Progress in Phosphine Oxide Catalysis

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PLAN

• Generalities about Phosphorous
• Redox-Neutral Phosphine Oxide Catalysis
• Development of $\text{P}^{\text{III}}/\text{P}^{\text{V}=\text{O}}$ 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: 1S² 2S² 2P⁶ 3S² 3P⁶ 3D⁰
  - larger than Nitrogen
  - vacant orbitals are accessible
- Hypervalency (penta, hexa and even hepta) possible

Valence & VSEPR:

- 3 trigonal pyramidal
- 4 tetrahedral
- 5 tetrahedral
- 5 trigonal pyramidal
- 6 octahedral
Generalities about Phosphorous

Phosphines

\[ \begin{align*}
\text{Ph} & \quad \text{Me} \\
R & \quad P \quad R \\
R & \quad R
\end{align*} \]

- Very good nucleophile
- P-chiral phosphines exist but can racemize
- \( E_A = 33 \text{ kcal/mol} \) (100 °C)

Phosphine oxides

\[ \begin{align*}
\text{O} & \\
R & \quad P \quad R \\
R & \quad R
\end{align*} \]

- 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

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 N₂ or CO₂).

- **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

1st example of phosphine catalysis in 1962 (Campbell): conversion of Isocyanates to Carbodiimides

\[
\text{R}^1\text{N}=\text{C}=\text{O} \quad \text{R}^1 = \text{Ar}, \text{alkyl} \quad \text{R}^2 = \text{Me}, \text{Et}
\]

0.1 wt% neat, toluene or xylene, r.t. - 150 °C

\[
\text{R}^1\text{N}=\text{C}=\text{N}-\text{R}^1
\]

14 examples yield 52 - 99%

Driving force

2nd example almost 50 years after (Marsden): intramolecular method

\[
\text{R}^1\text{N}=\text{C}=\text{O} \quad \text{R}^1\text{N}=\text{PR}_3
\]

VIA

15 examples yield 45 - 87%

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

Ding, M. W. Synthesis 2015, 47, 3522-3528.

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

Transformation discovered by Masaki and Fukui (1977)

Redox-Neutral Phosphine Oxide Catalysis

Using the ideal co-reagent

Dichlorination of Epoxides (2010)

\[
\begin{align*}
R^1\bigg\|_{\text{O}}^\text{O} \quad & \quad \text{R}^2 \\
\text{R}^1, R^2 = \text{Alk, Ar} \\
\text{Ph}_3\text{PO} & \quad (15 \text{ mol} \ %) \\
& \quad (\text{COCl})_2 \quad (1.3 \text{ equiv}) \\
& \quad 2,6\text{-BuPy} \quad (1.5 \text{ equiv}) \\
\xrightarrow{\text{CHCl}_3, \text{rt}} \\
\text{or C}_6\text{H}_6, 80 \text{ °C} \\
\rightarrow \\
\text{Cl} \quad \text{Cl} \\
\text{R}^1 \quad \text{R}^2 \\
10 \text{ examples,} \\
56-91\% \text{ yield}
\end{align*}
\]

Stereoselective 1,3 Dichlorination of Unsaturated Ketoesters (2014)

\[
\begin{align*}
\text{Ar} & \quad \text{O} \quad \text{CO}_2\text{Me} \\
& \quad 4\text{A MS, DCE} \\
& \quad \text{reflux, 24 h} \\
\xrightarrow{\text{Ph}_3\text{PO} \quad (10 \text{ mol} \ %)} \\
& \quad (\text{COCl})_2 \quad (3.4 \text{ equiv}), \\
\rightarrow \\
\text{Cl} \quad \text{Cl} \\
\text{Ar} \quad \text{Cl} \quad \text{CO}_2\text{Me} \\
18 \text{ examples} \\
\text{yield} 42-93\%
\end{align*}
\]

Dehydration of Amides to Nitriles (2018)

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\
\rightarrow \\
\text{MeCN, rt, 10 min} \\
\rightarrow \\
\text{R} \quad \text{N} \\
\text{R} = \text{Alk, Ar} \\
18 \text{ examples} \\
80\text{-}98\% \text{ yield}
\end{align*}
\]

