SOLVAY

Progress beyond

# Phosphorus Specialties: the cornerstone of synthesis for pharmaceutical applications

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# Overview

- Solvay Phosphorus Specialties, Strem Chemicals Inc. Partnership
- Chemistry for the Manufacture of Phosphine Ligands
- Applications in Pharmaceutical Catalysis
- Applications in Life Sciences
- Summary and Questions

***Solvay partners with Strem Chemicals for sample distribution***

# Strem Chemicals, Inc.

***Solvay partners with Strem Chemicals for sample distribution!***


Corporate Headquarters
Newburyport, MA USA

European Headquarters
Strasbourg, France

- Established in 1964
- More than 55 years of experience in manufacturing and handling high quality inorganics and organometallics
- 5,000+ specialty chemicals available
- Laboratory Chemicals for R&D
- cGMP Products Manufactured in Kilo-lab Suites
- High Pressure Materials
- Custom Synthesis Projects
- Customers include:
  - Academic, industrial and government R&D laboratories
  - Commercial scale businesses in the pharmaceutical, microelectronics, chemical & petrochemical industries

ISO 9001:2015 CERTIFIED

ChemStewards®



STREM CHEMICALS, INC.

*Samples available from Strem*

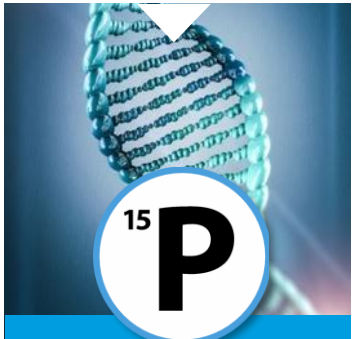
# Who We Are

- Putting our science to work for customers to develop differentiated products and technologies
- Dedicated on-site technical service and applications expertise to support our customers' needs
- Deep customer relationships and ongoing collaborations to solve demanding industry challenges

## Mining Solutions

Premier supplier of specialty reagent-based solutions to the mining industry with more than 100 years of commitment

## Phosphorus Specialties




Global supplier of differentiated products and technologies based on phosphorus chemistries

## Polymer Additives

Leader in the UV stabilization of polymers with more than 60 years of experience

# Global Leader in Phosphorus Chemistry

## Innovation:

160 years of know-how and innovation in phosphorus chemistry

## Partnership:

We work closely with customers to translate their needs into concrete solutions


## Differentiated products and technologies:

We offer a wide range of phosphorus-based chemistry to meet precise application requirements

## Secure and consistent supply source:

Stringent quality control standards and timely order fulfillment due to global footprint and supply chain

## Scale-up capabilities:

From R&D to large scale; largest capacity in the industry

# Our Portfolio

## Agriculture

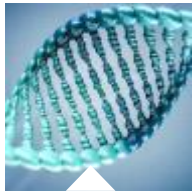
$ECO_2FUME^®$ | $VAPORPH3OS^®$

- ✔ Cylinderized phosphine gas fumigants that efficiently eradicate insects at all life stages
- ✔ Used on post-harvest products or storage structures

## Textiles

PROBAN® | THPC

- ✔ P-chemistry imparting flame-resistance to textiles & garments
- ✔ THPC for leather treatment applications



## Life Sciences

CYTOP® | RhodaPhos®

- ✔ Specialty phosphorus compounds for applications requiring stringent purity profiles
- ✔ Catalysis; oligonucleotide synthesis; reagents; intermediates

## Electronics

CYPURE® | CYTOP® | CYPHOS® IL

- ✔ High-purity phosphine gases & derivatives used throughout the electronics supply chain
- ✔ Dopants for LED & semi-conductors; capping ligands; solvents; quantum dot materials

## Biocides

TTPC | THPS

- ✔ TTPC & THPS for control of microorganisms*
- ✔ Oilfield & industrial wastewater treatment applications

## Chemical Processing

CYPHOS® | CYTOP® | RhodaPhos®

- ✔ Phosphine derivatives used in the manufacture of chemical compounds
- ✔ Organic extraction, catalysis, ligands and additives

## Plastics, Epoxy & Coating

CYPHOS® | AMGARD® | Albritect®

- ✔ Phosphorus additives optimizing the performance of plastics, epoxy, and coating systems
- ✔ Epoxy resin curing; flame retardant polymers; surface coating treatment; catalysts

## Other

Phos Acid | CYTOP® | CYPHOS® IL

- ✔ Phosphorus-based chemistries for commodity and niche applications
- ✔ Metal extraction & recycling; liquid extractions; ionic liquids; fertilizer; other applications



*Supplied via Novecare GBU

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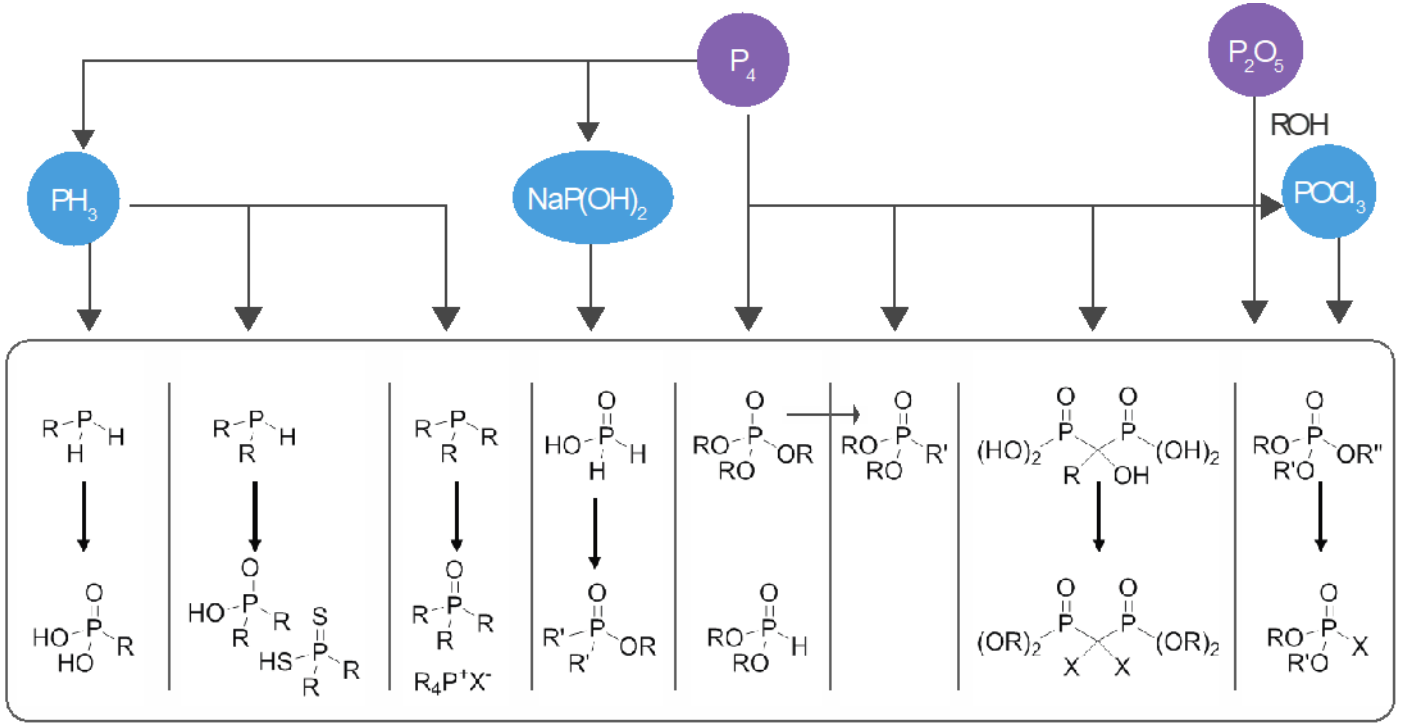
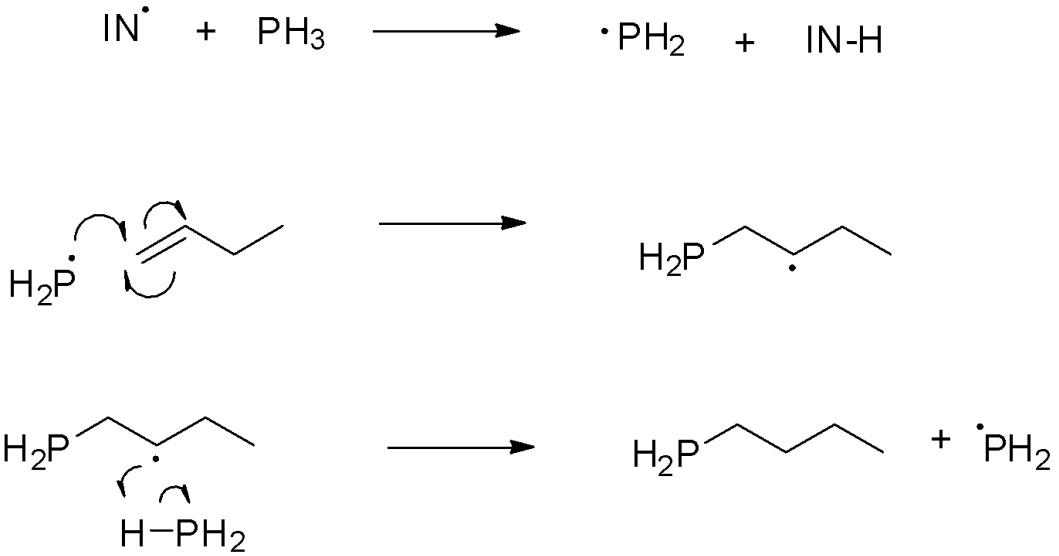
# Chemistry for the Manufacture of Phosphine Ligands

