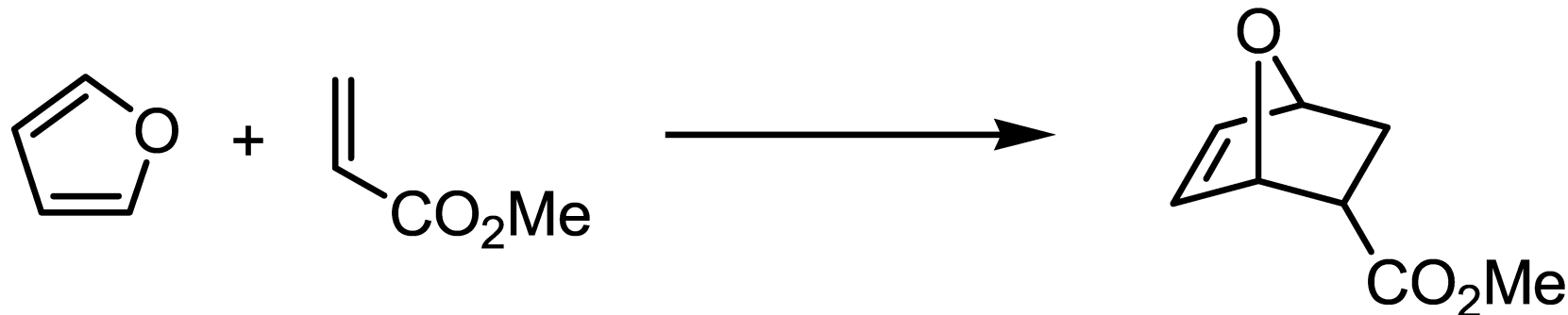


High Pressure in Organic Synthesis



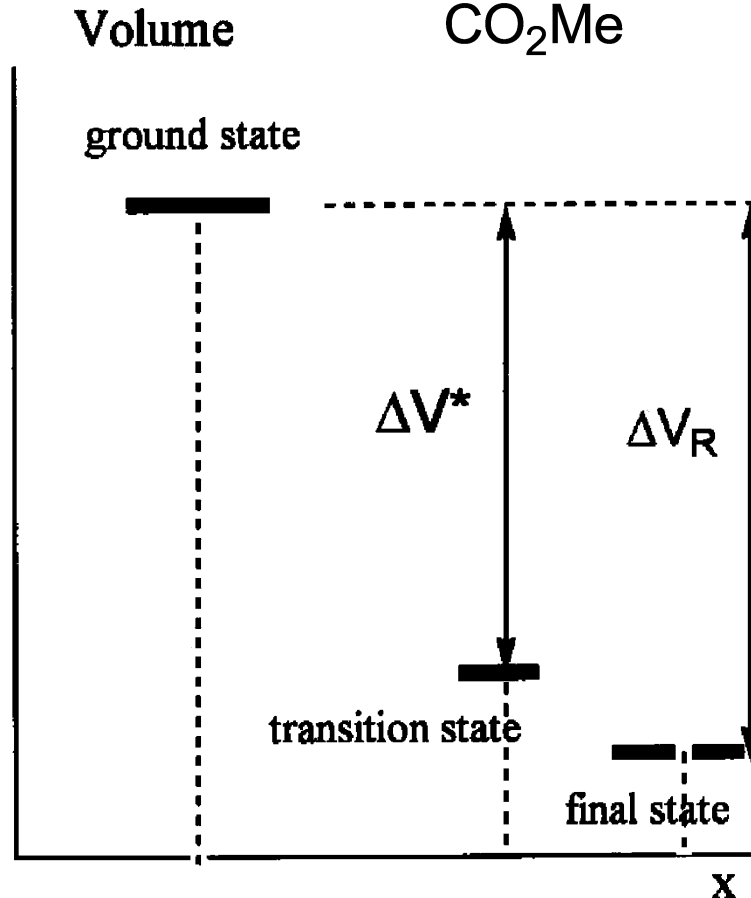
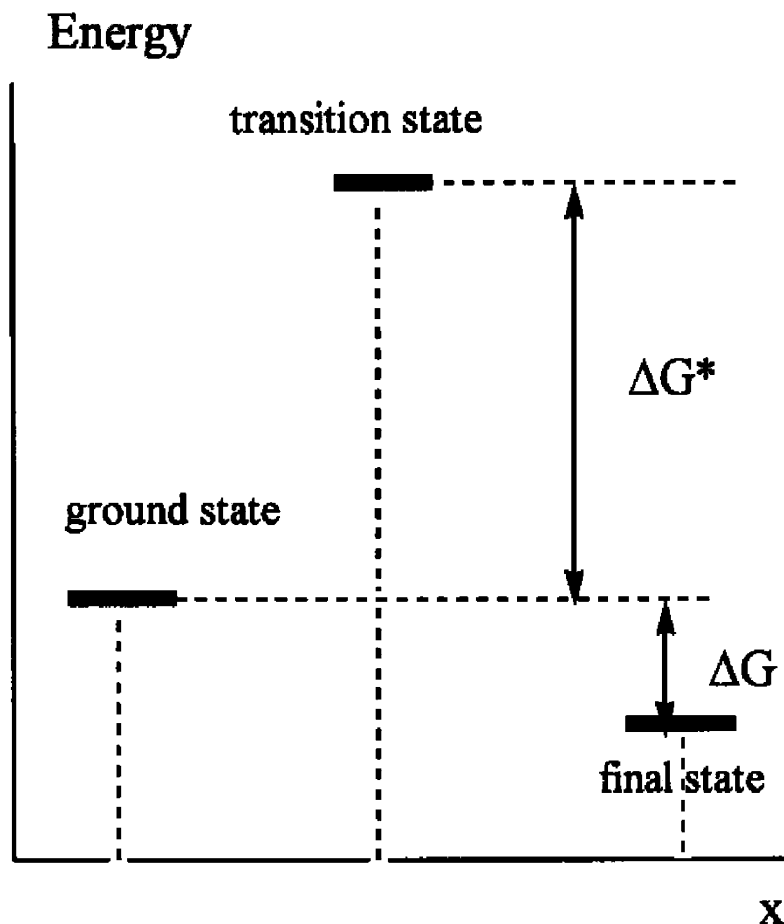
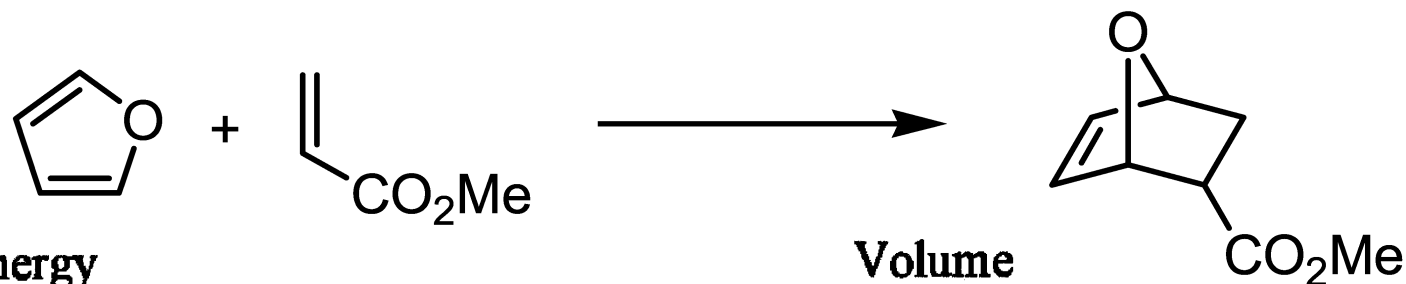
1 bar, 25 °C, 2-3 months - 50%

15 kbar, 25 °C, 4 h - 62%

Justin I. Montgomery

8/30/5

Reaction Profiles - Volume



$$\Delta V_R = \text{Volume of Reaction} = \sum V_{\text{products}} - \sum V_{\text{reactants}}$$

$$\Delta V^* = \text{Volume of Activation} = V_{\text{TS}} - \sum V_{\text{reactants}}$$

Thermodynamics: Pressure Effects on Equilibria

$$\left(\frac{\partial \ln K}{\partial P} \right)_T = - \frac{\Delta V}{RT}$$

ΔV = volume of reaction

Derive this equation given:

$$G = H - TS$$

$$H = U + PV$$

$$dU = TdS - PdV$$

ΔV can be measured two ways – measuring individual partial molar volumes or by determining how pressure affects the equilibrium constant

Kinetics: Pressure Effects on Rate

$$\left(\frac{\partial \ln k}{\partial P} \right)_T = \frac{-\Delta V^\ddagger}{RT}$$

If $\Delta V^\ddagger < 0$, reaction is accelerated

If $\Delta V^\ddagger > 0$, reaction is retarded

TS's with negative ΔV^\ddagger

- associative
- bond formation
- concentration of charge
- ionization

TS's with positive ΔV^\ddagger

- dissociative
- bond cleavage
- dispersion of charge
- neutralization
- diffusion control

Process	Estimated Contribution to ΔV^\ddagger (cm ³ /mol)
Homolytic bond cleavage	+10
Homolytic association	-10
Ionization	-20
Neutralization	+20
Charge Concentration	-5
Charge Dispersal	+5
Steric hindrance	(-)
Diffusion control	>+20

solvent
dependent

Table 7.1 Typical values for the volumes of activation^a

Reaction	ΔV^\ddagger (cm ³ mol ⁻¹)
Homolysis	+5 to +20
Radical polymerization (propagation)	ca. -20
Cycloadditions	
Diels-Alder	-30 to -50
catalysed	-25 to -35
intramolecular	-25 to -30
dipolar	-40 to -50
(2+2)	-40 to -55
H ₂ transfer	-25
Neutral S _N 2	small
Solvolysis of RX	-15 to -25
Quaternization of RX	-30 to -50 ^a
Ester hydrolysis	
basic	-10 to -15
acidic	>-10
Epoxide-ring opening	-15 to -20
Hydration of alkenes	ca. -20
Aldol reactions	-10 to -30?
Baylis-Hillman reactions	<-50
S _N Ar reactions (ionogenic)	-30 to -40
Wittig reactions	-20 to -30

^aMany reported volumes of activation appear to show a considerable dependence on the structure, on the solvent, and on other conditions.

How Much Pressure is Enough?

