Flash Vacuum Pyrolysis

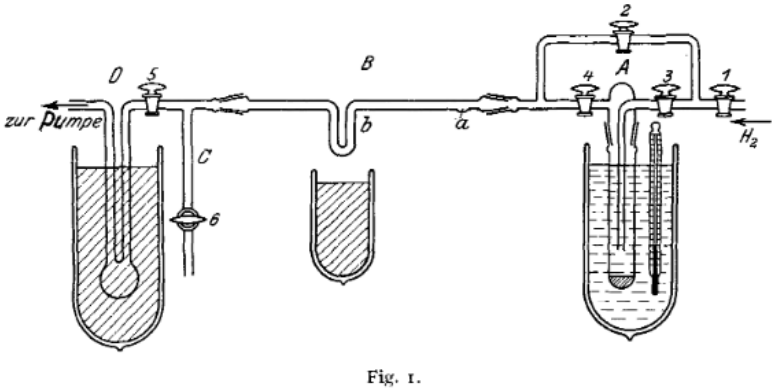
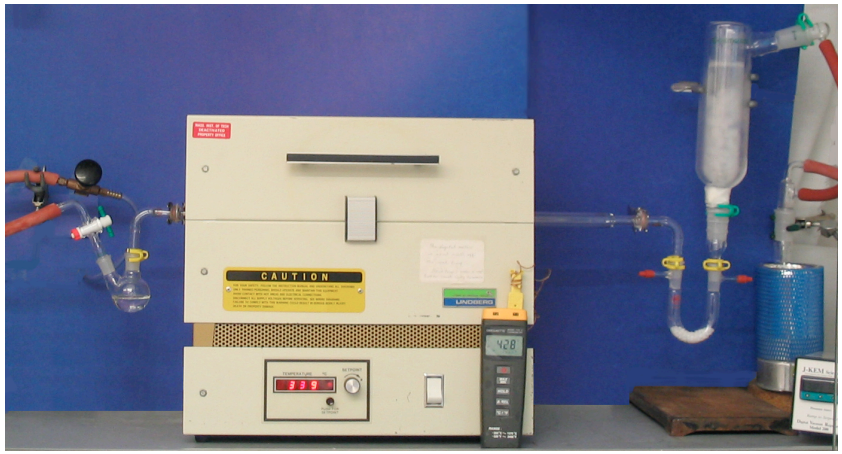
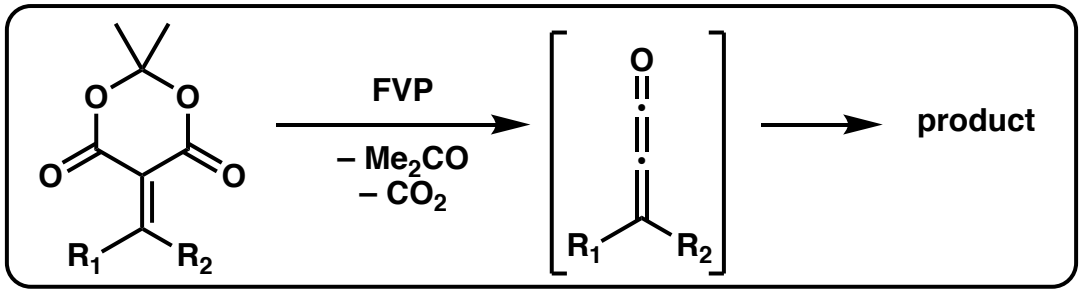


Fig. 1.





David Schuman
Stoltz, Reisman Literature Meeting
May 11th, 2018

Outline

- Background

- Key Concepts of FVP

- Examples of FVP Methodology

- FVP Use in Total Synthesis

-Related Reactivity

- Future Outlooks

"Organic chemists have enjoyed distilling compounds through hot tubes since the early days of the subject in the 19th century."
-McNab

McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

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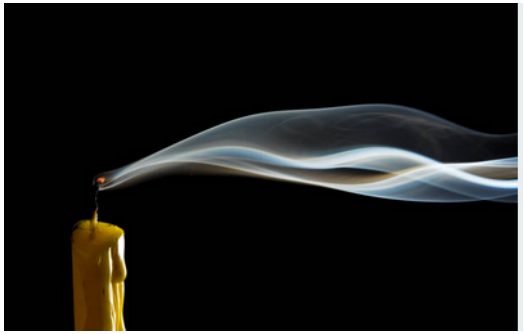
Combustion, Pyrolysis, and Flash Vacuum Pyrolysis (FVP)

"Combustion" or "burning"
Complex series of events including:



Pyrolysis
A series of, typically endothermic, chemical reactions, which occur at high temperature (and in this case produce flamable gas)

(Flaming) Gas Phase Combustion
Gas-Gas oxidation, exothermic, visible flames

Active Char, Oxidation of Char
Solid-Gas oxidation, highly exothermic, glowing coals

Photos reproduced from www.istockphoto.com, iStock by Getty Images
The Chemistry of Pyrolysis and Combustion; 1984; pp 489–529.
Harmathy, T. Z. *Fire Mater.* **1984**, *8*, 224–226.
Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.
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C. Graebe; F. Ullmann, *Justus Liebigs Ann. Chem.* **1896**, *291*,16–17.

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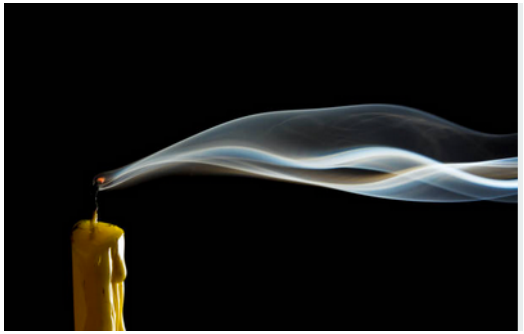

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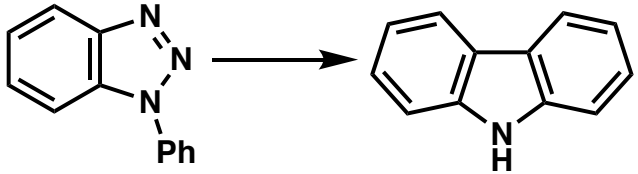
Pyrolysis

"Later, particularly during the 1800s, numerous investigations of 'pyrogenic reactions' were carried out by passing organic substances through red-hot glass, porcelain, or iron tubes at atmospheric pressure" -Wentrup



Graebe-Ullmann Reaction

Also includes processes such as dry distillation, destructive distillation, and hydrocarbon cracking not discussed here

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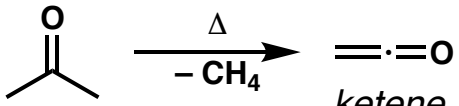
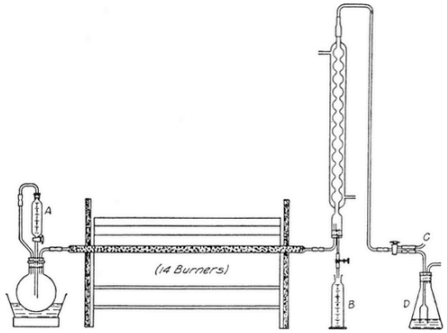
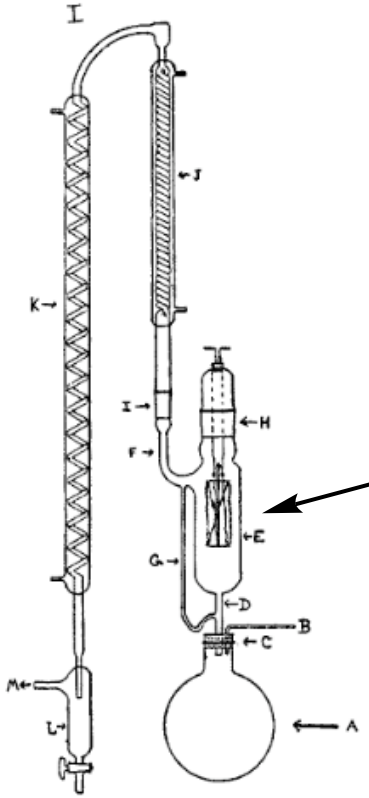
Development of Modern Flash Vacuum Pyrolysis

The Ketene Lamp
a lab scale use of pyrolysis



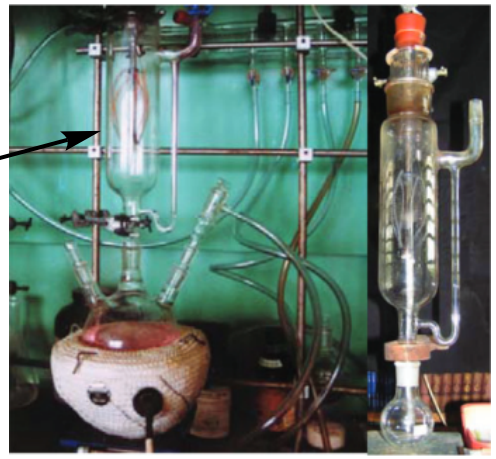


1925 Org. Synth. prep of ketene
"fourteen of the twenty burners of the combustion furnace are lighted…"
~700 ºC



Ketene Lamp described by Hurd

"dull red" glowing
metal filament



Ketene Lamp in use

Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.
Hurd, C. D. *Org. Synth.* **1925**, *4*, 35.
Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *5*, 122–125.

The Origins of FVP

Early experiments were designed for qualitative detection of free radicals

• Alkyl radicals generated by thermal conditions, under vacuum, are allowed to react with metallic mirror on the glass tube or cold trap

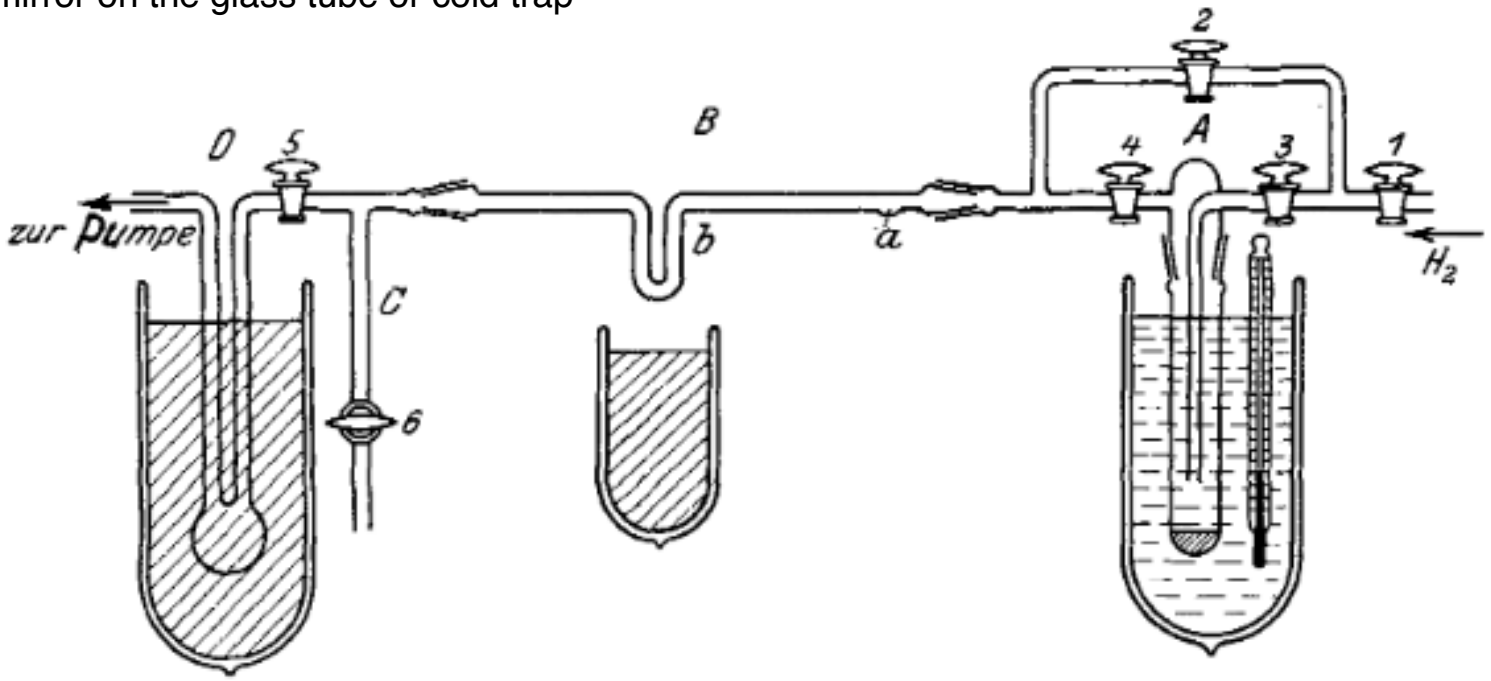
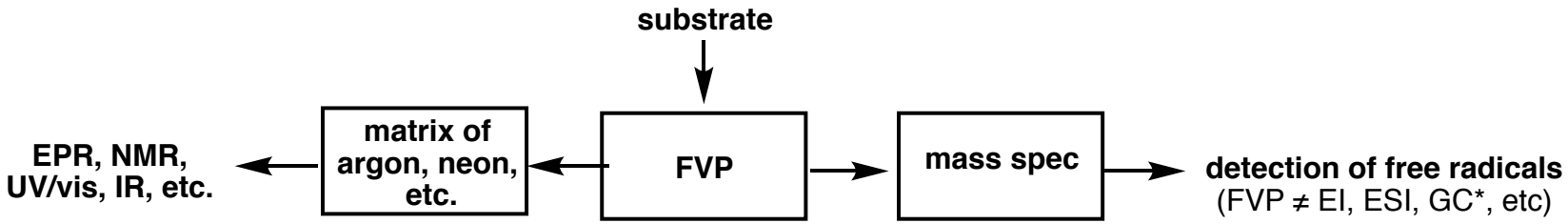


Fig. 1.