# Phosphorus Specialties Product Platform



# Foundational Chemistry

- Free radical addition of $PH_3$ to olefins is a major component of Solvay's alkylphosphine derivatives technology

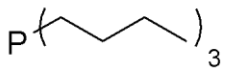




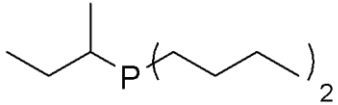
(1) Rahut, M. et.al., *J. Org. Chem*. **1961**, *26*, 5138
(2) Pellon, J., *J. Am. Chem. Soc*. **1961**, *83*, 1915

# Example – CYTOP® 340

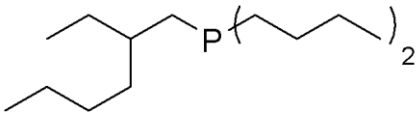
- Produce distribution is dependent on the nature of the olefin
- Initiator fragments and some olefin oligomers are formed
- Olefin diversity translates to product diversity



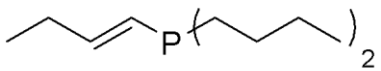
**94%**



**2.5 - 3.0%**



**0.8%**

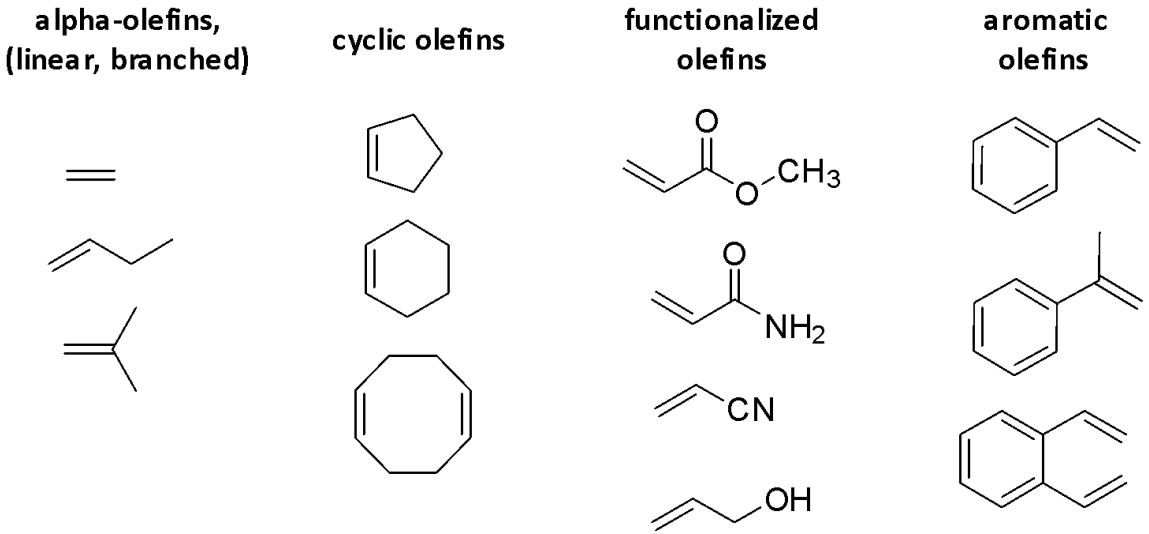


**0.5%**

- **CYTOP® 340** (Strem: 15-5801)
- Tri(n-butyl)phosphine
- CAS No. 998-40-3

# Foundational Chemistry – Olefin Examples

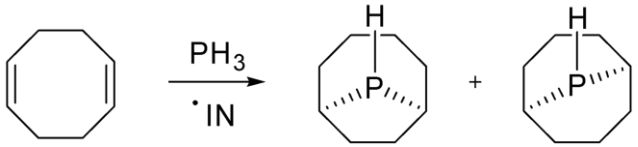
- Product distribution is dependent on the nature of the olefin



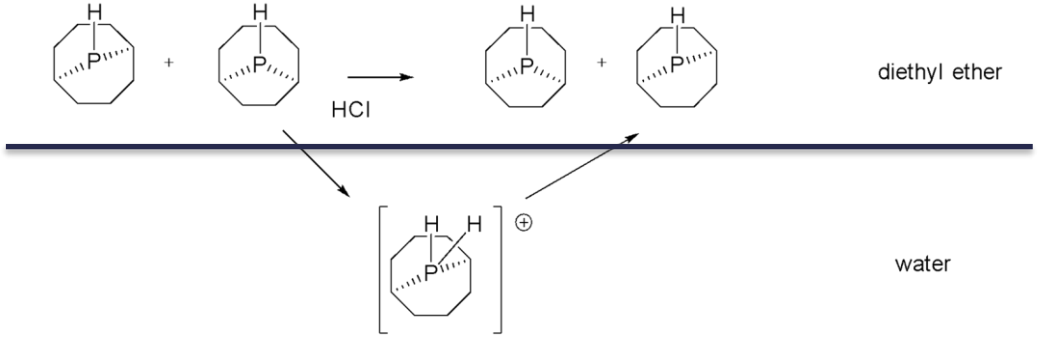

- Reactivity of olefins and the product compositions depend on number of double bonds and positions

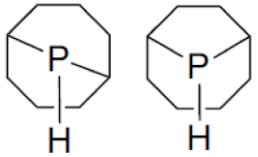
# CYTOP® 282T – Bulky Phosphine Ligand Precursor

- CYTOP® 282T– sterically bulky secondary phosphine
- Mixture of 9-phosphabicylononane [3.3.1] and [4.2.1]
- Synthetic route provides mixture of both isomers




- Isomers can be separated via selective protonation



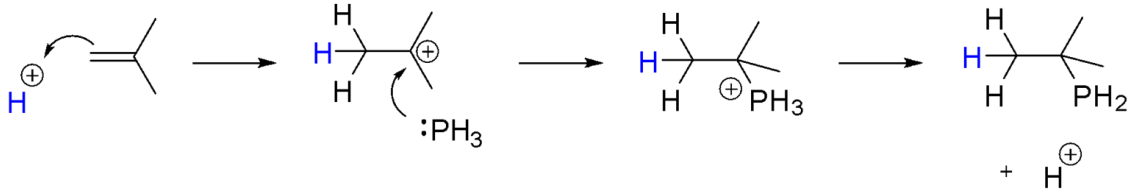



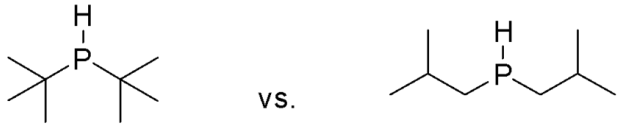

- **CYTOP® 282T** (Strem: 15-7535)
- 9-phosphabicyclononane [3.3.1] and [4.2.1]
- CAS No. 13887-02-0/ 13396-80-0

(1) Pringle, P.G. et al. *Adv. Synth. Catal.*, **2005**, *347*, 1345

# Acid Catalyzed Addition to Olefins

- Acid-catalyzed addition to olefins allows access to useful products not accessible through free radical routes



