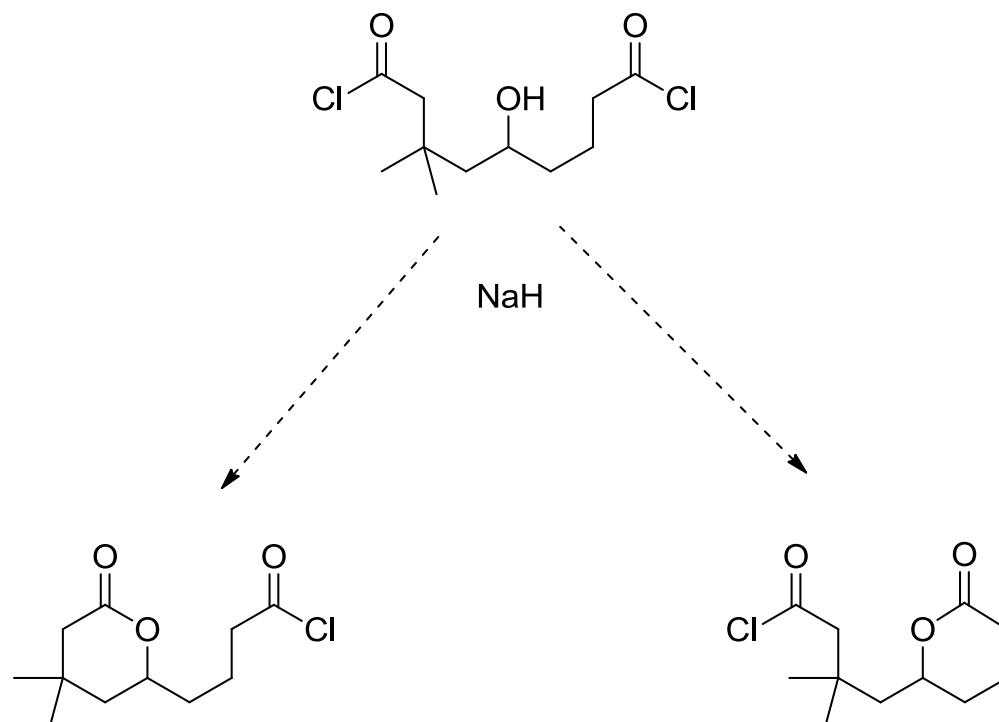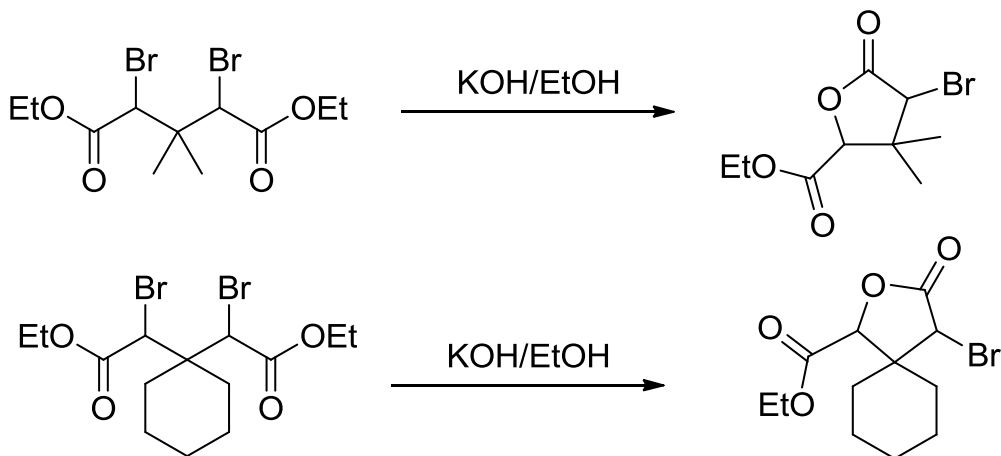# The Thorpe-Ingold Effect (*Gem*-dimethyl Effect)

