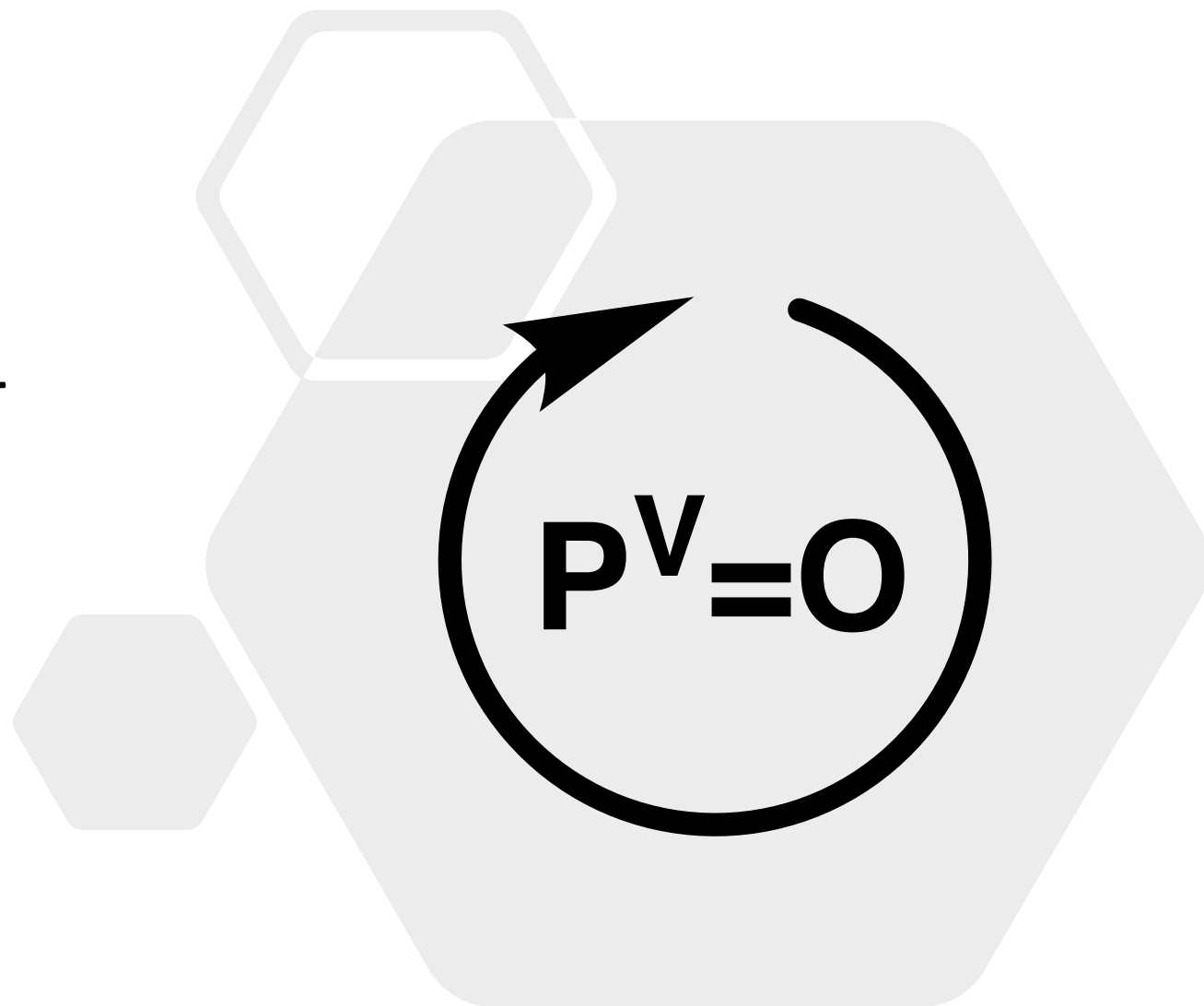


# Progress in -Phosphine Oxide- Catalysis

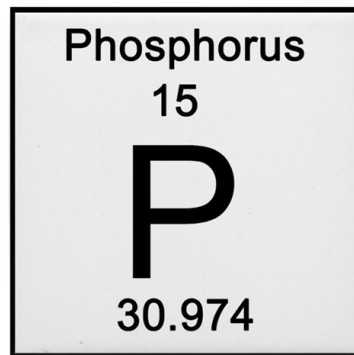
Remi LAVERNHE – 24/04/2020  
ZHU group



# PLAN

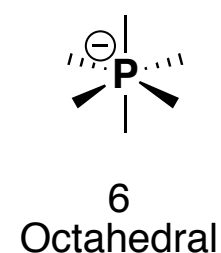
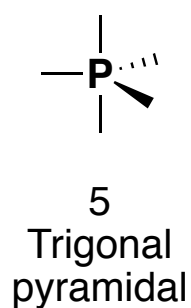
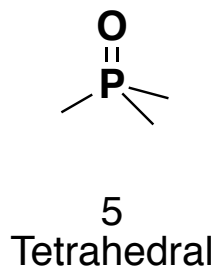
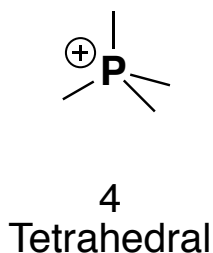
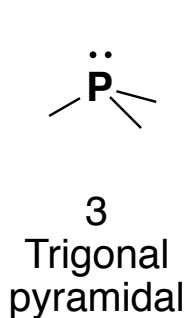
- Generalities about Phosphorous
- Redox-Neutral Phosphine Oxide Catalysis
- Development of  $P^{III}/P^V=O$  Redox Cycling
- Conclusion

# Generalities about Phosphorous



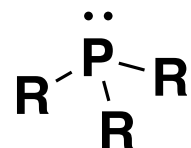
- Isolated in 1669
- Sources: Phosphates (China, Morocco, South Africa and USA)
- One of 6 element essential for life (C, H, N, O, **P**, S)
- Potential shortage of Phosphorus in around 80 years
- Electronic configuration:  $1S^2 2S^2 2P^6 3S^2 3P^6 3D^0$ 
  - larger than Nitrogen
  - vacant orbitals are accessible
- Hypervalency (penta, hexa and even hepta) possible

Valence & VSEPR:

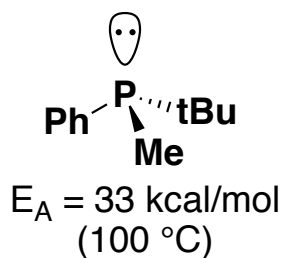


# Generalities about Phosphorous

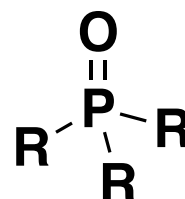
## Phosphines



- Very good Nucleophile
- P-chiral phosphines exist but can racemize



## Phosphine oxides



- P—O very strong, 350 kJ/mol (compared to 264 for P—C)
- P=O formation is used as driving force (Wittig, Appel..)
- But associated with:
  - Poor atom economy
  - Hampered purification
  - Recycling difficult
  - Few enantioselective process

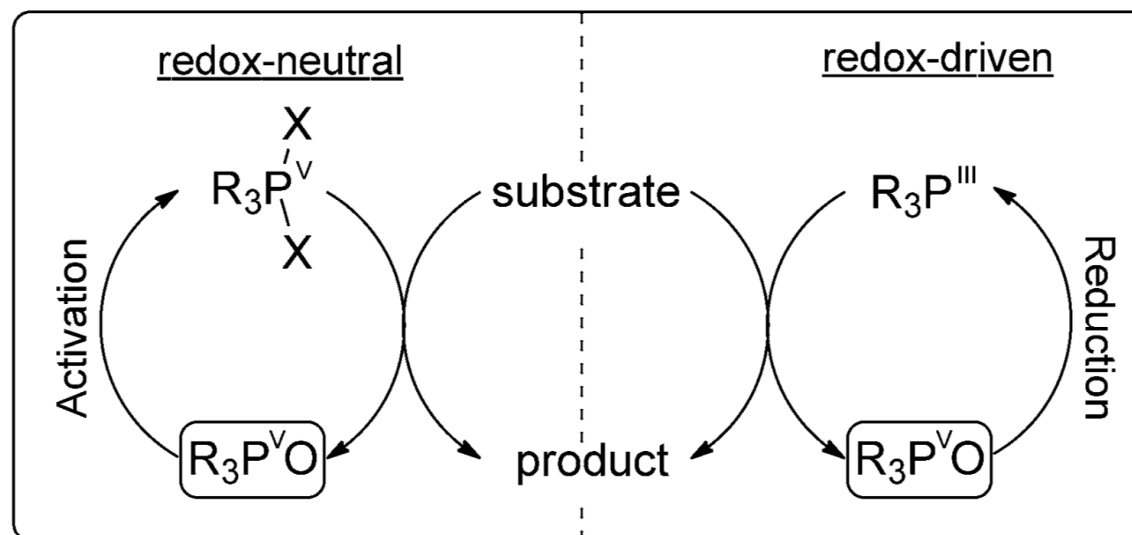
Arsenic is not viable alternative due to toxicity

Catalytic processes needed at an industrial level and at an environmental level

Rutjes, F. P. J. T. *ChemSusChem*. **2013**, 1615–1624.

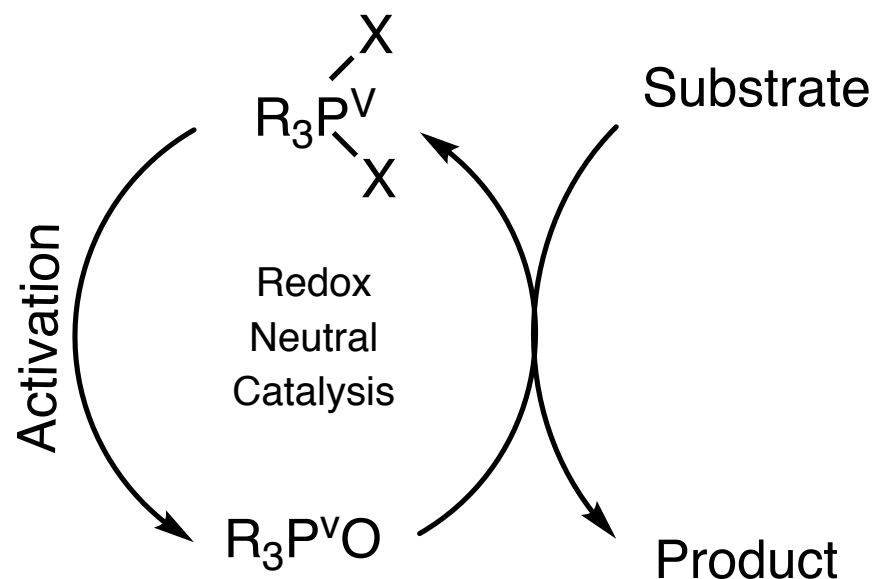
# Generalities about Phosphorous

- **Nucleophilic Phosphine Catalysis:** thoroughly investigated and no phosphine oxide involved. (Morita–Baylis–Hillman type reaction).
- **Redox-Neutral Catalysis:** in situ activation of a phosphorus(V) reagent without affecting the phosphorus oxidation state. Need to be entropically favored (release of gas such as  $N_2$  or  $CO_2$ ).
- **Redox-Driven Catalysis:** in-situ reduction of phosphine oxide (V) reagent to phosphine (III).



