OZONOLYSIS

THE ODOR OF ELECTRICITY

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Tyler Lab Group Meeting

6/19/13

Homer, 750 B.C.

Rubin, M. B. *Bull. Hist. Chem*, **2001**, *26*, 40.

Outline

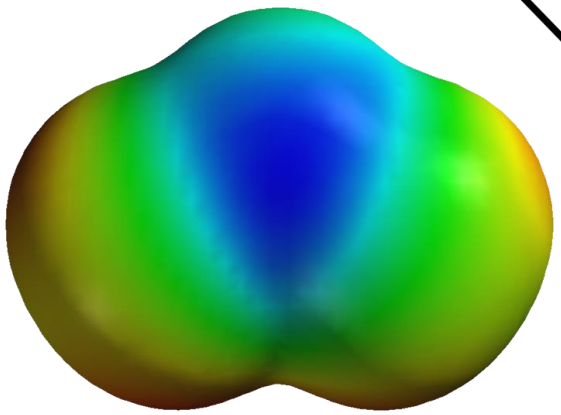
- Ozonolysis & ozone
- History of ozonolysis
  - Major discoveries
  - Intermediates and mechanism
  - General reactivities
- Modern ozonolysis
  - Regio- and stereoselective ozonolysis
  - Pharmaceutical applications
  - New methodologies
- Flow reactors for ozonolysis
- Summary & Conclusions

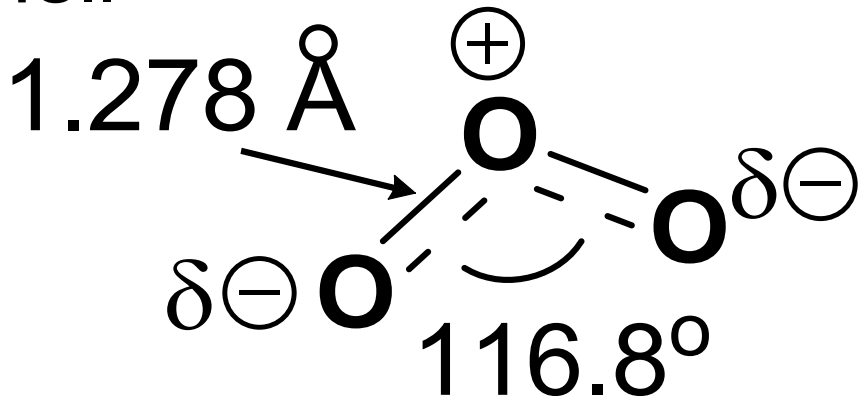
Ozonolysis

- *"the cleavage of an alkene or alkyne with ozone"*
- A "green" oxidant
  - Decomposes to O_2, H_2O_2, H_2O
  - Readily generated from O_2
- Avoids the use of metals and hypervalent halogens
  - Good for pharmaceutical syntheses
- Very strong oxidant (+2.07 eV vs. SHE)

Properties O_3

- BP: -112ºC
- Highly toxic
  - 100 ppb
- Oxidize all metals
  - Except: Au, Pt, Ir
- Diamagnetic, closed shell

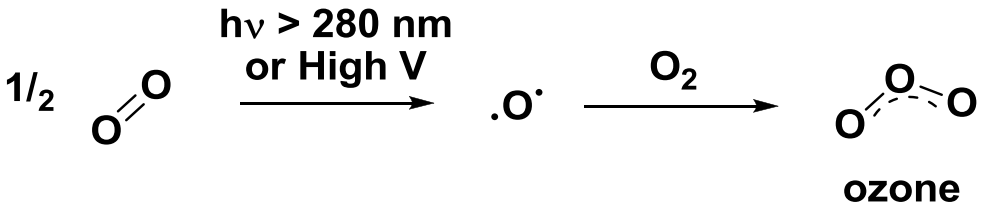




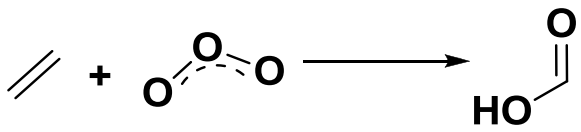
Hughes, R. H. *J. Chem. Phys.* **1956**, *24*, 131.
Trambarulo, R.; Ghosh, S. N.; Burrus, C. A.; Gordy, W. *J. Chem. Phys*. **1953**, *21*, 851.

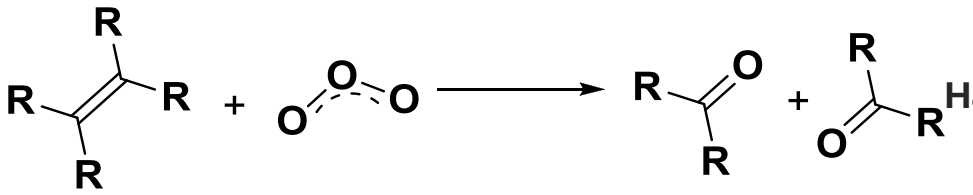
History of Ozonolysis

- Discovered 1840
  - Name “ozone” from *ozein* (greek: to smell)



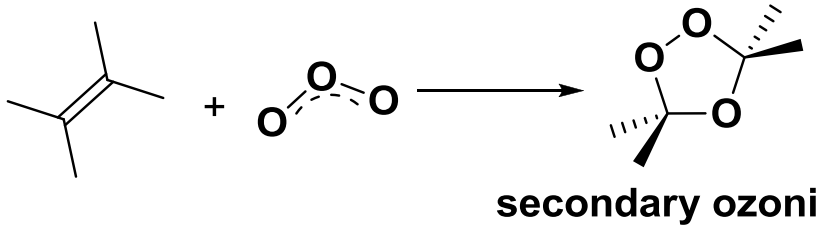
Schönbein *(1840-1868)*





Harries & Molinari *(1903-1916)*

Reiche, Pummerer, & Briner *(1932-1949)*

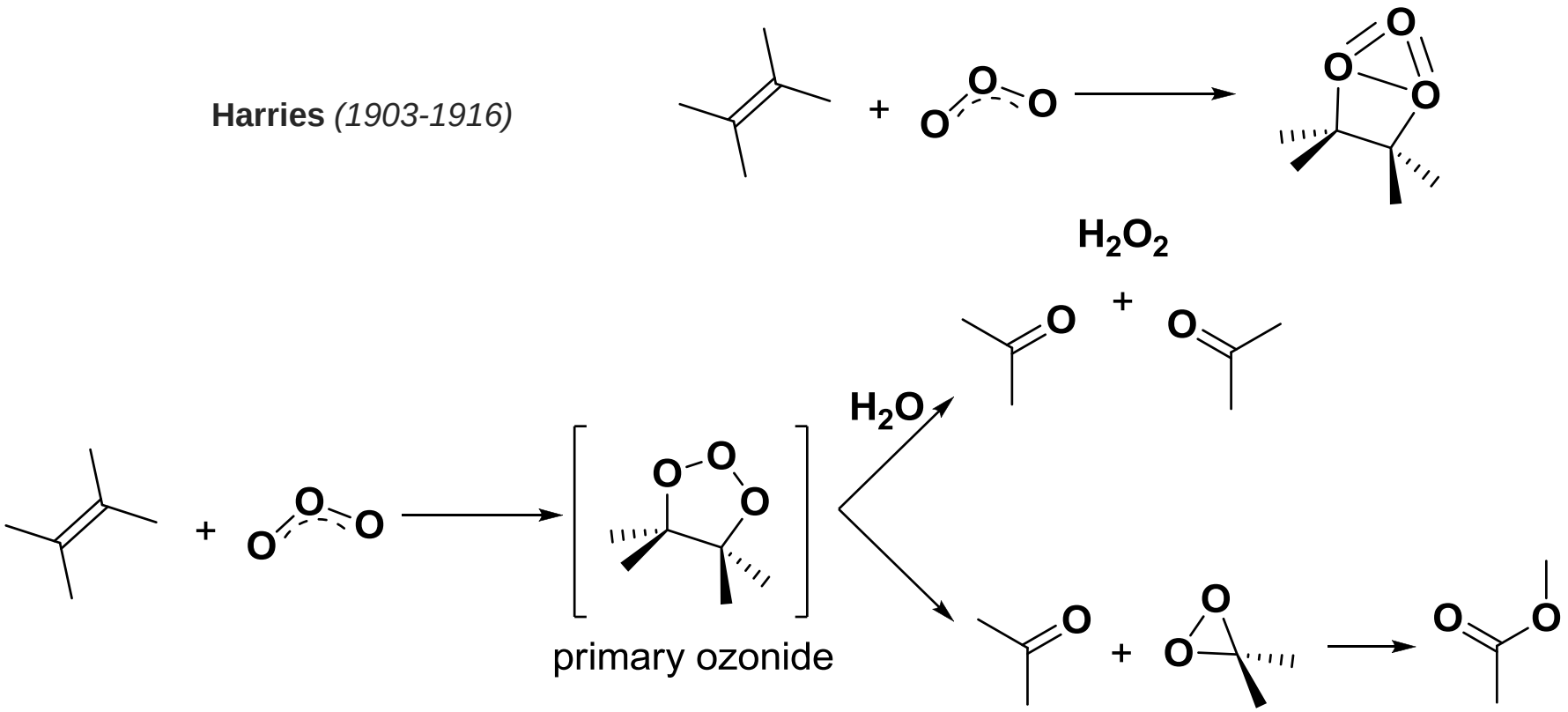


Schönbein, C. F. *C. R. Hebd. Seances Acad. Sci.* **1840**, *10*, 706.
Long, L. *Chem. Rev.* **1940**, *27*, 437.

Early Mechanism Theories

- Mechanism of ozonolysis
  - No basis for assumptions

Harries *(1903-1916)*

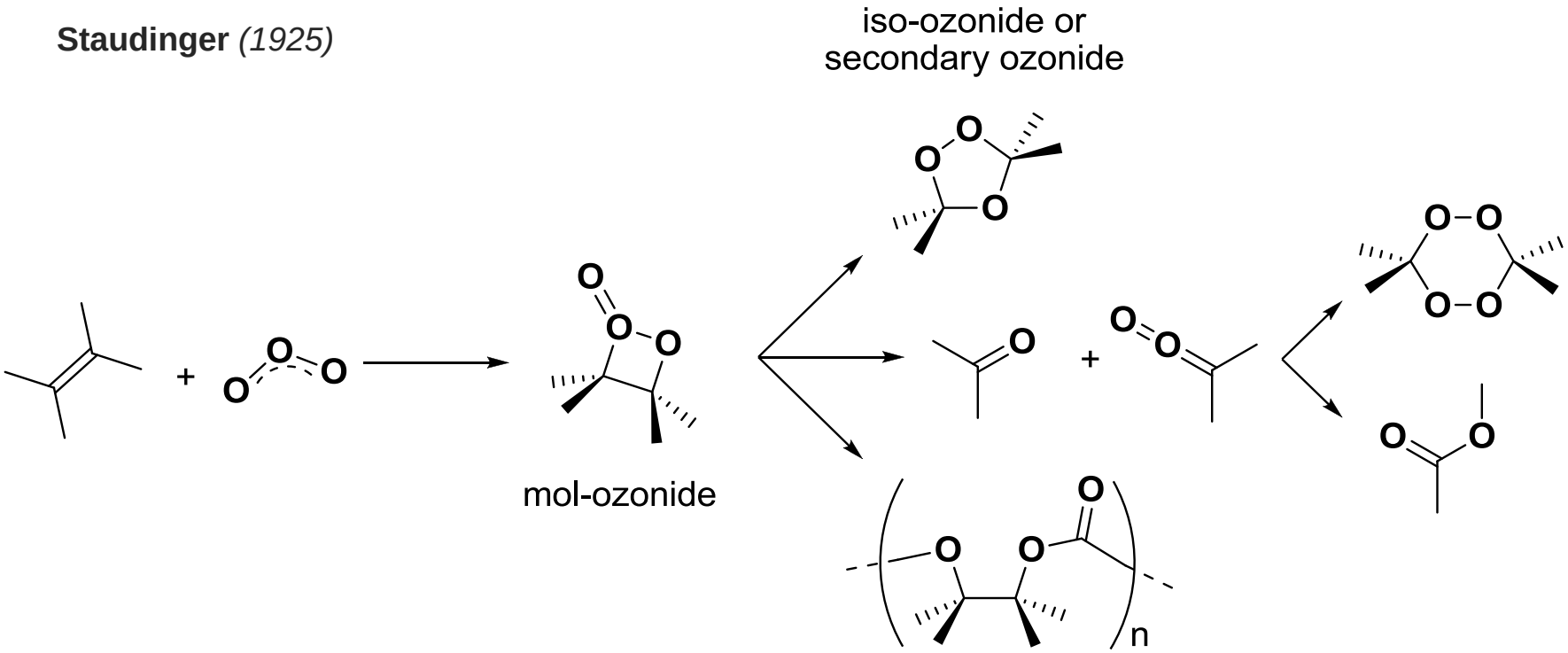


Harries, C. D. *Justus Liebigs Ann. Chem.* **1905**, *343*, 311.
Koetschau, R. Z. *Angew. Chem.* **1924**, *37*, 110.

