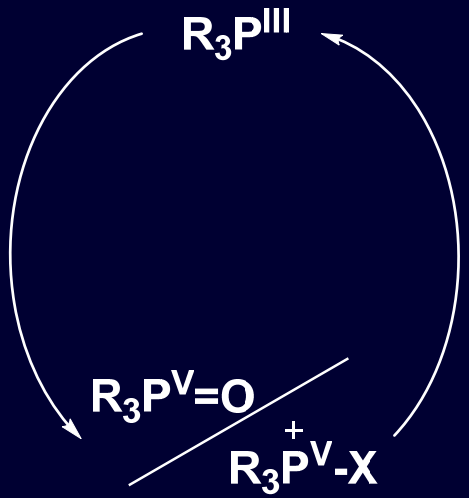
Progress of P^{III}/P^{V} Cycle: the Last Decade



Hang Yu

College of Chemistry and Molecular Engineering

12/4/2020

Outline

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- In situ P^{III}/P^{V}=O cycle
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- Constrained Bicyclic Phosphines
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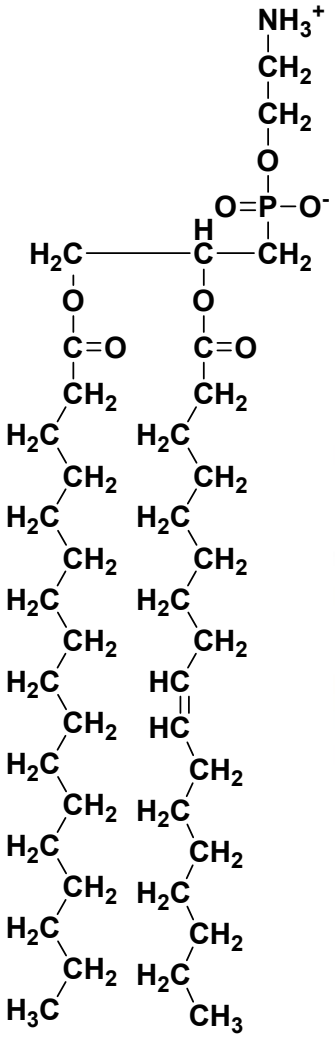
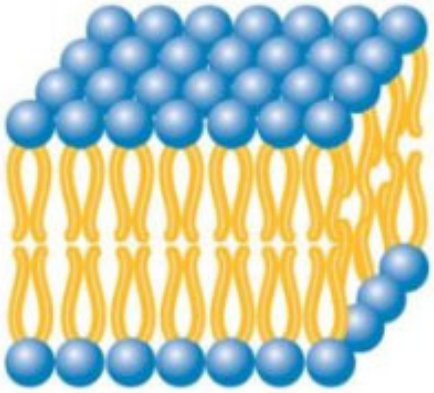
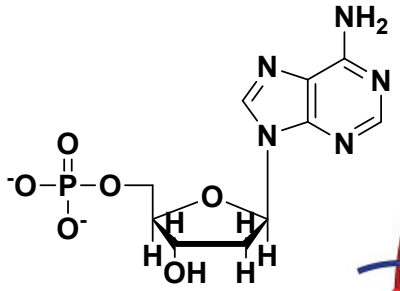
Introduction: Phosphorus in Organisms



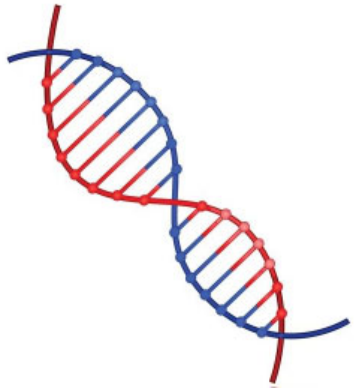
phospholipids

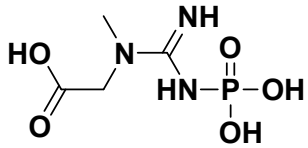


Lipid bilayer



nucleotide

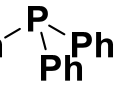


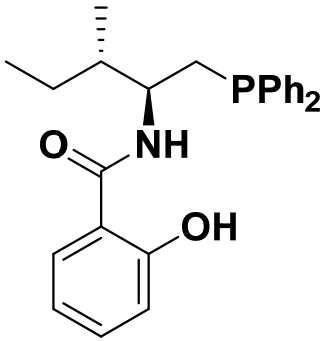


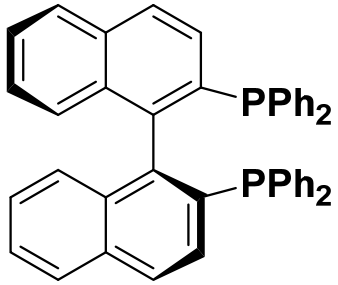
Creatine phosphate

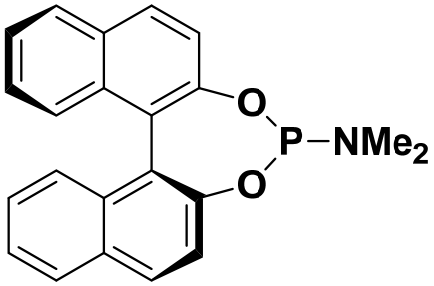
Phosphorus in Organic Chemistry

Ability of coordination:

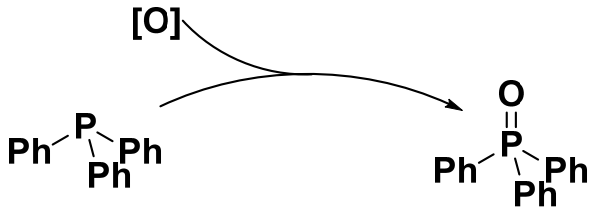
ML_2, M = Pd, ect, L =  , ect.



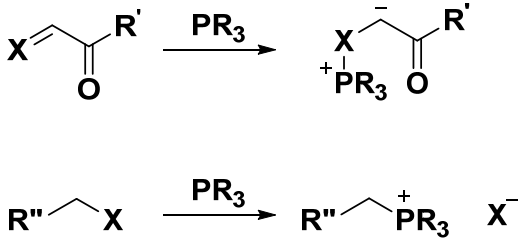




Reducing capability:

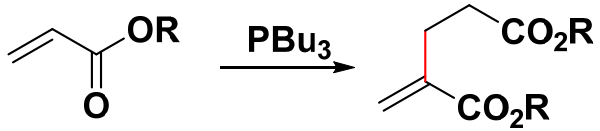


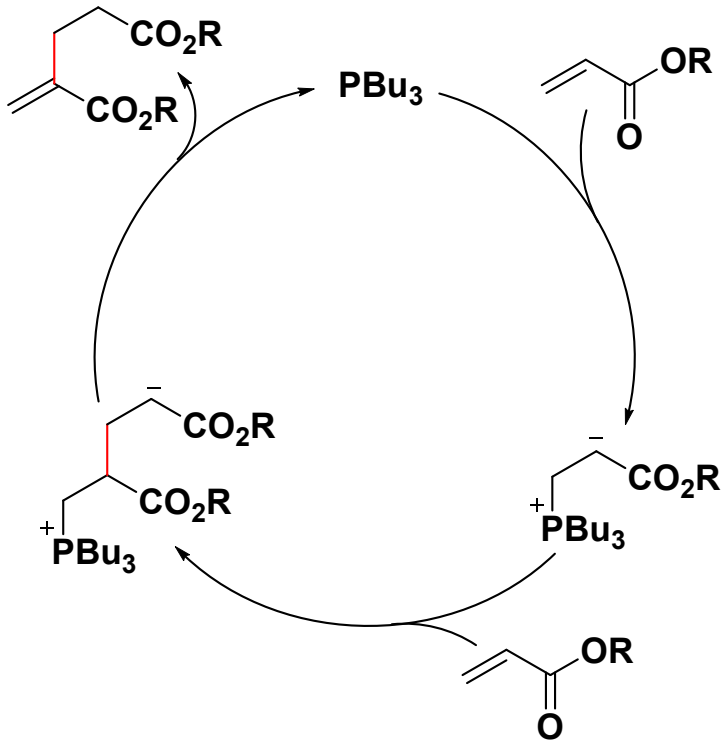
Nucleophilicity:



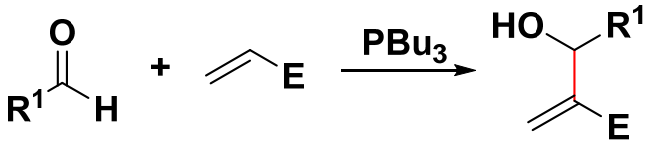
P(III) Catalysis: Nucleophilicity

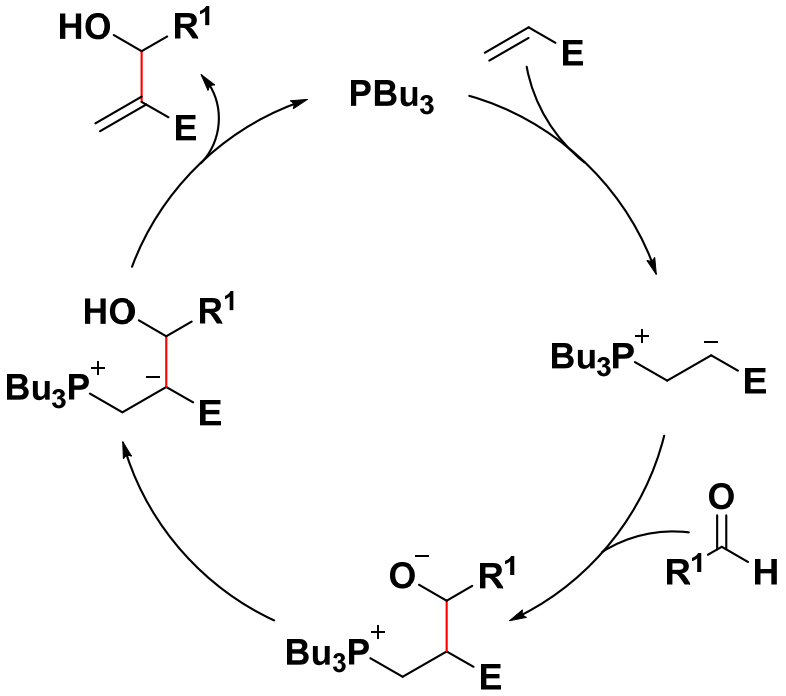
1963 Rauhut-Currier:





Morita-Baylis-Hillman reaction:



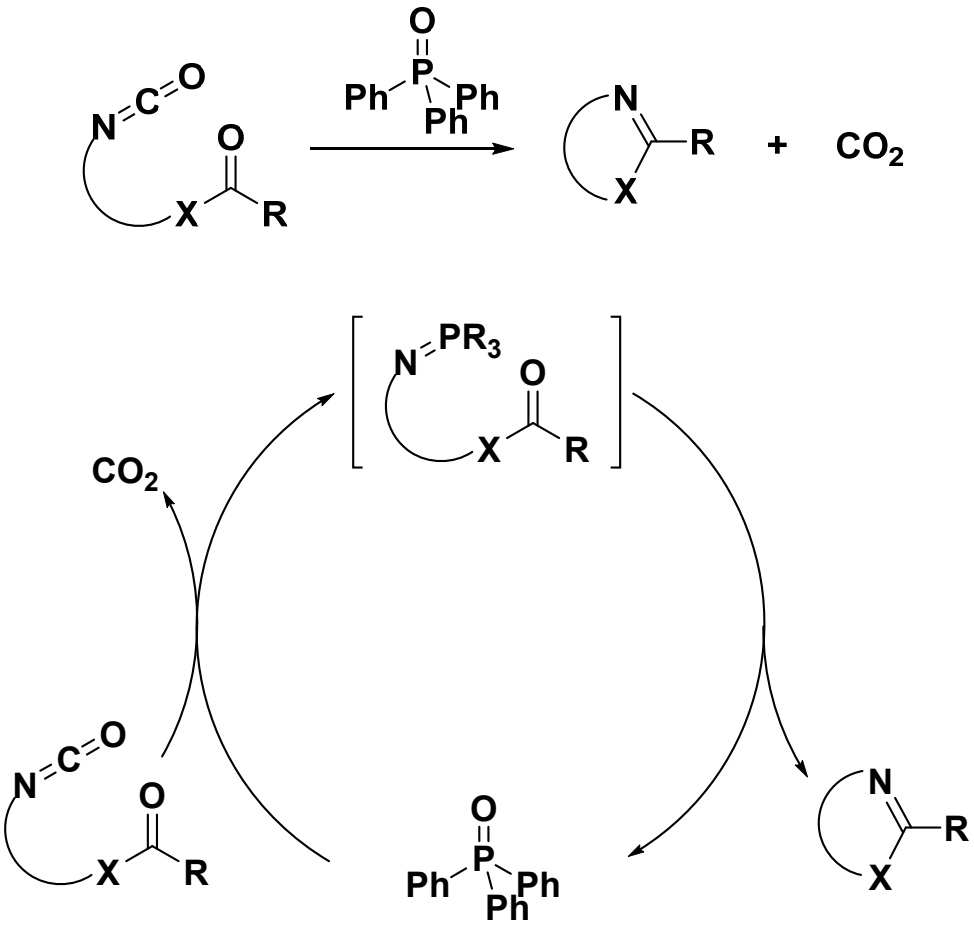


Rauhut, M. M.; Currier, H. *U.S. Patent 3074999*, **1963**.

Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

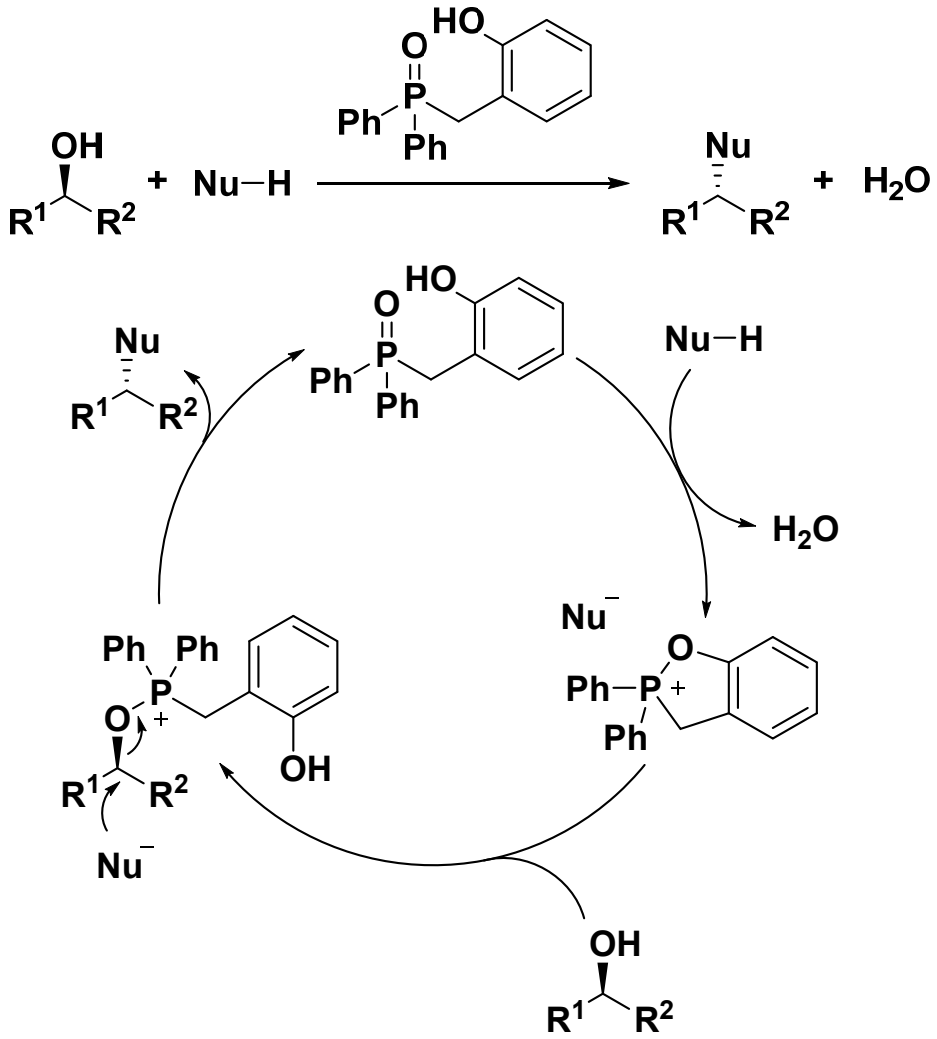
P(V) Catalysis: Eletrophilicity

Aza Wittig



Marsden S. P.; McGonagle A. E.; McKeever-Abbas B. *Org. Lett.* **2008,** *10*, 2589.

Catalytic Mitsunobu



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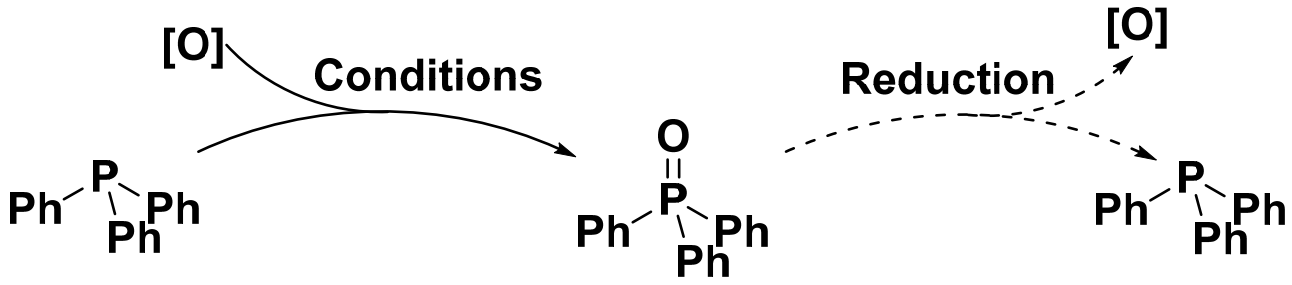
P(III) as the Reductant

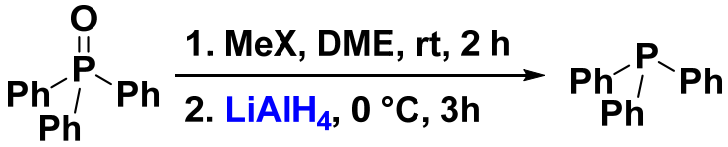
Reducing capability:



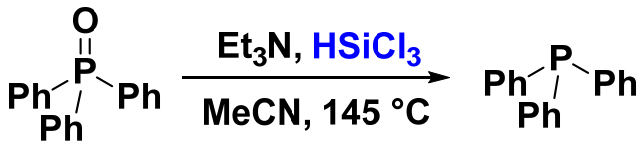
1.Numerous organic transformations (eg. Appel, aza-Wittig, and Staudinger reaction) are based on the use of stoichiometric amounts of phosphorus reagents.

2. The separation of the phosphine oxide waste can be challenging and sometimes significantly hampers product purification.

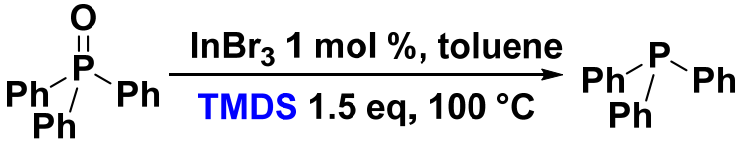
Reduction Method of P(V)=O



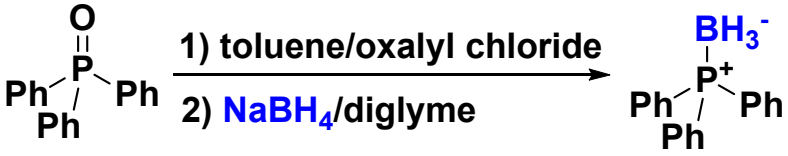
Imamoto T.; Kikuchi S.; Miura T.; Wada Y. *Org. Lett.* **2001**, *3*, 87.



Damian K.; Clarke M.L.; Cobley C.J. *J. Mol. Catal. A: Chem.* **2008**, *284*, 46.



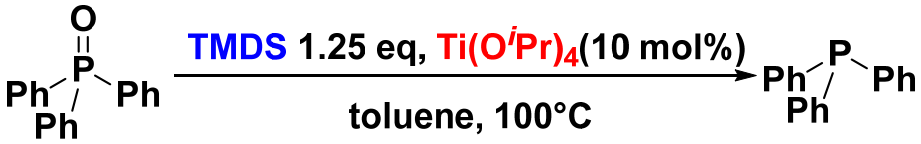
Pehlivan L.; Metay E.; Delbrayelle D.; Mignani G.; Lemaire M. *Tetrahedron* **2012**, *68*, 3151.

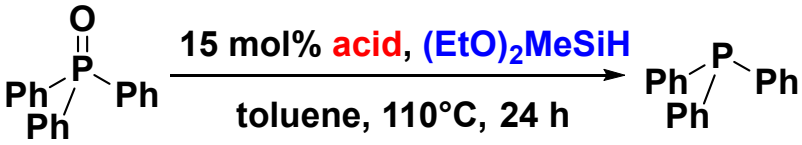


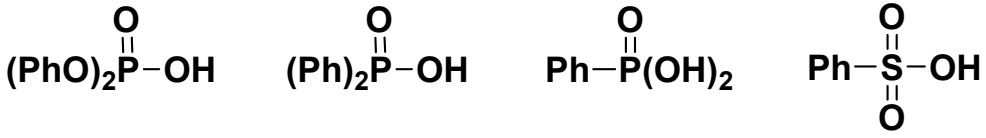
Rajendran K. V.; Gilheany D. G. *Chem. Commun.* **2012**, *48*, 817.

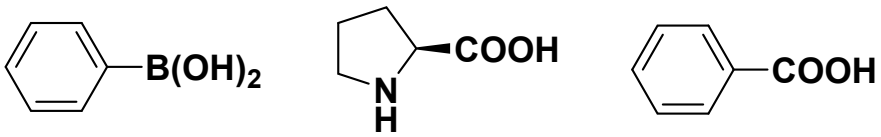
- P(V)=O with high bond energy results in the need to use very strong reduction conditions.
- In situ reduction method is required to accomplish the P^{III}/P^{V}=O catalysis.

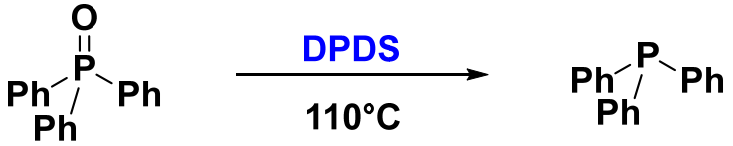
Reduction Method of P(V)=O

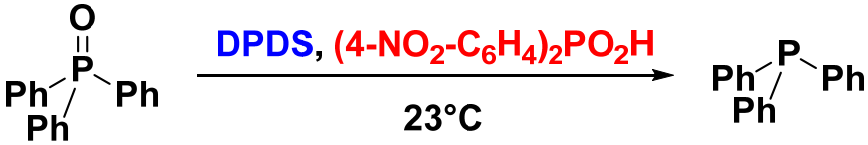












- Acidic additive can help silane to reduce P(V)=O.

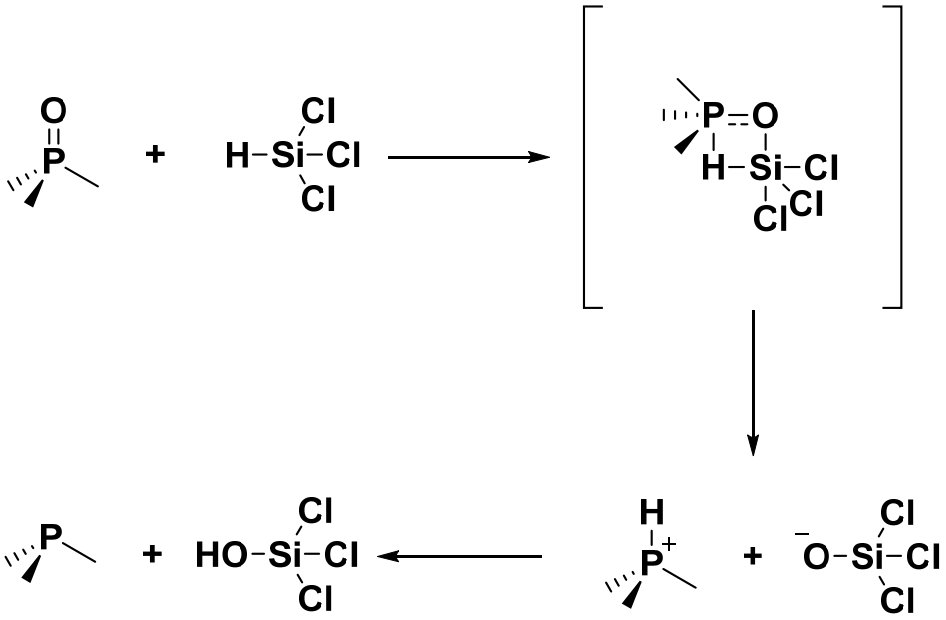
Li Y.; Lu L.; Das S.; Pisiewicz S.; Junge K.; Beller M. *J. Am. Chem. Soc.* **2012**, *134*, 18325.

Schirmer M-L.; Jopp S.; Holz A.; Spannenberg A.; Werner T. *Adv. Synth. Catal*. **2016**, *358*, 26.

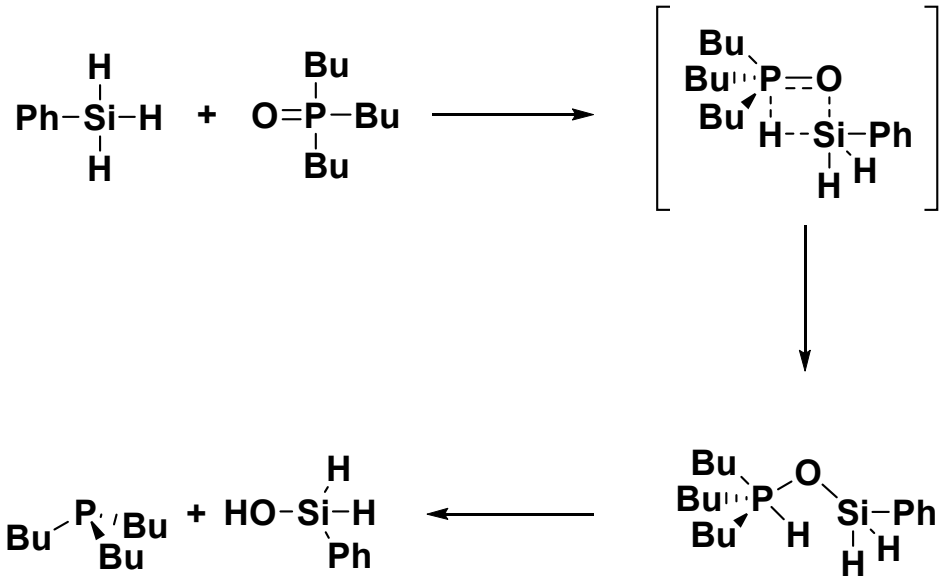
Buonomo J. A.; Eiden C. G.; Aldrich C. C. *Chem. Eur. J.* **2017**, 23, 14434.