Very recent research area: mostly after 2010

# Redox-Neutral Phosphine Oxide Catalysis

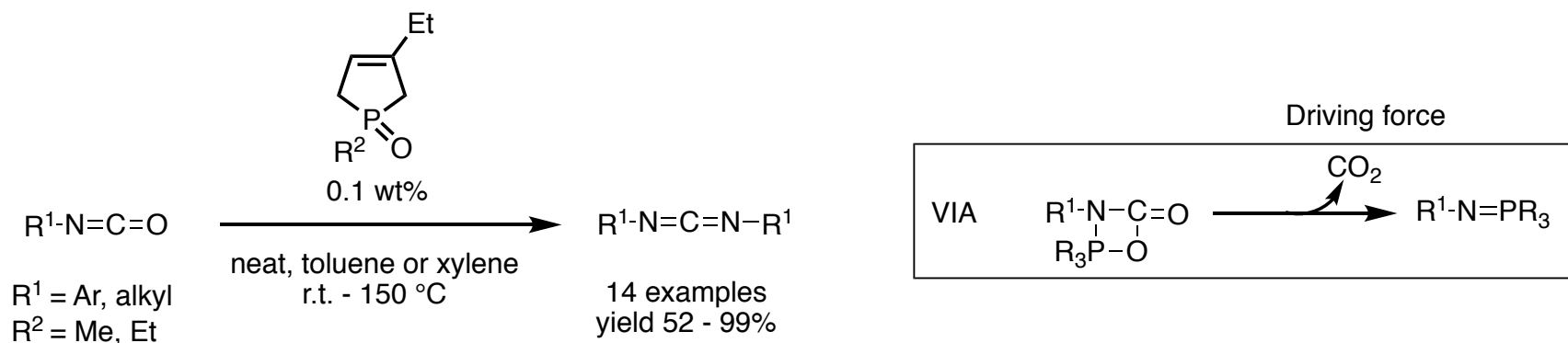


- Three different strategies:
- Finding the appropriate substrate
  - Using the ideal co-reagent
  - Designing the specific catalyst

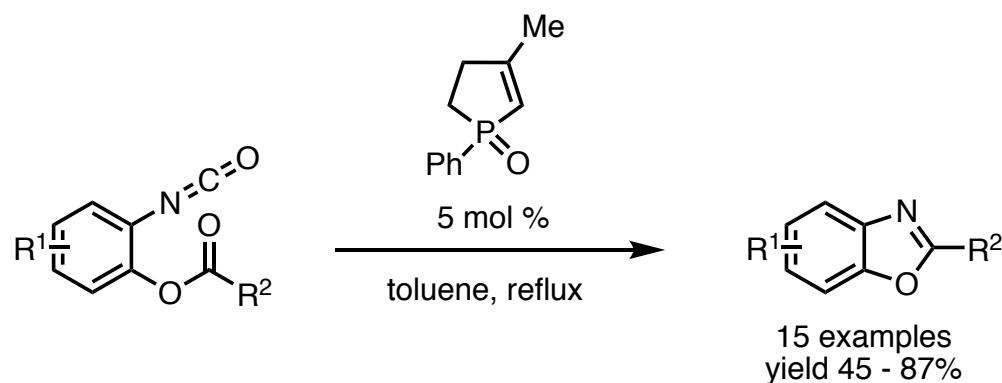
# Redox-Neutral Phosphine Oxide Catalysis

Finding the appropriate substrate

1<sup>st</sup> example of phosphine catalysis in 1962 (Campbell): conversion of **Isocyanates** to Carbodiimides



2<sup>nd</sup> example almost 50 years after (Marsden): intramolecular method



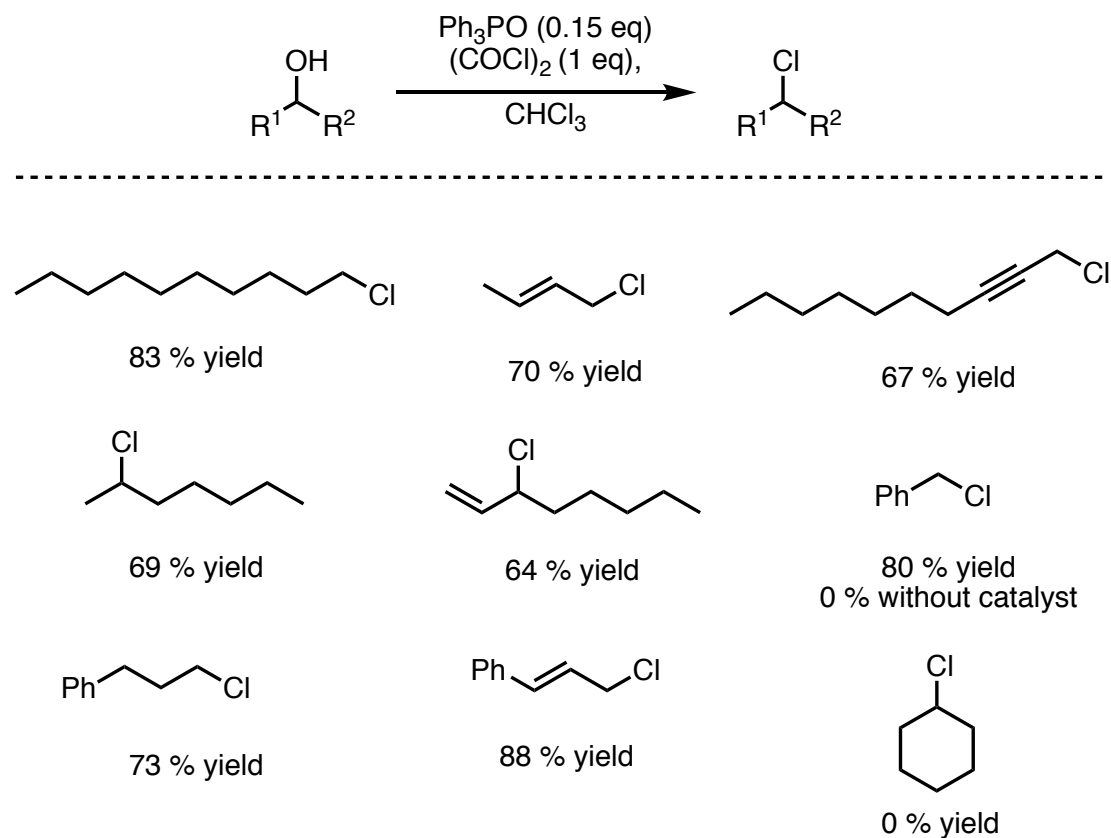
Same strategy: Access to Benzodiazepin-5-ones and Benzimidazoles

Campbell, T. W. *J. Am. Chem. Soc.* **1962**, *84*, 1493.  
Campbell, T. W. *J. Am. Chem. Soc.* **1962**, *84*, 3673–3677.  
Marsden, S. P. *Org. Lett.* **2008**, *10*, 2589–2591.  
Ding, M. W. *Synthesis* **2015**, *47*, 3522–3528.  
Ding, M. W. *J. Org. Chem.* **2016**, *81*, 1263–1268.

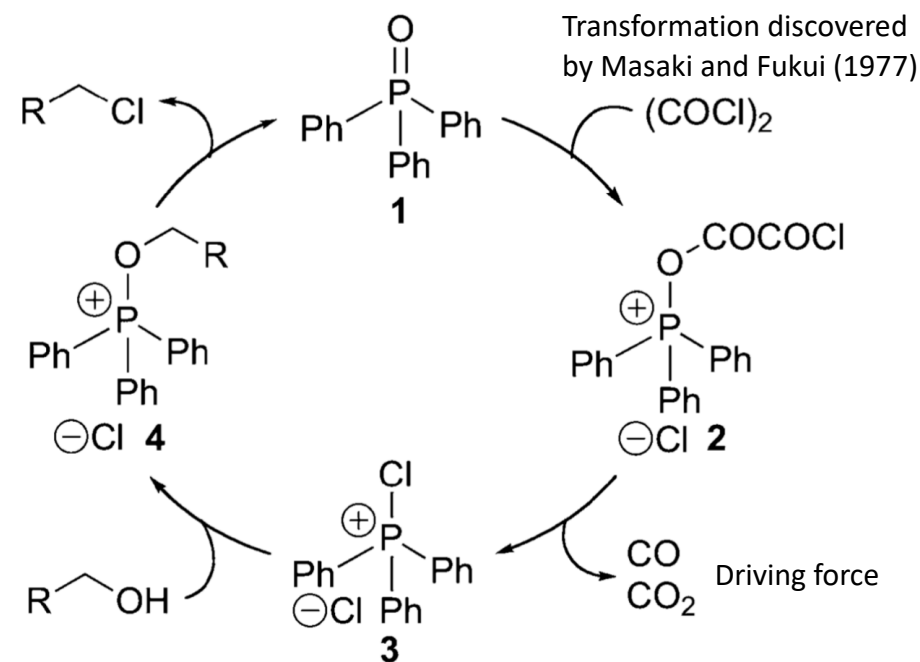
# Redox-Neutral Phosphine Oxide Catalysis

Using the ideal co-reagent

Denton first to show the utility of oxalyl chloride (2010)



Catalytic Appel reaction:  
Proposed Mechanism



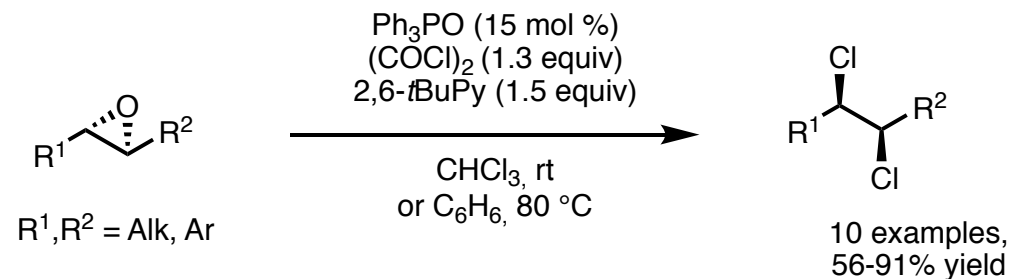
Masaki, M.; Fukui, K. *Chem. Lett.* **1977**, 6, 151 – 152.  
Denton, R. M. *Chem. Commun.* **2010**, 46, 3025–3027.  
Denton, R. M. *J. Org. Chem.* **2011**, 76, 6749–6767.



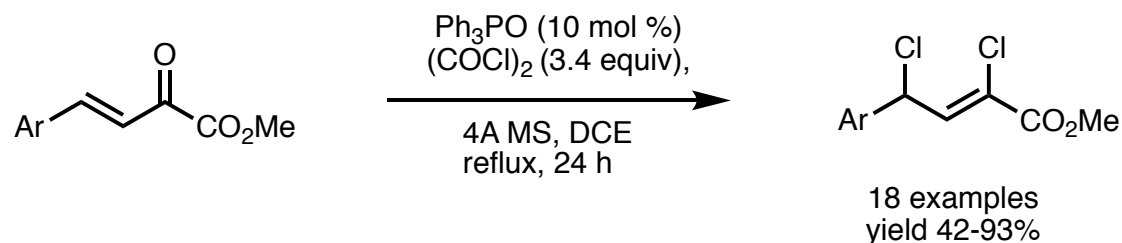
# Redox-Neutral Phosphine Oxide Catalysis

Using the ideal co-reagent

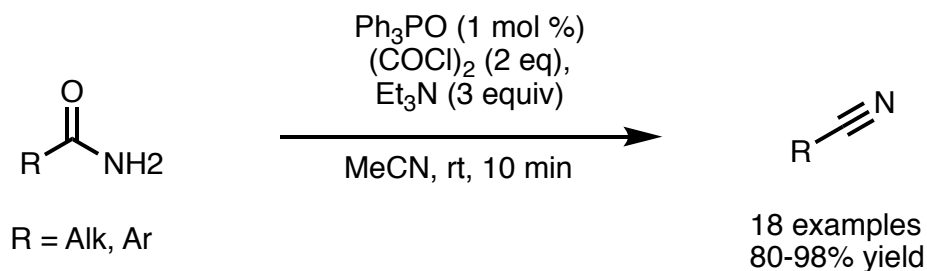
Dichlorination of Epoxides (2010)



Stereoselective 1,3 Dichlorination of Unsaturated Ketoesters (2014)



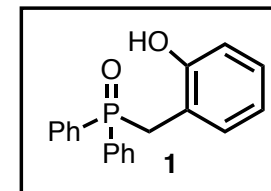
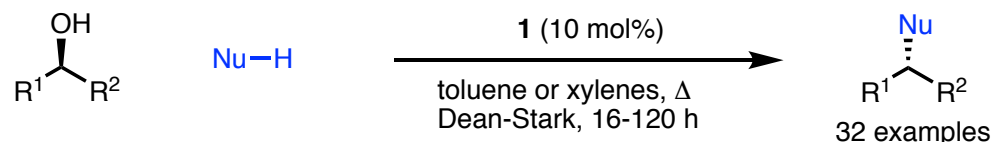
Dehydration of Amides to Nitriles (2018)



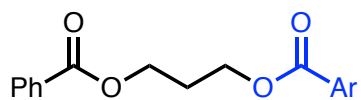
Denton, R. *Org. Lett.* **2010**, *12*, 4678–4681.  
Xu, P. F. *Chem. - A Eur. J.* **2014**, *20*, 98–101.  
Malkov, A. V. *Org. Lett.* **2018**, *20*, 728–731.