Early Mechanism Theories (cont.)

- Mechanism of ozonolysis

Staudinger *(1925)*

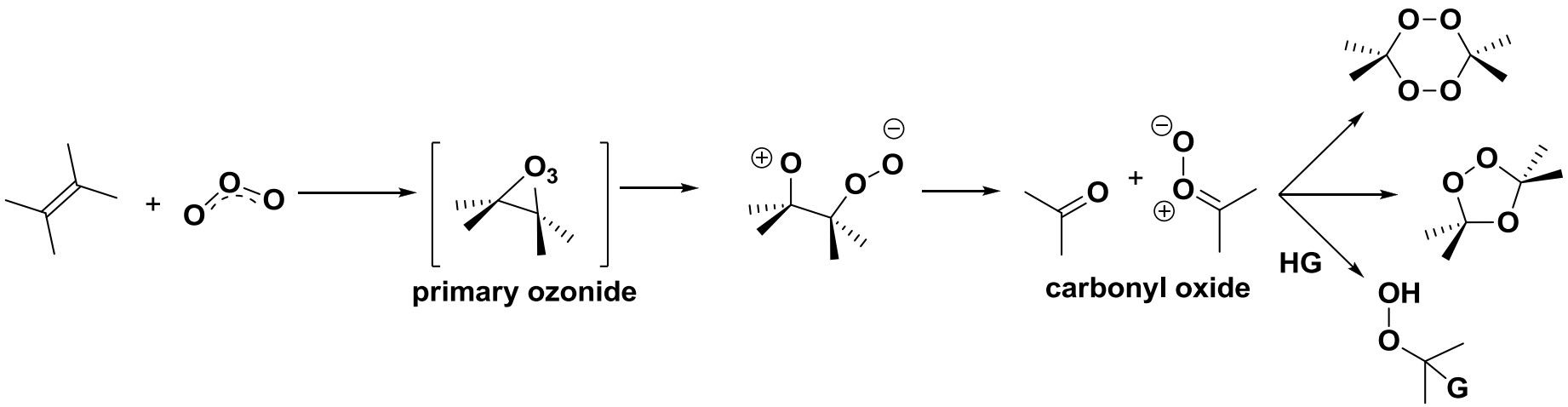


Staudinger, H. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 1088.

Early Mechanism Theories (cont.)

- Mechanism of ozonolysis

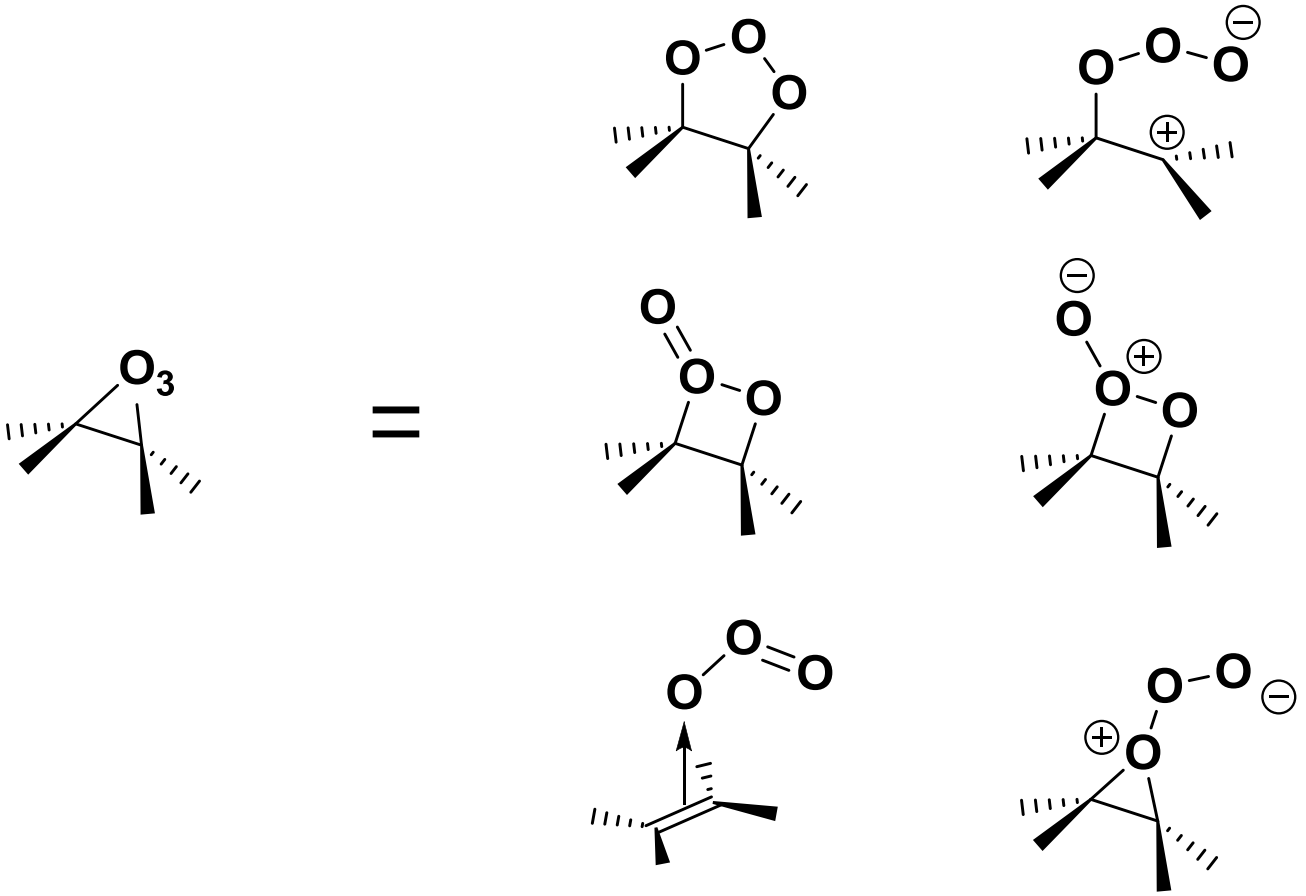
Criegee *(1949-1957)*



Criegee, R. *Justus Liebigs Ann. Chem.* **1953**, *583*, 1.
Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925.

Primary Ozonide

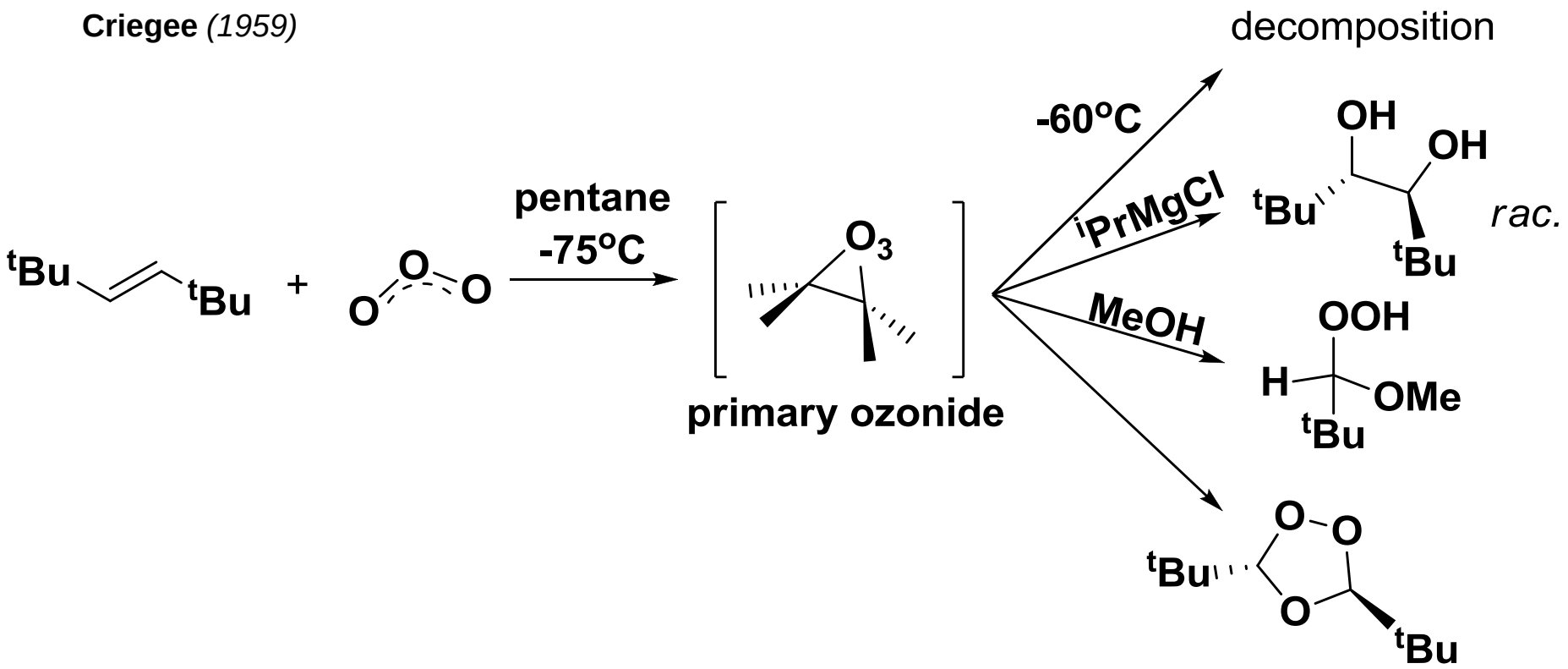
- Identity of the primary ozonide



Criegee, R. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 745.

Primary Ozonide (cont.)

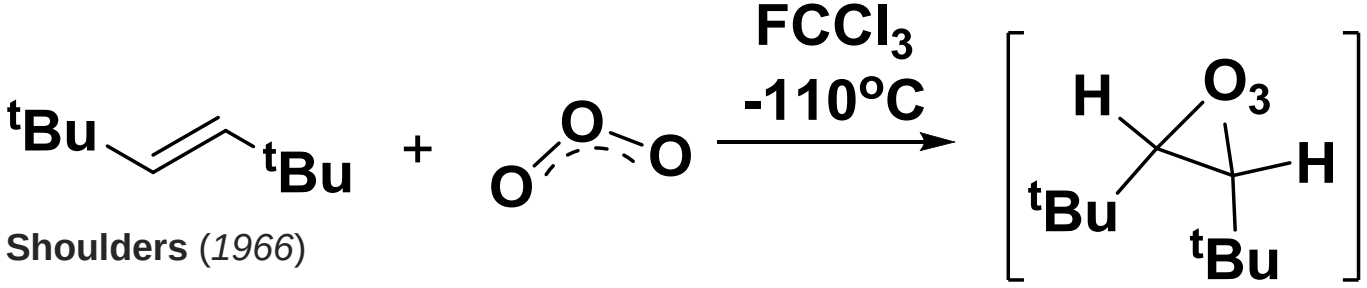
- Isolation of the primary ozonide



Criegee, R. *Angew. Chem.* **1959**, *71*, 525.

Primary Ozonide (cont.)