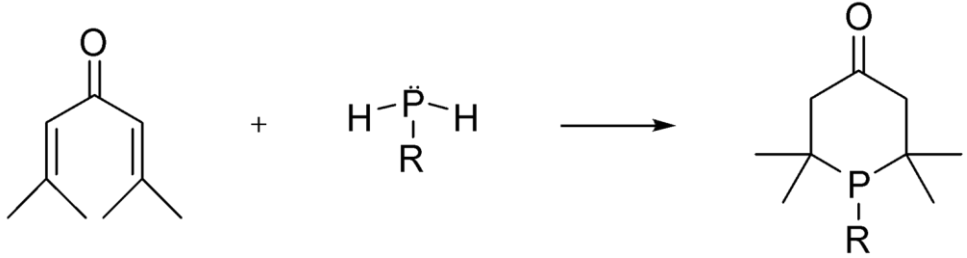




- **CYTOP® 341** (Strem: 15-5750)
- tri(isobutyl)phosphine
- CAS No. 4125-25-1

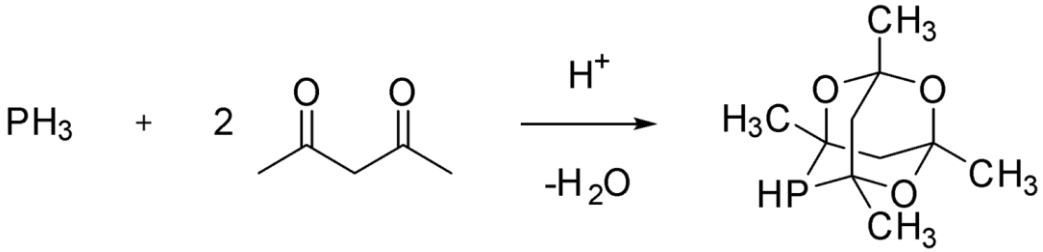
- Tri-*tert*-butylphosphine cannot be prepared under acid catalysis
- Tri-*iso*-butylphosphine is readily accessible (CYTOP® 341 [Strem: 15-5750])

# Other Chemistries

- Michael Addition to activated olefins




- Addition to 2,4-pentadione




- **CYTOP® 216X** (Strem: 15-1310)
- 1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane
- CAS No. 26088-25-5


(1) Welcher, J. Org. Chem. 1962, 27, 1824
(2) Epstein, B, *J.Am.Chem.Soc.*, **1961**, *83*, 3279

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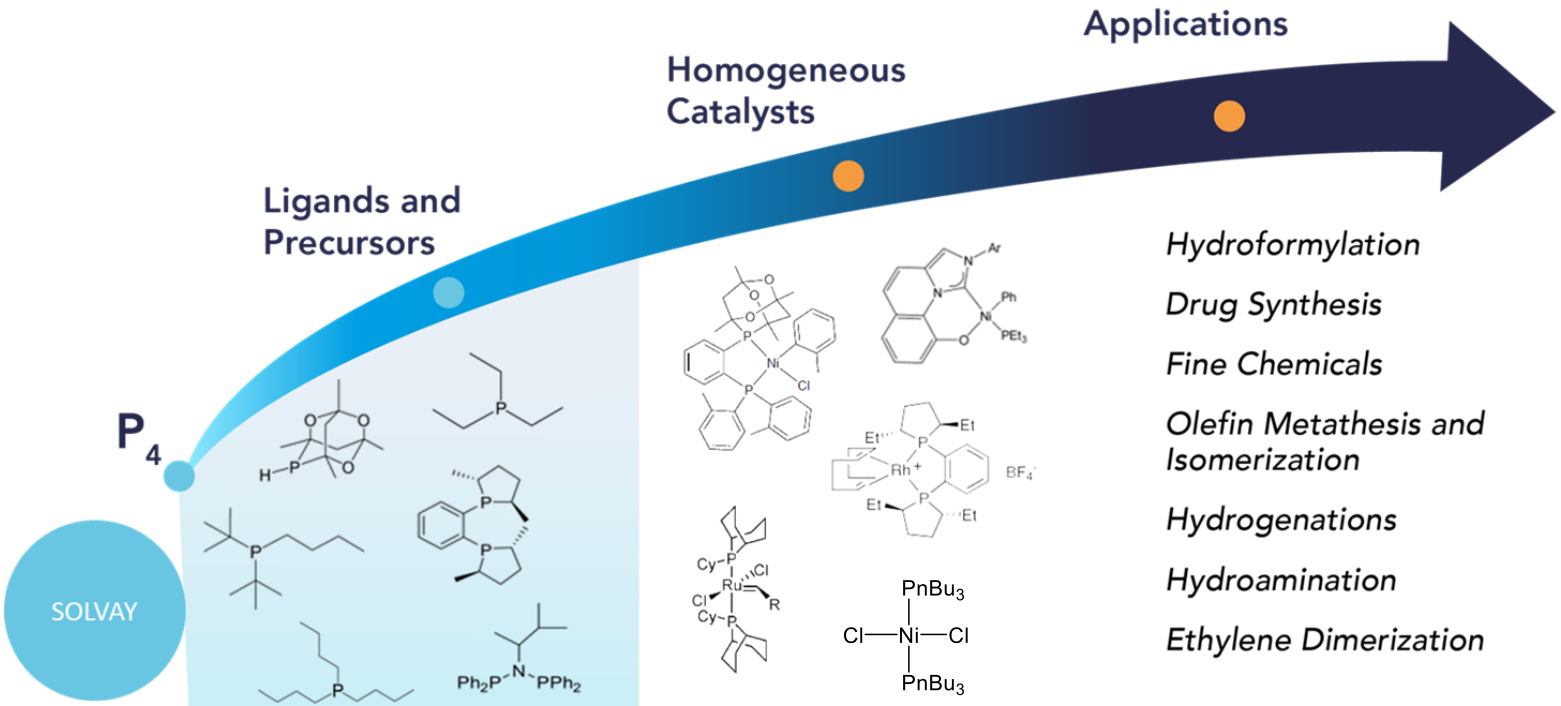
Progress beyond

# Applications in Pharmaceutical Catalysis and Life Sciences

STREM CHEMICALS, INC.

*Samples available from Strem*

# Solvay in Phosphorus Catalysis



# Why the interest in Phosphorus for Catalysis?

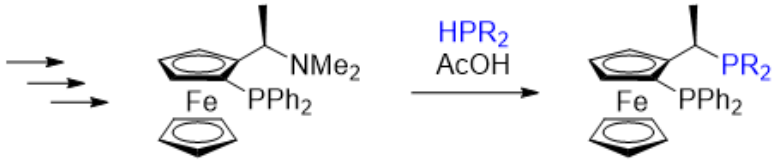
- Diversity of Structure, tunability (steric, electronic), thermal stability
- Liquid materials for ease of handling (product stewardship, safety, etc.)
- Established manufacturing routes, large scale availability
- Key balances between P ligands and metals employed (Cr, Co, Rh, Ni, etc.)
  - Solubilize and stabilize organometallics

***Solvay is a leader in supplying phosphine ligands to the market safely!***

# Ligand Diversity

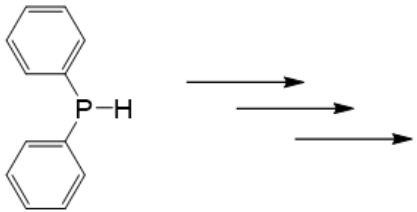
## Multifunctional building blocks

- Ability to tune ligand/catalyst properties via changes in ligand composition is a key feature in all successful ligand families
- Modularity leads to breadth in applications i.e. Josiphos™

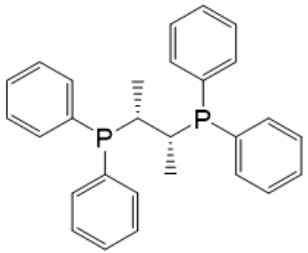



R = c-hex, t-Bu, c-pent, 2-adamantyl, phobyl

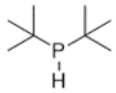
- Achiral primary and secondary phosphines can be made into chiral motifs for life sciences catalysis