# Redox-Neutral Phosphine Oxide Catalysis

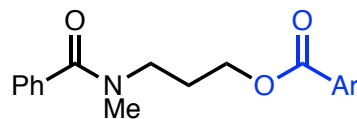
Designing the specific catalyst: a catalytic Mitsunobu reaction



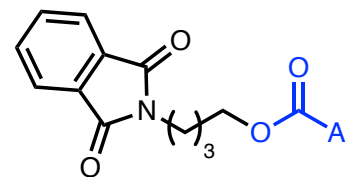
Selected examples:



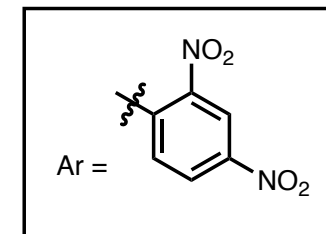
79% yield



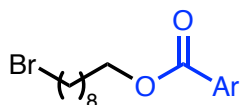
53% yield



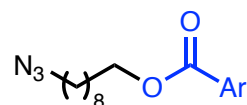
85% yield



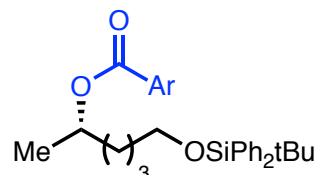
Phosphine-sensitive substrates



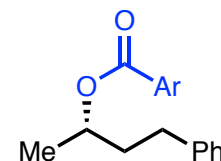
59% yield



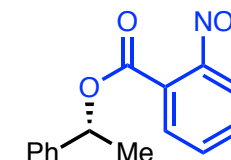
79% yield



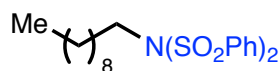
86% yield  
alcohol: 99% e.e. (R)  
product: 97% e.e. (S)



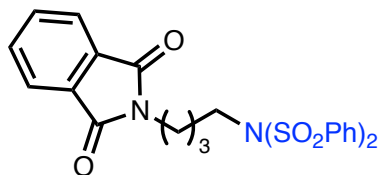
82% yield  
alcohol: 92% e.e. (R)  
product: 91% e.e. (S)



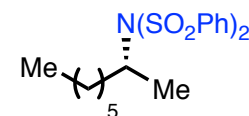
92% yield<sup>a,b,c</sup>  
alcohol: 99% e.e. (R)  
product: 85% e.e. (S)



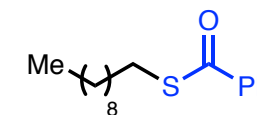
83% yield



88% yield



42% yield<sup>b,c</sup>  
alcohol: 99% e.e. (R)  
product: 92% e.e. (S)



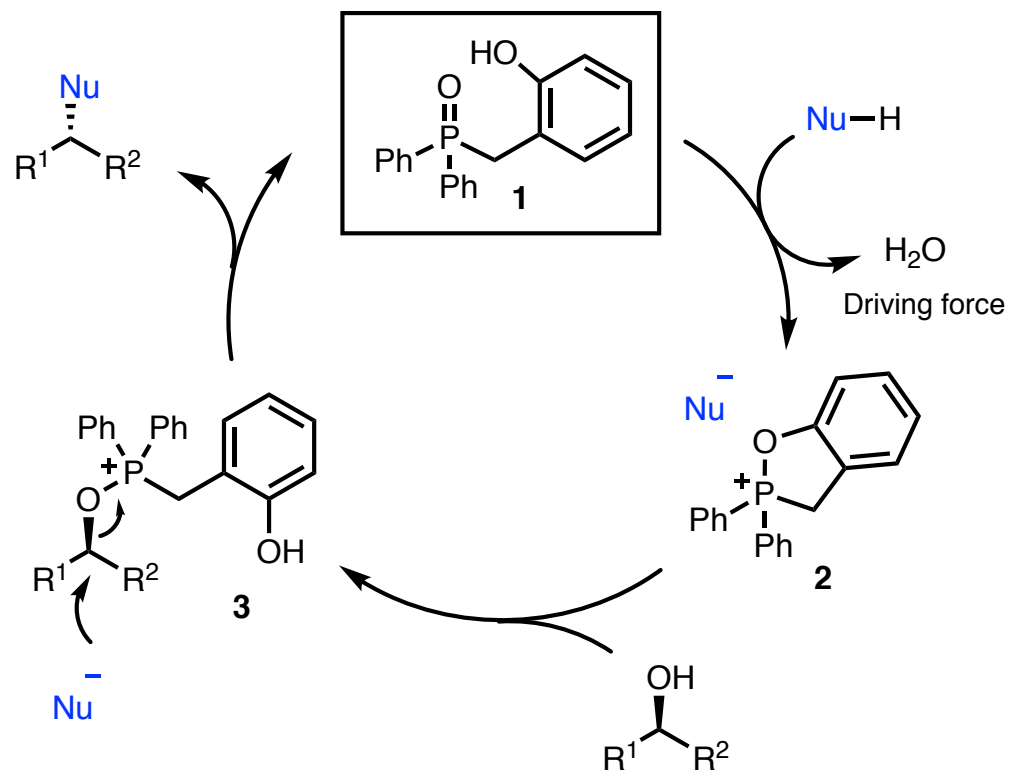
35% yield<sup>d</sup>

Denton, R. M. *Science*. **2019**, 365, 910–914.

# Redox-Neutral Phosphine Oxide Catalysis

Designing the specific catalyst: a catalytic Mitsunobu reaction

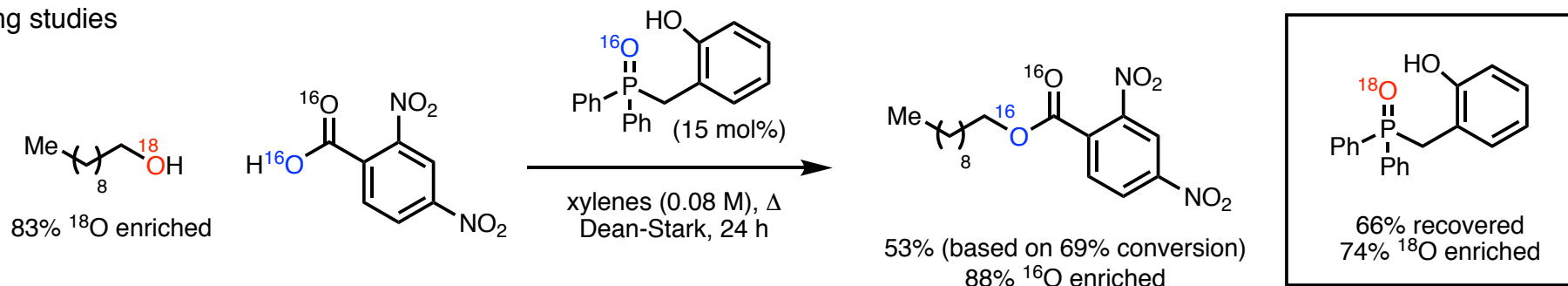
Proposed Mechanism:  
Redox-neutral dehydration platform



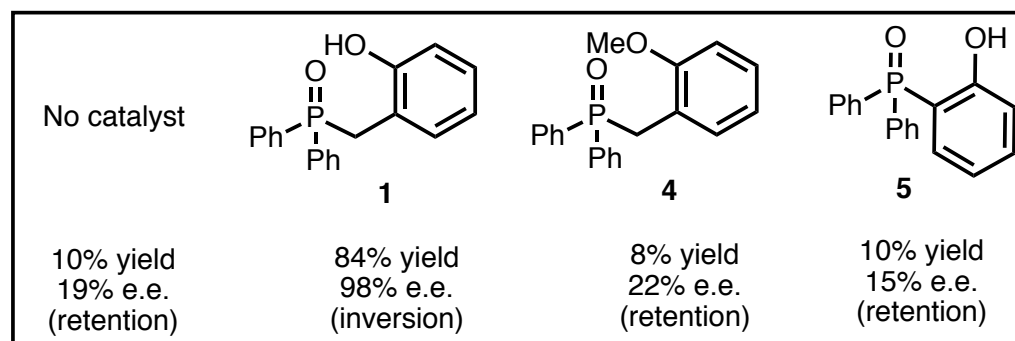
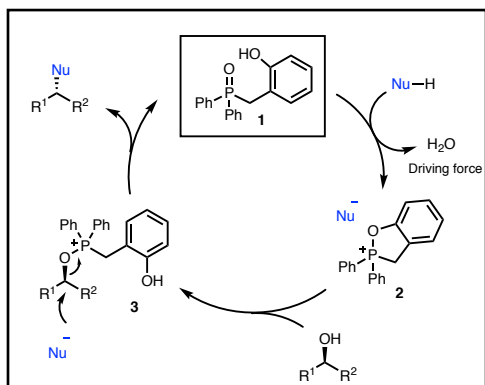
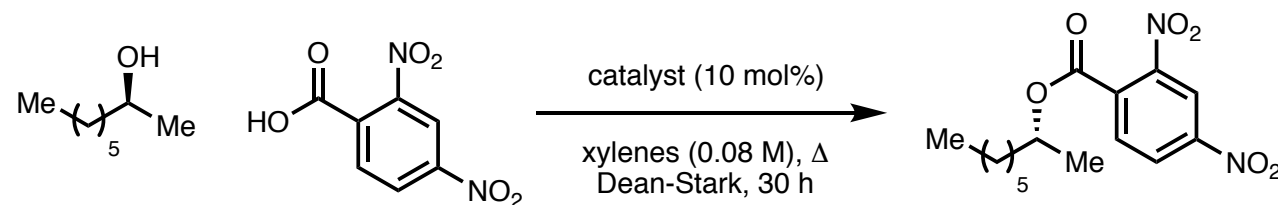
# Redox-Neutral Phosphine Oxide Catalysis

