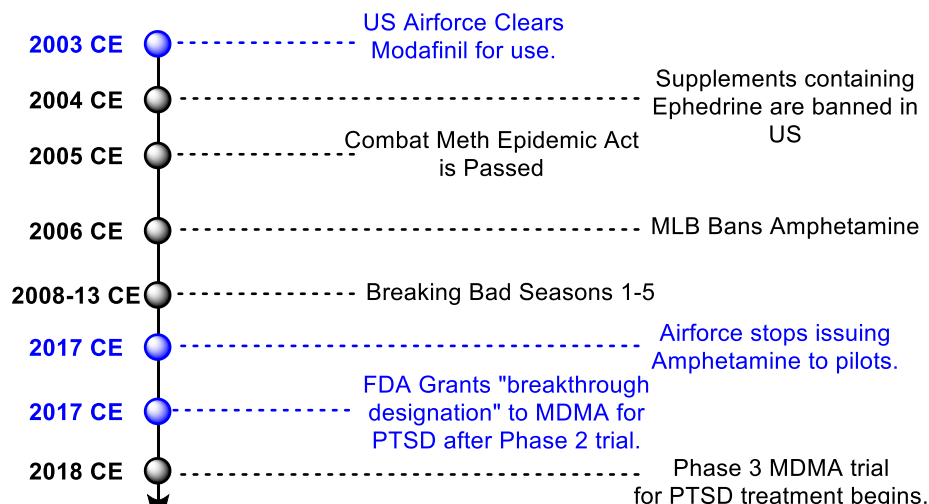
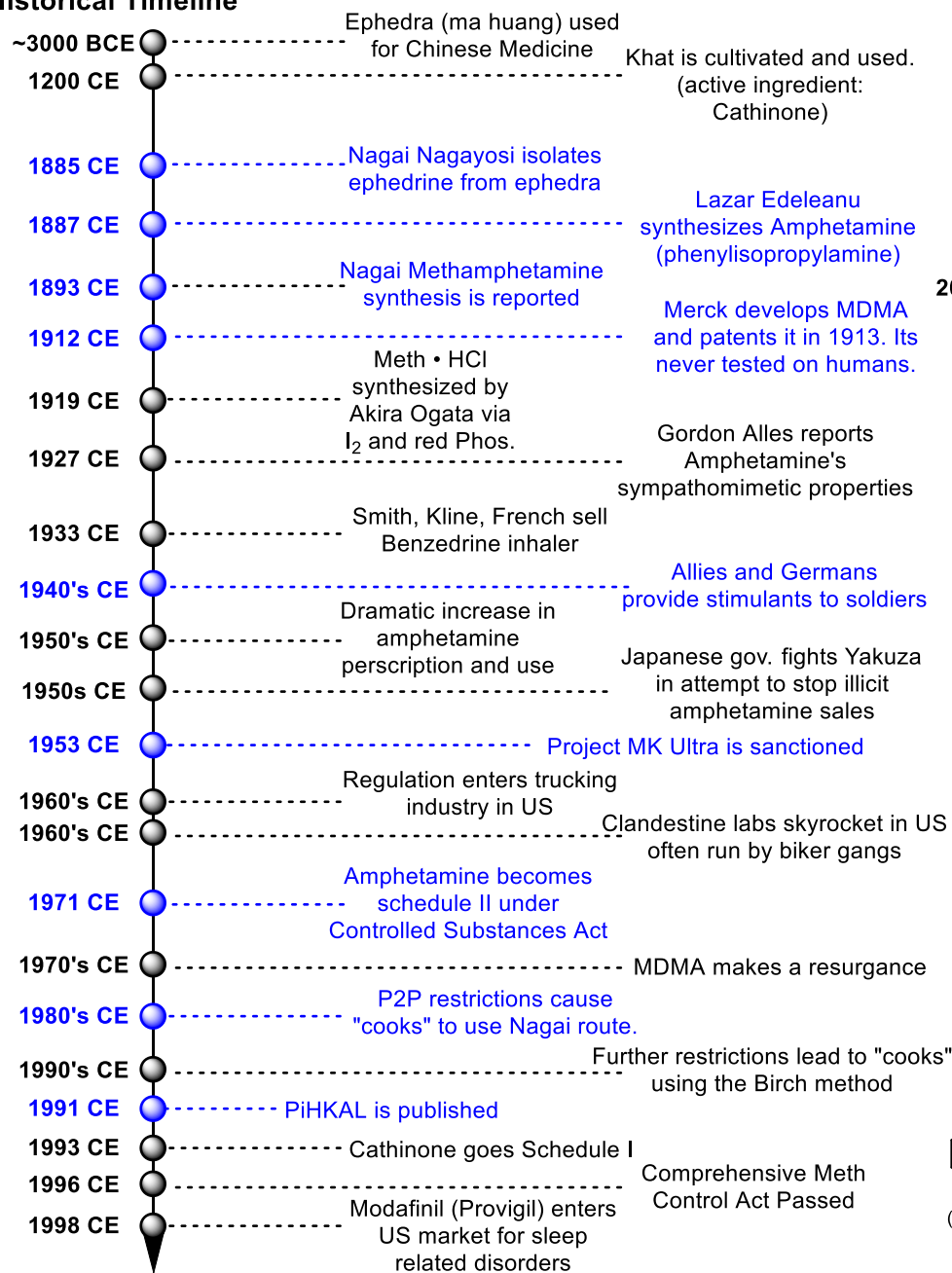


# Amphetamines and Trace Amines

Stephen Harwood

Baran Group Meeting  
1/11/2020

## Historical Timeline

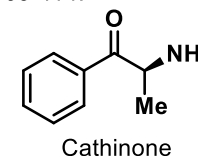


### Isolation of Ephedrine from Ma Huang

1kg of powdered Ma Huang is extracted with cold benzene and dilute sodium carbonate. The organic layer is washed with dilute HCl, which is then basified with potassium carbonate to liberate the basic residues. Extraction with chloroform followed by distillation yields 2.6g of crude pdt. Fractional crystallization of the HCl salt in alcohol was used for purification.

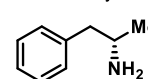
*J. Biol. Chem.* **1926**, 70, 109-114.

**Khat** contains cathinone which has moderate stimulant properties. It is very popular around the red sea regions. Approximately 40% of Yemen's total water supply goes to the cultivation of the khat plant.

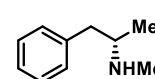


**Methamphetamine** is seeing a resurgence in the US. Illicit Meth today is nearly 100% pure. In 2015 nearly 6,000 people died from meth use, a 255% increase from 2005.

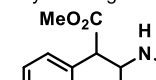
[www.nytimes.com/2018/02/13/us/meth-crystal-drug](http://www.nytimes.com/2018/02/13/us/meth-crystal-drug)



(+)-amphetamine (Adderall)

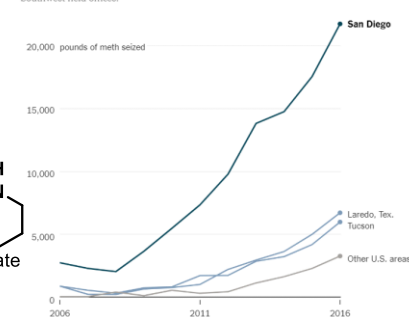


(+)-methamphetamine (Desoxyn, Methedrine)



methylphenidate (Ritalin)

**Meth Seizures Are on the Rise Across the Nation**  
The amount of methamphetamine seized by U.S. authorities has been increasing, especially in Southwest field offices.