Daniel Tao
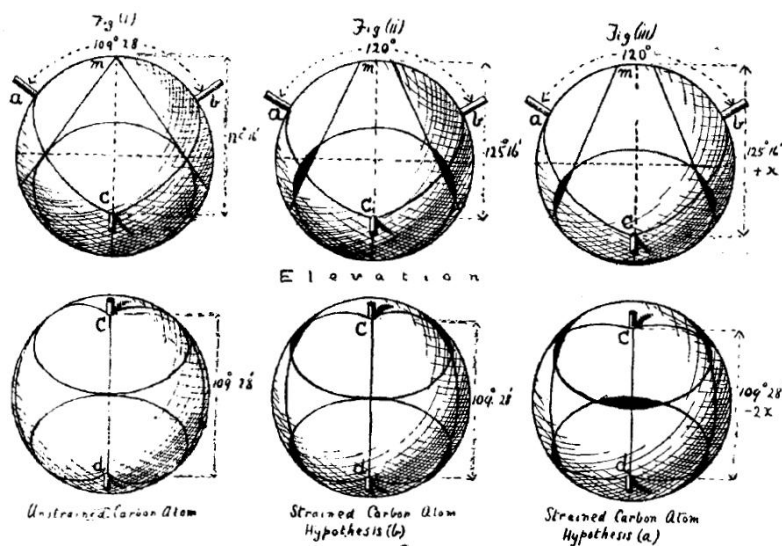
Overman Group Meeting

4/30/12

Question: What would be the major product in this cyclization?
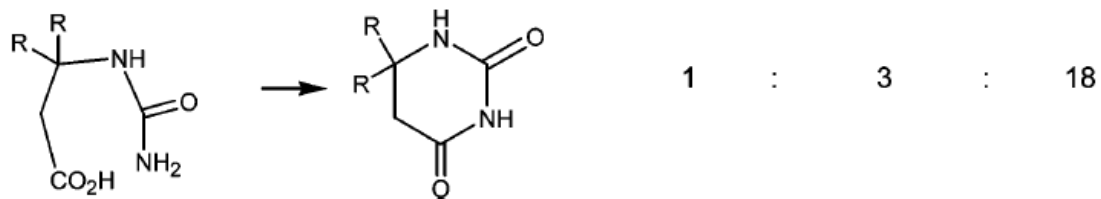
A Surprising Discovery in 1915

•Thorpe, Ingold, and Beesley noticed that cyclizations with quaternary carbons were faster than other substrates

•Their calculations estimated that the bond angle at strained carbon atoms was 109.5° while methylene's was 112.2 °

•The paper concluded that this decreased bond angle forces a more suggestive positioning for ring formation

Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*,1080–1106.

Examples of the *Gem*-Dimethyl Effect

Kaneti, J.; Kirby, A.J.; Koedjikov, A.H.; Pojarlieff, I.G. *Org. Biomol. Chem.*, **2004**, *2*, 1098–1103.
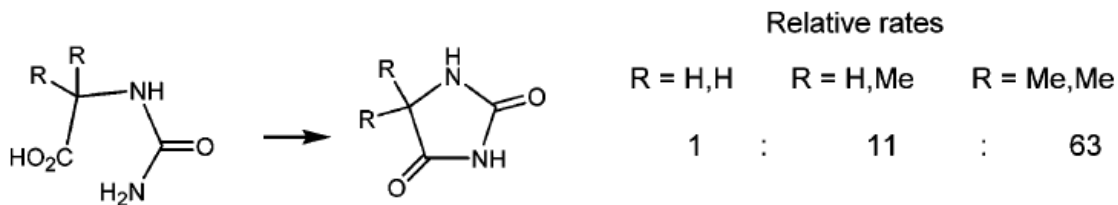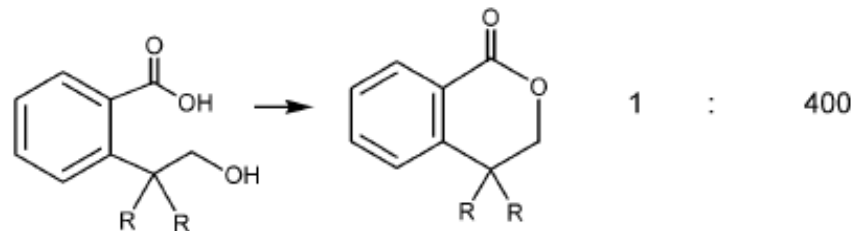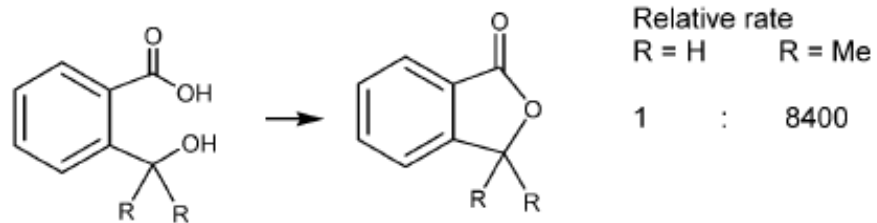
Looking for a Better Explanation