Redox-Neutral Phosphine Oxide Catalysis

Designing the specific catalyst: a catalytic Mitsunobu reaction

\[
\begin{align*}
\text{R}_1\text{R}_2\text{OH} + \text{Nu-H} & \xrightarrow{\text{1 (10 mol\%)} \quad \text{toluene or xylenes, } \Delta \quad \text{Dean-Stark, 16-120 h}} \text{Nu} \quad \text{R}_1\text{R}_2
\end{align*}
\]

32 examples

Selected examples:

- 79% yield
- 53% yield
- 85% yield
- 79% yield
- 86% yield
- 82% yield
- 92% yield
- 83% yield
- 88% yield
- 42% yield
- 35% yield

Phosphine-sensitive substrates

- Portion-wise addition of the acid.
- 25 mol % of catalyst used.
- 2 equivalent of alcohol used.
- 20 mol % of catalyst used.

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

18O enriched

53% (based on 69% conversion)
88% 18O enriched

2) Catalyst structure activity relationship

84% yield 19% e.e. (retention)
22% e.e. (inversion)
10% yield 15% e.e. (retention)

No catalyst

Redox-Neutral Phosphine Oxide Catalysis
Designing the specific catalyst: a catalytic Mitsunobu reaction

3) Validation of catalytic intermediates

\[
\begin{align*}
& \text{HO} \text{P} \text{O} \text{Ph} \text{Ph} \quad 1 \\
& \quad 31P \delta = 38.3 \text{ ppm}
\end{align*}
\]

\[
\begin{align*}
& \text{Tf}_2\text{O} (1.2 \text{ equiv}) \\
& \text{CDCl}_3, \text{ r.t.}
\end{align*}
\]

\[
\begin{align*}
& \text{HO} \text{P} \text{O} \text{Ph} \text{Ph} \quad 2 \\
& \quad 31P \delta = 92.9 \text{ ppm}
\end{align*}
\]

\[
\begin{align*}
& \text{TfOH} \quad \text{OTf} \\
& \text{MeOH}
\end{align*}
\]

\[
\begin{align*}
& \text{Me} \text{OH} \quad 8 \\
& \quad 31P \delta = 68.0 \text{ ppm}
\end{align*}
\]

\[
\begin{align*}
& \text{HO} \text{P} \text{O} \text{Ph} \text{Ph} \quad 3 \\
& \quad \text{78\% yield with 1}
\end{align*}
\]

\[
\begin{align*}
& \text{Me} \text{OH} \quad 8 \\
& \quad \text{78\% yield with 2}
\end{align*}
\]

\[
\begin{align*}
& \text{Me} \text{OH} \quad 8 \\
& \quad \text{34\% yield without catalyst}
\end{align*}
\]

Development of $\text{P}^{\text{III}}/\text{P}^{\text{V}=\text{O}}$ 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:
Development of P^{III}/P^{V}=O Redox Cycling

- First report as early as 1964 (Fritzsche)

  \[
  \text{Ph}_3\text{PO} \xrightarrow{\text{PMHS}} \text{Ph}_3\text{P} \quad \text{86\% yield}
  \]

  \[
  \text{Ph}_3\text{PO} \xrightarrow{\text{PhSiH}_3(2 \text{ equiv})} \text{Ph}_3\text{P} \quad \text{82\% yield}
  \]

  \[
  \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Ph}_3\text{PO} \xrightarrow{\text{PhSiH}_3(0.7 \text{ equiv})} \quad \text{Me} \quad \text{Me} \quad \text{Ph}_3\text{P} \quad \text{82\% yield}
  \]


- Strained phosphine oxides are easier to reduce

- No optical purity erosion of catalysts

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

- New generation of phosphine oxide catalysts

Development of $\text{P}^{\text{III}}/\text{P}^\text{V}=\text{O}$ Redox Cycling
A platform for improvement of existing methodologies: evolution of the Wittig reaction

A. Pioneering work of O'Brien (2009)

$$\text{R}_1^1 \text{H} + \text{R}_2^2 \text{Br} \rightarrow \text{R}_1^1 \text{R}_2^2 \text{R}_3^3$$

1 (10 mol %)
$\text{Na}_2\text{CO}_3$ (1.5 equiv)
$\text{Ph}_2\text{SiH}_2$ (1.1-1.5 equiv)
toluene 100 °C, 24h

