Club Phosphorus

No “Guys” Allowed

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Group Meeting
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Isolation

-Herring Brand discovered phosphorus in 1669 - allowed urine to putrify, boiled it down to a paste, finally heated to high temps and collected the vapors. The white waxy substance that resulted would glow in the dark. Thus phosphorus = "light bearer"

1) \((\text{NH}_4)\text{NaHPO}_4\) \rightarrow \text{NaPO}_3 + \text{NH}_3 + \text{H}_2\text{O}
2) 8 \text{NaPO}_3 + 10\text{C} \rightarrow 2 \text{Na}_4\text{P}_2\text{O}_7 + 10\text{CO} + \text{P}_4

-Robert Boyle later improved upon this synthesis by adding sand to the urine

4 \text{NaPO}_3 + 2\text{SiO}_2 + 10\text{C} \rightarrow 2 \text{Na}_2\text{SiO}_3 + 10\text{CO} + \text{P}_4

-Today it's a little more fun to isolate

1) \text{Ca}_5(\text{PO}_4)_3\text{F} + 5\text{H}_2\text{SO}_4 \rightarrow 3\text{H}_3\text{PO}_4 + 5\text{CaSO}_4 + \text{HF}

or

2) 2 \text{Ca}_3(\text{PO}_4)_2 + 6\text{SiO}_2 + 10\text{C} \rightarrow 6\text{CaSiO}_3 + 10\text{CO} + \text{P}_4
Applications

- Most useful as phosphoric acid for fertilizer
- White phosphorus was a main ingredient in matches from 1840s to 1910. However, its use led to “phossy jaw” where the jawbone rots away and can actually glow green
- Calcium phosphate used in production of fine china
- Red phosphorus used for matchbook strikers, flares, cap gun caps, street methamphetamine
- Dopant for N-type semiconductors
- $^{32}\text{P}$ and $^{33}\text{P}$ used as radioactive tracers

-Nerve Gases

\[
\begin{align*}
\text{Sarin} & : \begin{array}{c}
\text{O} \\
\text{O} \\
\text{P} \\
\text{F} \\
\text{C}_3\text{H}_7
\end{array} \\
\text{VX} & : \begin{array}{c}
\text{O} \\
\text{P} \\
\text{S} \\
\text{CH}_3 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{N}
\end{array} \\
\text{Soman} & : \begin{array}{c}
\text{O} \\
\text{P} \\
\text{F} \\
\text{C}_3\text{H}_7
\end{array}
\end{align*}
\]

- And of course.....organic chemistry!
Fun Facts about Phosphorus

- Several allotropes: white (aka yellow), red, and black. White most reactive
- Common oxidation states: -3, -1, 1, 3, 5
- Fun with names:

- Phosphine
- Phosphine Oxide
- Phosphite
- Phosphonate
- Phosphinate
- Phosphinite
- Phosphate
- Phosphonite

- Phosphines have a higher barrier to inversion (~30 kcal/mol) than amines (~5 kcal/mol) = phosphines can display optical isomerism
Phosphine Organocatalysis

-In the 1960s, 70, and 80s, phosphines behaving as nucleophilic catalysts reported sporadically but field grown significantly in the last ten years.

-Ph$_3$P used traditionally (low cost, air stable), but outperformed by the more air-sensitive trialkylphosphines when greater nucleophilicity is required (at least partially due to cone angle).

- Due to high barrier of inversion, can have chiral phosphine catalysts.

-Phosphines are less basic, more nucleophilic, and softer than amines.

-Typical reactions include

- Rauhut-Currier and Morita-Bayless-Hillman reactions
- Michael additions to activated alkenes and alkynes
- Cycloadditions
- Alcohol acylation and kinetic resolution
Rauhut-Currier Reaction

- Dimerization of activated alkenes reported in 1963
- Intermolecular version gave yields ~50%

\[
2 \text{CO}_2\text{Et} \xrightarrow{\text{PBU}_3 \text{ cat.}} \text{MeCN} \rightarrow \text{Co}_2\text{Et} \quad \text{Co}_2\text{Et}
\]


- 1970, McClure reports first cross-coupling reaction between ethyl acrylate and acrylonitrile

\[
\text{CN} + \text{CO}_2\text{Et} \xrightarrow{\text{PBU}_3 \text{ tBuOH, 100 °C}} \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN}
\]

