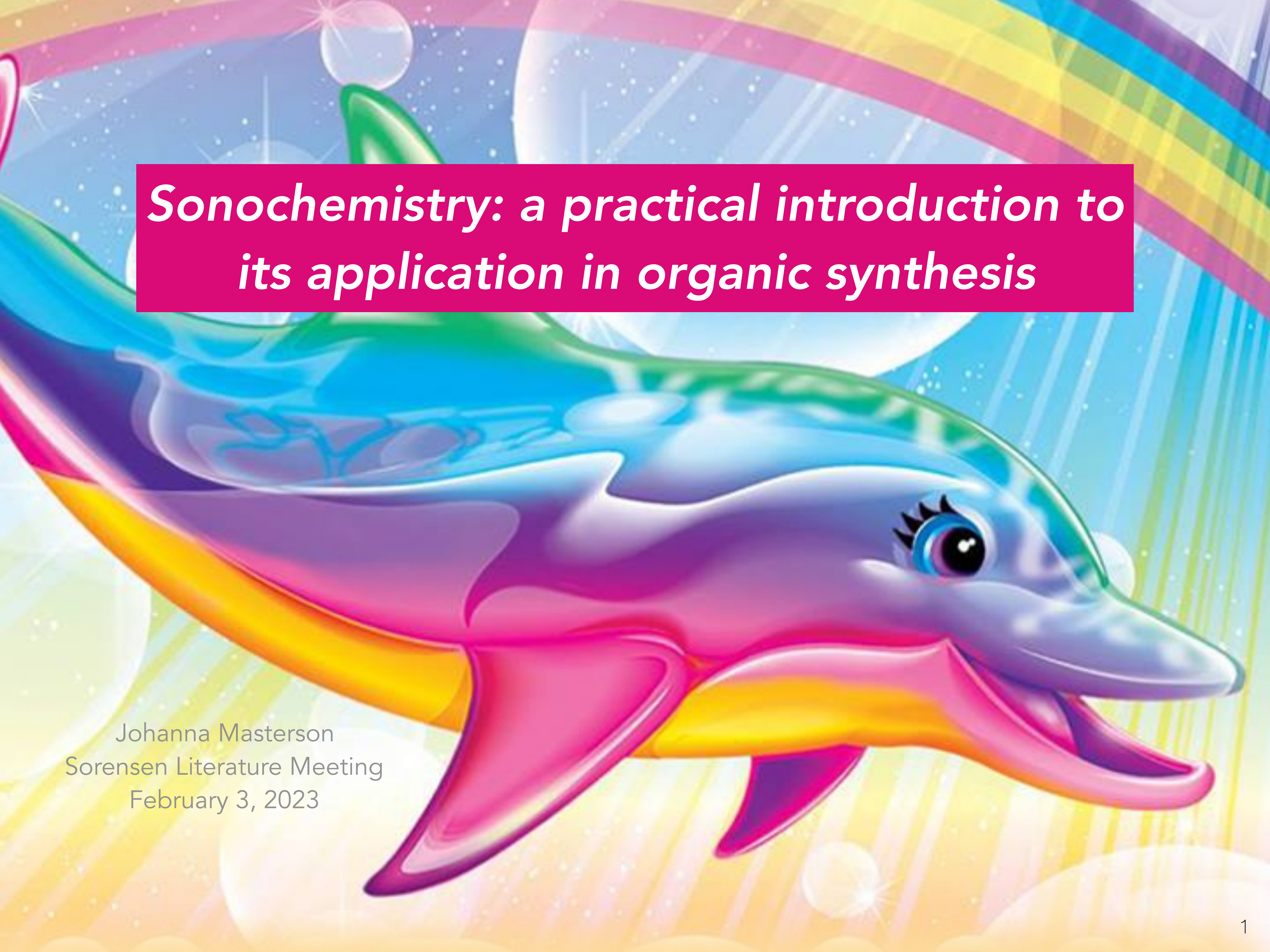


Sonochemistry: a practical introduction to its application in organic synthesis

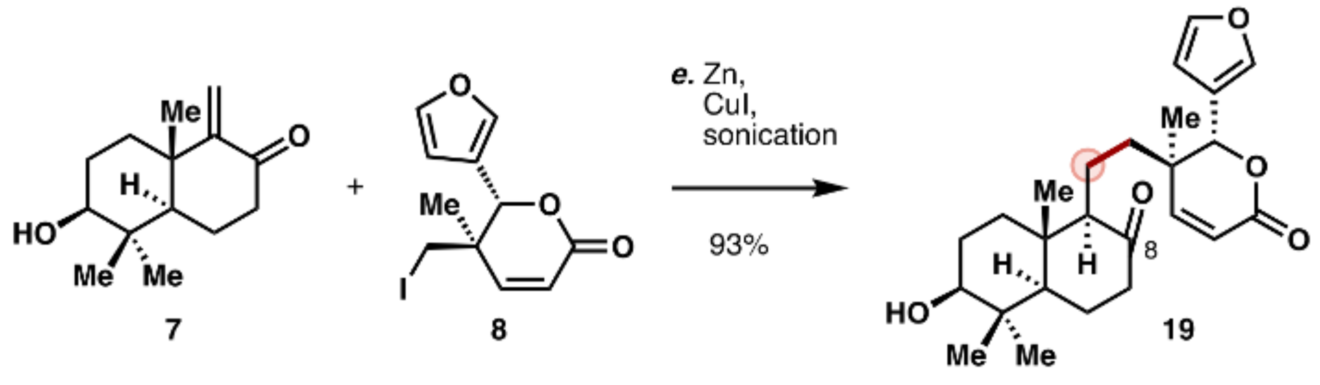
Johanna Masterson
Sorensen Literature Meeting
February 3, 2023

Introduction to Sonochemistry

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

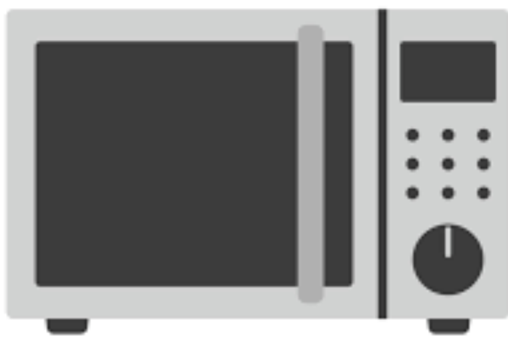
Concise Chemoenzymatic Synthesis of Gedunin

Jian Li, Fang Chen, and Hans Renata*

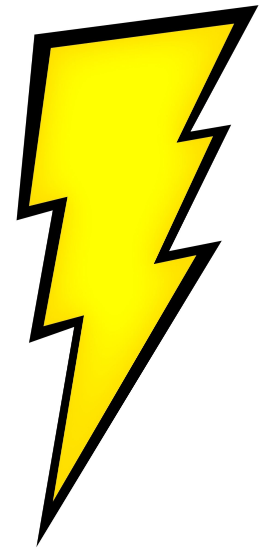


J. Am. Chem. Soc. 2022, 144, 42, 19238–19242

Introduction to Sonochemistry



microwave
(requires polarizable molecules)



electrochemistry
(requires conducting medium)

photochemistry
(requires chromophore)

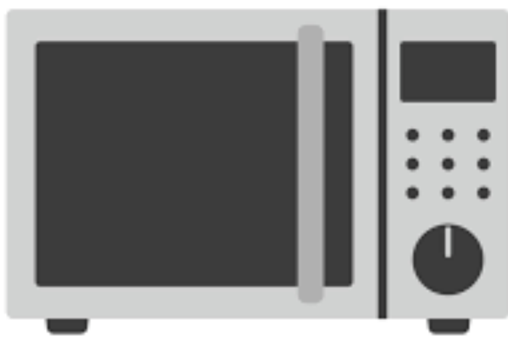
heat
(general activation)

pressure
(general activation)

sonochemistry
(general activation)

References

Introduction to Sonochemistry



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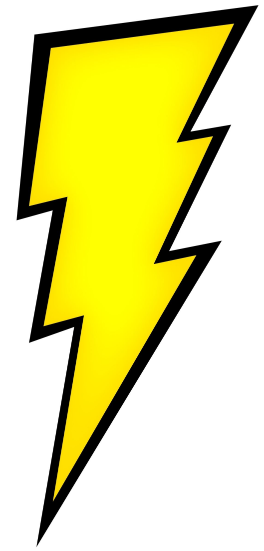

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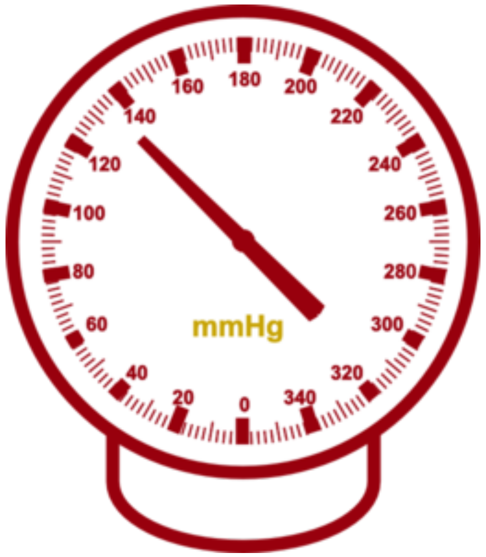

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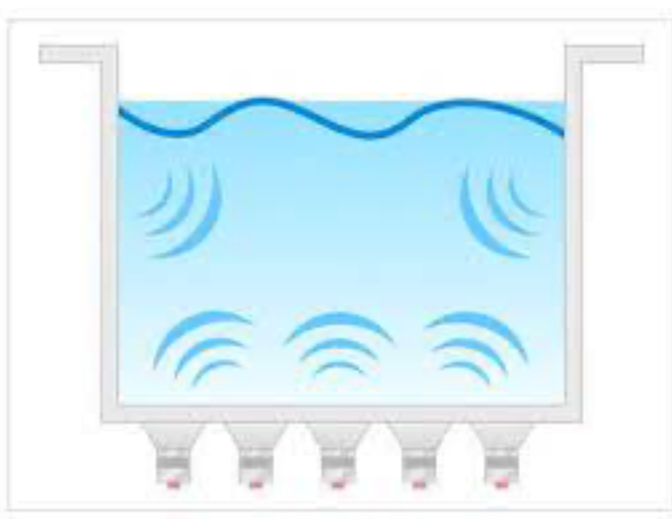

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Introduction to Sonochemistry

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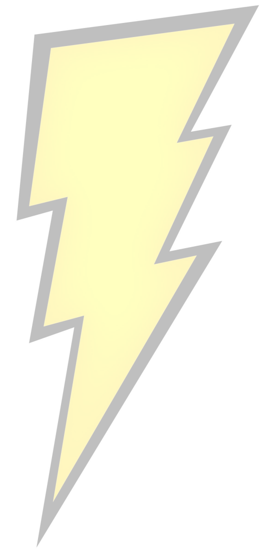

medium)

chemistry
chromophore)

Sonochemistry describes the effects of ultrasound irradiation on chemical reactions.

heat
(general activation)

pressure
(general activation)

sonochemistry
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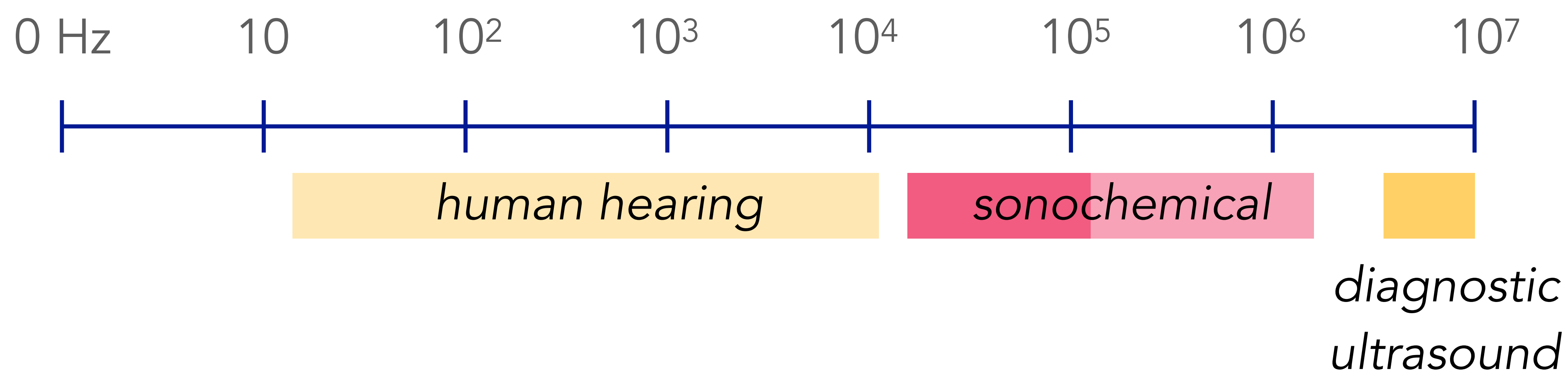
Introduction to Sonochemistry



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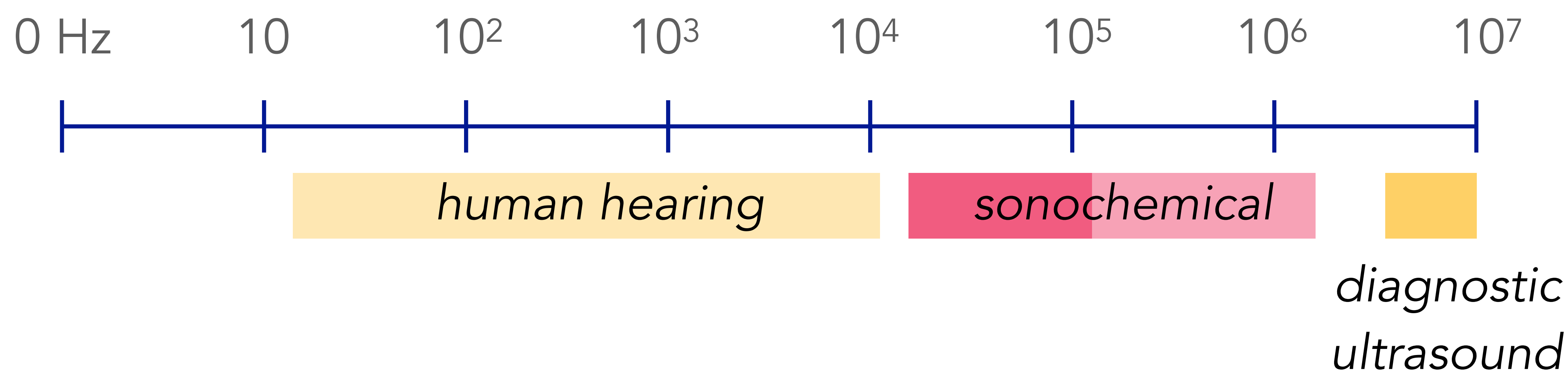

Sonochemical reactivity cannot be from direct coupling with the sound field, as this energy is too low for excitation of even molecular rotation! Reactivity can be traced to *cavitation* in the reaction medium.