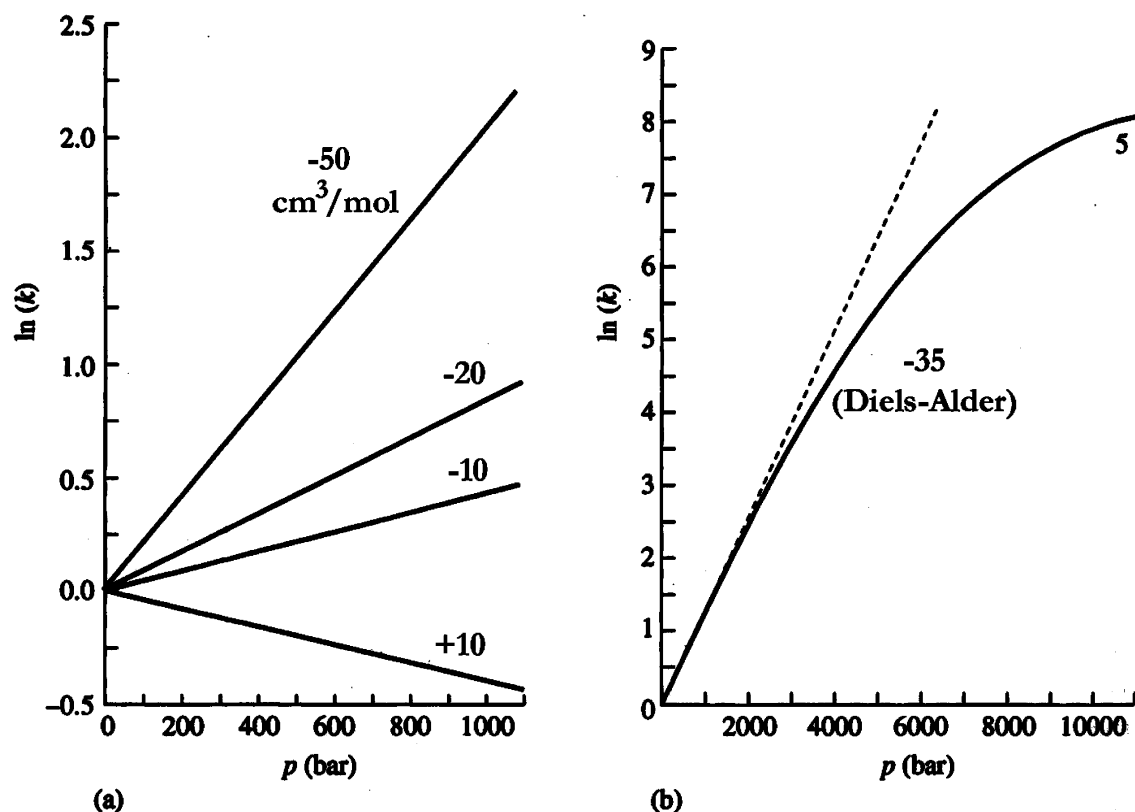


Fig. 7.1 (a) The kinetic response to pressure predicted from eqn (7.1.3) of reactions with the following volumes of activation: *curve 1*, 10 $\text{cm}^3 \text{mol}^{-1}$; *curve 2*, -10 $\text{cm}^3 \text{mol}^{-1}$; *curve 3*, -20 $\text{cm}^3 \text{mol}^{-1}$; and *curve 4*, -50 $\text{cm}^3 \text{mol}^{-1}$. (b) A schematic curve giving: (---) the linear response, and (—) a more realistic (nonlinear) response, *curve 5*, for $\Delta V^\ddagger = -35 \text{ cm}^3 \text{mol}^{-1}$.

For $\Delta V^\ddagger = -35 \text{ cm}^3/\text{mol}$ (if linear)

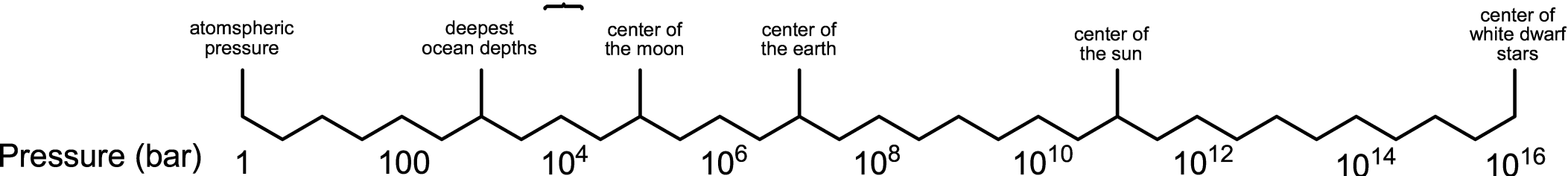
Pressure (Relative Rate)

1 bar (1)
 10 bar (1.01)
 100 bar (1.15)
 1 kbar (4.26)
 10 kbar (1,980,000)

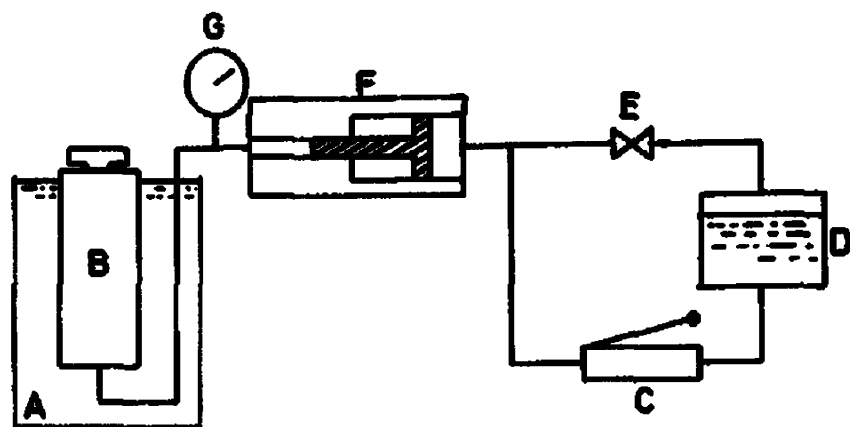
5-20 kbar normally used
 for organic synthesis

tire = 2-3 bar
 hydrogenators = 28 bar
 Ar tank = 210 bar

5-20 kbar

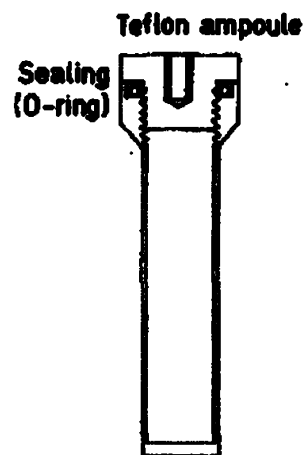


Reactor Design

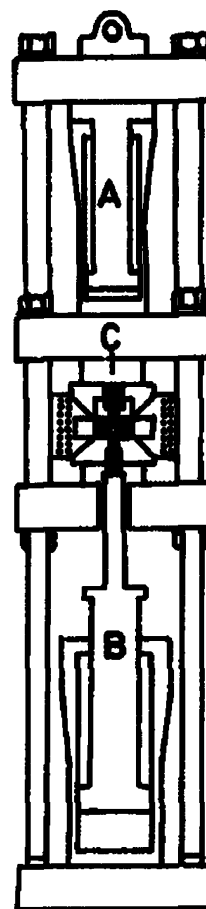


- A: Thermostatted bath
- B: High pressure vessel
- C: Hand pump
- D: Oil reservoir
- E: Valve
- F: Intensifier
- G: Bourdon gauge

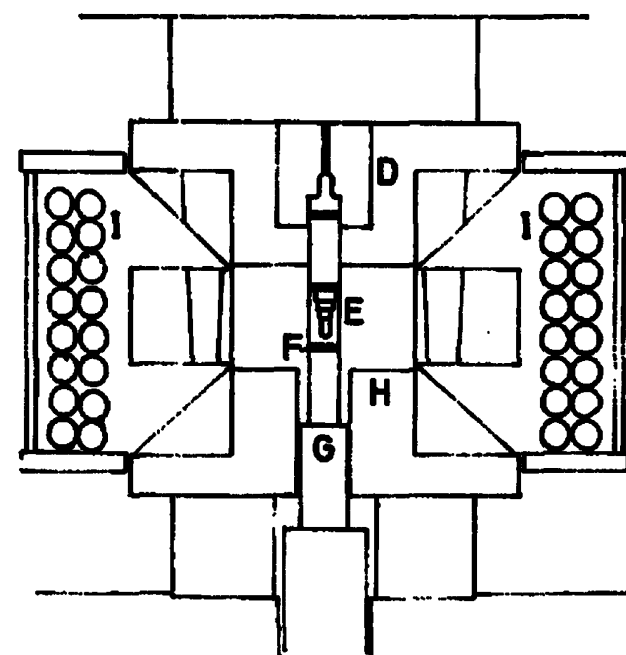
le Noble-type
apparatus



Reaction vessels (compressible)



- A: Upper hydraulic press
- B: Lower hydraulic press
- C: Spacer
- D: Upper lid
- E: Sample container



Enlarged View of Apparatus

- F: Sample
- G: Piston
- H: Lower lid
- I: Induction heater

Direct piston-cylinder equipment

Safety Considerations

- Compression of a fluid like water or hydraulic oil to 3-4 kbar causes compression of 10% (25% at 10 kbar)
 - Stored energy is about $0.5 \text{ kJ mol}^{-1} \text{ kbar}^{-1}$
 - A gas (He) stores about $2000 \text{ kJ mol}^{-1} \text{ kbar}^{-1}$
 - Leakage of a small portion of liquid would relieve pressure while leakage of a huge amount of gas would be required
- Some risk of injury from pin-hole jets of pressurized oil (can penetrate human body) or valve stems blowing out of valves

Overall, high pressure liquids are much less hazardous than high pressure gases

Effects of High Pressure on Solvent

- melting points increase ~15-20 °C per 1 kbar
- solubility of gases in liquids is increased, solids ??
- viscosity of liquid increases ~ 2X per 1 kbar (diffusion-controlled steps)
- compressibility of liquids is 4-18% at 1 kbar (rapidly approaching an upper limit at higher pressure)

For more details, see:

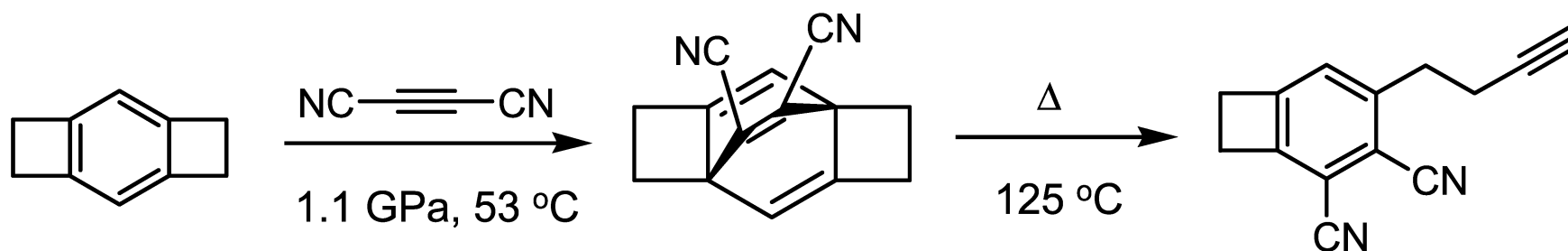
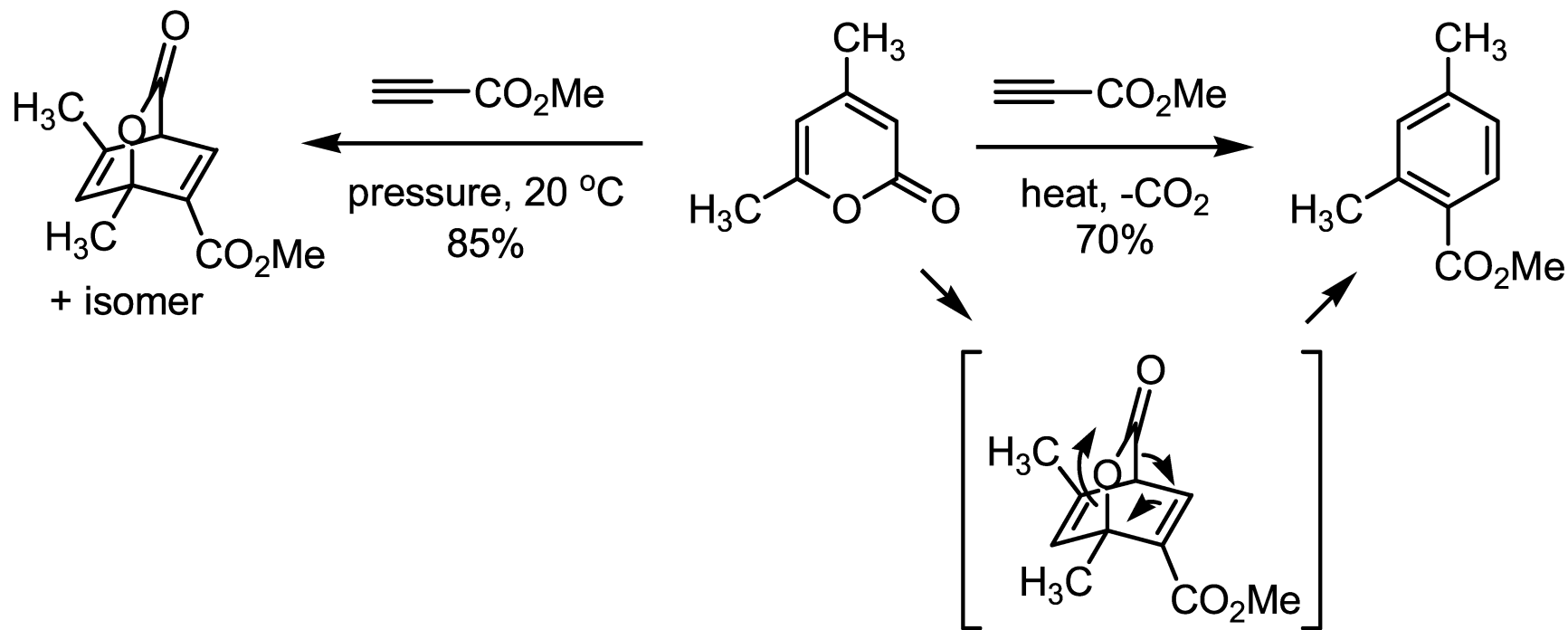
G. Jenner "Role of the Medium in High Pressure Organic Reactions. A Review" *Mini-Reviews in Organic Chemistry*, **2004**, 1, 9-26.