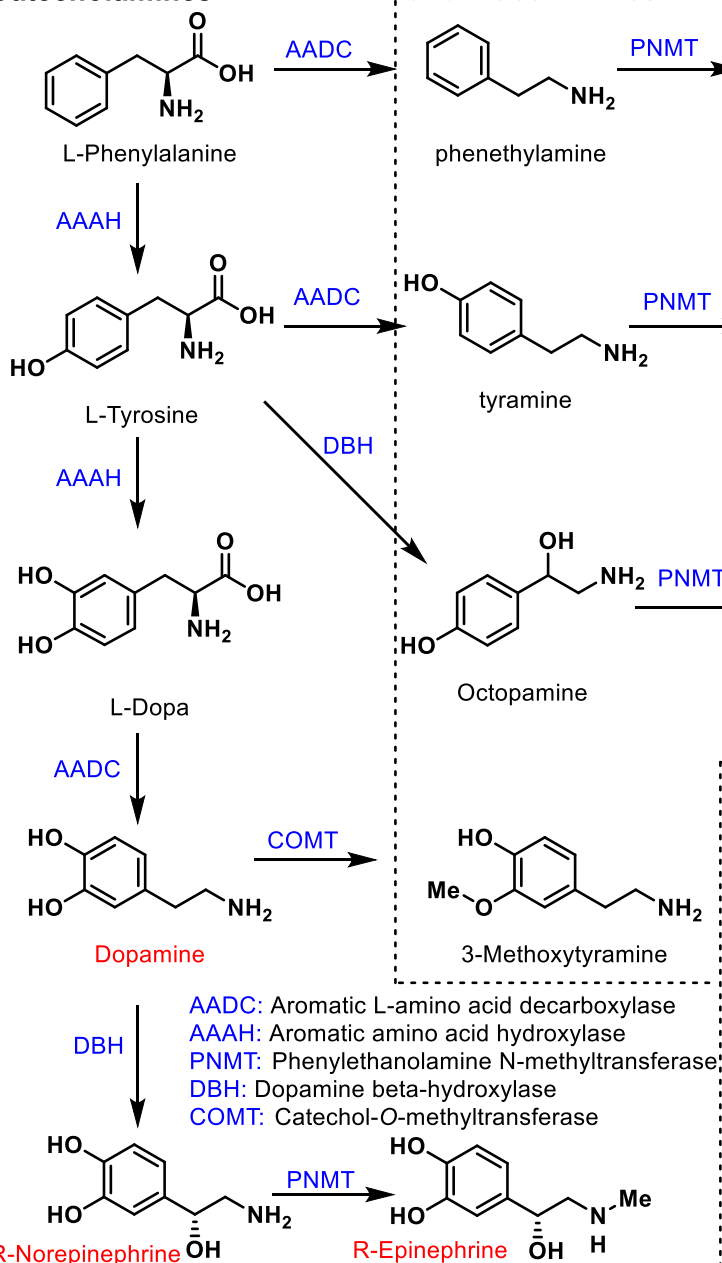


# Amphetamines and Trace Amines

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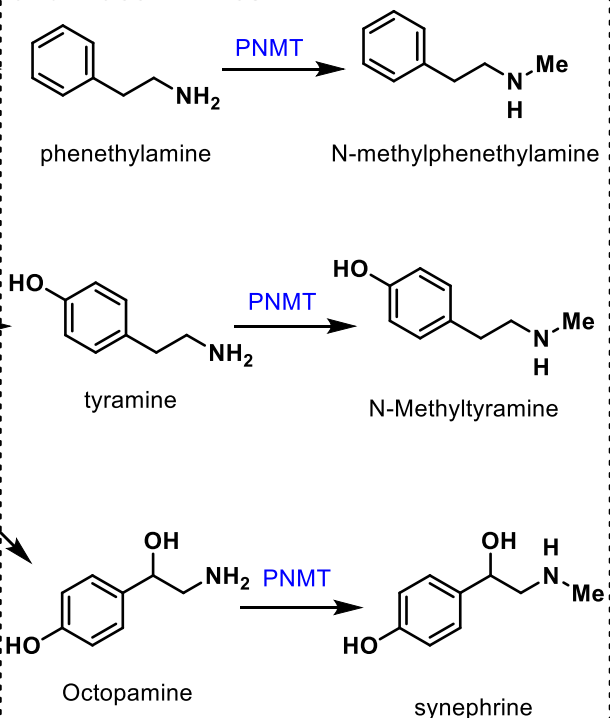
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## Catecholamines



Trends Pharmacol. Sci. 2005 274–281

## and Trace Amines



## Dopamine

Trends in Neurosciences. 2007, 30, 194-202

- Synthesized in the medulla of the adrenal glands and in neurons where it is a neurotransmitter and precursor to epinephrine and norepinephrine.
- It does not cross the BBB.
- Two known types of receptors D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-Like (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>)
- Binding to D<sub>1</sub>-like receptors is excitatory
- Binding to D<sub>2</sub>-like receptors is inhibitory.
- D<sub>1</sub> receptors are most common, D<sub>2</sub> are common and D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub> are least common.
- Its Major functions are: Motor Control, Motivation, Arousal, Reinforcement and Reward
- Its Minor Functions are: Sexual Drive, Nausea, and Lactation.
- Produced in the Ventral Tegmental Area (VTA) and released in the Frontal Cortex, Nucleus accumbens and Hippocampus.
- Produced in the Substantia Nigra and released in the dorsal striatum. (motor functions pathway)
- Higher levels of dopamine in pathways of the Basal Ganglia indicate easier activation. This area of the brain is responsible for initiation of behaviors. Thus dopamine plays a critical role in operant conditioning to reward signals.

## Epinephrine

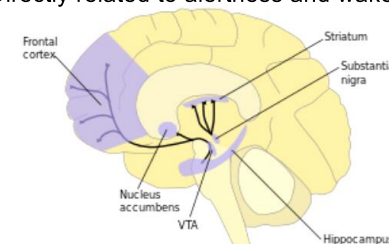
N. Engl. J. Med. 1980; 303:436-444

- Produced in adrenal glands and neurons in the medulla oblongata.
- Regulates visceral functions like respiration.
- In fight or flight, interacts with the sympathetic nervous system: increases blood flow to muscles and cardiac output, dilates pupils, releases blood sugar.
- Binds  $\alpha$  and  $\beta$  receptors but does not cross BBB.
- Not produced in the brain. Peripheral system only.
- Effects long term memory of stressful events through peripheral excitation.

## Norepinephrine

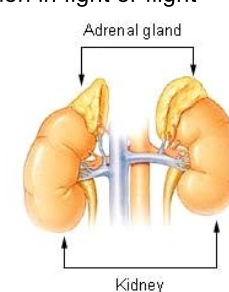
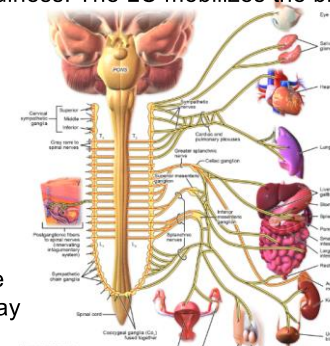
Comprehensive Physiology 2015, 5, 1-15

- Produced in the locus coeruleus (pons/brain), utilized by sympathetic ganglions along spinal cord.
- Redirected by adrenal glands back into blood, similar effects as epinephrine by binding adrenergic receptors
- Effects include: pupil dilation, increased cardiac output, adipose tissue thermogenesis, vasoconstriction, sugar production in liver, release of glucagon in pancreas
- Directly related to alertness and wakefulness. The LC mobilizes the brain for action in fight or flight



Above: Neural Pathway of Dopamine  
Right: Norepinephrine Neural Pathway

ACS Chem. Neurosci. 2015, 6, 16-26



Above: Epinephrine  
Produced in Adrenal gland

# Amphetamines and Trace Amines

Stephen Harwood

Baran Group Meeting

1/11/2020

## Trace Amine Biology

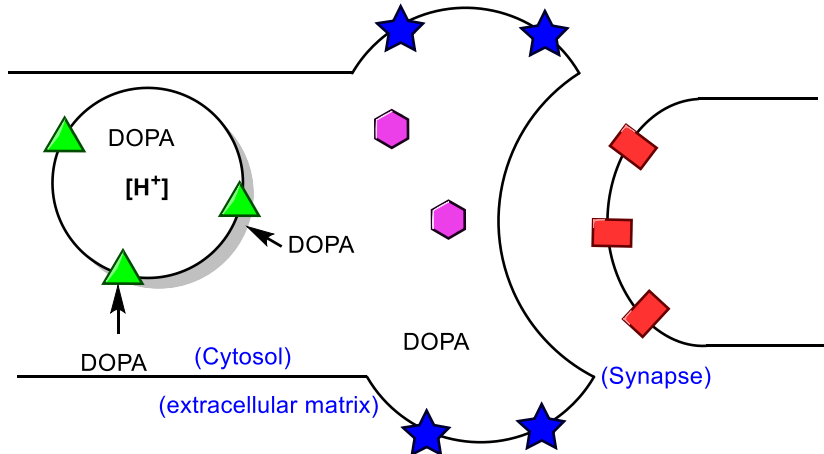
- 9 Genes/Pseudogenes in humans that are known to be related to trace amines.
- Genes: TAAR1, TAAR2, TAAR5, TAAR 6, TAAR8 and TAAR9
- Pseudogenes: TAAR3, TAAR4, TAAR5.
- Mostly orphan genes with little understood about their role and natural substrates.
- TAAR1 is most well understood and is found in the VTA, Frontal Cortex, hypothalamus and elsewhere.
- Binds tyramine >  $\beta$ -phenethylamine > dopamine = octopamine. It is also known to bind synthetic amphetamines.
- It exerts a negative control on dopaminergic activity indicating trace amines may act as neuromodulators.
- TAAR2 sometimes has a nonsense mutation in schizophrenic patients.
- TAAR5 is most highly conserved among mammals, found in olfactory epithelium.
- TAAR6 has been associated with schizophrenia, depression and bipolar.
- TAAR8 may be stimulated by lipopolysaccharides, making it potentially unique.
- No reliable information is known on TAAR9's role.

*Biomed. & Pharmacotherapy* **2016**. 83. 439-449

*Progress in Neurobiology*. **2006**. 79. 223-246

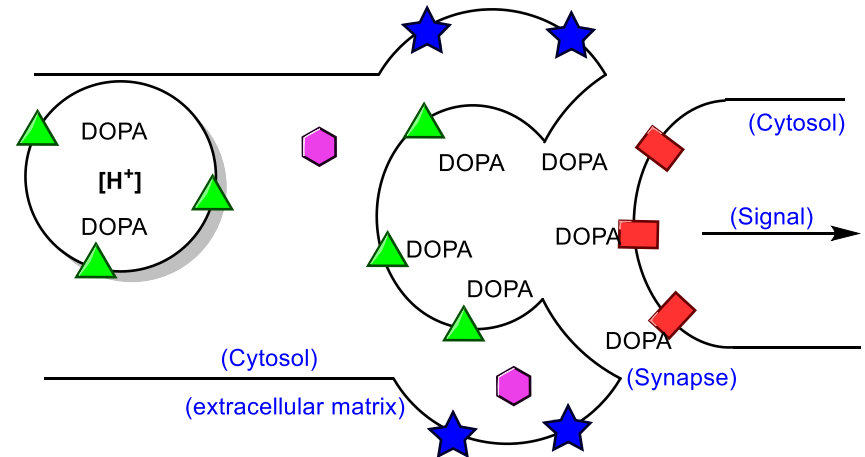
*Trends Pharmacol. Sci.* **2005** 274-281

## Cellular Role of Dopamine

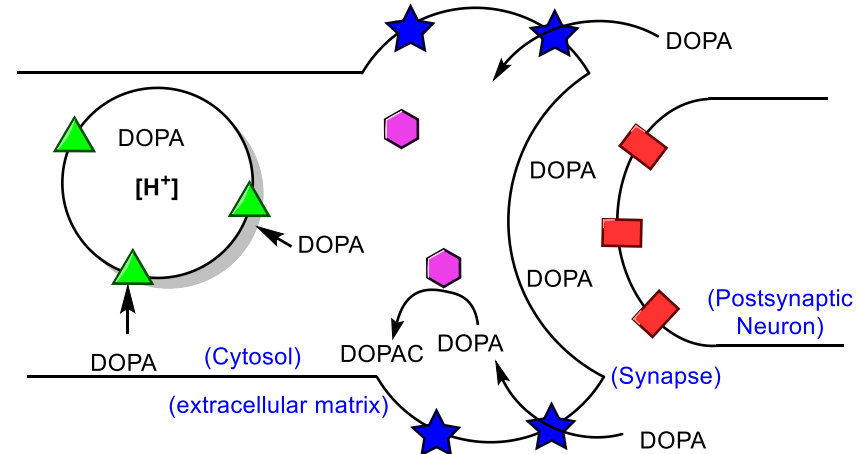


1. Using a proton gradient established by an ATPase, VMAT antiports DOPA into the vesicle and a proton to the cytosol.

- ▲ Vesicle monoamine transporter (VMAT)
- Dopamine Receptor ( $D_1$ -like or  $D_2$ -like)
- ★ Dopamine Transporter (DAT) ("reuptake pump")
- ◆ Monoamine Oxidase (MAO)



2. The vesicle travels down the axon reaching the terminal where exocytosis releases dopamine into the synapse when signaled. The extracellular dopamine binds the dopamine receptor, transmitting the signal to another neuron.