References

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[A CONTRIBUTION FROM THE ALFRED LOOMIS LABORATORY OF TUXEDO, NEW YORK, AND THE CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

THE CHEMICAL EFFECTS OF HIGH FREQUENCY SOUND WAVES
I. A PRELIMINARY SURVEY

BY WILLIAM T. RICHARDS AND ALFRED L. LOOMIS

RECEIVED AUGUST 30, 1927 PUBLISHED DECEMBER 10, 1927

1954: Sonochemical effects are ascribed to acoustic cavitation

THE JOURNAL OF CHEMICAL PHYSICS VOLUME 25, NUMBER 5 NOVEMBER, 1956

Chemical Effects of Ultrasonics—"Hot Spot" Chemistry*

MARY EVELYN FITZGERALD, VIRGINIA GRIFFING, AND JAMES SULLIVAN
Chemistry Department, Catholic University of America, Washington 17, D. C.
(Received September 27, 1954)

The present work was undertaken with the purpose of considering why and how reaction takes place in an ultrasonic field, rather than studying the chemical kinetics of such reactions. Experimental evidence is presented which supports the conclusions that chemical processes brought about by ultrasonics require cavitation. Furthermore, the experiments were planned so as to show whether the reactions take place in the bubble

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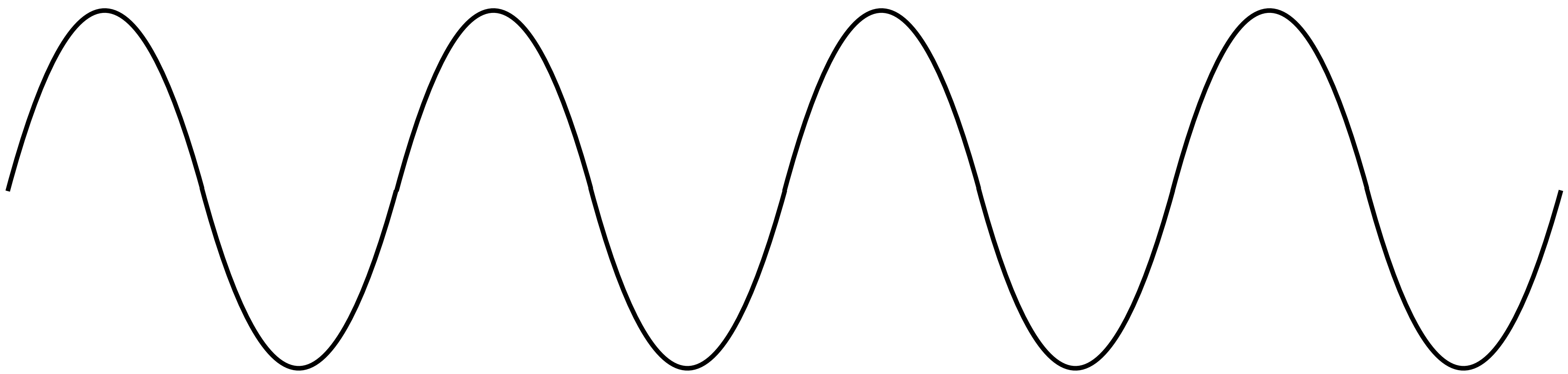

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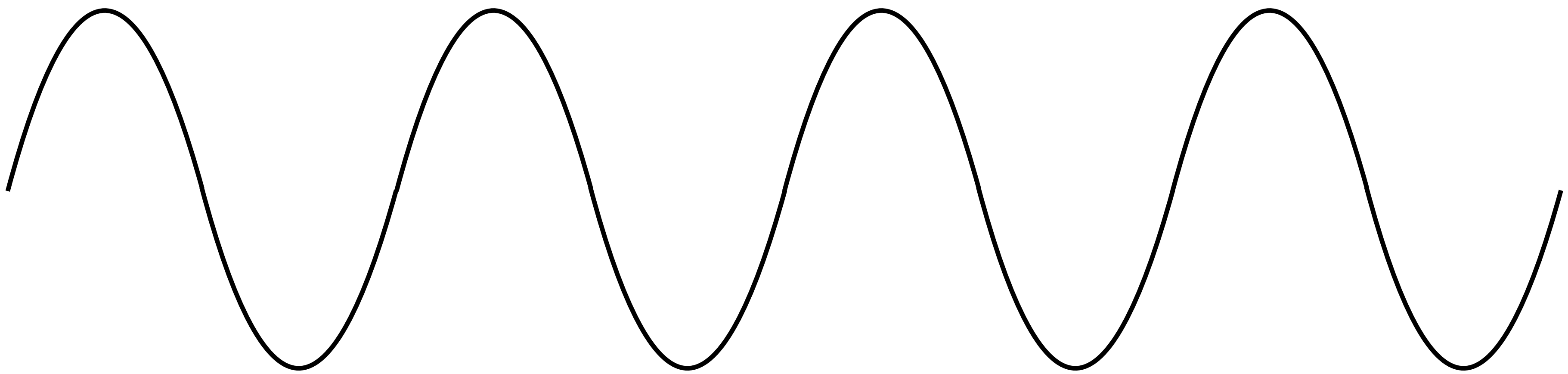

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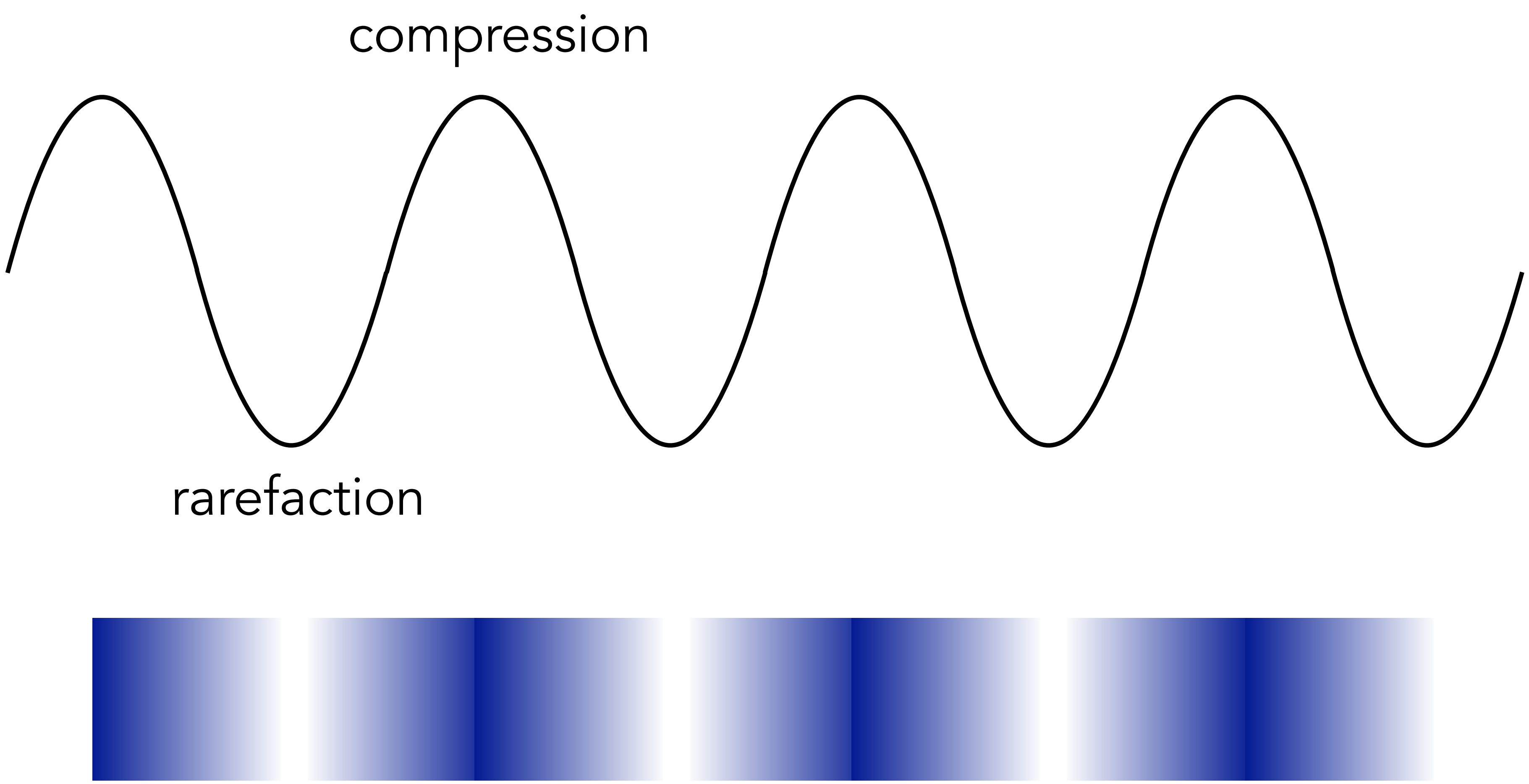

compression and rarefaction
of liquid media

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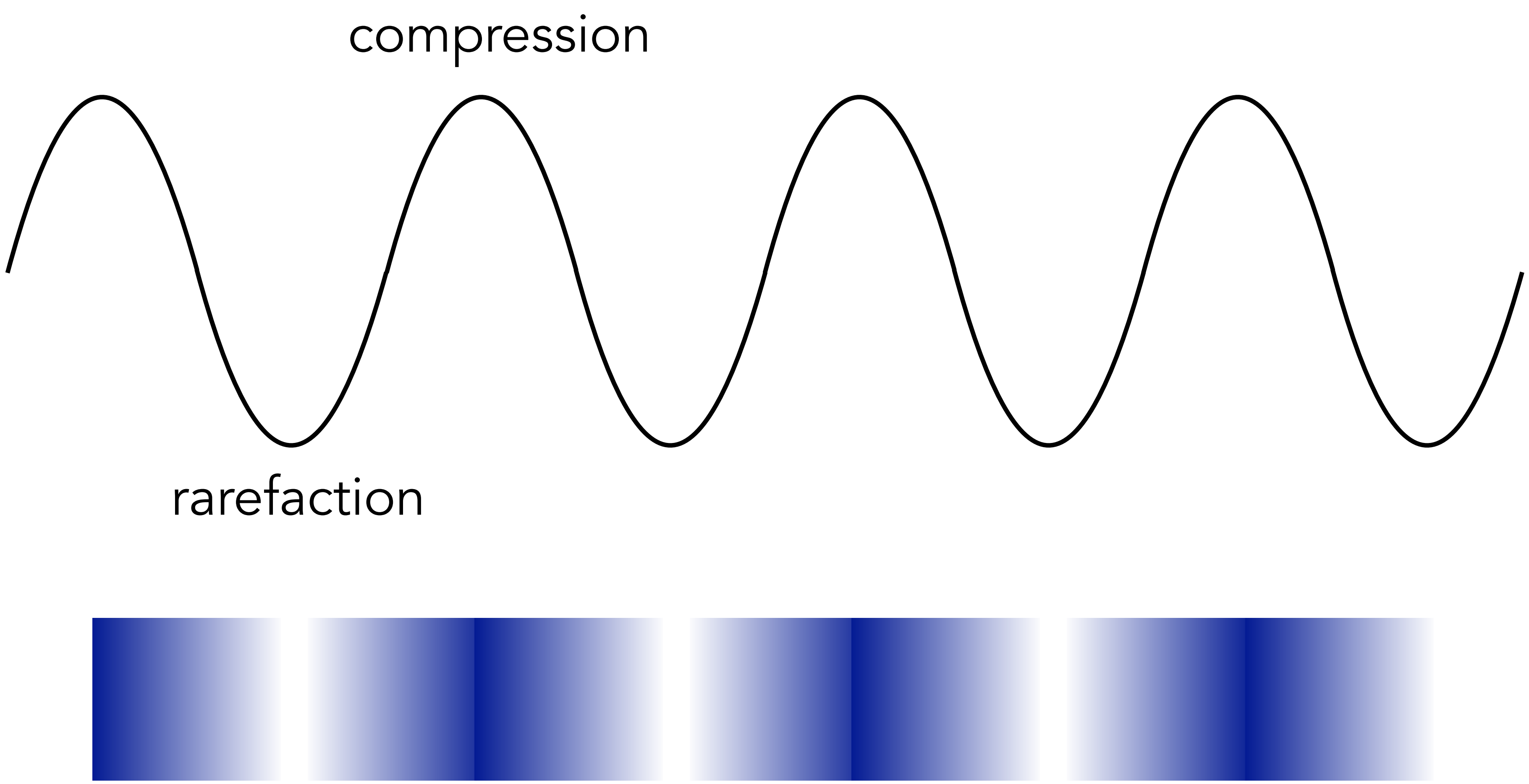

compression and rarefaction
of liquid media

When rarefaction is strong enough to overcome intermolecular forces holding the solvent together, ***cavitation*** occurs. *(cavitation threshold)*