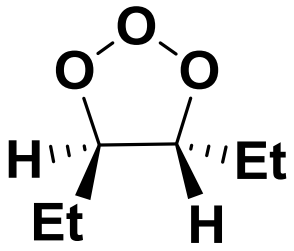
- NMR spectrum of the primary ozonide
  - ^{1}H: 2 singlet peaks (1:9)
  - Decomposition T > -60^{o}C



Bailey, Thompson, & Shoulders (*1966*)

primary ozonide

- IR Data
  - $t_{1/2}$ 55 min. at -100^{o}C

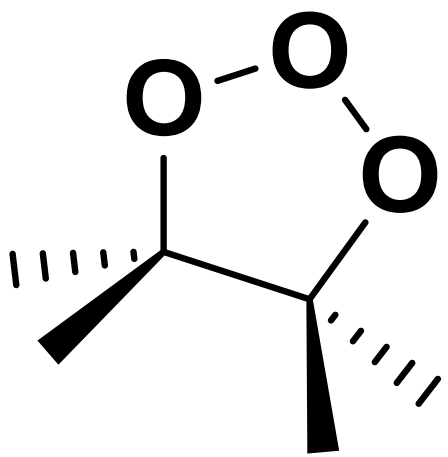


Alcock & Mile (*1973*)

Bailey, P. S.; Thompson, J. A.; Shoulders, B. A. *J. Am. Chem. Soc.* **1966**, *88*, 4098.
Alcock, W. G.; Mile, B. *J. Chem. Soc., Chem. Commun.* **1973**, 575.

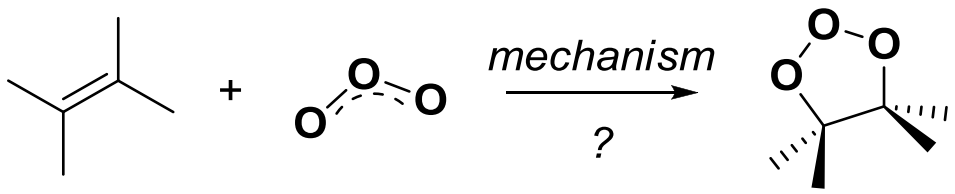
Primary Ozonide (cont.)

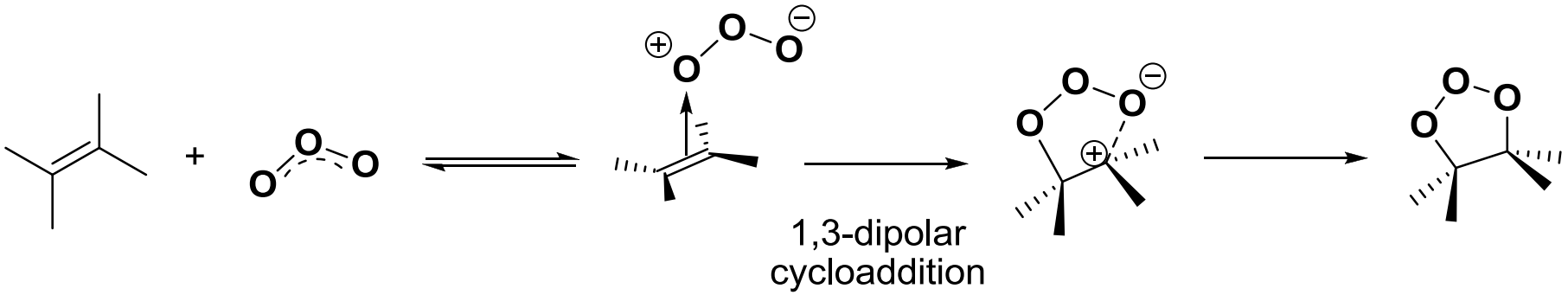
- First intermediate
  - Primary ozonide
  - 5 member ring, symmetric

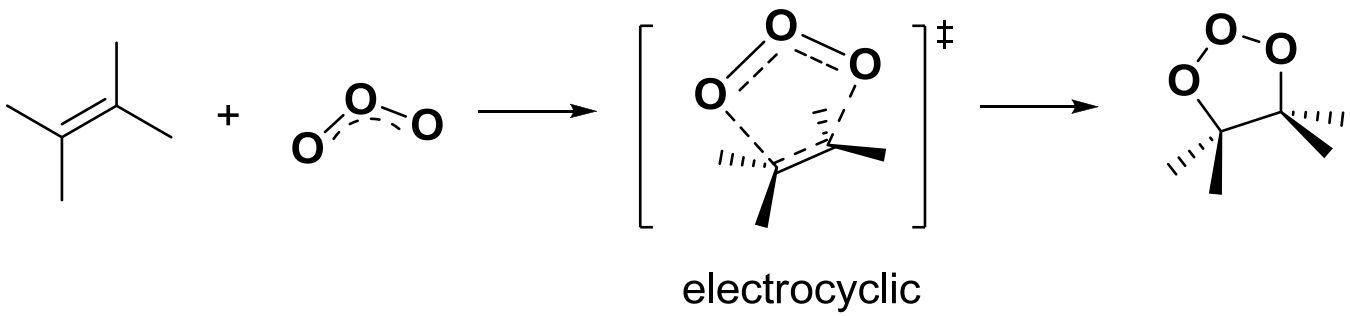


Durham, L. J.; Greenwood, F. L. *Chem. Commun.* **1967**, 843.
Durham, L. J.; Greenwood, F. L. *J. Org. Chem.* **1968**, *33*, 1629.
Greenwood, F. L.; Durham, L. J. *J. Org. Chem.* **1969**, *34*, 3363.

Intimate Mechanism

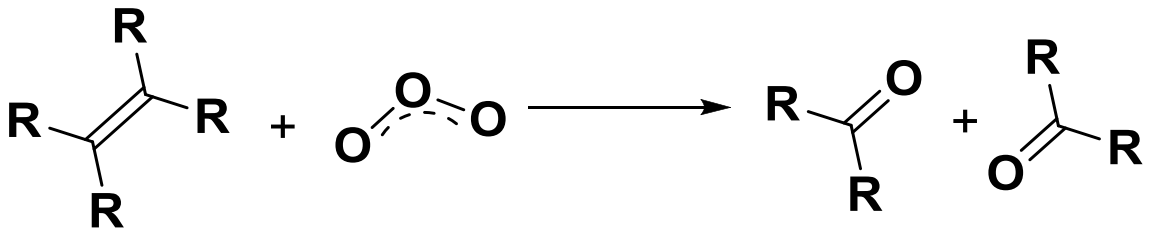






Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925.

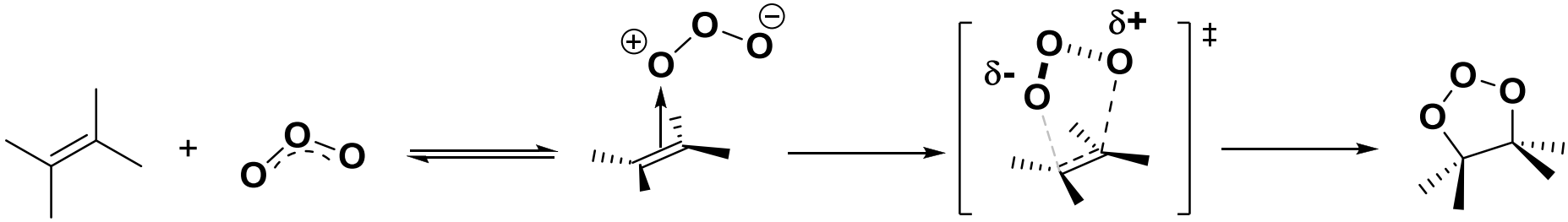
Intimate Mechanism (cont.)



- Rate information:
  - Overall 2nd order - $[O_3][alkene]$
  - Faster when R = EDG
    - O_3 acts as electrophile
    - Hammet plot $\rho = -1$
- Reaction faster in polar solvent (polar intermediate)
- Stereochemical retention (suggests $4_\pi+2_\pi$)
- Large $-\Delta S^\ddagger$

Cvetanovic, R. J. *J.Am. Chem. Soc.* **1968**, *90*, 3668–3672

Accepted Intimate Mechanism

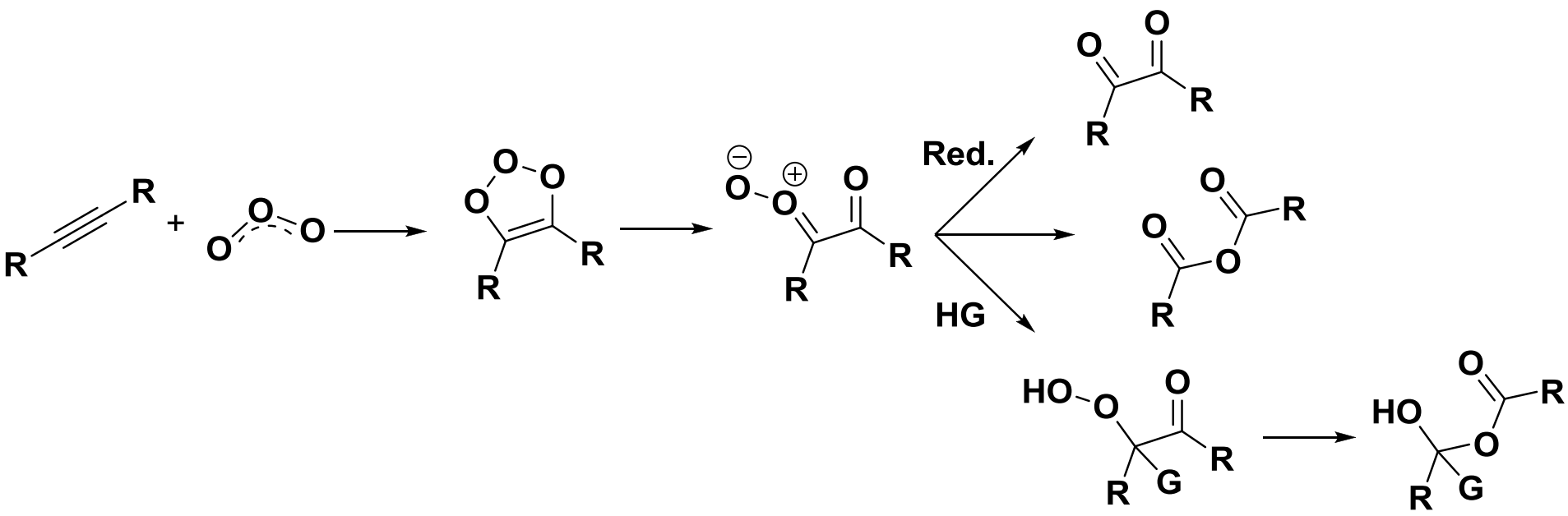


- Diels-Alder type [4_π+2_π]
- 1,3-Dipolar cycloaddition
  - Polar/ asymmetric TS‡

Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.
Bailey, P. S. *Ozonation in Organic Chemistry: Olefinic Compounds*; Academic Press: New York, 1978; Vol. 1.

Ozonolysis of Alkynes

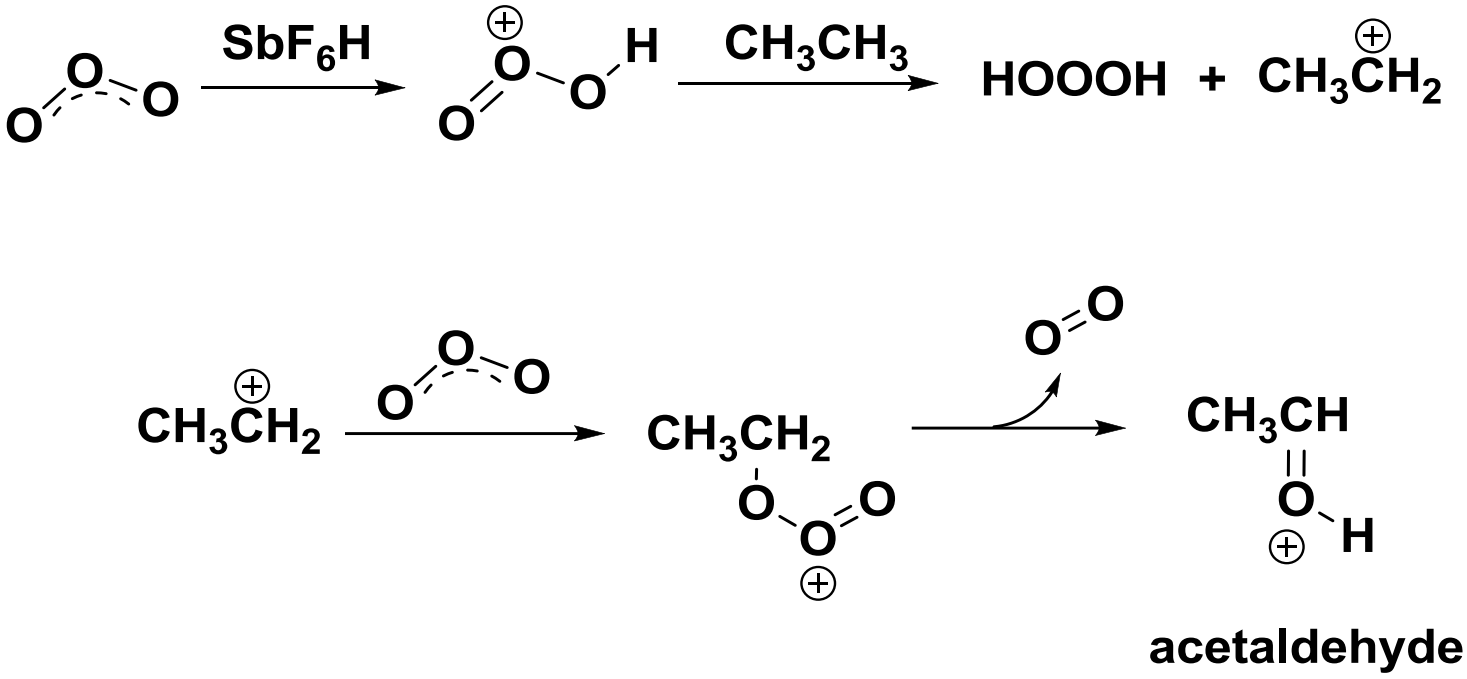
- React ~10x more slowly than alkenes



Criegee, R.; Lederer, M. *Liebigs Ann. Chem.* **1953**, *583*, 29.
Bailey, P. S. *Ozonation in Organic Chemistry: Nonolefinic Compounds*; Elsevier Science, 1982; Vol. 2.