Designing the specific catalyst: a catalytic Mitsunobu reaction

## 1) Labelling studies



## 2) Catalyst structure activity relationship

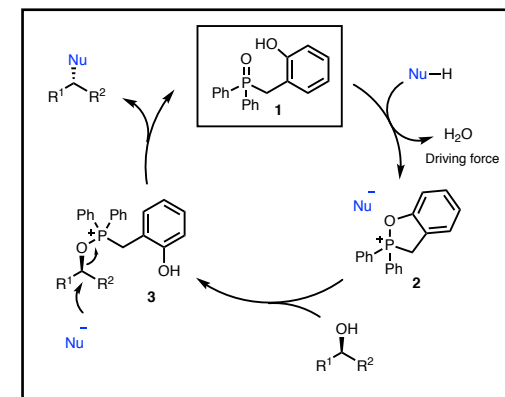
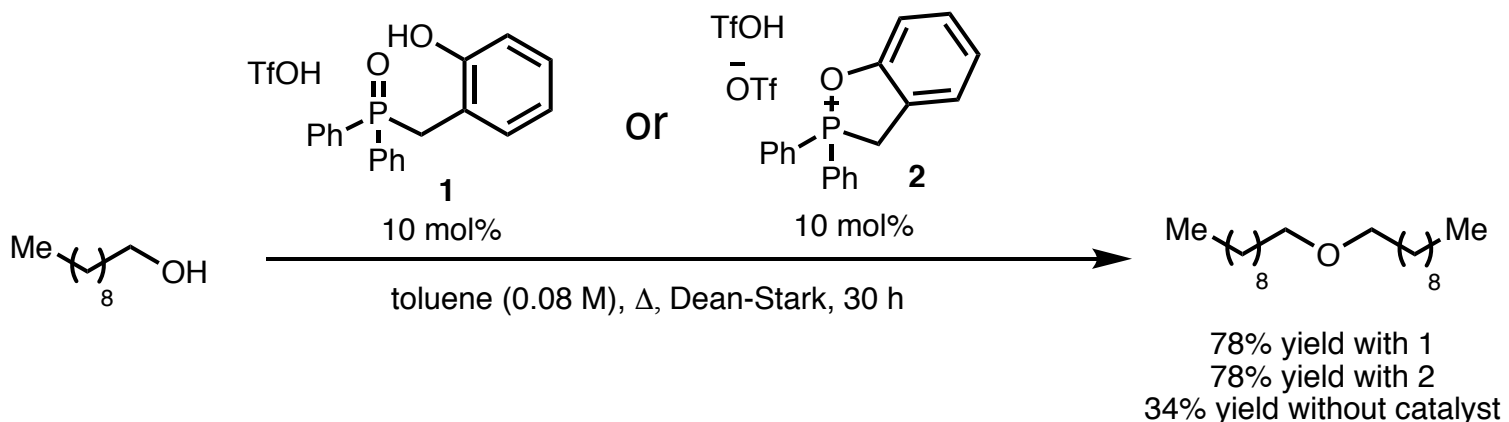
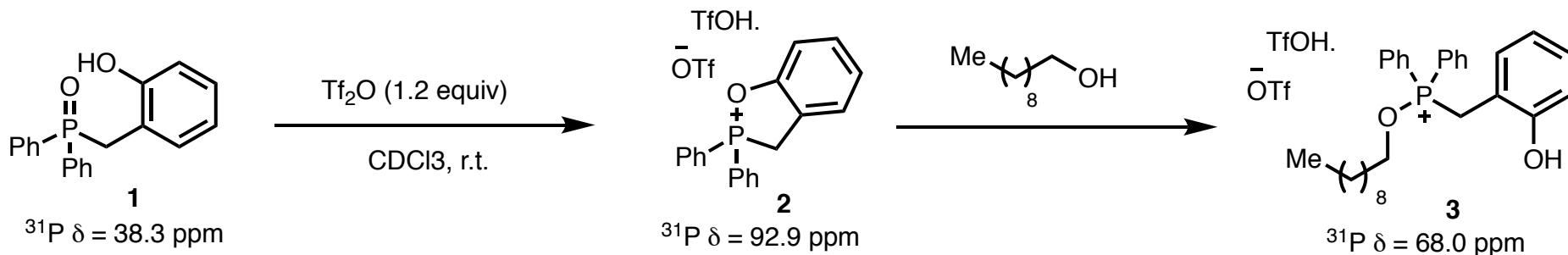


Denton, R. M. *Science*. **2019**, *365*, 910–914.

# Redox-Neutral Phosphine Oxide Catalysis

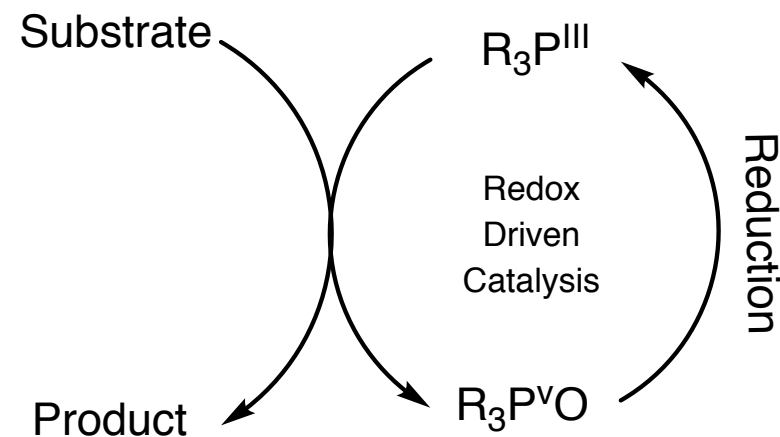
Designing the specific catalyst: a catalytic Mitsunobu reaction

## 3) Validation of catalytic intermediates



Denton, R. M. *Science*. **2019**, *365*, 910–914.

# Development of $P^{III}/P^V=O$ Redox Cycling



Challenging chemistry:

- Phosphine oxygen bond is strong so hard to reduce
- High number of report of phosphine oxide reduction (Borane Electroreduction, Metal hydrides, Metals, Silanes..)
- However: very few methods are applicable to organic synthesis (compatibly / loss of optical purity)
- Silanes: the most selective reducing agent

For reviews:

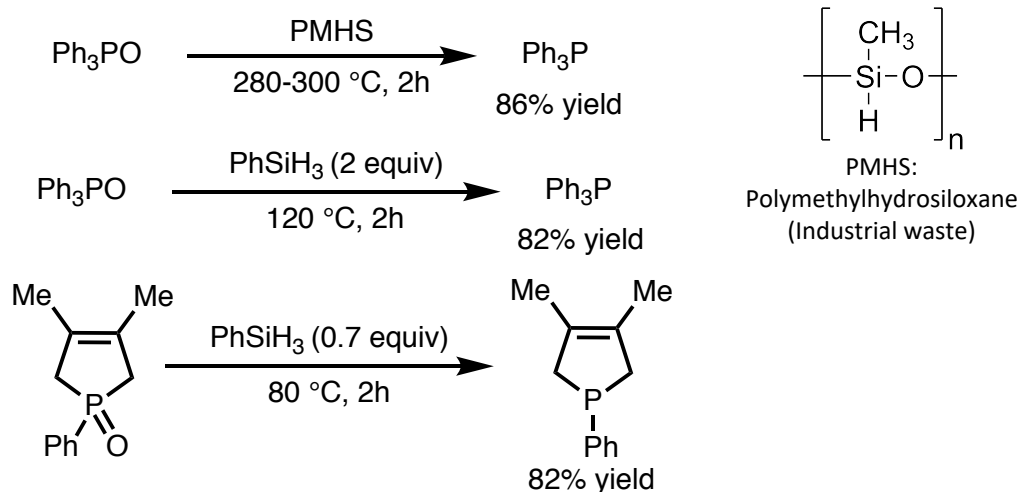
Rutjes, F. P. J. T. *ChemSusChem*. **2013**, 1615–1624.

Buono, G. *Chem. Soc. Rev.* **2015**, 44, 2508–2528.

Chusov, D. *Tetrahedron Lett.* **2019**, 60, 575–582.

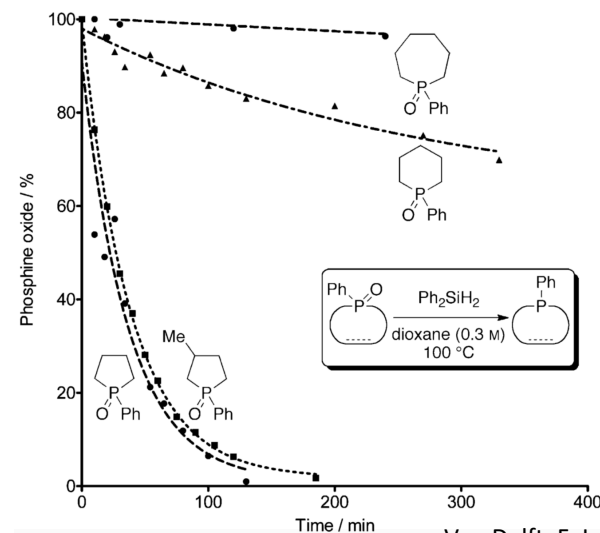
# Development of $P^{III}/P^V=O$ Redox Cycling

- First report as early as 1964 (Fritzsche)



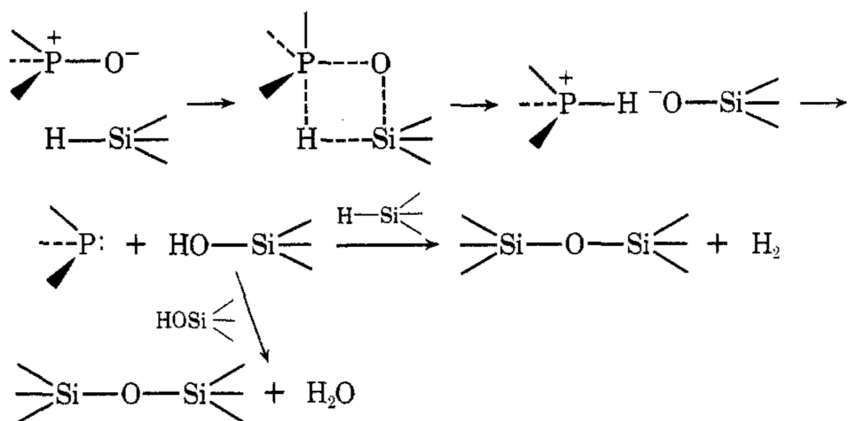
Fritzsche, et al. *Chem. Ber.* **1964**, 97, 1988 – 1993.

- Strained phosphine oxides are easier to reduce



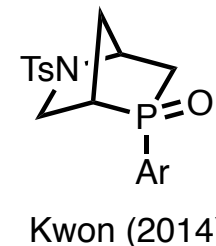
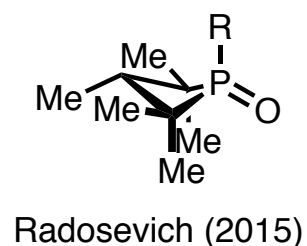
Van Delft, F. L. *Chem.- A Eur. J.* **2011**, 17, 11290–11295.

- No optical purity erosion of catalysts



Marsi, K. L. *J. Org. Chem.*, **1974**, 39, 265–267.

- New generation of phosphine oxide catalysts



- Available
- Highly strained
- Easy reduction
- Active
- Good enantioselectivity

McBride, J.J. *J. Org. Chem.* **1962**, 27, 606.

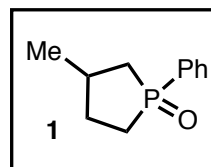
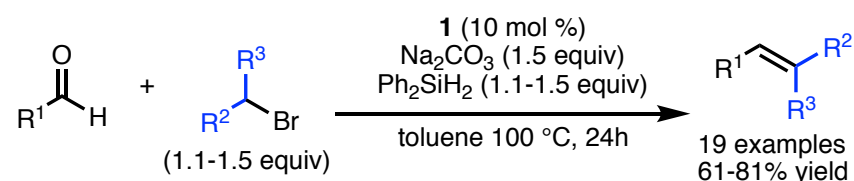
Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, 137, 616–619.