Table 7.2 The freezing pressures⁷ of some organic solvents at 25°C

Solvent	p_f (kbar)
Cyclohexane	0.355
<i>p</i> -Xylene	0.36
Acetic acid	0.39
Benzene	0.72
Nitrobenzene	0.84
<i>N,N</i> -dimethylaniline	0.93
Carbon tetrachloride	1.462
Dioxan	1.2
<i>o</i> -Xylene	2.29
Decane	3.0
Mesitylene	3.5
Chlorobenzene	4.55
Octane	5.3
Chloroform	5.5
Heptane	11.1
Diethyl ether	ca. 11
Dichloromethane	>20
1-Butanol	11.7
Methylcyclohexane	13.8
Ethanol	30
Methanol	50

"High Pressure Techniques..." 1997 p. 315.

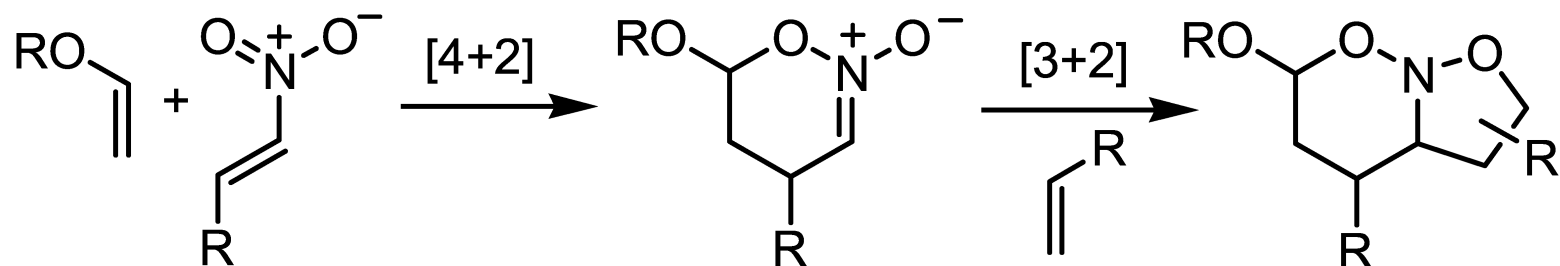
Pressure for Mild Reaction Conditions 1



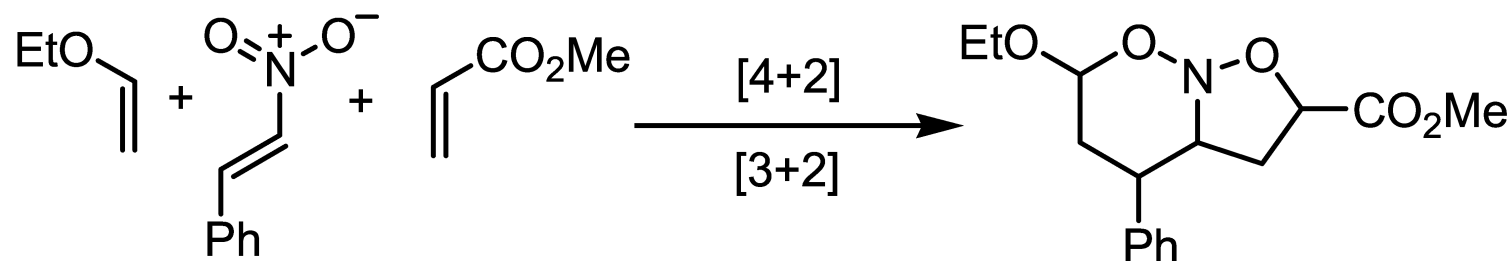
High pressure can allow for isolation of intermediates that would not be stable under conditions necessary for reaction at ambient pressure

Pressure for Mild Reaction Conditions 2

Tandem [4+2]/[3+2] Cycloadditions of Nitroalkenes



Lewis acid, high temp, or excess of reagents/long rxn time needed.
If Lewis acid, decomplexation needed before [3+2].



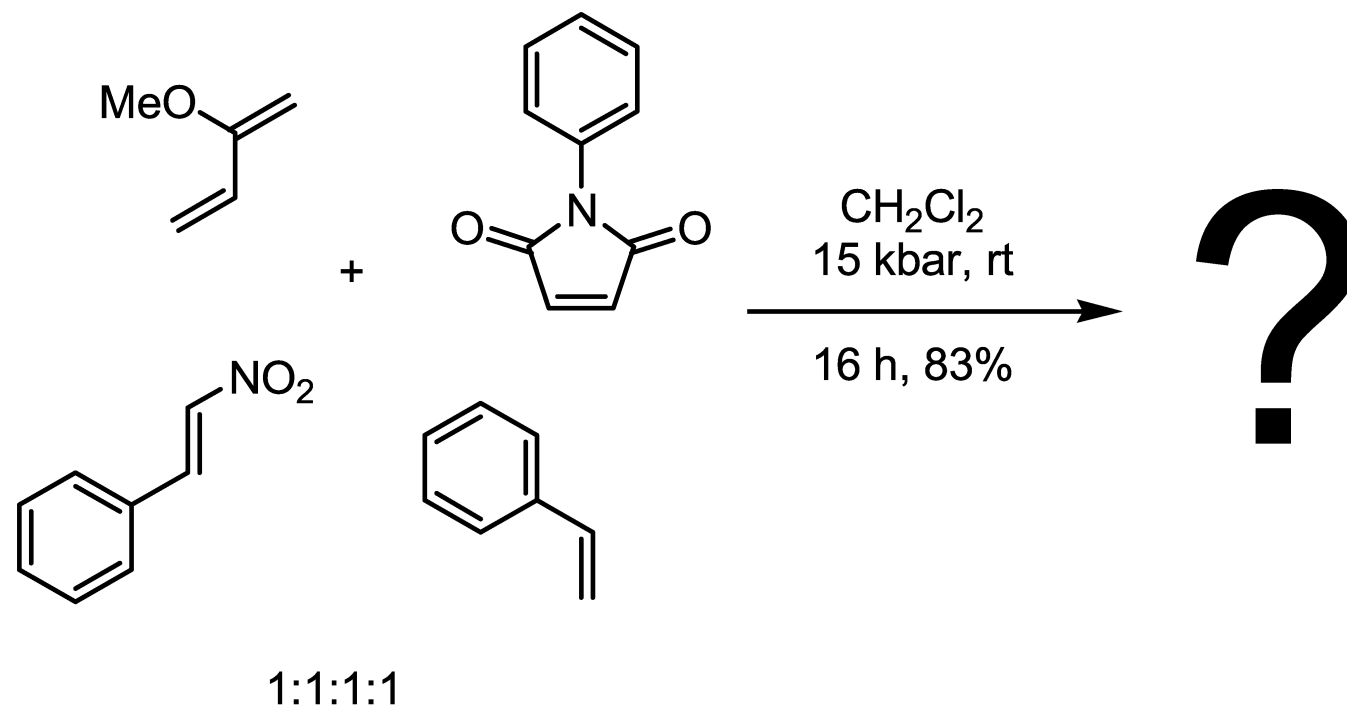
1 bar, 30 equiv. EVE, 37 equiv. MA, 20 days, 43%
15 kbar, 4 equiv. EVE and MA, 1 h, 62%

[4+2] – complete *endo* selectivity,
[3+2] – 2.6:1 ratio of diastereomers.

See “High Pressure Chemistry” **2002** pp. 284-304 (Chapter 9) for additional examples.

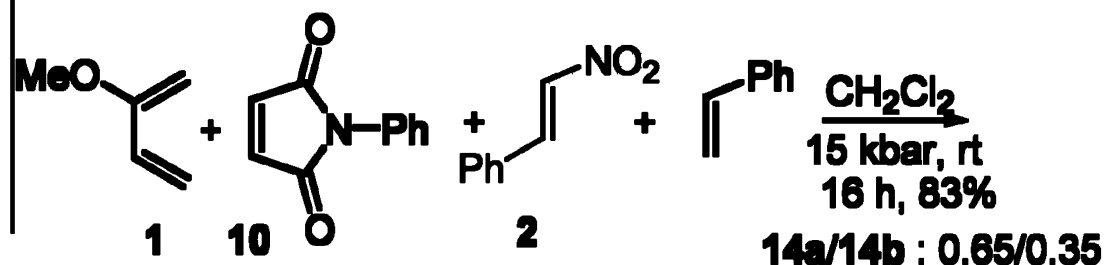
High pressure significantly extends the synthetic utility of the uncatalyzed reaction.

Riddle Me This...

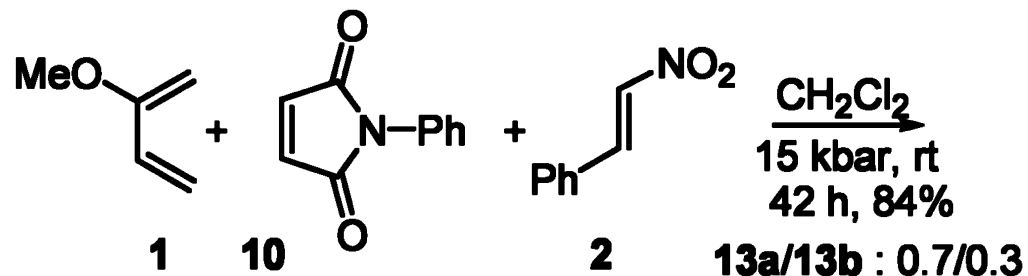
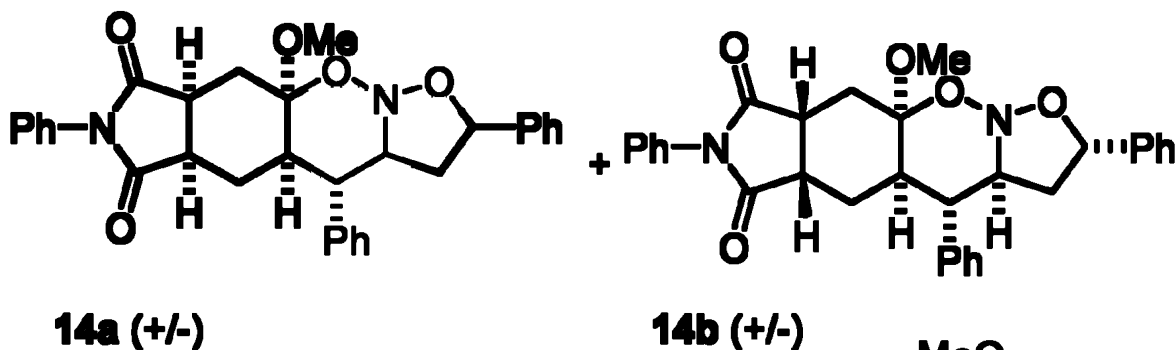


Predict the outcome of this reaction.