Reduction Mechanism of P(V)=O

Charge Separation Mechanism:



Nonionic Mechanism:

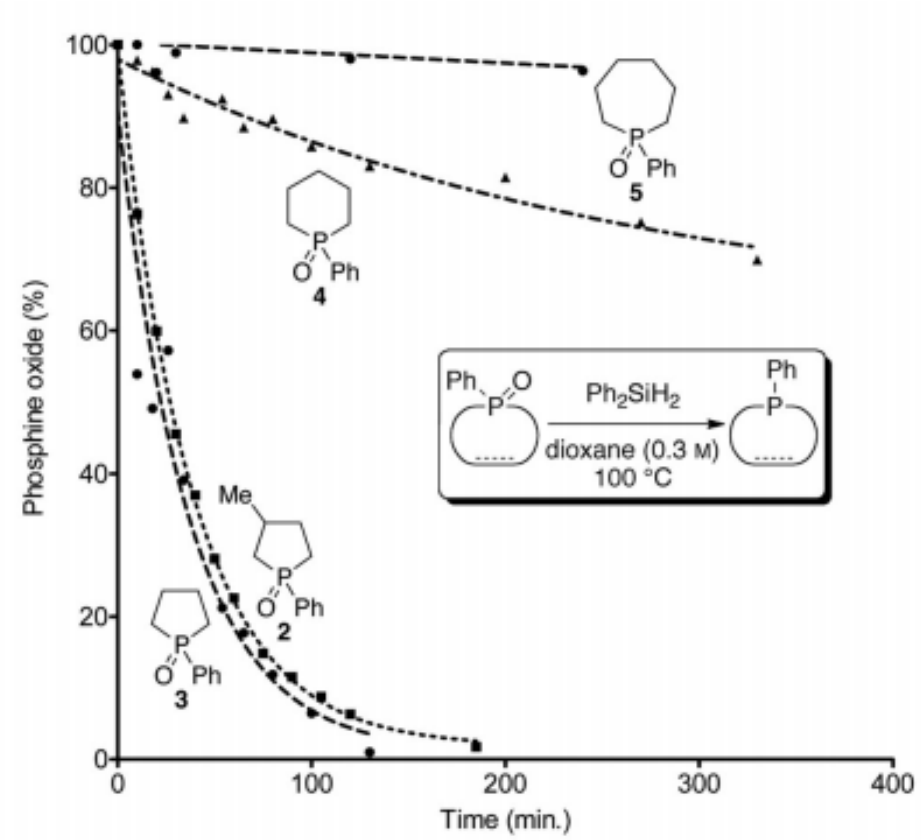


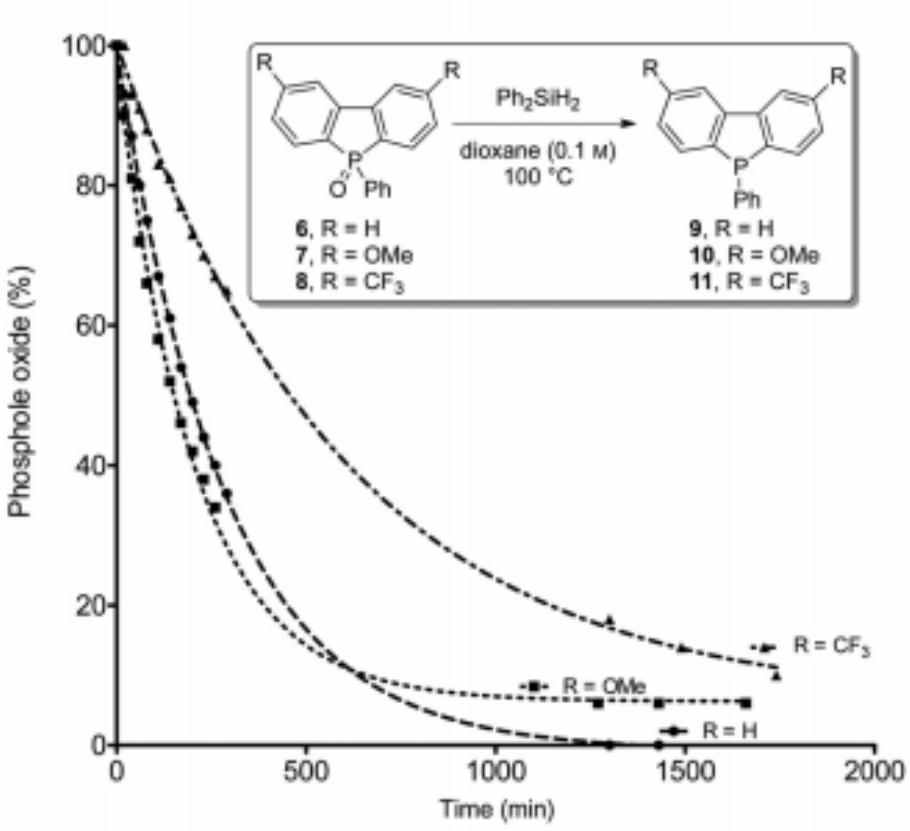
Retention of configuration!

Naumann K.; Zon G.; Mislow K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

Demchuk O. M.; Jasinski R.; Pietrusiewicz K. M. *Heteroat. Chem.* **2016**, *26*, 441.

Reduction Rate Curve





Kalkeren H. A. V.; Delft F. L. V.; Rutjes F. P. J. T. *Pure Appl. Chem.* **2013**, *85*, 817.

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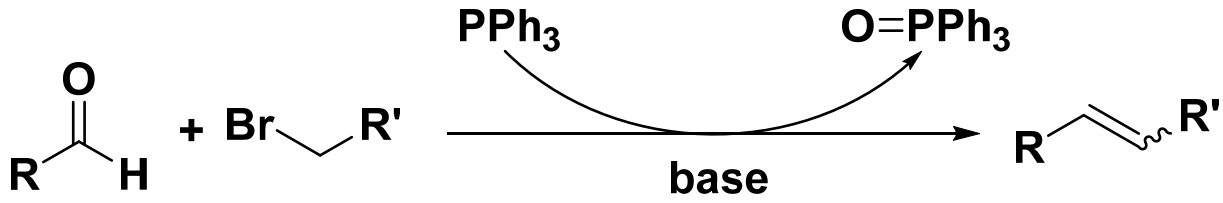
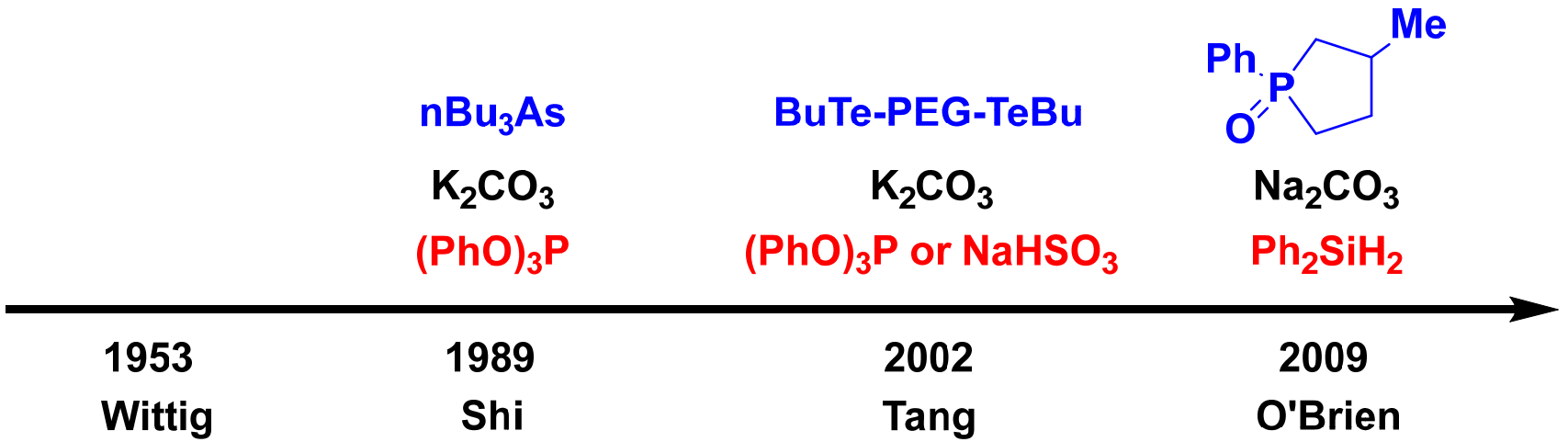
Catalytic Wittig Reaction

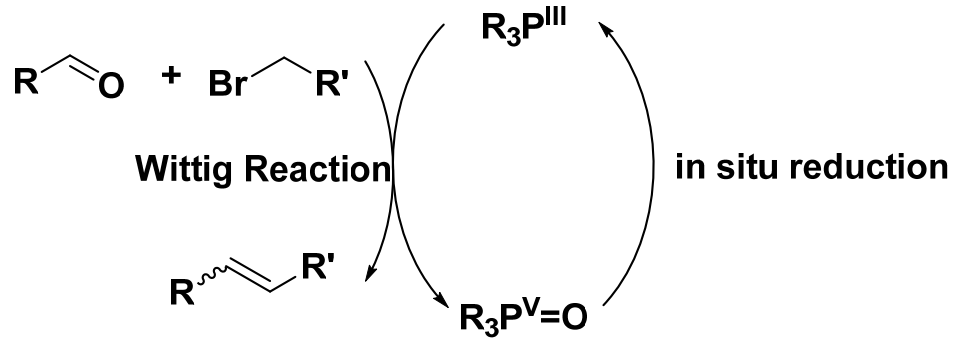


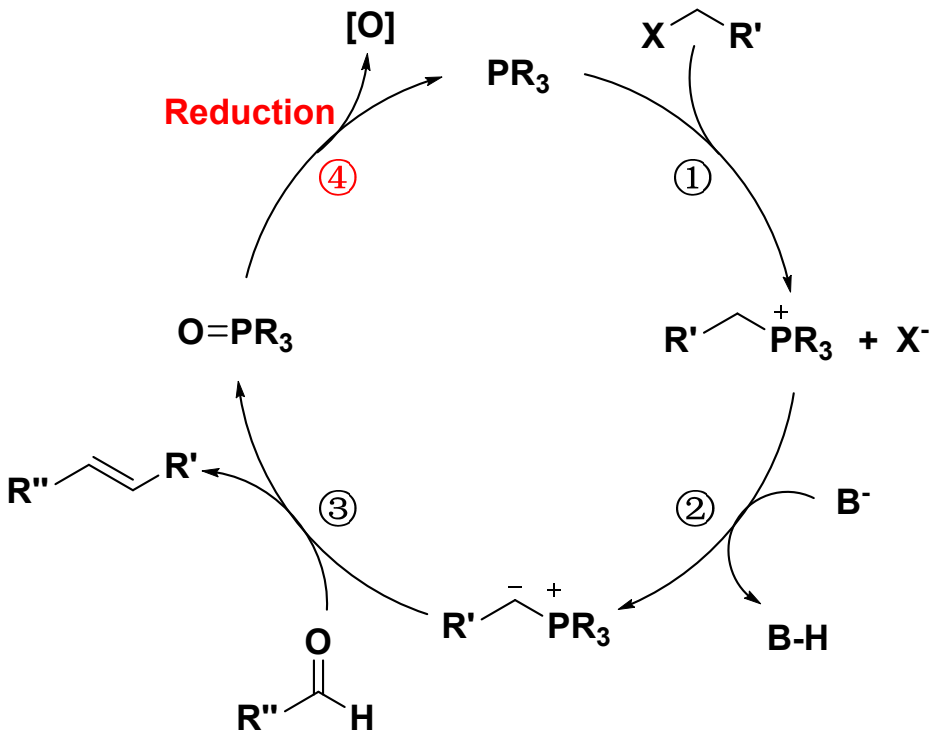
In industry, Wittig reactions occur in the synthesis of several compounds such as vitamin A.



Longwitz L.; Werner T. *Pure Appl. Chem.* **2019**, *91*, 95.

Catalytic Wittig Process





① Phosphate salts are produced as precursors to ylide.

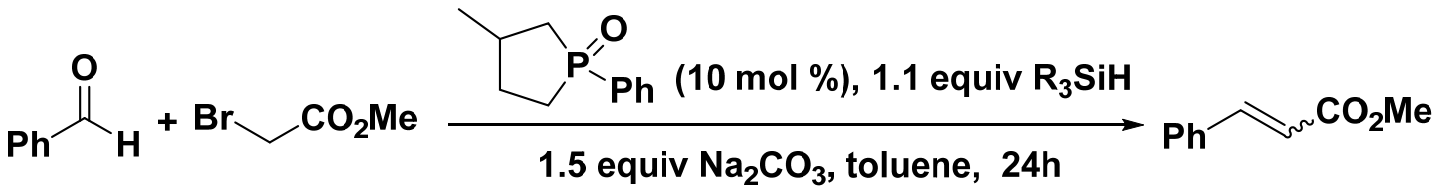
② Deprotonation to produce phosphorus ylide.

③ Obtain the product olefin and phosphorus oxide.

④ In the presence of other functional group (eg. aldehyde or bromine), complete the ***in situ*** reduction of phosphorus oxide.

Longwitz L.; Werner T. *Pure Appl. Chem.* **2019**, *91*, 95.