Practical Sonochemistry: Power Ultrasound Uses and Applications, 2nd edition

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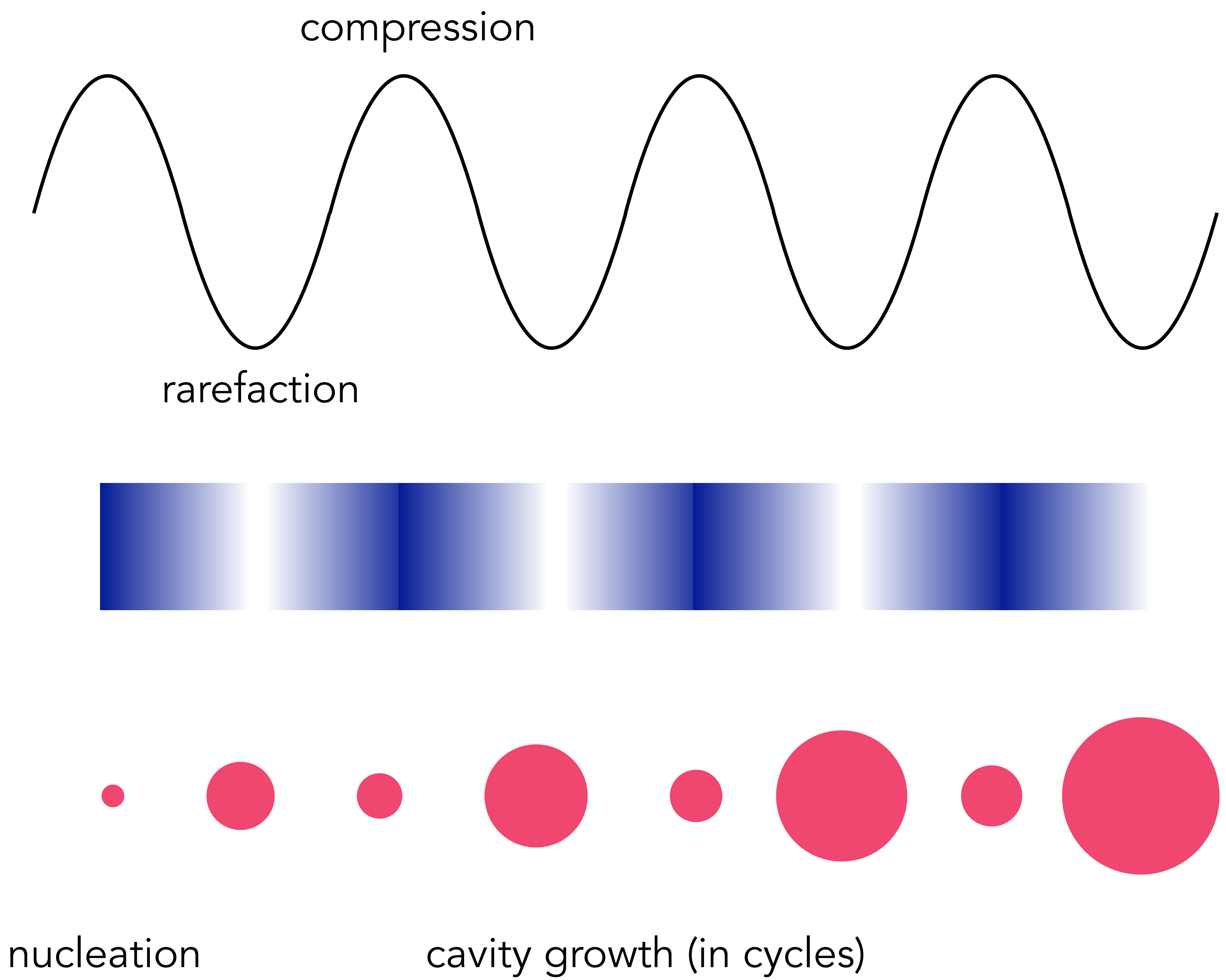

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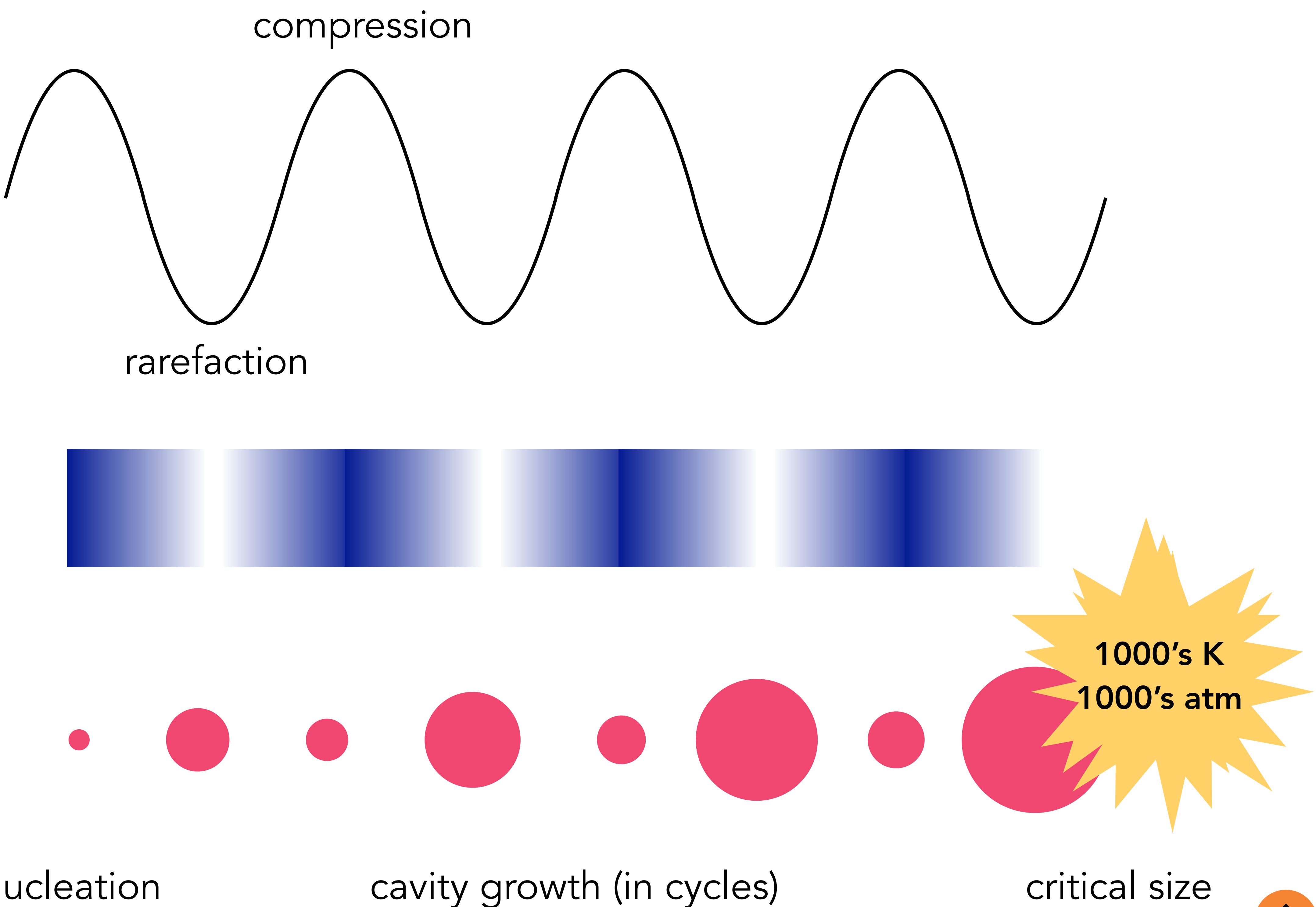
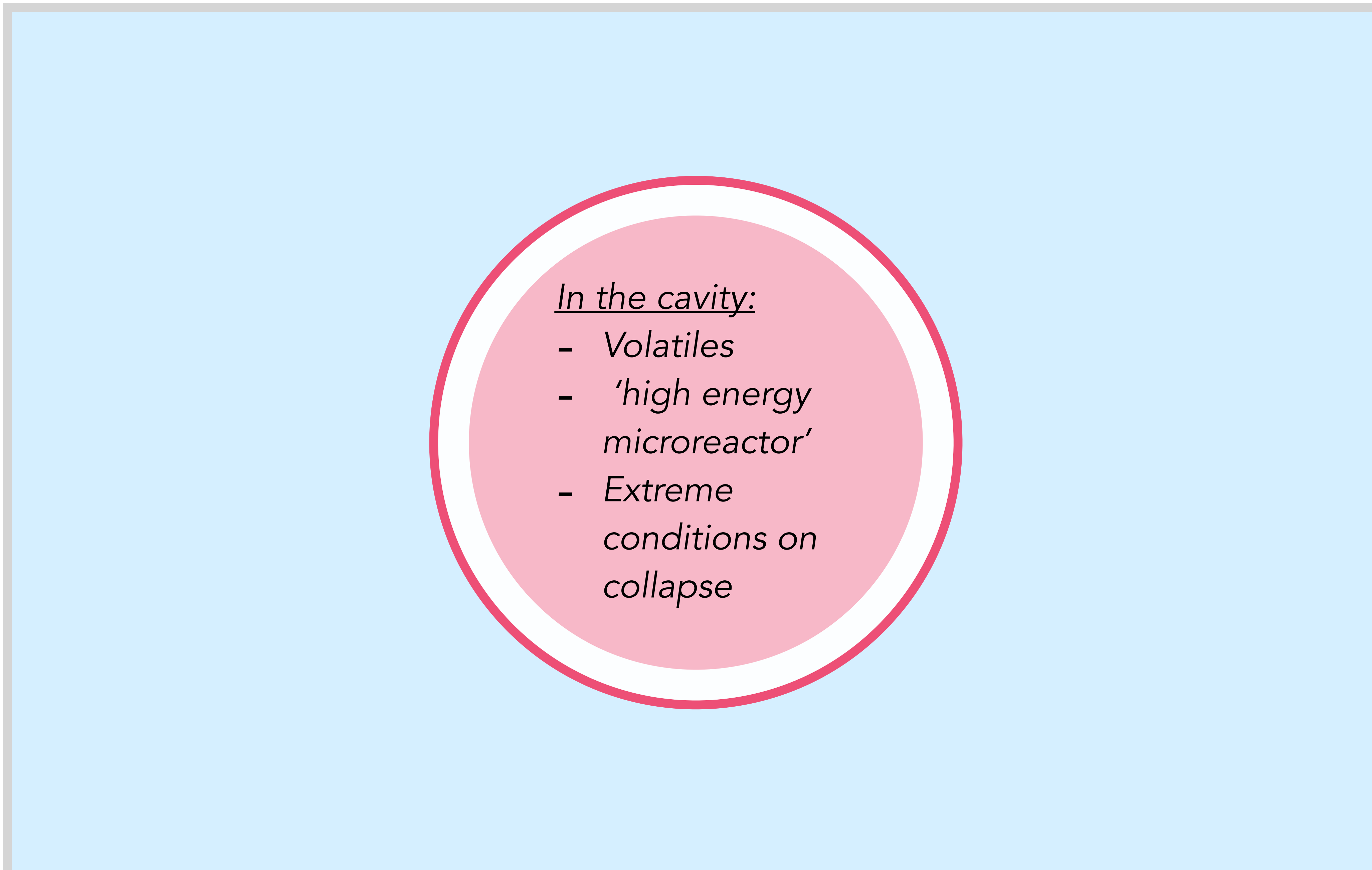


Cavitation: The Origin of Sonochemical Effects

Case 1: Homogeneous Solution



Cavitation: The Origin of Sonochemical Effects

Case 1: Homogeneous Solution

At the interface:
- *Intermediate conditions*
- *High-energy intermediates produced in cavity can react with substrates dissolved in bulk*

In the cavity:
- *Volatiles*
- *'high energy microreactor'*
- *Extreme conditions on collapse*

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Cavitation: The Origin of Sonochemical Effects

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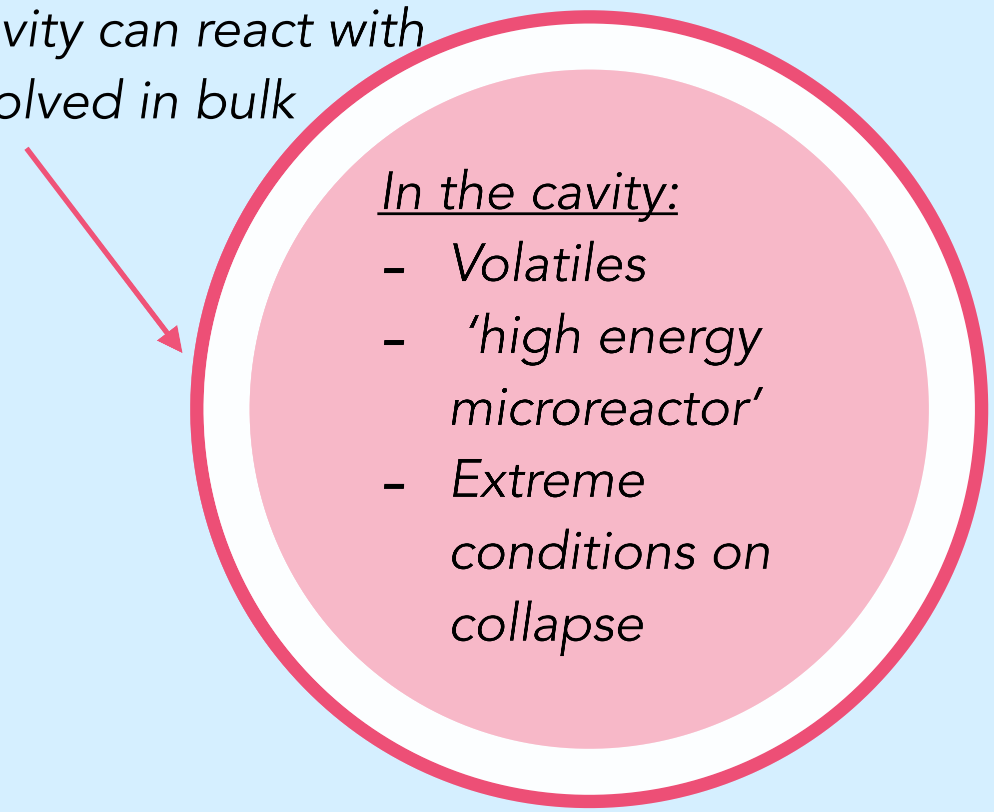
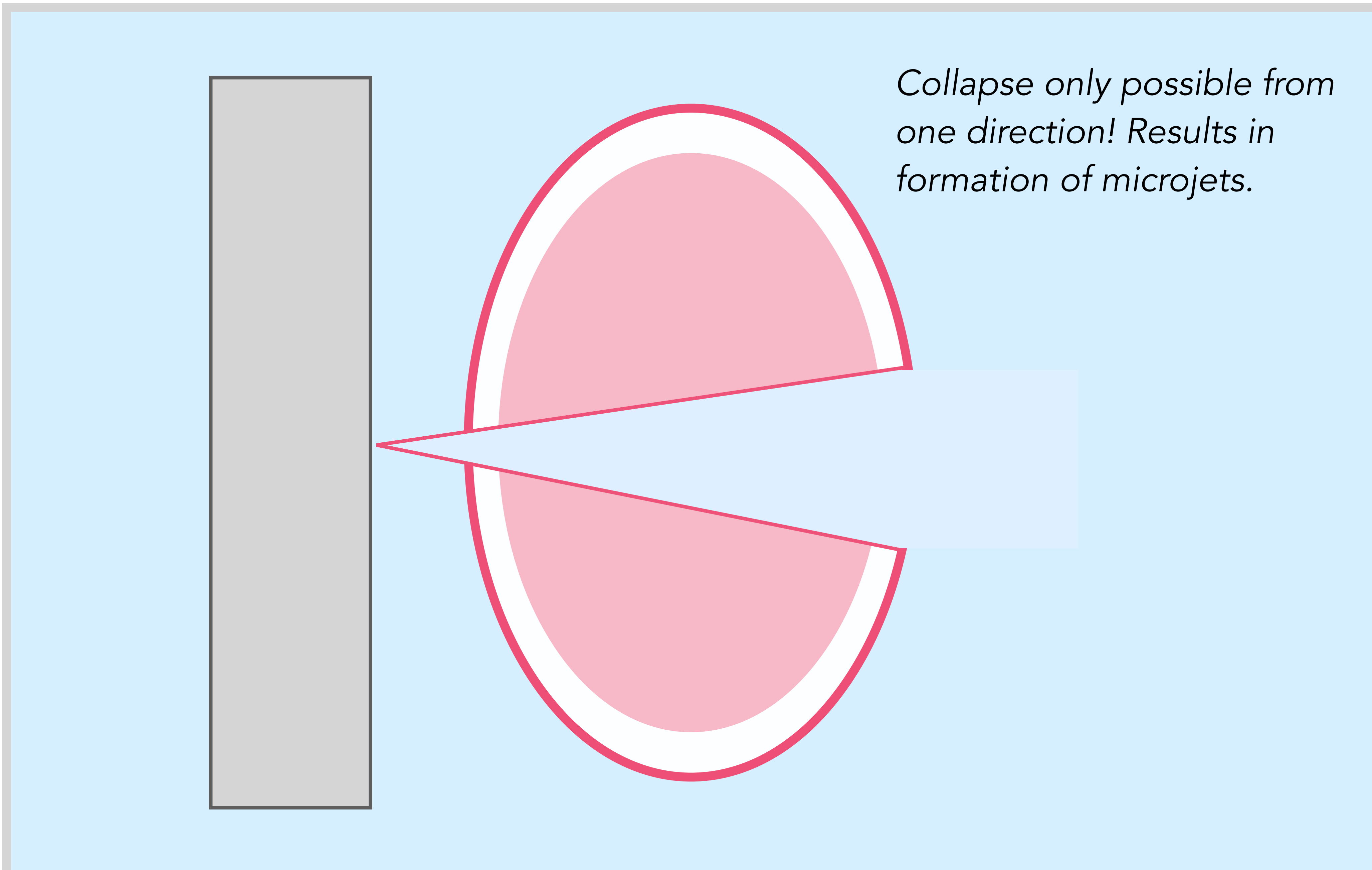