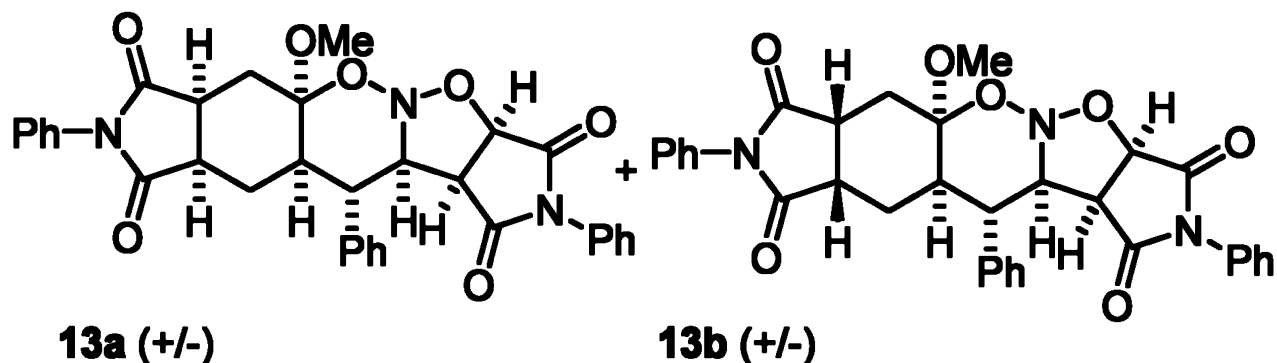
Domino [4+2]/[4+2]/[3+2] Under High Pressure



- Four-component reaction
- Complete selectivity for one electronic outcome



Pentacyclic product formed in one step from readily available starting materials



Volume of Activation in More Detail

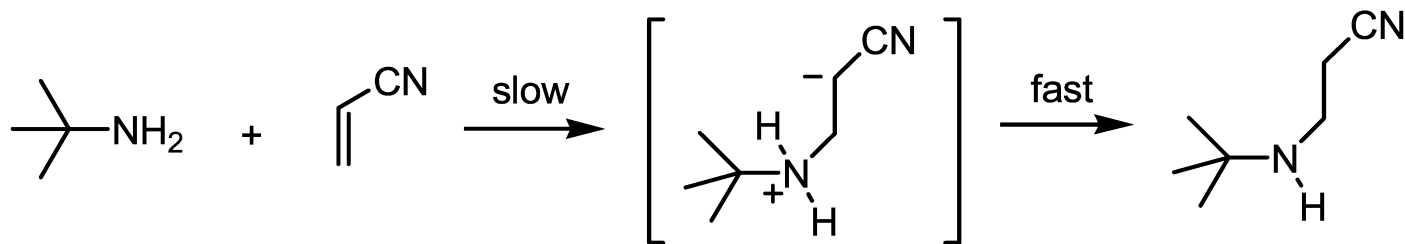
ΔV^* is a reflection of all volume changes that occur during progression from ground state to transition state and within the transition state.

There are two main volume effects: molecular reorganization (ΔV_s^*) and interactions of the reactants and activated complex with the medium (ΔV_m^*)

$$\Delta V^* = \Delta V_s^* + \Delta V_m^*$$








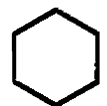

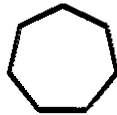

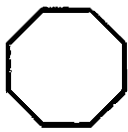

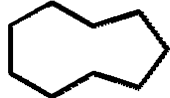

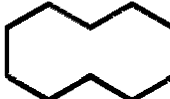

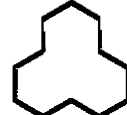


ΔV_s^* - change in intrinsic volume of reacting molecules (van der Waals spheres and voids around them)

ΔV_m^* - *electrostriction* – In a heterolytic bond dissociation, attractive interactions between the generated ion and solvent molecules lead to a contraction of volume that is much bigger than the expansion of volume resulting from the dissociation.



For an ionogenic reaction, how does solvent polarity affect ΔV^* ?

Relationship Between ΔV and Ring Size

			ΔV_W^a	ΔV_{Ra}	ΔH^b	ΔS^c	ΔG^b
	→		-1.7	-5.5	7.86	-7.0	9.95
	→		-2.5	-6.6	6.43	-10.3	9.50
	→		-3.8	-14.7	-13.46	-13.1	-9.56
	→		-4.4	-16.5	-19.47	-21.0	-13.21
	→		-4.7	-21.2	-13.41	-19.6	-7.57
	→		-4.9	-25.6	-9.88	-18.8	-4.28
	→		-4.7	-30.9			
	→		-4.6	-32.3			
	→		-4.7	-32.8			
	→		-4.7	-32.3			

• ΔV decreases as ring size increases from 3 to 10

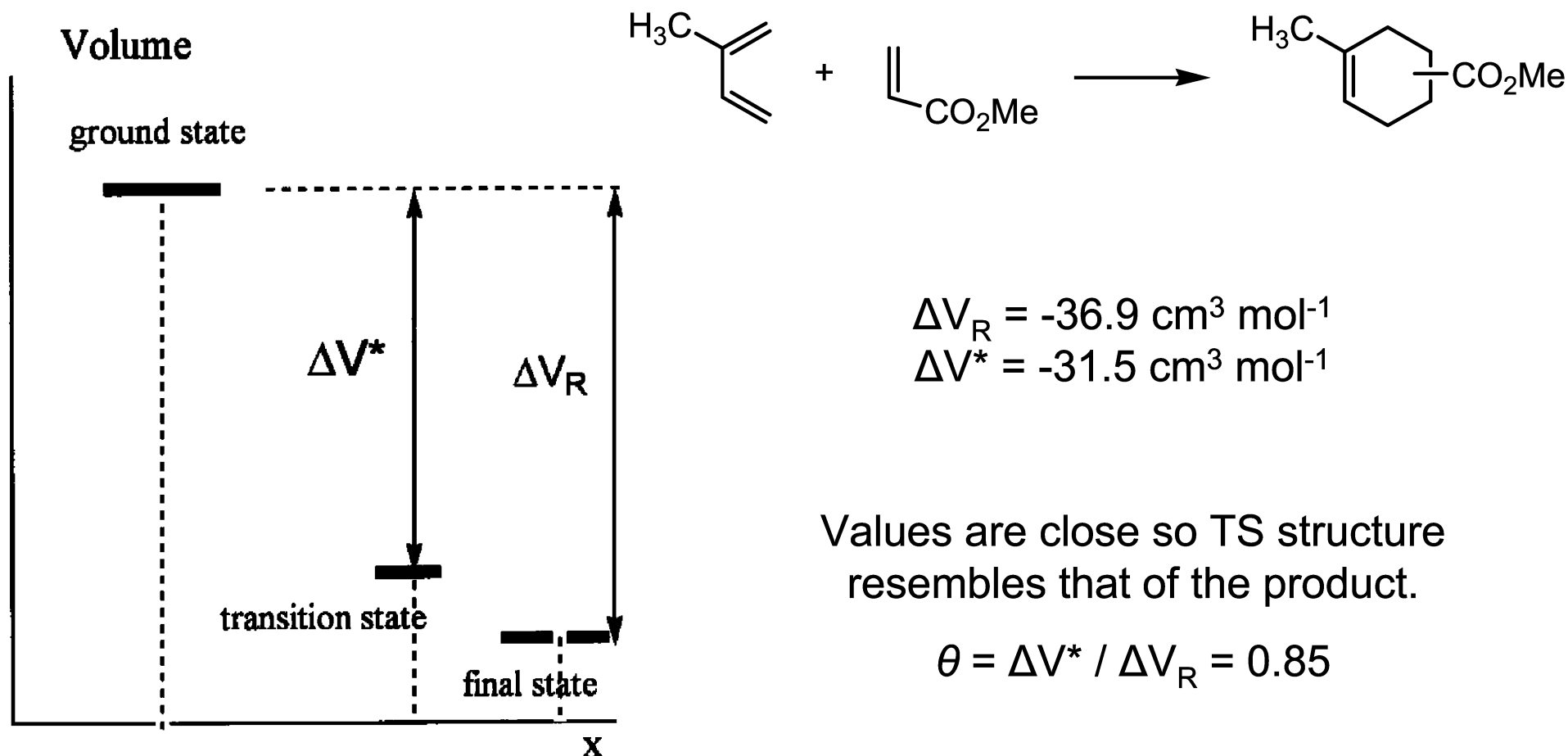
• van der Waals volume of reaction stays about the same

• change is from different packing of cyclic/open chain forms

• doesn't track with other thermodynamic parameters

Probably due to restriction of rotational degrees of freedom – the larger the ring, the more degrees of freedom are restricted upon cyclization – synthetic uses?

High Pressure as a Tool for Delineating Mechanism



However, only ΔV_s^* can be used for transition state location! ΔV_m^* (electrostriction) and other effects (steric, solvophobic) must not be present.

Mechanism: Solvent Effects and θ

Diene ^a	Dienophile	Solvent effect	θ^b
Isoprene	Methyl acrylate	Weak	0.85
Isoprene	Acrylonitrile	Weak	0.96
Isoprene	Methyl vinyl ketone	Moderate	1.02
DMB	<i>n</i> -Butyl acrylate	Weak	0.89
MOB	Maleic anhydride	Fairly strong	0.99 (in MeCN)
MOB	Maleic anhydride	Fairly strong	1.66 (in CH ₂ Cl ₂)

^a DMB = 2,3-dimethyl-1,3-butadiene; MOB = 1-methoxy-1,3-butadiene.

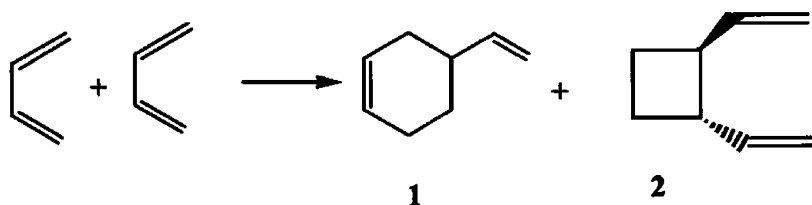
^b θ Values ($\theta = \Delta V^*/\Delta V$) are standardized to 20–25°C.

If solvent effect is weak, $\Delta V_m^* \sim 0$, $\Delta V^* \sim \Delta V_s^*$ and θ can locate TS.

If θ is ~ 1 in these cases, reactions are concerted processes.

If solvent effect is strong, $\Delta V_m^* < 0$ (electrostriction), $\Delta V^* = \Delta V_s^* + \Delta V_m^*$ and θ can be > 1 (ΔV_s won't contribute to ΔV since product is not charged).

The presence of a solvent effect indicates a polar TS – less concertedness.



Dimerization of 1,3-Butadiene
(no solvent effect)

What can be concluded from the θ values observed for compounds **1** & **2**?
Propose mechanisms and an additional experiment to support your argument.