• "While the fact that alkyl substitution tends to promote the rate of formation of a cyclic system from its noncylic analog... has been recognized for nearly half a century, no convincing explanation has been forthcoming."
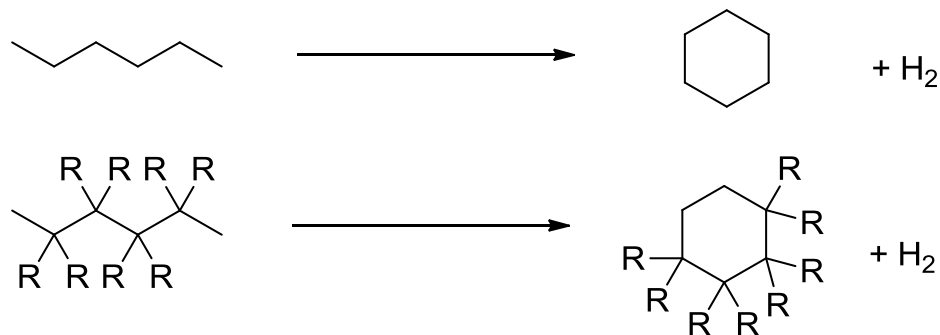
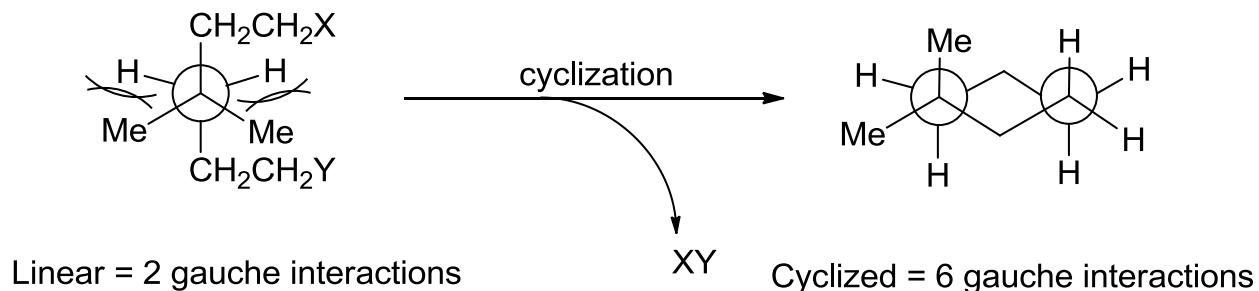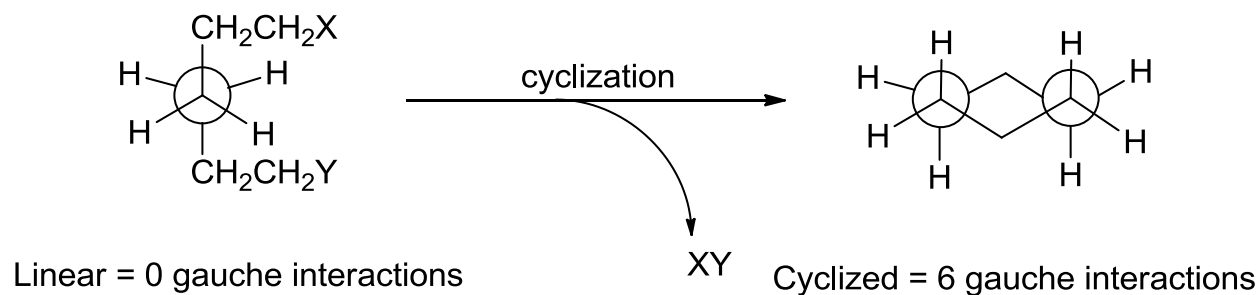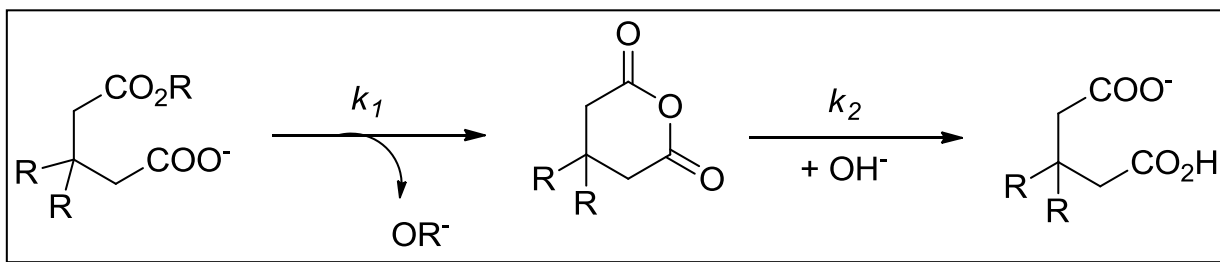-Norman Allinger, 1960

