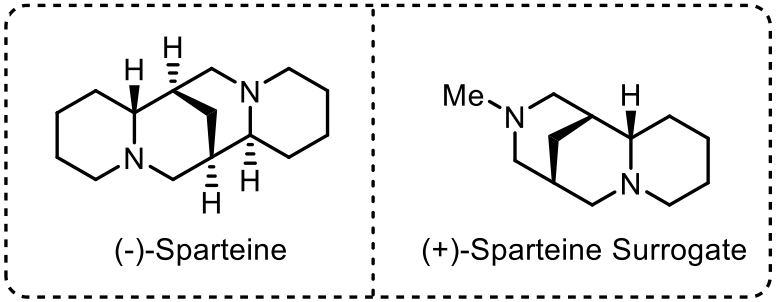
Entry	n	Ar	t (hours)	Yield (%)	ee
1	1	Ph	2	93	99.4 (R)
2	0	Ph	2	90	91.0
3	1	*p*-$CF_3C_6H_4$	2	96	96.0
4	1	*p*-$MeOC_6H_4$	2	99	98.4

Imamoto, T, *et. al. Angew. Chem Int. Ed.* **2007**, *46*, 8636.

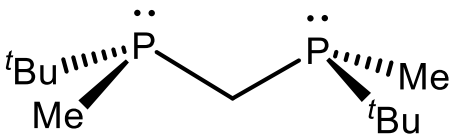
Catalytic Deprotonation of a Phosphine Borane

O'Brien at York University, 2011

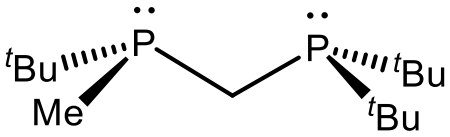




94% yield, 86:14 er (-)-Sparteine
84% yield, 12:88 er (+)-Sp Surrogate



Mini-PHOS
40% yield, 99:1 er



Trichickenfootphos
71% yield, 93:7 er

O'Brien, P. *et. al. J. Org. Chem.* **2011**, *76*, 4794.

References

Reviews of Note:

1.) *P-Stereogenic Ligands in Enantioselective Catalysis*, Arnald Grabulosa. Royal Society of Chemistry, Cambridge, 2011.

2.) Kolodiazhnyi, O. *Tetrahedron: Asymmetry.* **2012**, *23*, 1.

Articles are cited on the relevant slide.