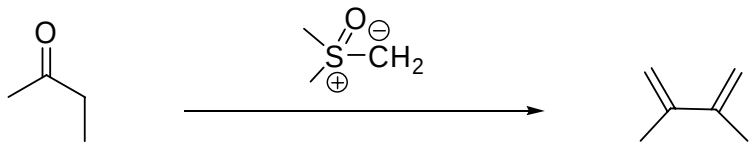
Beyond Corey Reaction:

Direct Diolefination of Ketones with Sulfur Ylides

Dr. Katerina Butova

Giessen 17.03.06

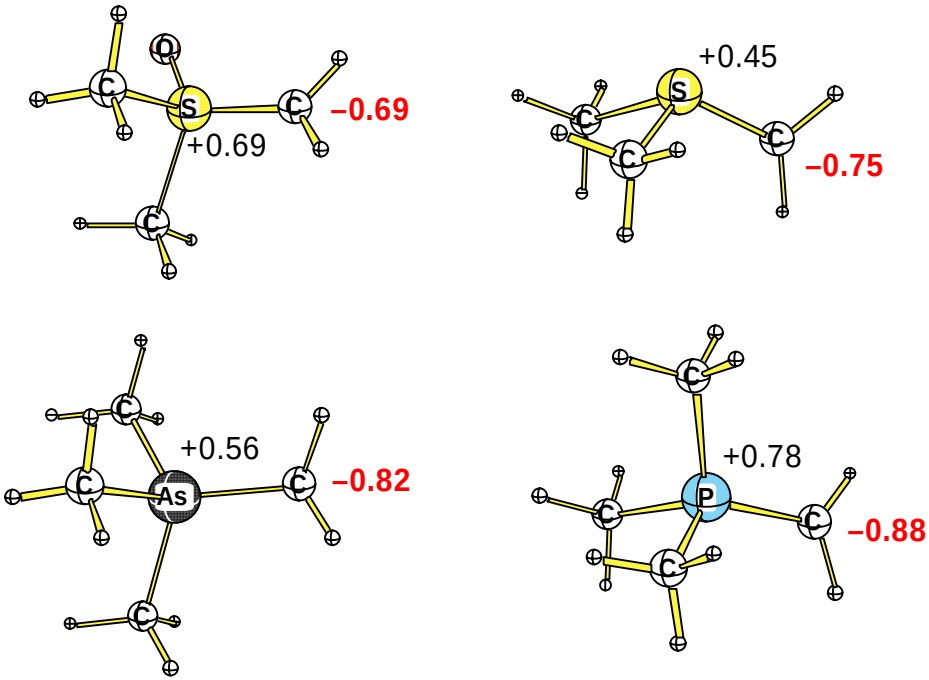
YLIDES: ELEKTRONIC STRUCTURE



1 **2**

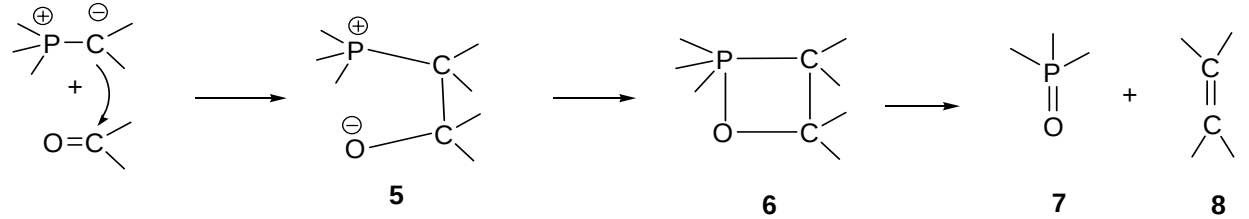
3 ylide ⇌ **4** yline

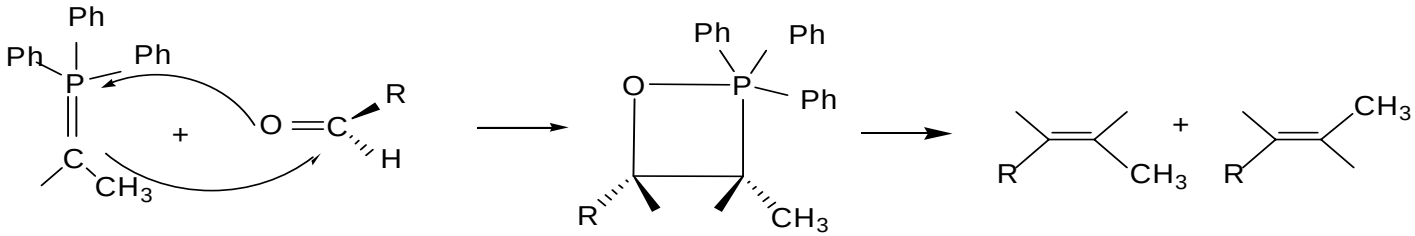
X : P , S, As, N

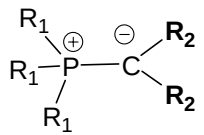


NBO charges at B3LYP/6-31+G*

Wittig reaction







nonstabilized ylide: **R_1** = Ph; **R_2** = H, Alk

stabilized ylide: **R_1** = Ph or Alk; **R_2** = CHO, COR, CO_2R, CN, SO_2R

E.Vedejs,K.A.Snoble, J.Am.Chem.Soc, 1973, 95, 5778

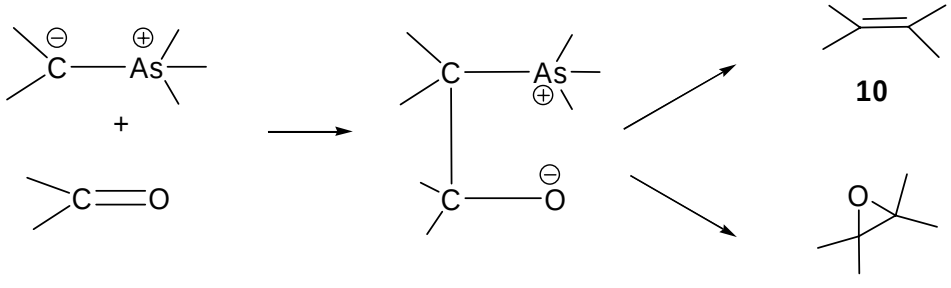