3. The Dopamine Transporter pumps DOPA into the cytosol of the presynaptic neuron. Here, the DOPA can be reused by transport into another vesicle by VMAT or destroyed by MAO.

DOPAC= Dihydroxyphenylacetic acid

Mechanisms of neurotransmitter release by amphetamines: a review.

*Progress in Neurobiology*. **2005**. 75. 406-433

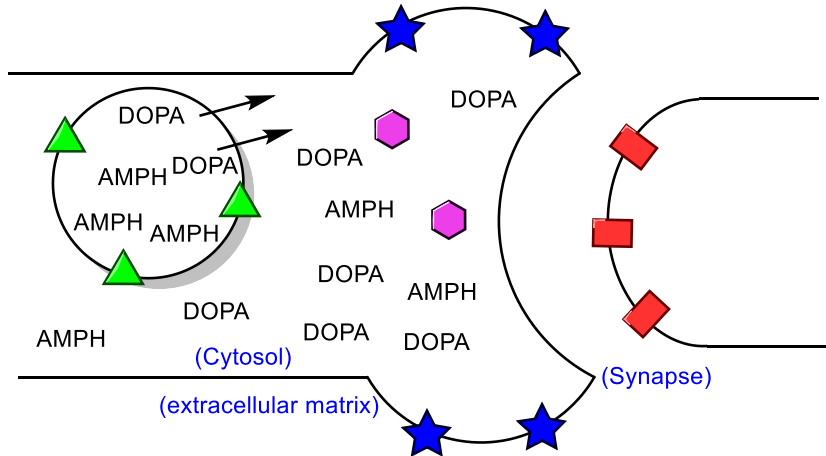
# Amphetamines and Trace Amines

Stephen Harwood

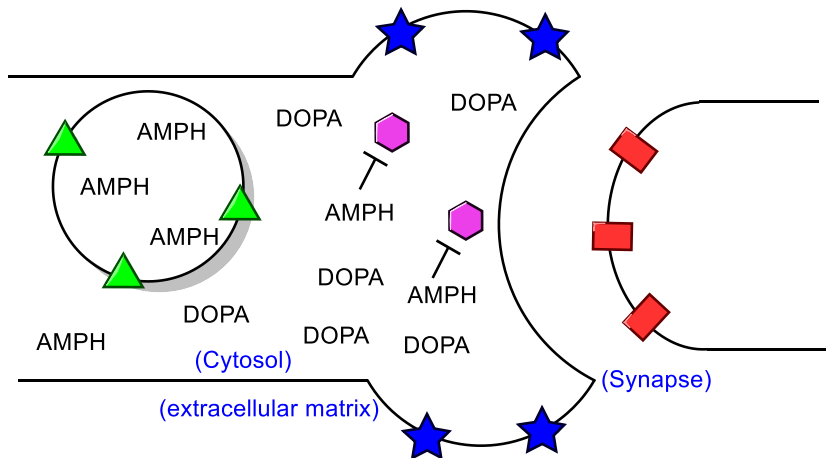
Baran Group Meeting

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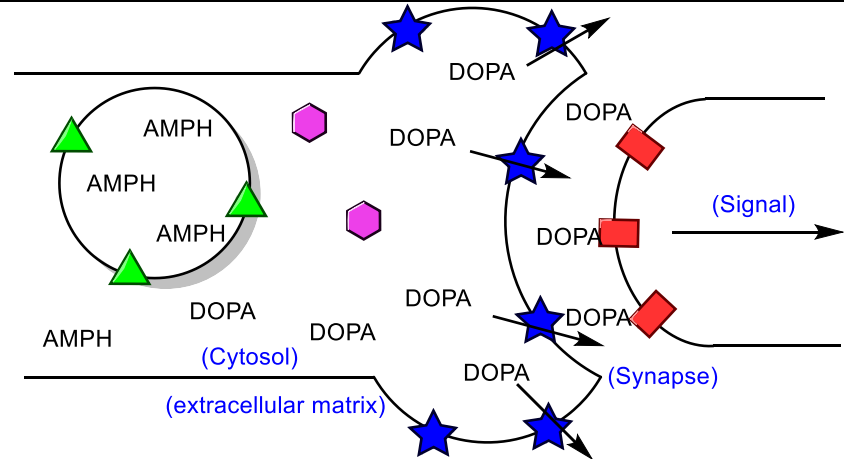
## Modulation of Dopamine by Amphetamine



1. Amphetamine destroys the proton gradient in vesicles leading to dopamine release into the cytosol.



2. Amphetamine inhibits MAO, protecting cytosolic DOPA.



3. AMPH causes DAT to actively transport DOPA into the synapse, the wrong way. The exact mechanisms for this are not yet known. AMPH also slightly blocks reuptake of DOPA. This leads to an increase in extracellular dopamine recognized by nearby neurons.

4. AMPH stimulates the production of DOPA, further amplifying the drugs effects.

In addition to DOPA, AMPH affects the pathways of the other catecholamines and even tryptamines like serotonin. The effects of other stimulant producing substituted amphetamines like METH are mechanistically similar.

"Therapeutic doses are normally given up to about 60 mg. ... [I have] never gone over 40 mg, but based on the experiences of others who have, [I recommend] this estimated dosing schedule: (1) Light increase in motivation: 10–15 mg. (2) 'Good' club buzz: 20–40 mg (add 1-2 drinks and [you are] set!). (3) Highway speeds: 60–80 mg (might start cleaning the club/party your [sic] at, lol). (4) TWEAKED OUT: 100–120 mg (not recommended). \*\*Based on Instant-release pills take orally... as always tolerance and body-type depending..."

*Pharmacol Rev.* **2014**, 66, 193–221

- ▲ Vesicle monoamine transporter (VMAT)
- Dopamine Receptor (D<sub>1</sub>-like or D<sub>2</sub>-like)
- ★ Dopamine Transporter (DAT) ("reuptake pump")
- ◆ Monoamine Oxidase (MAO)

## Theories of Dopamine Receptor Evolution

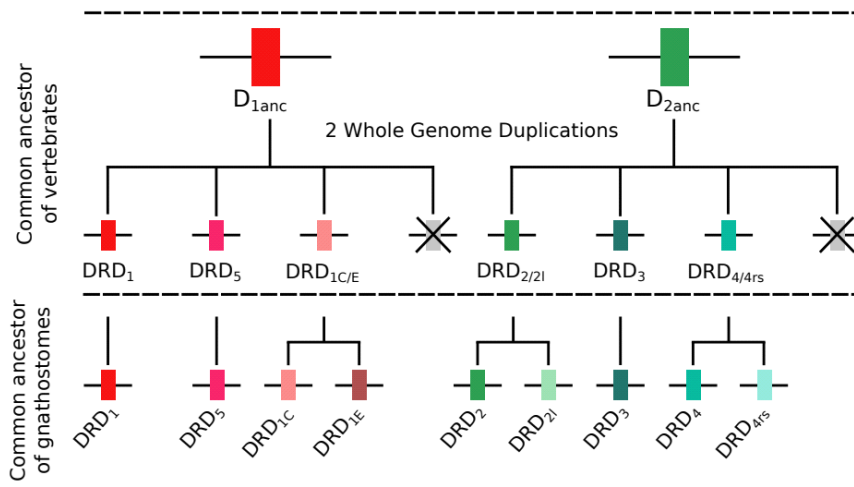
- D<sub>1</sub>-Like and D<sub>2</sub>-Like receptors are thought to have completely independent lineages indicating that the ability to bind dopamine was **acquired twice**

### D<sub>1</sub>-Like: DRD<sub>1</sub>, DRD<sub>5</sub>, DRD<sub>1C</sub>, DRD<sub>1E</sub>,

- Lack of introns
- Activates G $\alpha_{s/oif}$  G-proteins **causing** cAMP production.
- D<sub>1</sub> has sister relationships with D<sub>5</sub> and the D<sub>1C/E</sub> clade.
- D<sub>1C</sub> and D<sub>1E</sub> have a sister relationship.
- Over time, the binding pocket of D<sub>1</sub> has become more refined for DOPA.

### D<sub>2</sub>-Like: DRD<sub>2</sub>, DRD<sub>2L</sub>, DRD<sub>3</sub>, DRD<sub>4RS</sub>,

- Up to 6 introns.
- Activates G $\alpha_{i/o}$  G-proteins **inhibiting** cAMP production.
- D<sub>2</sub> has sister relationships with D<sub>3</sub>.
- D<sub>4</sub> and the D<sub>2/3</sub> clade have a sister relationship..