Suitable Phosphorus and Reductant

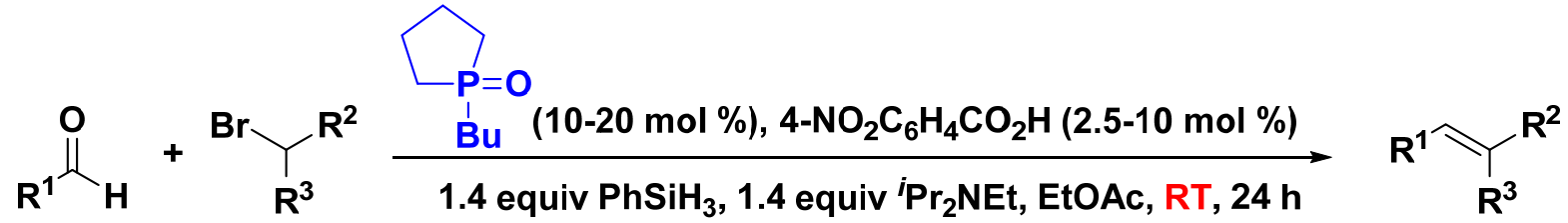


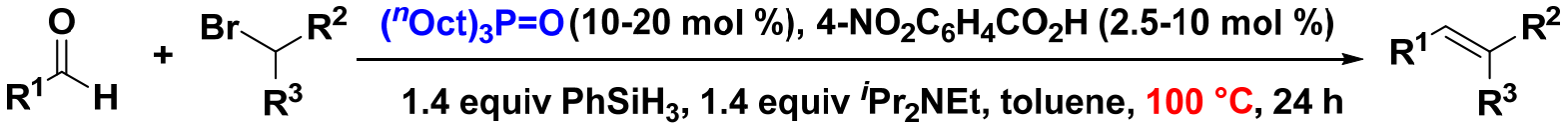
Entry	Silane	T/ °C	phosphorus cat.	Yield	E/Z
1	Ph_2SiH_2	100	standard	60	>95:5
2	$PhSiH_3$	100	standard	46	>95:5
3	Ph_3SiH	100	standard	trace	n.d.
4	Ph_2SiH_2	80	standard	62	67:33
5	Ph_2SiH_2	100	none	0[a]	n.d.
6	Ph_2SiH_2	100	PPh_3	0[a]	n.d.

[a] substance recovered.

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

Alkali and Acid Additive



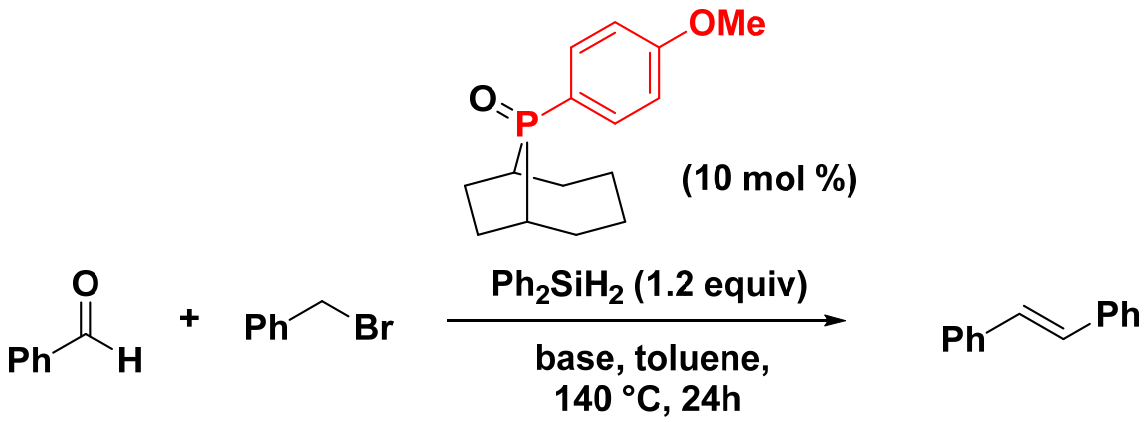


In the presence of alkali, ***acid*** as additive can still accelerate the reduction of phosphorus oxide.

Stabilized ylide: R^2 = EWG

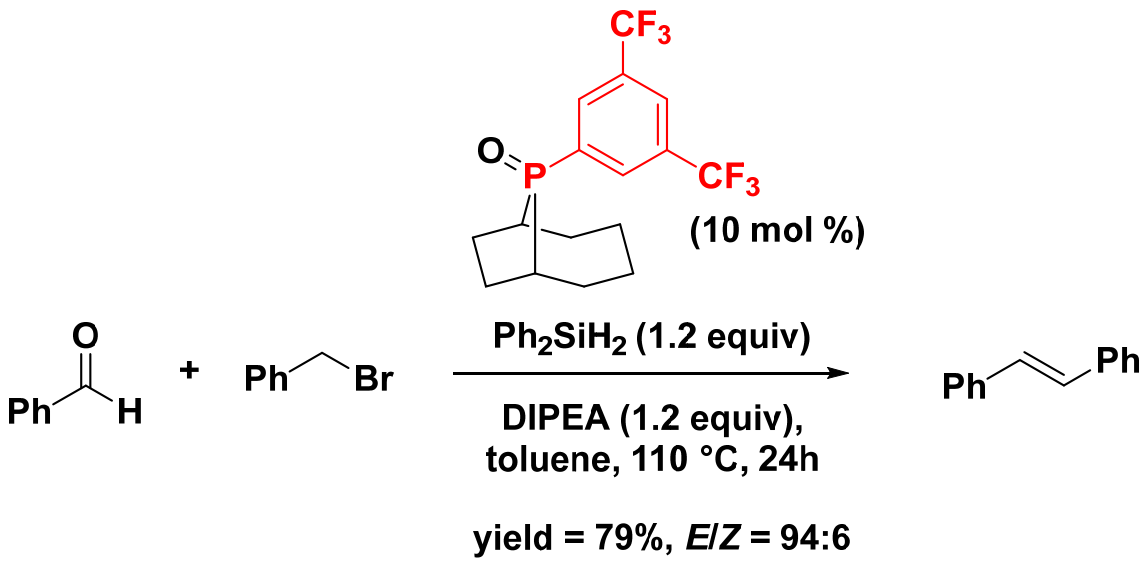
O'Brien C. J.; Lavigne F.; Coyle E. E.; Holohan A. J.; Doonan B. J. *Chem. Eur. J.* **2013**, *19*, 5854.

Unstabilized Ylide: Phosphorus and Base



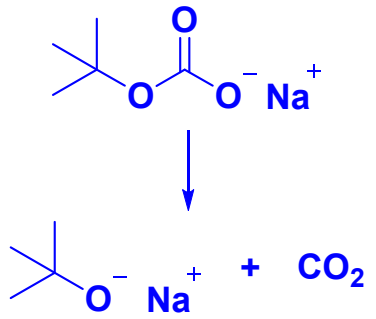
base = ^{t}BuOCO$_2$Na (2.0-3.5 equiv), yield = 80%, *E*/*Z* = 95:5

base = DIPEA (1.2 equiv), yield = 42%, *E*/*Z* = 94:6



yield = 79%, *E*/*Z* = 94:6

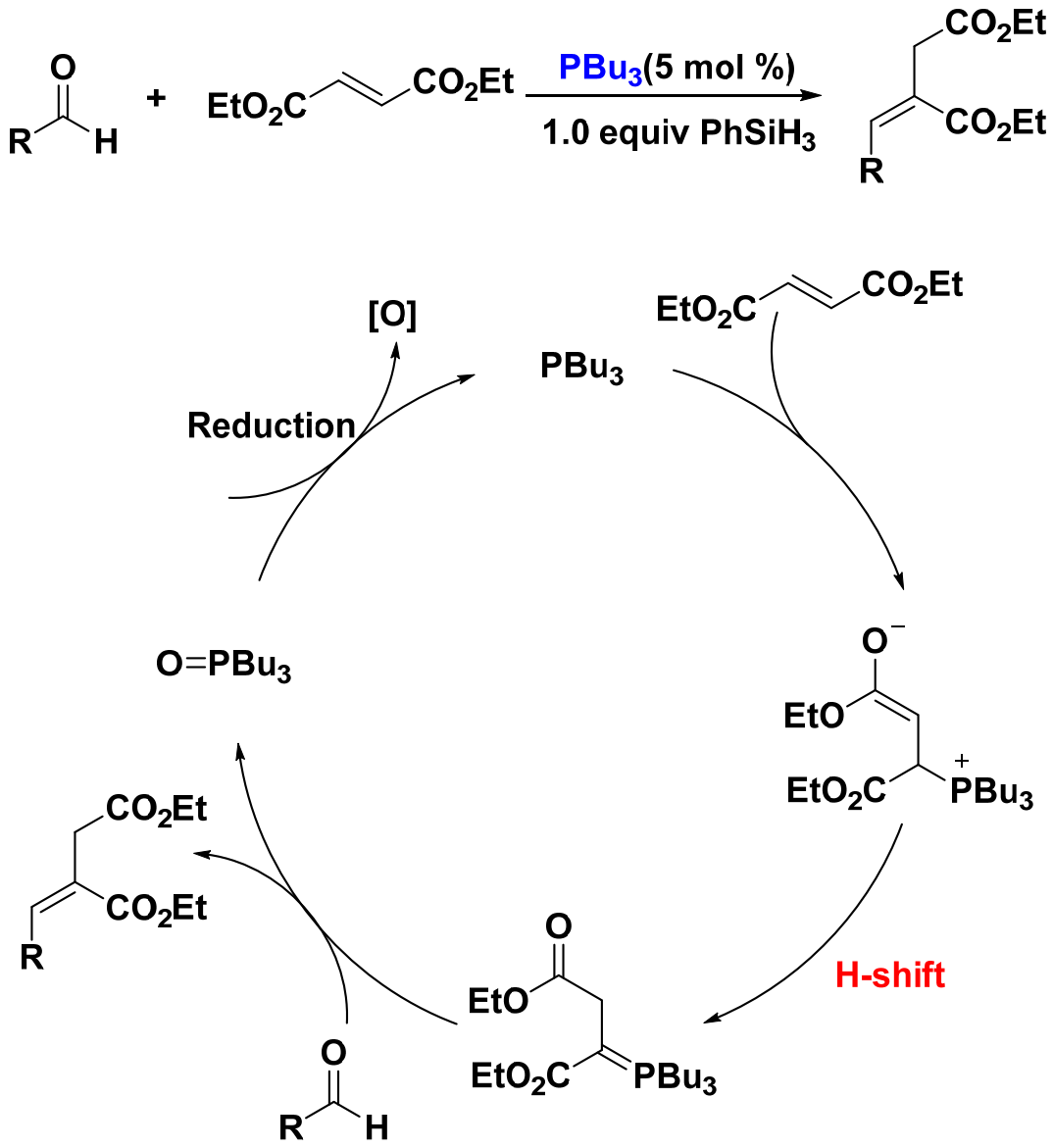
1. "Masked base" is necessary given a strong base can destroy the substrate



2. Electron-withdrawing group is required to be linked to the phosphorus catalyst.

Coyle E. E.; Doonan B. J.; Holohan A. J.; Walsh K. A.; Lavigne P.; Krenske E. H.; O'Brien C. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 12907.

An Alternative Way to Ylide

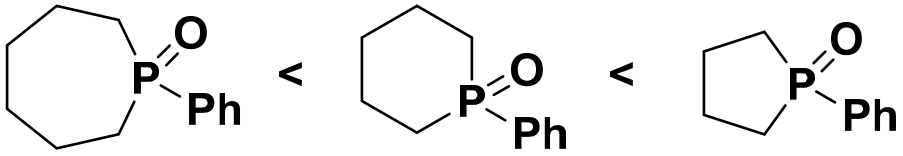


1. First base-free catalytic Wittig reaction.
2. Commercially available alkyl phosphorus was used, but at the expense of high temperatures.
3. The reaction can be done at room temperature if five-membered cyclic phosphorus is used.

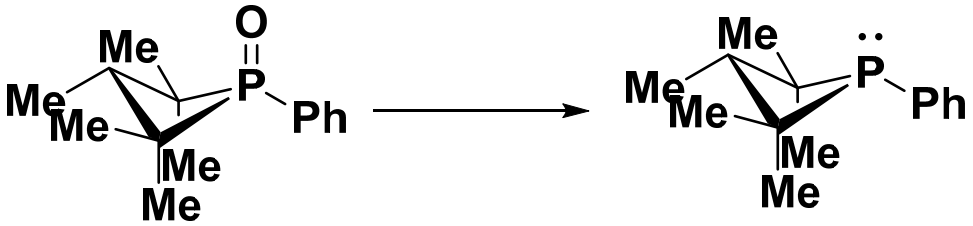
Schirmer M-L.; Adomeit S.; Werner T. *Org. Lett.* **2015**, *17*, 3078.

Ring Size and Phosphorous Reduction

The reduction of phosphane oxide is reported as the rate-determining step in the catalytic Wittig reaction.