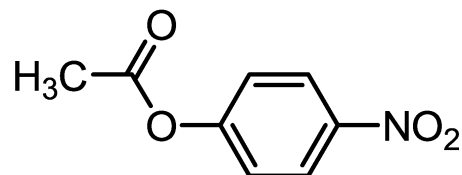
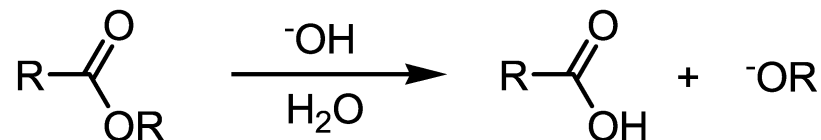
Table 8. Activation volumes in butadiene dimerization

Formation of	ΔV_{25}^* (cm ³ mol ⁻¹)	θ_{25}
1	-26.5	0.79
2	-14.4	0.59

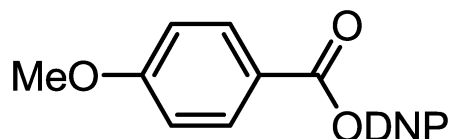
1,3-Butadiene Dimerization: Answer

Mechanism: The Sign of ΔV^*

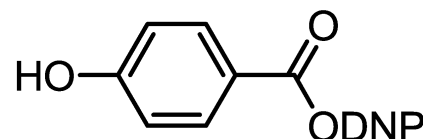
Base-catalyzed hydrolysis of esters:
DNP = 2,4-dinitrophenyl



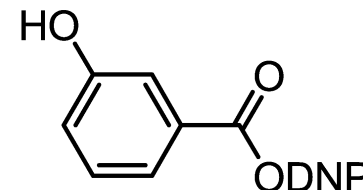
$$\Delta V^* = -20 \text{ cm}^3/\text{mol}$$



$$\Delta V^* = -19 \text{ cm}^3/\text{mol}$$



$$\Delta V^* = +16 \text{ cm}^3/\text{mol}$$



$$\Delta V^* = -15 \text{ cm}^3/\text{mol}$$

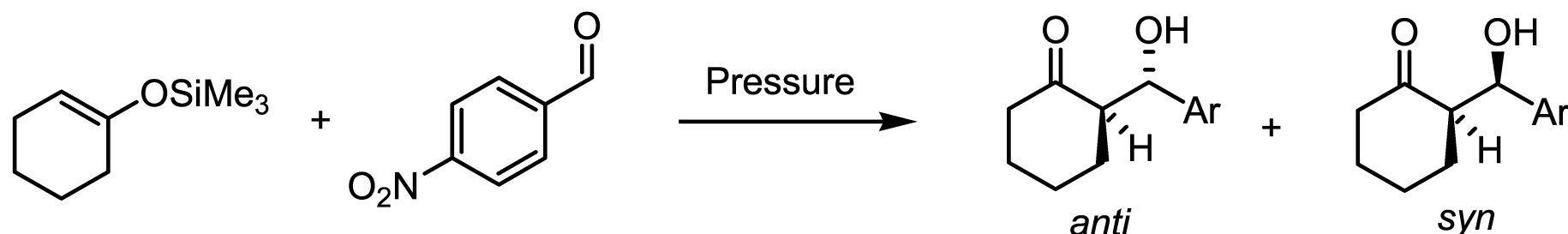
Explain these results with a mechanistic proposal.

Influence of High Pressure on Selectivity

- Thermodynamic control
 - Favorable difference of the reaction volume of the products
- Kinetic control (*nearly all the examples to date*)
 - Formation of isomers via different mechanisms: e.g. concerted vs. radical or ionic cyclization (pressure effect)
 - Favorable difference of activation volumes of the reactions leading to the isomers by the same mechanism (pressure effect) ($\Delta\Delta V^*$)
 - Favorable difference of enthalpy of the reactions leading to the isomers. Improvement of selectivity by performing the reaction at lower temperature (temperature effect, enabled by pressure)

$\Delta\Delta V^*$ ($\text{cm}^3 \text{ mol}^{-1}$)	p (MPa)	1 kbar	5 kbar	10 kbar
				1 GPa
	0.1	100	500	1000
	c_1/c_2	c_1/c_2	c_1/c_2	c_1/c_2
1	1.00	1.04	1.22	1.50
5	1.00	1.22	2.74	7.52
10	1.00	1.50	7.52	56.6

Selectivity: Mukaiyama Type Aldol

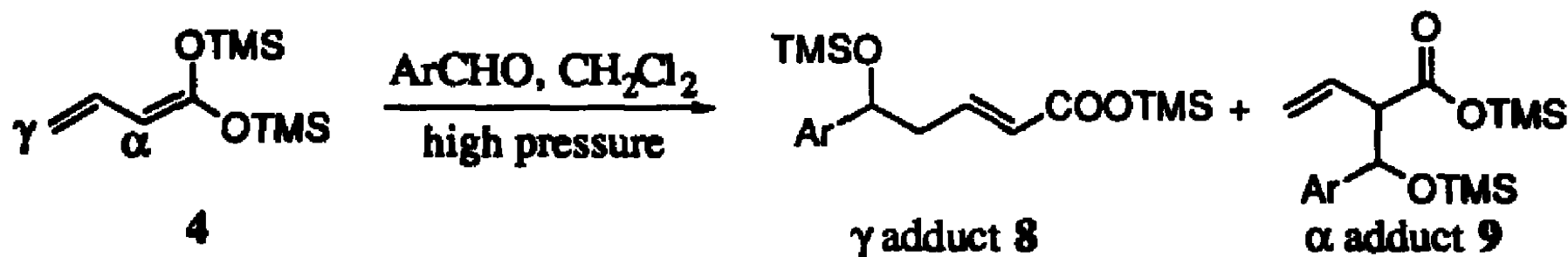


Pressure (MPa)	% syn
300	20
500	31
800	67
1000	76
1200	80

- Ar = *p*-NO₂Ph
- Low conversion at low P
- Low yield for all
- Long reaction times (days)

Proposed change in selectivity is due to switch from chair (low P) to boat (high P) TS – boat must be more compact.

Selectivity: Mukaiyama Type Aldol w/ Dienolate



Entry	Ar	Conditions	γ Adduct 8	: α Adduct 9	Yield %
1	Ph	17 kbar, 65° C, 3 days	25	75	68
2	Ph	12 kbar, 65° C, 3 days	35	65	51
3	Ph	5 kbar, 65° C, 6 days	83	17	57
4	Ph	2 kbar, 65° C, 3 days	88	12	41

TS leading to γ -adduct 8 is less compact than TS leading to α -adduct 9

Selectivity, Mechanism: Cycloheptatriene Reactions

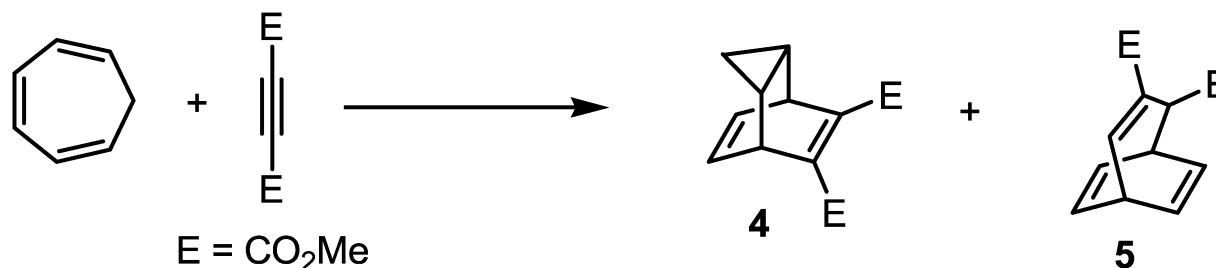


Table I. Pressure Effect on Product Distribution^a

<i>p</i> , MPa	time, h	% 4	% 5
0.1	8-48	68	32
100	6-20	73	27
200	15	78	22
400	1	82	18
400	5	90	10
400	16	90	10
600	5.5	95	5
800	3	97	3
800	15	99	1
900	1	100	0

^a At 80 °C, in CH₂Cl₂ solution.

$$\Delta V_4^* = -33.8 \text{ mL/mol}$$

$$\Delta V_5^* = -28.8 \text{ mL/mol}$$

Predicts 74:26 **4:5** at 800 MPa

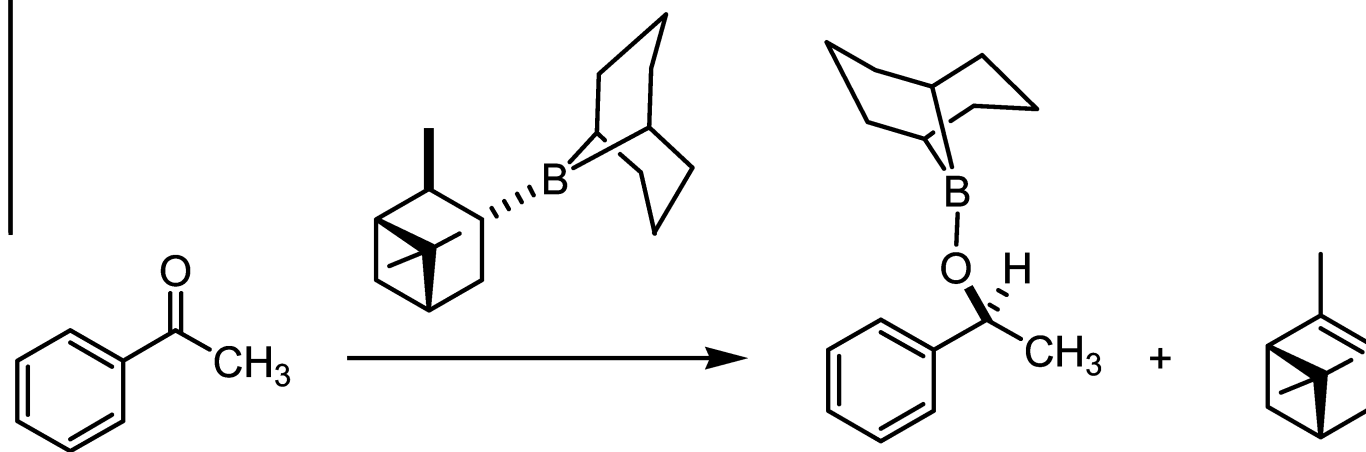
Draw a mechanism for formation of both compounds. Explain the pressure/time effect on product distribution.

M. J. Goldstein, A. H. Gevertz *Tetrahedron Lett.* **1965**, 4413.

G. Jenner, M. Papadopoulos *J. Org. Chem.* **1986**, 51, 585.

"High Pressure Chemistry" **2002**, pp. 246-247.

Selectivity: Alpine-Borane Reduction of Ketones



Pressure accelerates
reaction
AND improves ee%

Explain with a
mechanistic proposal.

Table I. Reductions of Prochiral Ketones with Neat *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane at 6000 atm (92% ee (+)- α -Pinene)