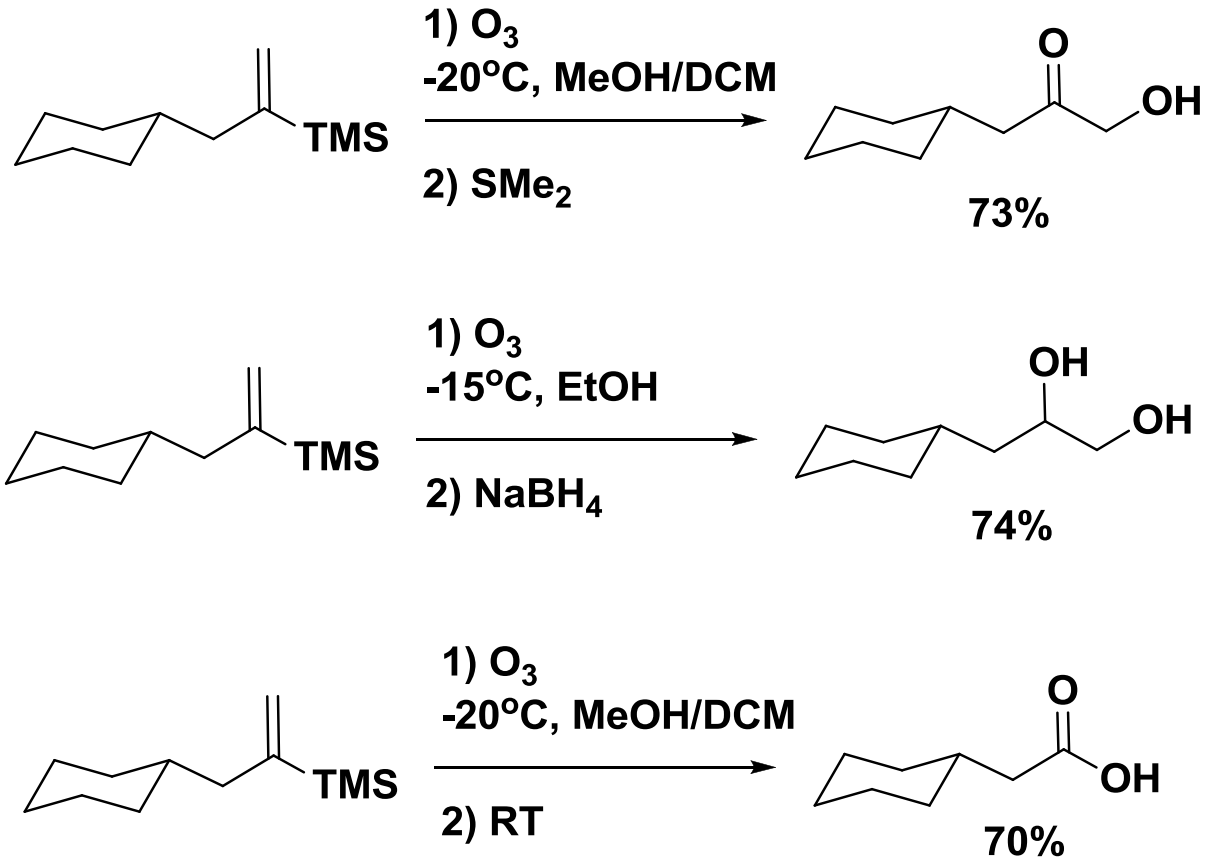
Ozonolysis of Alkanes

- Requires “magic acid” at -78°C



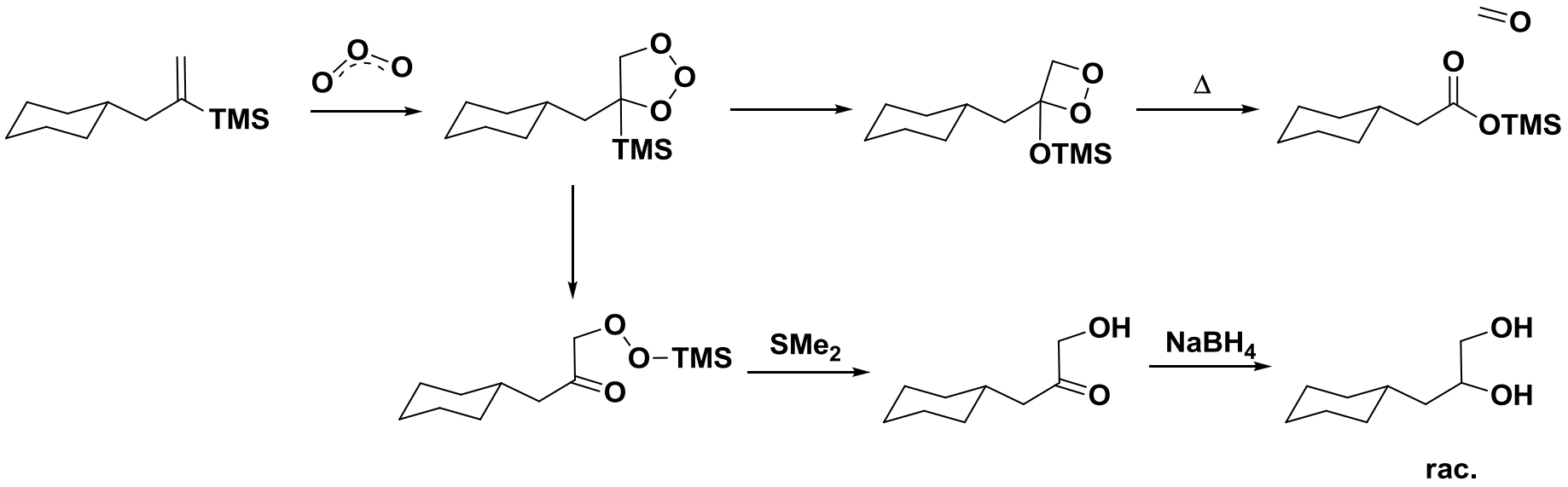
Olah, G. A.; Yoneda, N.; Parker, D. G. *J. Am. Chem. Soc.* **1976**, *90*, 5261.
Yoneda, N.; Olah, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 3113.

Ozonolysis of Vinyl-Silanes



Büchi; Wüest *J. Am. Chem. Soc.* **1978**, *100*, 294.

Ozonolysis of Vinyl-Silanes (cont.)



Büchi; Wüest *J. Am. Chem. Soc.* **1978**, *100*, 294.
Bailey, P. S. *Ozonation in Organic Chemistry: Nonolefinic Compounds*; Elsevier Science, 1982; Vol. 2.

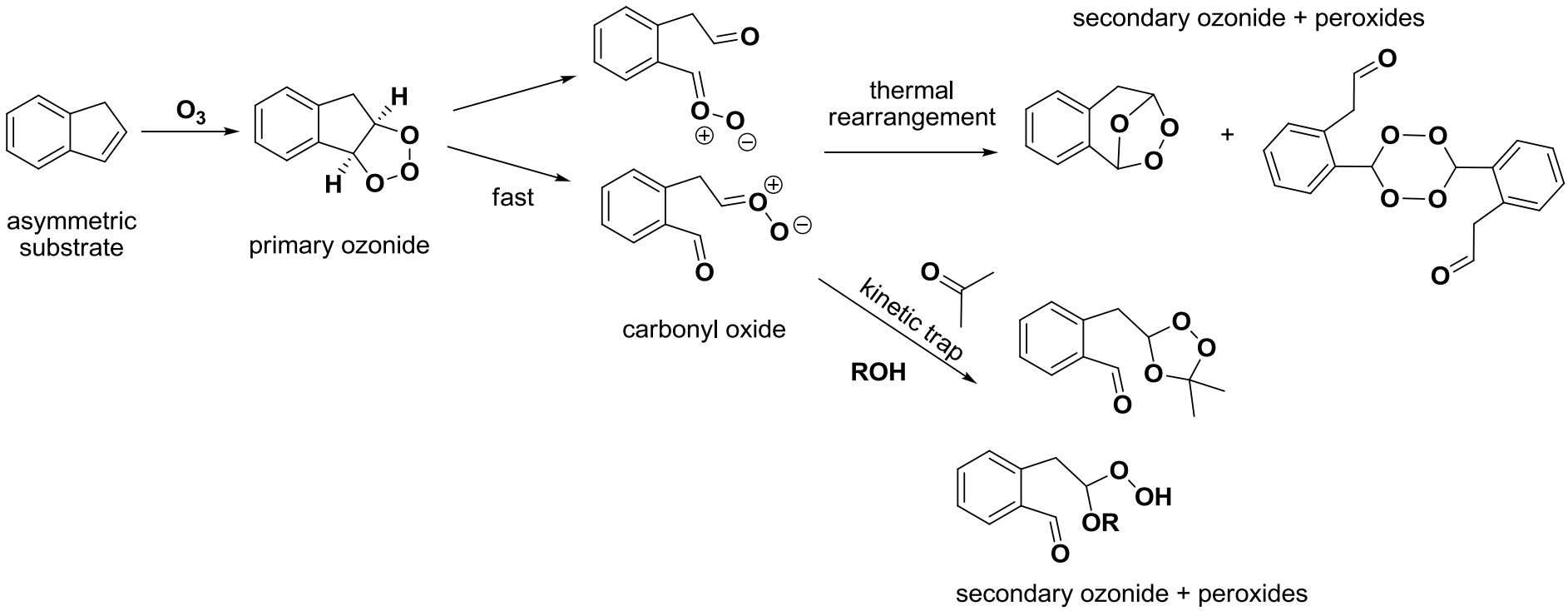
Modern Ozonolysis (cont.)

- Temperature: 0°C to -20°C
  - Prefers peroxy intermediates that can be more safely reacted out
- Reductive workup: SMe_2, $P(OMe)_3$, $NaBH_4$
  - Forms aldehydes or alcohols
- Oxidative workup: *m*-CPBA, H_2O_2, O_2, Ag_2O
  - Forms aldehydes or carboxylic acids

Testero, S. A.; Suarez, A. G.; Spanevello, R. A.; Mangione, M. I. *Trends in Organic Chemistry* **2003**, *10*, 35–49.
Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001.