Edwin Vedejs, J.Org.Chem., 2004, 69, 5159-5167

B.E.Maryanoff, A.B.Reitz, B.A. Duhl-Emswiler, J.Am.Chem.Soc.,107,217, 1985

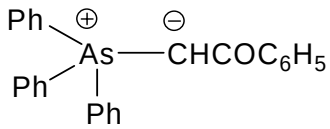
F.Volatron and O.Eisenstein, J.Am.Chem.Soc.,1984, 106, 6117-6119

F.Volatron and O.Eisenstein, J.Am.Chem. Soc. 1987, 109. 14-21

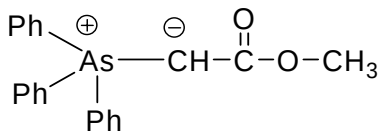
Arsonium ylides



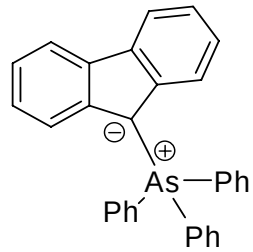
9 **10** **11**



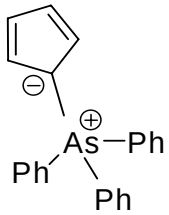
12



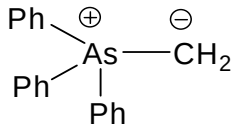
13



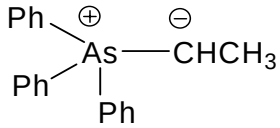
14



15



16

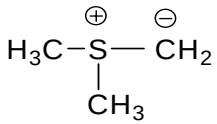


17

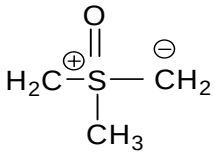
B.Malcolm C.Henry and George Wittig, J.Am.Chem.Soc.,82, 563, 1960