Hexane	σ_H	σ_C	Optical Isomers H	Optical Isomers C	$-\Delta H$ Calcd.	$-\Delta H$ Found	ΔS Calcd.	ΔS Found	$-\Delta F$ Calcd.	$-\Delta F$ Found
n	2	6	1	1	0.0	0.0	0.0	0.0	0.0	0.0
2-CH₃	1	1	1	1	0.8	0.9	3.4	3.3	1.8	1.9
3-CH₃	1	1	2	1	1.6	1.6	2.0	2.2	2.2	2.2
2,2-(CH₃)₂	3	1	1	1	0.0	0.1	6.8	5.7	2.0	1.8
2,3-(CH₃)₂ᵃ	1	2	2	2	1.6	2.4	3.2	4.1	2.6	3.6
2,3-(CH₃)₂ᵇ	1	1	2	2	0.0	0.6	4.6	5.0	1.4	2.0
2,4-(CH₃)₂ᵃ	1	1	2	2	0.8	0.3	4.6	5.0	2.2	1.8
2,4-(CH₃)₂ᵇ	1	1	2	1	2.4	2.3	3.2	3.6	3.4	3.3
2,5-(CH₃)₂ᵃ	2	2	1	1	1.6	1.4	4.6	3.8	3.0	2.6
2,5-(CH₃)₂ᵇ	2	1	1	1	0.0	−0.5	3.2	5.2	1.0	1.1
3,3-(CH₃)₂	1	1	1	1	1.6	1.2	4.6	4.1	3.0	2.4
3,4-(CH₃)₂ᵃ,ᶜ	2	2	2	2	3.2	2.6	4.6ᶜ	3.0	4.2	3.6
3,4-(CH₃)₂ᵇ,ᶜ	1	1	1	2	0.8	0.8	6.0ᶜ	3.9	2.2	2.0
2-C₂H₅	1	1	2	2	0.8	0.8	3.4	2.7	1.8	1.6
3-C₂H₅	1	1	1	2	1.6	1.2	4.8	3.5	3.0	2.2

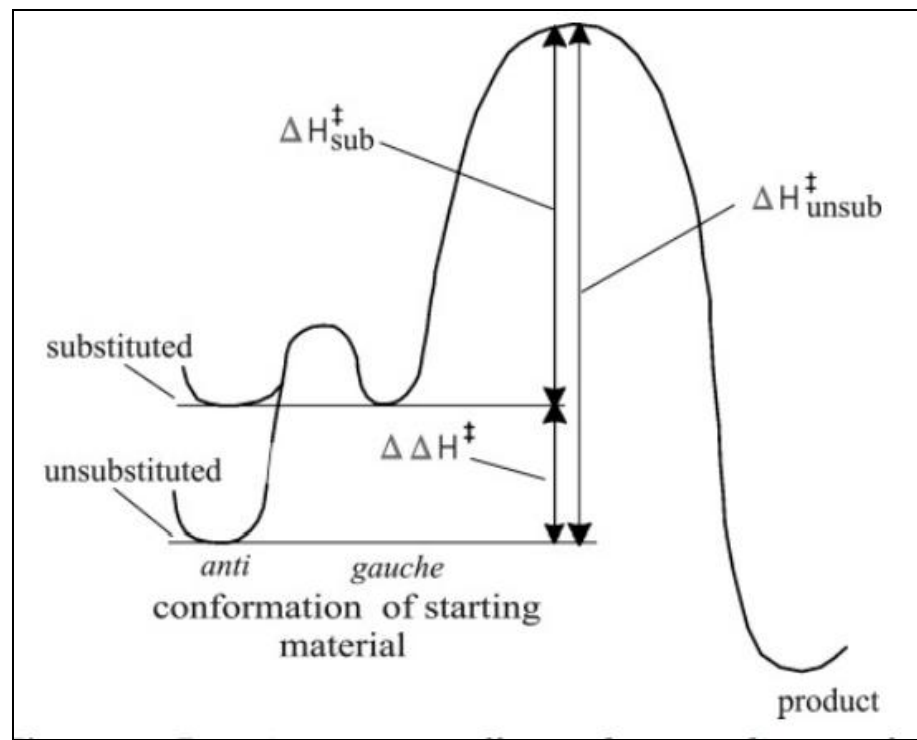Allinger, N.L.; Zalkow, V. *J. Org. Chem.*, **1960**, *25*, 701–704.
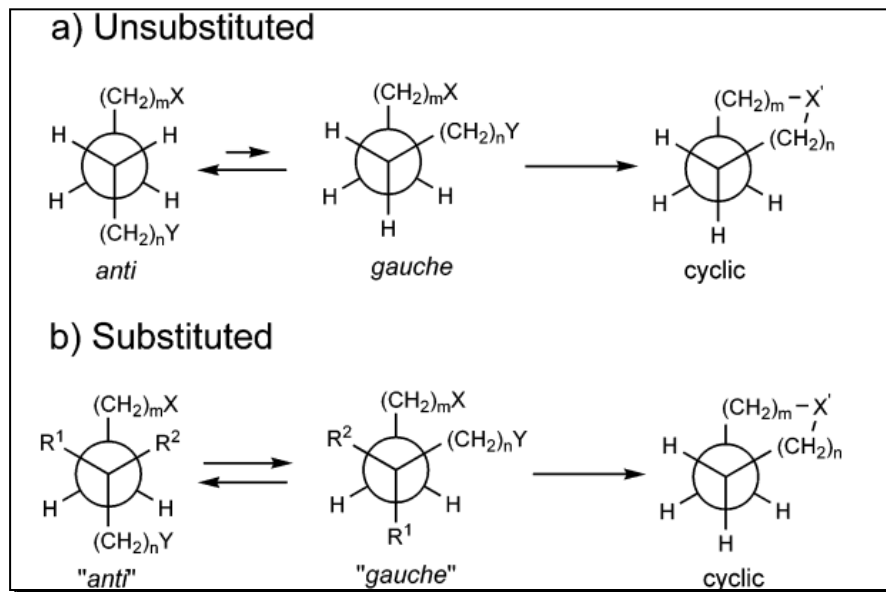
Looking for a Better Explanation