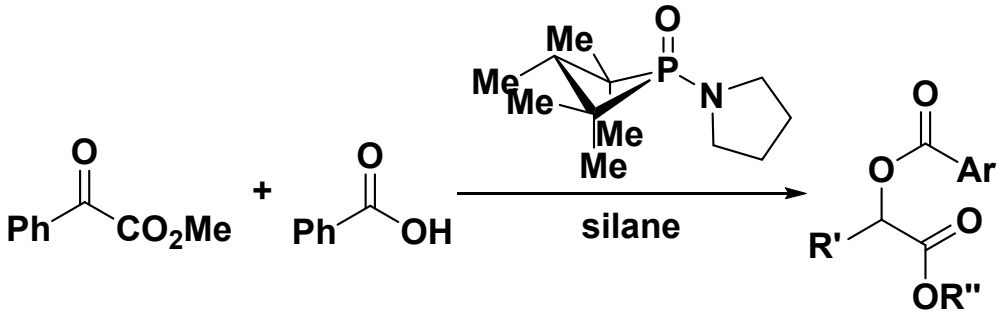


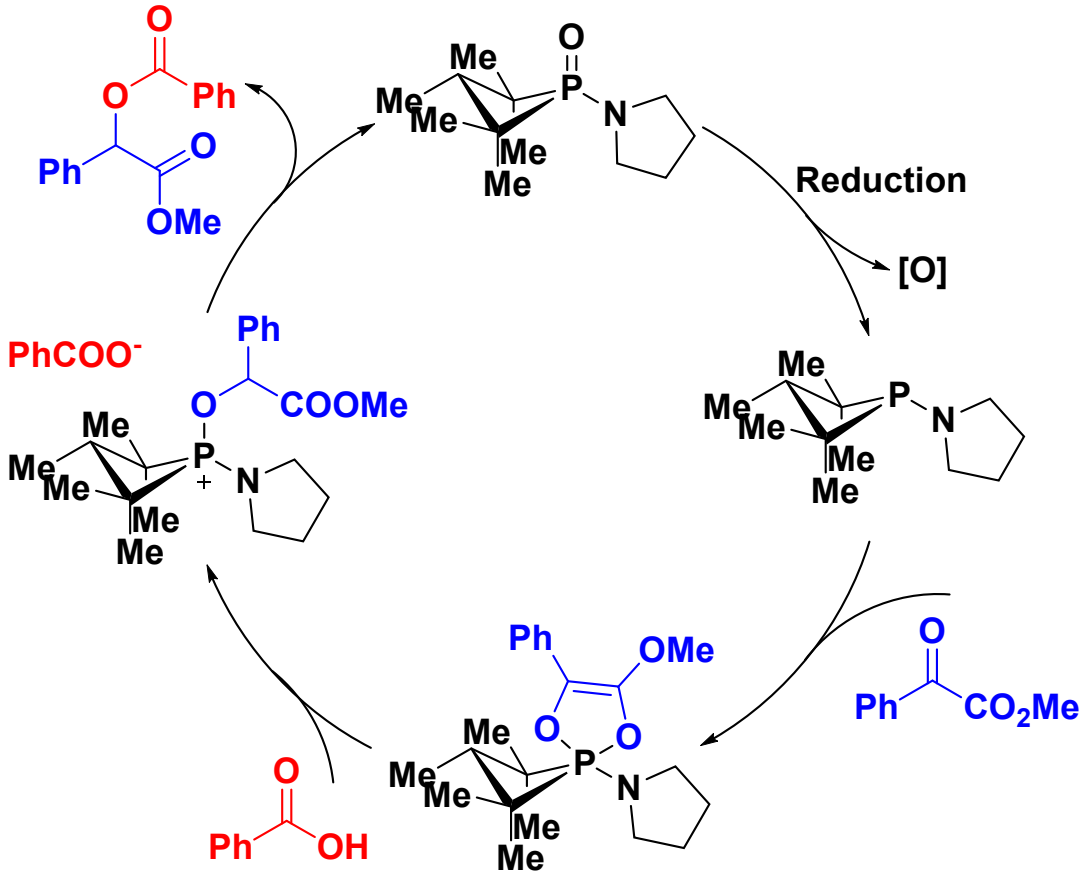
As for 4-membered ring phosphorous, the reduction was reported in as early as 1967.



Cremer, S.E.; Chorvat, R.J. *J. Org. Chem.* **1967**, *32*, 4066.

4-Membered Ring Phosphorous

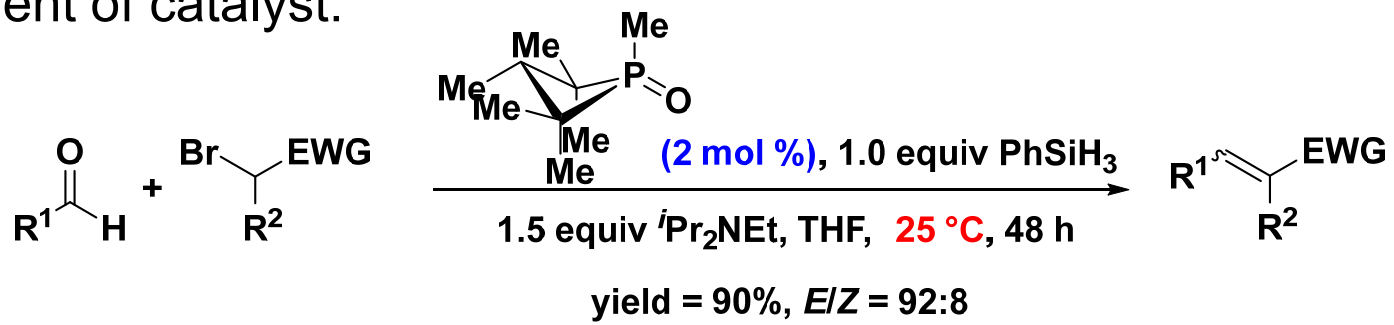




Zhao W.; Yan P. K.; Radosevich A. T. *J. Am. Chem. Soc.* **2015**, *137*, 616.

4-Membered Ring Phosphorous

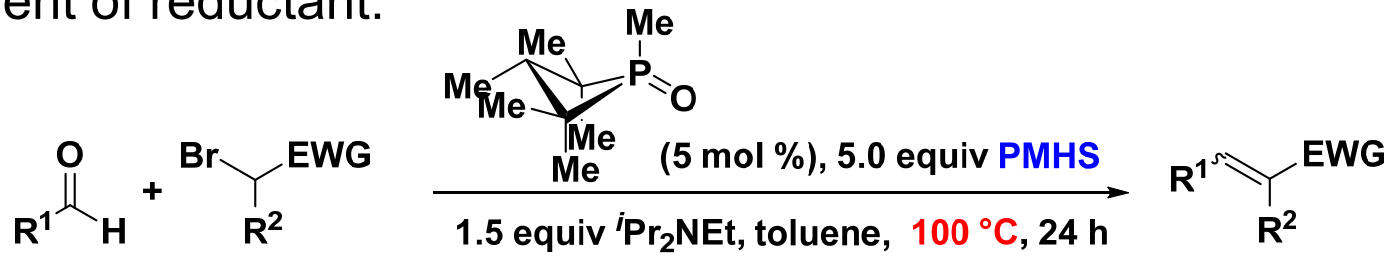
Improvement of catalyst:



yield = 90%, *E*/*Z* = 92:8

1. Mild condition
2. Additive-free
3. Low catalyst loading

Improvement of reductant:



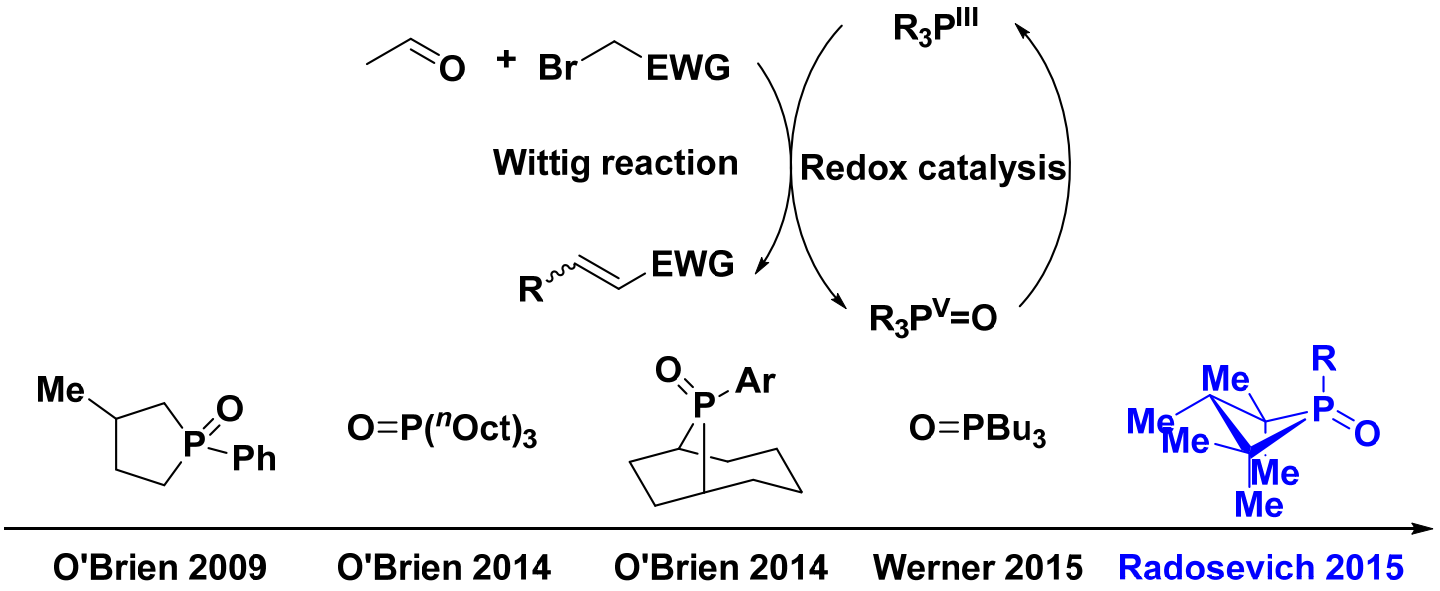
yield = 92%, *E*/*Z* = 87:13

PMHS: PolyMethylhydrosiloxane, a by-product of industrial production of silicones.

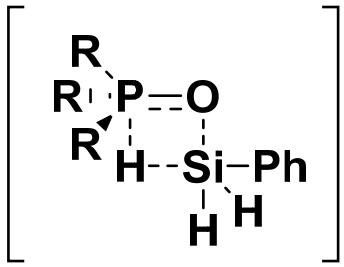
Longwitz L.; Spannenberg A.; Werner T. *ACS Catal.* **2019**, *9*, 9237.

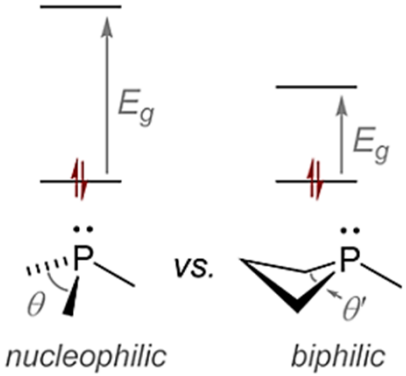
A Brief Summary

Improvement of catalyst:



The properties of phosphorus was improved in terms of electric and steric effects.