1:1 ratio of reactants

yields calculated based on 21% conversion of both reactants

48%  25%  22%  0%


- Lack of ability to control cross-coupling remained a problem
- Roush and Krische revisited the reaction using an intramolecular version that gave good results

\[ \text{Ph}O \text{O} \text{Ph} \]

\[ \text{10 mol % PBu}_3, \text{EtOAc} \rightarrow \text{Ph} \text{O} \text{C} \rightarrow \text{Ph} \]

86%

\[ \text{J. Am. Chem. Soc. 2002, 124, 2402.} \]

\[ \text{J. Am. Chem. Soc. 2002, 124, 2404} \]

- phosphines behaved better than DABCO, DBU, and DMAP b/c activated alkenes = soft electrophile and phosphine = softer nuc than amines

- unsymmetric / electronically differentiated bis(enones) undergo chemoselective addition of the more electrophilic alkene onto the less electrophilic alkene as shown below

\[ \text{O} \text{O} \text{H} \]

\[ \text{O2N} \text{O2N} \]

- Can even do tandem Rauhut-Currier/Aldol reactions

\[ \text{PR}_3 \rightarrow \text{O} \text{Bn} \]

ROH

33-79%

\[ \text{Org. Lett. 2004, 6, 1857.} \]
Morita-Baylis-Hillman Reactions

- Initially Morita used phosphines to couple an activated alkene with an aldehyde while Baylis and Hillman used tertiary amines (DABCO)
- Phosphines have come back to life and in some cases perform better than amines

\[
\begin{align*}
\text{R} & \quad \text{cat. PBU}_3 & \quad \text{time} & \quad \text{yield (\%)} \\
\text{Ph} & \quad 20 & \quad 17 \, \text{h} & \quad 20 \\
\text{OEt} & \quad 40 & \quad 28 \, \text{d} & \quad 40 \\
\text{Ph} & \quad 20 & \quad 2 \, \text{h} & \quad 75 \\
\text{OEt} & \quad 20 & \quad 24 \, \text{h} & \quad 50 \\
\end{align*}
\]

Slow cyclization of unsaturated esters, but thiol esters cyclize nicely

*Tet. Lett.* **1999**, *40*, 3279
Catalytic Asymmetric M-B-H Reactions

- Most of the focus to date has been on coupling aldhydes and acrylates using sultam auxiliaries, quinidine-derived chiral nucleophilic amines, or chiral lanthanide lewis acids
- Schaus found that mild acids (phenol, BINOL) speed up M-B-H reactions of cyclic enones

Catalysts:

\[
\text{Catalyst: } \begin{array}{c}
\text{(not good)} \\
\text{(best)} \\
\text{(diminished activity)}
\end{array}
\]

\[
\begin{align*}
\text{Catalysts:} & \quad \begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{X = H, Br, Ph}
\end{array} \\
\text{diminished activity}
\end{align*}
\]

- Shi and co-workers replaced aldehydes with the more reactive N-arylidine-4-methylbenzenesulfonamides with good results

Yields up to 96%, ee's up to 94%

Related Reactions

phosphonium silyl ketene acetal undergoes Ireland-Claisen rearrangement


Combination of the M-B-H reaction and a Tsuji-Trost for intramolecular allylation

*J. Am. Chem. Soc.** 2003, 125, 7758.*
Cycloadditions

- Phosphines used as nucleophilic catalysts in lots of [3+2] cycloadditions.

- Allows for facile construction of cyclopentenes using 2-butynoates or 2,3-butadienoates (commercially available) as simple 3 carbon moiety in the [3+2] reaction.

no reaction here if triethylamine used instead of phosphine

EWG = CO₂Me  81%   80:20  
EWG = CO‴Me  59%  63:17  
EWG = CN        79%   83:17

\[ \text{J. Org. Chem. 1995, 60, 2906.} \]
Asymmetric [3+2] Variants

- Asymmetric variants developed based on chiral phosphines

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{i-Bu} \\
10 \text{ mol % cat.} & \\
\end{align*}
\]

- Stereochem of starting E or Z olefin preserved in the product. Authors conclude a concerted mechanism.

\[
\begin{align*}
\text{R group (isopropyl) blocks bottom face}
\end{align*}
\]