In the bulk:
- *Intense shear forces capable of bond-breaking*
- *Enhanced heat and mass transfer*
- *Disturbance of solvation layer around molecules*

Cavitation: The Origin of Sonochemical Effects

Case 2: Heterogeneous Solution



Cavitation: The Origin of Sonochemical Effects

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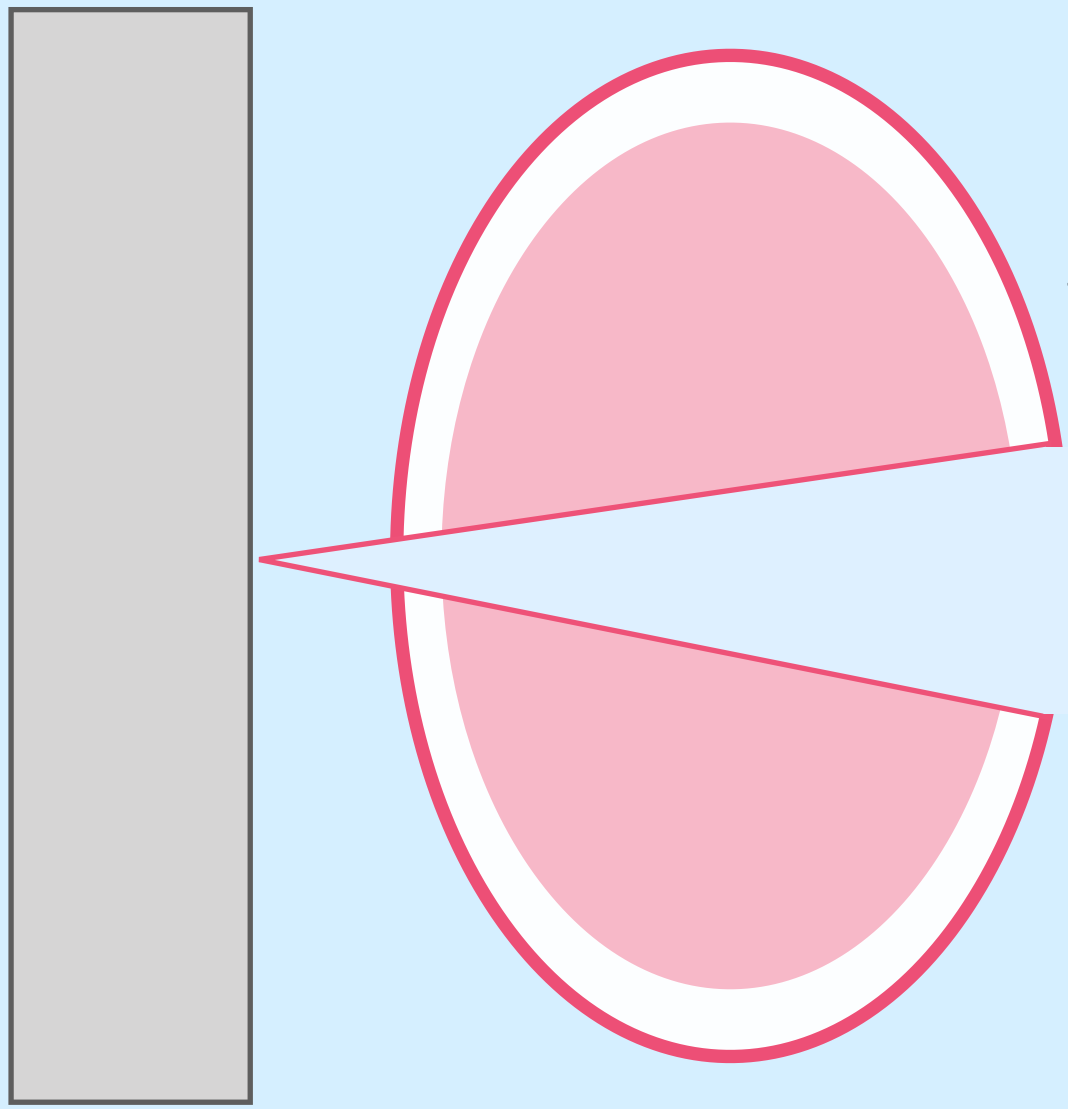


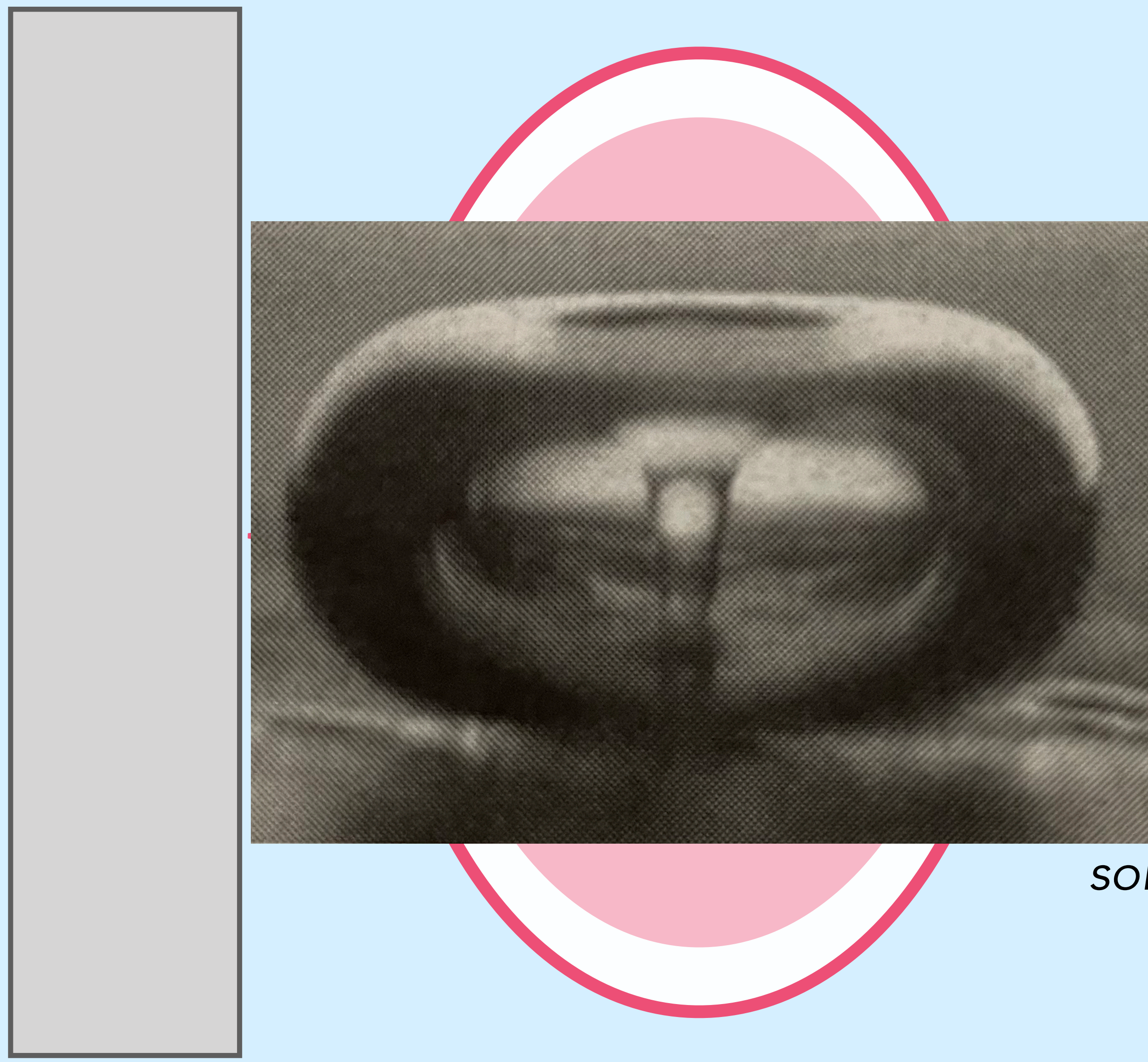
<u>Microjet formation:</u>

- *High-pressure jetting*
- *Increases surface area available for reactivity*
- *Useful for prep of organometallics, activating heterogeneous catalysts, and increasing heat/mass transfer to solid surface*

Practical Sonochemistry: Power Ultrasound Uses and Applications, 2nd edition

Cavitation: The Origin of Sonochemical Effects

Case 2: Heterogeneous Solution



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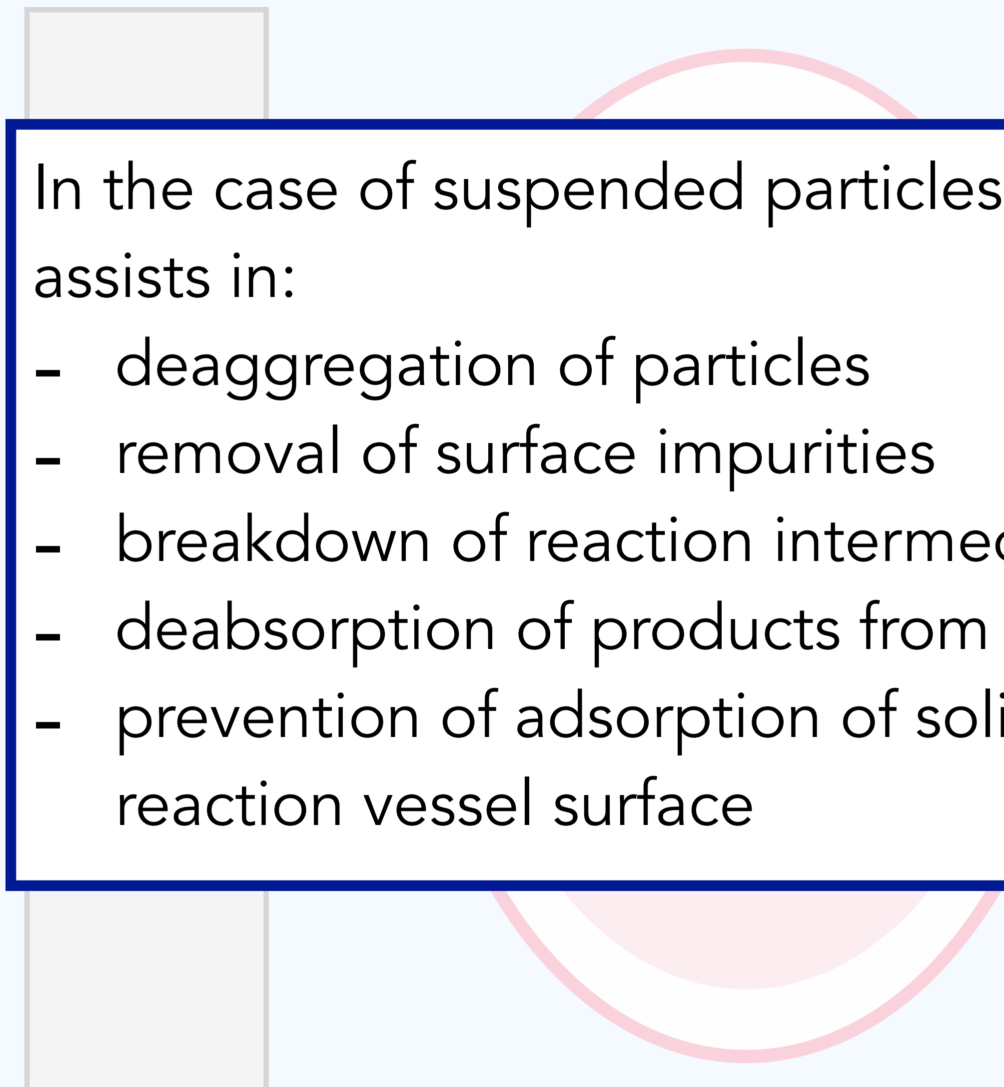