Independently reported by Paneth and Rice

Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.
Paneth, F.; Hofeditz, W. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 1335–1347.
Rice, F. O.; Rice, K. K. *The Aliphatic Free Radicals* **1935** (The Williams and Wilkins Co.: Baltimore, MD).

Analytical Flash Vacuum Pyrolysis



Analytical FVP, specifically FVP-MS. was a major driving force in the early devlopment of modern FVP

Eltenton, G. C. *J. Chem. Phys*. **1942** , *10* , 403–404.
Eltenton, G. C. *J. Chem. Phys*. **1947** , *15* , 455–481.
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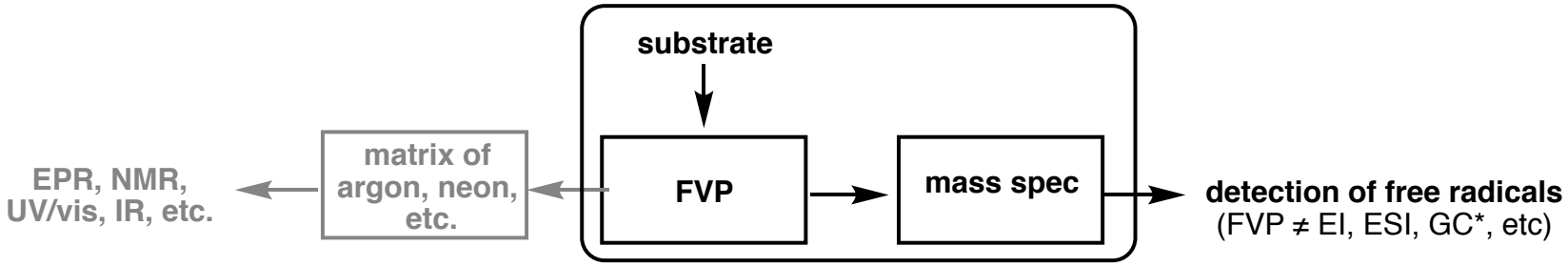

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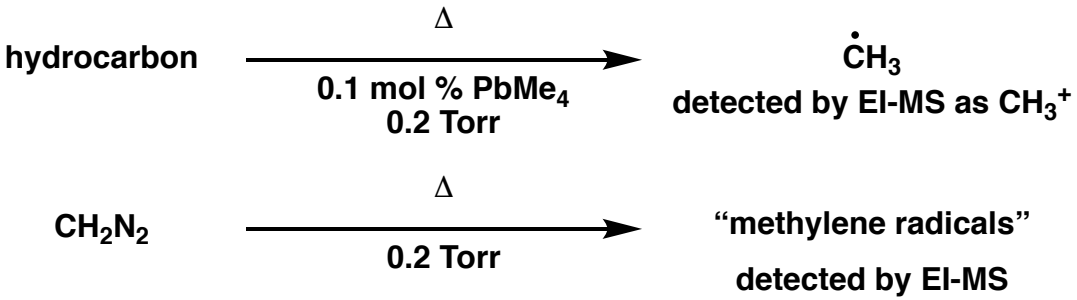
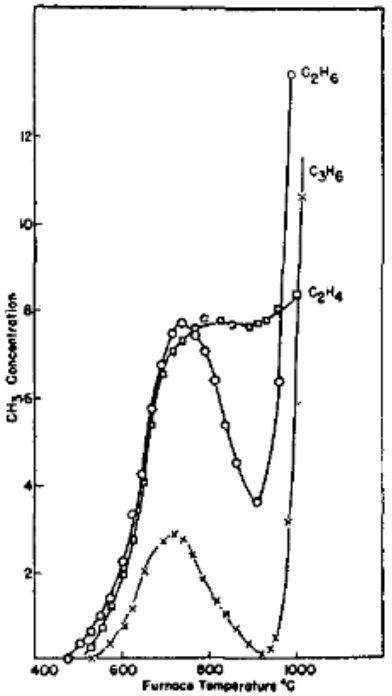
Example study by Eltenton





Later studies showed $PbMe_4$ was not required for alkyl radical formation.
Studies often involved complex, custom apparatuses for MS detection of alkyl radicals.

Eltenton, G. C. *J. Chem. Phys.* **1942** , *10* , 403–404.
Eltenton, G. C. *J. Chem. Phys.* **1947** , *15* , 455–481.
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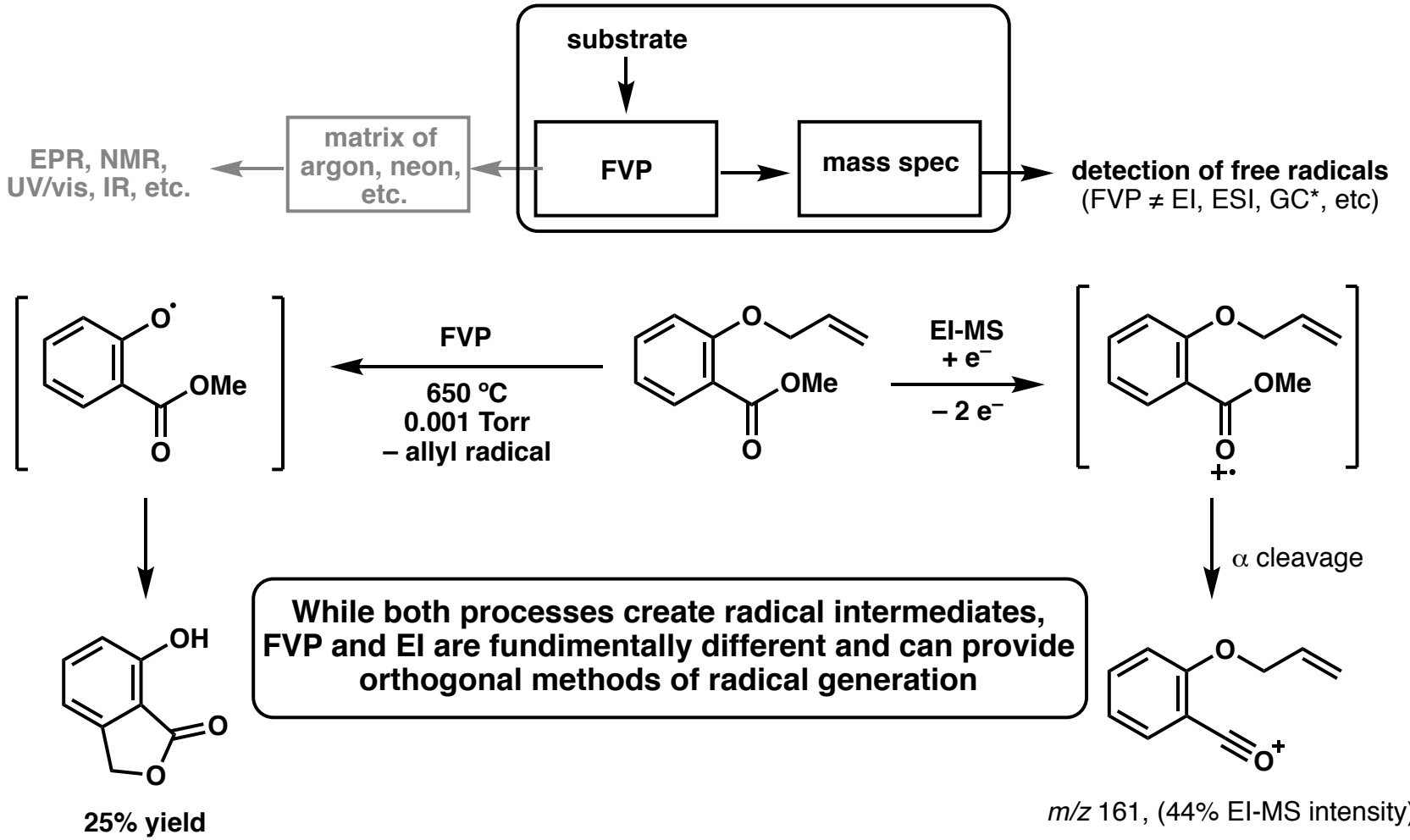

McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26
Black, M.; Cadogan, J. I. G.; McNab, H. *J. Chem. Soc. Perkin Trans. 1* **1994**, 155–159.
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Flash Vacuum Pyrolysis

"It's getting hot in here" -Nelly

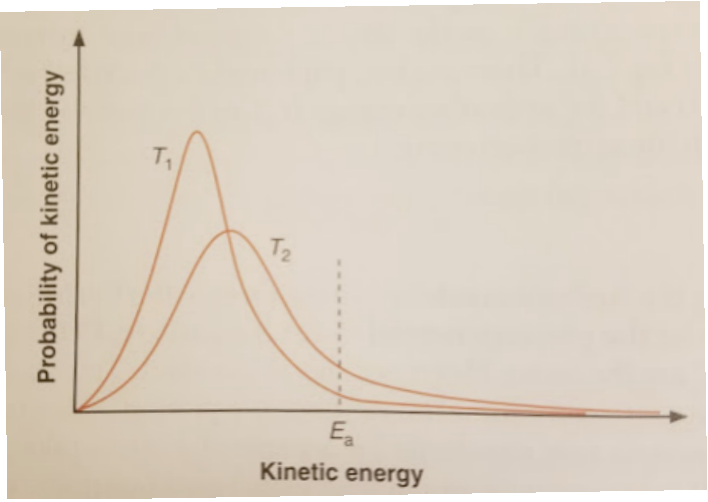
Temperature is relative in FVP

• Tube or oven temperature ≠ temperature of the reactants. Recall vaccum is a poor conductor of heat

• Molecules gain energy by wall collisions so both oven temperature and number of collisions determine "effective temperature"

• Number of collisions is influenced by tube size, pressure, contact time, and if used, carrier gas (deactivating) and packing material (activating)

• Reactions can be difficult to replicate using a different apparatus, >100 ºC differences are often seen



Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.
Benson, S. W.; Spokes, G. N. *J. Am. Chem Soc.* **1967**, *89*, 2525–2532.
D. M. Golden, G. N. Spokes, S. W. Benson, *Angew. Chem. Int. Ed.* **1973**, *12*, 534–546.
Figure replicated from Anslyn, E. A.; Dougherty, D. A. *Modern Physical Organic Chemistry* University Science Books: USA, 2006.

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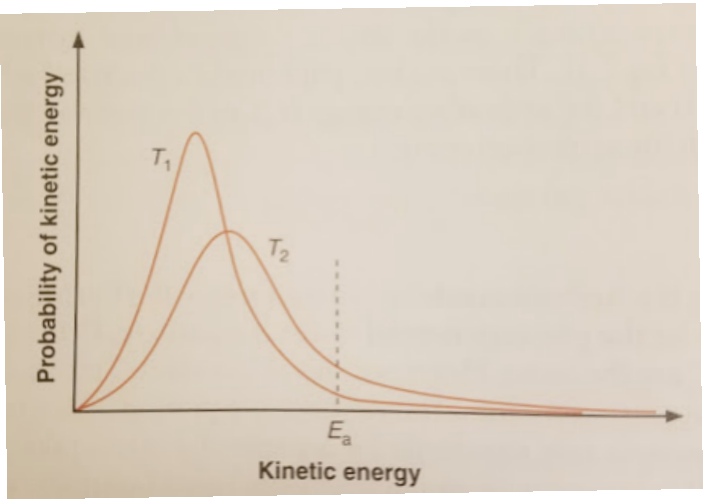

Very Low Pressure Pyrolysis (VLPP)

A method of quantitative kinetic investigations of FVP reactions

Multiple chambers with varying exit hole sizing and known internal area allow perdiction of number of wall collisions

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Benson, S. W.; Spokes, G. N. *J. Am. Chem Soc.* **1967**, *89*, 2525–2532.
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Figure replicated from Anslyn, E. A.; Dougherty, D. A. *Modern Physical Organic Chemistry* University Science Books: USA, 2006.

Flash Vacuum Pyrolysis

What is this an exotherm for ants?