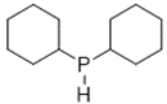

**RhodaPhos® DPP**
(Strem: 15-1701)



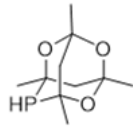

**RhodaPhos® CP100R**
(Strem: 15-0165)



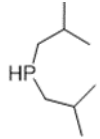

**CYTOP® 242**
(Strem: 15:1040)



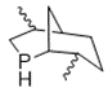

**CYTOP® 266**
(Strem: 15-1120)



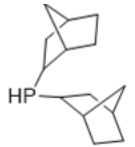

**CYTOP® 216X**
(Strem: 15-1310)




**CYTOP® 241**
(Strem: 15-1030)




**CYTOP® 170**
(Strem: 15-7605)

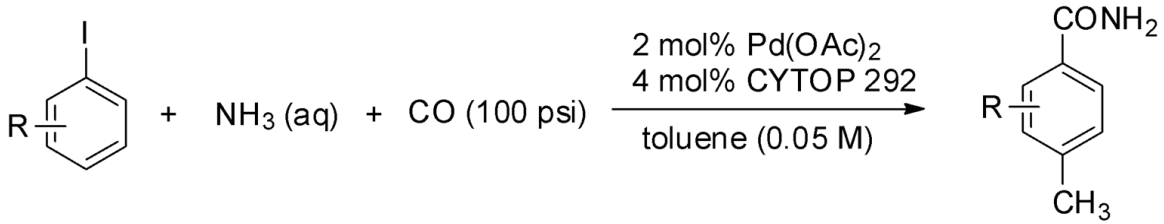


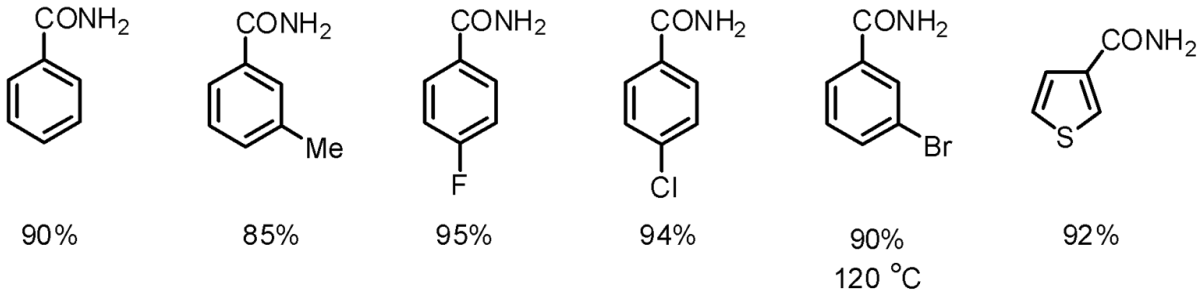

**CYTOP® 222**
(Strem: 15-1460)

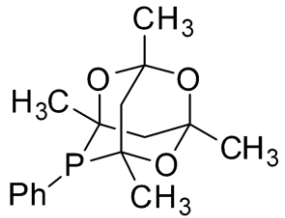
STREM CHEMICALS, INC.
*Samples available from Strem*

# Aminocarbonylation

- Importance of Pd-catalyzed coupling methods cannot be understated – they are critical in the preparation of many important products
- Significant limitation is the direct use of ammonia for amination protocols – catalyst deactivation and uncontrolled amination




CYTOP 292

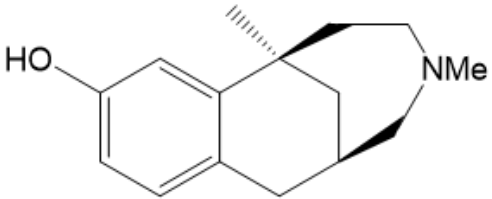
- **CYTOP® 292** (Strem: 15-5375)
- 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane
- CAS No. 97739-46-3

Samples available from Strem

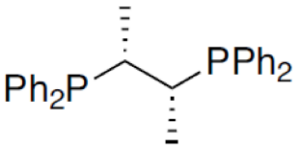
# Carbon-Carbon Bond Formation

## Synthesis of (-)-eptazocine

- Bulky Chiral Bidentate Ligand
- (2R,3R)-(+)-bis(diphenylphosphino)butane
- Support several industrial and academic relevant chiral transformation
- Synthesis of (-)-eptazocine, commercially available analgesic
- Construction of both benzylic quaternary carbons and C-CN bond in a single operation (arylcyanation)




(-)-eptazocine



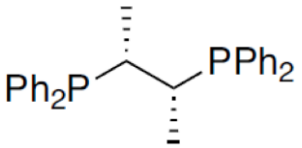

- **RhodaPhos® CP100R** (Strem: 15-0165)
- (2R,3R)-(+)-Bis(diphenylphosphino)butane
- CAS No. 74839-84-2

(1) *JACS*. **2008**, *130*, 12874

# Carbon-Carbon Bond Formation

## Synthesis of (-)-eptazocine

- Chemistry was shown effective with a variety of ligands, however only RhodaPhos® CP100R gave yields as high as 98% and ee% of 92%
- 7 step synthesis




- **RhodaPhos® CP100R** (Strem : 15-0165)
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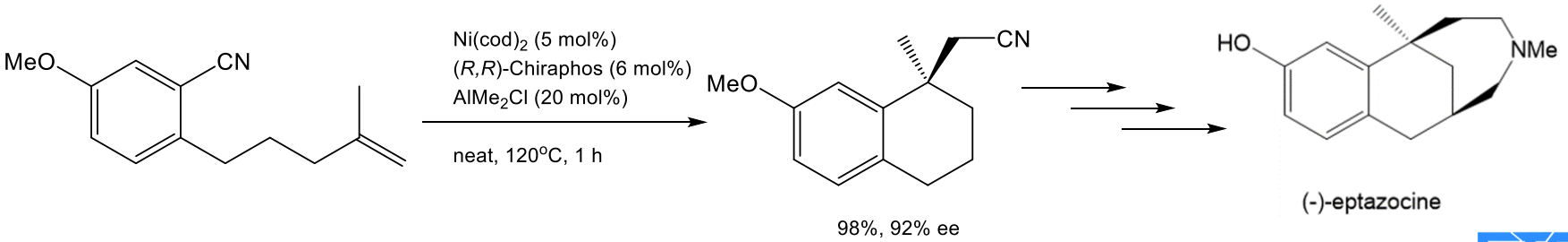
- CAS No. 74839-84-2

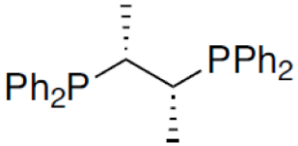


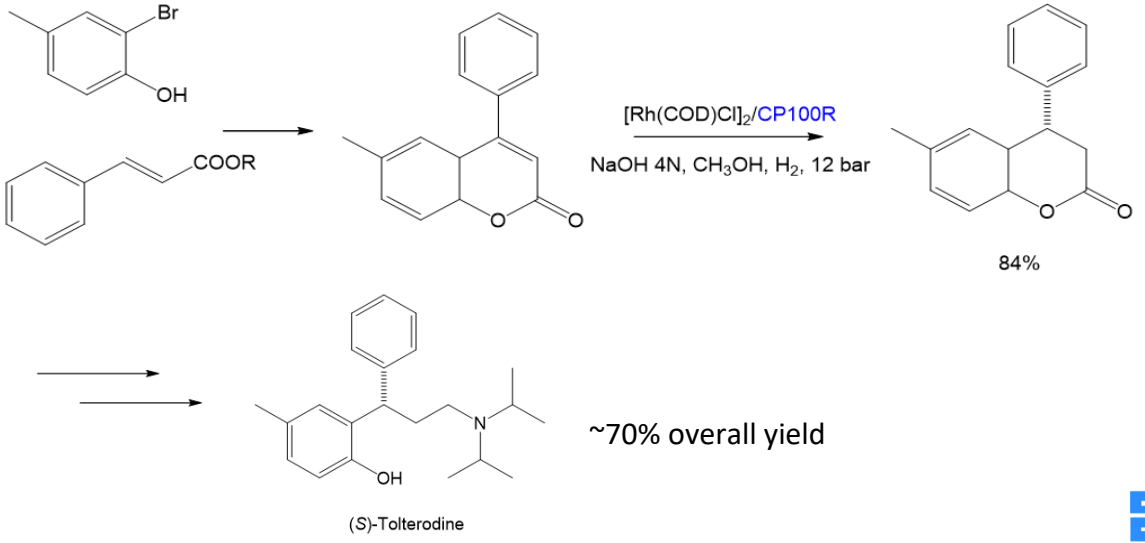

(1) *JACS*. **2008**, *130*, 12874

# Chiral Hydrogenations

## Synthesis of (*S*)-Tolterodine

- (*R*)-Tolterodine is a potent treatment for overactive bladder disorder (muscarinic antagonist), while (*S*)-Tolterodine is weaker with less side effects (dry mouth, tachycardia)
- Efficient and short enantioselective synthesis (84% isolated yields, 80 ee% etc.) (4 step synthesis)
- Commonly referred to as “Chiraphos”




- **RhodaPhos® CP100R** (Strem: 15-0165)
- (2R,3R)-(+)-Bis(diphenylphosphino) butane
- CAS No. 74839-84-2