Modern Ozonolysis

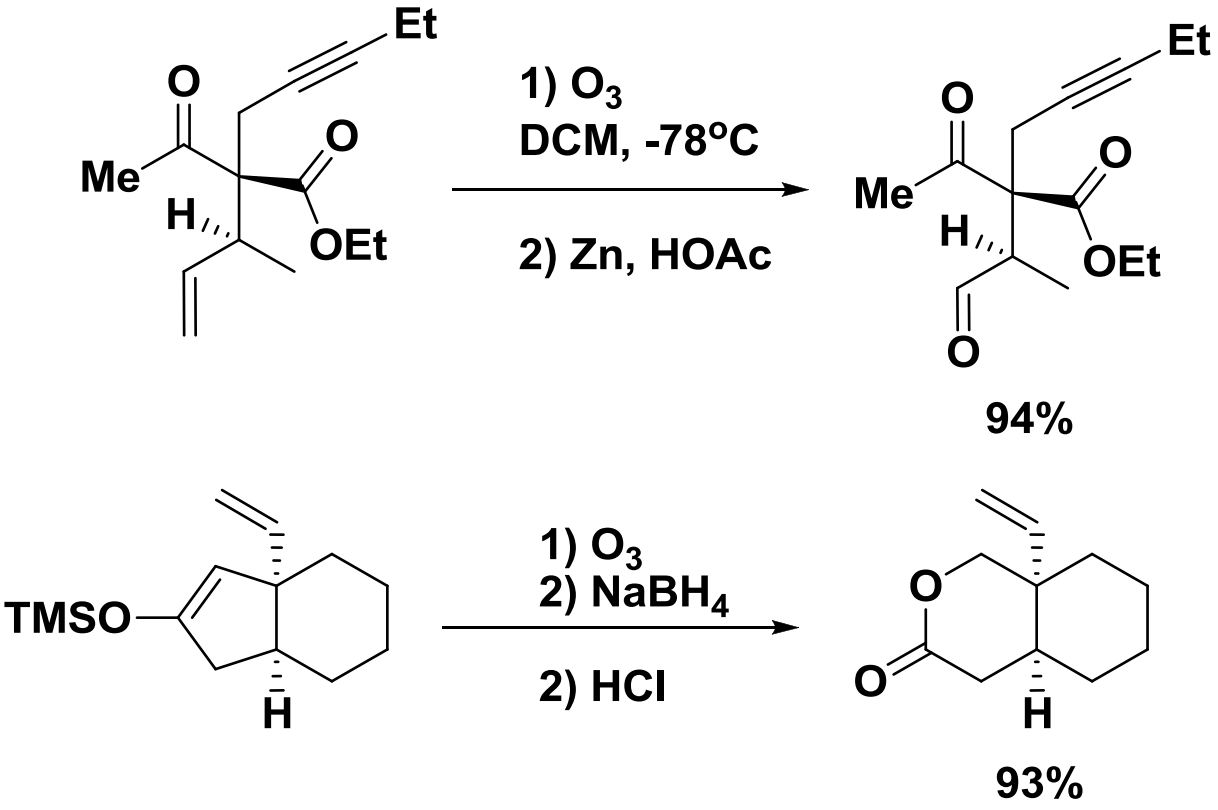
- Trap kinetic product before rearrangement
  - ROH, RC(O)R
  - Stereoselctivity



Testero, S. A.; Suarez, A. G.; Spanevello, R. A.; Mangione, M. I. *Trends in Organic Chemistry* **2003**, *10*, 35–49.

Modern Ozonolysis

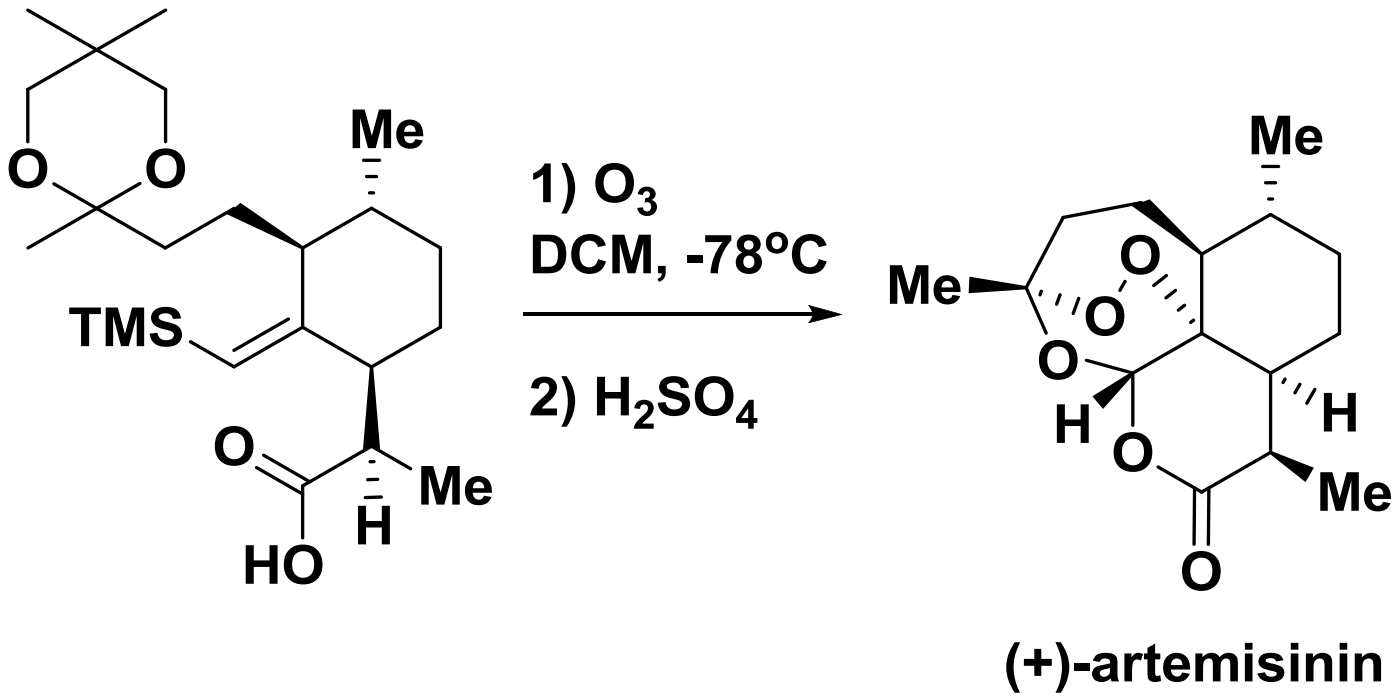
- Selectively ozonate
  - Regioselctivity, kinetic driven reaction



McCurry, P. M.; Abe, K. *Tetrahedron Lett.* **1974**, 1387.
Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 2027.

Advanced Synthesis: (+)-Artemisinin

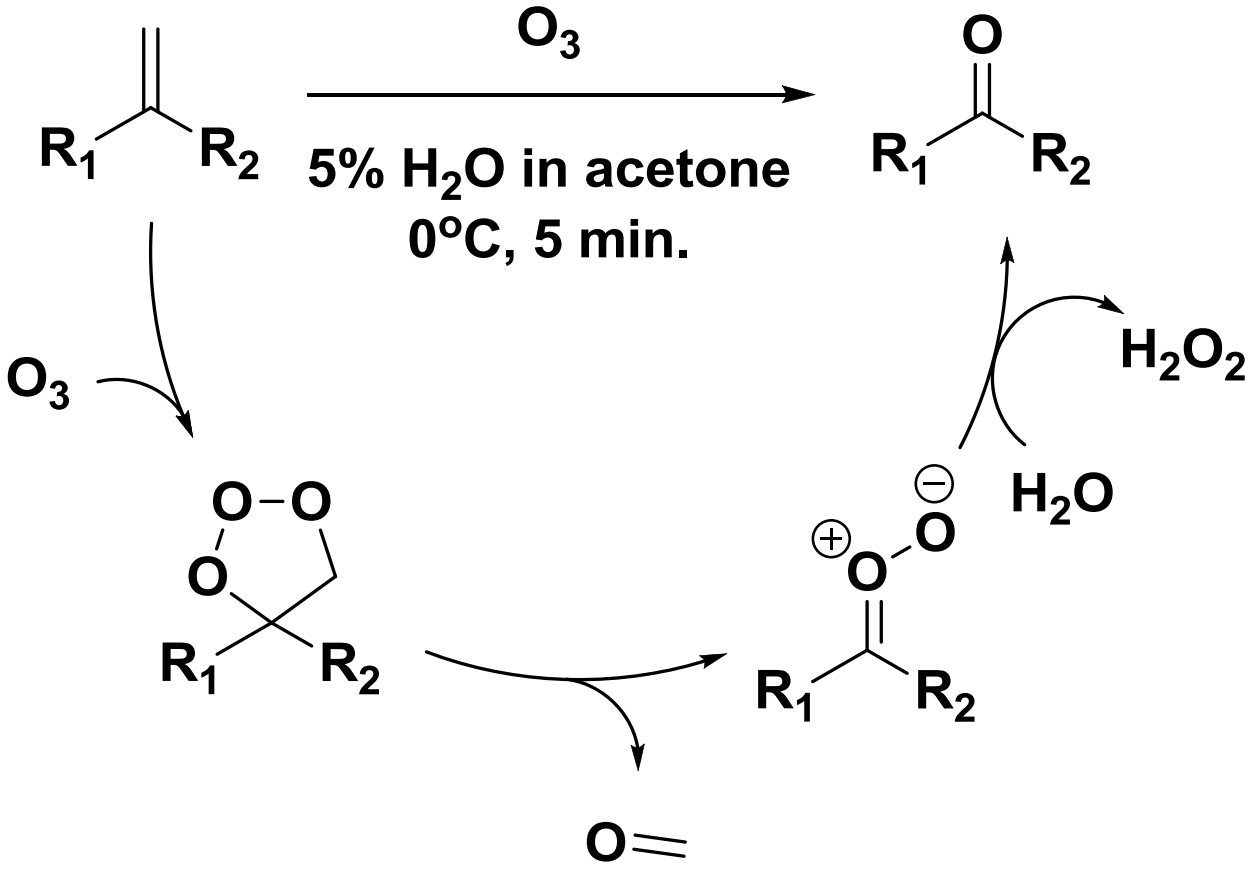
- Anti-malarial (100 ton/year)
  - 500g scale batch process



Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001.

Modern Ozonolysis (cont.)

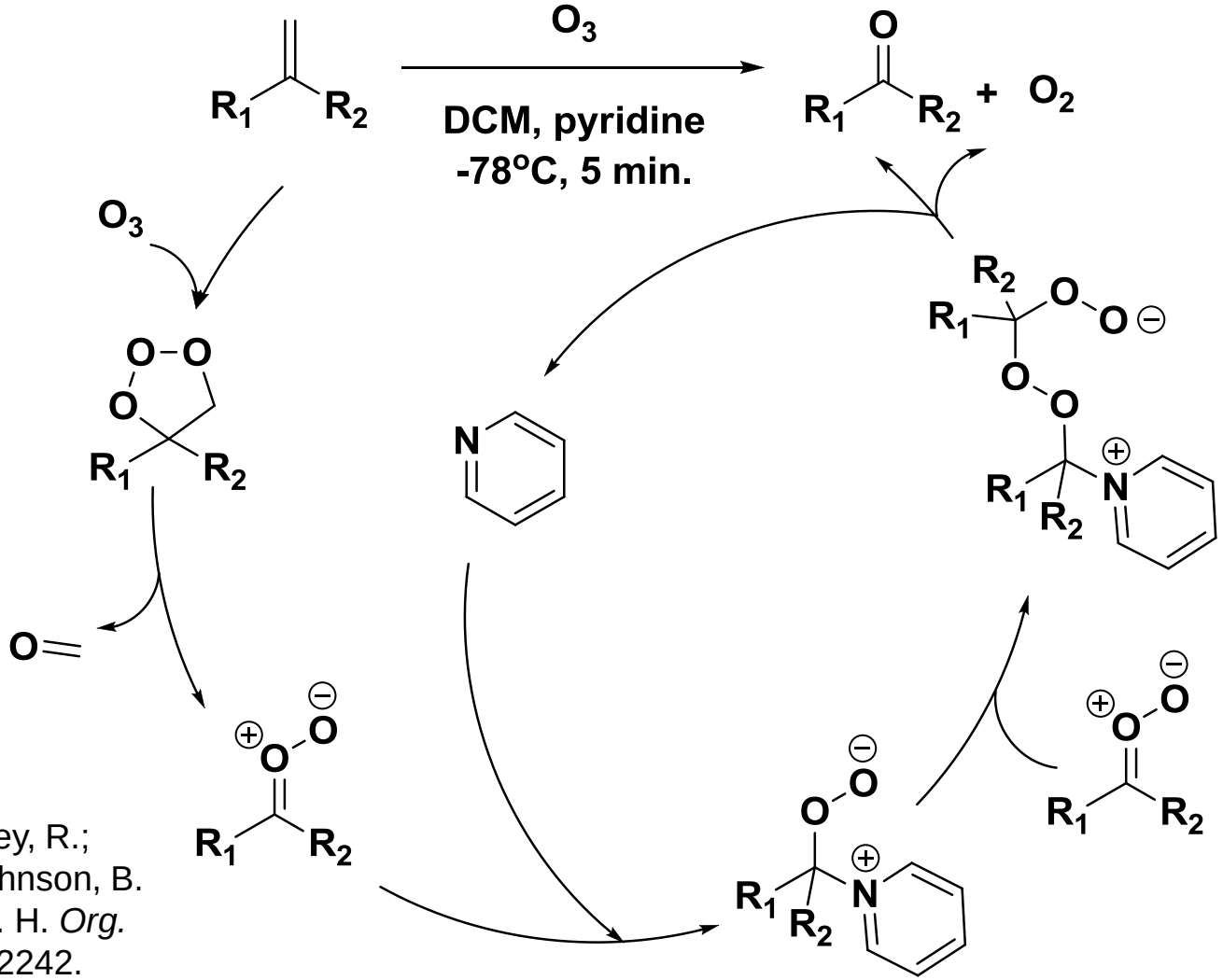
- *In-situ* peroxide quench (H_2O)



Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*,4688.