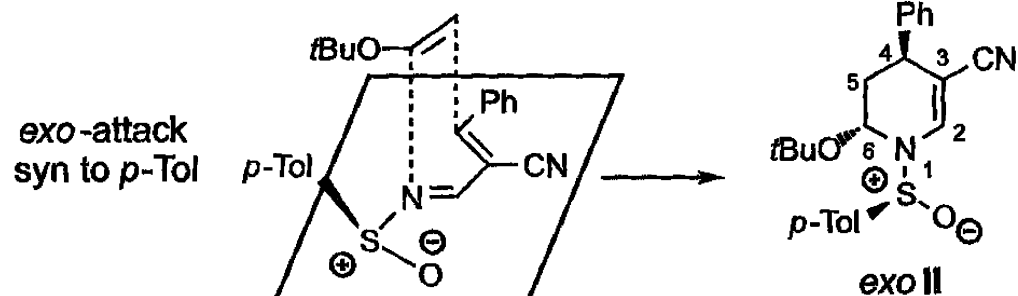
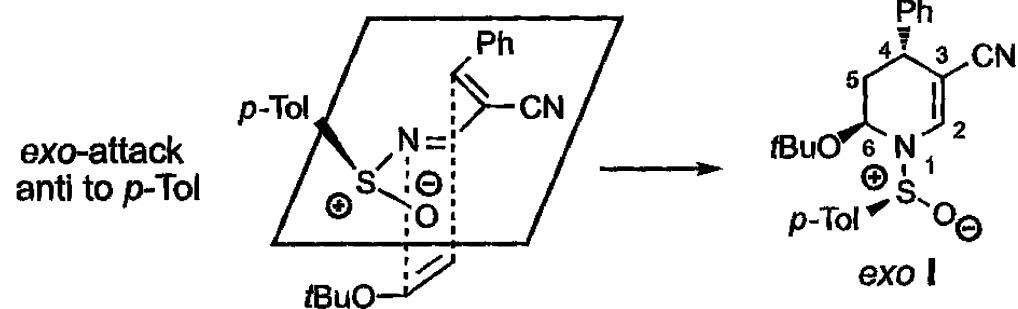
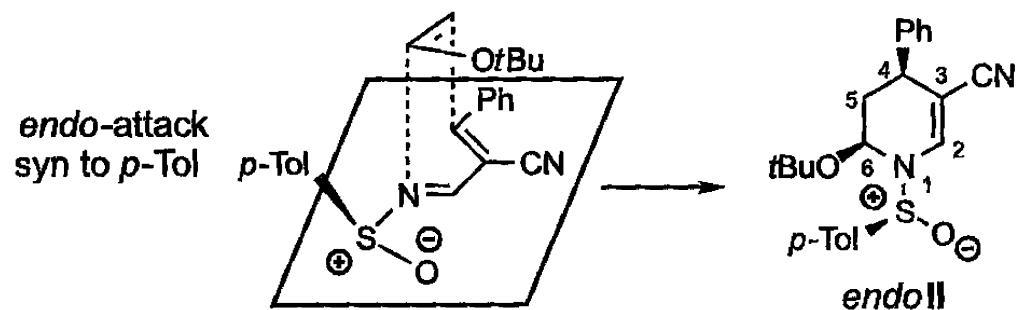
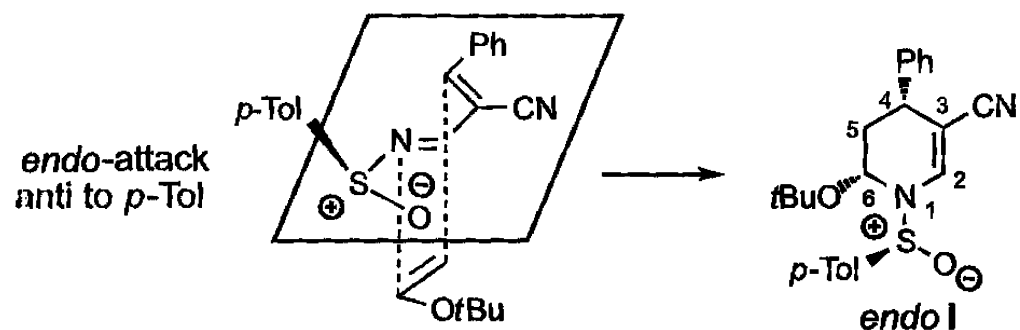
ketone	reaction time, days		%ee ^c			isolated yield	abs config ^e
	6000 atm ^a	1 atm ^b	6000 atm	(corrected ^d)	1 atm		
acetophenone	1	7 ^{4a}	92	(100)	78 ^{4a}	80	<i>S</i>
acetophenone	1		98.4 ^f			83	<i>S</i>
3-acetylpyridine	1.5 ^g	2	92	(100)	90	67	<i>S</i>
2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one	2.5 ^h	NR ⁱ	92	(100)	<i>i</i>		(<i>R</i>) ^j
3-methyl-2-butanone	1	14 ^{4a}	83	(90)	57 ^{4a}	47	<i>S</i>
α -tetralone	3	29	82	(89)	52	43	<i>S</i>
cyclopropyl methyl ketone	5.5	NR ⁱ	69	(75)	<i>i</i>	65	(<i>S</i>) ^j
<i>trans</i> -4-phenyl-3-buten-2-one	<1	3	65	(71)	58		<i>S</i>
2-octanone	<1	7 ^{4a}	58	(63)	44 ^{4a}	63	<i>S</i>

^a Reaction carried to >97% completion. ^b Reaction typically carried to 60–75% completion except as noted in ref 4a.

^c %ee determined by proton chiral shift study at 200 MHz with Eu(hfc)₃. ^d Corrected for 92% ee (+)- α -pinene. ^e Determined by sign of rotation. ^f 98.5% ee (+)- α -pinene was used. ^g 1.0 mL of THF added per 10.0 mmol of borane. ^h Reaction was 83% complete. ⁱ Reaction at 1 atm too slow to be useful. ^j Configuration based on proposed mechanism.

Selectivity: Alpine Borane Reduction- Explanation

Selectivity: [4+2] Cycloaddition of Sulfinimines



<i>p</i> (GPa)	Yield (%)	Ratio of diastereomers <i>endo I</i> : <i>endo II</i> : <i>exo I</i> : <i>exo II</i>
1.1	99	2.77:1.00:0.54:0.31
0.9	87	2.45:1.00:0.50:0.30
0.7	81	2.13:1.00:0.52:0.35
0.5	44	2.21:1.00:0.55:0.37
0.4	24	2.01:1.00:0.52:0.52
0.3	11	2.01:1.00:0.55:0.35
0.2	26 ^a	1.75:1.00:0.50:0.36
1·10 ⁻⁴	4	1.46:1.00:0.50:0.43

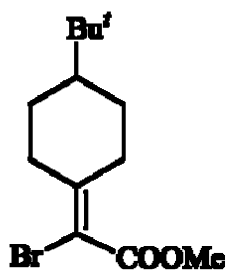
2 days except ^a4 days

$$\Delta\Delta V^* (\text{endo I} - \text{exo II}) = -2.0 \text{ cm}^3 \text{ mol}^{-1}$$

$$\Delta\Delta V^* (\text{endo I} - \text{endo II}) = -1.8 \text{ cm}^3 \text{ mol}^{-1}$$

Pressure has a significant effect on yield. Also, a measureable $\Delta\Delta V$ is observed, but actual influence on selectivity is low.

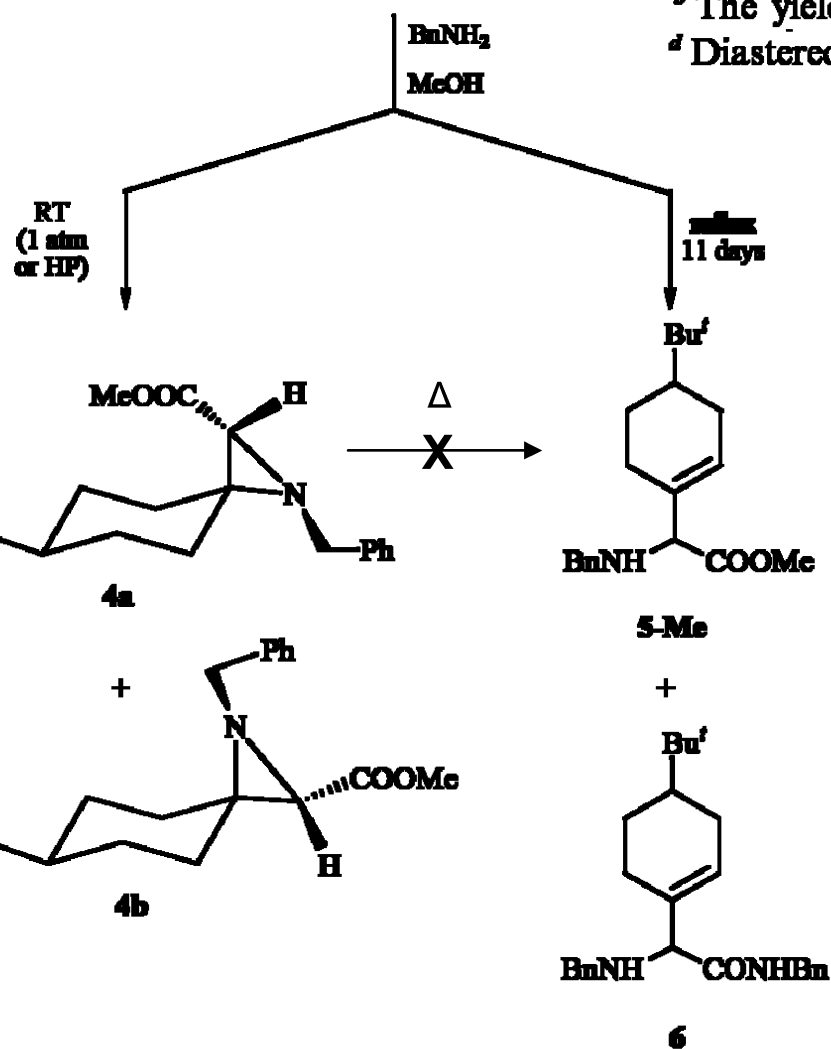
Selectivity: Michael Addition



Reagents		Reaction conditions			Yields (%) ^a	
Ester 3	Amine	Solvent		t/d	4	5
Me	BnNH ₂	MeOH	reflux, <i>P</i> atm	11		34 ^b
Me	BnNH ₂	MeOH	RT, <i>P</i> atm	60	85 ^c	
Me	BnNH ₂	MeOH	RT, 11 kbar	4	83 ^d	

^b The yield of amide 6 is 18%. ^c Diastereomeric ratio 4a:4b = 1.7:1.

^d Diastereomeric ratio 4a:4b = 10:1.

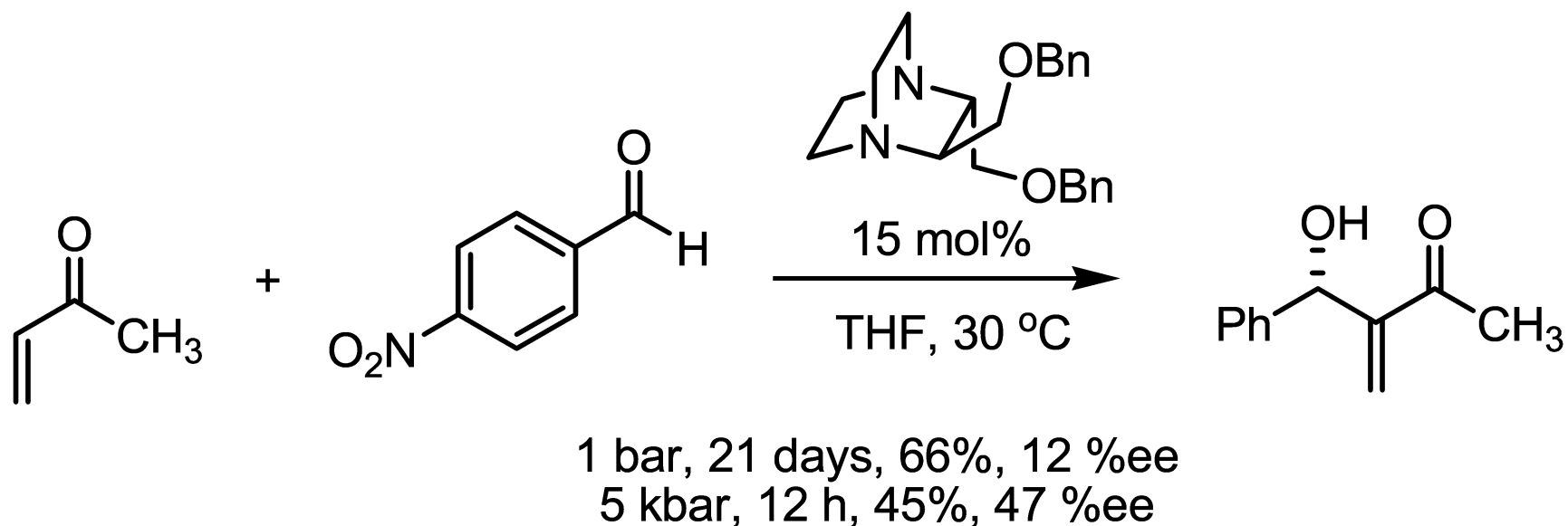
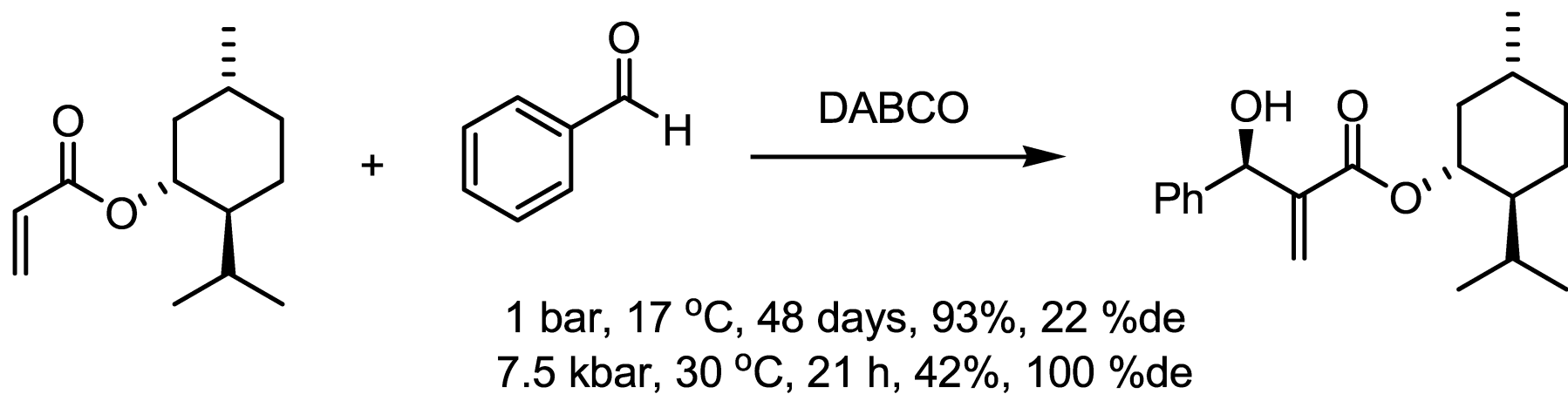


Addition to a β,β -disubstituted (also tetra-substituted double bond) α,β -unsaturated ester is facile under high pressure.