(1) *J. Org. Chem*. **2007**, *72*, 6056

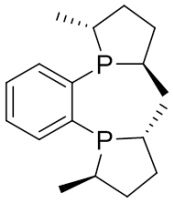
# Chiral Hydrogenation

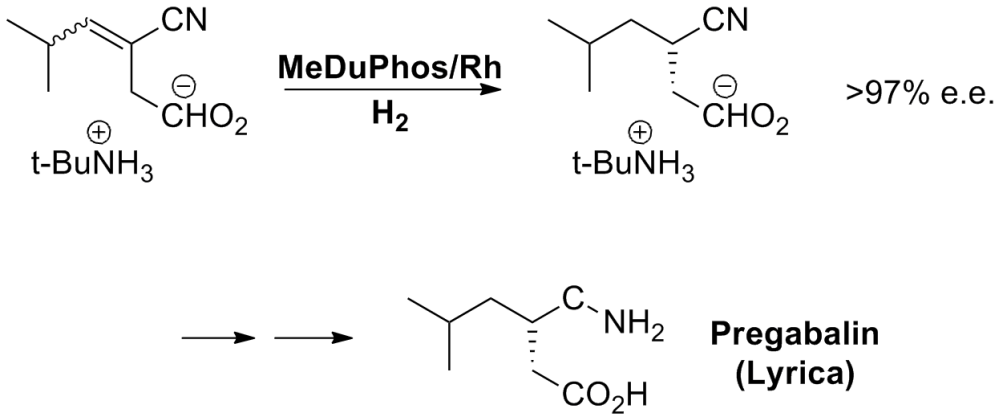
## API Synthesis

- DuPhos ligands are among the most extensively studied for chiral hydrogenations
- Broad range of substrates with direct relevance to important target molecules

### RhodaPhos® (R,R) MethylDuPhos

- 1,2-Bis(2R,5R)-2,5-dimethyl(phospholano)benzene;
- CAS No. 393801-72-4;

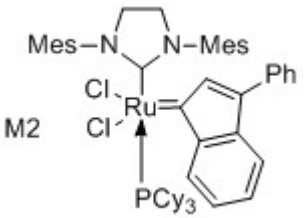


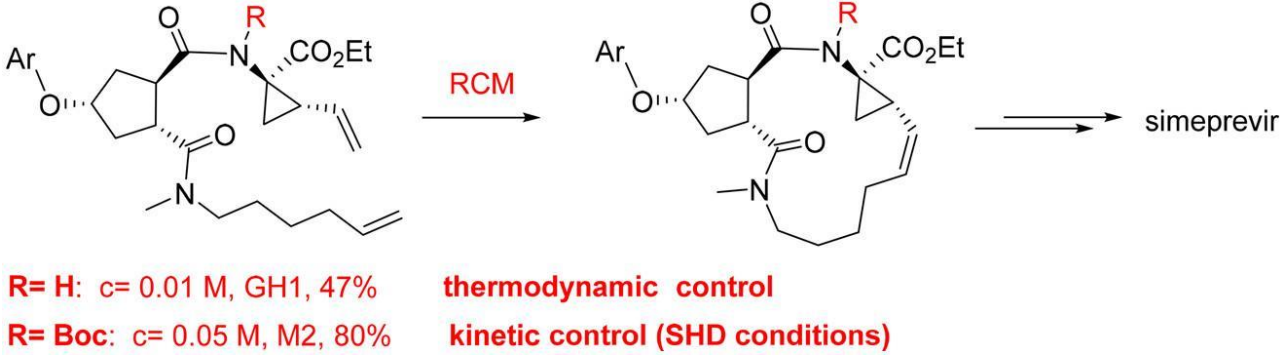



- Leveraged in a concise, enantioselective synthesis of pregabalin (anti-convulsant)
- Key step is the asymmetric hydrogenation of the 3-cyano-5-methylhex-3-enoic acid salt shown.

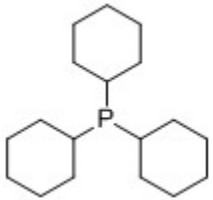
# Metathesis

## Synthesis of HCV Protease Inhibitor




- **CYTOP® 366** (Strem: 15-6152)
- Tricyclohexylphosphine
- CAS No. 2622-14-2



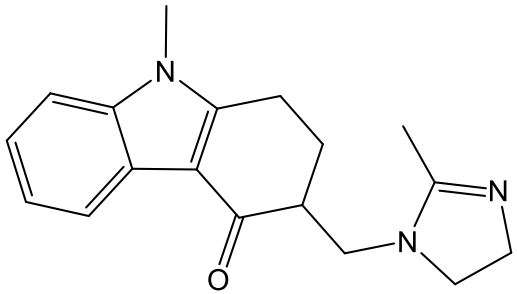

- Switch to Boc derivative and M2 catalyst improved space-time-yield 15 fold (14 Kg / $m^3$ / hour vs. 0.86).
- GH1 and M2 are both Ru based RCM Catalysts with CYTOP® 366
- Trials were compared to 5 other RCM catalysts

(1) Horvath, A. et al. *J. Org. Chem.*, **2019**, *84*, 4932-4939

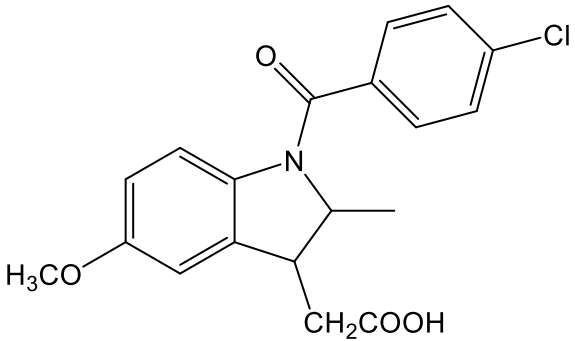
# Indole Synthesis

## Important class of compounds for pharma

- Indole derivatives represent one of the most important structural classes in drug discovery
- Indoles are prevalent in both biologically active compounds as well as natural products leading to strong demand for synthetic methodologies
- Challenging via traditional routes when substituting at C5 (such as Fischer Indole synthesis)
- Metal catalysts with phosphine ligands are attractive solution




Ondansetron

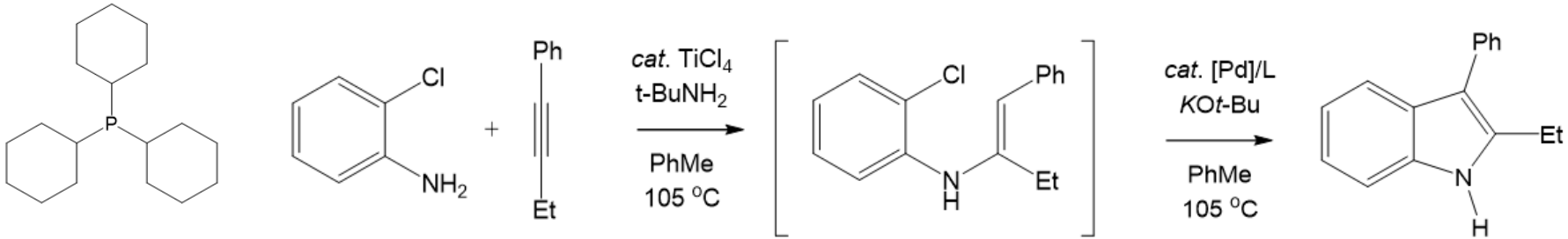



Indomethacin

# Indole Synthesis - Important class for Pharma

## Important class of compounds for pharma

- Phosphine ligand supported palladium coupling is an effective route to substituted indoles
- Tricylohexylphosphine (CYTOP® 366) gave higher yields (71%) in intramolecular cyclizations to form indole compared to carbenes (55%), triphenylphosphine (2%), and other monophosphine biaryl ligands (10-55%) in the presence of base



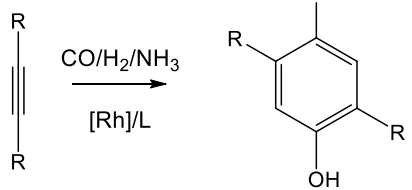

- **CYTOP® 366** (Strem: 15-6152)
- Tricyclohexylphosphine
- CAS No. 2622-14-2

(1) *Tetrahedron* **2008**, 50, 769-777

# Hydroquinone Synthesis

## Cost effective and practical catalysis solutions

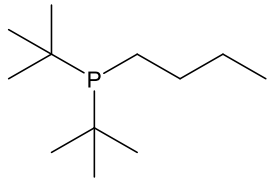
- Synthesis of hydroquinones are industrially relevant in pharmaceuticals
- CYTOP® 202 is a bulky phosphine ligand suitable for cyclocarbonlyation
- For ring forming reaction from alkynes, CYTOP® 202 had performance improvement over cataCXium® A at a significant ligand cost advantage