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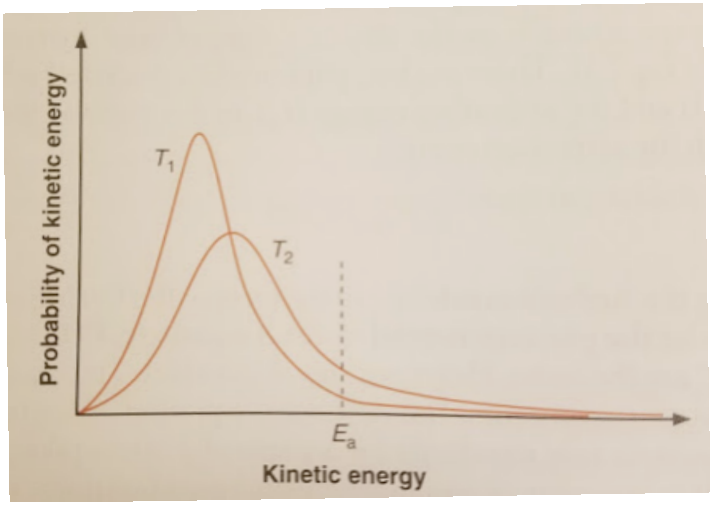
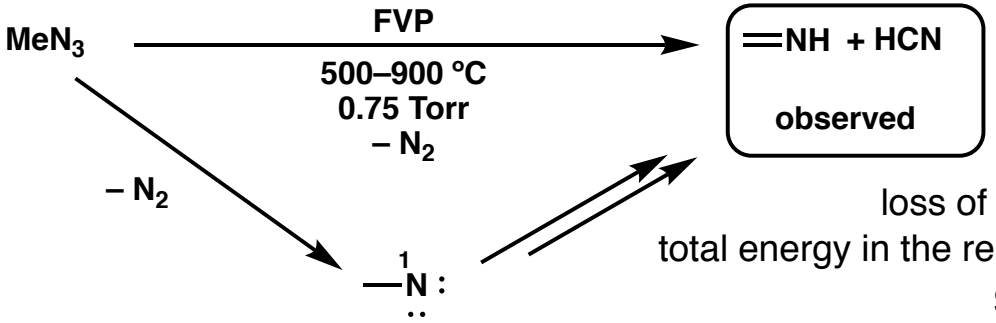
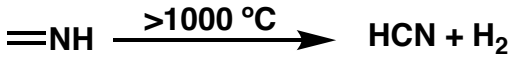


Chemical Activation can cause undesired secondary reactions





loss of N_2 is 51 kcal mol^{-1} exothermic

total energy in the reaction intermediate is 2–3x expected amount

Solution is carrier gas

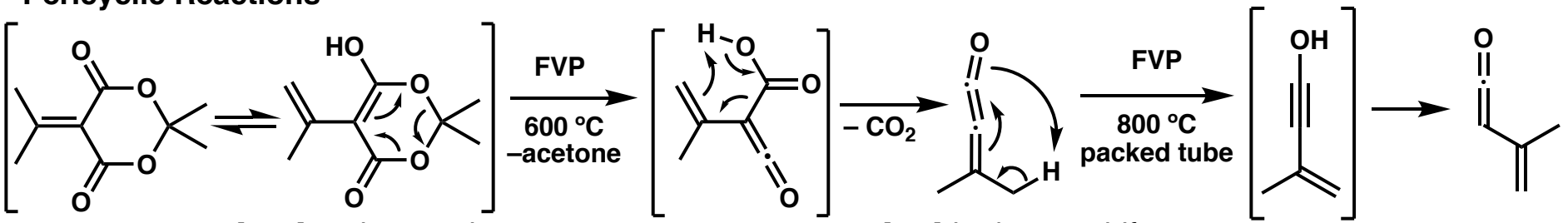
Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165. Wentrup, C.; Winter, H. W. *Angew. Chem. Int. Ed.* **1978**, *17*, 609–610. Wentrup, C. *Aust. J. Chem.* **2013**, *66*, 852–863. Billups, W. E.; Bachman, R. F. *Tetrahedron Lett.* **1992**, *33*, 1825–1826. Figure replicated from Anslyn, E. A.; Dougherty, D. A. *Modern Physical Organic Chemistry* University Science Books: USA, 2006.

Modes of Reactivity

Typical modes of reactivity in FVP reactions fall into three broad categories, with some overlap

Recall FVP reactions are unimolecular as the vacuum limits gas phase interactions.
Without solvent, ionization energy is very high and ionic intermediates are not implicated.

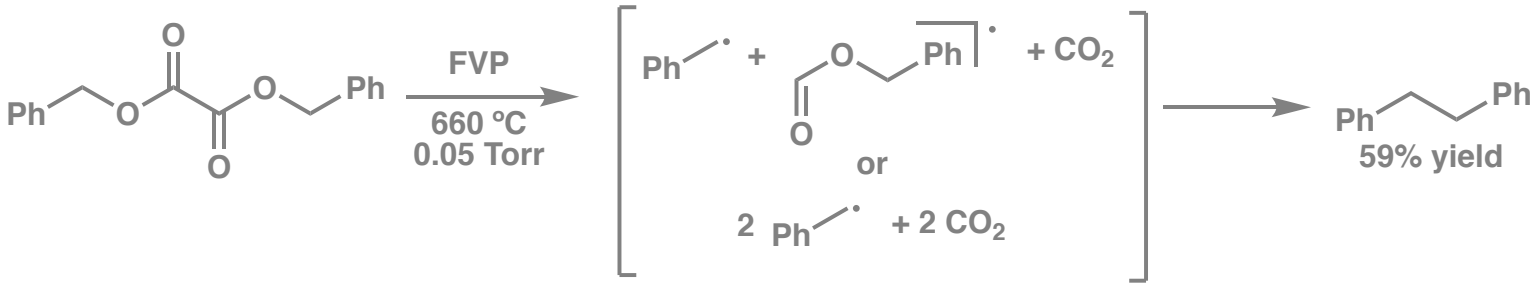
Pericyclic Reactions



[4+2] cycloreversion *retro ene* *[1,5]-hydrogen shift*

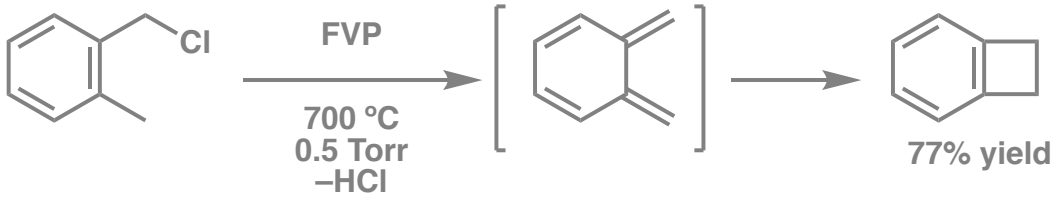
Radical Reactions

• Cleavage of the weakest bond to form a diradical



Cleavage of small molecule

• Typically extrusion of N_2, CO, CO_2, etc. to generate a reactive intermediate (i.e. diradical, carbene, nitrene, etc)



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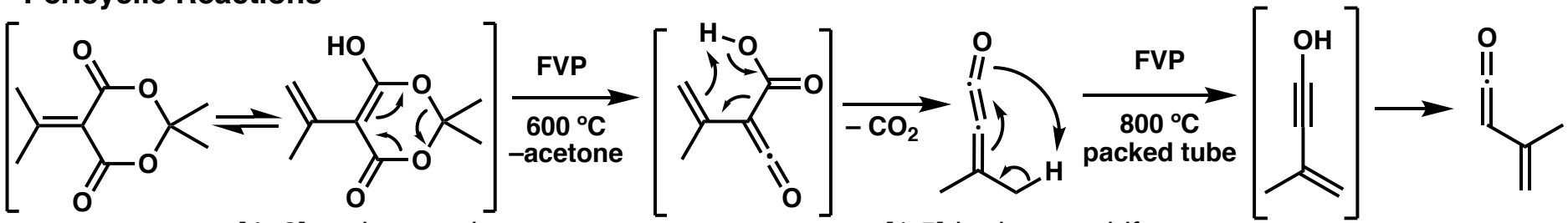
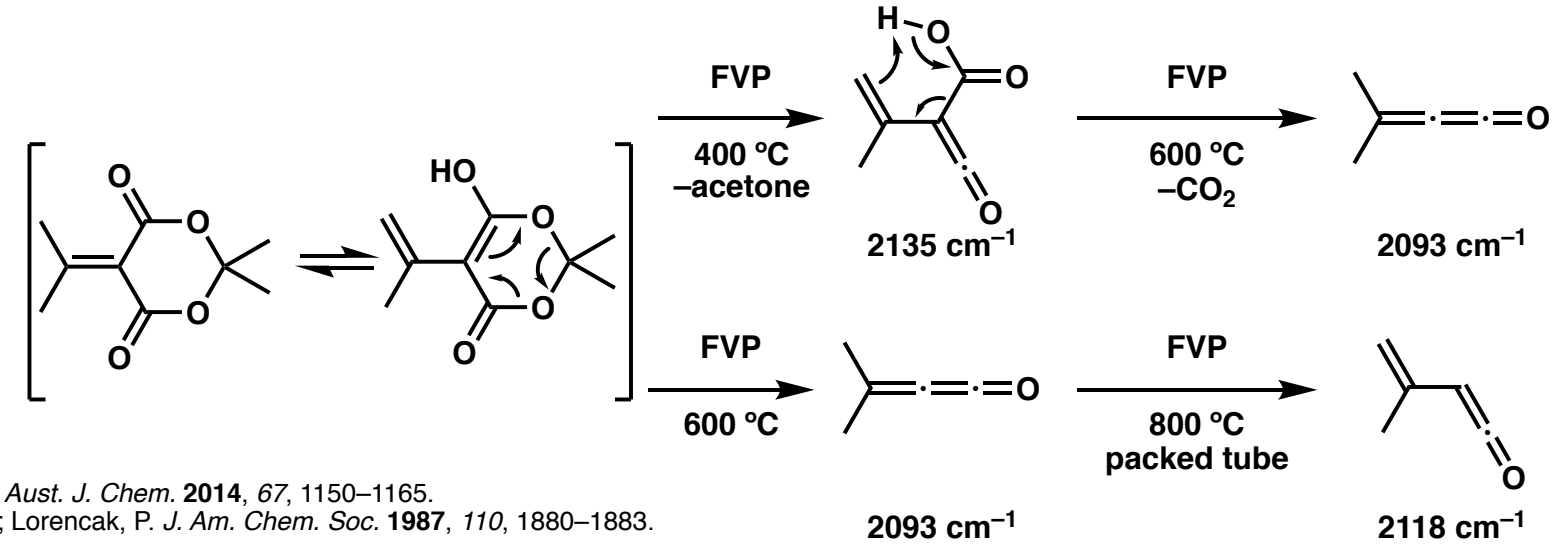


Double Pyrolysis



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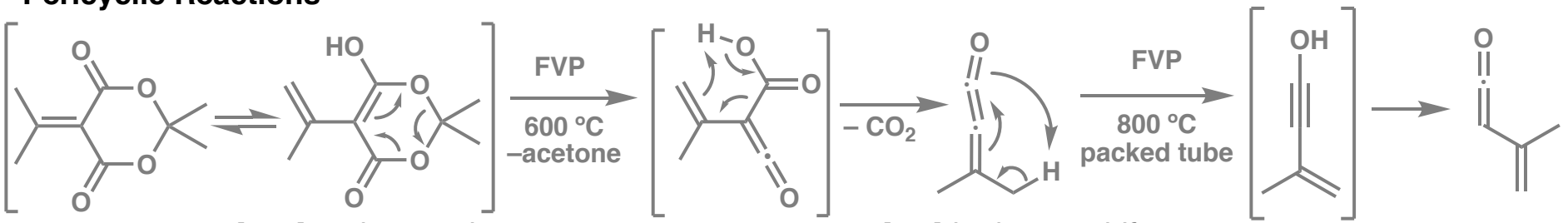

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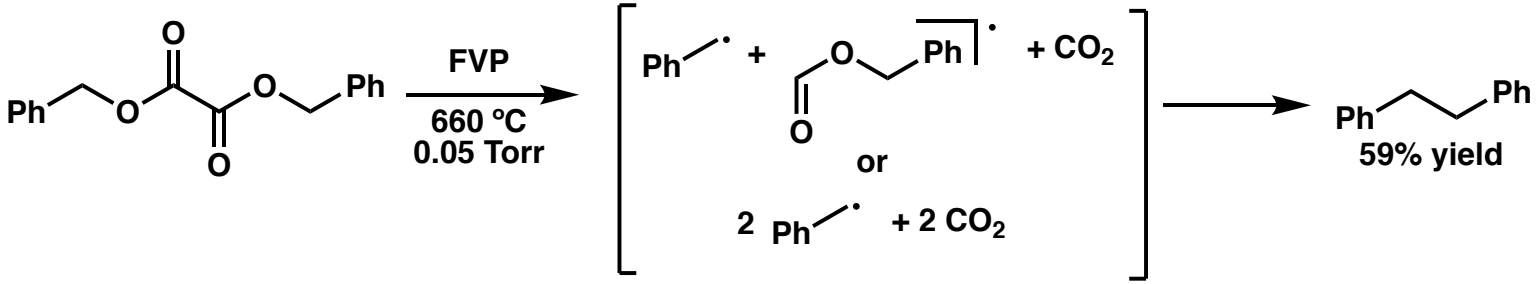

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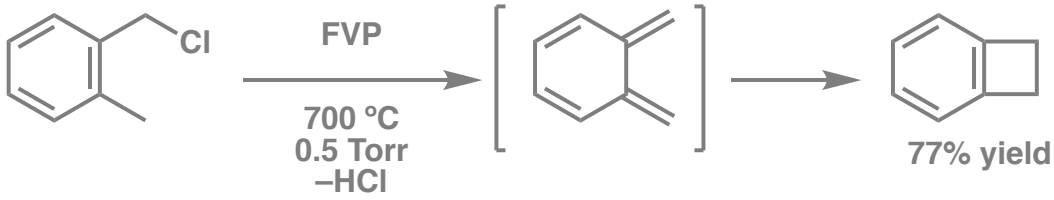

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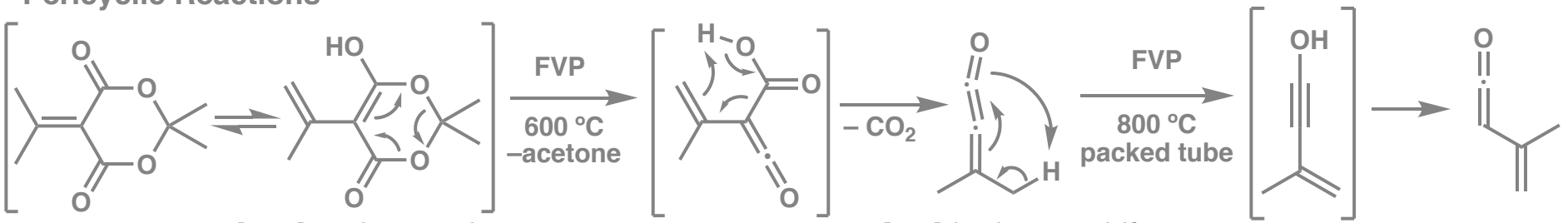