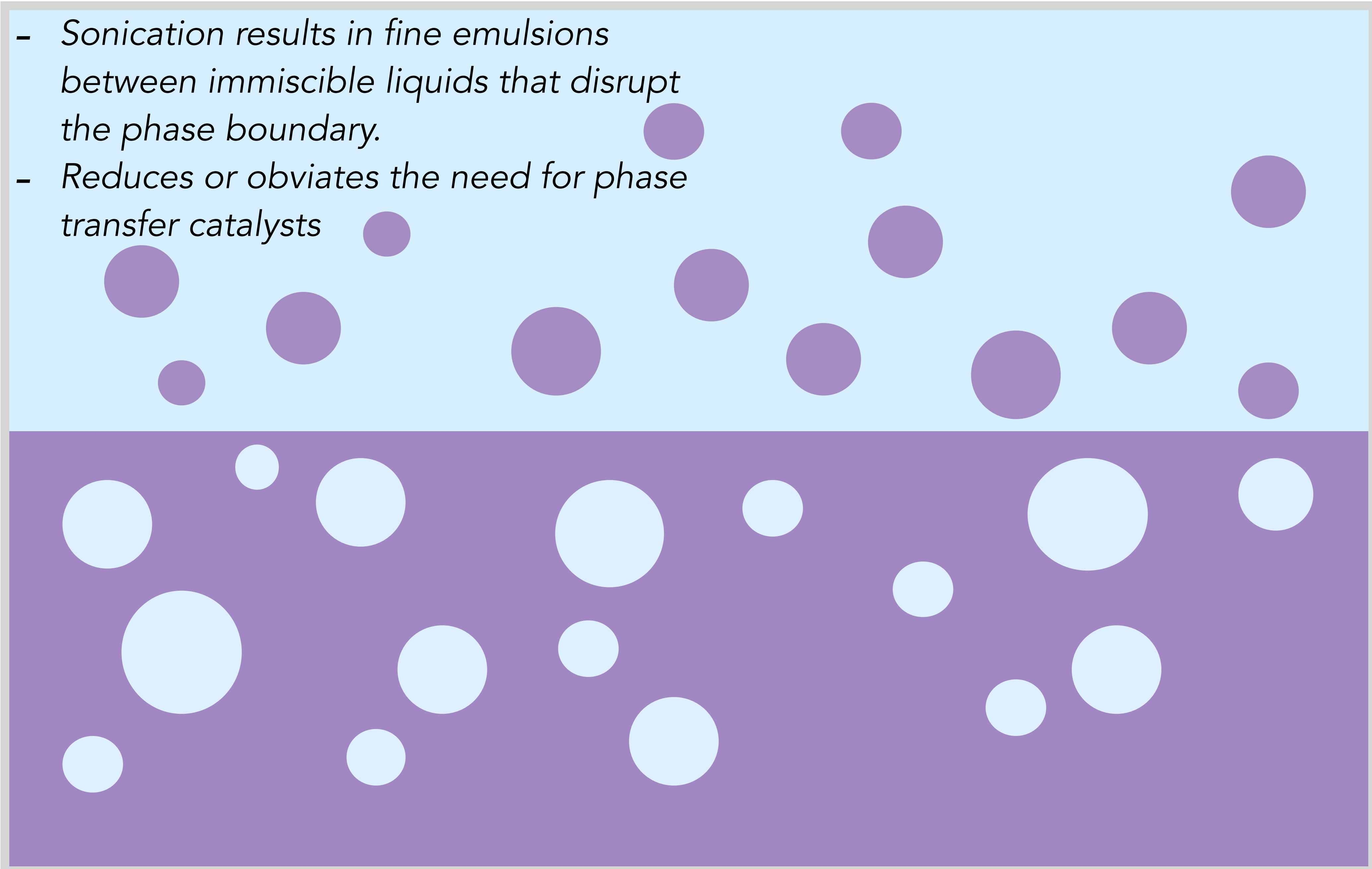
In the case of suspended particles, cavitation assists in:

- deaggregation of particles
- removal of surface impurities
- breakdown of reaction intermediates
- deabsorption of products from particle surface
- prevention of adsorption of solids onto reaction vessel surface

Cavitation: The Origin of Sonochemical Effects

Case 3: Biphasic Solution

- *Sonication results in fine emulsions between immiscible liquids that disrupt the phase boundary.*
- *Reduces or obviates the need for phase transfer catalysts*



Sonochemistry in Organic Synthesis: Overview

- Although examples of sonochemistry in organic synthesis in the 1950's and 60's exist, this methodology was understudied (lack of reproducibility and availability of equipment)
- The 1980's saw a resurgence in organic sonochemistry, led in part by J.L. Luche
- Luche categorized sonochemical reactions into two types
    - *i. True sonochemistry*, which occurred when key reactive intermediates were generated directly from cavitation effects
    - *ii. False sonochemistry*, which occurred when reactivity was the result of mechanical effects of ultrasound

Molecules, 2021, *26*, 755
Tet Lett, 1990, *31*, 4125

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Sonochemistry in Organic Synthesis: Overview

- Luche and Mason also postulated three 'rules' governing the use of sonochemistry:
    i. In homogeneous solutions, reactions involving radical or radical ion intermediates will be sensitive to sonochemical effects
    ii. In heterogeneous systems, polar reactions can benefit from the mechanical effects of sonication
    iii. In cases with mixed mechanisms (radical and ionic), sonication will enhance the radical pathway. In cases where the mechanisms converge to give the same products, this results in a rate increase. In cases where the mechanisms diverge to give different products, this results in *sonochemical switching*

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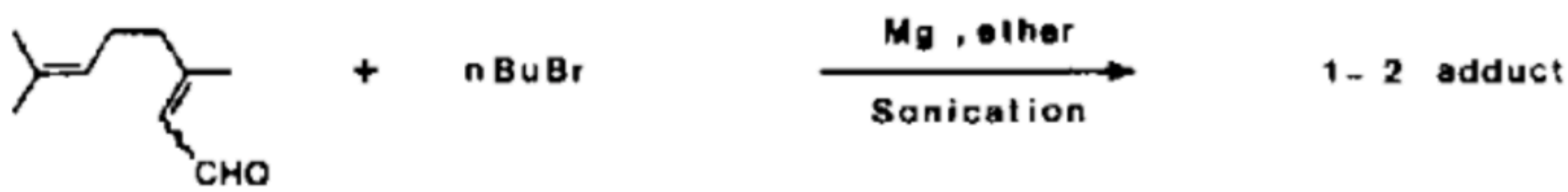
<u>Advantages to using sonochemistry:</u>

- Accelerate rate of reaction
- Use of less forcing conditions
- Use less pure/cheaper reagents
- Initiate a reaction
- Reduction of induction period
- Alternate reaction pathways

Ultrasound as a New Tool for Organic Chemists
Chem Soc Rev, 1987, *16*, 275

Sonochemistry in Organic Synthesis: Examples

- Grignard and Barbier-type reactions

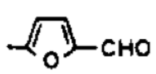
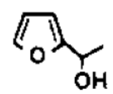
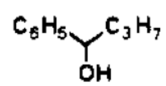
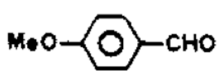
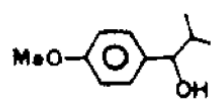
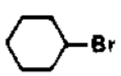
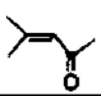
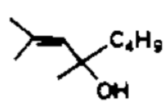
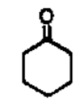
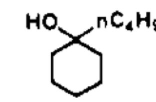
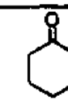
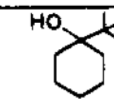
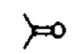
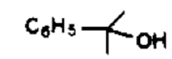
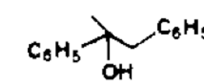
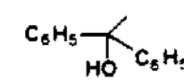
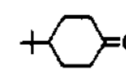
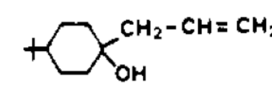


Ultrasonics, 1987, *25*, 40
J. Am. Chem. Soc. 1980, 102, 27, 7926–7927

Sonochemistry in Organic Synthesis: Examples

- Grignard and Barbier-type reactions

Table I. Modified Barbier Reaction with Ultrasonic Irradiation

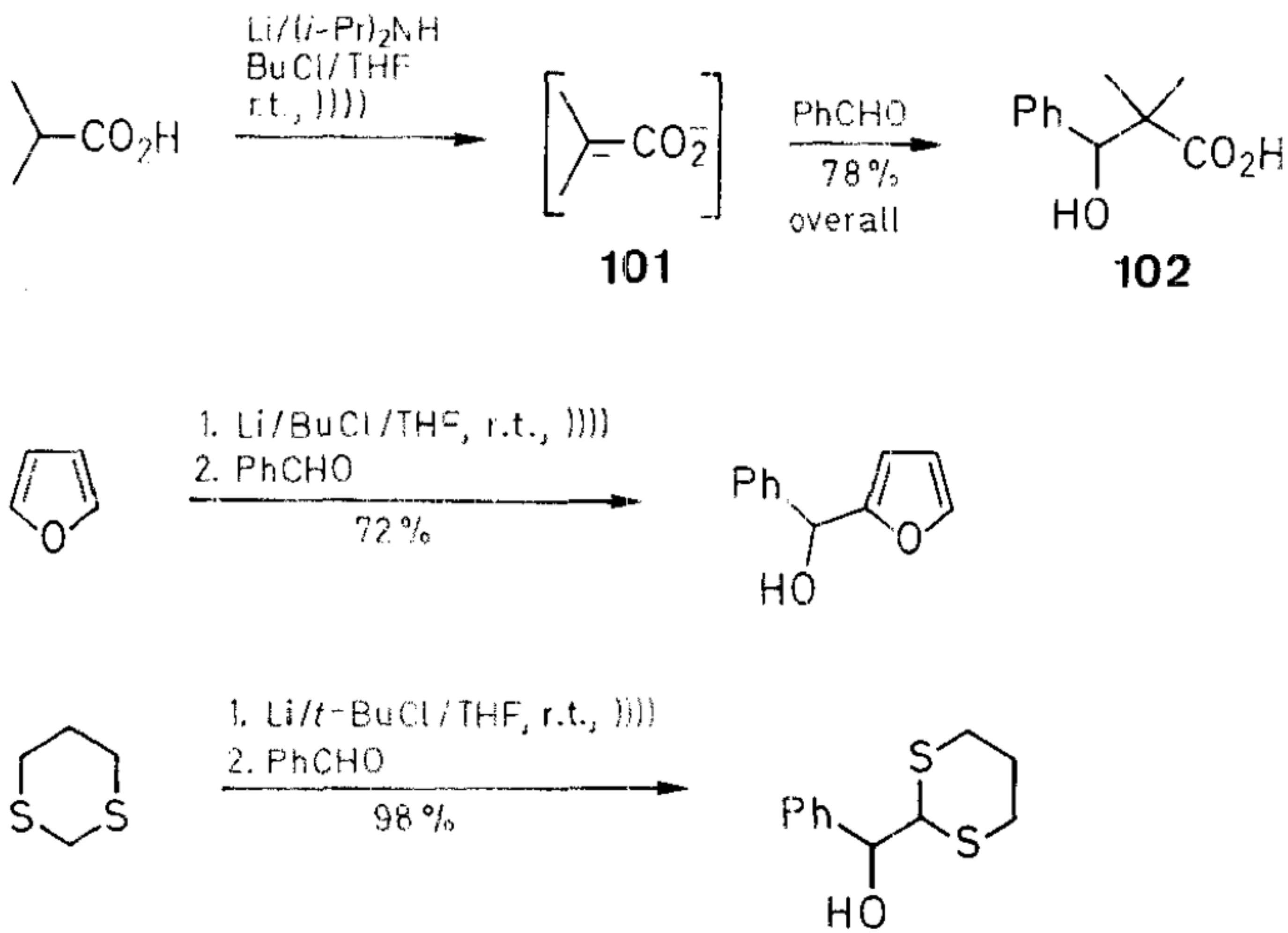
R-X	Carbonyl compound	Product	Reaction time (min)	Yield[a]
CH_3I			10	100 (92)
n-C_3H_7Br	C_6H_5-CHO		10	100
s-C_3H_7Br			15	100 (96)
n-C_4H_9Br	$(n\text{-}C_4H_9)_2\ C=O$	$(n\text{-}C_4H_9)_3\ C-OH$	15	100 (90)
			30	80 (68)
n-C_4H_9Br			15	100 (80)
n-C_4H_9Br			15	84
t-C_4H_9Br			30	76
C_6H_5Br			30	100 (95)
$C_6H_5CH_2Br$	$C_6H_5-COCH_3$		10	95
C_6H_5Br	$C_6H_5-COCH_3$		30	92 (83)
$CH_2=CH-CH_2Br$			15	76 (60)[b]
$CH_2=C(CH_3)Br$	$C_5H_{11}-CHO$	$C_5H_{11}-CH(OH)-C(CH_3)=CH_2$	40	96 (71)
$CH_3-CH=CH-Br$	$C_5H_{11}-CHO$	$C_5H_{11}-CHOH-CH=CH-CH_3$	40	95 (79)