William Jonson and Hans Schubert, J.Org.Chem., Vol 35, pp.2678, 1970

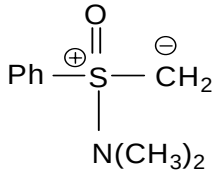
COREY REAGENTS



18

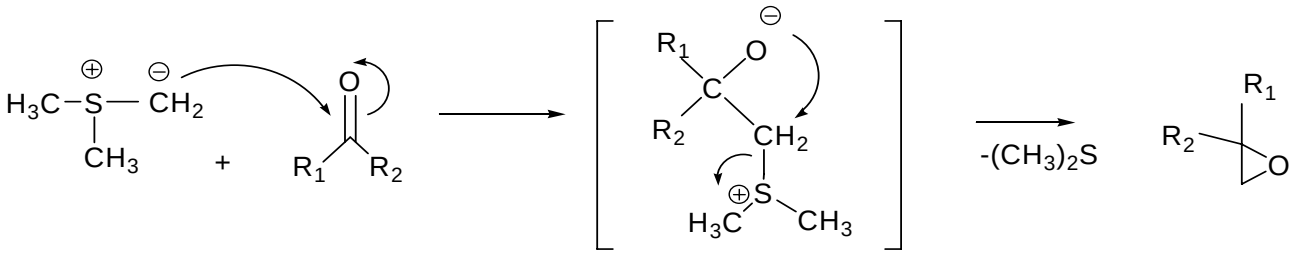


19

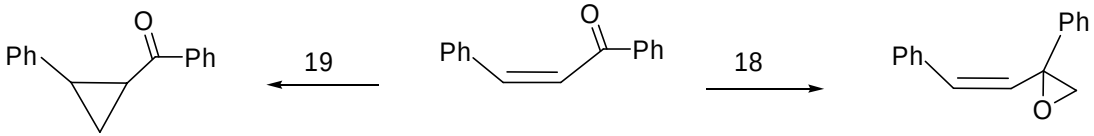


20

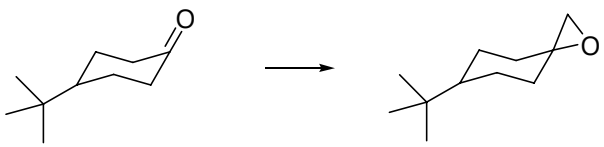
The mechanism of the Corey - Chaykovsky reaction:



21 **22**



25 95% **24** **26** 87%



23 **27**

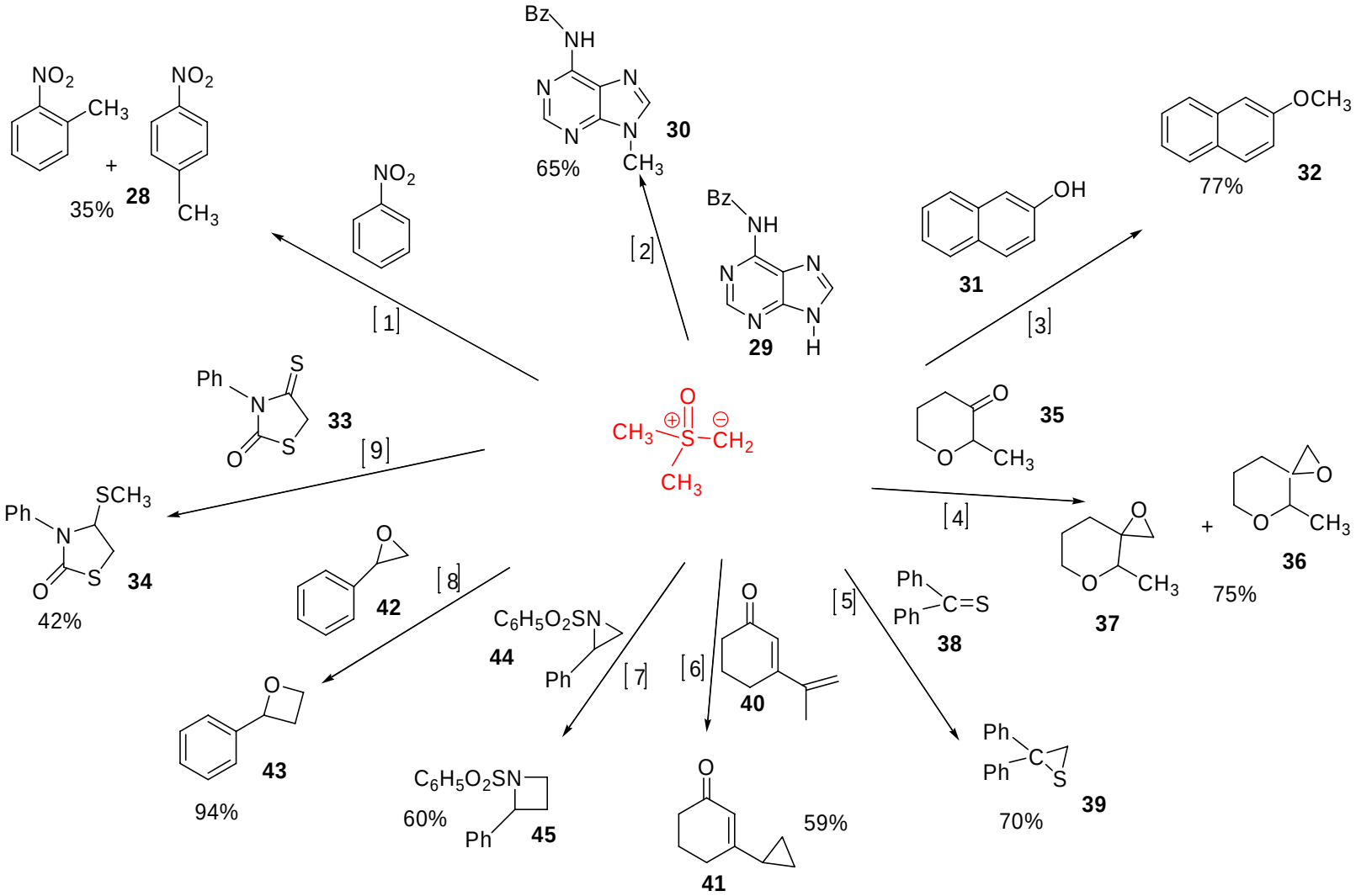
Tabl.1

Substrat	S-ylide	(E)-oxirane %	(Z)-oxirane %
23	$Me_2S(O)CH_2$		100
23	$Me_2S\text{-}CH_2$	83	17
23	$PhS(O)CH_2$ $N(CH_3)_2$		100