19 examples
61-81% yield

B. Most recent paper (2019)

$$\text{R}_1^1 \text{H} + \text{R}_2^2 \text{Br} \rightarrow \text{R}_1^1 \text{R}_2^2 \text{R}_3^3$$

2 (2.0 mol %)
$i\text{Pr}_2\text{NEt}$ (1.1 equiv)
$\text{PhSiH}_3$ (1.0 equiv)
THF, 25 °C, 48h

25 examples
54-97% yield

Selected examples:

- **A**: 74% yield, >95:5
  - 77% yield, 83:17
  - 65% yield, >95:5
- **B**: 97% yield, 93:7%
  - 90% yield, 94:6
  - 69% yield, >95:5
- **A**: 80% yield, 75:25
  - 68% yield, >95:5
  - 68% yield, >95:5
- **B**: 60% yield, 94:6
  - 66% yield, >95:5
  - 90% yield, 94:6

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Proposed Mechanism:

Classical Wittig reaction


For each product the compound number, yield, E/Z ratio, and halide are given.
Development of $\text{P}^{\text{III}}/\text{P}^{\text{V}}=\text{O}$ Redox Cycling

A platform for improvement of existing methodologies: the Cadogan cyclization

Classical Cadogan cyclization (1965)

$$\text{2 PR}_3, \Delta \rightarrow$$

Radosevich work (2017): Cadogan for heterocyclization

$$\begin{align*}
\text{R}^1 & \text{N}^2 \text{R}^2 \\
\text{NO}_2 & \overset{1 \text{ (15 mol \%)} \text{ PhSiH}_3 \text{ (2.0 equiv)}}{\text{PhMe (1.0 M)}} \overset{100^\circ \text{C}, 3-16 \text{ h}}{\rightarrow} \text{R}^1 \text{N}^2 \text{R}^2
\end{align*}$$

Selected examples:

- 92% yield
- 94% yield
- 79% yield
- 86% yield
- 73% yield
- 99% yield
- 92% yield
- 78% yield

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

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

A platform for improvement of existing methodologies: the Cadogan cyclization

Selected examples:

- **77% yield**
  - ![Chemical structure](image1)

- **63% yield**
  - ![Chemical structure](image2)

- **56% yield**
  - ![Chemical structure](image3)

- **82% yield**
  - ![Chemical structure](image4)

- **58% yield**
  - ![Chemical structure](image5)

- **60% yield**
  - ![Chemical structure](image6)

Proposed mechanism:

- **Resting state**
  - ![Chemical structure](image7)

- **Reduction fast**
  - ![Chemical structure](image8)

- **DFT studies** (exp and calc Hammet in correlation)

- **oxazaphosphirane (IV)**
  - ![Chemical structure](image9)

- **observed by low temp Heteronuclear NMR**

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

A platform for improvement of existing methodologies: Overview

Catalytic Staudinger Ligation of Carboxylic Acids and Azides (2012)

\[
\begin{align*}
\text{R}^1\text{OH} & \xrightarrow{\text{PPh}_3 (10 \text{ mol%), R}^2\text{N}_3 (1.2 \text{ equiv), PhSiH}_3 (1.0 \text{ equiv})} \text{PhMe, 60-110 °C} \\
\text{R}^1\text{O} & \xrightarrow{17 \text{ examples}} \text{NHR}^2
\end{align*}
\]

0.3 mmol scale

36-97% yield

17 examples

12036 – 12040.


Catalytic Staudinger/Aza-Wittig sequence (2013)

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Ph}_2\text{SiH}_2 (1.1 \text{ equiv})} \text{dioxane, 101 °C} \\
\text{Ph} & \xrightarrow{12 \text{ examples}} \text{N}^\text{R}^2\text{R}'^1\text{R}^3
\end{align*}
\]

(10 mol%)

53-95% yield

14 examples

37-98% yield

A catalytic Mitsunobu reaction (2015)

\[
\begin{align*}
\text{R}^1\text{OH} & \xrightarrow{\text{Ph}_3\text{P} (10 \text{ mol%), PhSiH}_3 (1.0 \text{ equiv})} \text{THF, 80 °C, 18 h} \\
\text{Nu} & \xrightarrow{14 \text{ examples}} \text{R}^1\text{NHR}^2
\end{align*}
\]