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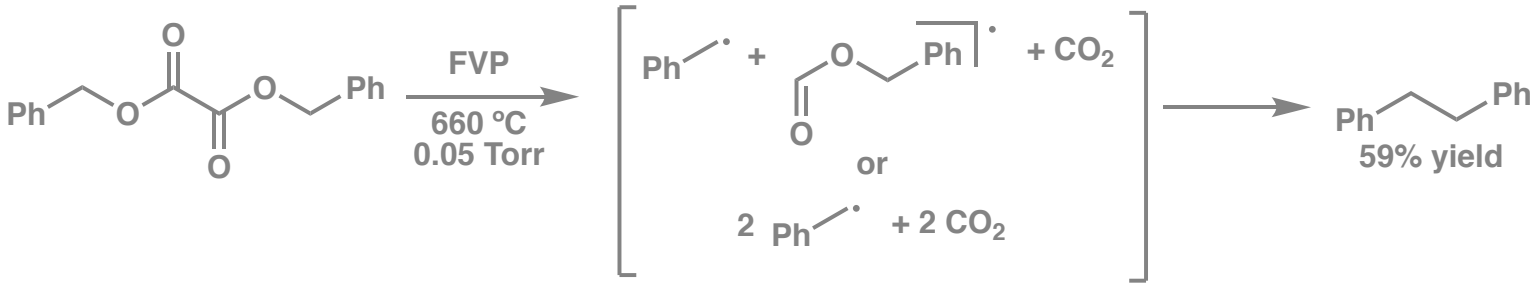

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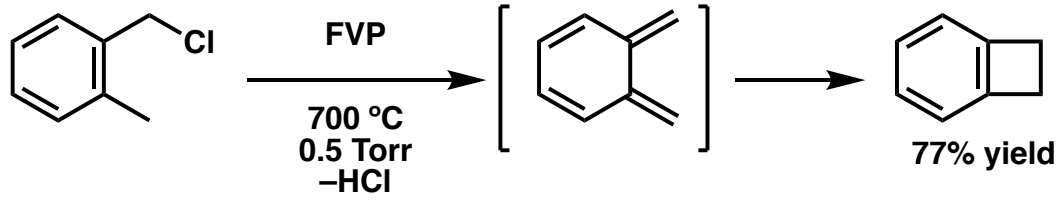
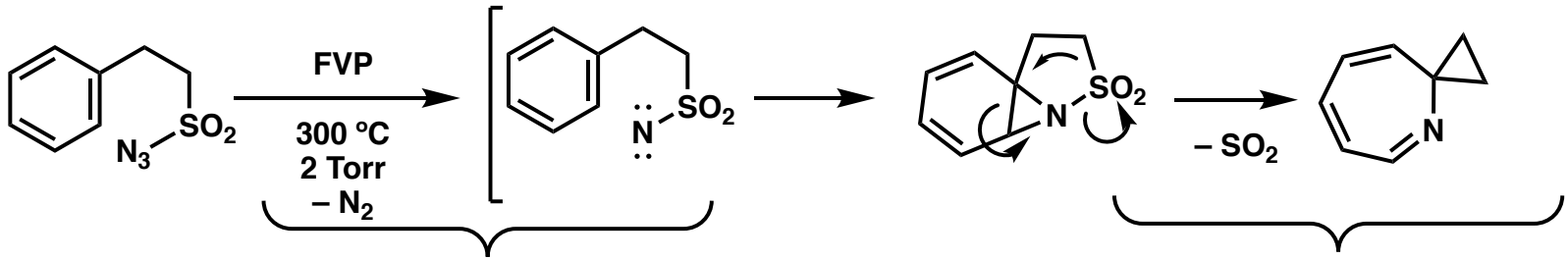
• Typically extrusion of N_2, CO, CO_2, etc. to generate a reactive intermediate (i.e. diradical, carbene, nitrene, etc)



Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165. Wentrup, C.; Lorencak, P. *J. Am. Chem. Soc.* **1987**, *110*, 1880–1883. Wentrup, C.; Gross, G.; Berstermann, H. M.; Lorencak, P. *J. Org. Chem.* **1985**, *50*, 2877–2881. Trahanovsky, W. S.; Ong, C. C.; Lawson, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 2839–2842. Schiess, P.; Heitzmann, M.; Rutschmann, S.; Staheli, R. *Tetrahedron Lett.* **1978**, 4569–4572. McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

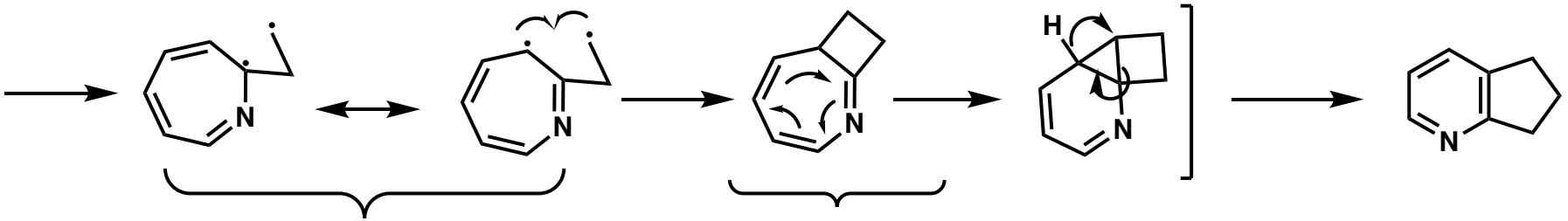
Modes of Reactivity

Often a reaction will include multiple common reaction modes



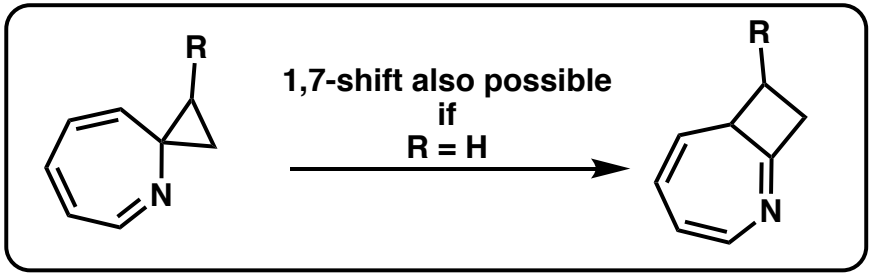
loss of small molecule to generate nitrene

loss of small molecule to generate cyclopropane



homolytic bond cleavage to form diradical

6π-cyclization



Abramovitch, R. A.; Holcomb, W. D. *J. Am. Chem. Soc.* **1975**, *97*, 676–677.

Outline

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- Key Concepts of FVP

- Examples of FVP Methodology

- FVP Use in Total Synthesis

-Related Reactivity

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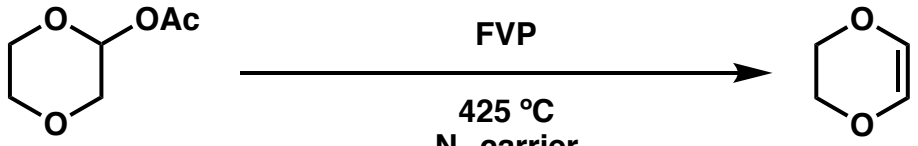
"Organic chemists have enjoyed distilling compounds through hot tubes since the early days of the subject in the 19th century."
-McNab

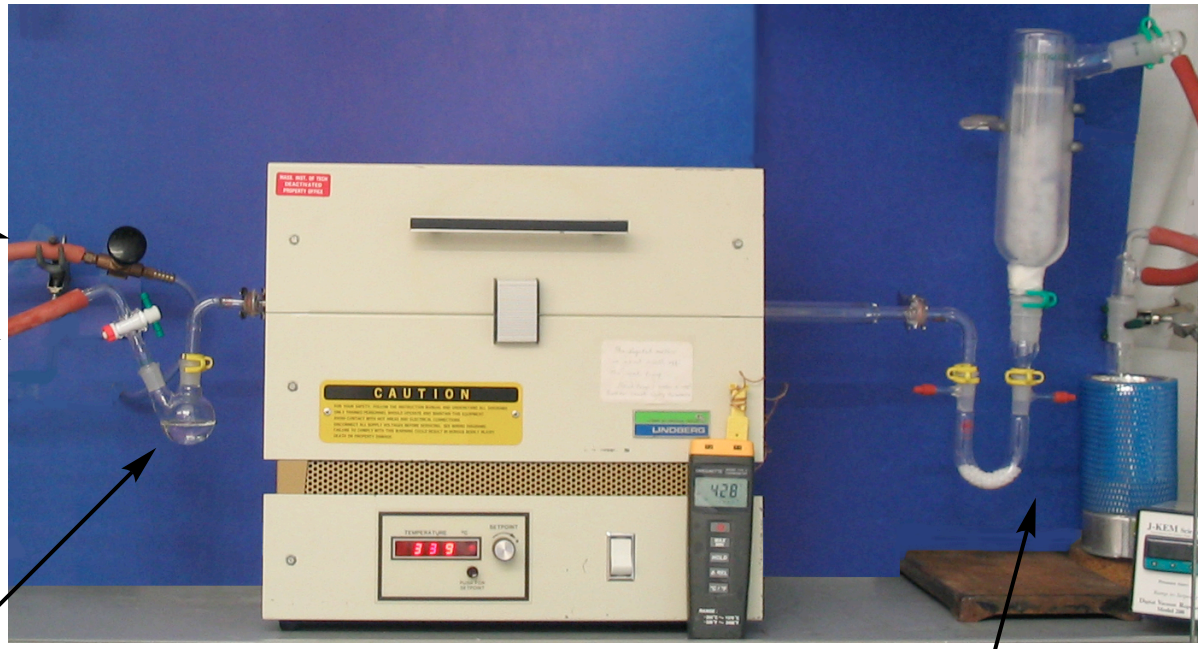
McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

Modern Flash Vacuum Pyrolysis

A Typical FVP Preparative Setup



44–61% yield
~ 5g
~ 30 min reaction time



needle valve used to control pressure

carrier gas (if used)

flask of starting material often heated to vaporize

electric tube furnace containing quartz reaction tube

~200 – >1,000 °C

N_2-cooled trap used to collect product

Vacuum controler <0.1 – >100 Torr

Total Cost:
$5,000–10,000
(commercial)

<$2000
(built)

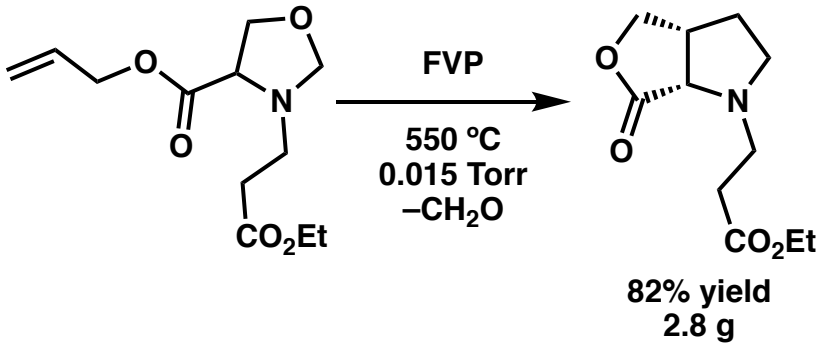
Special Equipment
- quartz tube
- tube oven
- needle valve

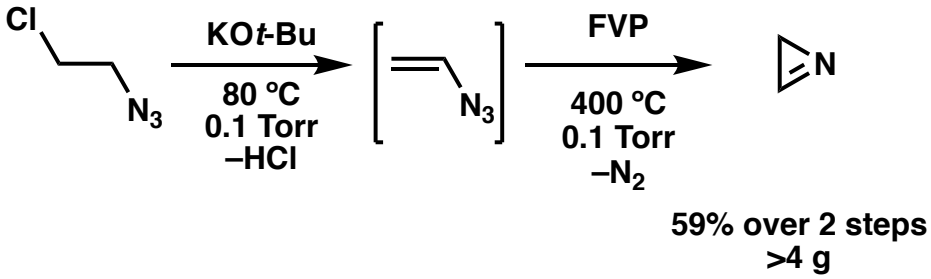
Kreilein, M. M.; Eppich, J. C.; Paquette, L. A. *Org. Synth.* **2005**, *82*, 99–107.