From the organolithium

Ultrasonics, 1987, *25*, 40
J. Am. Chem. Soc. 1980, 102, 27, 7926–7927

Sonochemistry in Organic Synthesis: Examples

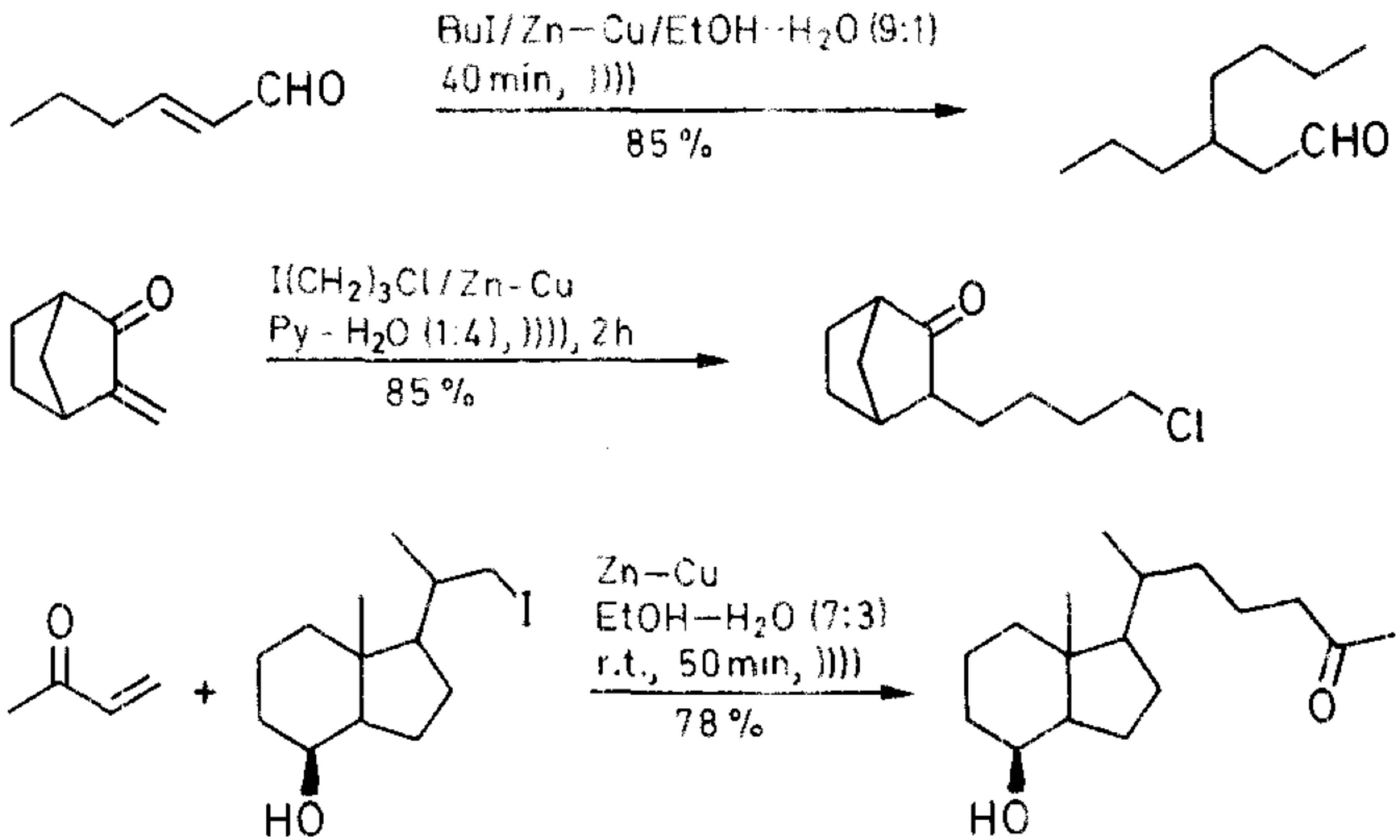
- Grignard and Barbier-type reactions



Synthesis, 1989, *11*, 787

Sonochemistry in Organic Synthesis: Examples

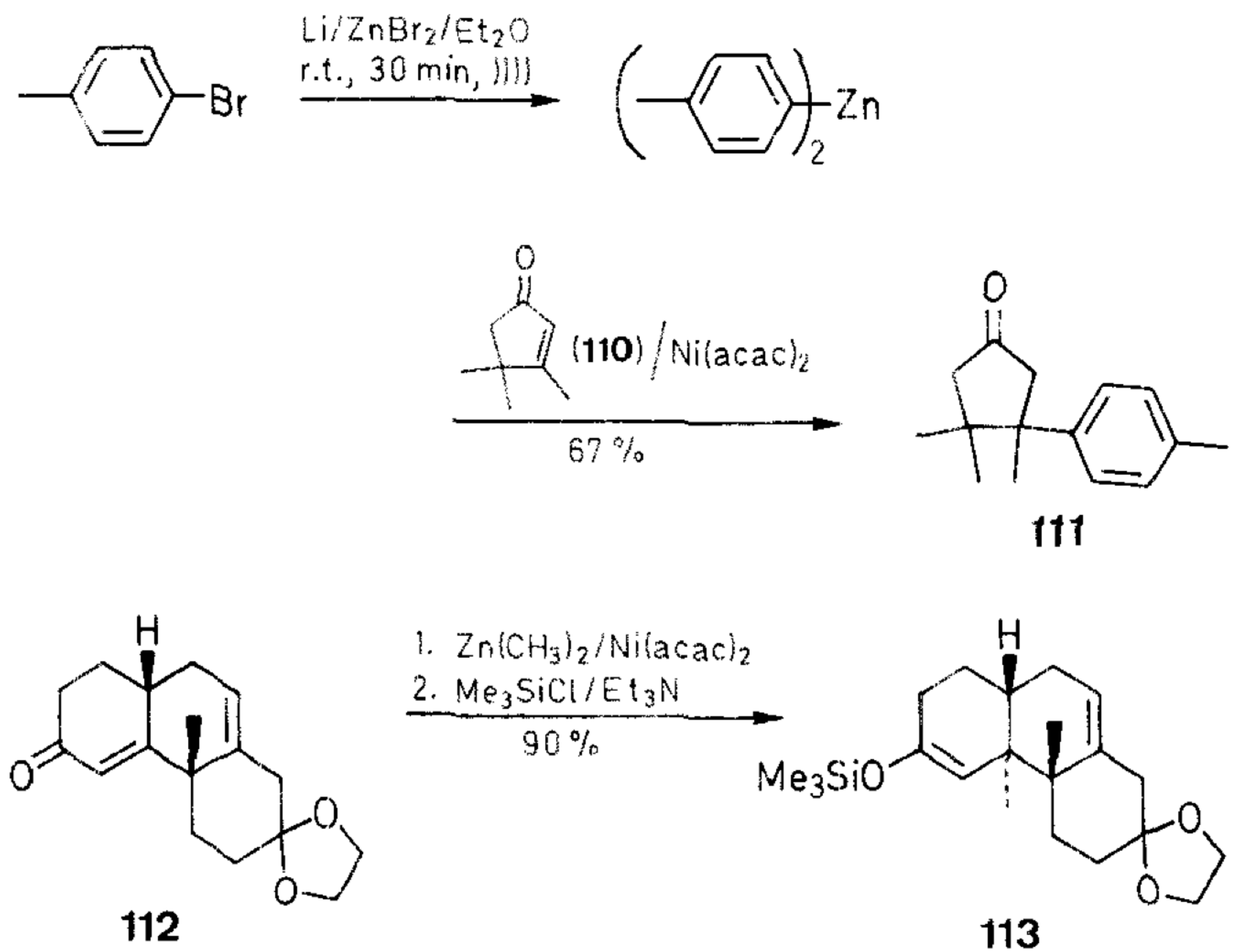
- Conjugate Additions



Synthesis, 1989, *11*, 787

Sonochemistry in Organic Synthesis: Examples

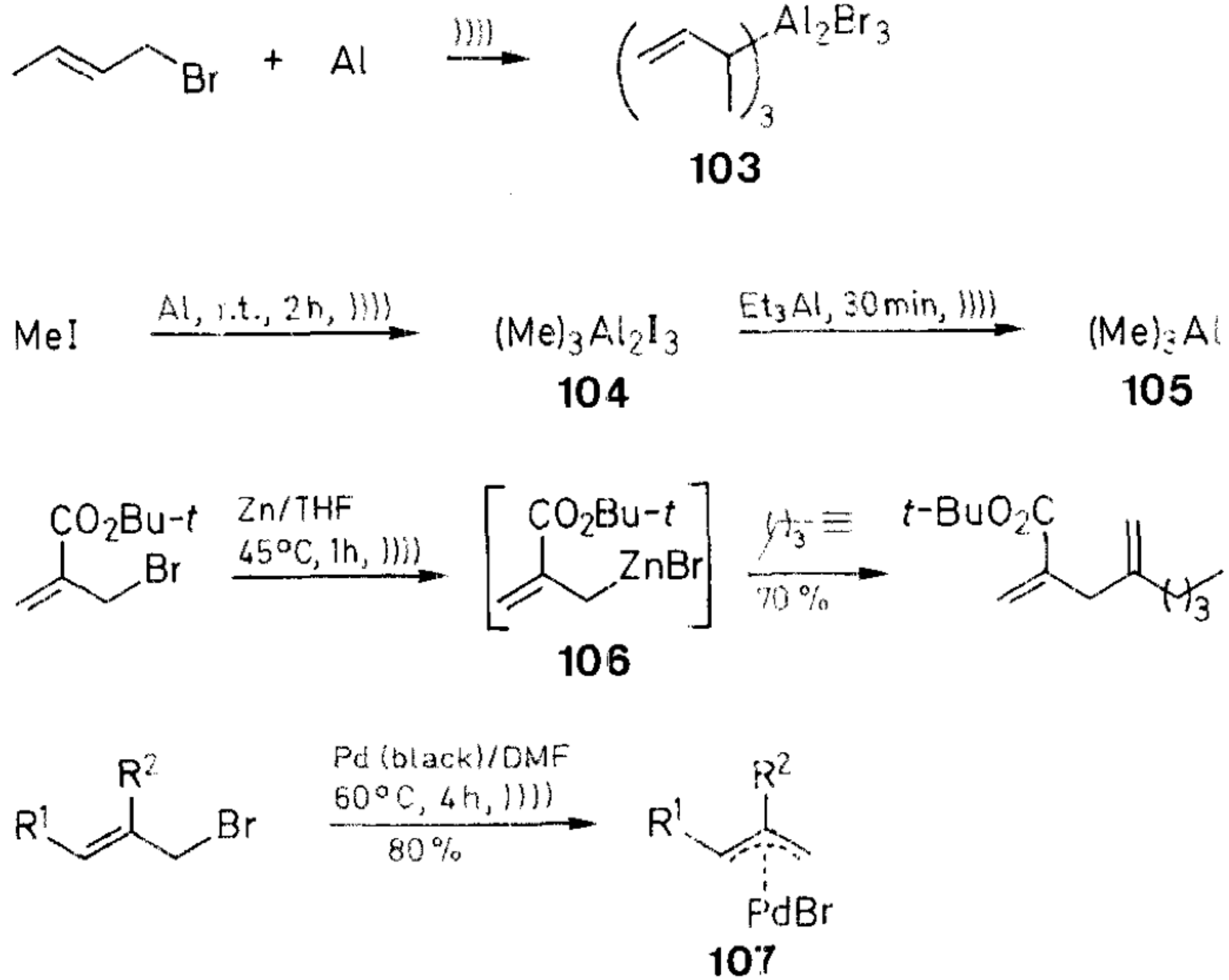
- Conjugate Additions



Synthesis, 1989, *11*, 787

Sonochemistry in Organic Synthesis: Examples

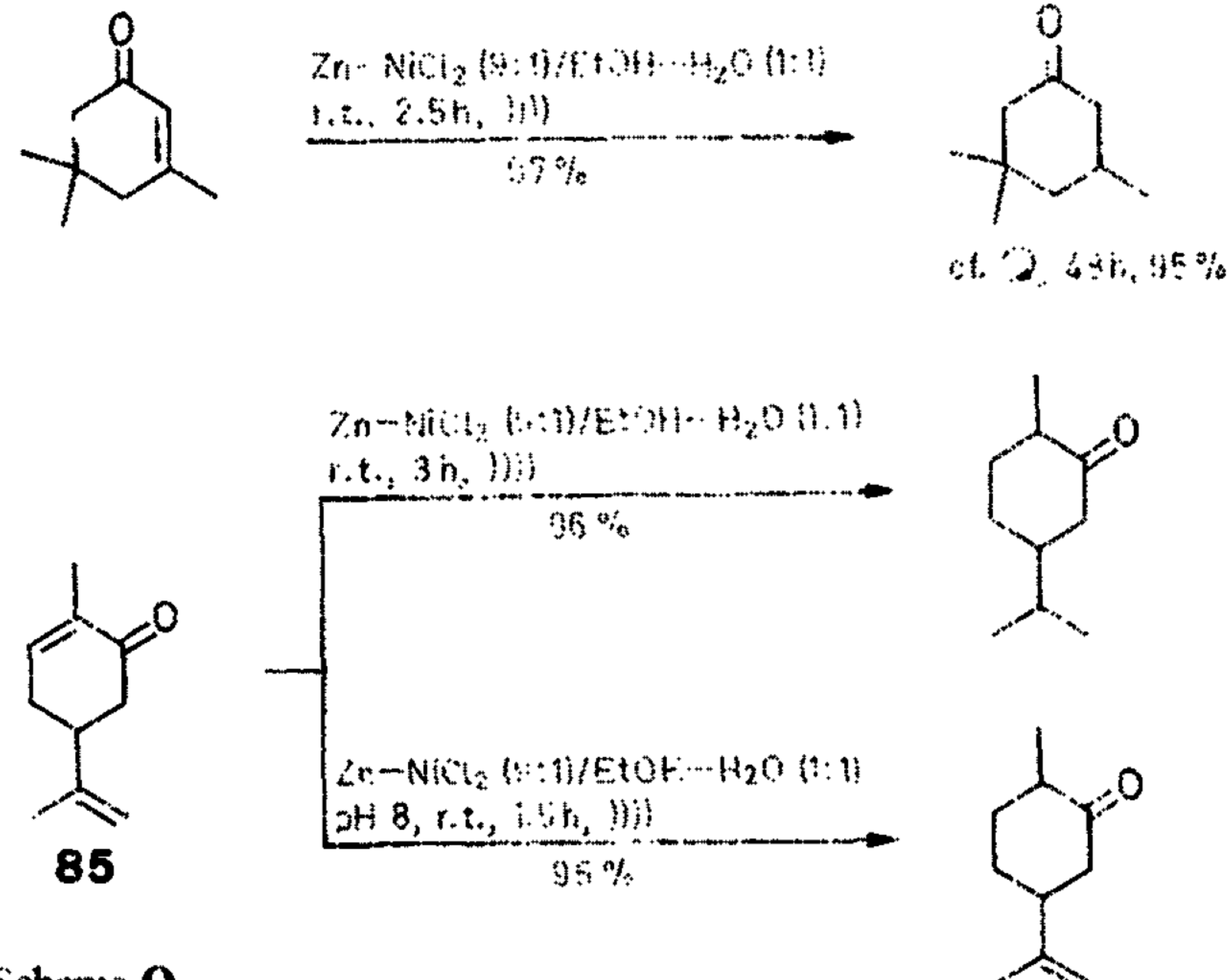
- Preparation of Organometallic Reagents