During the two episodes of vertebrate whole genome duplication, 4 copies of D<sub>1</sub>-like and D<sub>2</sub>-like receptors were produced (8 total). In both the D<sub>1</sub> and D<sub>2</sub> lineages, one of the copies was lost. Later, in the gnathostome ancestor, the DRD<sub>1C/E</sub> ancestor was duplicated. Also in the gnathostome ancestor, the DRD<sub>2/2L</sub> and DRD<sub>4/4RS</sub> ancestors were duplicated giving rise to the 5 D<sub>2</sub>-like receptors we know today.

- Note: Research on this topic is still very active and the theories presented may change. Additionally, an opinion exists that eukaryotic cells acquired cell-cell signaling machinery through late horizontal gene transfer from bacteria (similar to the way eukaryotic cells gained mitochondria).

PeerJ **2018** DOI: 10.7717/peerj.4593; *Biol. of the Cell* **2003**, 95, 489-502  
*Trends in Genetics* **2004**, 20, 292-299

## ADHD and Amphetamines

- Amphetamines have become the first-choice treatment for ADHD.

### Attention Deficit Hyperactivity Disorder (ADHD)

- Today, 4-10% of children are affected in US. Boys are 2X diagnosed compared to girls.
- Three categories: Predominantly inattentive (ADHD-PI), Predominantly Hyperactive-impulsive (ADHD-PD or ADHD-HI), and Combined type (ADHD-C).
- 30-50% of people have ADHD symptoms continue into Adulthood.
- Genetics determine roughly 75% of cases, indicating a genetic component although ADHD is very poorly understood today.
- Difficult to diagnose because the behaviors exist on a continuum, leading to its controversy as a diagnosis.

### Genetic Variance

- Some individuals with ADHD possess DAT and/or DRD<sub>4</sub> variants and decreased levels of D<sub>2</sub>/D<sub>3</sub> receptors. This makes them effectively less receptive to dopamine signals.
- Some studies have found differences in brain structure in the left frontal cortex and regions responsible for long-term memory.
- Some potential, not yet clinically validated biomarkers are:
  - Phenethylamine levels in urine
  - Platelet levels of MAO
  - Zinc and Iron levels.

### Prenatal Stress in Mothers

- A variety of neurodevelopmental and behavioral phenotypes may be associated with prenatal stress, including ADHD.
- Individual fetuses may respond differently to prenatal stress hormones. Some may show no effect based on their genetic composition.
- Some researchers theorize that this could be an evolutionary mechanism to make offspring better prepared for the environment they are entering by responding to the mother's signaling.

### Evolution and ADHD

- Many theories exist based around the idea that ADHD gave a selective advantage to either individuals or groups with individuals who were more vigilant, more risk taking, more exploratory, more energetic, or more impulsive.
- Some speculate that it may have been an individual disadvantage, but an advantage to the group.
- The most culturally popular is the "**Hunter vs. Farmer Hypothesis**" first suggested by Thom Hartmann in his book *Attention Deficit Disorder: a Different Perspective*. Thom Hartmann is a political commentator and his book was not a scientific work. Nevertheless, it postulated a theory that some researchers have adopted.
  - The idea is that Hunters had to be vigilant and hyperfocused on their environment to catch prey and not become prey. When humans became farmers this was no longer an advantage in a sedentary society and became a maladaptation that some humans still have today.

*The Lancet Psychiatry* **2018** 5, 727-738

*JAMA* **2009**, 302, 1084-1091

*Nature Reviews: Neuroscience* **2008**, 9, 957-964

*J. of Child Psychology and Psychiatry* **2011**, 356-367

*Current Opinion in Genetics and Development* **2007**, 17, 234-238

# Amphetamines and Trace Amines

Stephen Harwood

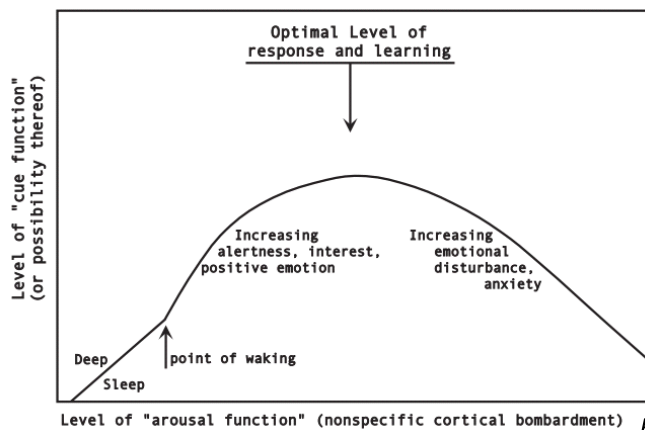
Baran Group Meeting  
1/11/2020

## Performance Enhancing Effects?

- Evidence shows that Amphetamine stimulants can have positive effects on *Physical Performance*.
  - Increase in physical strength
  - Decrease in muscle fatigue
  - Increase in endurance
  - Decreased reaction time
  - Increased alertness and focus
  - Increased acceleration
- Because of these performance effects and their dangerous side effects, most professional and collegiate sports have banned amphetamines.
- In addition to their positive effects, there are several side effects which can hurt performance
  - Decreased heat tolerance (disrupts thermoregulation leading to increased core temperature).
  - Increased risk of cardiac arrhythmias, dyskinesia, seizures, hallucinations.
  - If too much is taken it can negatively impact focus, reaction time, and decision making. **These negative effects can prove fatal under physical exertion.**

## Cognitive Enhancers: A Limitless Pill?

- Research is inconclusive on the impact of phenethylamines on short and long term memory and focus in healthy individuals. Meta-studies find evidence of bias in the results and draw inconclusive conclusions.
- Results are highly dose dependent on an individual level. High doses hinder performance broadly.
  - Modafinil has gained attention recently as a safer amphetamine with potentially small cognitive enhancing effects. However, this has yet to be proven.
  - Amphetamine (Adderall) and Ritalin (Methylphenidate) are frequently employed as study drugs by college and high school students.
  - Between 5 and 35% of students college students use phenethylamines illegally.
  - Between 3 and 10% of grade school students use phenethylamines illegally.



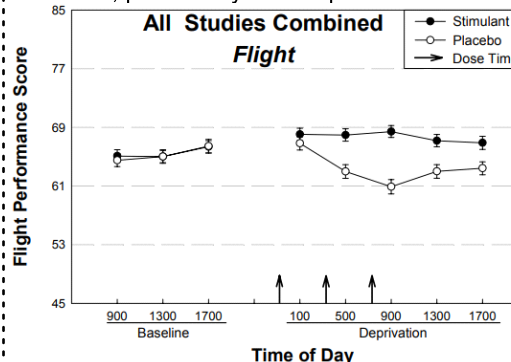
Addict. Behav. **2017** 245-249  
*J. Cog. Neurosci.* **2015**  
 27, 1069-1089  
*Prim. Care Clin. Office Pract.*  
**2013**, 40, 487-505  
*Addiction.* **2013** 109, 547-557

**On Left:** Yerkes-Dodson Theory

*Pharmacol. Rev.* **2014** 193-221

## Use to Fight Fatigue

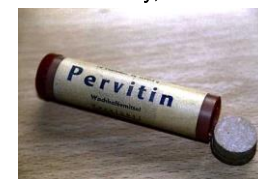
- Amphetamines have been used historically and contemporarily to fight fatigue in militaries (particularly in aviation), long-haul trucking, oil rigs, med. residency, etc.
- While controversy exists in the literature on the extent to which phenethylamines have been used in the military, clear documentation of their widespread useage in WWII exists.
- Recently, Modafinil has been gaining attention and useage by militaries around the world, US included.
- They are most often used in aviation for long bombing missions. Although, they are also used in long ground missions, particularly in the special forces.



"Overall, modafinil maintained flight accuracy within approximately 15-30% of baseline levels, whereas performance under the no-treatment/placebo condition declined by as much as 60-100%. Benefits were most noticeable after 24 to 32 h of continuous wakefulness"

Jacobson's "miracle tissue regenerator" shots, consisted of amphetamines, animal hormones, bone marrow, enzymes, human placenta, painkillers, steroids, and multivitamins. Although, he had many important and famous clients, his most famous was JFK who recieved his "miracle tissue regenerator" shot on over 30 occasions.  
 "I don't care if it's horse piss! It's the only thing that works."  
 - JFK

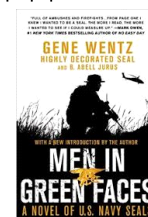
*Aviat Space Environ Med.* **2004** 75 9, 777-784.  
*Psychopharmacology* **2000**, 150, 272-282  
*Labor: Studies in Working-Class History of the Americas.* **2014**, 11, 63-90 DOI 10.1215/15476715-2801097  
*J. Interdisciplinary His..* **2011**, 205-233  
*Bulletin of Anesthesia History.* April **2011**, 21-32



Methamphetamine issued by the Nazi's in WWII. Called "Panzerschokolade" or "Stuka-Tabletten"



Amphetamine issued by Allied Forces. Called "go pills" "Bennies" or "pep-pills"



Max Jacobsen (Dr. Feelgood)

## Disclaimer:

The following information was legally obtained under the First Amendment of the US Constitution. HOWEVER, attempting to act on this information through the purchasing of precursor chemicals with intent to manufacture, synthesis of controlled substances or their derivatives, and consumption of these chemicals are **all felony crimes** and should not be committed. ADDITIONALLY, many of these chemicals are highly **reactive** and many of the portrayed chemical reactions produce **dangerous** gases and other byproducts. These reactions **should NOT be attempted** for safety reasons.