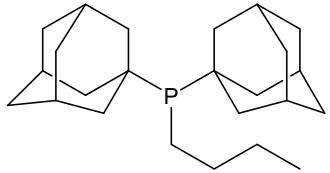

1. R = H
2. R = Ph

| R | CYTOP® 202 | cataCXium® A |
|---|---|---|
| H | 70% | 66% |
| Ph | 58% | 53% |

L =




vs



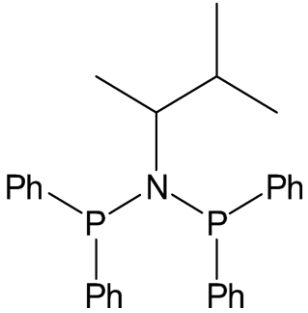

- CYTOP®202 (Strem: 15-1128)
- di-tert-butyl(n-butyl)phosphine
- CAS No. 29949-72-2

**cataCXium® A**

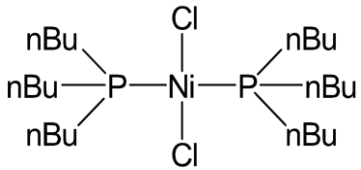
- CYTOP® 202 outperforms in the synthesis of substituted hydroquinones

(1) *Beller, M. et al. ChemCatChem* **2011**, 3, 1273-1276

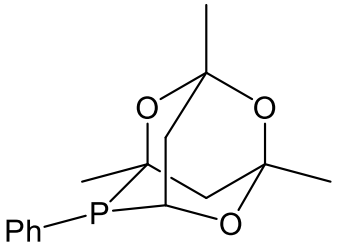
# Other Phosphines, Catalysts and Applications




- **RhodaPhos® PNP12M**
  (Strem: 15-0745)
- N,N'-bis(diphenylphosphino)-1,2-dimethyl propylamine
- CAS No. 872187-64-9
- Olefin Oligomerization Ligand



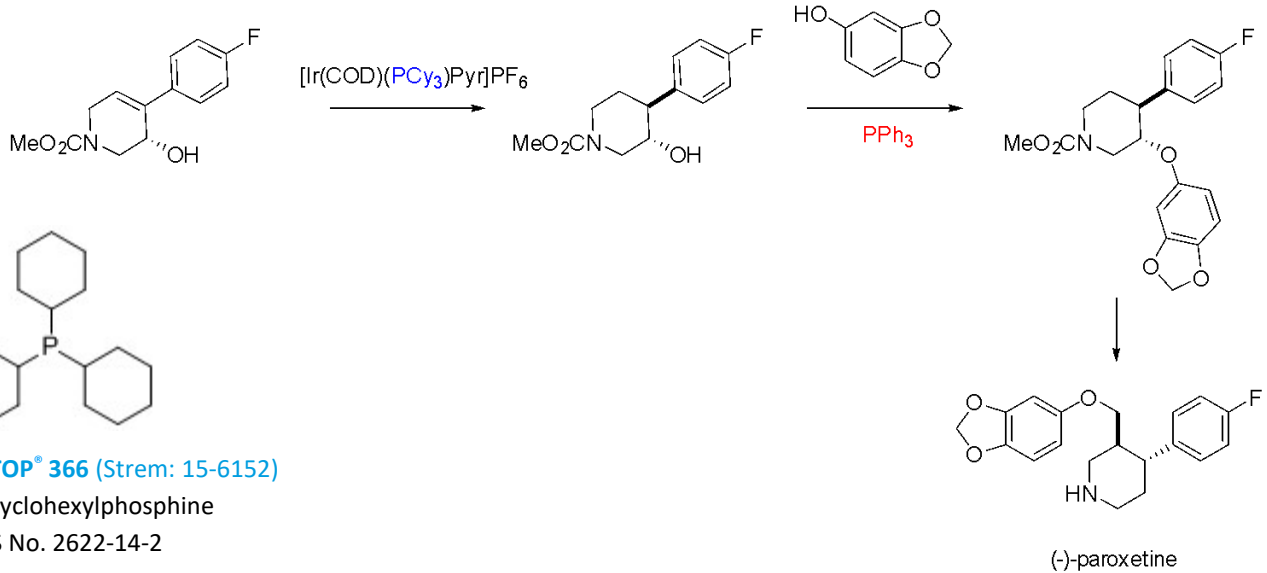

- **RhodaPhos® NICAT**
  (Strem: 28-0075)
- Dichlorobis(tributylphosphine) nickel
- CAS No. 15274-43-8
- Olefin Oligomerization




- **CYTOP® 292**
  (Strem: 15-5375)
- 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-phosphaadamantane
- CAS No. 97739-46-3
- Telomerization Ligand

# Total Synthesis of PAXIL

- Total synthesis of paroxetine (PAXIL) serves as an excellent example of the utility of P-based reagents in synthesis
  - Ir-catalysed hydrogenation of the tri-substituted olefin using $PCy_3$ (CYTOP® 366)
  - Coupling to sesamol using Mitsunobu conditions
    - Option to use alkylphosphine (e.g. CYTOP ® 330) for water-soluble by-products







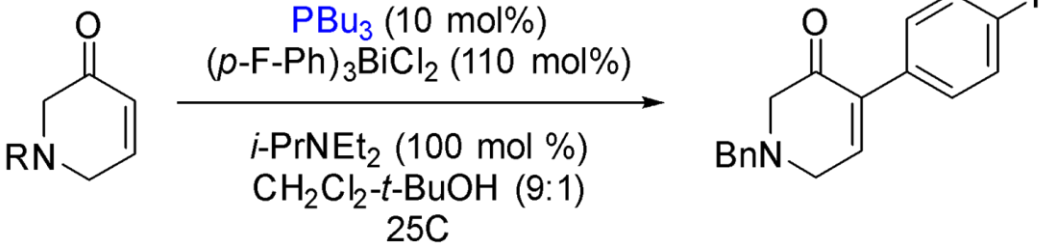
- **CYTOP® 366** (Strem: 15-6152)
- Tricyclohexylphosphine
- CAS No. 2622-14-2

(-)-paroxetine

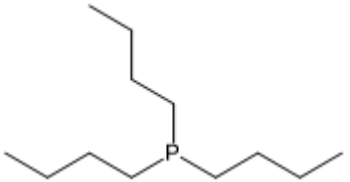
(1) Krische et al., *Tetrahedron*, **2006**, 62, 10594

# Total Synthesis of PAXIL

- Total synthesis of paroxetine (PAXIL) serves as an excellent example of the utility of P-based reagents in synthesis
  - Key step is the phosphine-catalyzed enone α-arylation
  - Tri-*n*-butylphosphine = CYTOP® 340
  - This protocol has been applied to a range of cyclic enones and β-substituted enals




*single regioisomer*
*79% yield*

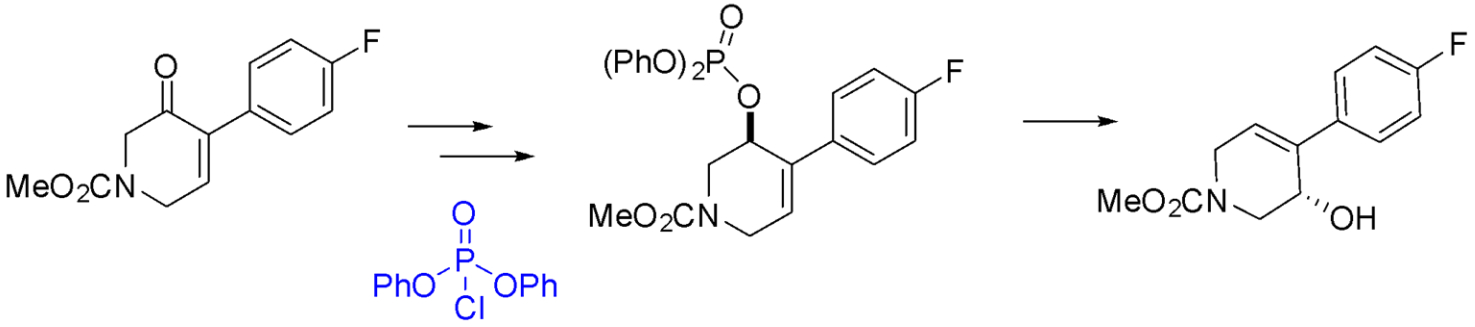



- **CYTOP® 340**
  (Strem: 15-5801)
- Tributylphosphine
- CAS No. 4125-25-1

(1) Krische et al., *Tetrahedron*, **2006**, 62, 10594

# Total Synthesis of PAXIL

- Total synthesis of paroxetine (PAXIL) serves as an excellent example of the utility of P-based reagents in synthesis
  - *anti*-Selective copper-mediated allylic substitution employing DPCP
- Chiral alcohol intermediate in 92% ee