Synthesis, 1989, *11*, 787

Sonochemistry in Organic Synthesis: Examples

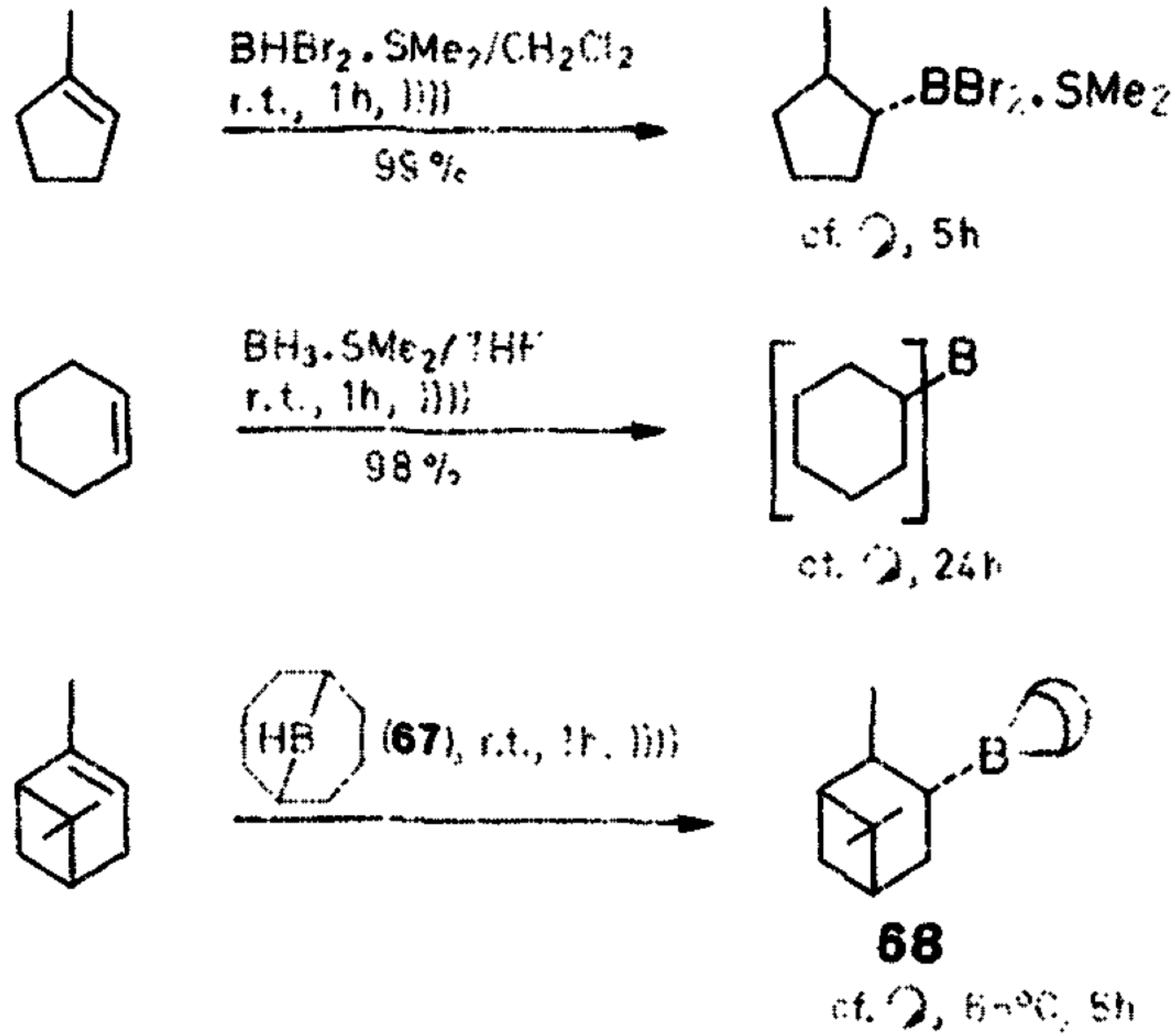
- Hydrogenations



Scheme Q

Sonochemistry in Organic Synthesis: Examples

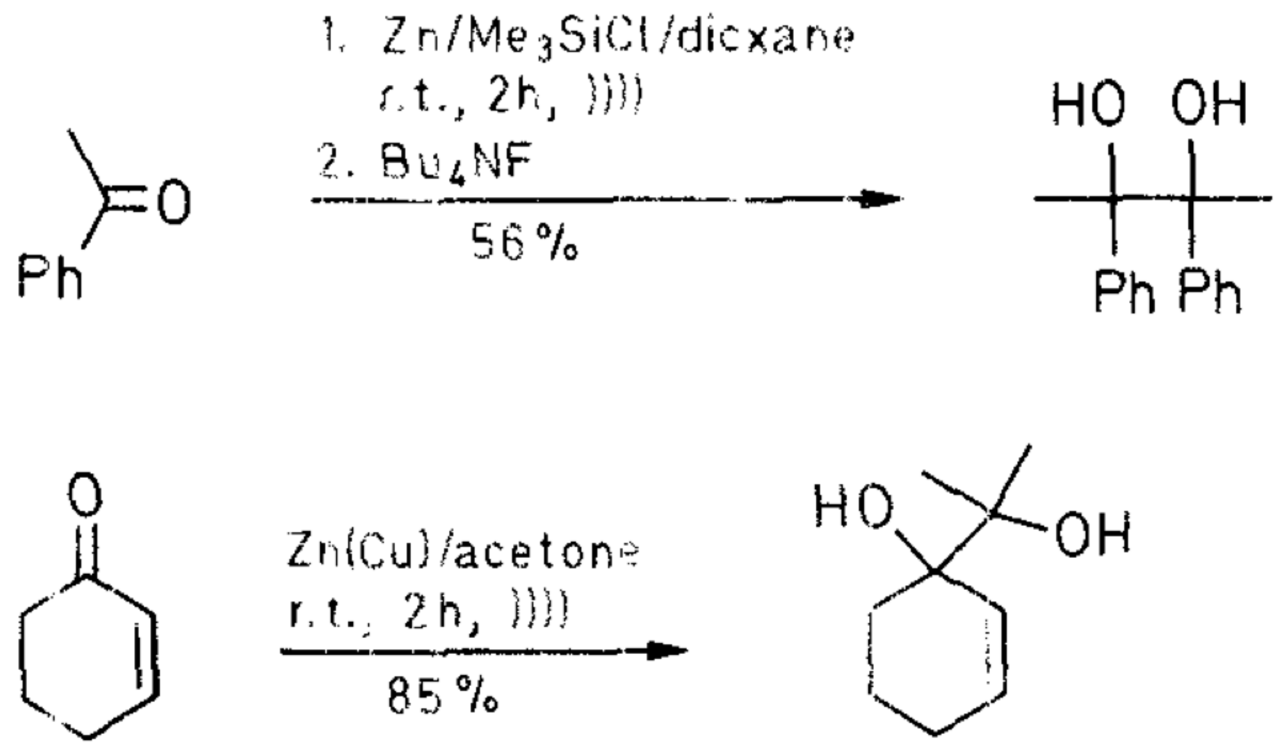
- Hydroborations



Synthesis, 1989, *11*, 787

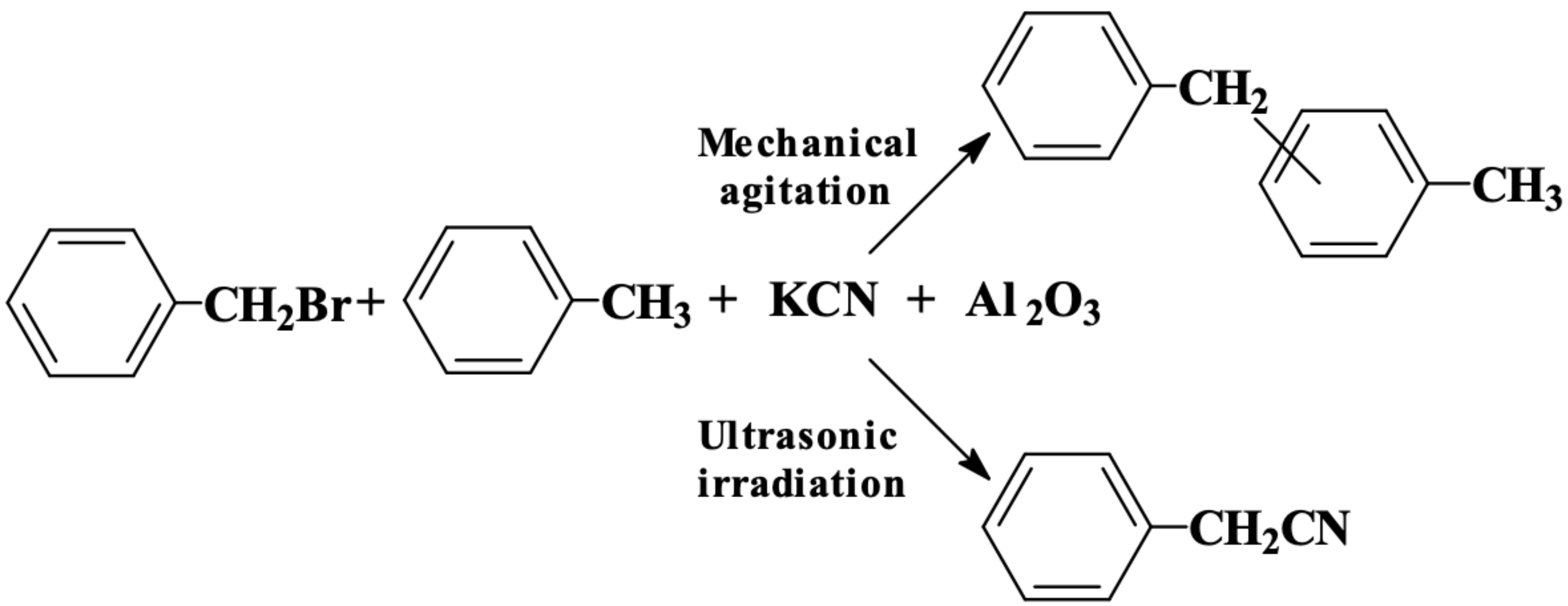
Sonochemistry in Organic Synthesis: Examples