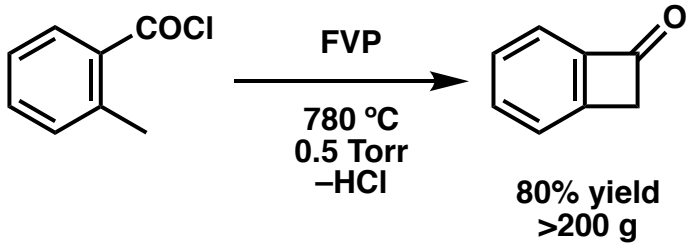
Preparative Flash Vacuum Pyrolysis

Benefits

- Constant flow reaction, same setup can run longer for scale up
- Products "isolated" by cold trapping, reduce secondary reactions
- Solvent-free, "green", avoid sealed, pressurized tubes
- Fast reaction times, ~1–2 g/hr for prep. scale
- Few parameters to optimized (temperature, pressure, and if used, carrier gas/packing material)





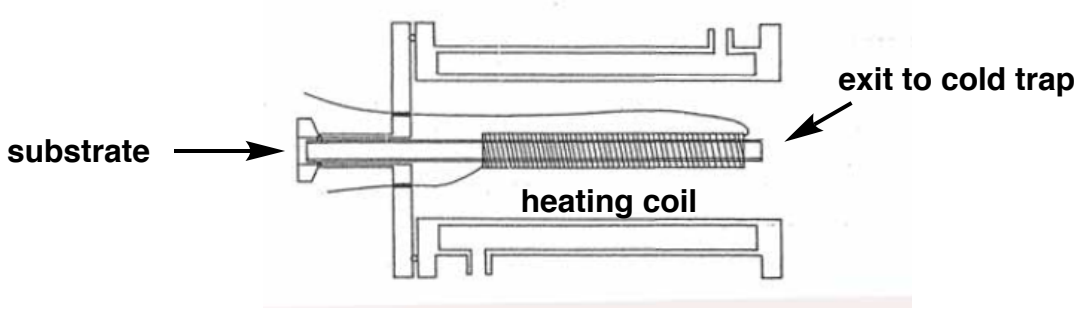


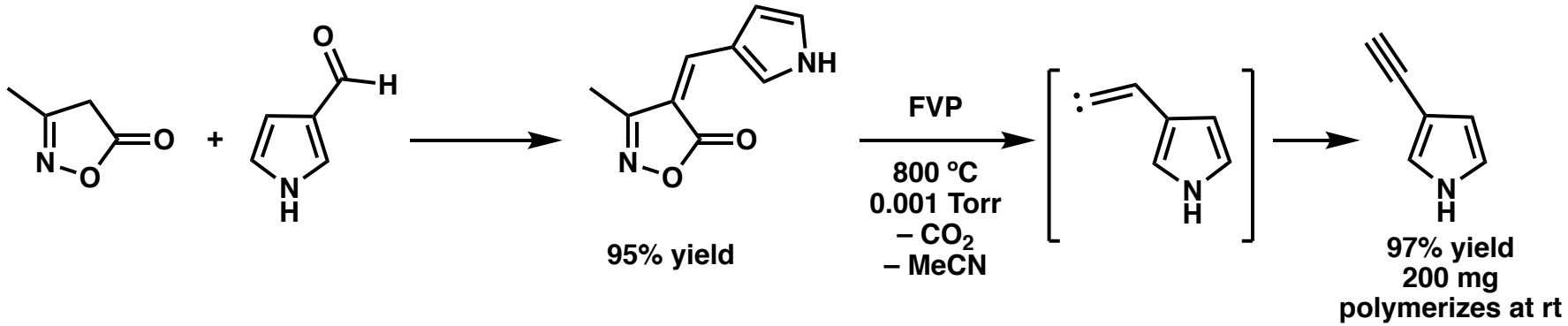
Kreilein, M. M.; Eppich, J. C.; Paquette, L. A. *Org. Synth.* **2005**, *82*, 99–107. Schiess, P.; Barve, P. V.; Dussy, F. E.; Pfiffner, A. *Org. Synth.* **1995**, *72*, 116. Suzzarini, L.; Lin, J.; Wang, Z. Y. *Tetrahedron Lett.* **1998**, *39*, 1695–1696. Bureau, R.; Mortier, J.; Joucla, M. *Tetrahedron* **1992**, *48*, 8947–8952. Guillemin, J.-C.; Denis, J.-M.; Lasne, M.-C.; Ripoll, J.-L. *J. Chem. Soc., Chem. Commun.* **1983**, *5*, 238–239.

Isolation of Reactive Compounds

Isolation of reactive intermediates is possible on synthetically relevent scale.

- Rapid low temperature quench limits secondary or intermolecular reactions
- Vacuum limits intermolecular collisions
- Carrier gas can be used to kinetically deactivate substrate, especially if chemical activation is suspected
- Even thermally unstable compounds may be isolated with optimization (contact time, carrier gas)



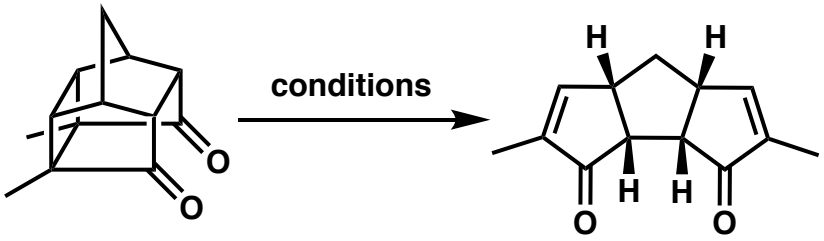


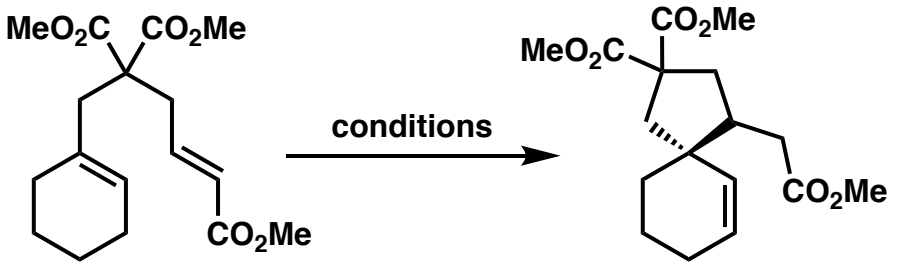
Wentrup, C.; Winter, H. W. Angew. Chem. Int. Ed. 1978, 17, 609–610. Wentrup, C. Aust. J. Chem. 2013, 66, 852–863. Billups, W. E.; Bachman, R. F. Tetrahedron Lett. 1992, 33, 1825–1826. Kreilein, M. M.; Eppich, J. C.; Paquette, L. A. Org. Synth. **2005**, 82, 99–107.

Comparison of FVP and Thermal Reactivity

Why should one use FVP versus typical heat/stir reactions?

FVP allows higher reaction temperature to achieve reactivity but significantly shorter reaction times to limit secondary reactions.





entry	condtions	yield
1	FVP 450 °C, 1 Torr	100%
2	sealed tube 260 °C, Ph_2O, 30 min	20% (based on recovered starting material)

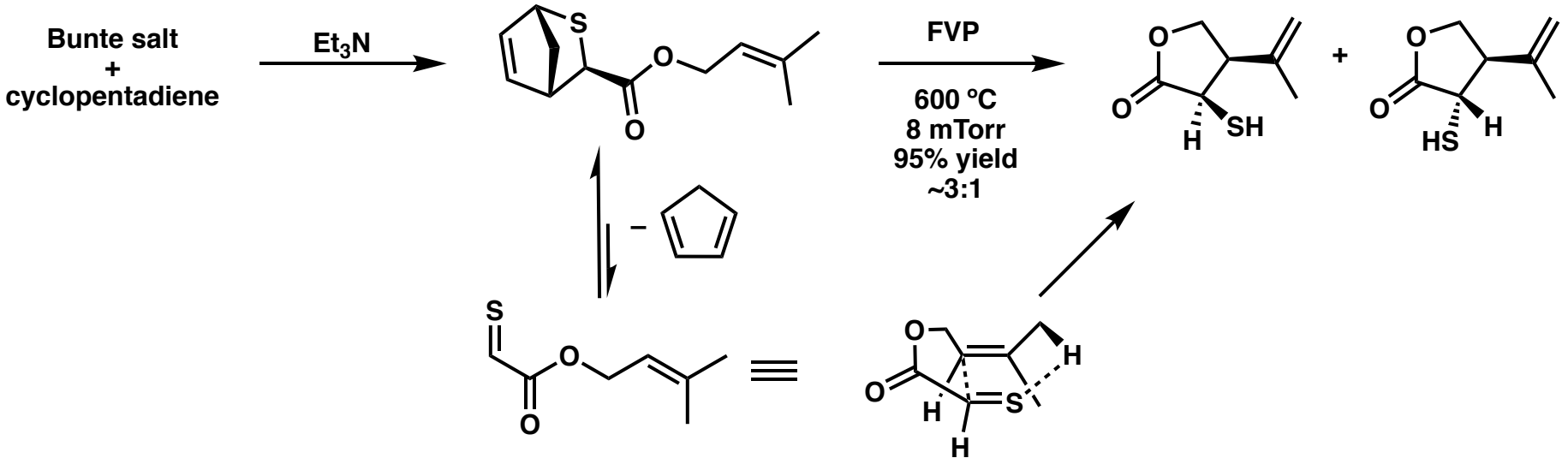
entry	condtions	yield
3	FVP 550 °C, 0.1 Torr	80%
4	up to 220 °C, mesitylene	no reaction or decomp

Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443–3452. Mehta, G.; Reddy, A. V. *J. Chem. Soc. Chem. Commun.* **1981**, 756–757. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543–4559. Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636–644.

FVP Methodology

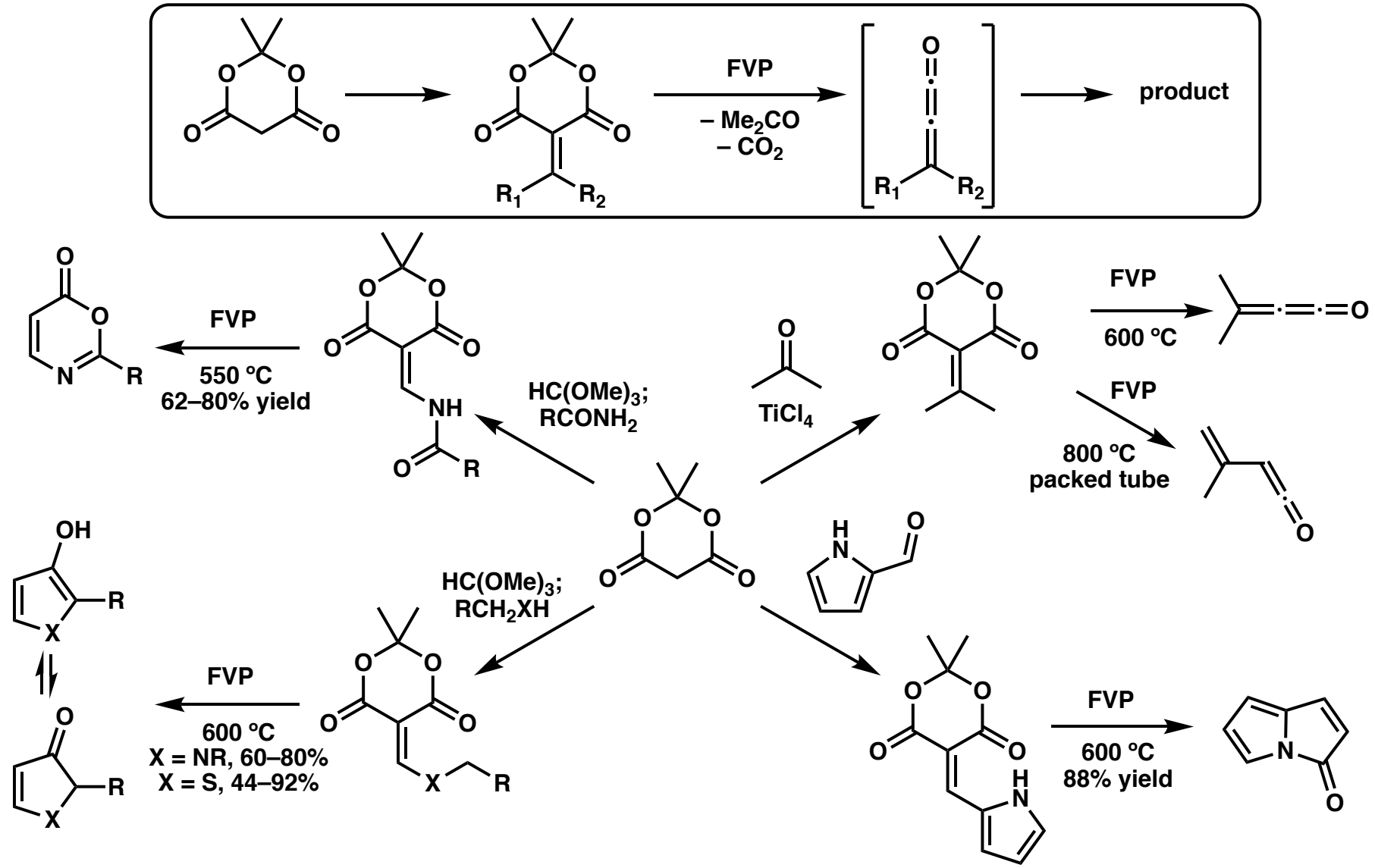
Using entropy and FVP to overcome reaction rates

Reaction is unimolecular and 1st order but complexation is fast and 2nd order overall.
Buildup of diene during reaction limited reaction size and concentration in batch.



Choi, A. S.-M.; Kirby, G. W. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 3225–3233.

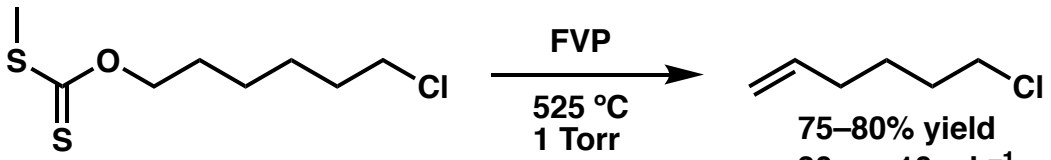
FVP of Meldrum's Acid Derivatives



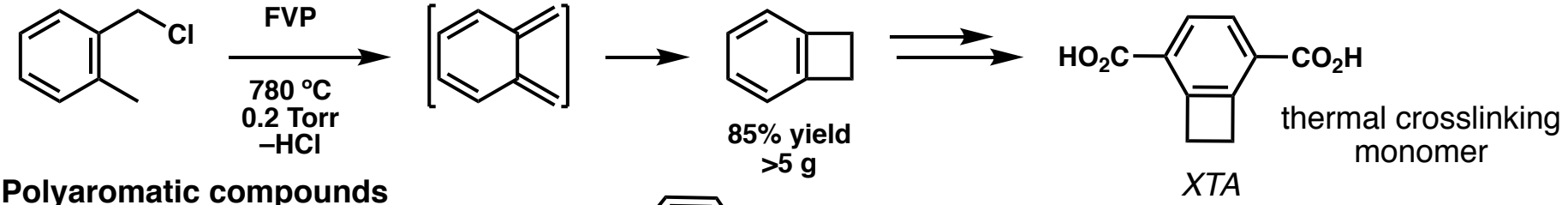
McNab, H. Aldrichim Acta 2004, 37, 21–26. McNab, H.; Withell, K. Tetrahedron 1996, 52, 3163–3170. McNab, H.; Monahan, L. C. J. Chem. Soc., Perkin Trans. 1 1988, 863–868. Hunter, G. A.; McNab, H. J. Chem. Soc., Perkin Trans. 1 1995, 1209–1214. McNab, H. J. Org. Chem. 1981, 46, 2809. Wentrup, C. Aust. J. Chem. 2014, 67, 1150–1165. Wentrup, C.; Lorencak, P. J. Am. Chem. Soc. 1987, 110, 1880–1883.