• This study concluded that gauche interactions play a key role in increasing rate of alkyl chain cyclization

Linear = 0 gauche interactions   Cyclized = 6 gauche interactions

Linear = 2 gauche interactions   Cyclized = 6 gauche interactions

Allinger, N.L.; Zalkow, V. *J. Org. Chem.*, **1960**, *25*, 701–704.

Looking for a Better Explanation

• In the same year, Bruce and Pandit founded the "reactive rotamer" hypothesis. When R = Me, k_1 for ring-closing increased while k_2 for hydrolytic ring-opening decreased,

Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.
Jung, M.E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
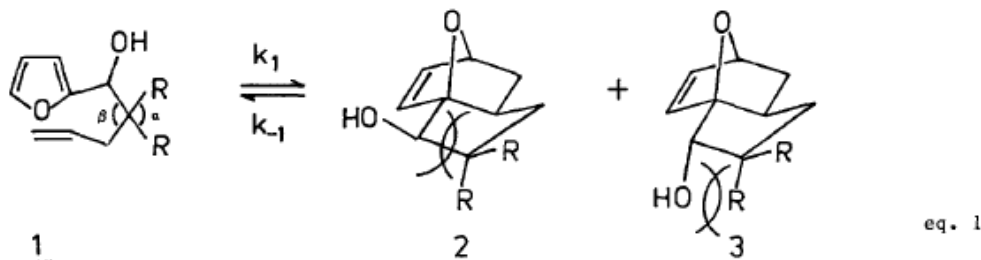
Disproving Thorpe-Ingold Angle Effect

Table I. Substituent Effects on Rates and Equilibria of Intramolecular Diels-Alder Reactions

	R	$k_1 \times 10^6 s^{-1}$ [a]	rel. rate	$K^b_{eq.}$	$t_{1/2}(h)$	%yield
A	H	--	--	no reaction	--	
B	$-CH_3$	--	--	<0.05	--	<5
C	$-CH_2CH_2$ CH_2 $-CH_2CH_2$	1.46	1	0.9	131	47
D	$-CH_2-CH_2CH_3$	2.73	1.8	1.4	71	58
E	$-SCH_2$ CH_2 $-SCH_2$	5.95	4.1	3.2	32	76
F	$-SCH_2CH_3$	6.94	4.8	5.7	28	85
G	$-OCH_2CH_3$	14.3	9.8	4.7	13	82

• Sternbach and Rosanna looked a variety of substituents to increase the rate of an intramolecular Diels-Alder

• Thioacetal 1E characterized by crystallography to show bond angle at 111.7°

• First data correlating a larger bond angle with increased reactivity in *gem*-dimethyl system, disproving the initial Thorpe-Ingold hypothesis

Sternbach, D.D.; Rossana, D.M. *Tetrahedron Lett.* **1988**, *29*, 2429.

Disproving Reactive Rotamer Hypothesis

• Parrill and Dolata took a detailed look at these intramolecular Diels-Alder studies with a conformational search program, WIZARD


• The program calculated the percentages of reactive rotamers based on the energies from the substituents

• They found no consistent correlation between the reactive rotamer population and rate