Kwon, O. *J. Am. Chem. Soc.* **2014**, 136, 11890–11893

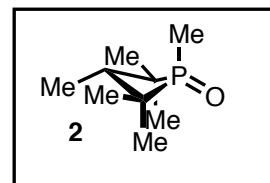
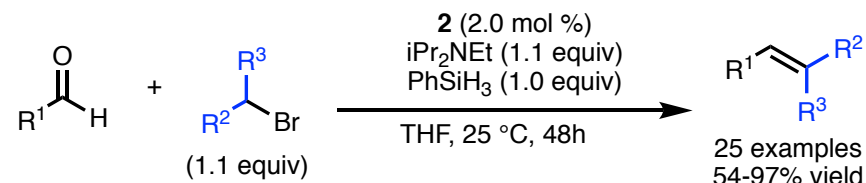
# Development of P<sup>III</sup>/P<sup>V</sup>=O Redox Cycling

A platform for improvement of existing methodologies : evolution of the Wittig reaction

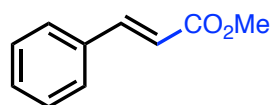
## A. Pioneering work of O'Brien (2009)



## B. Most recent paper (2019)

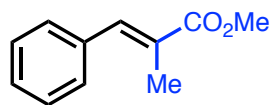


Selected examples:



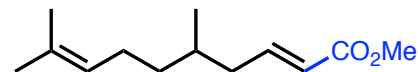
A: 74% yield, >95:5

B: 97% yield, 93:7<sup>a</sup>



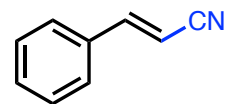
A: 77% yield, 83:17

B: 54% yield, >95:5



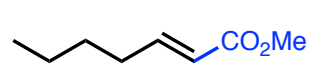
A: 65% yield, >95:5

B: 69% yield, >95:5



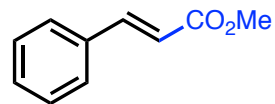
A: 80% yield, 75:25

B: 60% yield, 94:6



A: 68% yield, >95:5

B: 66% yield, >95:5

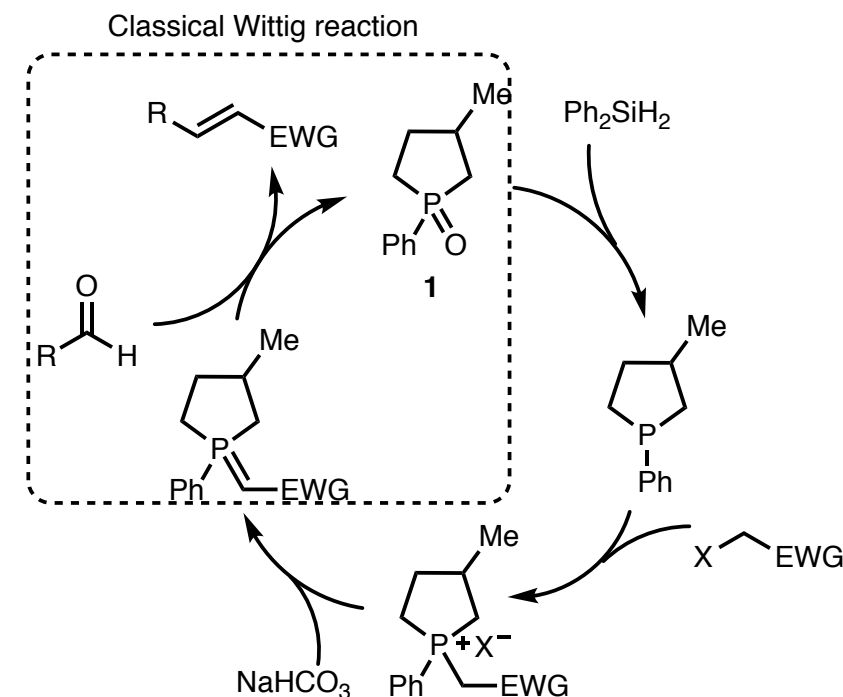


A: 68% yield, >95:5, Cl

B: 90% yield, 94:6, Cl

<sup>a</sup> For each product the compound number, yield, E/Z ratio, and halide are given.

## Proposed Mechanism:



O'Brien, C. J. *Angew. Chemie - Int. Ed.* **2009**, *48*, 6836–6839.

Van Delft, F. L. *Chem. - A Eur. J.* **2011**, *17*, 11290–11295.

O'Brien, C. J. *Chem. - A Eur. J.* **2013**, *19*, 15281–15289.

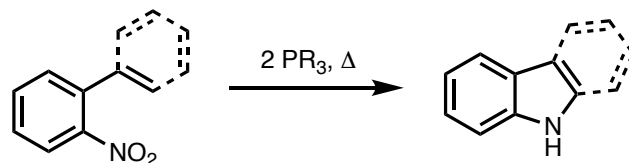
Werner, T. *ACS Catal.* **2019**, *9*, 9237–9244.



# Development of P<sup>III</sup>/P<sup>V</sup>=O Redox Cycling

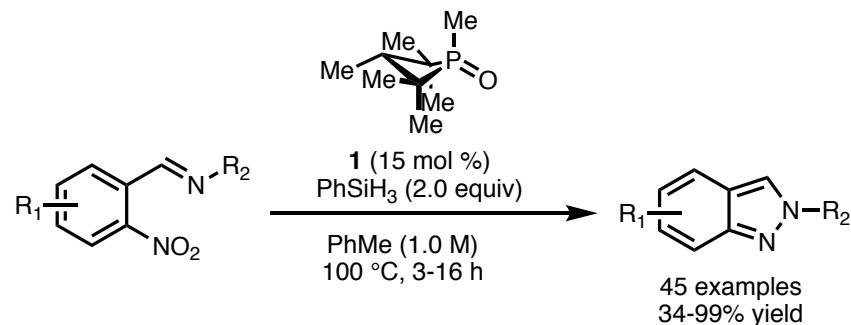
A platform for improvement of existing methodologies: the Cadogan cyclization

Classical Cadogan cyclization (1965)

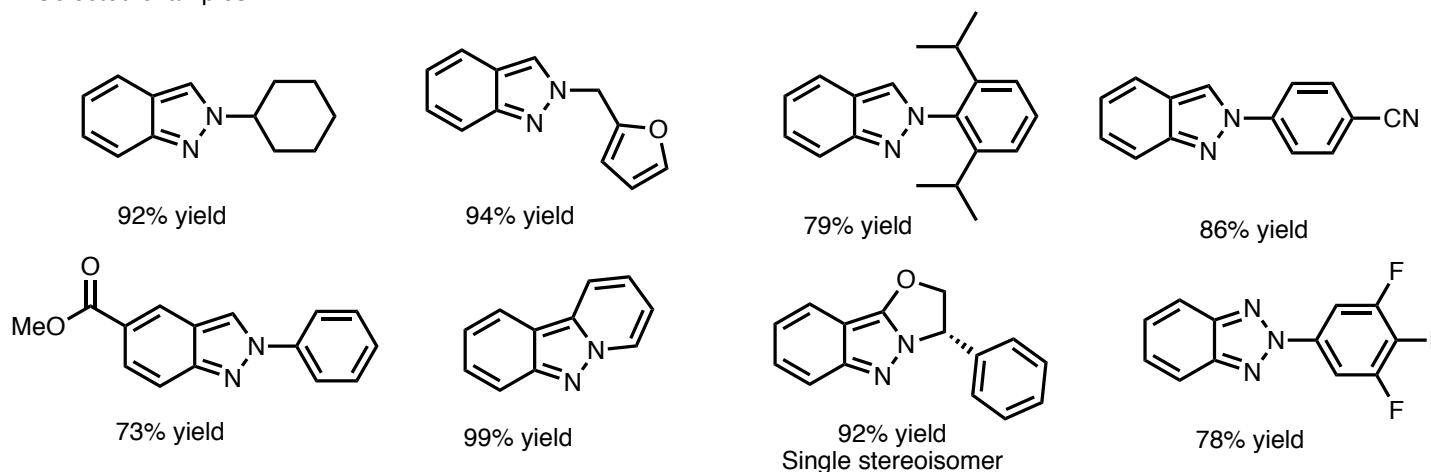


- Superstoichiometric amount of phosphorous reagent
- Harsh conditions (neat refluxing of triethylphospite)

Radosevich work (2017): Cadogan for heterocyclization



Selected examples:

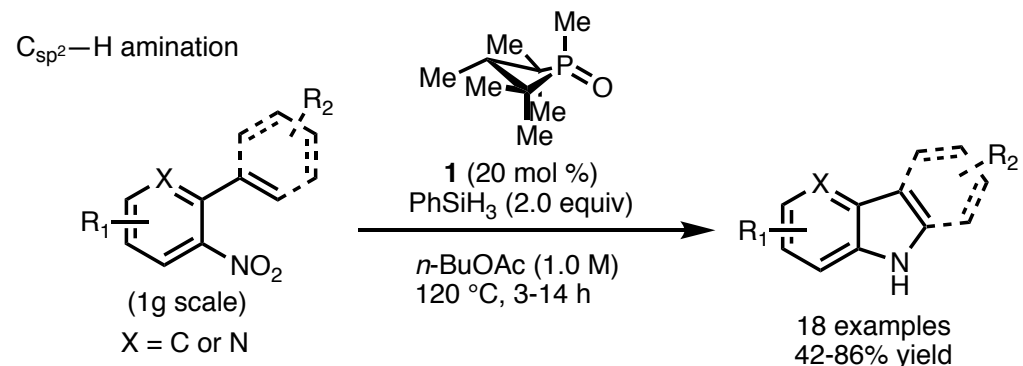


Kadogan J. I. G. *J. Chem. Soc.*, **1965**, 4831-4837

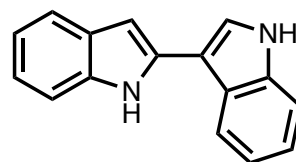
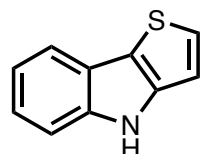
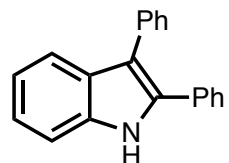
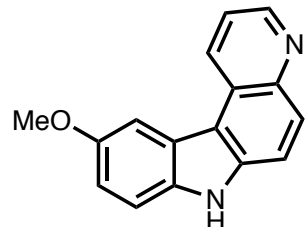
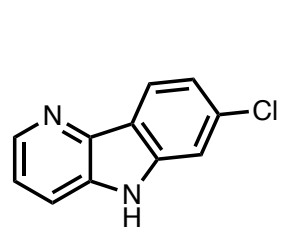
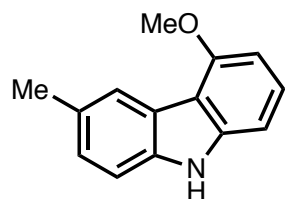
Radosevich, A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6839-6842

# Development of P<sup>III</sup>/P<sup>V</sup>=O Redox Cycling

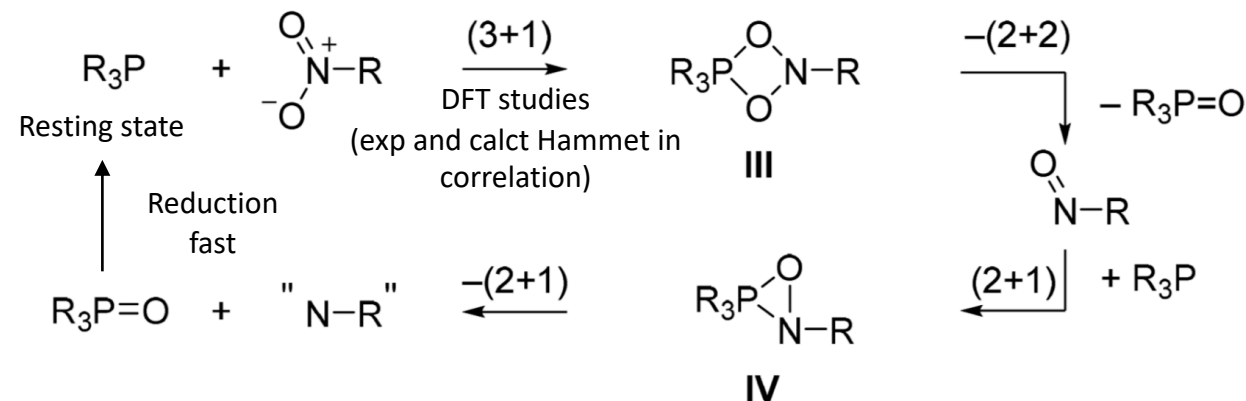
A platform for improvement of existing methodologies: the Cadogan cyclization



Selected examples:



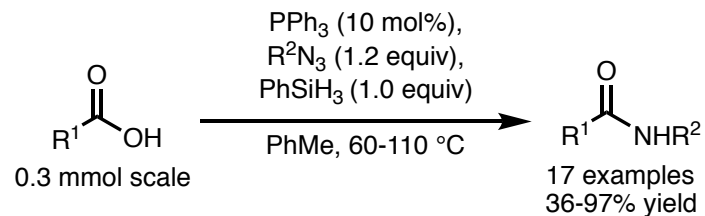
## Proposed mechanism



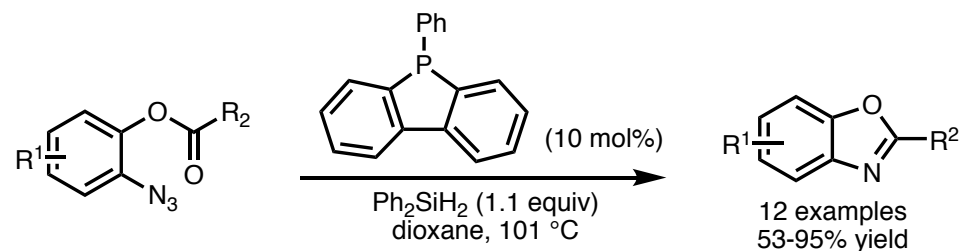
# Development of P<sup>III</sup>/P<sup>V</sup>=O Redox Cycling

A platform for improvement of existing methodologies: Overview

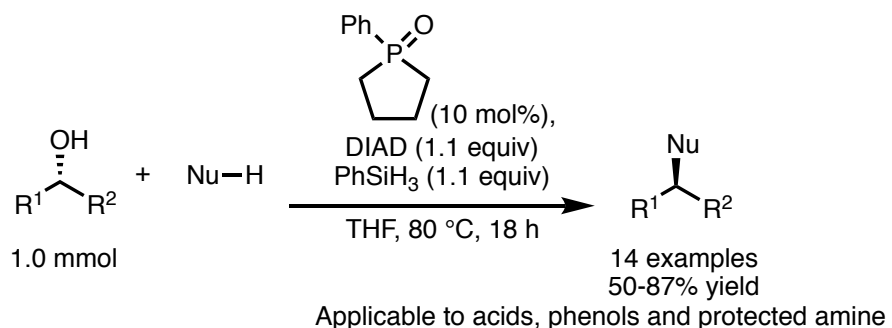
Catalytic Staudinger Ligation of Carboxylic Acids and Azides (2012)



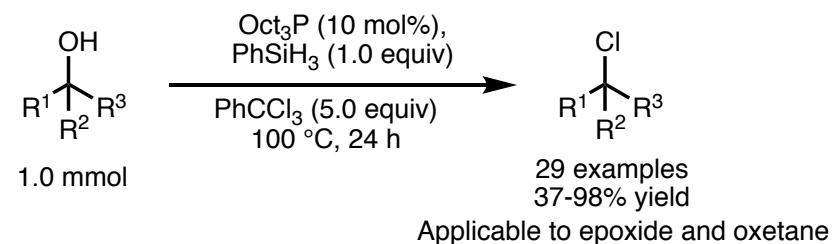
Catalytic Staudinger/Aza-Wittig sequence (2013)



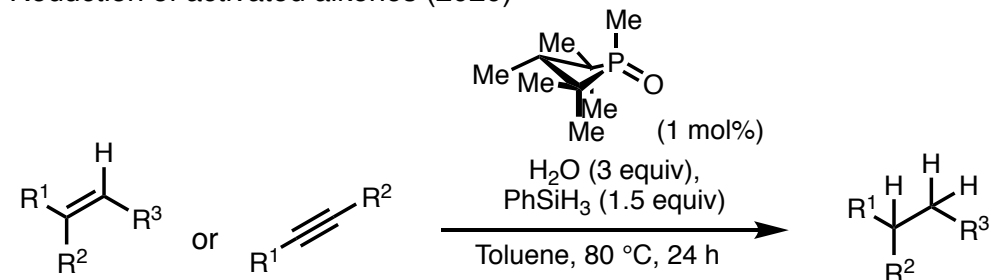
A catalytic Mitsunobu reaction (2015)



A catalytic solvent-free Appel reaction (2019)



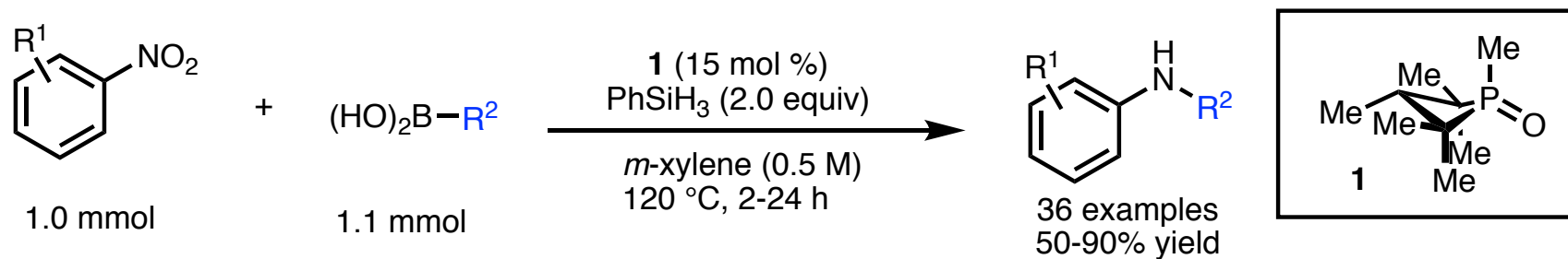
Reduction of activated alkenes (2020)



Ashfeld, B. L. *Angew. Chemie - Int. Ed.* **2012**, *51*, 12036–12040.  
Van Delft, F. L. *European J. Org. Chem.* **2013**, No. 31, 7059–7066.  
Aldrich, C. C. *Angew. Chemie - Int. Ed.* **2015**, *54*, 13041–13044.  
Werner, T. J. *Org. Chem.* **2019**, *84*, 7863–7870.  
Werner, T. *Angew. Chemie - Int. Ed.* **2020**, *59*, 2760–2763.

# Development of $P^{III}/P^V=O$ Redox Cycling

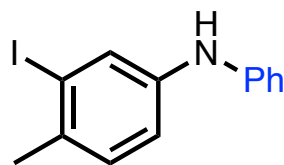
Development of new methods: New reaction of C-N cross-coupling (2018)



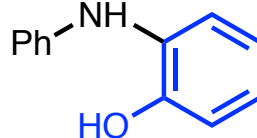
Selected examples:



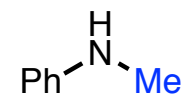
71% yield



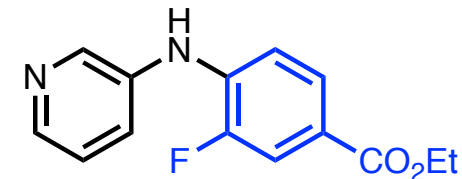
86% yield



56% yield



50% yield



56% yield

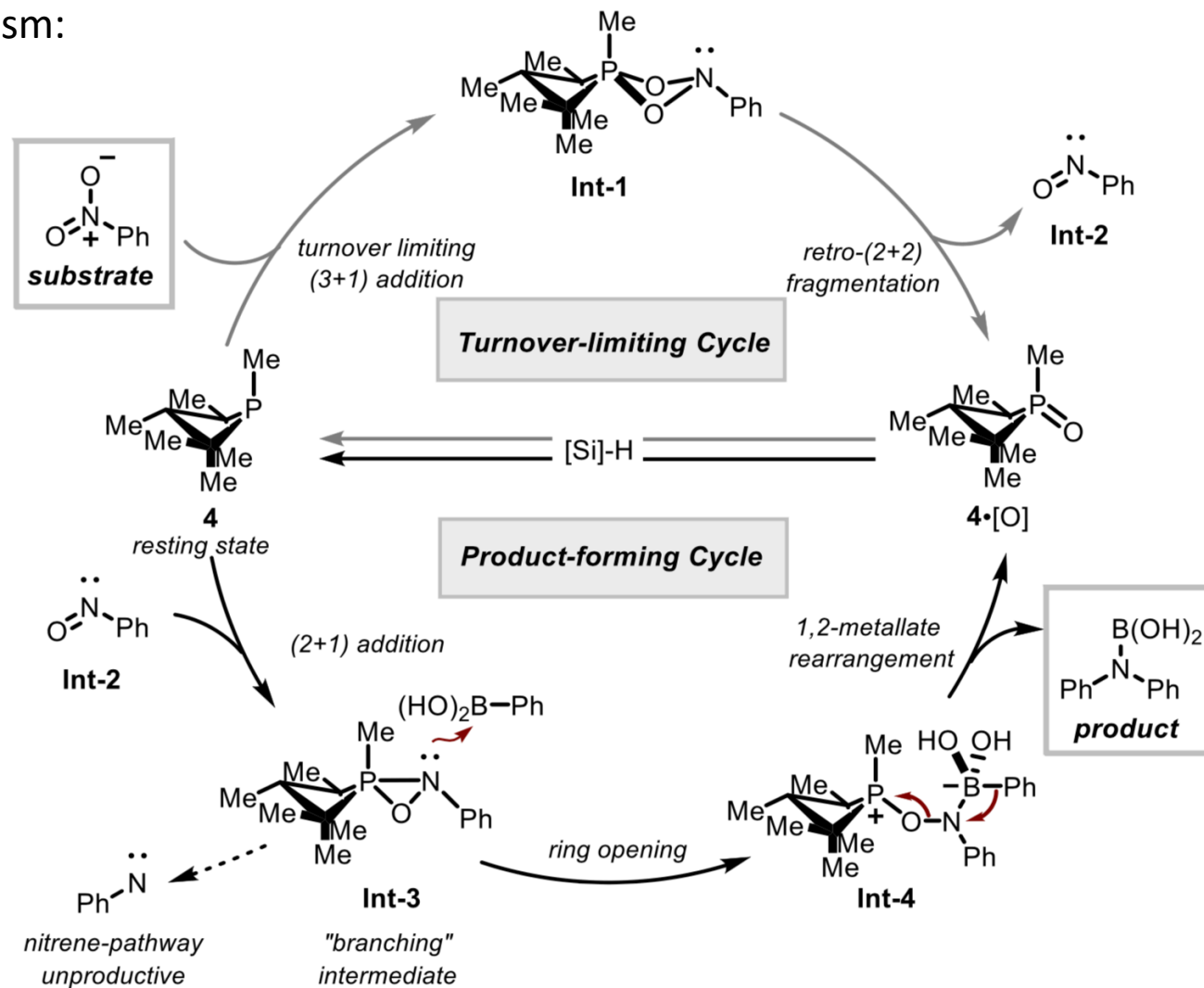
- Metal free cross-coupling
- Orthogonal to other methods
- Can be followed by intramolecular cyclization: highly functionalized indoles, oxindoles, benzimidazoles and quinoxalinediones
- Another paper showed improved conditions: PMHS (6 equiv) and CPME (0.25 M)

Radosevich, A. T. *J. Am. Chem. Soc.* **2018**, *140*, 15200–15205.  
Radosevich, A. T. *Angew. Chemie - Int. Ed.* **2020**, *59*, 4505–4510.  
Radosevich, A. T. *J. Am. Chem. Soc.* **2020**, *142*, 6786–6799

# Development of $P^{III}/P^V=O$ Redox Cycling

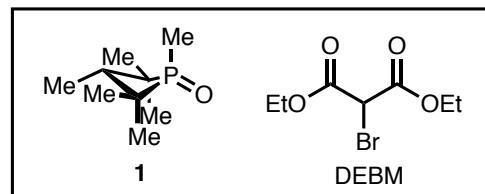
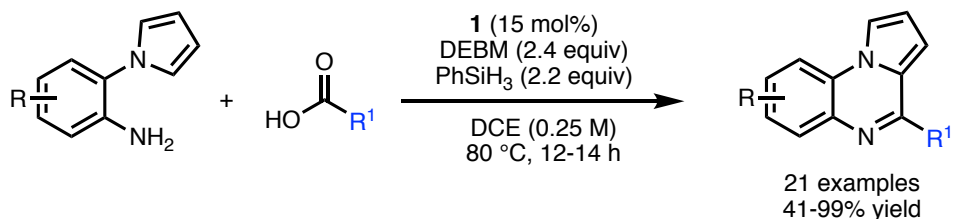
Development of new methods: New reaction of C-N cross-coupling (2018)