FVP Synthetic Use

Polymers

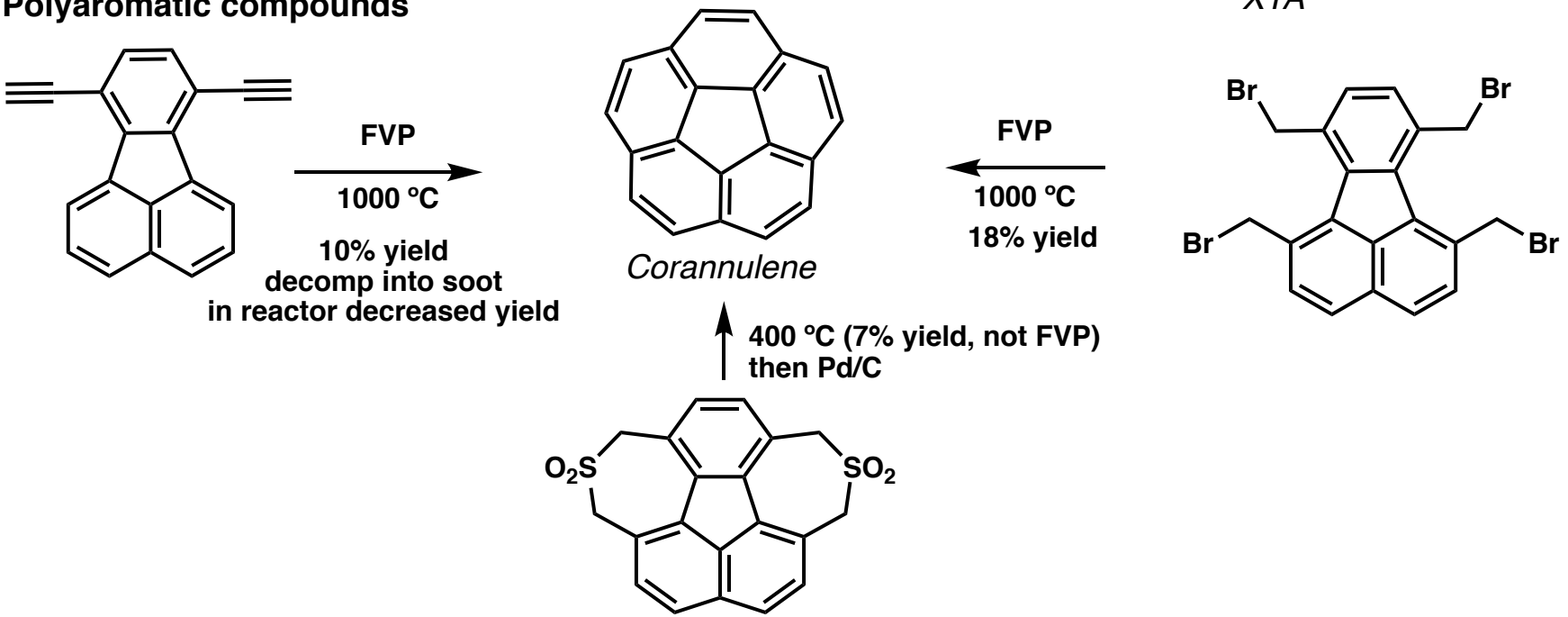


Modified Chugaev elimination
- clean reaction, even with primary xanthate
- high yield and scaleable
- used in polymer synthesis



thermal crosslinking monomer

Polyaromatic compounds



Jenneskens, L. W.; Hoefs, C. A. M.; Wiersum, U. E. *J. Org. Chem.*, **1989**, *54*, 5811–5814. Walker, K. A.; Markoski, L. J.; Moore, J. S. *Synthesis*, **1992**, 1265–1268. Tsefrikas, W. M.; Scott, L. T. *Chem. Rev.,* **2006**, *106*, 4868–4884.

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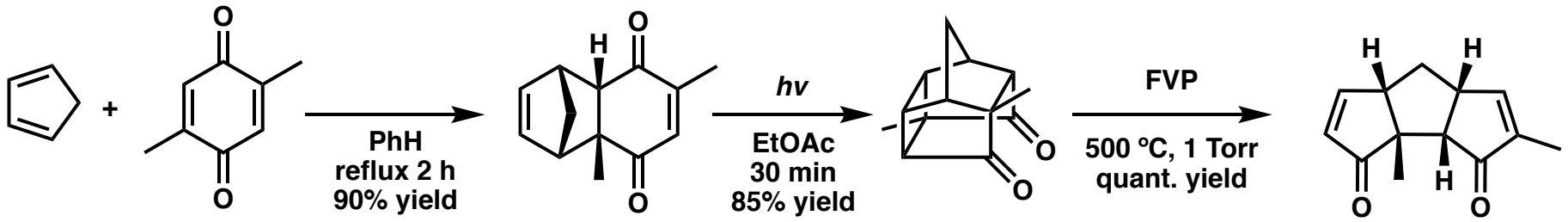
-McNab

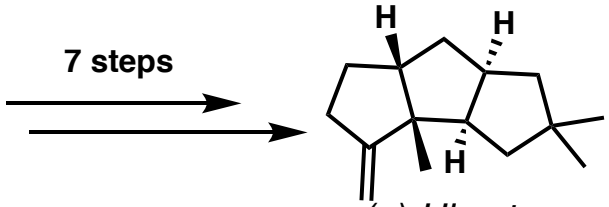
McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

FVP in Total Synthesis

Formal Thermal Cyclobutane Cycloreversion

Synthesis of *(±)-Hirsutene*
Mehta





(±)-Hirsutene
10 steps

"The key concept in our synthetic sequence to triquinanes is the novel photo-thermal olefin metathesis of cheap, abundantly available Diels-Alder adducts of 1,3 cyclopentadienes and p-benzoquinones." -Mehta

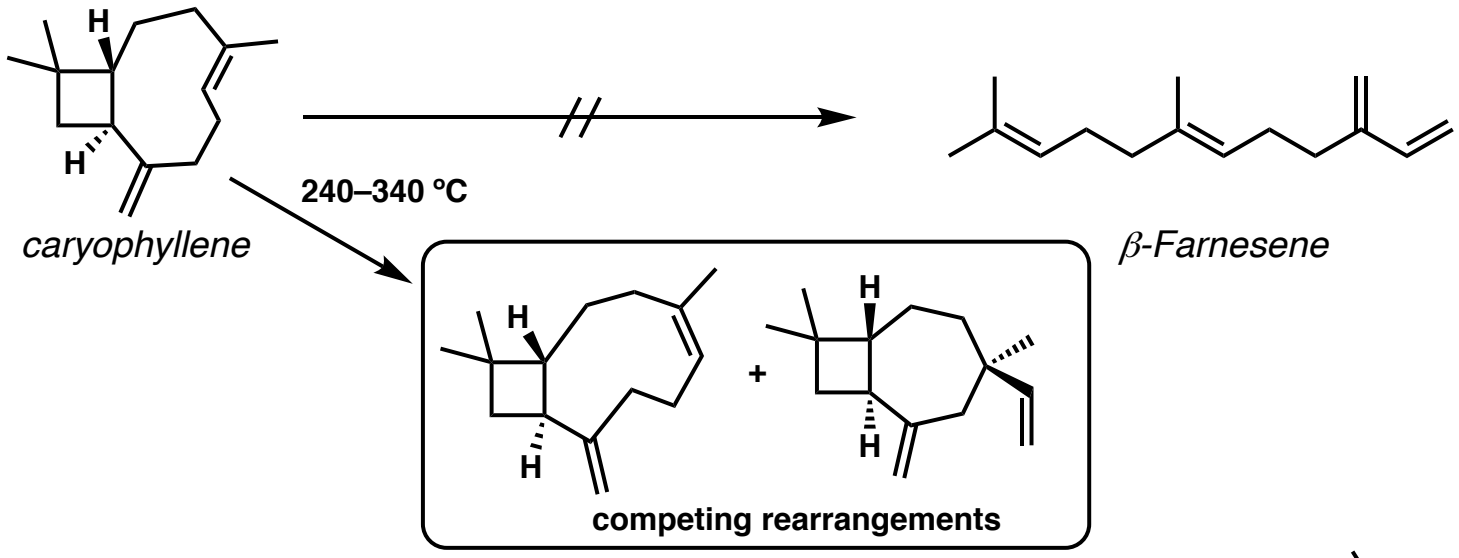
Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443–3452. Mehta, G.; Reddy, A. V. *J. Chem. Soc. Chem. Commun.* **1981,** 756–757. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543–4559.

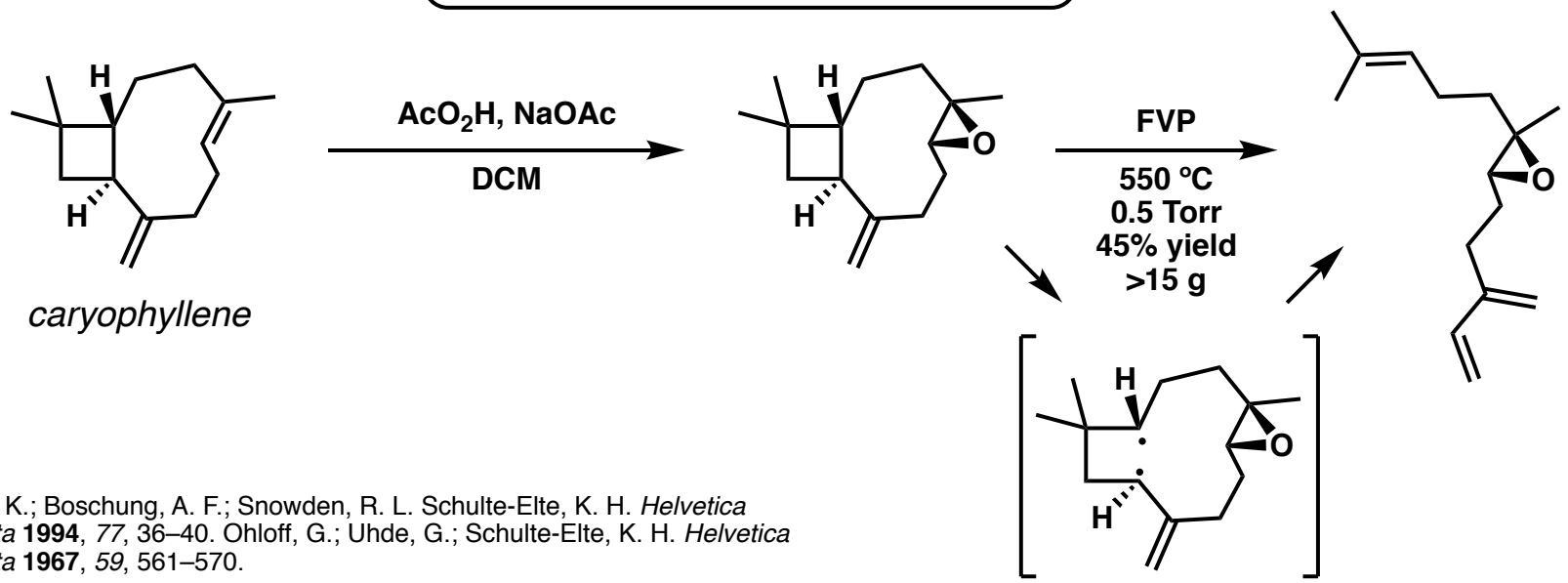
FVP in Total Synthesis

Formal Thermal Cyclobutane Cycloreversion

Conversion of Caryophyllene to Farnesene-Type Sesquiterpenes

Why not thermal cyclobutane fragmentation?



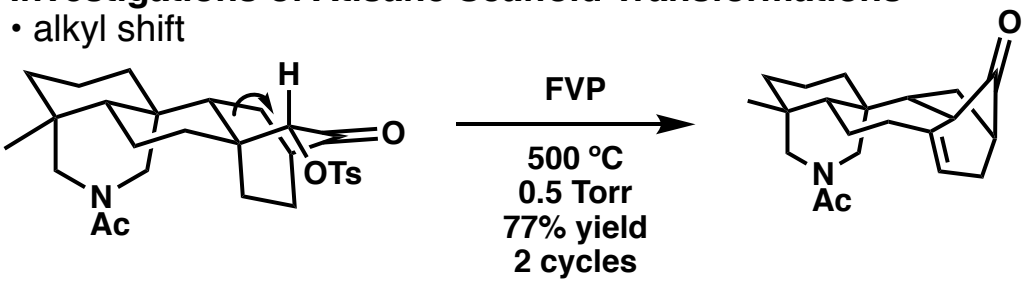


Giersch, W. K.; Boschung, A. F.; Snowden, R. L. Schulte-Elte, K. H. *Helvetica Chimica Acta* **1994**, *77*, 36–40. Ohloff, G.; Uhde, G.; Schulte-Elte, K. H. *Helvetica Chimica Acta* **1967**, *59*, 561–570.