1.0 mmol

50-87% yield

1.0 mmol

Applicable to acids, phenols and protected amine

A catalytic solvent-free Appel reaction (2019)

\[
\begin{align*}
\text{R}^2\text{R}^1\text{R}^3 & \xrightarrow{\text{Oct}_3\text{P} (10 \text{ mol%), PhSiH}_3 (1.0 \text{ equiv})} \text{PhCCl}_3 (5.0 \text{ equiv}) \\
\text{Cl} & \xrightarrow{29 \text{ examples}} \text{R}^1\text{R}^3
\end{align*}
\]

100 °C, 24 h

Applicable to epoxide and oxetane

Reduction of activated alkenes (2020)

\[
\begin{align*}
\text{R}^2\text{R}^1\text{R}^3 & \xrightarrow{\text{H}_2\text{O} (3 \text{ equiv), PhSiH}_3 (1.5 \text{ equiv})} \text{Toluene, 80 °C, 24 h} \\
\text{H} & \xrightarrow{29 \text{ examples}} \text{R}^1\text{R}^3
\end{align*}
\]

1 mol%

37-98% yield

53-95% yield

LSPN Seminar - 24/04/2020
Development of P^{III}/P^{V}=O Redox Cycling

- 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)

Selected examples:

- 71% yield
- 86% yield
- 56% yield
- 50% yield
- 56% yield

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


Proposed mechanism:

Radosevich, A. T. J. Am. Chem. Soc. 2020, 142, 6786−6799
Development of P^{III}/P^{V}=O Redox Cycling
Development of new methods: Annulation of amines with carboxylic acids

Proposed mechanism

selected examples:

- 90% yield
- 93% yield
- 85% yield
- 67%, 95:5 e.r.
- 86% yield
- 71% yield

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

The emergence of enantioselective processes

First enantioselective catalytic Wittig reaction (2014)

\[
\text{MeO} \text{O} \text{Br} \text{R}_3\text{P}^* (5-10\text{ mol}\text{%}) \\
\text{HSi(OMe)}_3, \text{Na}_2\text{CO}_3 \\
toluene, 125^\circ \text{C}, 20\text{ h}
\]

Moderate yield and selectivity

Catalytic Staudinger/aza Wittig reaction (2019)

\[
\text{O} \text{X} \text{Y} \text{N}_3 \text{PhSiH}_3 (2.0\text{ equiv}) \\
2\text{-nitrobenzoic acid (20 mol\%)} \\
toluene, 4\text{ A MS} \\
r.t., 48\text{h}
\]

28 examples
63-99\% yield
71-99\% ee

Selected examples

99\% (90\% ee) 97\% (95\% ee) 95\% (84\% ee) 92\% (87\% ee) 90\% (80\% ee)

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

The emergence of enantioselective processes

Asymmetric process via a Michael addition/Wittig (2019)

\[
\text{R}^1\text{O} = \text{CF}_3 \quad \text{R}^2\text{O}_2\text{C} = \text{CO}_2\text{R}^2
\]

\[
\text{R}^1\text{O} = \text{CF}_3 \quad \text{R}^2\text{O}_2\text{C} = \text{CO}_2\text{R}^2
\]

\[
\text{R}^1\text{O} = \text{CF}_3 \quad \text{R}^2\text{O}_2\text{C} = \text{CO}_2\text{R}^2
\]

34 examples
49-99% yield (79-95% ee)

Proposed mechanism

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?

\[ P^V = 0 \]
Preparation of phosphetane oxide catalysts

A. 

\[ \text{Phosphetane} + \text{PCl}_3 + \text{AlCl}_3 \xrightarrow{0 \, ^\circ \text{C}, \text{DCM}} \text{Cl} \xrightarrow{\text{then}, \text{H}_2\text{O}} \text{Me} \]

B. 

\[ \text{Me}_{12}\text{P} \xrightarrow{\text{MeMgBr}} \text{Me}_{12}\text{OP} \xrightarrow{35 \, ^\circ \text{C}, \text{THF/Et}_2\text{O}} \text{Me}_{12}\text{P} \]
Figure 4. Qualitative frontier molecular orbital diagrams depicting the electronic structure arising from nontrigonal perturbation of a model $\sigma^3$-P compound.