- **DPCP**
- Diphenylchlorophosphate
- CAS No. 2524-64-3

(1) Krische et al., *Tetrahedron*, **2006**, 62, 10594

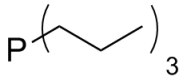
# Homologation of Aldehydes

## DualPhos

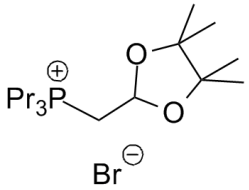
- Trialkylphosphines, like CYTOP® 330, have been successfully used to develop 2-carbon homologation strategies
- The approach has been applied to the synthesis of unsaturated aldehydes such as phomolide G, H

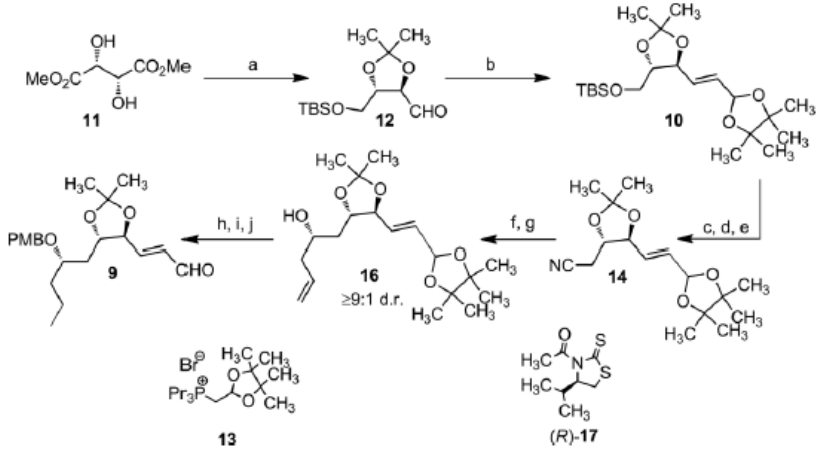
**CYTOP® 330** (Strem: 15-7610)

- tri-*n*-propylphosphine;
- CAS No. 2234-97-1;



- Applied in the development of **DualPhos**; reagent for the 2-carbon homologation of aldehydes;
- **DualPhos**:





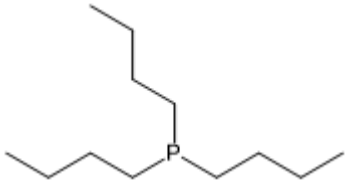
Scheme 2. Reagents and conditions: Yields are of isolated products. **a**) ref. 10; 51 % over four steps. **b**) **13**, KO*t*Bu, THF, 0 °C to 23 °C, 82 %. **c**) TBAF, THF, 0 °C, 93 %. **d**) $PPh_3$, $I_2$, 1*H*-imidazole, THF, 0 °C to 23 °C, 87 %. **e**) KCN, TBAI (10 mol-%), DMSO, 23 °C, 67 %. **f**) Allylzinc bromide, THF, 23 °C, 81 %. **g**) $LiAlH_4$, LiI, $Et_2O$, –100 °C, 92 % (*dr* ≥ 9:1). **h**) $(PPh_3)_3RuCl_2$, $H_2$ (1 atm), benzene/EtOH (1:1 v/v), 23 °C, 94 %. **i**) NaH, PMBCl, DMF, 0 °C to 23 °C, 84 %. **j**) $FeCl_3{\cdot}6H_2O$, acetone, 23 °C, 63 %. TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, PMB = *p*-methoxybenzyl.


McNulty et al., *Green Chem.*, **2013**, 15, 3146
McNulty et al., *R. Soc. Open Sci.* **2016**, 3, 160374.
McNulty et al. *Eur. J. Org. Chem.* **2017**, 29.

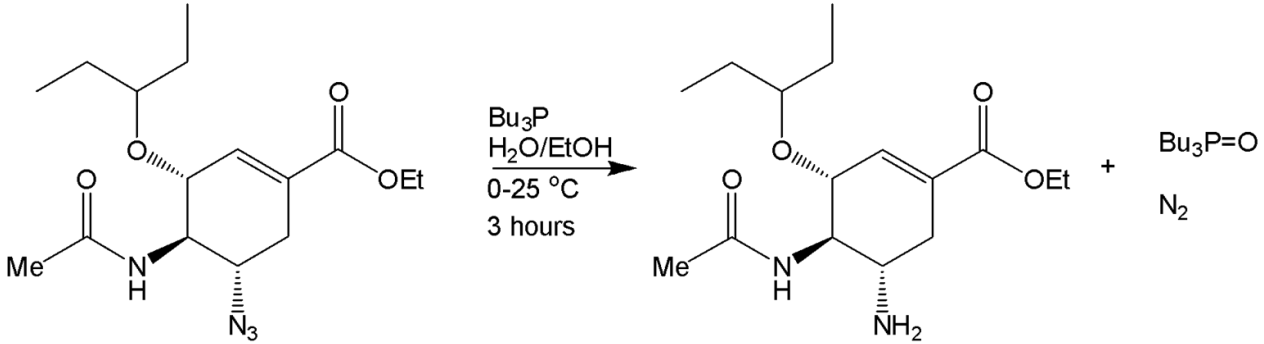
# Staudinger Reaction

## Synthesis of Tamiflu®

- Tributylphosphine successfully applied to total synthesis of oseltamivir phosphate (Tamiflu®)
- Improvements over conventional hydrogenation with Raney Nickel:
  - Fewer impurities
  - No hydrogenation of cyclohexene
  - Easier to process (no filtration)



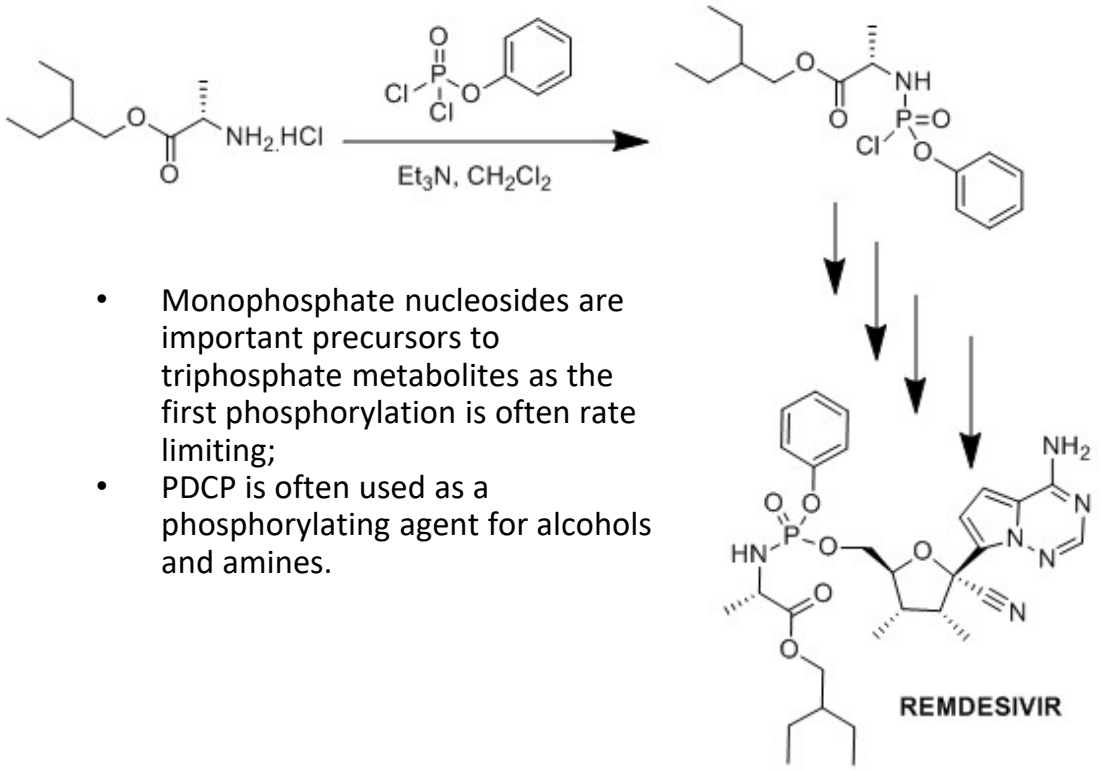
- **CYTOP® 340** (Strem: 15-5801)
- Tributylphosphine
- CAS No. 4125-25-1