Proposed mechanism:

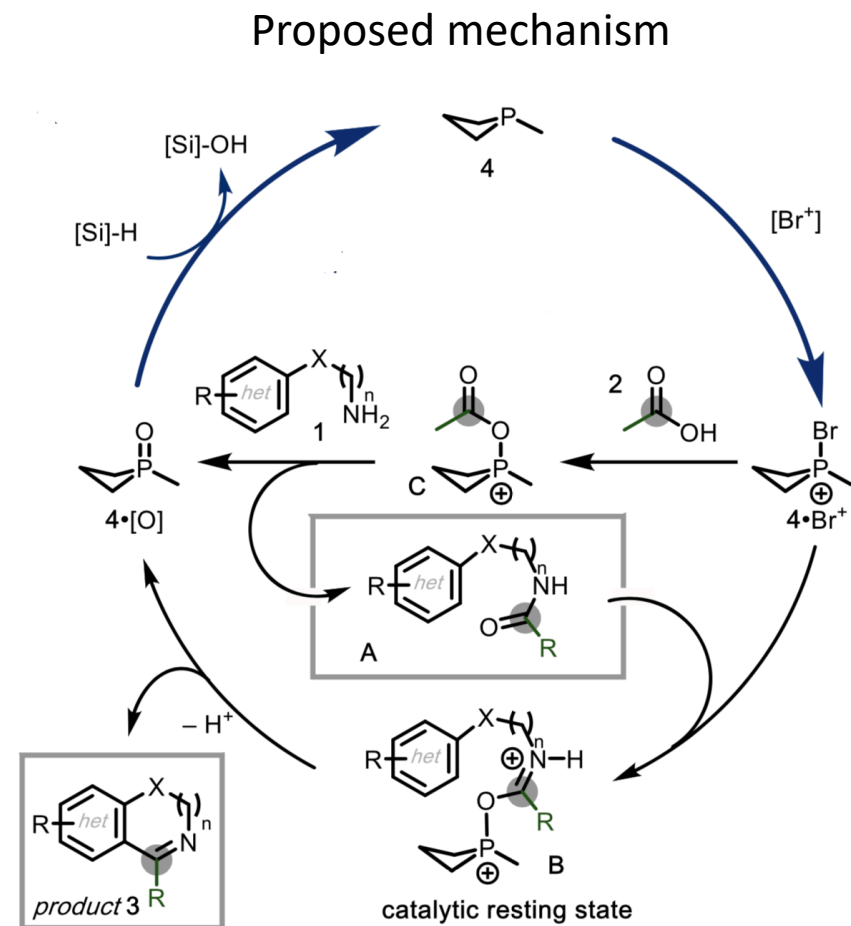
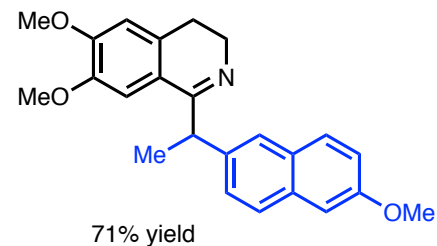
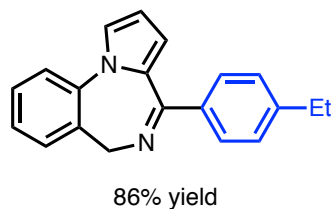
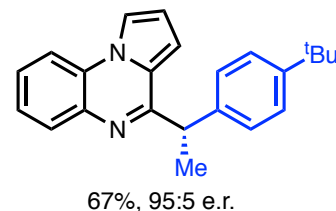
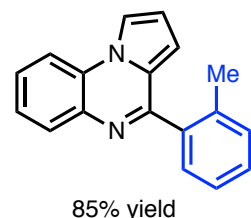
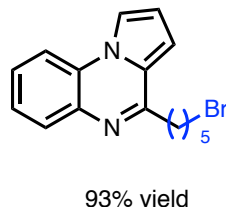
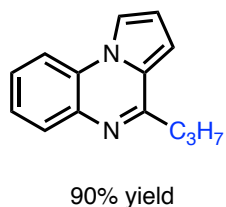


# Development of P<sup>III</sup>/P<sup>V</sup>=O Redox Cycling

Development of new methods: Annulation of amines with carboxylic acids



selected examples:

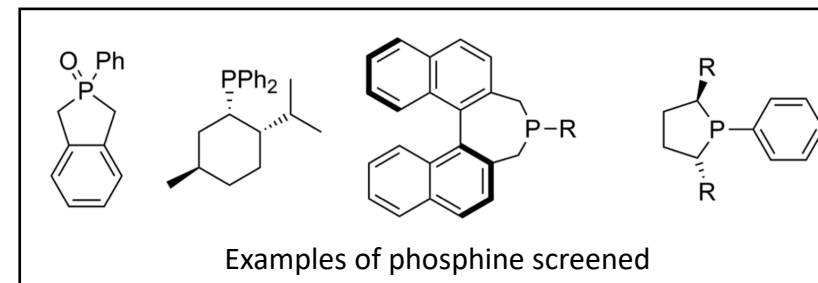
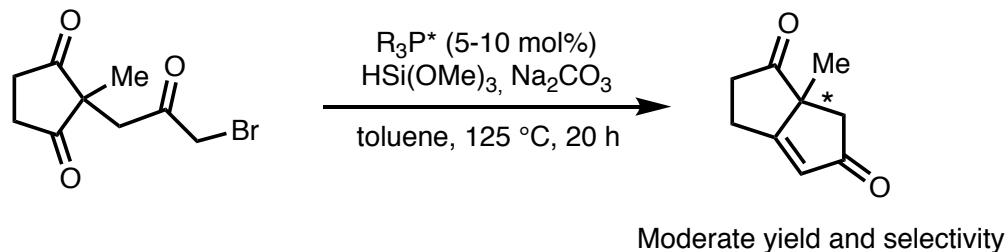


Radosevich, A. T. *J. Am. Chem. Soc.* **2019**, *141*, 12507–12512

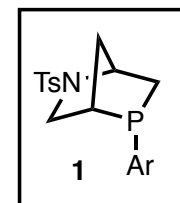
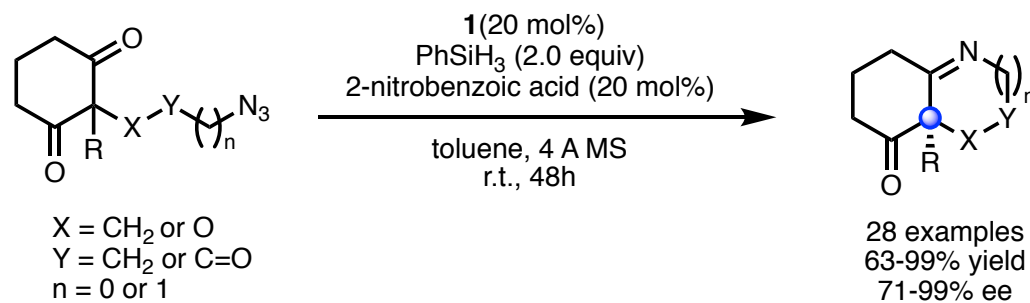
# Development of $P^{III}/P^V=O$ Redox Cycling

The emergence of enantioselective processes

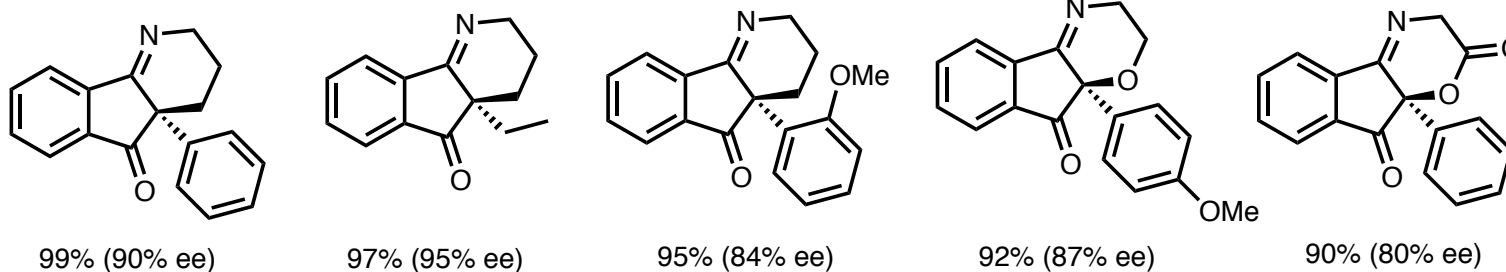
First enantioselective catalytic Wittig reaction (2014)



Catalytic Staudinger/aza Wittig reaction (2019)



Selected examples

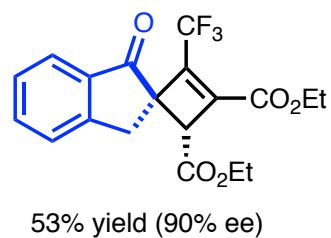
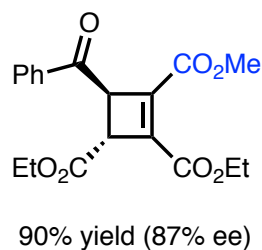
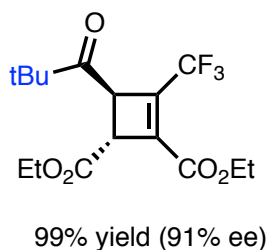
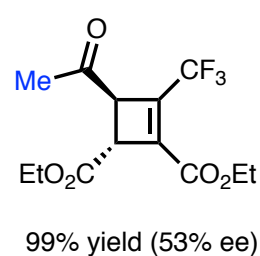
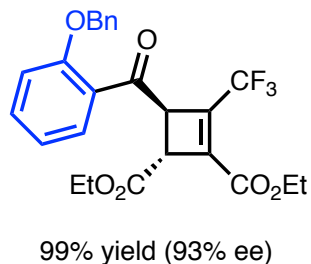
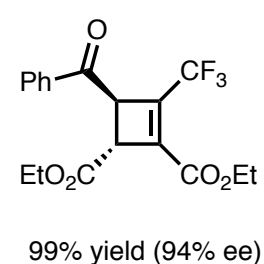
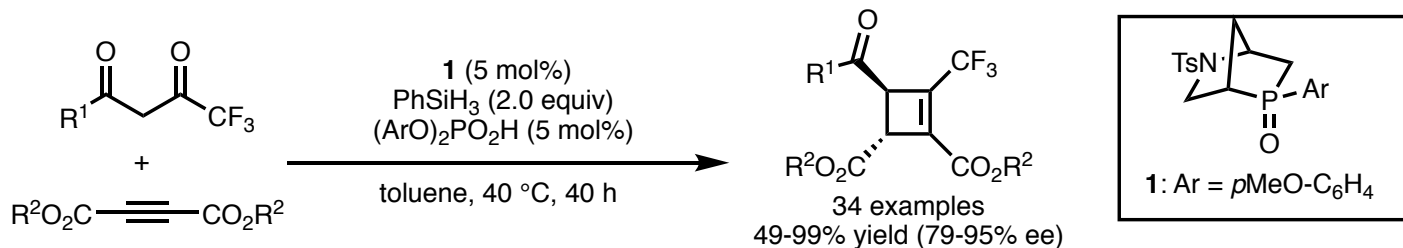


Werner, T. *European J. Org. Chem.* **2014**, 2014, 6630–6633.  
Kwon, O. *J. Am. Chem. Soc.* **2019**, 141, 9537–9542.