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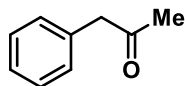
# Amphetamines and Trace Amines

Stephen Harwood

Baran Group Meeting

1/11/2020

## P2P Methods of Synthesis

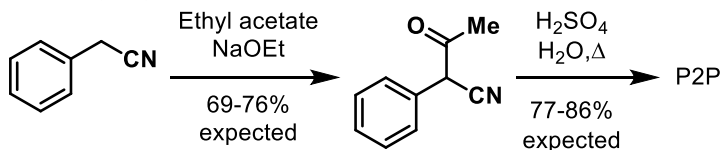


Phenyl-2-Propane (P2P)

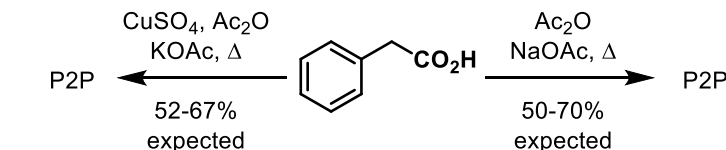
In 1980, P2P became a scheduled chemical, requiring clandestine labs to synthesize the precursor.

Procedures can be found at erowid.org

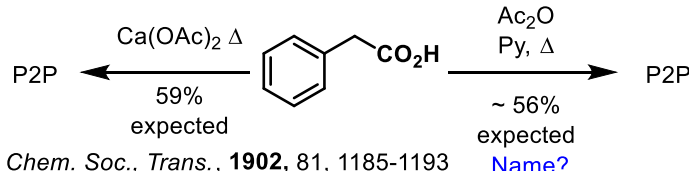
### From Benzyl Cyanide



### From Phenylacetic Acid

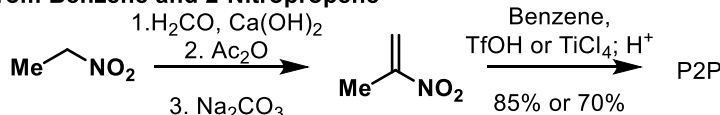


*Chemie Listy* **1990** 84 (9), 993-994 *Chem. Ber.* **1935**, 68, 2112



*J. Chem. Soc., Trans.*, **1902**, 81, 1185-1193

### From Benzene and 2-Nitropropene



Caution: High "fume off" risk.  
Very oxygen sensitive!

*Tet. Lett.* **1988**, 29, 2977-2978

*JOC* **1989**, 54, 733

*Tetrahedron* **1990**, 46, 7539-7555

*JACS* **1845**, 67, 205

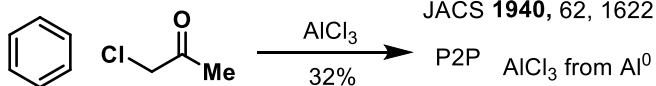
*Ind. Eng. Chem.* **1940**, 32, 34

*JOC* **1950**, 15, 8.

*JOC* **1961**, 26, 1348-1357

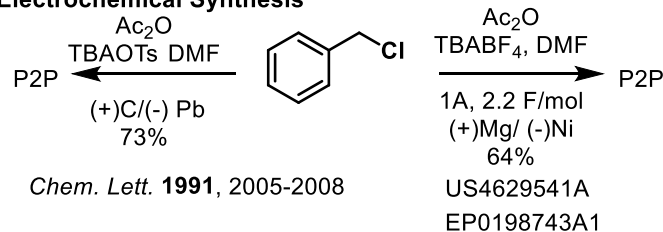
Procedure was reproduced  
by "Scooby Doo"

### From Benzene and chloroacetone



Chloroacetone from acetone, CuCl, LiCl and HCl  
or MeN<sub>2</sub> and AcCl. *JACS* **1955**, 5274 and *JACS* **1954**, 1186.

## Electrochemical Synthesis

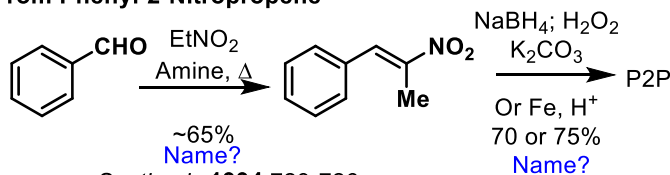


*Chem. Lett.* **1991**, 2005-2008

US4629541A

EP0198743A1

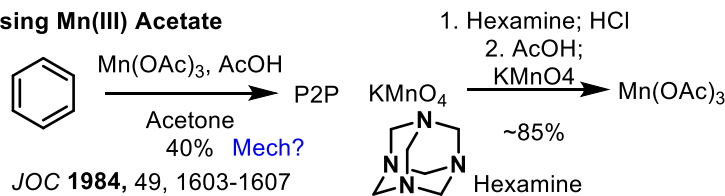
### From Phenyl-2-Nitropropene



*Synthesis* **1994** 723-726

Alexander Shylgin, Pihkal pg 734

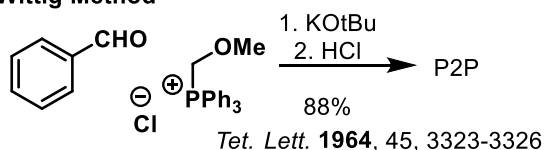
### Using Mn(III) Acetate



*JOC* **1984**, 49, 1603-1607

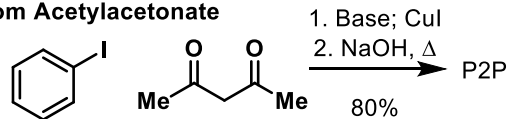
Hexamine

### Wittig Method



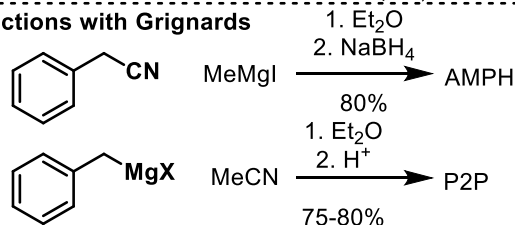
*Tet. Lett.* **1964**, 45, 3323-3326

### From Acetylacetonate



*Chem. Lett.* **1982**, 11, 597-600

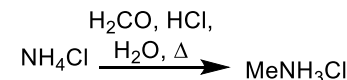
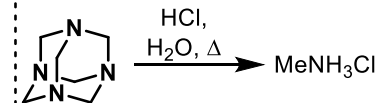
### Reactions with Grignards



*JACS* **1987** 109 3378-3387

*Tet Lett* **1980**, 21, 155-158

## Methylamine Synthesis



*J. Chem. Soc.* **1917**, 844-853

*JACS* **1918** 1411-1515

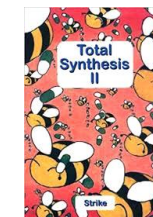
Yields range from 35 to 60%

### Other Feedstocks:

NH <sub>4</sub> NO <sub>3</sub>	Ice Packs
I <sub>2</sub> /HI	Povidone tincture
Red Phos.	H <sub>2</sub> O <sub>2</sub> , KI Fireworks and matchbooks
Pseudo/ephedrine	Decongestants ma huang extraction
Lithium	Online, batteries



Hobart Huson  
"Strike"



Became renowned as the founder of The Hive, an online web forum for clandestine chemists. Hive was referenced in Breaking Bad.



Uncle Fester is the author of several clandestine Chemistry books:

- Secrets of Methamphetamine
- Practical LSD Manufacture
- Advanced Techniques of Clandestine Psychedelic & Amphetamine Manufacture

Interview:

<https://www.youtube.com/watch?v=1PFQbckZivM>



Steve Preisler  
"Uncle Fester"

# Amphetamines and Trace Amines

Stephen Harwood

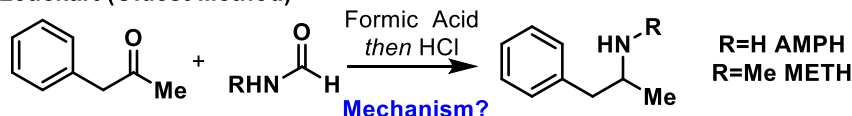
Baran Group Meeting

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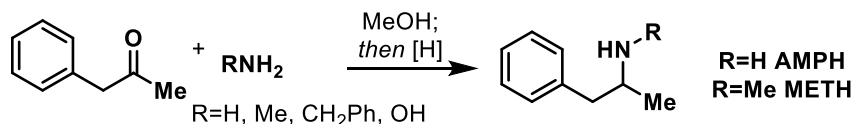
## Most Common Methods of (Meth)Amphetamine Synthesis

### P2P Methods

#### Leuckart (Oldest Method)



#### Reductive Amination



Various reductants can be used to reduce the Schiff Base. Common ones are:

- Aluminum amalgams (from aluminum foil)
- Hydrogen (Pt/C, Pd/C, Raney Ni, Pd/BaSO<sub>4</sub>)
- Metal Hydrides are occasionally used (NaBH<sub>4</sub> and LiAlH<sub>4</sub>)

Advantages of a P2P production method include its scalability. Resolution can be achieved using d-tartaric acid and ethanol.

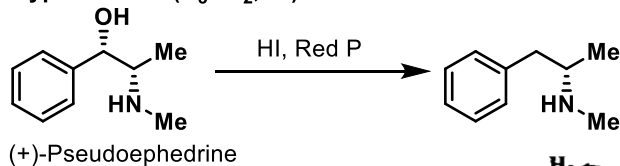
The major disadvantage is the required synthesis of P2P given its scheduled status.

### (Pseudo)Ephedrine Methods

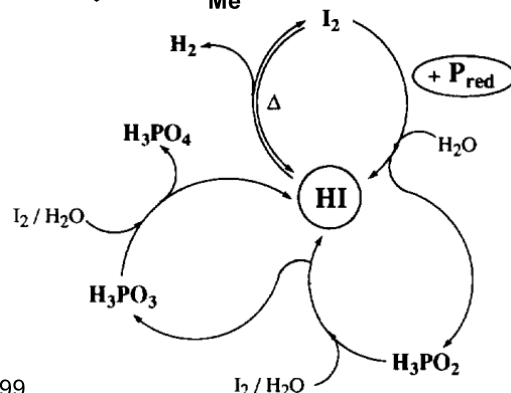
#### Nagai Method (HI, Red Phosphorus)

#### Moscow Method( I<sub>2</sub>, H<sub>2</sub>O, Red Phosphorus)

#### Hypo Method (H<sub>3</sub>PO<sub>2</sub>, HI)



Through the course of the reaction HI dissociates at high temperature to H<sub>2</sub> and I<sub>2</sub>. It is in this way that it acts as a reductant in the reaction. Red Phosphorus reacts with the I<sub>2</sub> produced to generate PI<sub>3</sub> which is hydrolyzed to regenerate HI and form phosphoric acid.