Parrill, A.L.; Dolata, D.P. *Tetrahedron Lett.* **1994**, *35*, 7319–7322.
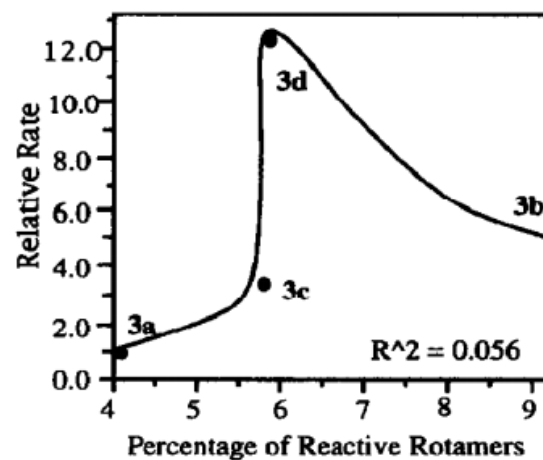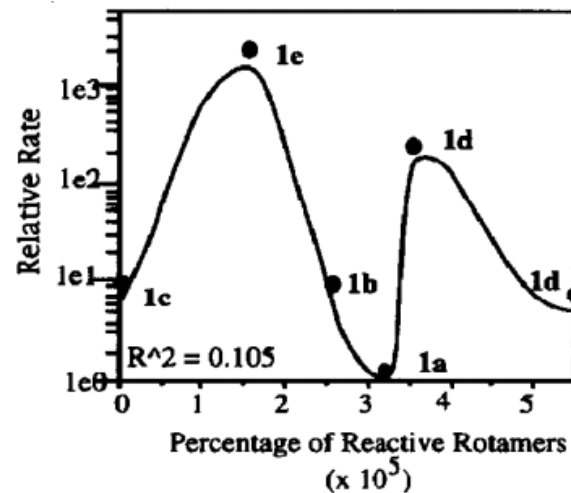
What explanation is left to believe in?