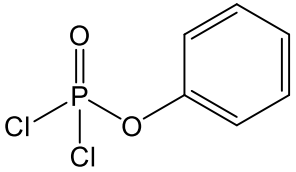

(1) Trussardi, R. US Patent 7531687

# Phosphorylation in Prodrug Synthesis

## Antiviral Remdesivir




- **Phenyl dichlorophosphate**
- PDCP
- CAS No. 770-12-7



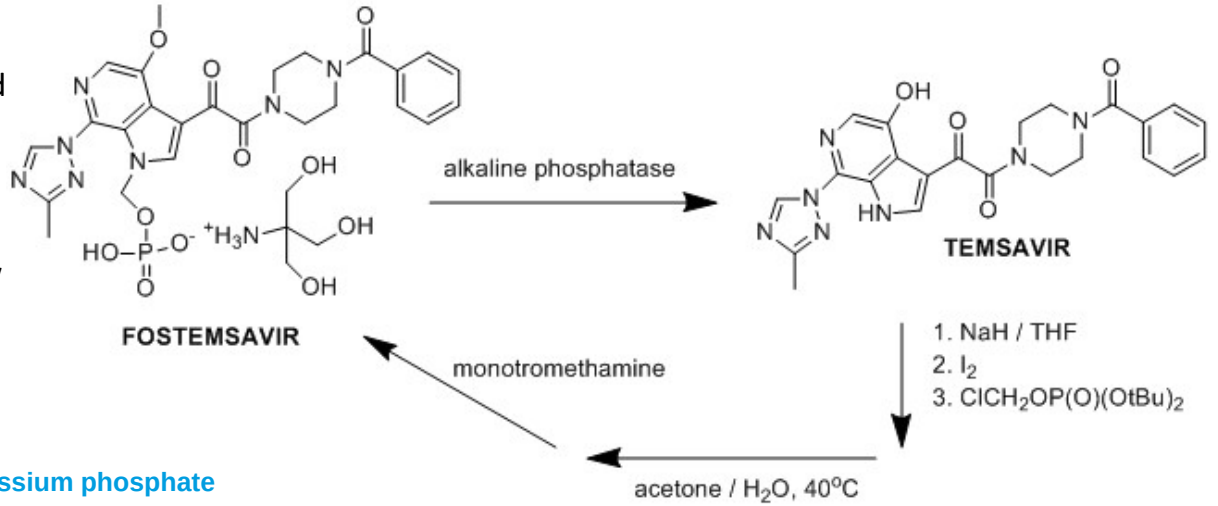
- Monophosphate nucleosides are important precursors to triphosphate metabolites as the first phosphorylation is often rate limiting;
- PDCP is often used as a phosphorylating agent for alcohols and amines.

(1) Siegel, D. et al. *J. Med. Chem.*, **2017**, *60*, 1648-1661

# Phosphorylation in Prodrug Synthesis

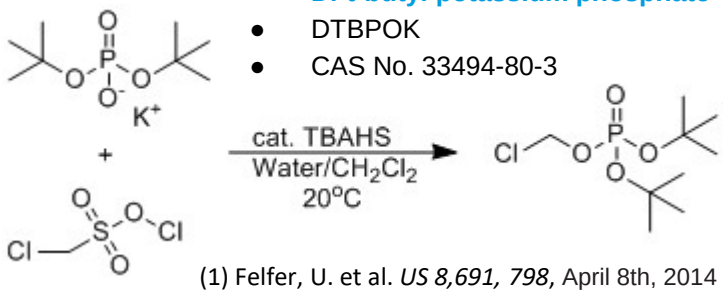
## HIV-1 attachment inhibitor

- Temsavir has limited exposure at higher doses due to dissolution and / or solubility / absorption issues;
- Fostemsavir developed as prodrug to address this;
- Recently FDA approved for treatment of HIV in adults with few treatment options available.




(1) Wang, T. et al. *J. Med. Chem.*, **2018**, *61*, 6308-6327

- **Di-t-butyl potassium phosphate**
- DTBPOK
- CAS No. 33494-80-3



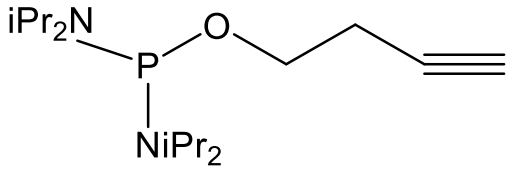

(1) Felfer, U. et al. *US 8,691, 798*, April 8th, 2014

# Phosphitylation in Oligonucleotide Synthesis

## Emerging area

- Phosphoramidites of DNA and RNA bases used to build oligos;
- Used in diagnostics (PCR, gene sequencing);
- Therapeutics (ASO, siRNA, LNA);
  - <10 approved drugs for small indications;
  - Inclisiran siRNA for cholesterol reduction (Novartis bet the house on this one).

- **RhodaPhos(R) Phos Reagent** (Strem: 15-0695)
- 2-Cyanoethyl N,N,N',N'–tetraisopropylphosphoramidite
- CAS No. 102691-36-1

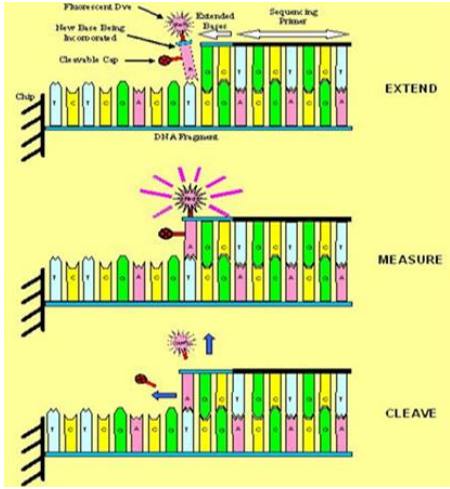



Samples available from Strem

# Disulfide Bond Reduction

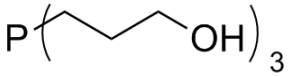
## Gene Sequencing

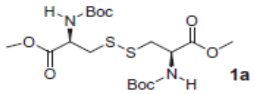
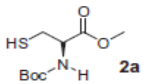
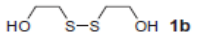
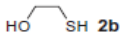
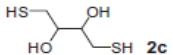
- DNA is fragmented, amplified, attached to a DNA sequence primer & affixed as a high-density array of spots on a glass chip.
- Array is subjected to reagents containing DNA bases modified with a dye and an end cap.




**CYTOP® 208 (Strem: 15-6375)**

- tris(3-hydroxypropyl)phosphine (“THPP”);
- CAS No. 4706-17-6;
- Quicker, more complete cleavage
- No odor
- Stable over wide pH range




| Entry | Disulfide, 1a–1g | Thiol, 2a–2g | Reducing agent | | |
|---|---|---|---|---|---|
| | | | THPP | TCEP | DTT |
| 1 |  1a |  2a | 99[c] | 77[c] | 35[c], 85[d] |
| 2 |  1b |  2b | 82[e] | 25[e] | 30[e] |
| 3 |  1c |  2c | 94[f] | 90[f] | – |

(1) McNulty et al., *Bioorg Med Chem Lett*, **2015**, 25, 4114.

# Why Work With Solvay?

- **Get the speed, flexibility and intimacy of a small company with strong corporate support**
- Ability to meet demanding purity, supply and scale-up needs, successfully transitioning chemistries from lab quantities to industrial scale production
- Proven track record of developing innovative and practical routes to market
- Diverse and expanding R&I organization prepared to support today's applications and tomorrow's innovations
- Safe handling and processing of laboratory and large scale air-sensitive material
- Logistics, registration support, toxicology support

Together, let's unlock the potential of phosphorus chemistry to support your sustainable growth

# Thank you.

Dino Amoroso, Ph.D., North American Account Manager
dino.amoroso@solvay.com

William Stibbs, Ph.D., Senior Business Development Manager
william.stibbs@solvay.com

Eamonn Conrad, Ph.D., Global Business Development Manager
eamonn.conrad@solvay.com

SOLVAY

Progress beyond

# Phosphorus Specialties: the cornerstone of synthesis for pharmaceutical applications

## *Samples available from Strem*


## *Industrial Scale from Solvay*

**Innovation:**

160 years of know-how and innovation in phosphorus chemistry

**Partnership:**

We work closely with customers to translate their needs into concrete solutions

**Differentiated products and technologies:**

We offer a wide range of phosphorus-based chemistry to meet precise application requirements