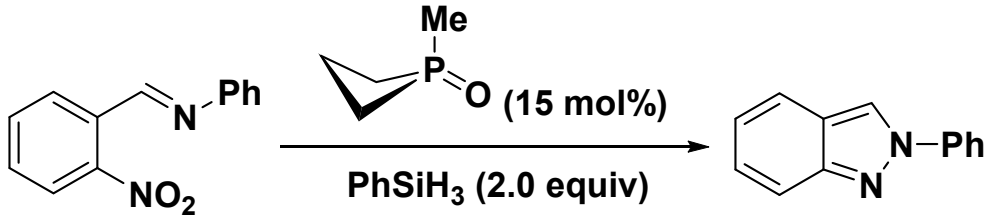


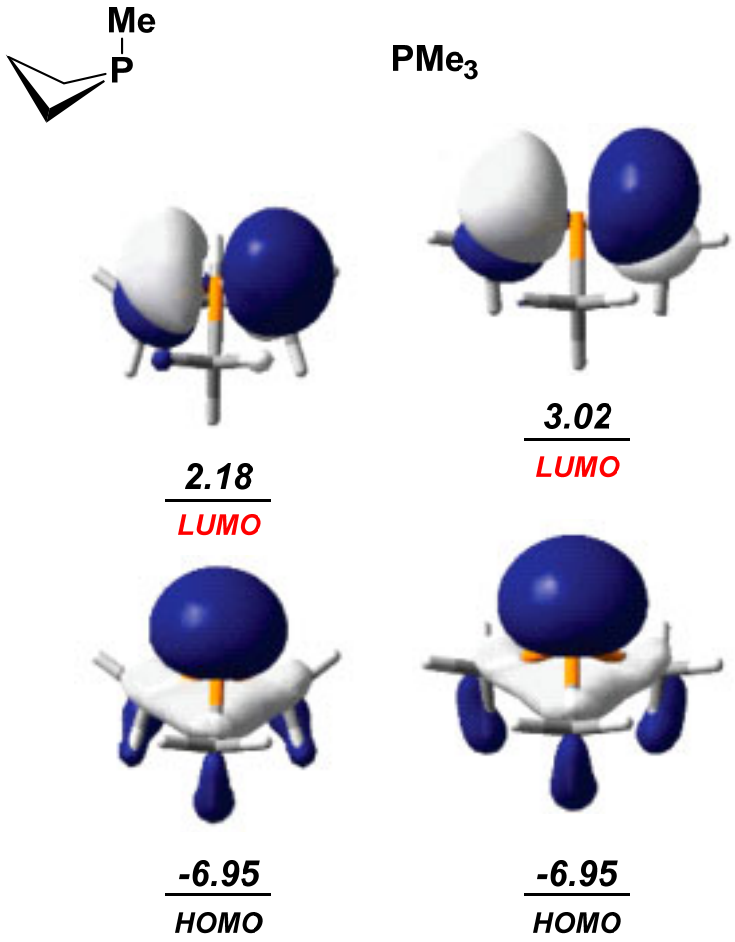


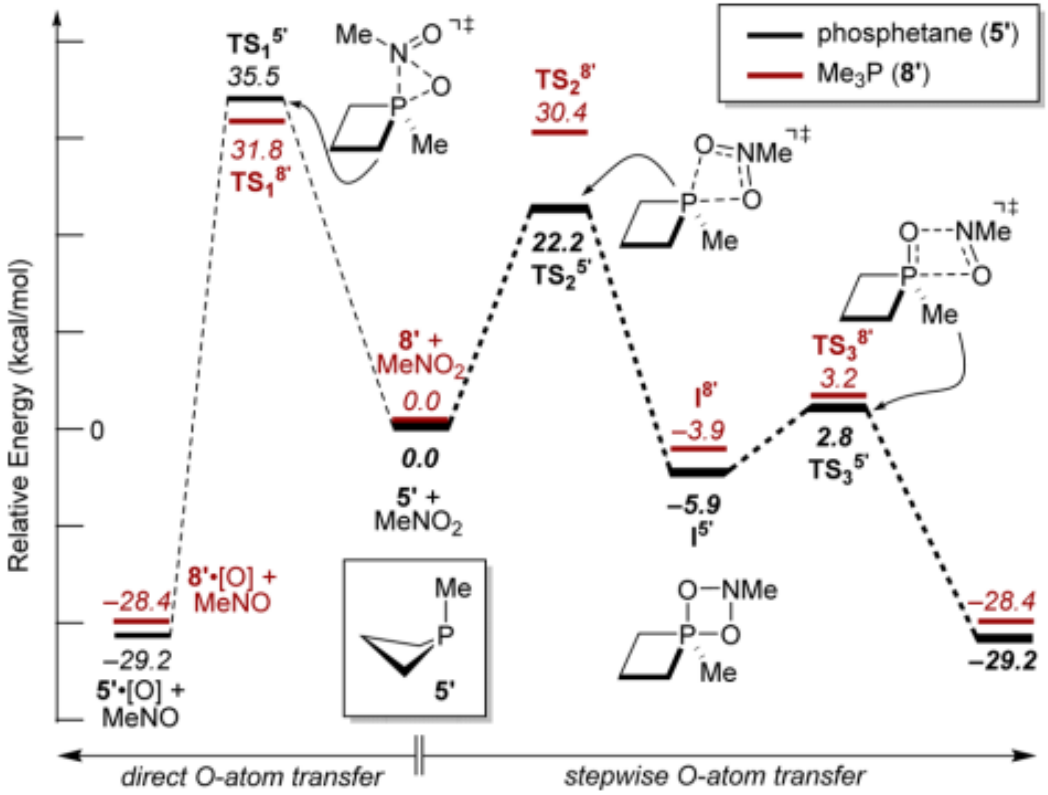
Nykaza T. V.; Harrison T. S.; Ghosh A.; Putnik R. A.; Radosevich A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6839.

Longwitz L.; Spannenberg A.; Werner T. *ACS Catal.* **2019**, *9*, 9237.

Catalytic Cadogen Reaction



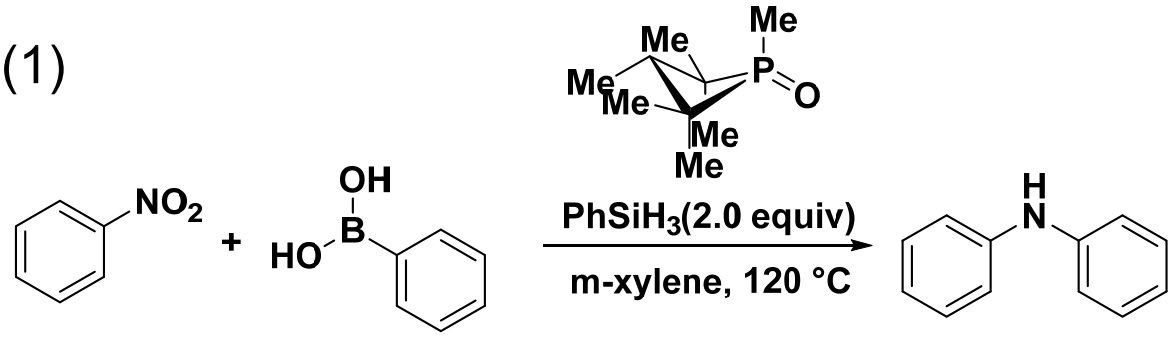




Nykaza T. V.; Harrison T. S.; Ghosh A.; Putnik R. A.; Radosevich A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6839.

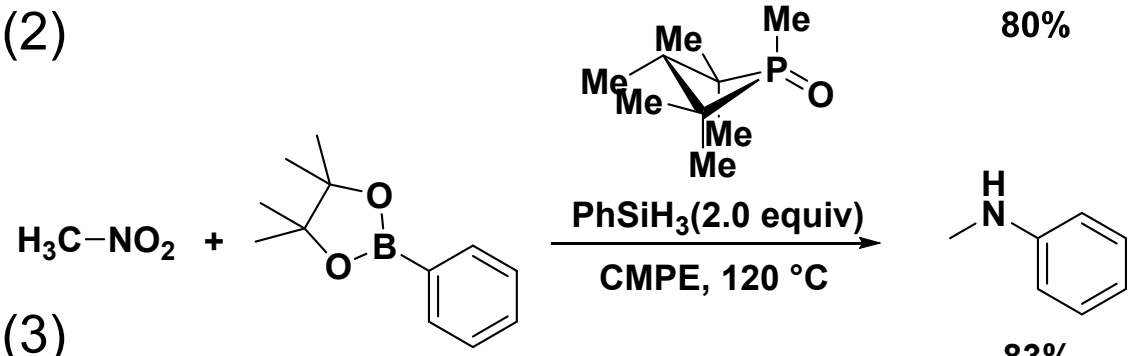
Reductive Coupling Based on the Idea

(1)



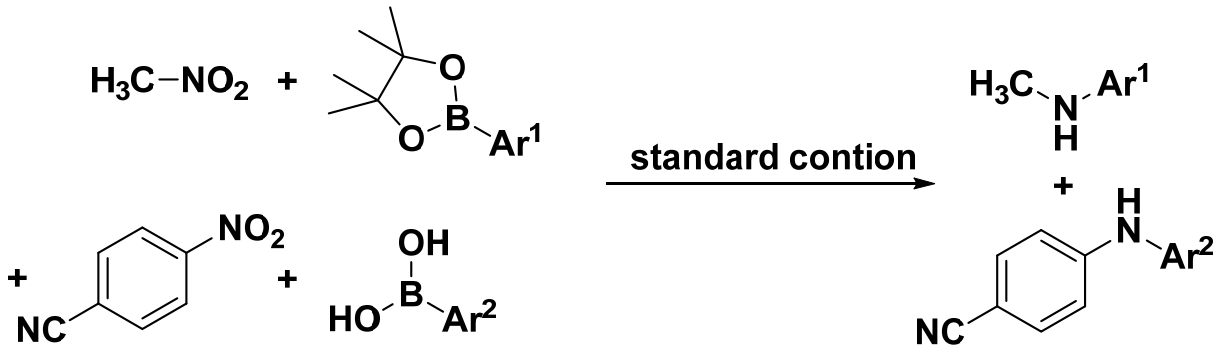
80%

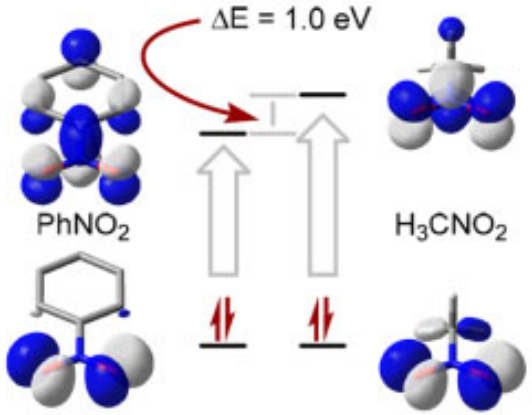
(2)

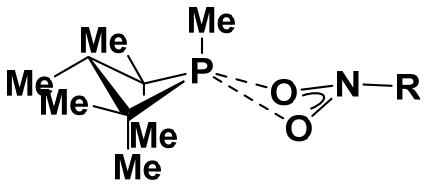


83%

(3)







(3+1) cheletropic addition leading $n_p \rightarrow \pi^*_{RNO2}$ interaction

Nykaza T. V.; Cooper J. C.; Li Z.; Mahieu N.; Ramirez A.; Radosevich A. T. *J. Am. Chem. Soc.* **2018**, *140*, 15200.

Li G.; Nykaza T. V.; Cooper J. C.; Ramirez A.; Luzung M. R.; Radosevich A. T. *J. Am. Chem. Soc.* **2020**, *142*, 6786.

Li G.; Qin Z.; Radosevich A. T. *J. Am. Chem. Soc.* **2020**, *142*, 16205.

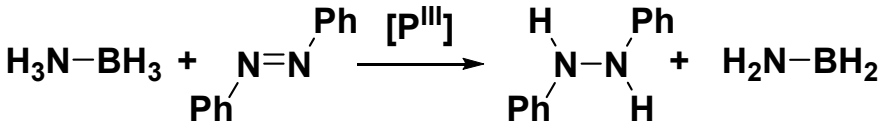
Summary of Catalytic Wittig Reaction

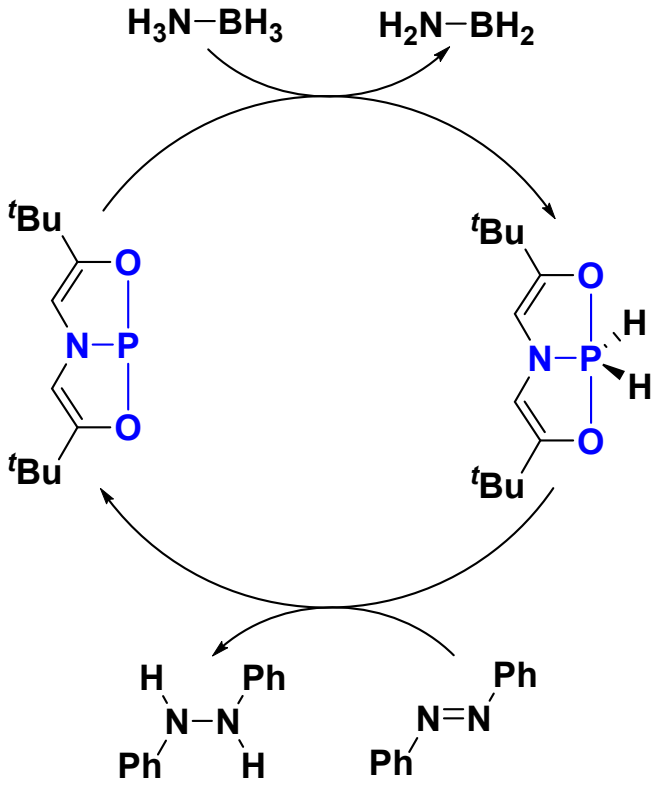
- The reduction of phosphorus oxide is usually the rate-determining step.
- As for catalytic ability, Small cyclophosphorus is much more higher than commonly used phosphorus such as PPh_3 or PBu_3.
- Silanes have excellent properties in reduced phosphorus oxide, such as non-toxicity, good functional group tolerance, predictable stereochemical results, etc.
- Further development is needed to make industrial waste PMHS as terminal reductant.

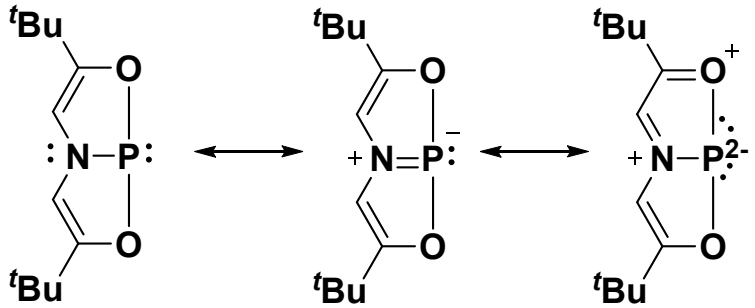
Outline

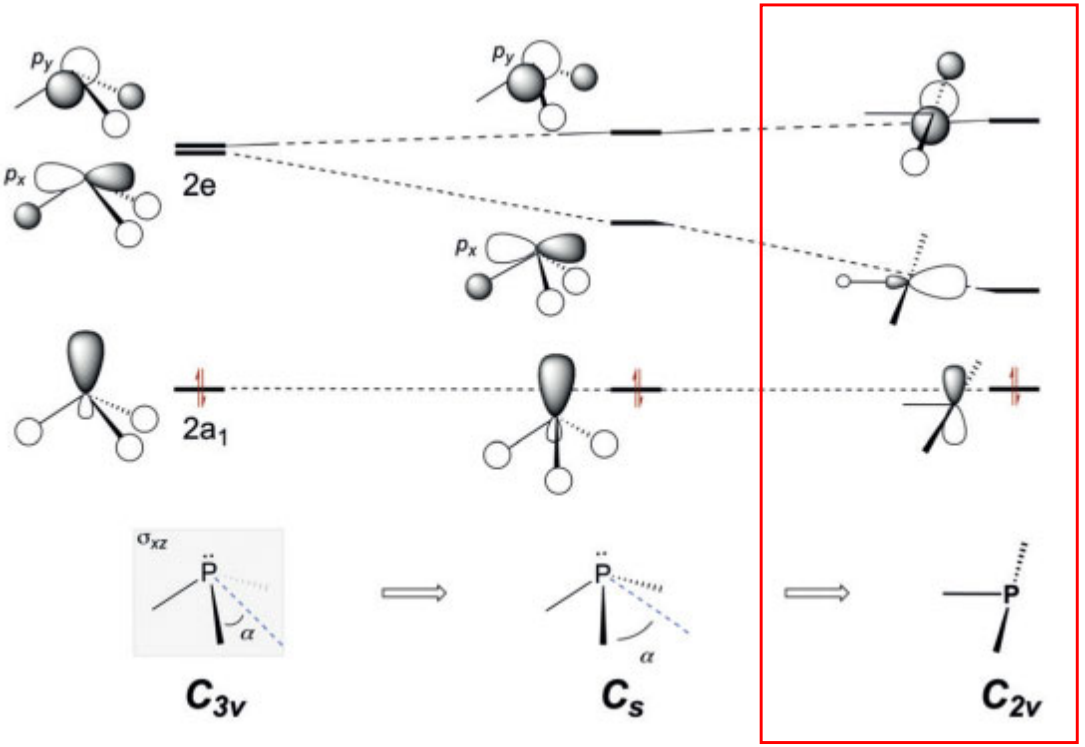
- Introduction
  - Typical Catalytic Reaction of P(III) and P(V)
- In situ P^{III}/P^{V}=O cycle
  - Reduction Methods of P^{V}=O
  - Catalytic Wittig Reaction
- Constrained Bicyclic Phosphines
- P^{III}/P^{V} Cycle via Pyridyl Phosphonium Salts
- Summary
- Acknowledgement