FVP in Total Synthesis

Investigations of Atisane Scaffold Transformations

• alkyl shift

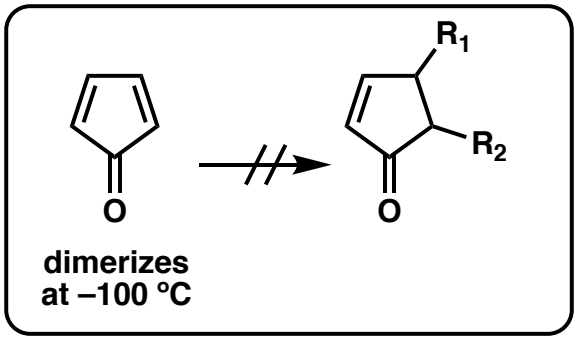


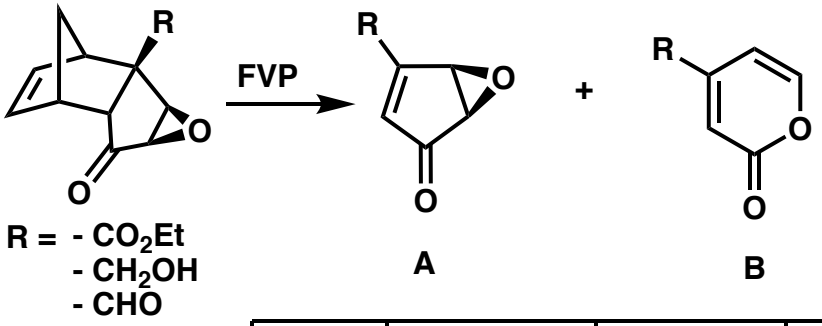
Other conditions attempted showed no reaction or decomposition.

• 180 °C sealed tube
• relux collidine 18h
• 300 °C collidine

Prostaglandins and Related Compounds

• use of D-A adduct as a surrogate for cyclopentadienone



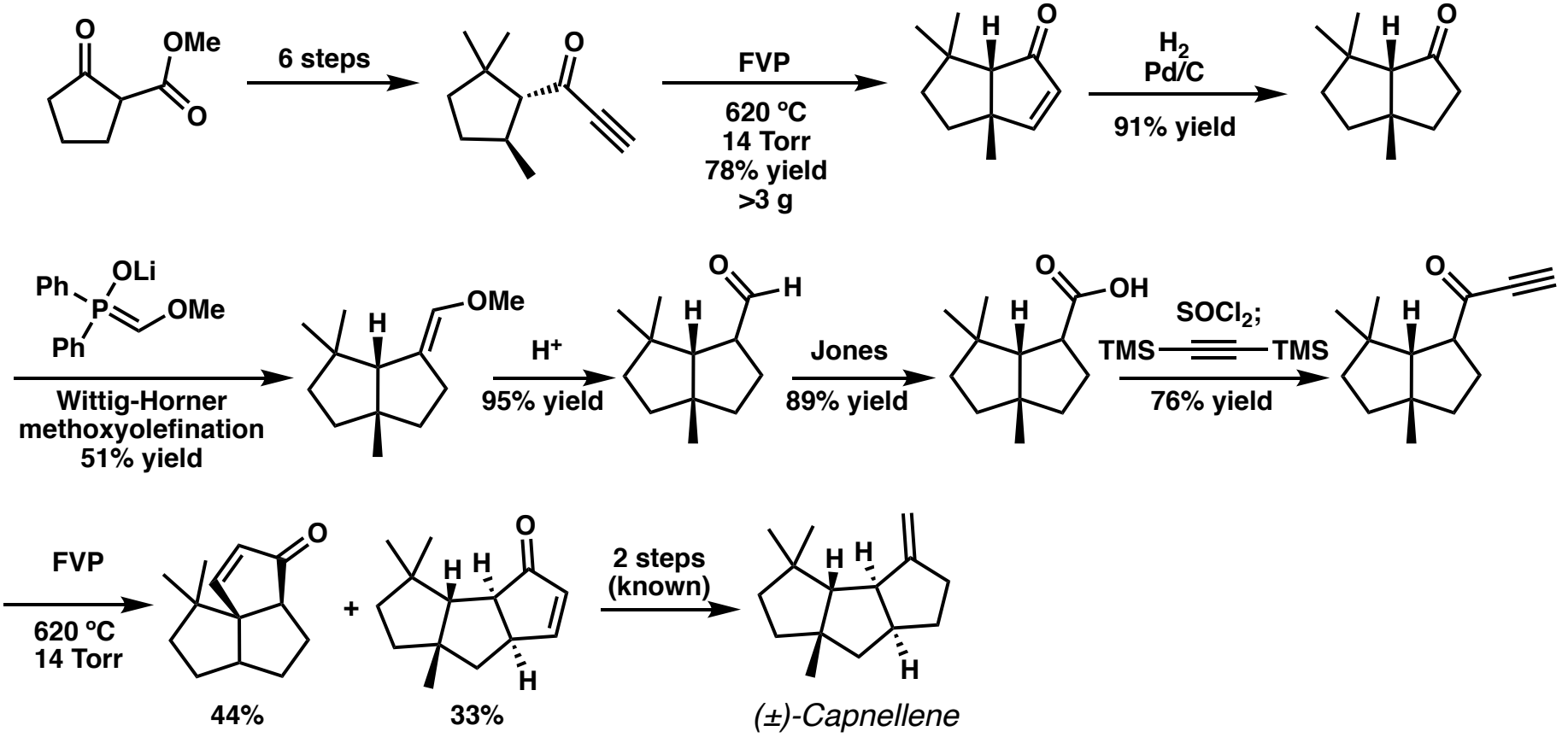


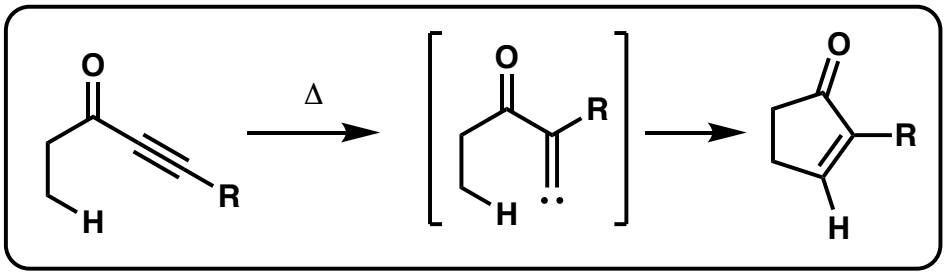
R =	conditions	product	yield
CO_2Et	430 °C	A	55%
	510 °C	B	95%
CH_2OH	540 °C	B	80%
CHO	420 °C	A	95%
	550 °C	B	95%

Johnston, J. P.; Overton, K. H. *J. Chem. Soc., Perkin Trans.* **1972**, 1490–1500. Klunder, A. J. H.; Bos, W.; Verlaak, J. M. M.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553–4556. Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557–4560.

FVP in Total Synthesis

Synthesis of *(±)-Capnellene*
FVP cyclization used twice
Forms (undesired) vicinal quat center





Huguet, J.; Karpf, M.; Dreiding, A. S. *Helvetica Chimica Acta* **1982**, *65*, 2413–2421. Karpf, M.; Huguet, J.; Dreiding, A. S.; *Helvetica Chimica Acta* **1982**, *65*, 13–25.

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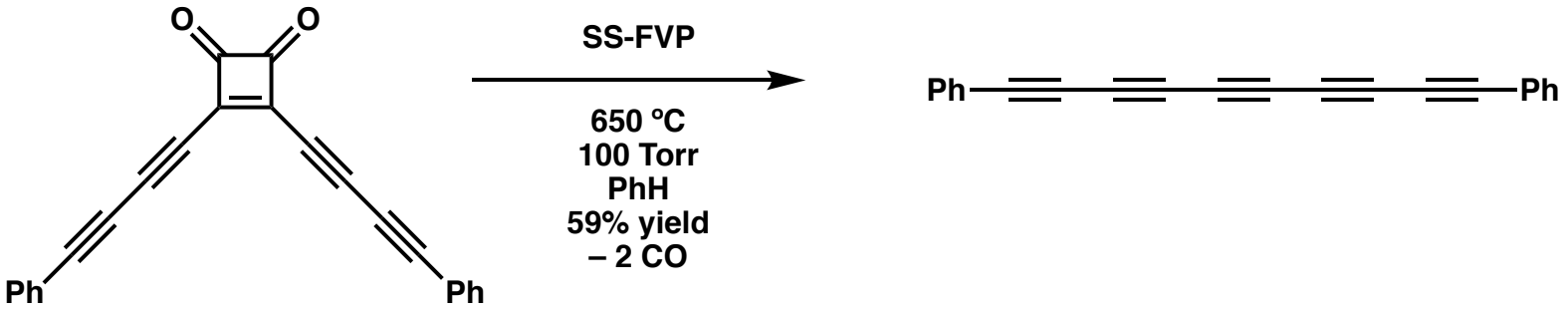
-McNab

McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

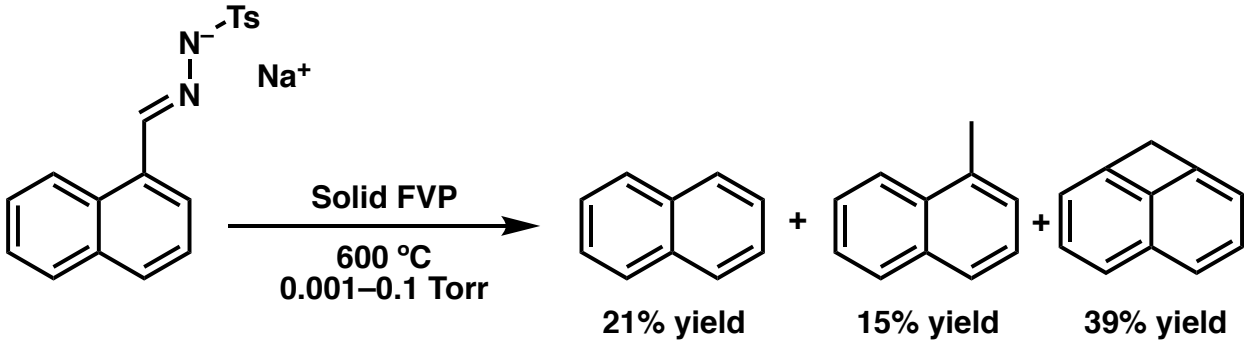
FVP Reactions of Low Volatility Substrates

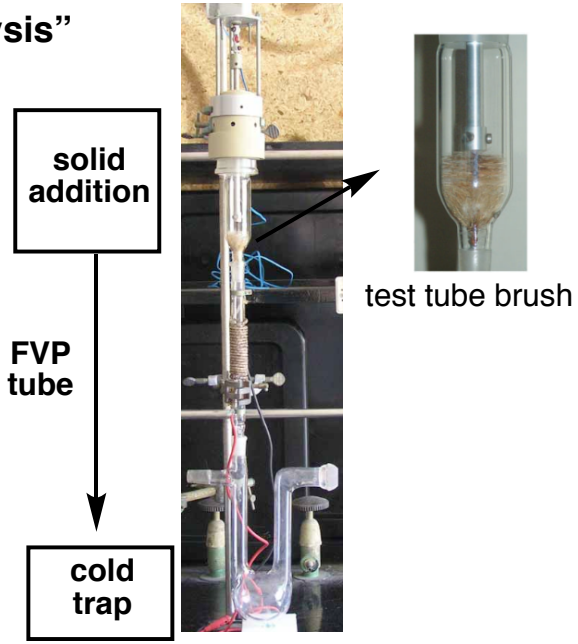
Solution spray flash vacuum pyrolysis
- solution of substrate in solvent is sprayed into FVP chamber as an aerosol

Solvent-assisted pyrolysis
- solution of substrate in solvent is quickly vaporized, substrate is carried with vapor
- solution is typically frozen then placed in >300 °C oil bath, similar to MALDI-MS



Direct useage of solid substrate, "Falling Solid Pyrolysis" or "Piptopyrolysis"
- numerous reports use solid addition funnels, but large chunks of solid falling to apparatus cause pressure spikes and undesired side reactions





Images replicated from SI of Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165. Wentrup. C.; Mayor, C.; Becker, J.; Linder, H. J. *Tetrahedron* **1985**, *41*, 1601–1612. Rubin, Y.; Lin,S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991** , *113* , 6943–6949.