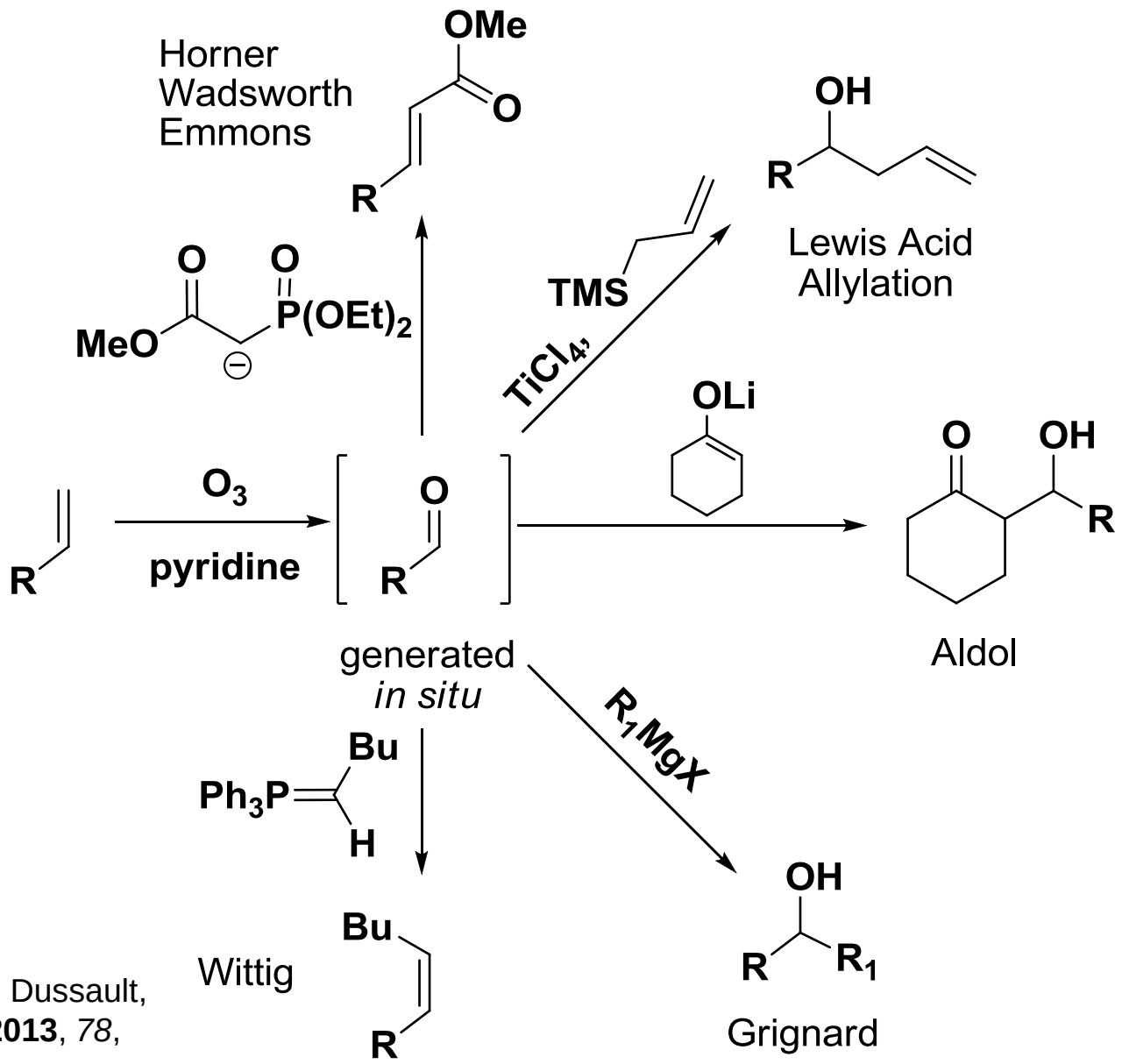
Modern Ozonolysis (cont.)

- *In-situ* peroxide quench (cat. Pyridine)



Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.* **2012**, *14*, 2242.

One-Pot Syntheses



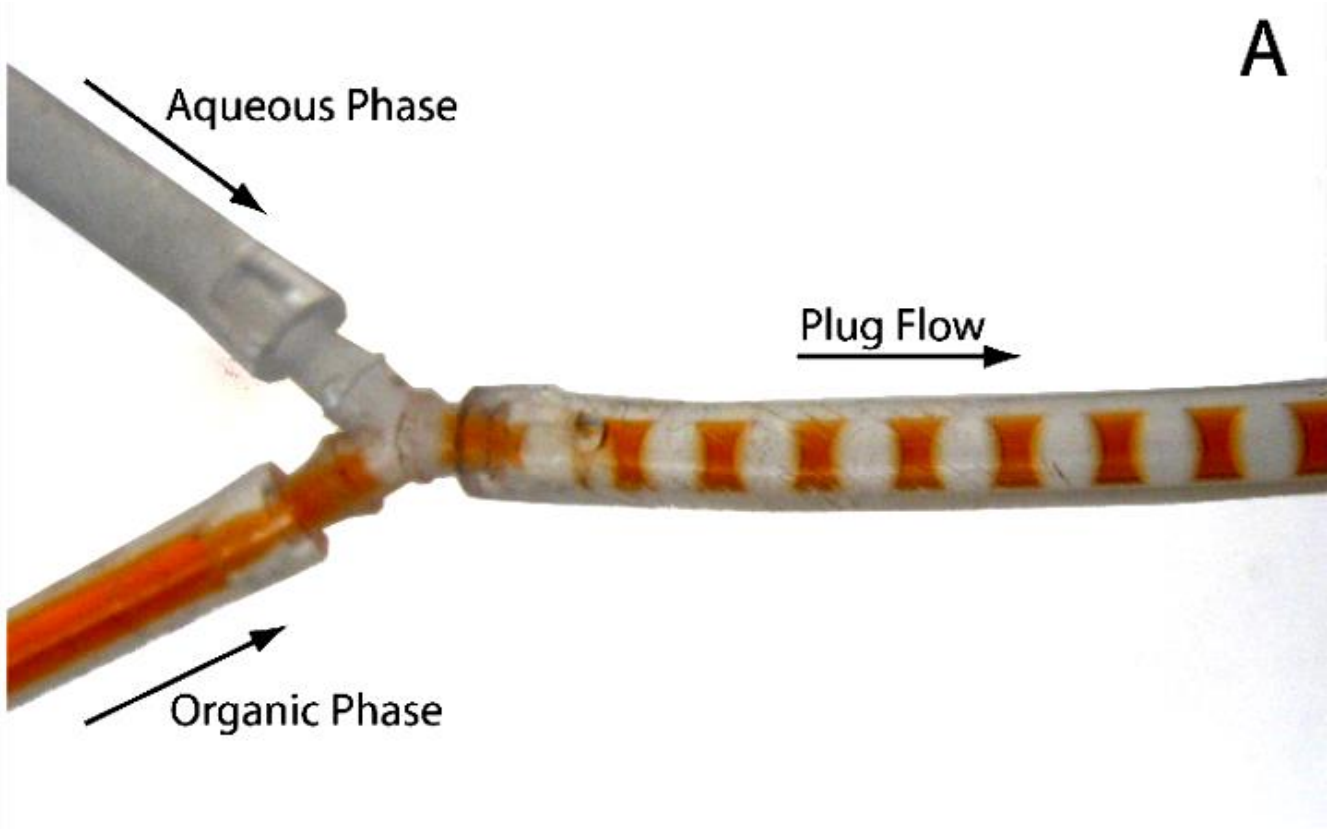
Willand-Charnley, R.; Dussault, P. H. *J. Org. Chem.* **2013**, *78*, 42.

Flozone

- Flow reactors for ozonolysis
  - Reduces the amount of peroxides present
  - Ease of ozone generation for flow process
  - Continuous flow operations
- Downside
  - Difficult due to heterogenous reaction
  - Cost to generate ozone
  - Requires extra steps to quench (batch workup)
  - Cryogenic temperatures

Current Flozone Reactors

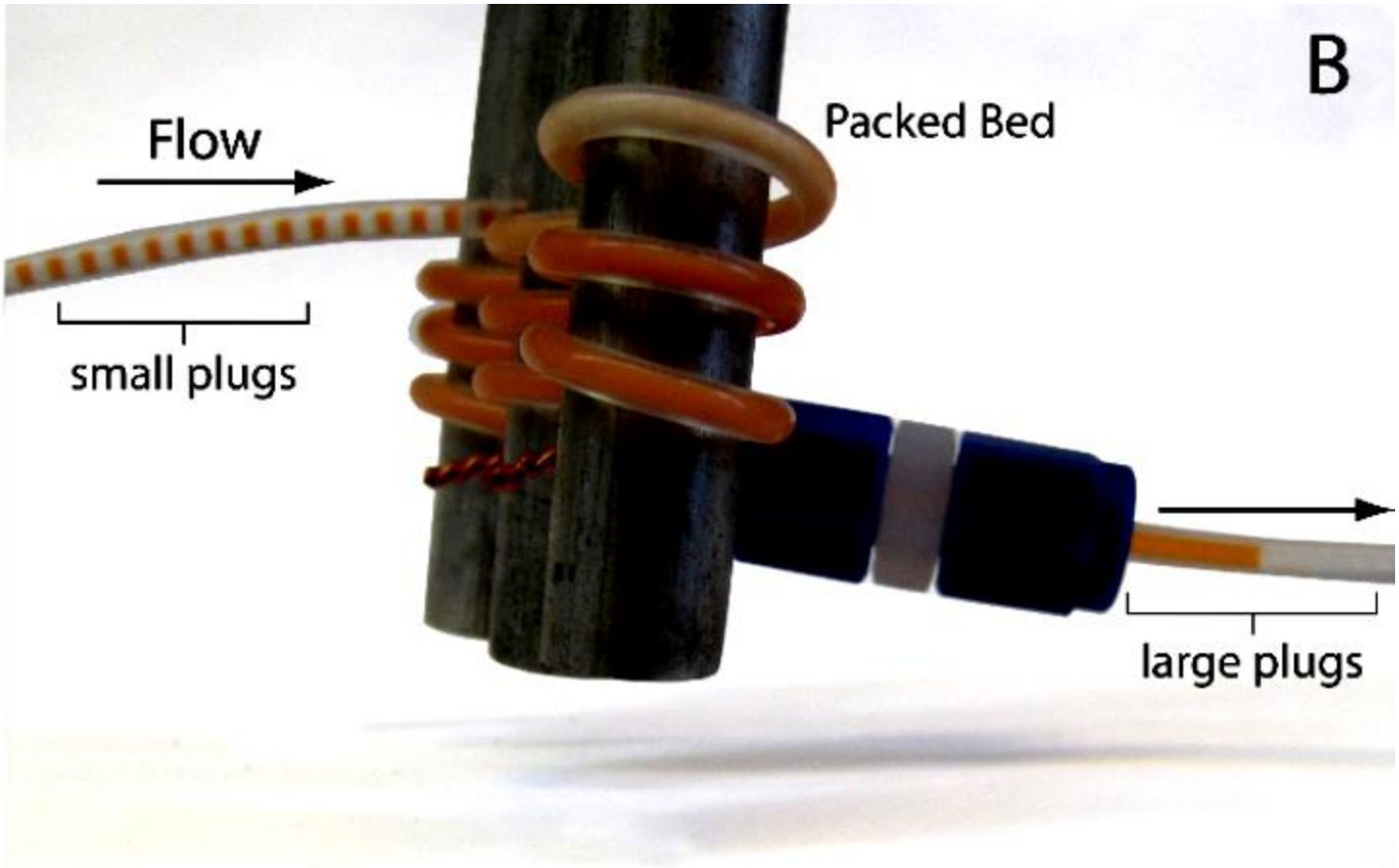
- Plug-flow reactor
  - Poor diffusion of O_3 to substrate



Bogdan, A.; McQuade, D. T. *Beilstein J. Org. Chem.* **2009**, *5*, 17.