Planar Phosphorus



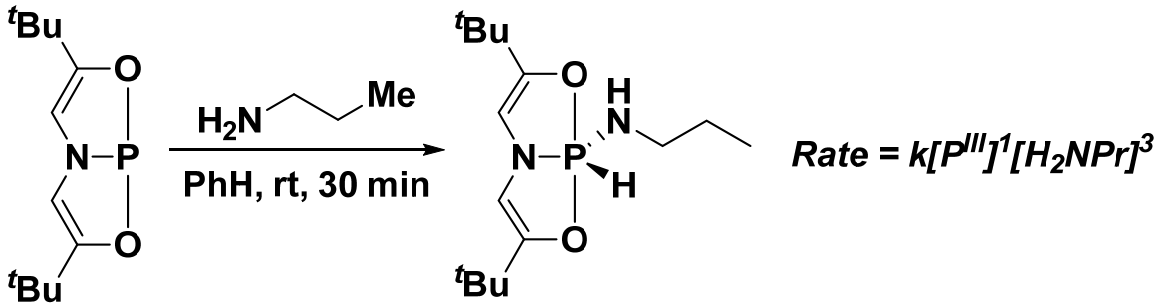




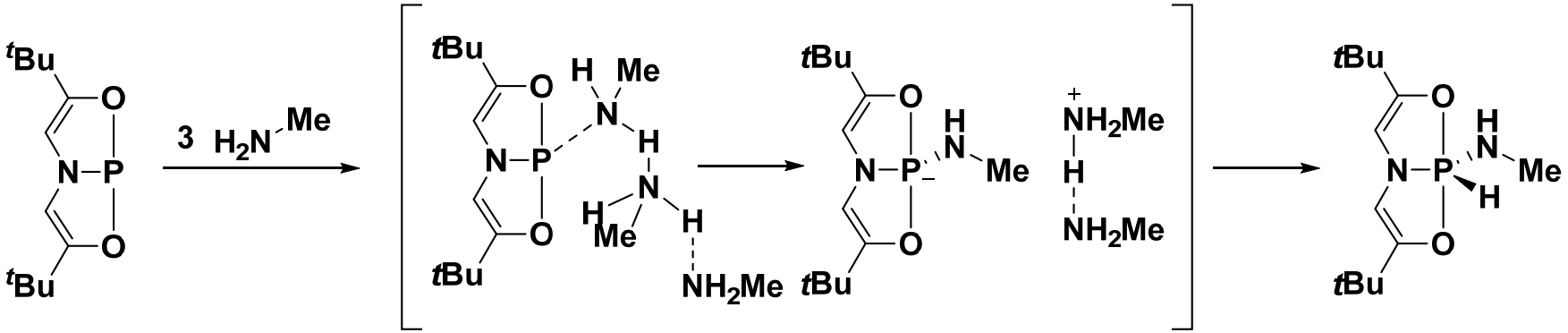


Dunn N. L.; Ha M.; Radosevich A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330.

“Oxidation Addition”



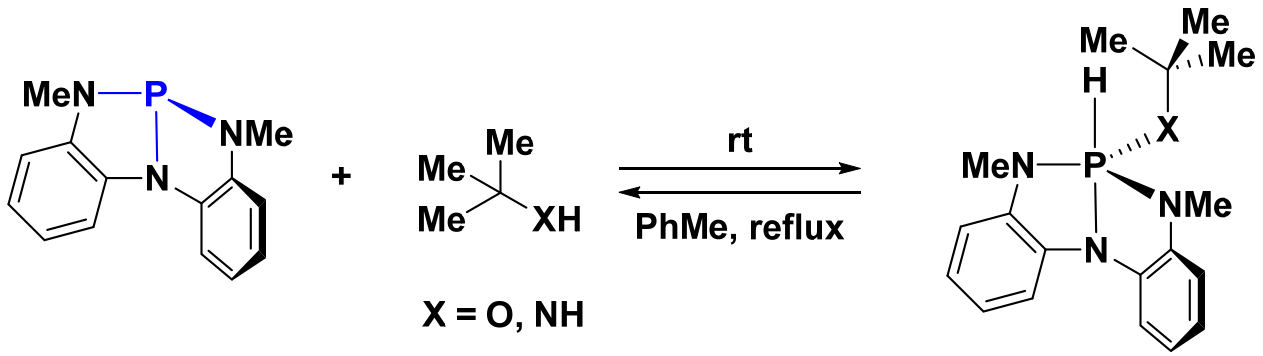
Kinetic studies show a third-order to amine!

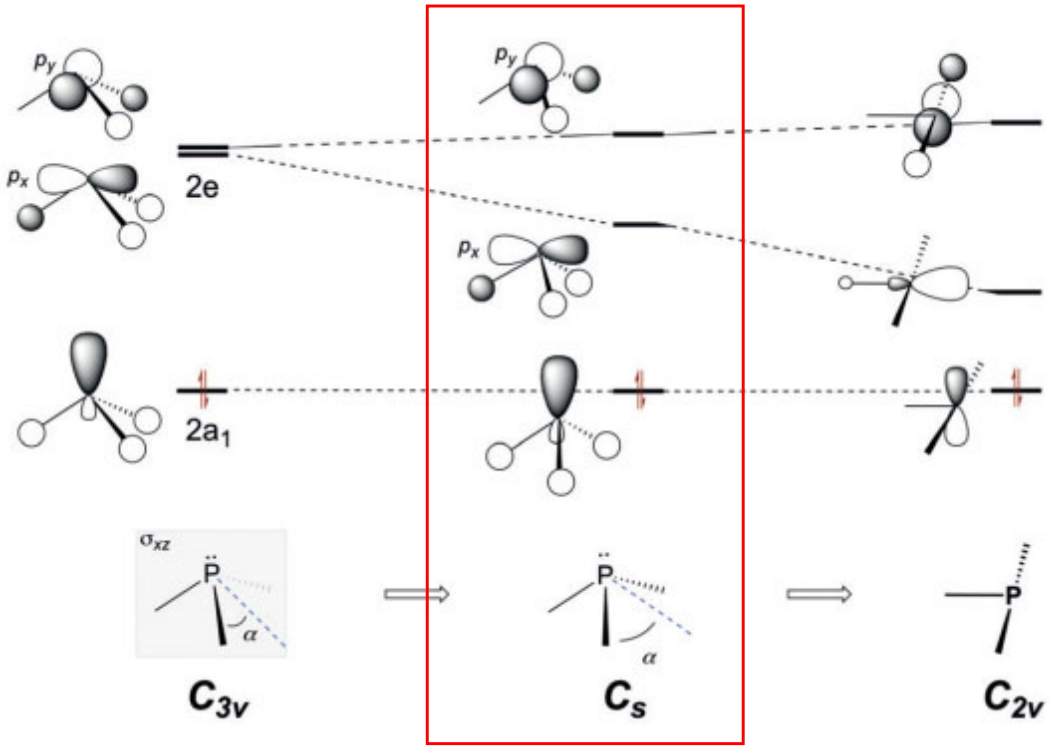


Mechanism reflects the electrophilicity of the P^{III} center.

McCarthy S. M.; Lin Y.; Devarajan D.; Chang J. W.; Yennawar H. P.; Rioux R. M.; Ess D. H.; Radosevich A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.

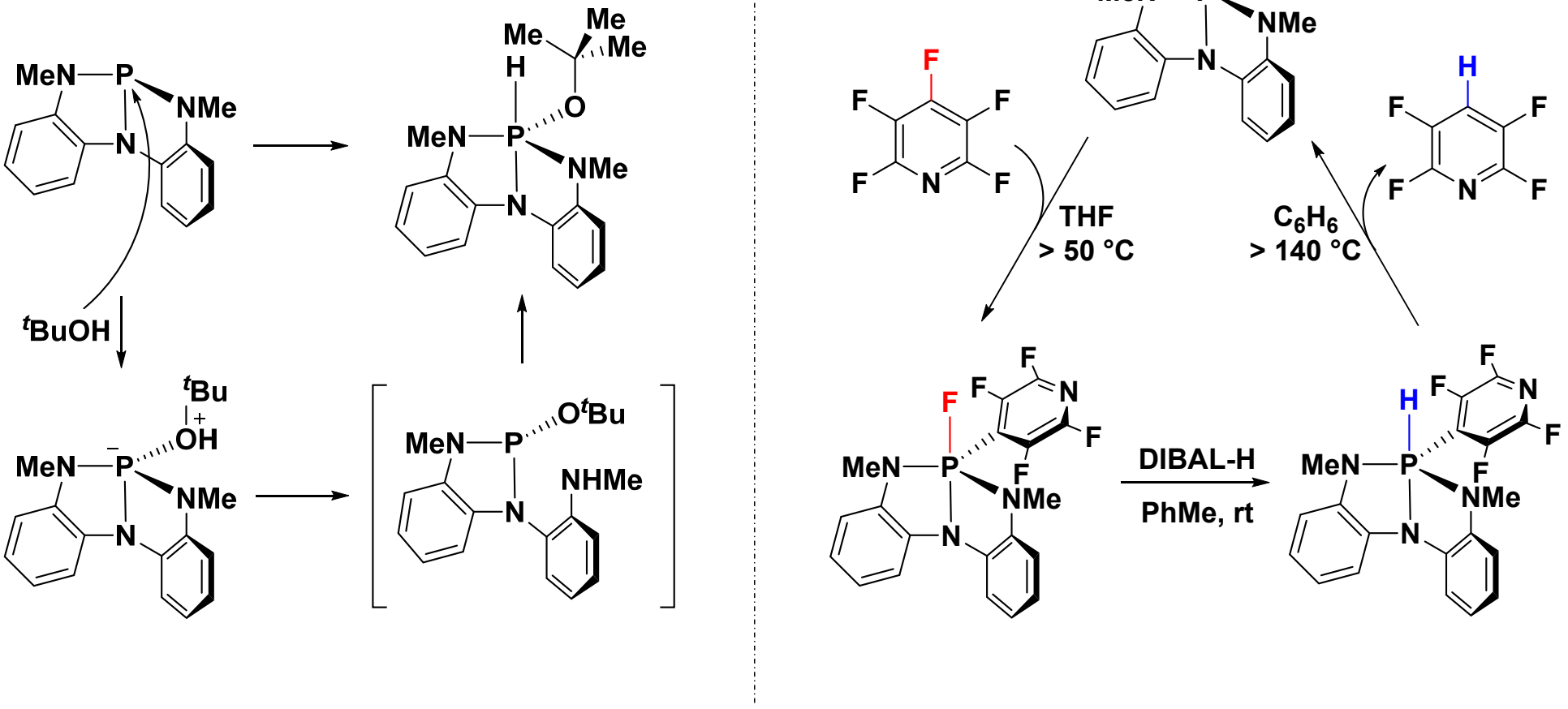
Bent Phosphorus





McCarthy S. M.; Lin Y.; Devarajan D.; Chang J. W.; Yennawar H. P.; Rioux R. M.; Ess D. H.; Radosevich A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.

Biphilic Bent Phosphorus



Biphilic

McCarthy S. M.; Lin Y.; Devarajan D.; Chang J. W.; Yennawar H. P.; Rioux R. M.; Ess D. H.; Radosevich A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.
Lim S.; Radosevich A. T. *J. Am. Chem. Soc.* **2020**, *142*, 16188.