• The same group plotted the $\Delta H^{\ddagger}$ as a function of rate, finding a very consistent pattern
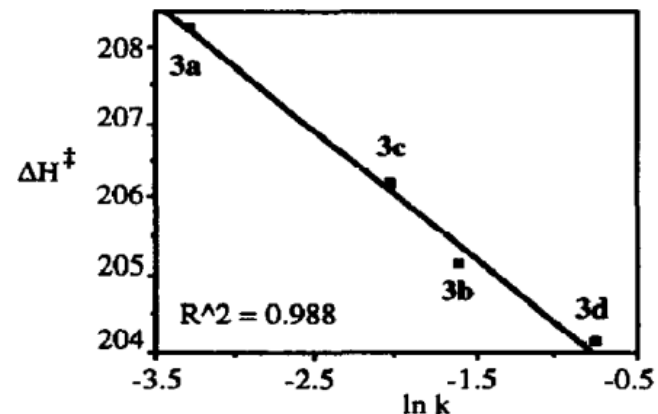
• In 2005, calculations run by Ringer and Mager suggested that dimethyl-substituted cyclobutane has 8 kcal/mol less ring strain than cyclobutane
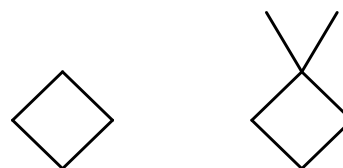
• In response to this publication, Bachrach commented, "There is no enthalpic stabilization, by this we mean no reduction in ring strain energy, afforded to rings by *gem*-substitution."
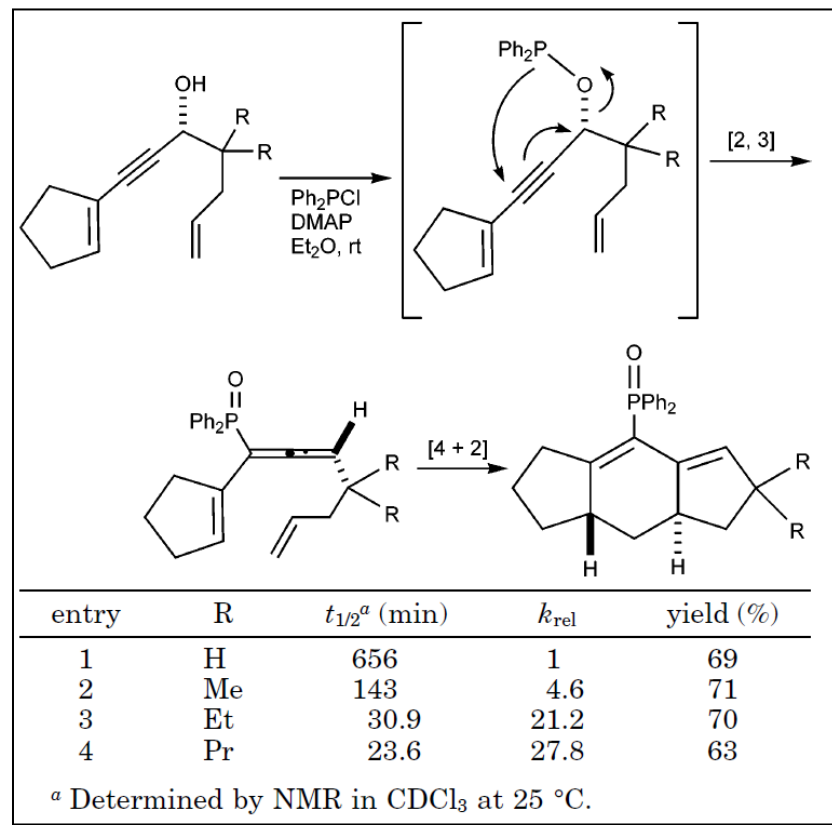
Parrill, A.L.; Dolata, D.P. *Tetrahedron Lett.* **1994**, *35*, 7319–7322.
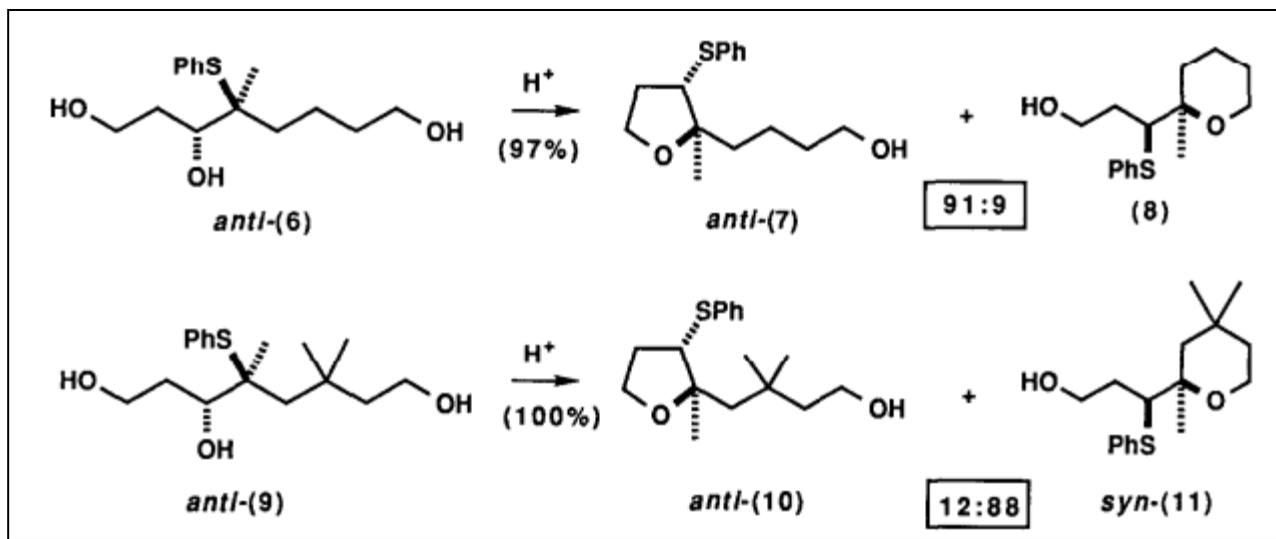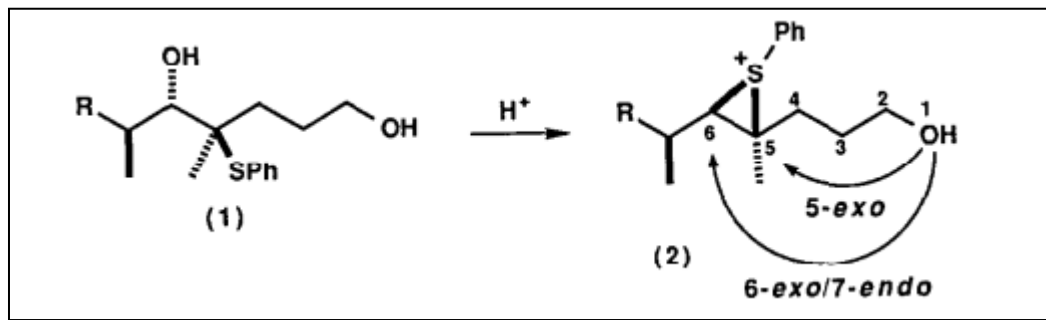Ringer, A.L.; Magers, D.H. *J. Org. Chem.* **2007**, *72*, 2533–2537.
Bachrach, S.M. *J. Org. Chem.* **2008**, *73*, 2466–2468
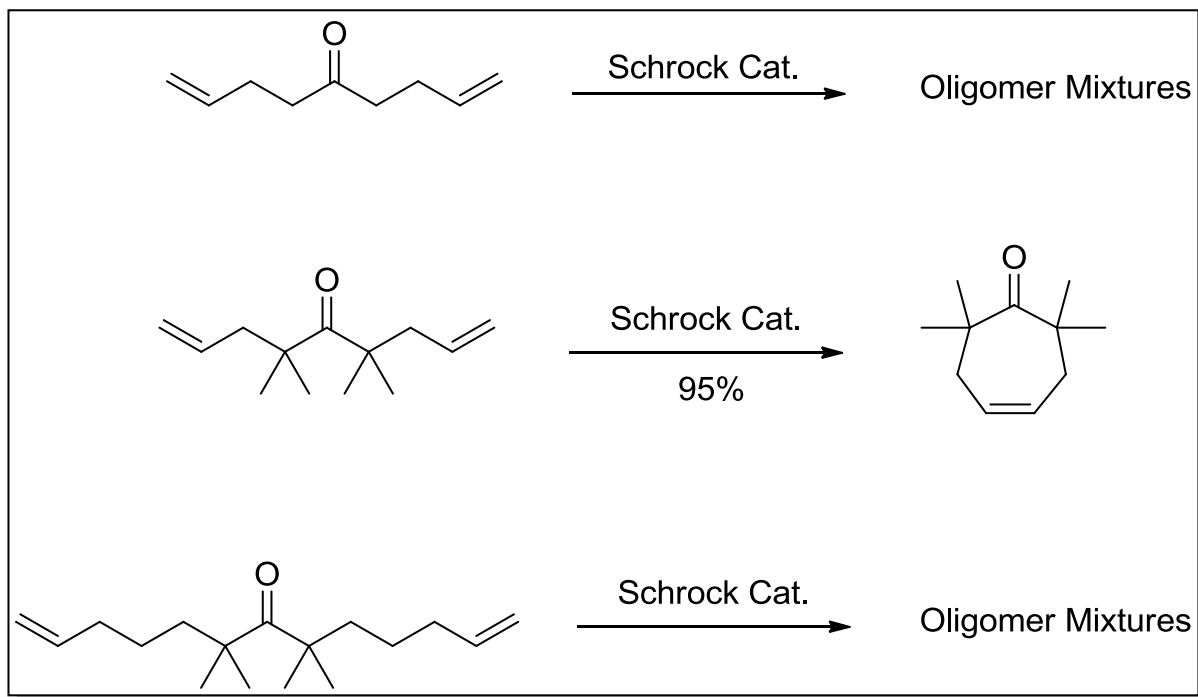
Applications in Synthesis