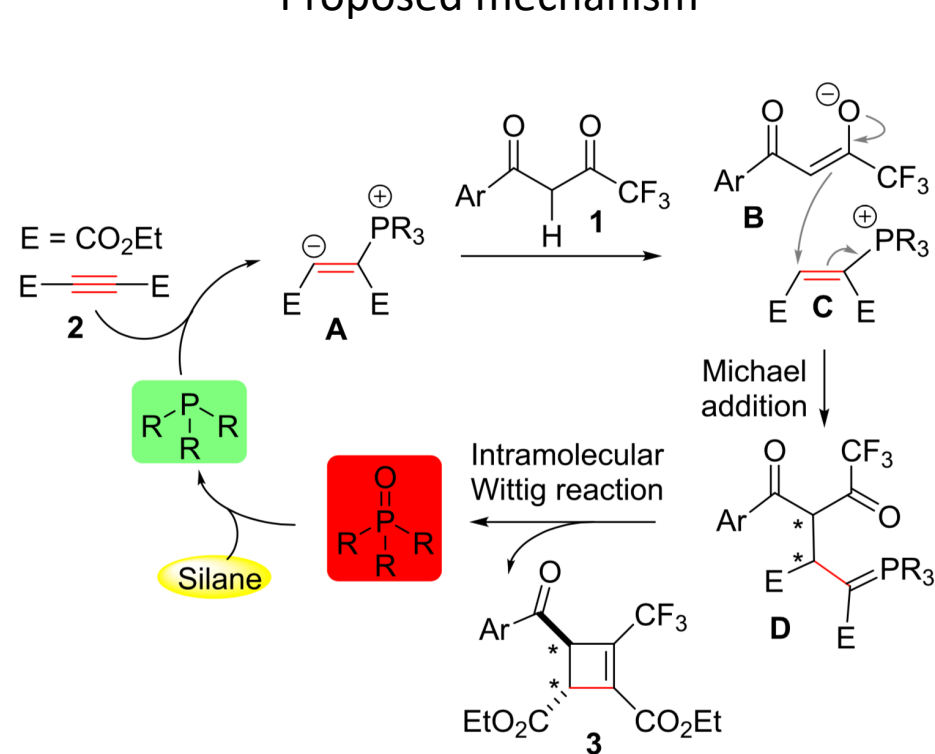
# Development of $P^{III}/P^V=O$ Redox Cycling

The emergence of enantioselective processes

Asymmetric process via a Michael addition/Wittig (2019)



Proposed mechanism

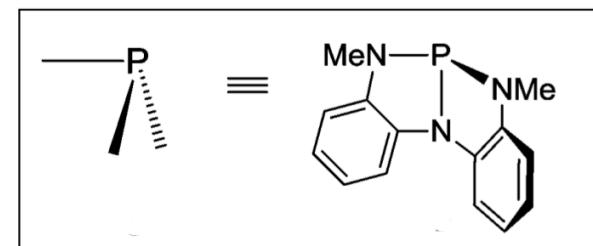
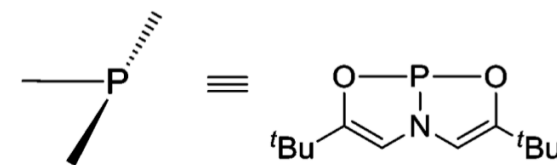


Voituriez, A. *J. Am. Chem. Soc.* **2019**, *141*, 10142–10147.

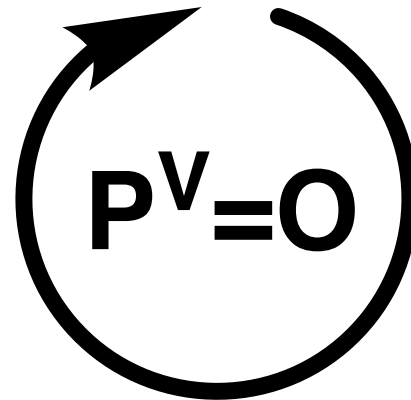


# Conclusion: Phosphine Oxide Catalysis

- Improvement of existing methods: important potential for **industrial use** + **environmental issues**
- Development of **innovative reactions** as well as new **enantioselective transformations**
- Holy Grail: universal use of **PMHS** as a reducing agent
- Future of Phosphorous catalysis: possible use as a catalyst with **elementary steps** like metals (oxidative addition, reductive elimination..)

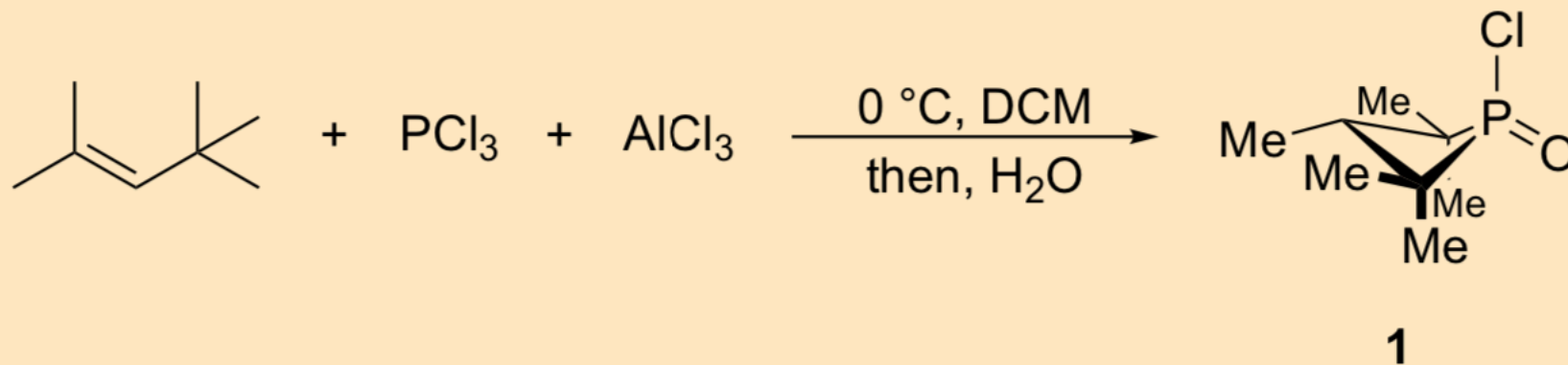


-Thank you for your attention-  
Any question?

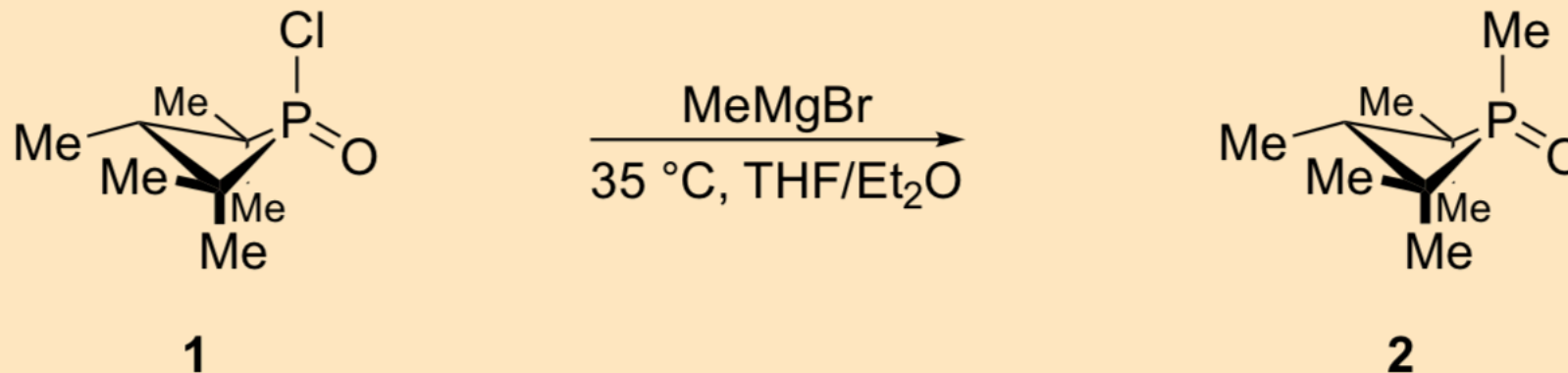


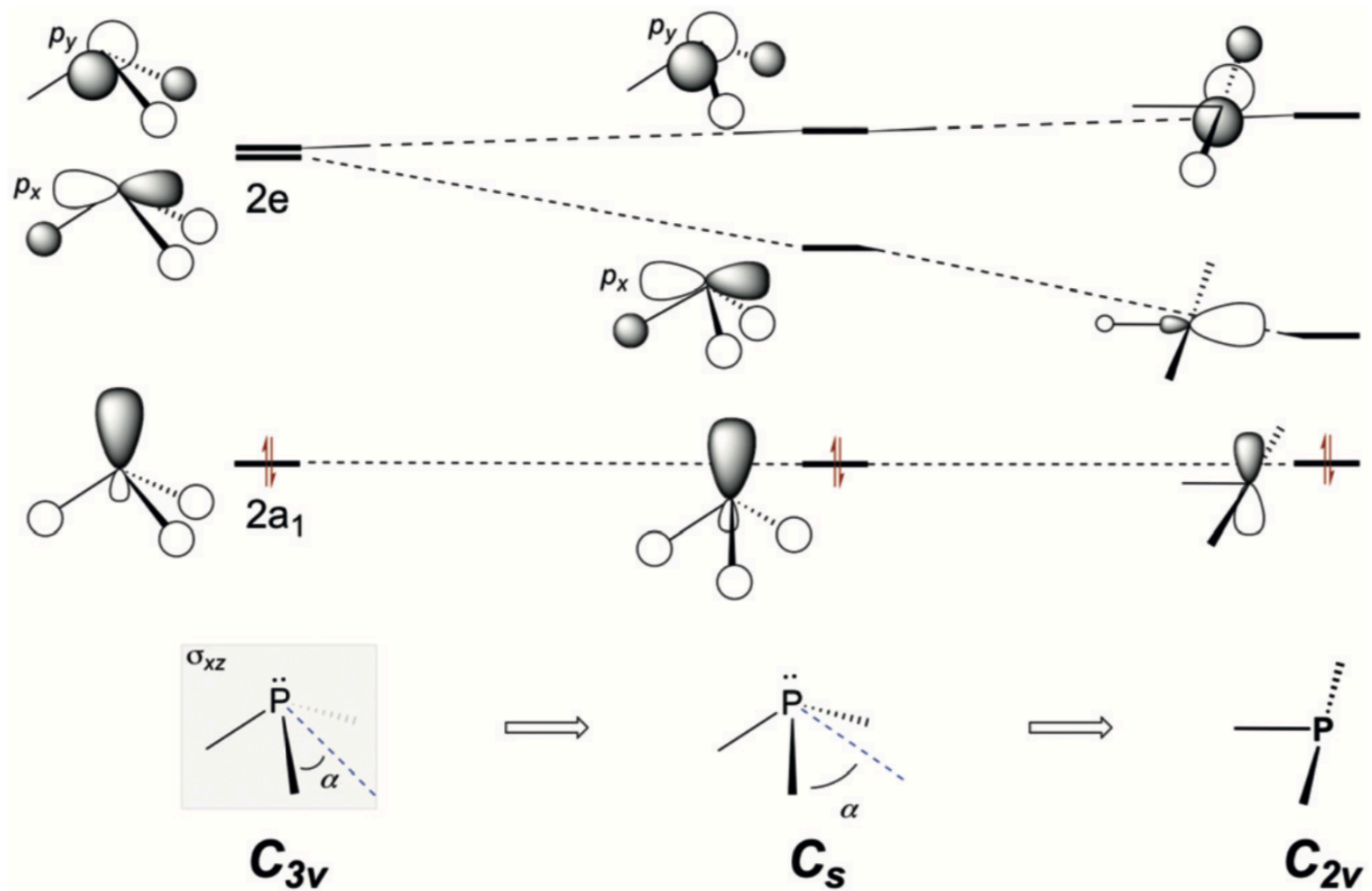
# Preparation of phosphetane oxide catalysts

A.



B.





**Figure 4.** Qualitative frontier molecular orbital diagrams depicting the electronic structure arising from nontrigonal perturbation of a model  $\sigma^3$ -P compound.