Outline

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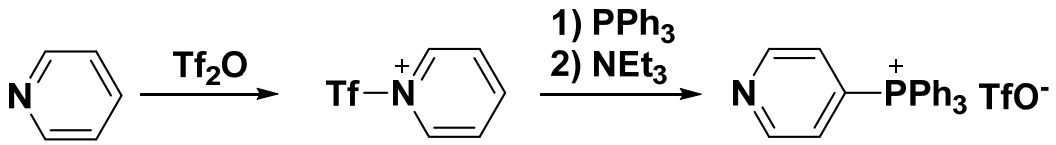
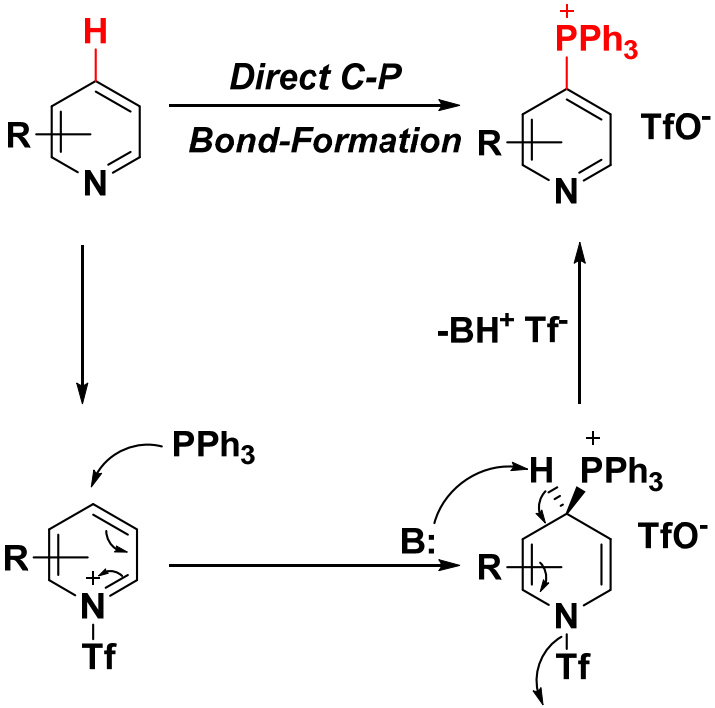
P(III)/P(V) Cycle via Pyridyl Phosphonium Salts



Anders, E.; Markus, F. *Tetrahedron Lett.* **1987**, *28*, 2675.

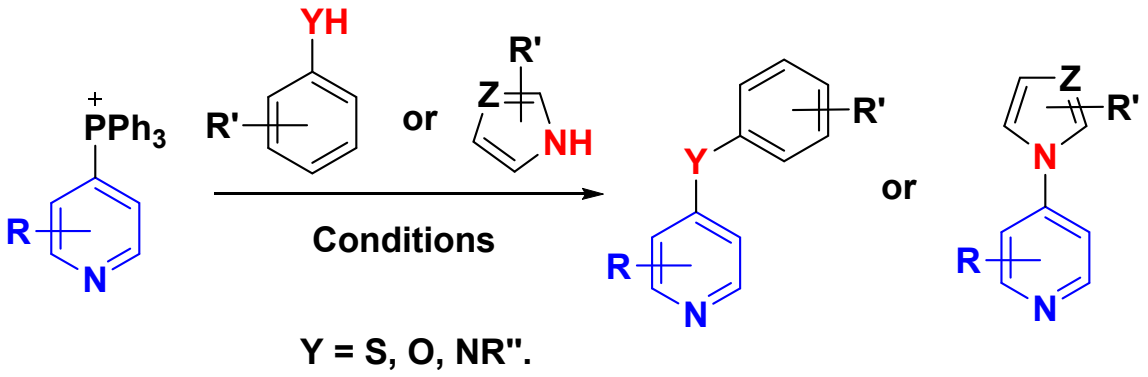


1.Regioselectivity is governed by favorable orbital interaction between the **4-position** and the phosphorus lone pair.

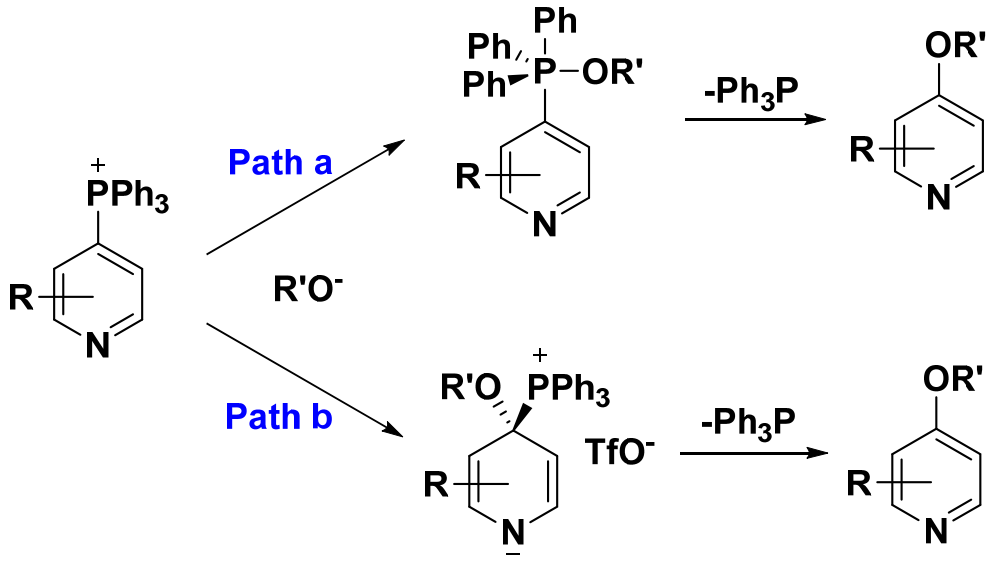
2.C-P will form at the **2-position** if the 4-position is blocked.

Hilton M. C.; Dolewsik R. D.; McNally A. *J. Am. Chem. Soc.* **2016**, *138*, 13806.

React Directly with Nucleophile



Y = S, O, NR''.



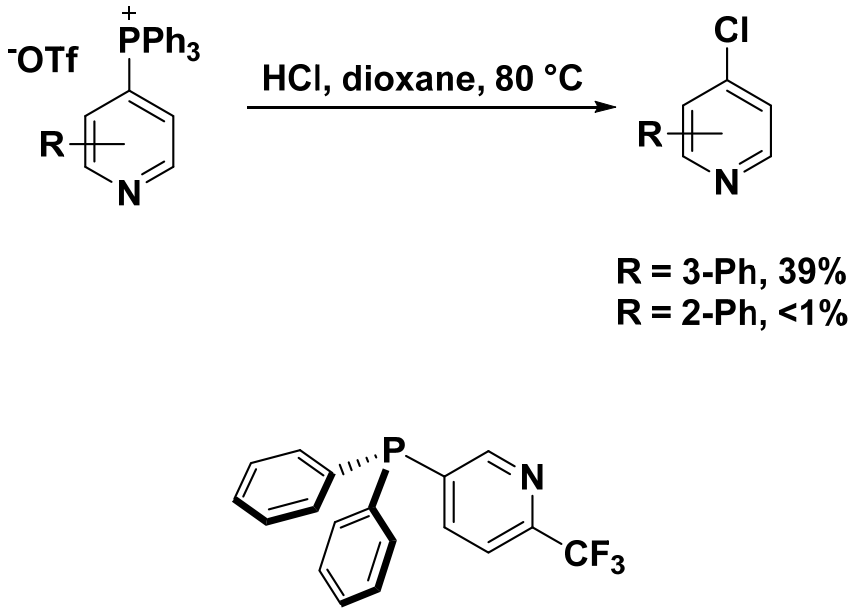
Path a: ligand-coupling process

Path b: S_NAr reaction

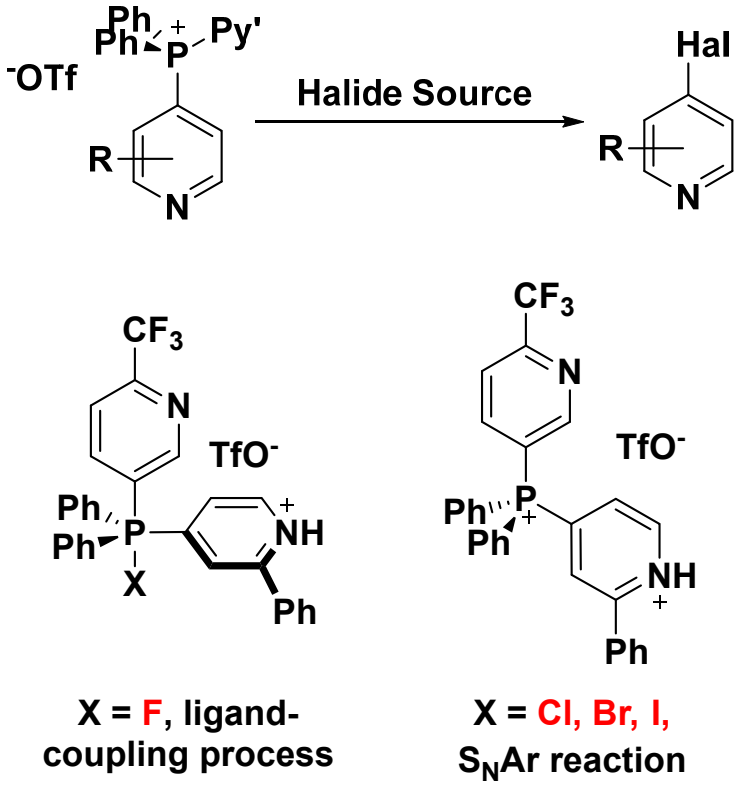
Hilton M. C.; Dolewsik R. D.; McNally A. *J. Am. Chem. Soc.* **2016**, *138*, 13806.

Anderson R. G.; Jett. B. M.; McNally A. *Angew. Chem. Int. Ed.* **2018**, *57*, 12514.

React Directly with Nucleophile



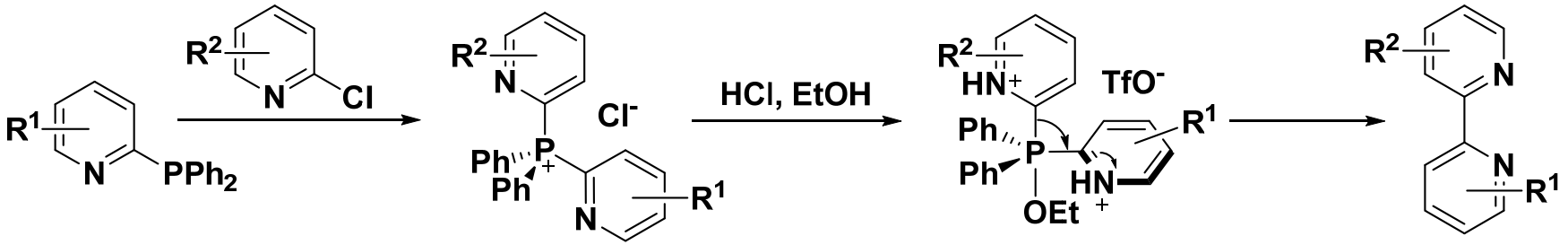
3-Pyridyl increases the electrophilicity of the resulting phosphonium salt; 2-CF_3 would prevent reaction with Tf_2O.



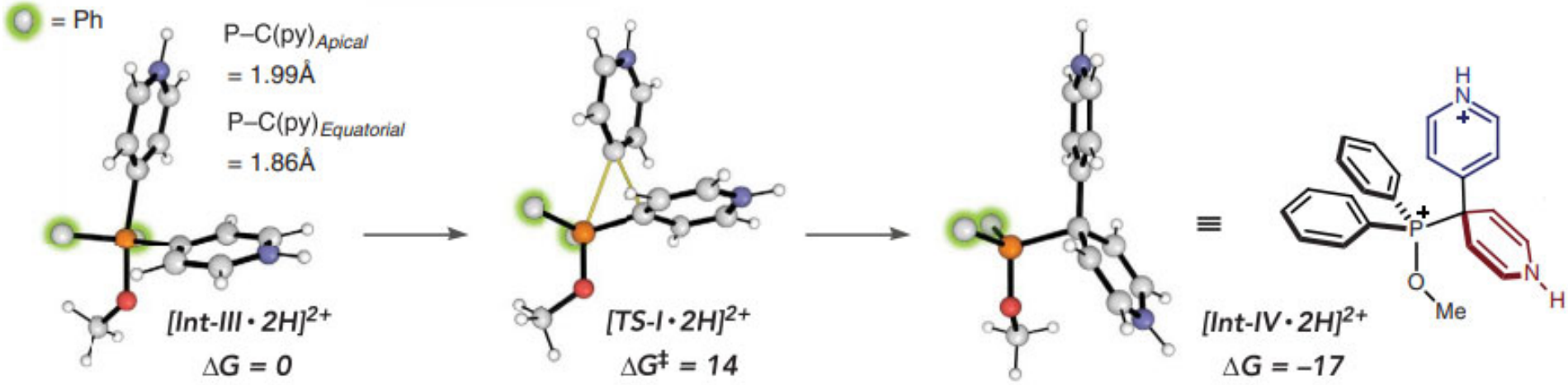
Excluding fluorination, the halides directly attack at carbon rather than via phosphorus ligand-coupling.

Levy J. N.; Alegre-Requena J. V.; Liu. R.; Paton. R. S.; McNally A. *J. Am. Chem. Soc.* **2020**, *142*, 11295.

Pyridine Coupling



Chlorine atom can be placed in 2-position or 4-position.



Hilton M.C.; Zhang X.; Boyle B. T.; Alegre-Requena J. V.; Paton R. S.; McNally A. *Science* **2018**, *362*, 799.

Boyle B. T.; Hilton M. C.; McNally A. *J. Am. Chem. Soc.* **2019**, *141*, 15441.

Outline

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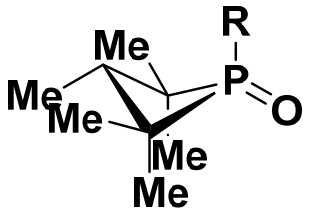
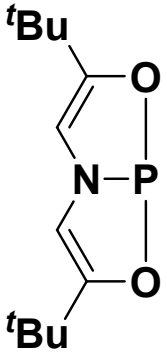
Summary

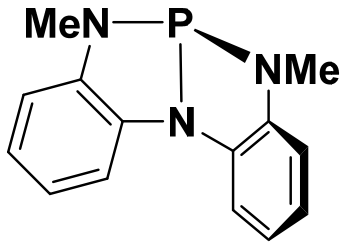
- A mature catalytic reduction system



- Constrained bicyclic phosphines are still studied



or



- A pyridine substitution method