gem-substituted substrate	ring size	$k_{intra}^{gem}/k_{intra}$
$Br(CH_2)_2CCH_2CO_2^-$ (with two CH_3)	6	38.5
$Br(CH_2)_5CCH_2CO_2^-$ (with two CH_3)	9	6.62
$Br(CH_2)_6CCH_2CO_2^-$ (with two CH_3)	10	1.13
$Br(CH_2)_7CCH_2CO_2^-$ (with two CH_3)	11	0.61
$Br(CH_2)_6C(CH_2)_7CO_2^-$ (with two CH_3)	16	1.22

entry	R	$t_{1/2}^a$ (min)	k_{rel}	yield (%)
1	H	656	1	69
2	Me	143	4.6	71
3	Et	30.9	21.2	70
4	Pr	23.6	27.8	63

^{a} Determined by NMR in CDCl$_3$ at 25 °C.

Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1980**, *14*, 102–109.
Curtin, M.L.; Okamura, W.H. *J. Org. Chem.* **1990**, *55*, 5278–5287.

Applications in Synthesis

McIntyre, S.; Sansbury, F.H.; Warren, S. *Tetrahedron Lett.* **1991**, *32*, 5409–5412

Applications in Ring-Closing Metathesis

Forbes, M.D. *et al. J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.

Applications in Medicinal Chemistry
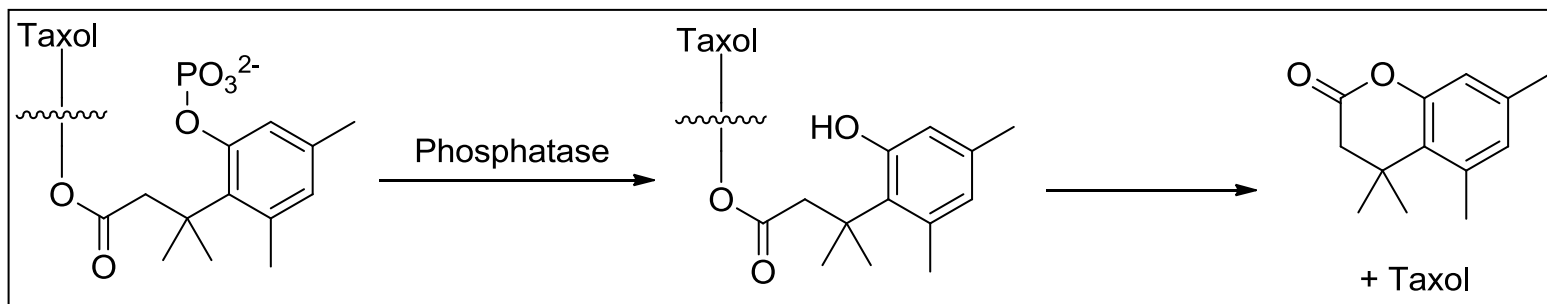
• "Pro drugs" which deliver hydrophobic molecules into the system with hydrophilic linkers which can be leaved

• Improved pharmacokinetic or biological activity in certain cases

Ueda, Y. *et al. Bioorg.Med. Chem. Lett.* **1995**, *5*, 247–252.
Jung, M.E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.