Catalyst Synthesis

Methodology in the Synthesis of Hirsutene

**Pyrrole Synthesis via Cycloaddition**

\[
\begin{align*}
\text{R}^1 \equiv \text{(CH}_2\text{)}_7\text{OTHP} & \quad \text{R}^2 = 1\text{-napthyl} \\
20 \text{ mol } \% \text{ PBu}_3 & \\
\text{Benzene, rt} & \\
\text{R}^1 & = \text{Ts} \\
\text{R}^2 & = \text{Ts} \\
75\% & \\
\end{align*}
\]

1) DDQ, benzene, reflux, 92%

2) NaOMe, 86% or TBAF, 71%

\[
\begin{align*}
\text{Ts} & \quad \text{Ph} \\
\text{Ts} & \quad \text{Ph} \\
\text{CO}_2\text{Et} & \\
\text{CO}_2\text{Et} & \\
\end{align*}
\]


Additions to Alkynes

- Triaryl Phosphines isomerize ynones to dienones. Originally performed with RuH$_2$(PPh$_3$)$_4$, later realized that only the phosphines doing any of the work.

\[
\begin{align*}
\text{R}_3\text{P} \quad &\quad \text{R}\text{C}O_2\text{Et} \\
\text{R}-\text{C}\equiv\text{C} \quad &\quad \text{R}_3\text{P} \quad \text{R}\text{C}O_2\text{Et} \\
\text{yields} \quad &\quad \text{~80\%}
\end{align*}
\]

Additions to Allenes

- Normally, addition of nucleophiles to electron-deficient allenes occurs at the alpha-beta double bond....but with triphenylphosphine the addition takes place at the beta-gamma double bond (effectively umpolung addition)

More Michael Additions

- Michael addition of carbon acids usually done with strong base, but phosphines can catalyze some additions

\[
\text{NO}_2^- + \text{R}= \text{Bu, Ph} \quad \text{PR}_3 \text{ cat} \quad \text{NO}_2^- \quad \text{EWG}
\]

\[\text{Tet. Lett. 1973, 14, 3597.}\]

- Toste showed alcohols and water could add to activated alkenes

\[
\text{R}= \text{H, Me, or Ph}
\]

\[\text{J. Am. Chem. Soc. 2003, 125, 8696.}\]
\[
\text{Reactivity of EWG} \quad \text{with PR}_3 \quad \text{leads to} \quad \text{R}_3^+\text{P-} \quad \text{EWG}
\]

\[
\text{R}_3^+\text{P-} \quad \text{EWG} \quad + \quad \text{NO}_2 \quad \text{leads to} \quad \text{NO}_2 \quad \text{R}_3^+\text{P-} \quad \text{EWG}
\]

\[
\text{NO}_2 \quad + \quad \text{EWG} \quad \text{leads to} \quad \text{NO}_2^- \quad \text{EWG}
\]

\[
\text{NO}_2^- \quad + \quad \text{EWG} \quad \text{leads to} \quad \text{NO}_2^- \quad \text{EWG}
\]

\[
\text{NO}_2^- \quad + \quad \text{R}_3^+\text{P-} \quad \text{EWG} \quad \text{leads to} \quad \text{NO}_2^- \quad \text{EWG} \quad + \quad \text{R}_3^+\text{P-} \quad \text{EWG}
\]
Additions to Alkynes

- Phosphines catalyze Michael addition of alcohols to activated alkynes as well

\[ \text{CO}_2\text{Me} + \text{ROH} \xrightarrow{15 \text{ mol} \% \text{PBU}_3} \text{RO}=\text{CO}_2\text{Me} \]  

- Used in the synthesis of coumarins (Yavari)

\[ \begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{OH}
\end{array}
\xrightarrow{\text{MeO}_2\text{C}=\text{CO}_2\text{Me}}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{CO}_2\text{Me}
\end{array}
\]  

- Used by Evans to make fused pyran structures

\[ \begin{array}{c}
\text{OH}
\end{array}
\xrightarrow{\text{PBU}_3}
\begin{array}{c}
\text{OTBS}
\end{array}
\xrightarrow{\text{steps}}
\begin{array}{c}
\text{SePh}
\end{array}
\text{H}
\text{H}
\text{H}
\text{H}
\]  
*J. Org. Chem. 1996, 61, 4880*
Conclusions

- Phosphines are good for more than just ligands, Wittig, and Mitsunobu

- Phosphines are more nucleophilic and less basic than amines

- Phosphines are excellent for Michael additions

- Can be used in asymmetric organocatalysis