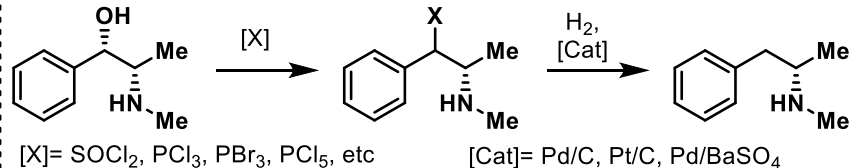
This method gained popularity after P2P became difficult to attain. The major advantage of this method is utilization of the "chiral pool" providing a more potent product per gram.

J. Organomet. Chem **1997**, 529, 295-299

Role of Red Phosphorus and I<sub>2</sub> in Nagai-type methods

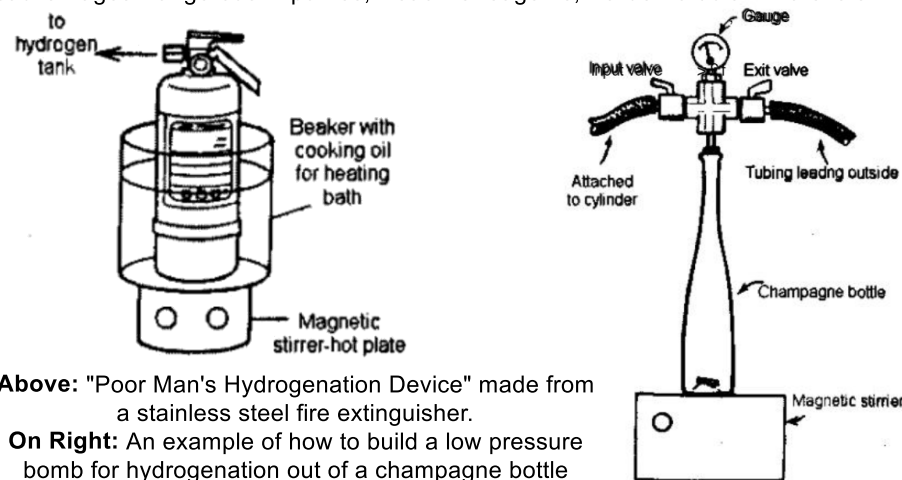
### (Pseudo)Ephedrine Methods (Cont.)

#### Chlorination/ Reduction



Advantages of this route: Chiral Pool materials

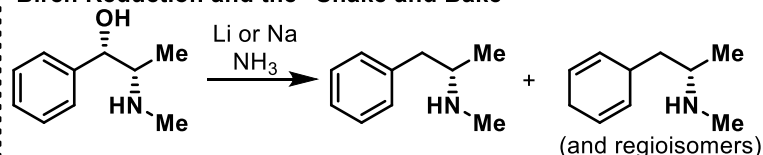
Disadvantages: Dangerous impurities, Reactive reagents, Harder to obtain materials.



Above: "Poor Man's Hydrogenation Device" made from a stainless steel fire extinguisher.

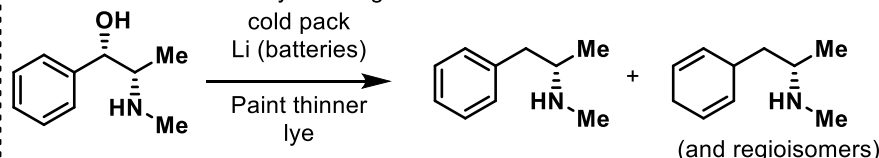
On Right: An example of how to build a low pressure bomb for hydrogenation out of a champagne bottle

#### Birch Reduction and the "Shake and Bake"



Traditional Birch requires free base, and can provide a very pure product. The main problem is the acquisition of ammonia.

This must usually be bought as fertilizer or stolen.



All the contents are placed in a soda bottle, shaken, and occasionally vented to prevent explosion. It has become the most popular method of synthesis for personal use in US. Yields are in the mid 30% range.

Shake and Bake method is VERY dangerous:

[youtu.be/oCZgG5VJdTQ](https://youtu.be/oCZgG5VJdTQ)

# Amphetamines and Trace Amines

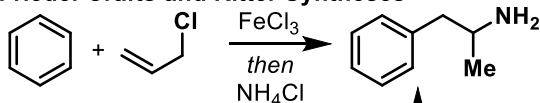
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## Most Common Methods of (Meth)Amphetamine Synthesis (Cont.)

### Friedel-Crafts and Ritter Syntheses



Rxn is messy and low yielding.  
JACS **1946**, 68, 1009-1011

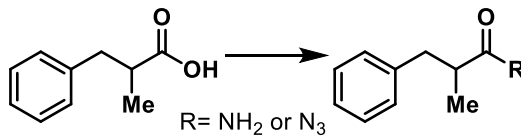
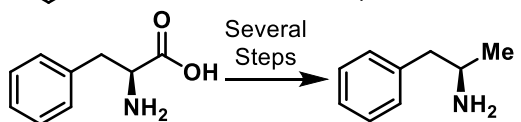
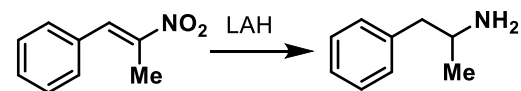


Ritter Reaction: JACS **1948**, 70, 4045-4050

3 main methods of allylbenzene synthesis:

- $\text{PhMgBr} + \text{AllylBr}$
- $\text{PhMgBr}$ ,  $\text{AllylBr}$ ,  $\text{CuI}$
- Cinnamaldehyde + Tosylhydrazine then  $\text{NaBH}_4$   
J. Biol. Chem. **1935**, 108, 619  
J. Organomet. Chem. **1987**, 133-138  
JOC **1978**, 43, 2310

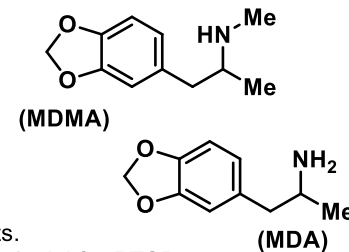
### Other common methods of synthesis



**Key Resources for Synthesis info:**  
*Secrets of Methamphetamine Manufacture 7th ed.*  
 Uncle Fester  
*Total Synthesis II Strike*  
 PIHKAL by Shulgin  
*Forensic Science International* **42**, **1989**, 183-199  
*ACS Chem. Neurosci.* **2018** 2307-2330  
 erowid.org

## 3,4-Methylenedioxy methamphetamine (MDMA) (aka Molly, E, Ecstasy, Adam)

- Synthesized 1912, rediscovered around 1950-60
- Tested on animals by the CIA in the MK Ultra program
- Used as a party drug to replace MDA ("the love drug")
- Shulgin was instrumental for its growth in popularity in the US.
- It became a Schedule I drug in 1985
- It can lead to death due to its body temperature elevating effects.
- Recently given "breakthrough designation" by FDA after Phase 2 trial for PTSD
- Biologically, it modulates the release of serotonin, norepinephrine and dopamine.
- It decreases activity in the amygdala, the fear center of the brain.



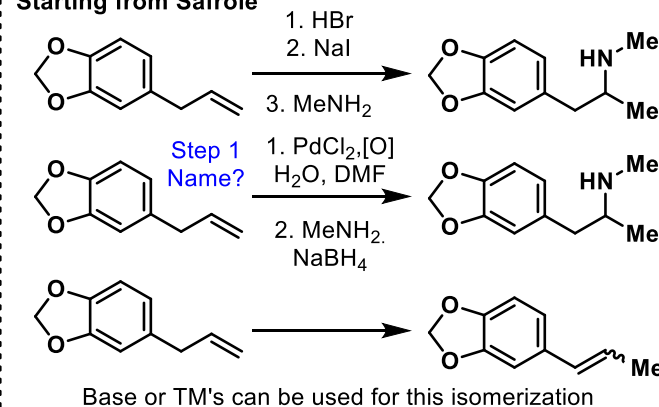
Dr. Alexander Shulgin  
Co-author of  
PIHKAL and TIHKAL

### Synthesis of MDMA

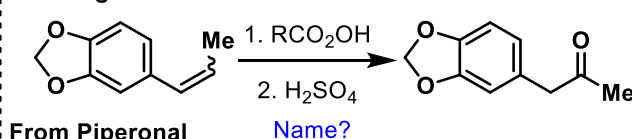
Many MDMA Syntheses are similar to the (meth)amphetamine analogs. They use commercial materials to arrive at a P2P equivalent:

- Halohydrations, Wacker, Condensations, and epoxidations are all utilized

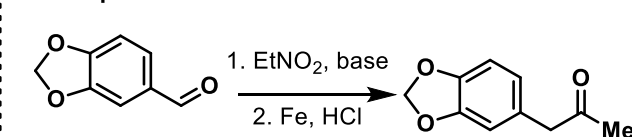
### Starting from Safrole



### Starting from isosafrole

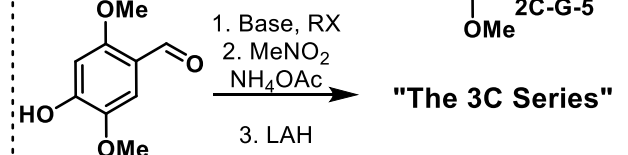
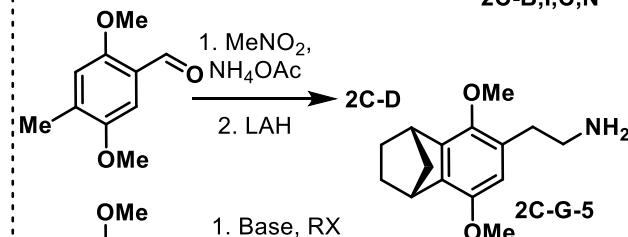
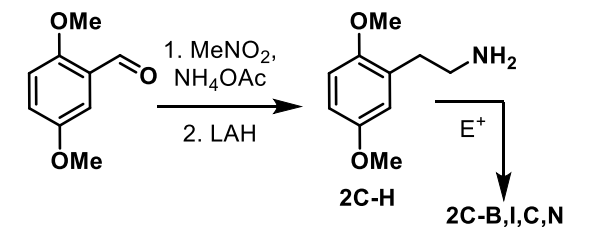
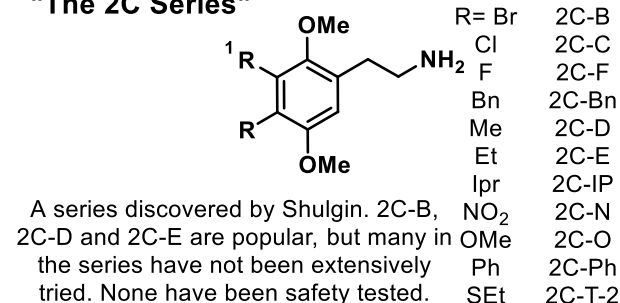


### From Piperonal



Piperonal can be derived from Piperine extracted from black pepper.