Selectivity increase?

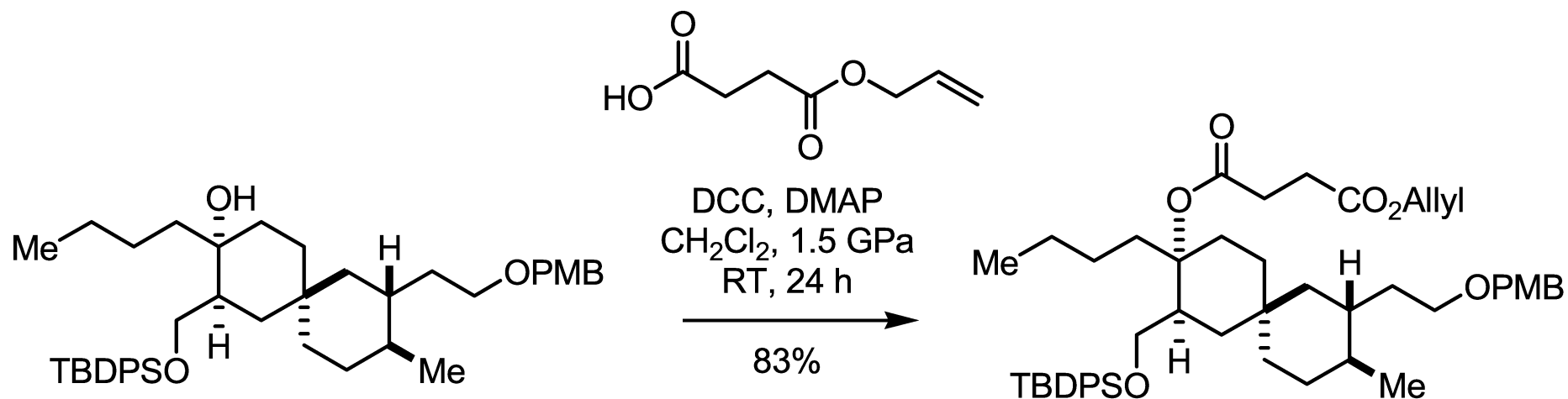
- Either a $\Delta\Delta V^*$ effect – one TS more compact, or perhaps the amine addition becomes irreversible under pressure, placing the reaction under kinetic control under these conditions.

Selectivity: Bayliss-Hillman Reaction

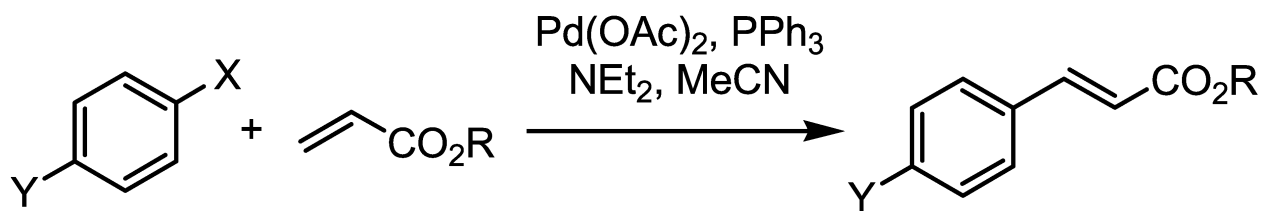


Bayliss-Hillman Reaction shows a very large pressure effect on reaction time and selectivity.

Pressure and Steric Interactions



T. Shimizu, T. Masuda, K. Hiramoto, T. Nakata *Org. Lett.* **2000**, 2, 2153.



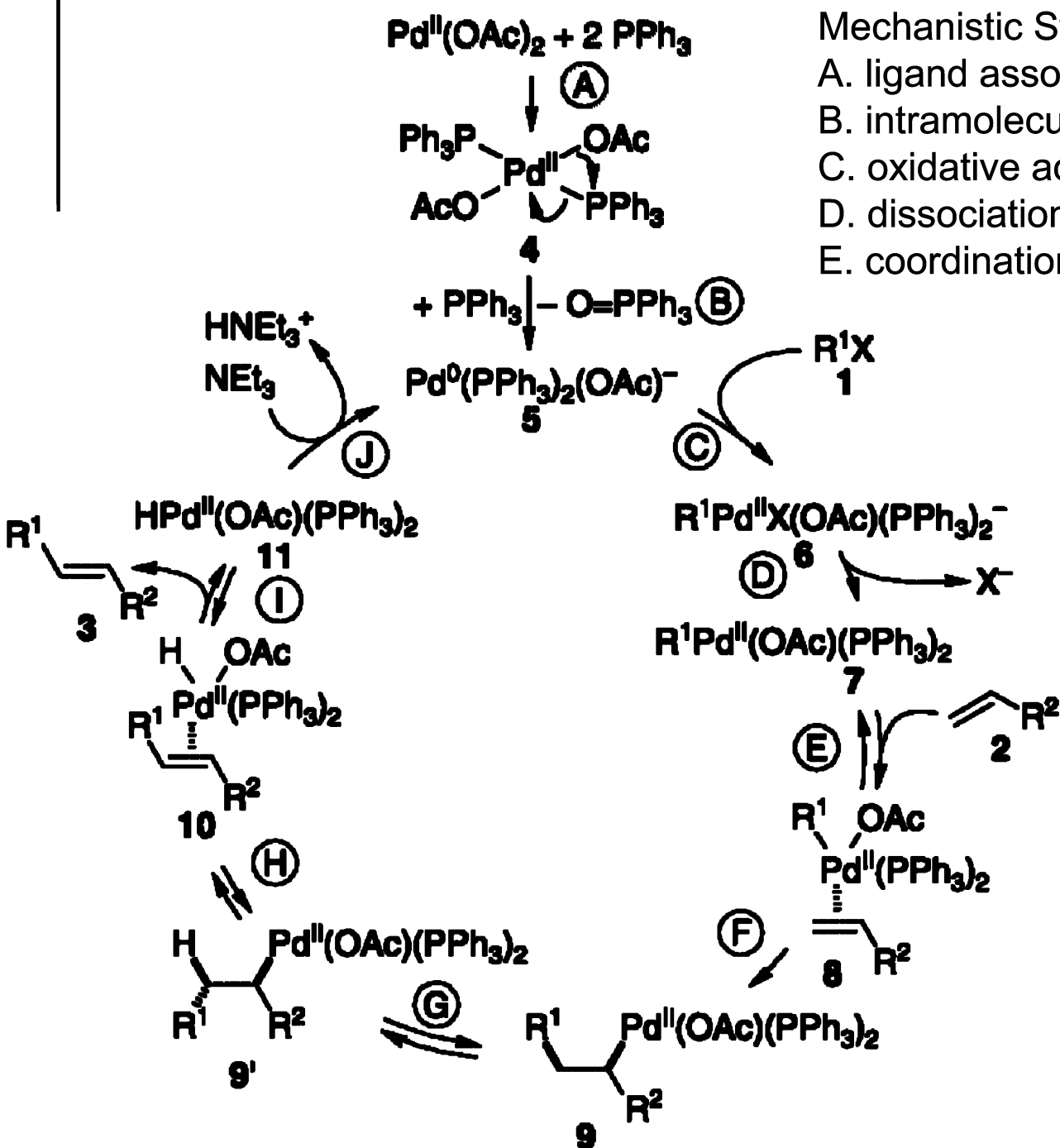
Aryl Halide	Acrylate	ΔV^*
Y = H, X = I	R = Me	-5
Y = H, X = I	R = Et	-7
Y = H, X = I	R = <i>t</i> Bu	-12
Y = NO ₂ , X = I	R = Me	-9
Y = NO ₂ , X = OTf	R = Me	-37

M. Buback, T. Perkovic, S. Redlich, A. de Meijere *Eur. J. Org. Chem.* **2003**, 2375.

Increased steric crowding leads to a decrease in ΔV^* (more negative value)

$$\Delta V^* = \Delta V_s^* + \Delta V_m^* + \Delta V_\sigma^*$$

Mechanistic Complexity: The Heck Reaction



Mechanistic Steps:

A. ligand association

B. intramolecular reduction

C. oxidative addition

D. dissociation of X^-

E. coordination

F. *syn* addition

G. internal rotation

H. *syn* elimination

I. decomplexation

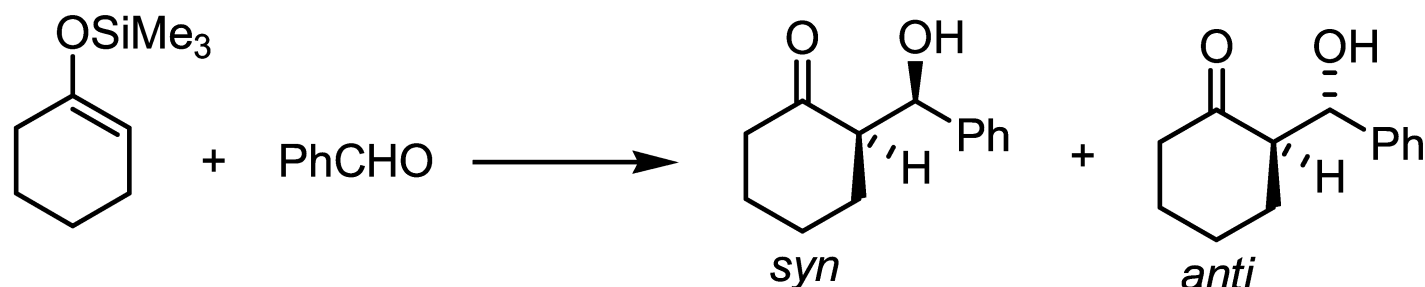
J. reductive elimination

Predict how each step is affected by high pressure.