- Pinacol Reactions



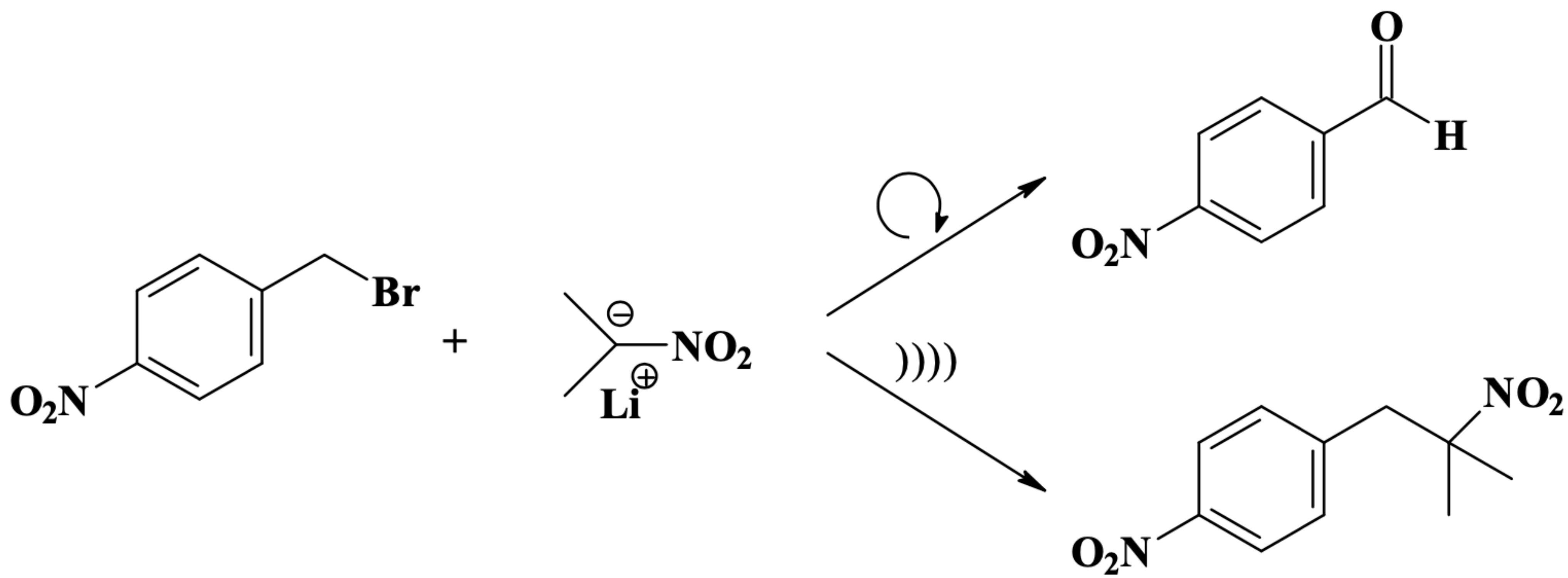
Synthesis, 1989, *11*, 787

Sonochemistry in Organic Synthesis: Sonochemical Switch



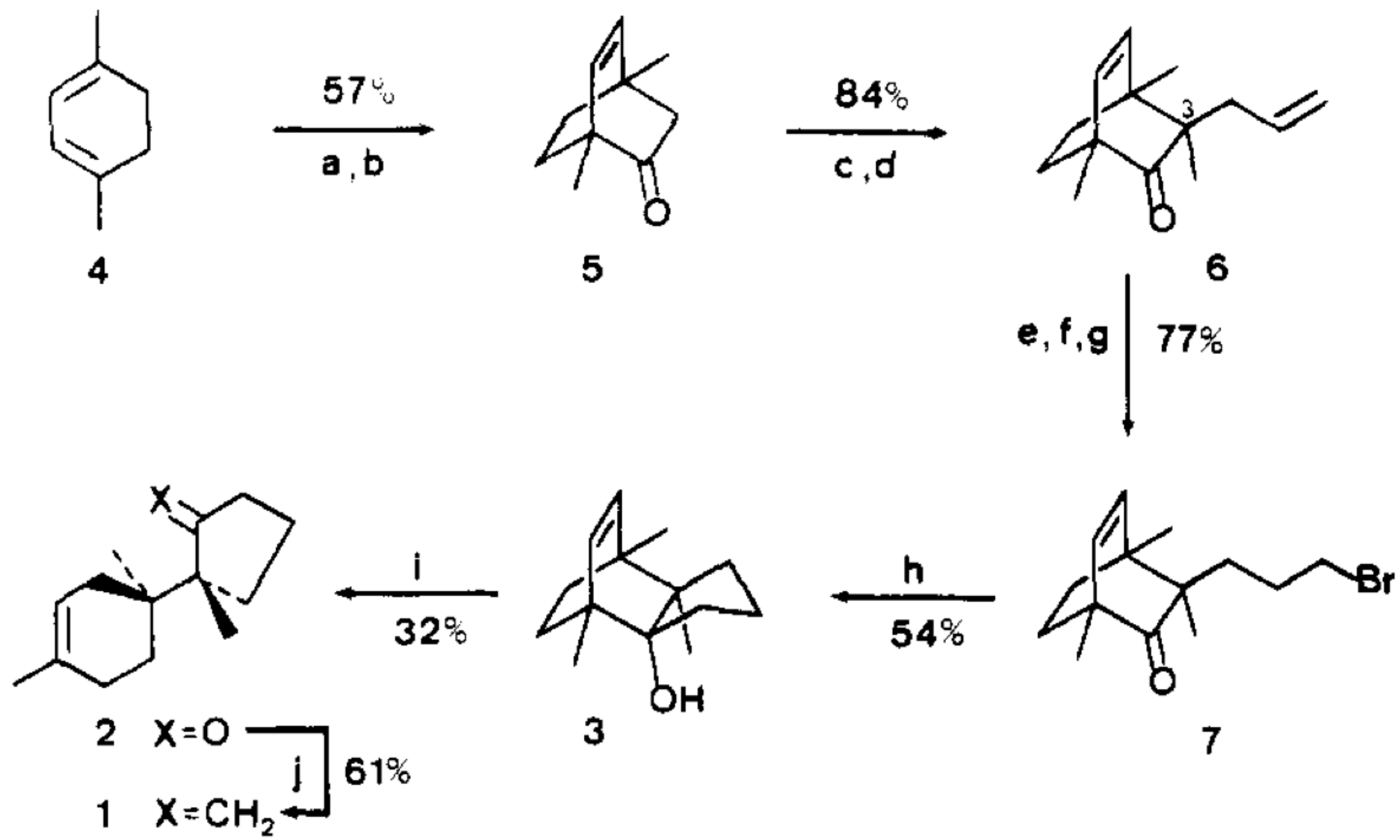
J. Chem. Soc. Ser. Chem. Commun. **1984**, 439–440.

Sonochemistry in Organic Synthesis: Sonochemical Switch



Tetrahedron Lett. **1991**, *32*, 4709–4712.

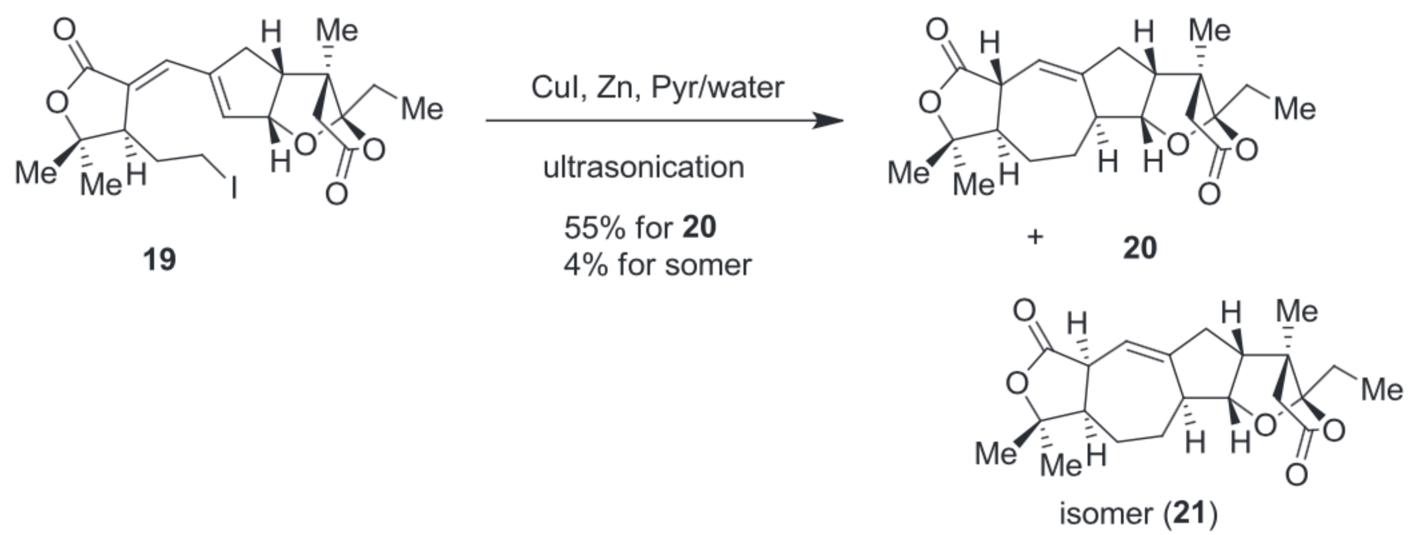
Sonochemistry in Organic Synthesis: Uses in Natural Product Synthesis

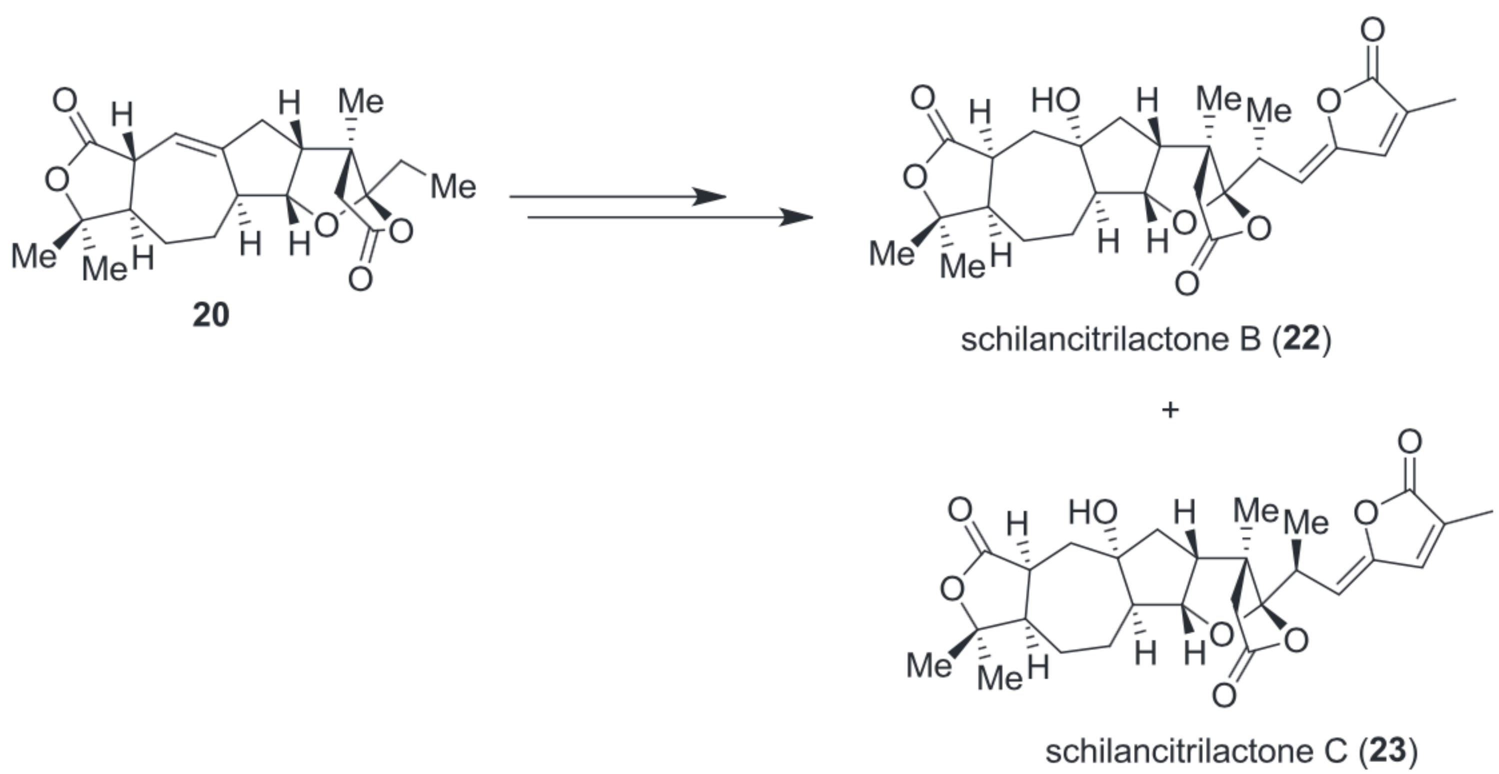


[a] Reagents: (a) CH_2=C(CN)Cl, toluene, 90 °C; (b) $Na_2S \cdot 9H_2O$, EtOH, reflux, 24 h; (c) LDA, THF, −70 °C, then CH_3I, HMPA, −30 °C; (d) LDA, THF, −70 °C, then CH_2=$CHCH_2I$, HMPA, −60 °C; (e) 9-BBN, THF, then 30% aqueous H_2O_2, NaOH; (f) TsCl, C_6H_5N; (g) LiBr, acetone, reflux, 1.5 h; (h) Li, THF, 0 °C; (i) KH, HMPA, 140 °C, 1 h; (j) Ph_3P=CH_2, Me_2SO, 80 °C.

J. Org. Chem. 1984, 49, 8, 1464–1465

Sonochemistry in Organic Synthesis: Uses in Natural Product Synthesis





ACIEE, 2015, *54*, 5732
Ultrasonics Sonochemistry, 2021, *77*, 105665

Parameters and their Effects on Cavitation

1. *Acoustic Effects*
2. *Solvent Effects*
3. *External Effects*

Parameters and their Effects on Cavitation

1. *Acoustic Effects*
   A. *Frequency:* higher frequency = shorter rarefaction cycles
      i. Increase in frequency requires an increase in amplitude to maintain cavitation levels
      ii. Higher frequencies result in smaller cavitation bubbles
      iii. Frequencies too high will result in no cavitation
   B. *Intensity:* greater intensity generally results in increase in cavitation
2. *Solvent Effects*
3. *External Effects*

Parameters and their Effects on Cavitation

1. *Acoustic Effects*
2. *Solvent Effects*
   A. *Viscosity:* cavitation is harder to induce in more viscous media
   B. *Surface Tension:* reduction in surface tension lowers cavitation threshold
   C. *Vapor Pressure:* solvents with higher vapor pressure have lower cavitation thresholds
   D. *Solvent purity:* dissolved impurities lower the cavitation threshold
3. *External Effects*

Parameters and their Effects on Cavitation

1. *Acoustic Effects*
2. *Solvent Effects*
3. *External Effects*
    A. *External Temperature:* alters the viscosity, surface tension, and vapor pressure of solvent
    B. *External Pressure:* greater external pressure requires greater rarefaction pressure to induce cavitation
    C. *Bubbled gas:* dissolved gas lowers cavitation threshold by providing sites of nucleation
        i. Generally, this reduces the intensity of the collapse of bubbles

Practical Sonochemistry: Power Ultrasound Uses and Applications, 2nd edition

Sonochemical Set-ups and Techniques

When Using a Bath Sonicator:

- Ensure the bath is filled to the level recommended
- Map out the powerful cavitation zones by sonicating a sheet of aluminum foil and noting where it degrades most severely
- Place reaction vessel at the same spot in the bath to ensure reproducible results
- Use flat-bottomed vessels and ensure they do not touch the bottom or sides of the bath
- Adjust solvent level to be even with the level of the bath

J. Org. Chem. 2021, 86, 20, 13833–13856

Sonochemical Set-ups and Techniques

Pros to Bath Sonicators:

- Widely available and inexpensive
- Even distribution of acoustic field
- Allows use of conventional glassware and methods

Cons to Bath Sonicators:

- Typically low power transmitted from bath to reaction
- Power is dependent on the size of bath, reaction vessel, and placement in bath (must be evaluated for each system)
- Baths do not have universal frequencies
- Temperature control can be an issue
- Typically do not have adjustable power

J. Org. Chem. 2021, 86, 20, 13833–13856
Practical Sonochemistry: Power Ultrasound Uses and Applications, 2nd edition

Sonochemical Set-ups and Techniques

When Using a Probe Sonicator:

- Ensure the probe is intact and change if damage is noted
- Use pulse conditions to help control temperature by allowing heat to dissipate
- Place probe in the center of the reaction vessel
- Round-bottom flasks are best
- Homogenize systems prior to sonication and slowly add any powders/solids

J. Org. Chem. 2021, 86, 20, 13833–13856

Sonochemical Set-ups and Techniques

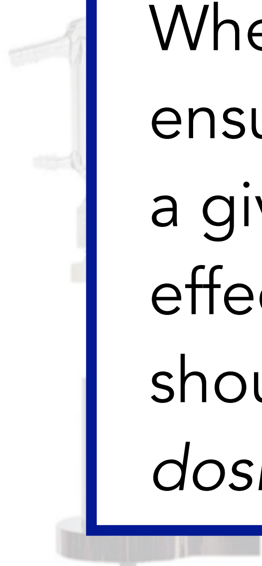
When Using a High-frequency Horn Sonicator:

- Must carefully control temperature! Double jacketed reactors are recommended
- Can operate as a probe or a bath (not recommended)
- Must avoid corrosive/hazardous liquids
- Acoustic efficiency is determined by height of liquid in the cup
- High-frequencies favor radical formation

J. Org. Chem. 2021, 86, 20, 13833–13856

Sonochemical Set-ups and Techniques

When Using a High-frequency Horn Sonicator:



When running sonochemical reactions, the user should ensure that the cavitation threshold is being reached in a given system. Additionally, for each system, the effective sonochemical power applied to the reaction should be measured to ensure reproducibility! (see *dosimetry* in further readings)

uble

eight of liquid in the cup

- High-frequencies favor radical formation

J. Org. Chem. 2021, 86, 20, 13833–13856

Further Reading

1. *For more comprehensive reviews on organic sonochemical transformations:*
   - Luche, J.L. *Synthesis*, 1989, *11*, 787
   - Low, C.M.R. *Ultrasonics Sonochemistry*, 1995, *2*, 153
   - Majhi, S. *Ultrasonics Sonochemistry*, 2021, *77*, 105665
2. *For more practical knowledge of techniques:*
   - Mason, *Practical Sonochemistry: Power Ultrasound Uses and Applications*, 2nd edition
   - Cintas, P. *et al. J. Org. Chem.*, 2021, 86, 20, 13833