### "The 2C Series"

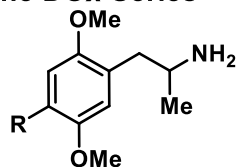


# Amphetamines and Trace Amines

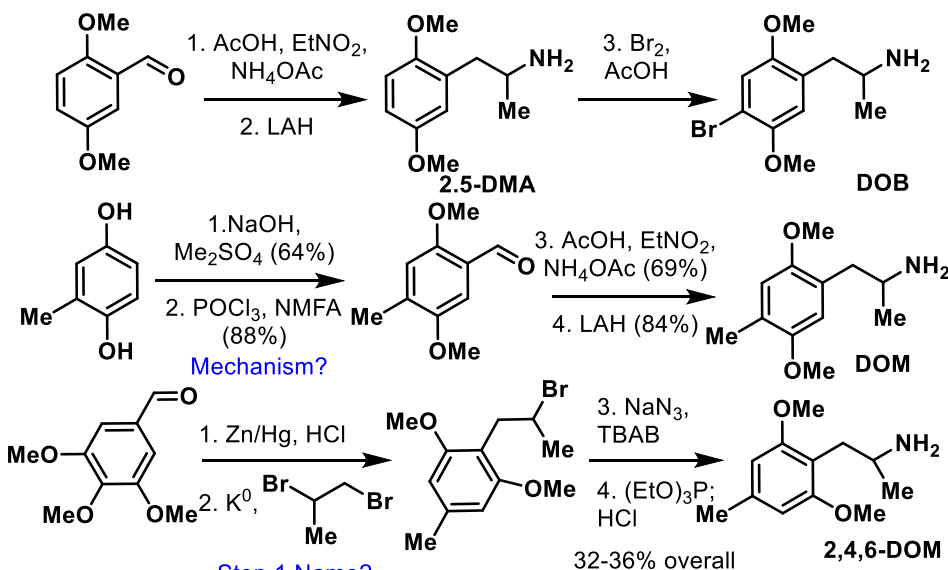
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## "The DOx Series"



- Another Series of Amphetamines pioneered by Shulgin.
- These compounds have high selectivity as 5-HT partial agonists, thus they modulate serotonin levels in the brain.
  - They have long lasting effects.
- DOB, DOC, and DOM are a few of the flagship members.
  - the R-enantiomer displays dramatically more activity.
  - Many are unscheduled in US due to low use.



Novel Synthesis of 2,4,6-DOM reported by "Labrat"

*JOC.* **1990**, 55, 5386-5390  
*Tet. Lett.* **1989**, 30, 1689-1690  
*Synthesis.* **1985**, 202

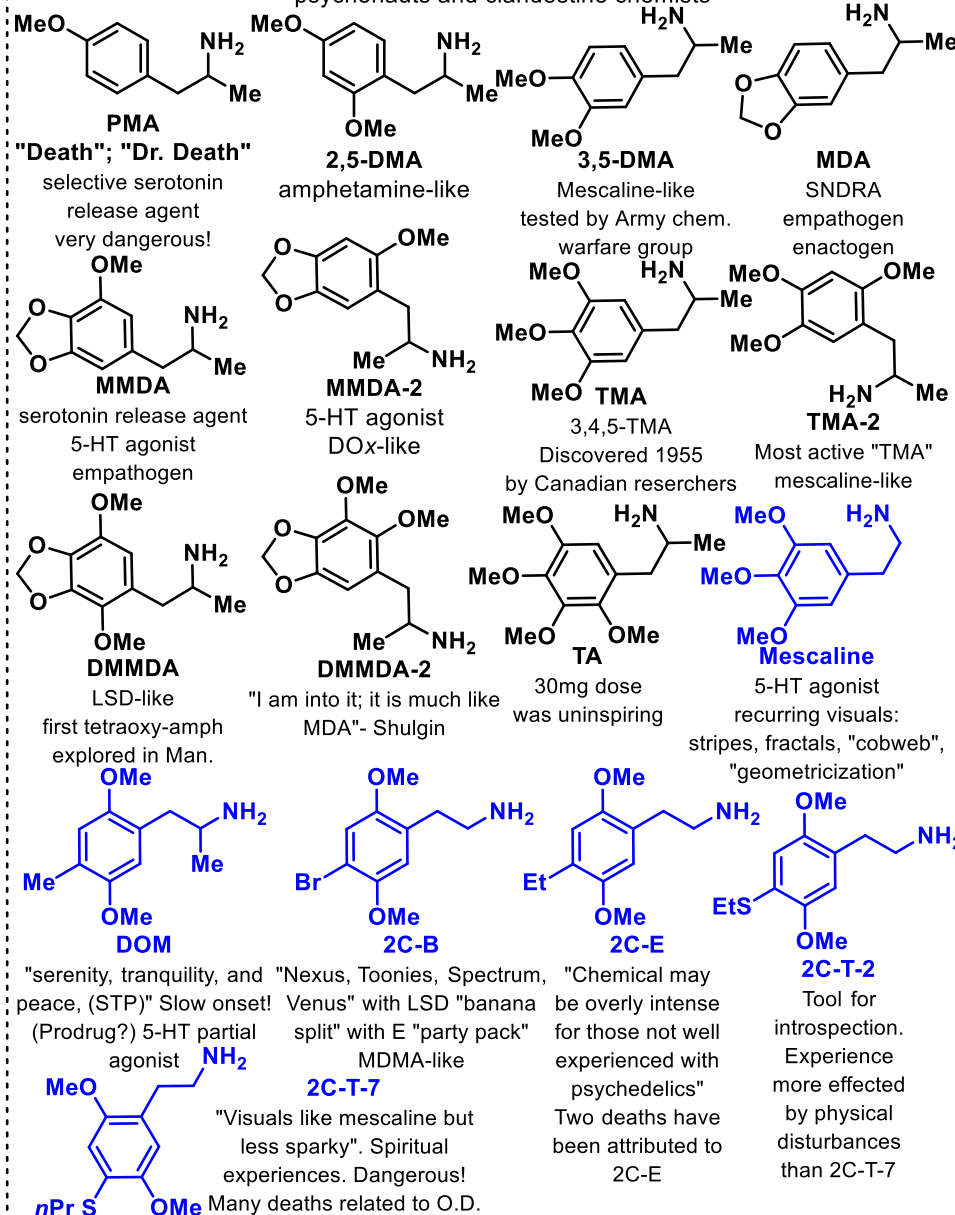
"(with 3 mg) In the middle of the experience I found that I was able to separate components of complex things so as to evaluate them separately. There is no need to respect their normal purpose. The sharpness of observation is enhanced, but one can focus at every different depth of a thing or a concept. Colors are not just brighter; there are more of them. There is a profoundness of meaning inherent in anything that moves. A line of thought or a bit of personal history ties the thinker to the objects that had been thought of, or once experienced. It is this relationship that will prove productive. Not like in a movie which is circular in its totalness, but as in true life where the future is the result of your own involvement with everything about you."

--Shulgin PiHKAL on the effects of DOM

**NOTE: DOB has considerable toxicity in humans and rats. People have gone into coma and have died from ingesting too large amounts of DOx compounds. It is not recommended these compounds be consumed**

## Shulgin's "Essential Amphetamines" and the "Magical Half-Dozen"

- Essential Amphetamines compounds differ from natural product oils by an amine group.
- Magical Half-Dozen (All Schedule I) are Shulgin's top compounds. Very Popular among psychonauts and clandestine chemists