(+, -, or 0)

Step	ΔV^*	Reason
A		
B		
C		
D		
E		
F		
G		
H		
I		
J		

Relationship Between ΔV and Reactions in H_2O



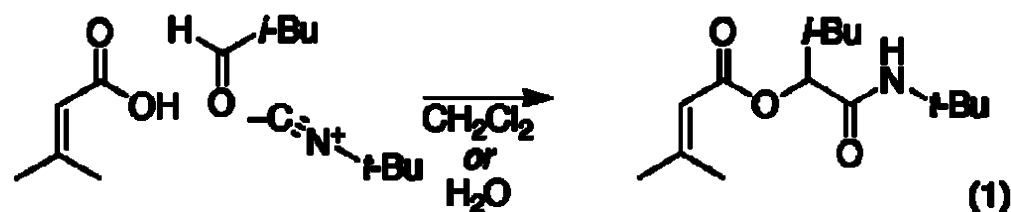
RT, 1 bar, CH_2Cl_2 or CH_3CN , no $TiCl_4$ – No Reaction after 15 days!

entry	1:2	solvent ^d	temp, °C	time	conditions	yields, ^b %	syn:anti ^b	ref
1	1:1	CH_2Cl_2	20	2 h	$TiCl_4$	82	25:75	1
2	1:1	CH_2Cl_2	60	9 days ^c	10 kbars	90	75:25	2
3	1:2	A	20	5 days	ST ^e	45 (43) ^f	74:26	
4	1:2	H_2O	20	5 days	ST	23	85:15	
5	1:2	A	55	2 days	US ^g	68	73:27	
6	1:5	A	55	2 days	US	61	72:28	
7	1:12	A	20	5 days	ST	40	67:33	
8	2:1	A	20	5 days	ST	37	78:22	
9	2:1	A	60	2 days	ST	47	73:27	
10	2:1	A	55	2 days	US	72	74:26	

^a All reactions in this work were carried out under atmospheric pressure at a concentration of 0.4 M of the limiting component. ^b As determined by NMR spectroscopy ($CDCl_3$, 90 MHz) using the following signals of methylene protons: δ 4.83 (d, $J = 9$ Hz, 1 H, anti), 5.40 (d, $J = 2.5$ Hz, 1 H, syn). Compounds 3 and 4 have been found identical in every respect with those prepared under the $TiCl_4$ -catalyzed aldol reaction.¹ ^c It may be significant that the time of reaction in water under an estimated 22 kbars (cohesive energy density of water) is smaller, at least of the same order as that of the reaction conducted under 10 kbars. ^d A refers to a mixture of oxolane–water (1:1). ^e Vigorous magnetic stirring or violent shaking. ^f Isolated yield after silica gel chromatography (1:1 ether–hexane). ^g In a Bransonic 220, 50-kHz cleaning bath.

Reactions that have $\Delta V^* < 0$ also seem to be accelerated in water.

Multicomponent Reactions in Water



(Ugi reaction also examined)

Table 1. Passerini Reaction (eq 1) under Various Reaction Conditions

solvent	time (h)	temp (°C)	conversion (%)	yield (%)	rate (M ⁻² s ⁻¹) ^a
CH₂Cl₂	18	25	50	45	0.01
H₂O	3.5	25	100	95	0.18
2.5 M aq LiCl	0.3	25	100	95	ND
1.0 M aq LiCl	0.8	25	100	95	2.86
1.0 M aq glucose	0.8	25	100	95	ND
0.5 M aq glucose	2	25	100	94	1.29

18 fold increase in going from CH₂Cl₂ to H₂O

High LiCl concentrations: reaction too fast to measure!

Also MeOH (no reaction) and formamide (15% conversion, 24 h)

What is responsible for the acceleration?

- Direct involvement of water in mechanism?
 - probably not, no reaction in MeOH, which should behave similarly
 - Dielectric constant?
 - no, formamide has a higher dielectric constant than water (but lower cohesive energy density)
 - Hydrophobic effect? (entropy-driven aggregation of two nonpolar molecules in water)
 - maybe, scales with solvent-accessible surface area in the TS
 - Cohesive energy density of water? (high energy needed to create a cavity in water)
 - maybe, scales with the volume of the TS, so it's difficult to distinguish w/ hydrophobic effects
- Probably a combination of hydrophobic effects and cohesive energy density effects.

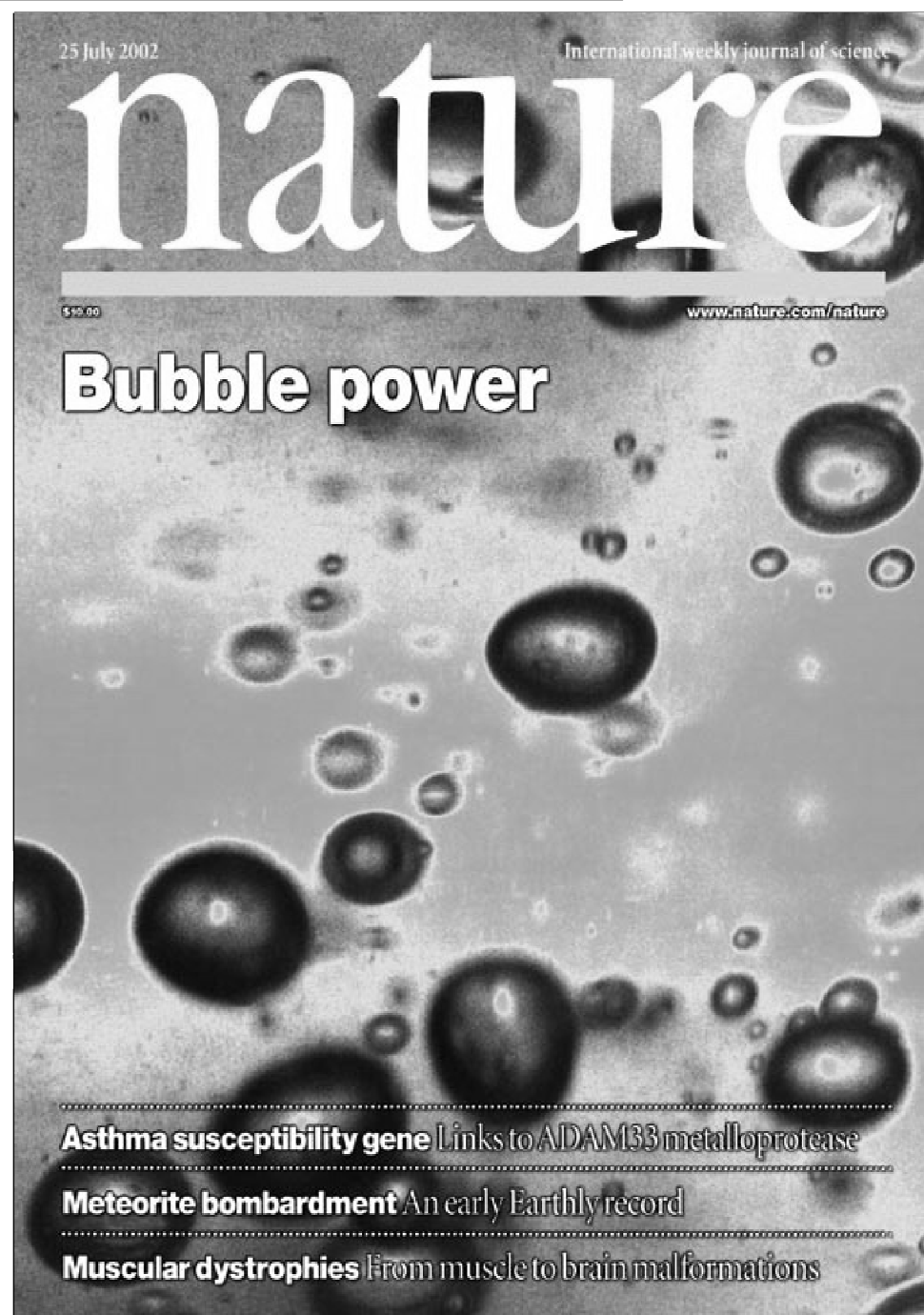
Sonochemistry for High Pressure Organic Reactions?

- Ultrasound – acoustic waves w/ frequencies from 20 – 100 MHz
- Produces acoustic cavitation
 - Cavitation collapse can produce local “hot spots” with high temperatures and pressures up to 1 kbar
- Some reactions with negative activation volumes have been favorably affected by ultrasound
 - cycloadditions
 - aldol reaction
- More information:

“Sonochemistry – The Use of Ultrasonic Waves in Synthetic Organic Chemistry” C. Einhorn, J. Einhorn, J.-L. Luche
Synthesis **1989**, 787-813.

“Comparative Activation Modes in Organic Synthesis. The Specific Role of High Pressure” G. Jenner
Tetrahedron **2002**, 58, 5185-5202.

<http://www.scs.uiuc.edu/suslick/> (Suslick group web pages)



Conclusions

- Reactions with $\Delta V^* < 0$ are accelerated under high pressure conditions
- Bond forming reactions, associative processes, and reactions with TS's with charge buildup generally show a $\Delta V^* < 0$
- Not much information has been reported on the effect of high pressure on systems at equilibrium
- 5-20 kbar is generally needed for a synthetically useful pressure effect
- High pressure can provide milder reaction conditions to allow for isolation of sensitive intermediates
- High pressure studies can help to delineate mechanism
- High pressure can lead to changes in mechanism
- High pressure can have a beneficial influence on selectivity (but usually low without a mechanism change)
- High pressure can accelerate sterically congested reactions
- Reactions with $\Delta V^* < 0$ are often accelerated in water at atmospheric pressure

Key References

Review Articles

- “Activation and Reaction Volumes in Solution” T. Asano, W. J. le Noble *Chem. Rev.* **1978**, 78, 407.
- “Organic Synthesis under High Pressure; I” K. Matsumoto, A. Sera, T. Uchida *Synthesis* **1985**, 1.
- “Organic Synthesis under High Pressure; II” K. Matsumoto, A. Sera *Synthesis* **1985**, 999.
- “The Pressure Effect on Strained Transition States” G. Jenner *J. Chem. Soc., Faraday Trans 1*, **1985**, 81, 2437.
- “Activation and Reaction Volumes in Solution. 2” R. Van Eldik, T. Asano, W. J. le Noble *Chem. Rev.* **1989**, 89, 549.
- “Sonochemistry – The Use of Ultrasonic Waves in Synthetic Organic Chemistry” Luche *et al. Synthesis* **1989**, 787.
- “Hydrophobic Effects. Opinions and Facts” W. Blokzijl, J. B. F. N. Engberts *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1545.
- “Pressure Dependence of Rate and Equilibrium Constants in Solution. A Guide to Analytical Equations” C. A. N. Viana, J. C. R. Reis *Pure & Appl. Chem.* **1996**, 68, 1541.
- “High Pressure and Selectivity in Organic Reactions” G. Jenner *Tetrahedron* **1997**, 53, 2669.
- “A Few Questions on the Sonochemistry of Solutions” J. L. Luche *Ultrasonics Sonochemistry* **1997**, 4, 211.
- “Activation and Reaction Volumes in Solution. 3” A Drljaca, C. D. Hubbard, R. van Elkik, T. Asano, M. V. Basilevsky, W. J. le Noble *Chem. Rev.* **1998**, 98, 2167.
- “Comparative Activation Modes in Organic Synthesis. The Specific Role of High Pressure” G. Jenner *Tetrahedron* **2002**, 58, 5185.
- “High-Pressure Mechanistic Delineation Based on Activation Volumes” G. Jenner *J. Phys. Org. Chem.* **2002**, 15, 1.
- “Role of the Medium in High Pressure Organic Reactions. A Review” G. Jenner *Mini-Reviews in Org. Chem.* **2004**, 1, 9.
- “Correlation Between Pressure and Steric Interactions in Organic Reactions” G. Jenner *Tetrahedron* **2005**, 61, 3621.

Books:

- “Organic Synthesis at High Pressure” Ed. by K. Matsumoto, R. M. Acheson, ©1991 by John Wiley & Sons, Inc., New York.
- “High-Pressure Techniques in Chemistry and Physics – A Practical Approach” Ed. by W. B. Holzapfel, N. S. Isaacs, Series Ed. by L. M. Harwood, C. J. Moody, ©1997 by Oxford University Press, New York.
- “Sonochemistry and Sonoluminescence” Ed. by L. A. Crum, T. J. Mason, J. L. Reisse, K. S. Suslick, ©1999 by Kluwer Academic Publishers, The Netherlands.
- “High Pressure Chemistry – Synthetic, Mechanistic, and Supercritical Applications” Ed. by R. van Eldik, F.-G. Klärner, ©2002 by Wiley-VCH, Germany.

Perhaps of Interest:

- “High Pressure and the Origin of Life” Hazen, Bector, Brandes, Cody, Hemley, Sharma, and Yoder Jr *J. Physics: Condensed Matter* **2002**, 14, 11489.