Current Flozone Reactors (cont.)

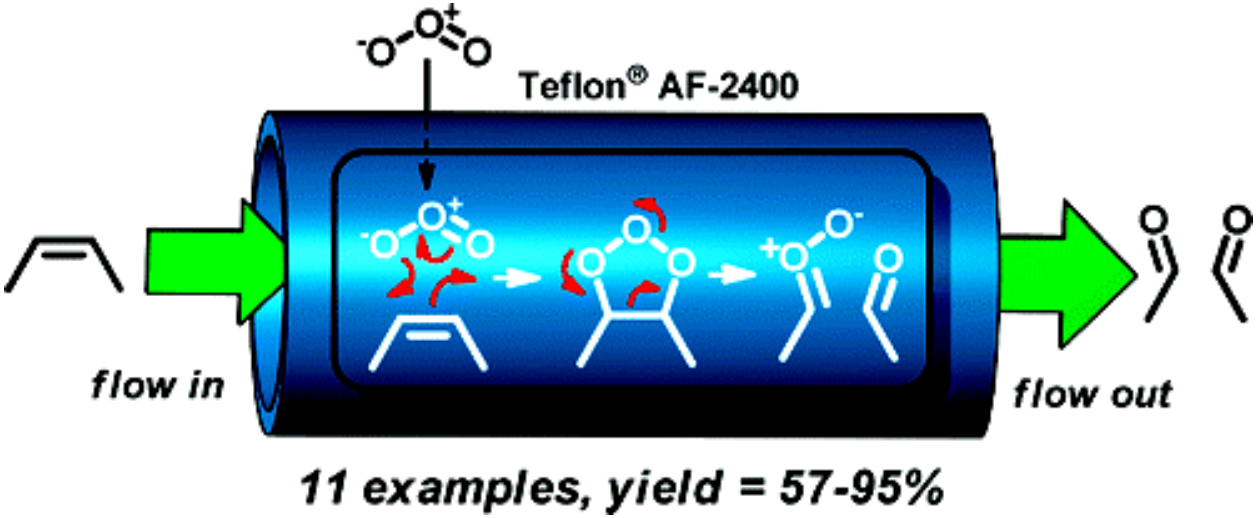
- Packed bed reactor
  - Provides better mixing, slower flow rates



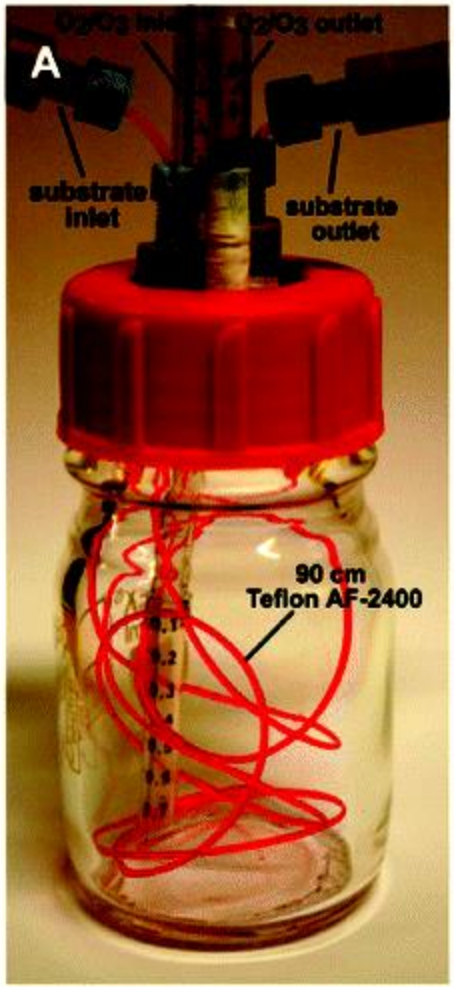
Bogdan, A.; McQuade, D. T. *Beilstein J. Org. Chem.* **2009**, *5*, 17.

Current Flozone Reactors

- Semi-permiable teflon tubing
  - Very slow, poor permiation



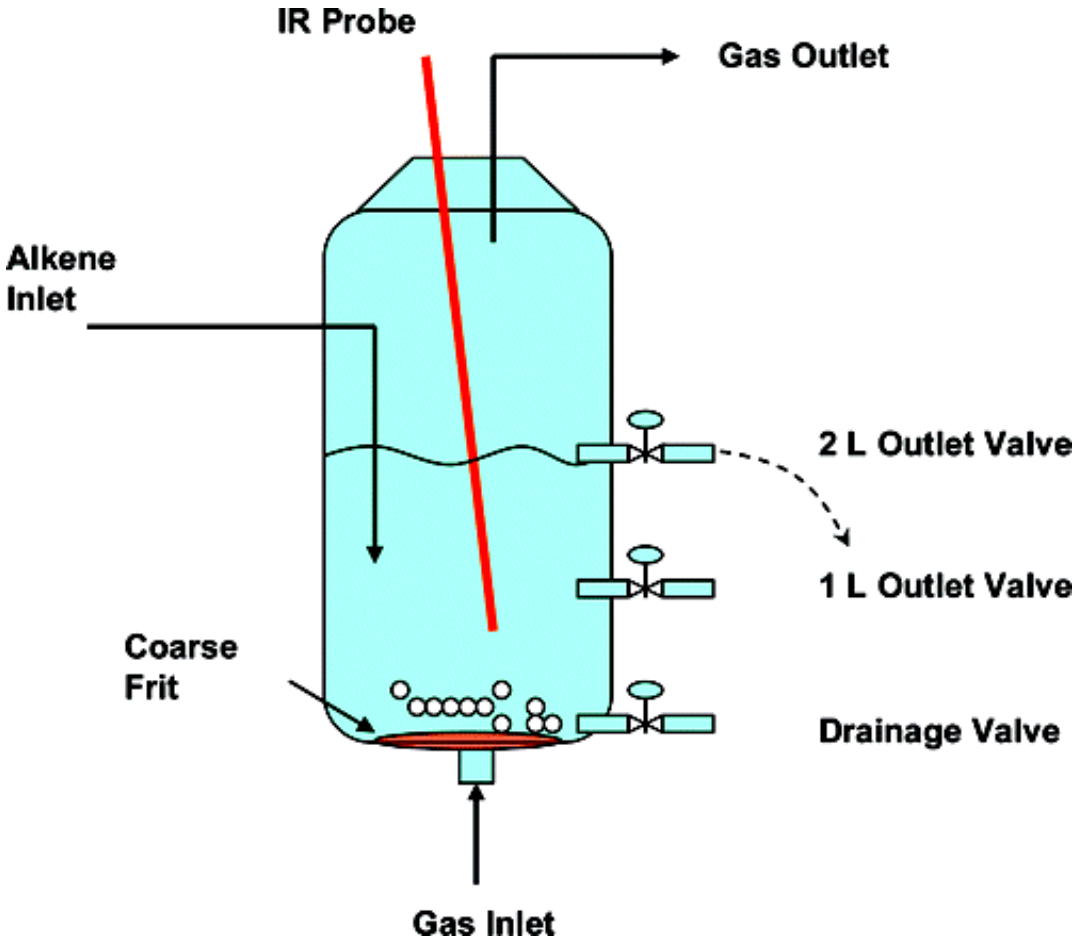
11 examples, yield = 57-95%



O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596.

Current Flozone Reactors

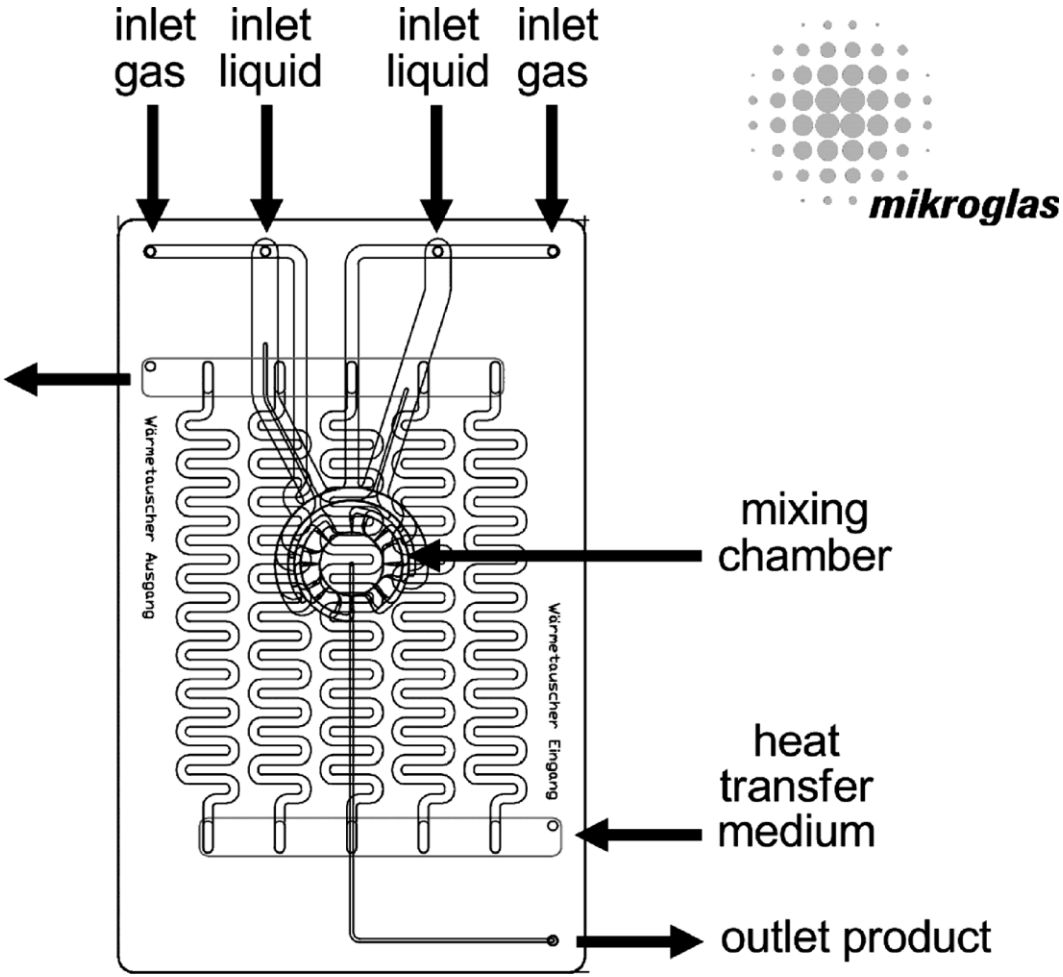
- Overflow batch
  - Buildup of peroxides



Allian, A. D.; Richter, S. M.; Kallemeyn, J. M.; Robbins, T. A.; Kishore, V. *Org. Process Res. Dev.* **2011**, *15*, 91.