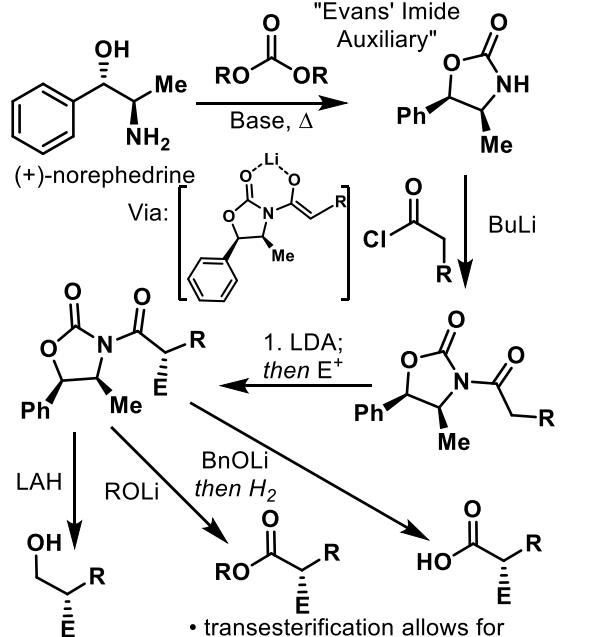
# Amphetamines and Trace Amines

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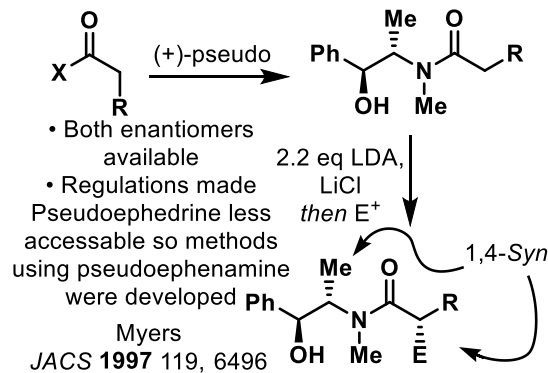
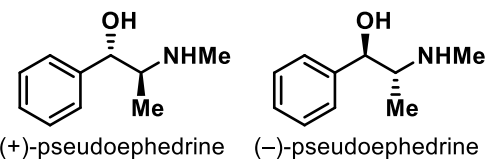
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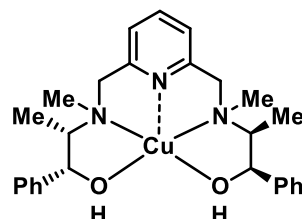
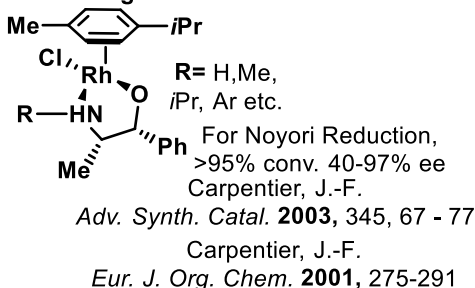
## Use as Auxiliaries



Evans JACS **1982**, 104, 1737, JACS **1985**, 107, 4349  
JACS **1990**, 112, 4011



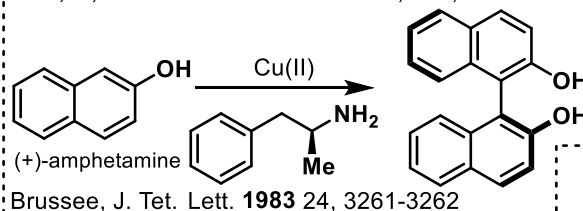
## Use as Ligands



For Chiral cyclopropanation

92% yield, 86:14 *trans*:*cis*, 89% ee

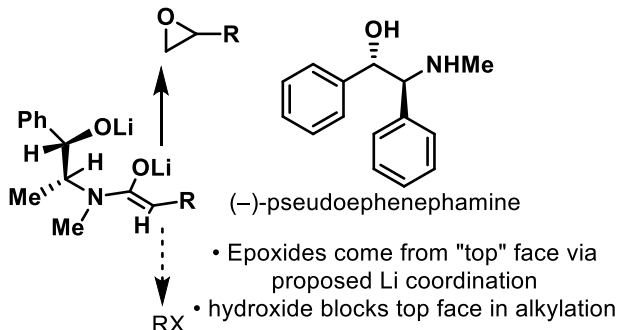
Gao, J.; J. Mol. Cat. A: Chem. **2003**, 191, 23-27



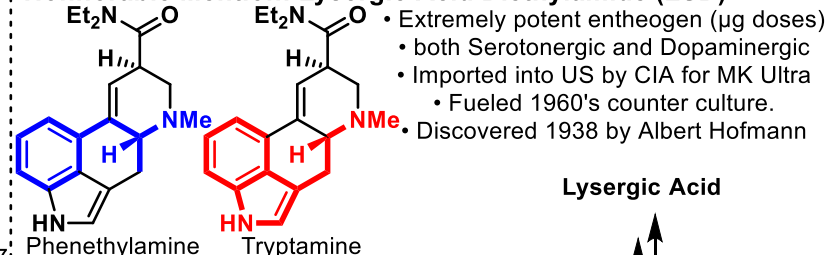
**Reviews on (pseudo)ephedrine auxiliaries:**

Myers notes Chem 115 on Asymmetric Alkylation

Current Organic Syn. **2018**, 15, 38-83

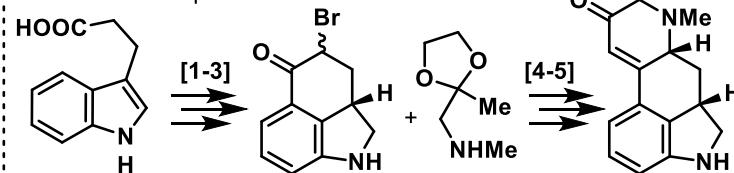


## Honorable Mention: Lysergic Acid Diethylamide (LSD)



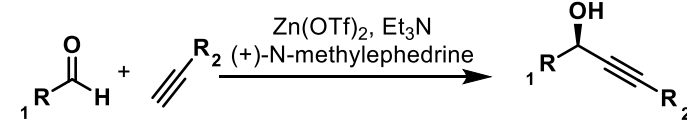
## R.B. Woodward's Lysergic Acid Synthesis

14 steps total. JACS **1956** 75 5256



KEY STEPS: 1. [H] 2. Friedel-Crafts 3. [Br] 4.  $S_N2$

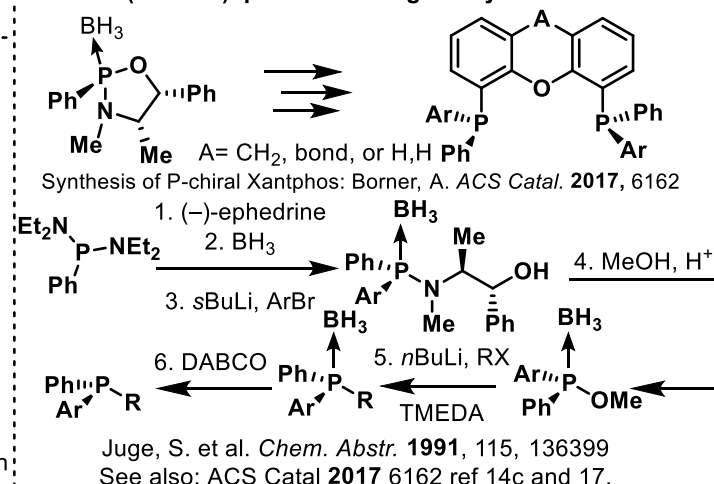
5.  $-H_2O$ ,  $-(OHCH_2)_2$  6. [H] 7.  $SOCl_2$  8.  $S_N2$  w/ [CN] 9.  $H^+/H_2O$  10. [O]



Substituted alkynes: Carreira, E. JACS **2000**, 122, 1806-1807

Terminal alkynes: Carreira, E. Org. Lett. **2000**, 4233-4236

## (Pseudo)ephedrine for ligand synthesis



Stephen Harwood

## The "Battle" Against Clandestine Chemistry

### "Small Toxic Networks" (STN's)

- Centered around individual cooks
- More primitive precursor acquisition strategies
- STN's grew domestically in number until 2006 Combat Meth Act.
- Rarely turn large profits, enough to sustain cooking and personal use.
- STN's are difficult to disrupt. Loose associations for tradecraft, not much intranetwork contact.
- Decentralization of information on internet has helped spread clandestine methods.
- The recent "Shake and Bake" method led to an increase in STN's

### "Mexican-Run Drug Trafficking Organizations" (MDTO's)

- Today, only 20% of meth is made domestically. The rest is from Global Production Networks.
- These networks obtain precursors from international sources and produce on an industrial scale.
- They have several cells which operate as a conglomerate: Production, Smuggling, Trafficking, and Distribution.
- After the Chemical Diversion and Trafficking Act of 1988, MDTO's appeared in Southwestern US.
- "Super Labs" are capable of 10 lbs to 100 lbs batches and operate continuously.
- DEA works internationally to halt supply of precursor chemicals.
- Super labs moved out of US and down south after constricting pseudo supply.
- After global restriction of pseudo, the Mexico based labs switched back to the P2P production method.

### Opinions of Policy Experts

- Specifics are debated but there is a general consensus:
  - Make Pseudo and epinephrine prescription medication only.
  - More restricted control of P2P and its precursors internationally, including rarer precursor chemicals which MDTO's have access to.
- Some Experts suggest a re-examination of federal funding distribution is necessary. Vermont, 9 lab busts in 10 years receives the same amount of funding as Tennessee with 14,836 busts (half of all busts). That's \$648,709 per bust vs. \$388 per bust.
- Additionally, experts disagree on how pseudo should be controlled: Local regulation (State level) or Federal regulation?

"At that moment, when I had the TV sound off, I was in a 382 mood; I had just dialed it. So although I heard the emptiness intellectually, I didn't feel it. My first reaction consisted of being grateful that we could afford a Penfield mood organ. But then I realized how unhealthy it was, sensing the absence of life, not just in this building but everywhere, and not reacting—do you see? I guess you don't. But that used to be considered a sign of mental illness; they called it 'absence of appropriate affect.' So I left the TV sound off and I sat down at my mood organ and I experimented. And I finally found a setting for despair. So I put it on my schedule for twice a month; I think that's a reasonable amount of time to feel hopeless about everything, about staying here on Earth after everybody who's smart has emigrated, don't you think?"

--Philip K. Dick, *Do Androids Dream of Electric Sheep?*



Left: Small chemistry lab  
Right: "Super Lab"



*Philip K. Dick's High Life* by Stephen Bitsoli, The Fix, 2017

From Soda Bottles to Super Labs: An Analysis of North America's Dual Methamphetamine Production Networks *Geographical Review* 2015, 105,4, 511-517  
Reducing Illicit Methamphetamine Labs: Is Precursor Control the Answer? *J. Drug Policy Analysis*. 2016, 9, 31-54