Mimicking FVP Reactivity in Solution

Flash Flow

- Use of high pressure (>100 bar) and temperature (>200 ºC) in fluid flow microreactor

Microwave superheating

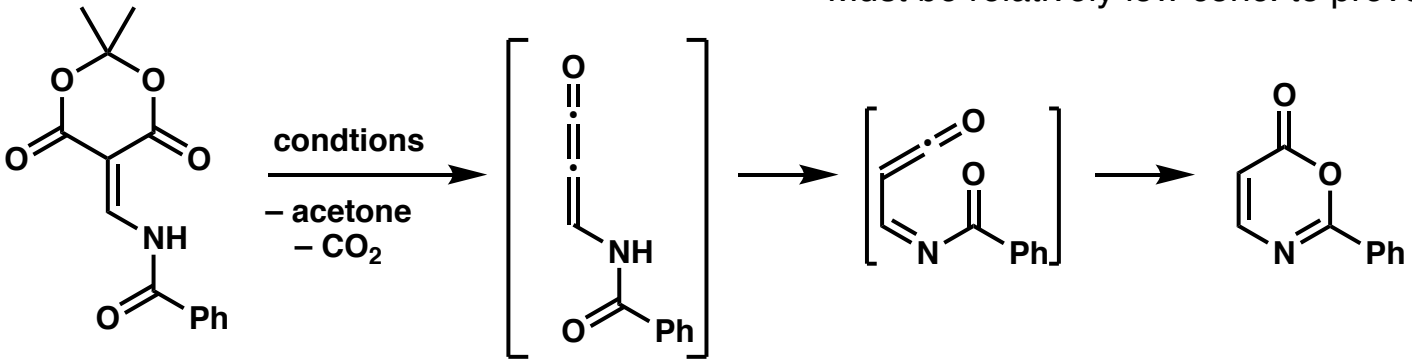
- High pressure (< 30 bar) and temperature (>200 ºC) in a microwave batch reactor
- Thermal sensitizer (i.e. graphite) can be used

Advantages over FVP

- Can be easier to optimize, especially retention time
- Can use solid or non volatile substrates
- More familiar reaction

Disadvantages to FVP

- Often temperature/pressure limited by solvent or reaction
- Products must be thermally stable
- Must be relatively low conc. to prevent reaction

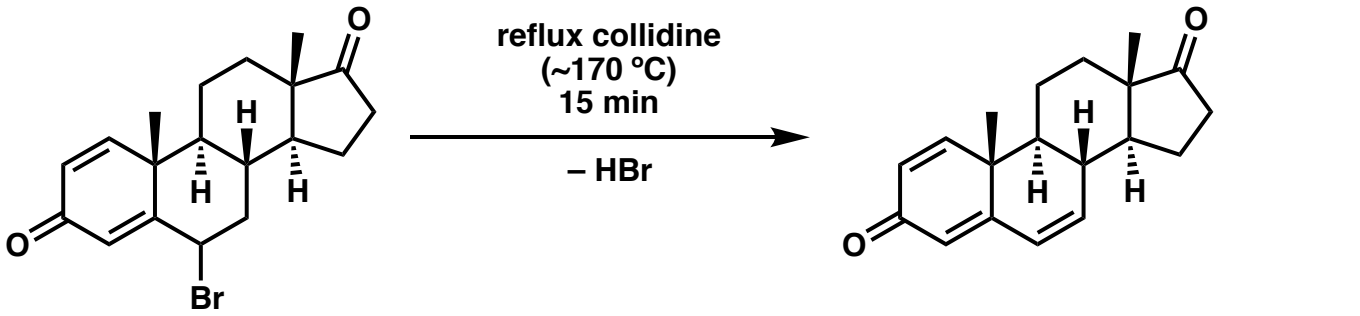


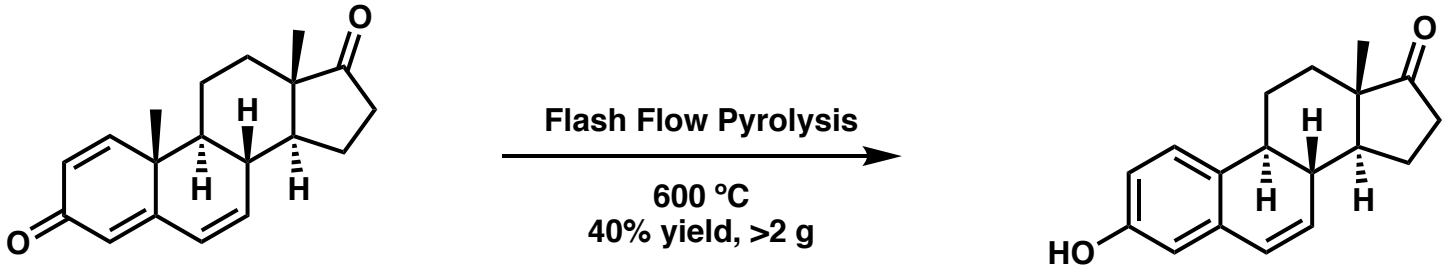
entry	reaction type	temperature (ºC)	pressure	yield (%)	
1	μw batch	240	< 30 bar	88	~100 mg scale
2	μw batch	250	< 30 bar	90	
3	flow	250	>30 bar	87	
4	flow	260	>30 bar	85	
5	flow	270	>30 bar	88	
6	FVP	550	0.01 Torr	79	500 mg scale

Cantillo, D.; Sheibani, H; Kappe, C. O. *J. Org. Chem.* **2012**, *77*, 2463–2473. McNab, H.; Withell, K. *Tetrahedron* **1996**, *52*, 3163–3170. McNab, H.; Morrow, M.; Parsons, S.; Shannon, D. A.; Withell, K. *Org. Biomol. Chem.* **2009**, *7*, 4936–4942.

Flash Flow Pyrolysis in Total Synthesis

What talk doesn't include 1950s steroid chemistry?





$\Delta^{1,4,6}$-androstatriene-3,17-dione

Δ^{6}-dehydroestrone

Solution of substrate in mineral oil (10 mg ml^{-1}) was flowed through glass tube packed with helicies at 2 ml s^{-}

The authors propose direct loss of methyl radical requires such forcing conditons

Kaufmann, S.; Pataki, J.; Rosenkranz, G.; Romo, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950** , *72* , 4531–4534.

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- FVP Use in Total Synthesis

- Future Outlooks

"Organic chemists have enjoyed distilling compounds through hot tubes since the early days of the subject in the 19th century."
-McNab

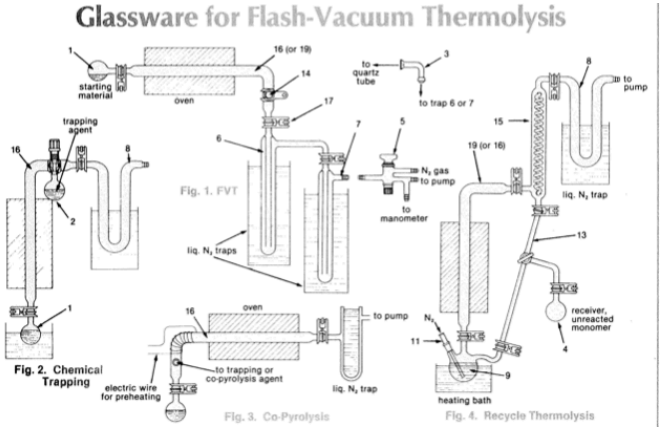
McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.

Commercial FVP Systems

ThalesNano kit
- tube furnace
- vacuum controller
- quartz reactor tube
- cold trap
- vacuum pump

"Contact for quote" = $$$$

Seybold apparatus
- unavailable, was marketed by Normag AG (Germany)
- all glass system, hard to prevent leaks, fragile
- pyrolysis tube ends at N_2 trap, very efficient trapping
- $$$$

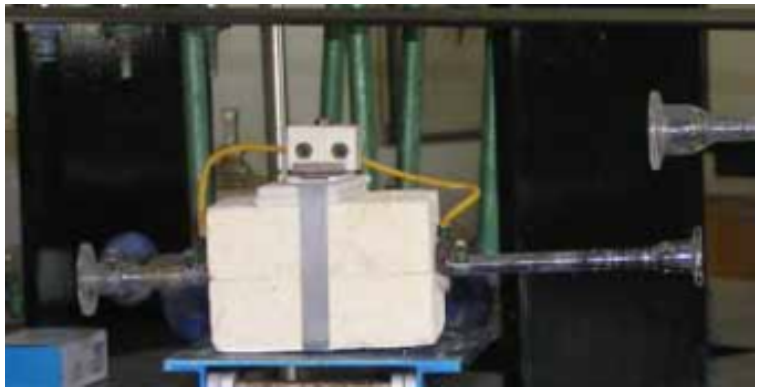


FVP Glassware from Sigma Aldrich
- unavailable in current catalog
- "commercial" homebuild system

photo replicated from www.thalesnano.com/products/Flash%20Reactor%20Plus Wiersum, U. E. *Aldrichchemica Acta* **1984**, *17*, 31–41. Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.

Standardized FVP Reactor

A standard FVP reactor is needed for consistency across labs
- Replication of experiments can be difficult between systems
- Tube size, length, surface area, inlet and outlet can all affect contact time



Wentrup homebuild brick pyrolyzer

The ideal commercial FVP system would
- have standardized quartz tubes
- digital pressure, temperature, flow control
- rapid product trapping
- low cost

Commercial FVP challanges
- niche technique
- safety issues for industry
- homebuild units already more common in academia
- competing flash flow and microwave

photo replicated from Wiersum, U. E. *Aldrichchemica Acta* **1984**, *17*, 31–41. Wentrup, C. *Aust. J. Chem.* **2014**, *67*, 1150–1165.

FVP References

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Wentrup, C. *Chem. Rev.* **2017**, *117*, 4562–4623.
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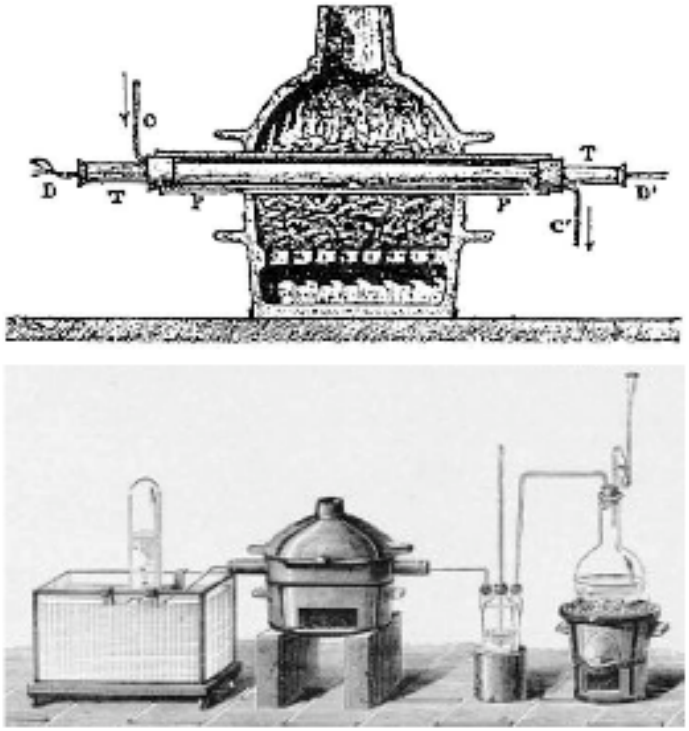
Brown, R. F. C.. *Aust. J. Chem.* **2010**, *63*, 1002–1006.
McNab, H. *Aldrichim Acta* **2004**, *37*, 21–26.
McNab, H. *Aldrichim Acta* **1984**, *17*, 24–41.
McNab, H. *Contemp. Org. Synth.* **1996**, *3*, 373–396.
Tsefrikas, V. M.; Scott, L. T. *Chem. Rev.* **2006**, *106*, 4868–4884.

Other resources

Baran Group meeting, Apr. 21, 2012
http://www.scripps.edu/baran/images/grpmtgpdf/Holte_Apr_12.pdf



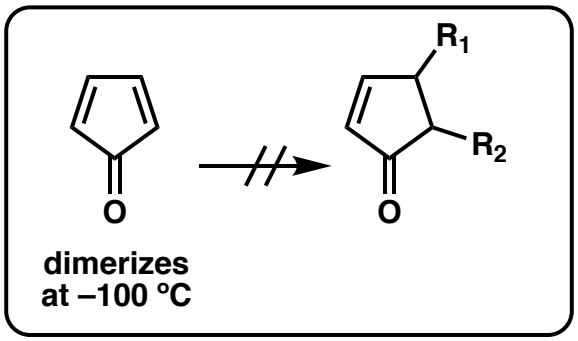
1864 pyrolysis apparatus used by Deville

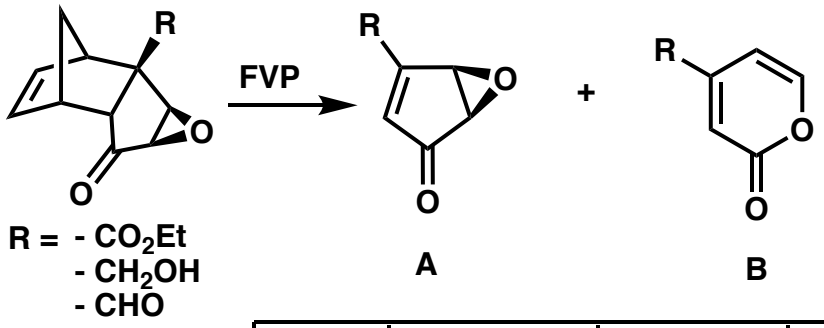
Image replicated from Wentrup, C. *Chem. Rev.* **2017**, *117*, 4562–4623.

FVP in Total Synthesis

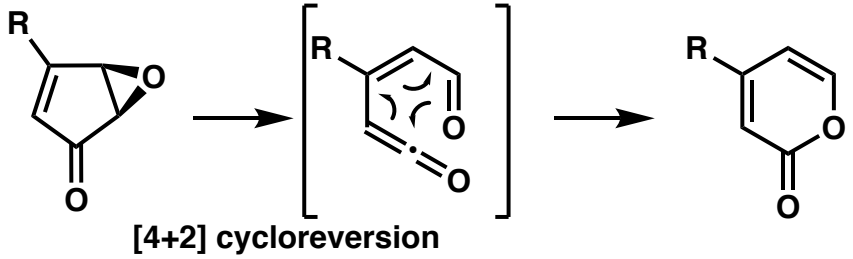
Prostaglandins and Related Compounds

• use of D-A adduct as a surrogate for cyclopentadienone





R =	conditions	product	yield
CO_2Et	430 °C	A	55%
	510 °C	B	95%
CH_2OH	540 °C	B	80%
CHO	420 °C	A	95%
	550 °C	B	95%



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