Current Flozone Reactors

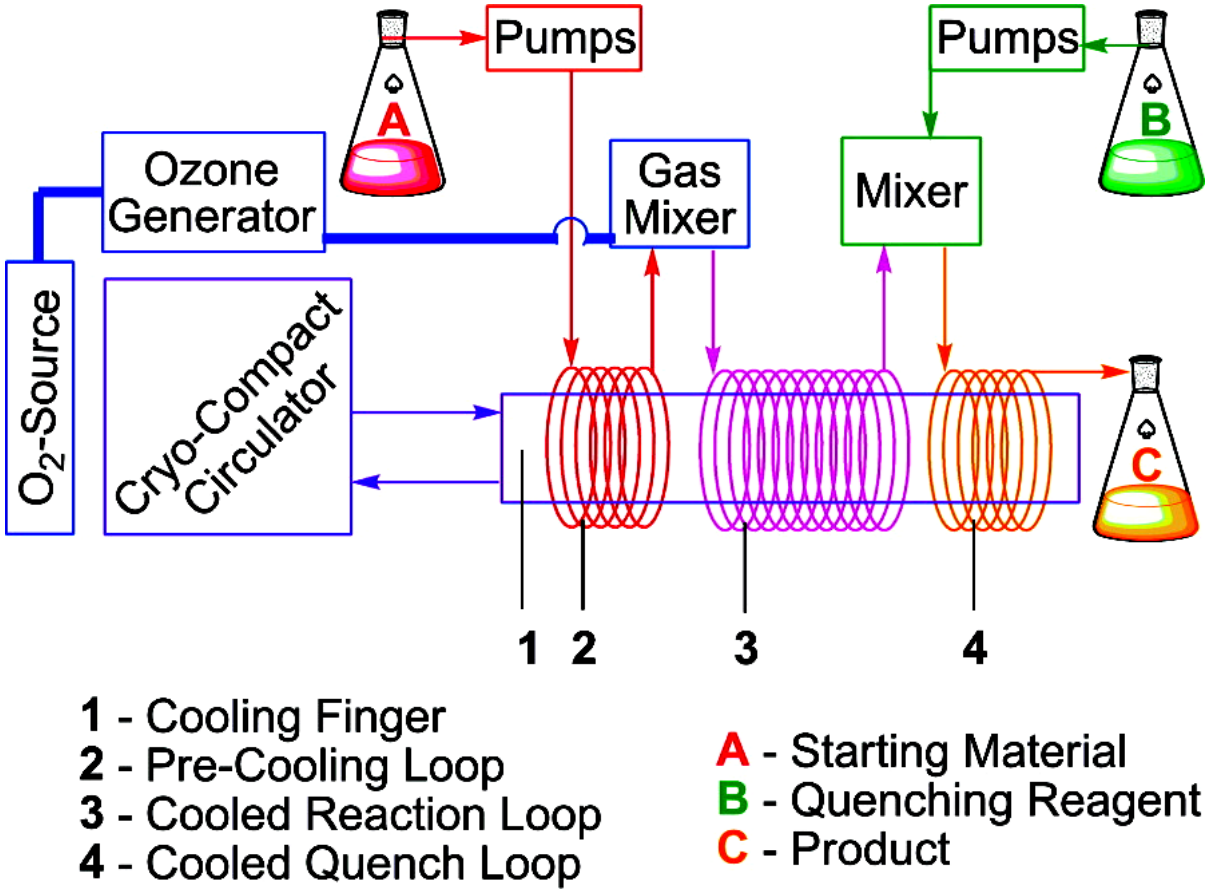
- Microstructured device



Hubner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Kupper, L.; Jahnisch, K. *Org. Process Res. Dev.* **2009**, *13*, 952.

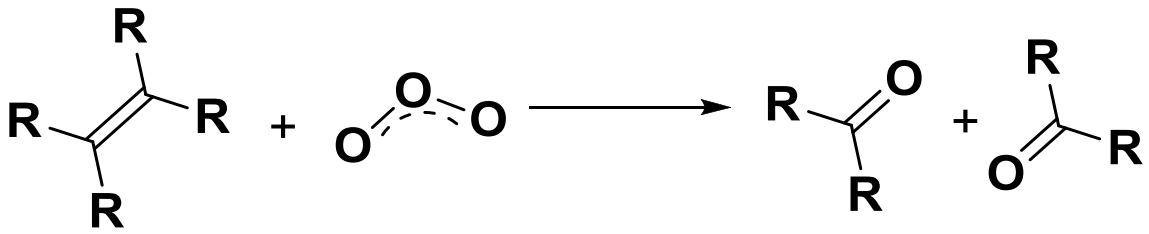
Current Flozone Reactors

- Microreactors
  - 1mL/min, 50 mM (70-90%)

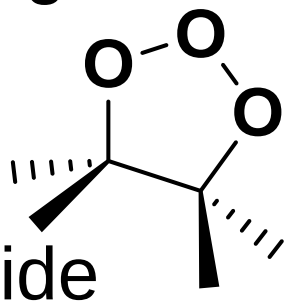


Irfan, M.; Glasnov, T. N.; Kappe, O. C. *Org. Lett.* **2011**, *13*, 984.

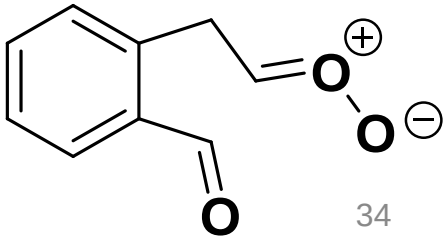
Summary and Conclusions

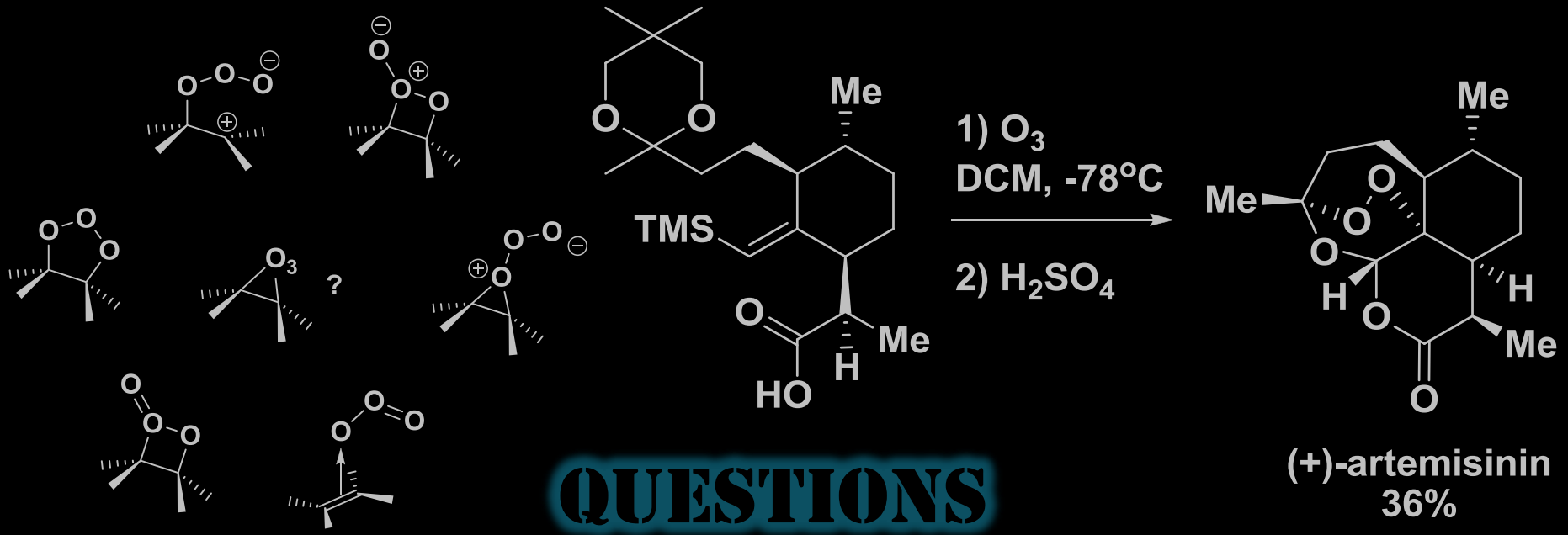


- O_3 is an efficent oxidizing agent
  - Toxic, generated on site, naturally occuring
- Mechanism and organo-oxidation
  - O_3 electrophillic, 1,3-cycloaddition
  - Primary ozonide decomps to carbonyl oxide

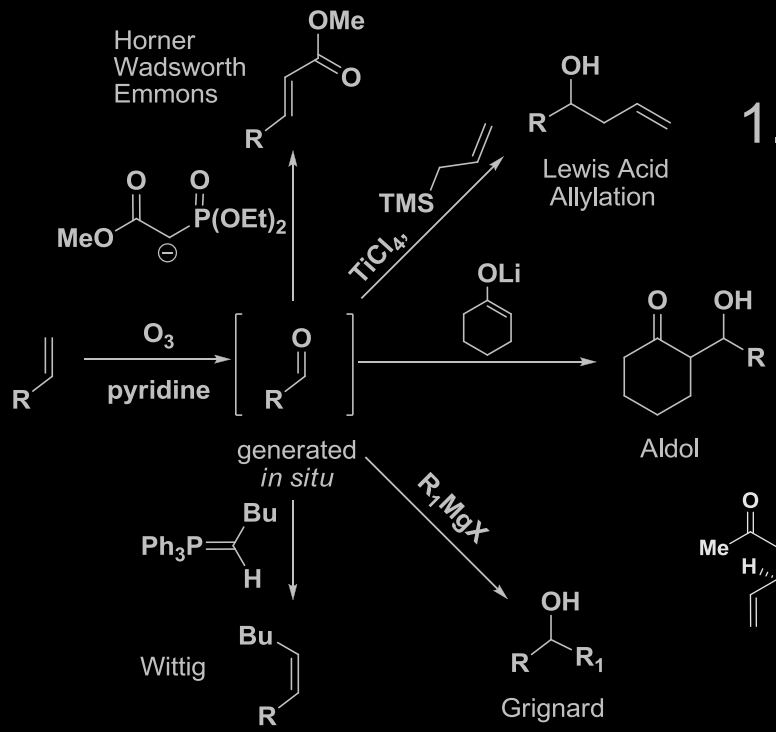


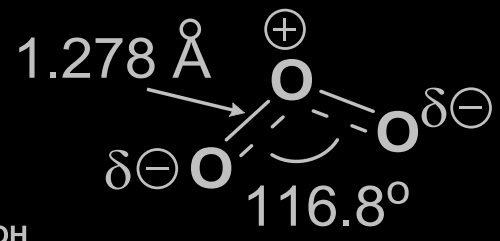
- Trapping the carbonyl oxide
  - Selectivity of products, clean reactions
- Flow reactors
  - Offer new approach to avoid peroxy intermediates

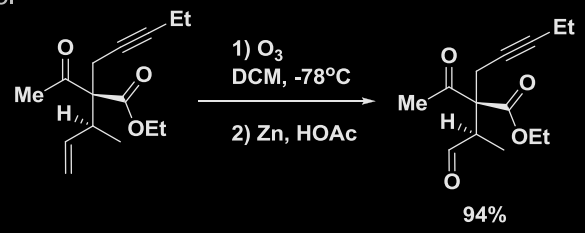


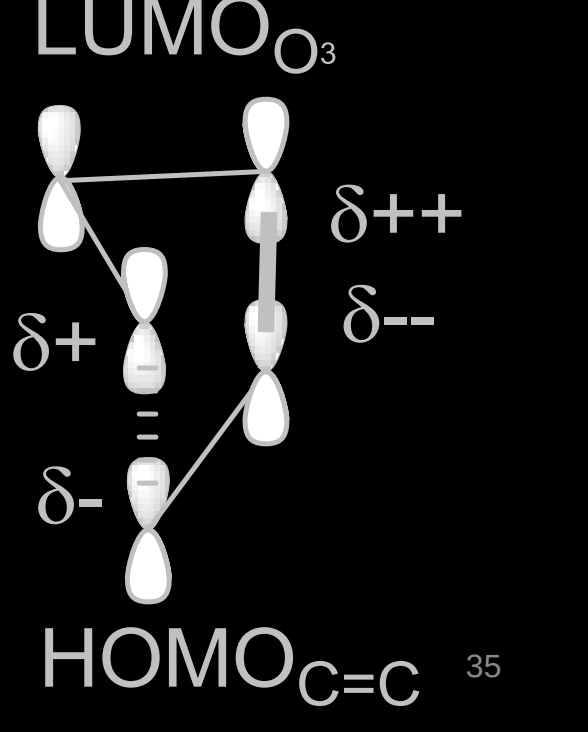

1) O_3
DCM, -78°C
2) H_2SO_4
TMS
Me
HO
?
(+)-artemisinin
36%

QUESTIONS


Horner
Wadsworth
Emmons
OMe
MeO
P(OEt)2
TMS
TiCl4,
Lewis Acid
Allylation
OH
O3
pyridine
OLi
Aldol
generated
in situ
R1MgX
Ph3P
Bu
Wittig
Grignard


1.278 Å
116.8°
δ⊖


1) O_3
DCM, -78°C
2) Zn, HOAc
94%


$LUMO_{O_3}$
δ++
δ--
δ+
δ-
$HOMO_{C=C}$