C.R.Johnson, C.W.Schroeck, J.Am.Chem.,Soc., 93, 5303-5305, 1971

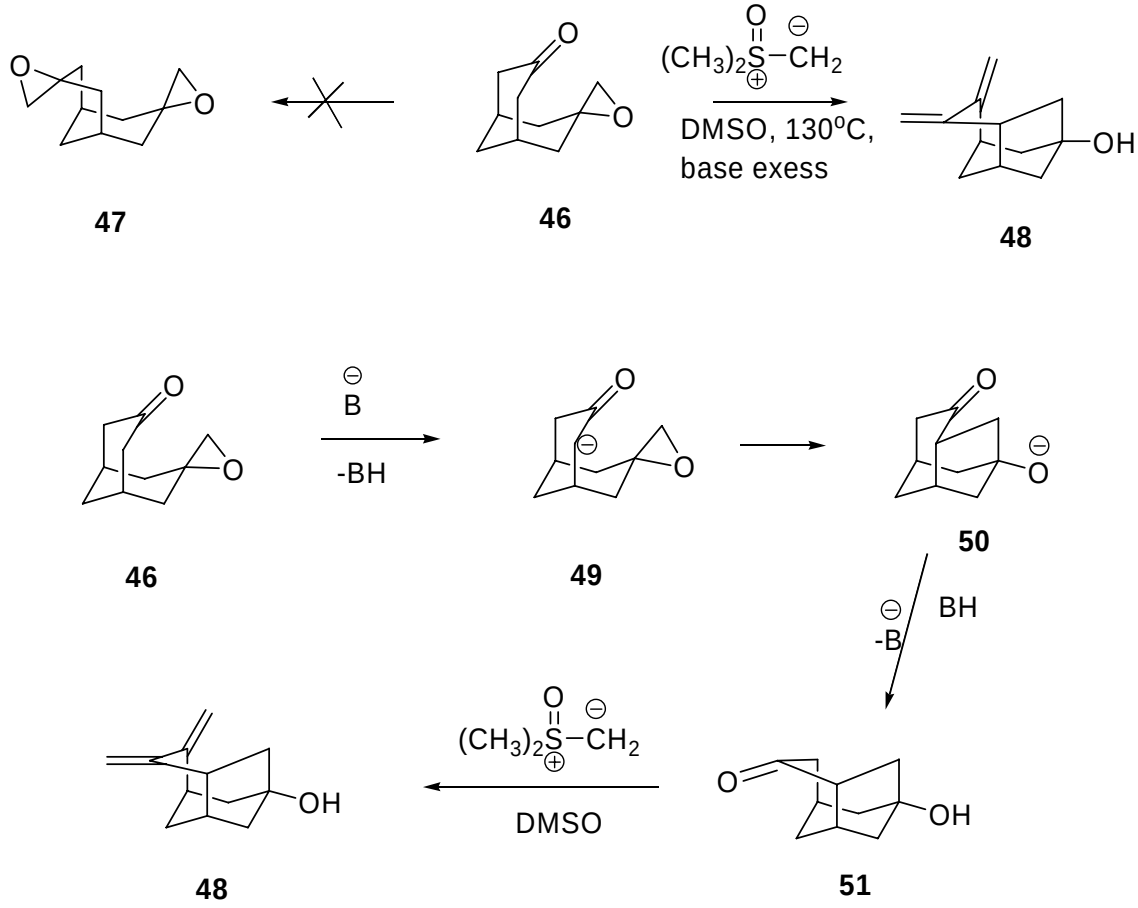
C.R.Johnson, C.W.Schroeck, J.R.Shanklin, J.Am.Chem.Soc., 95, 7424-7431, 1973

Chemical properties of the dimethilsulfoxonium methylide



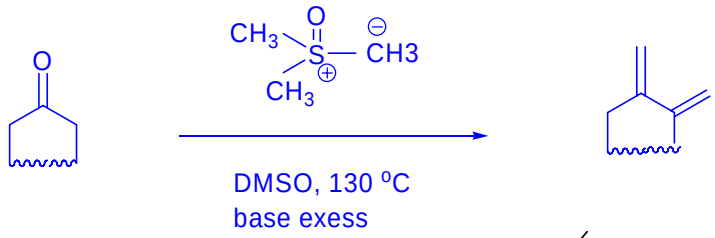
1.V.J.Traynelis and J.V.McSweeney, J.Org.Chem, 31, 243,(1966)
2.Takehisa Kunieda, Bernhard Witkop, J.Org.Chem, 35, 3981,(1970)
3.Horat Metzger, H.König, Kurt Seelert, Tetrahedron Lett., 5, 867, (1964)
4.D.S. Fullerton, Chi-Ming Chen, I.H.Hall, J Med.Chem.,19,1391 (1976)
5.Corey E.J. and Chaykovsky M., J.Am.Chem.Soc 87,1353 (1965)
6.Piers E., Banville J, Can.J.Chem. 60,2965 (1982)
7.Nadir U.K., Koul K V., J.Chem.Sos.Chem.Commun, 417, (1981)
8.Okuma K.,Tanaka Y, Kaji S.,Ohta H., J.Org.Chem.,48, 5133 (1983)
9.Zhtar B.E., Rudik O.I., Baeva I.G., Ukr.Khim.Zh. 49, 97 (1983)

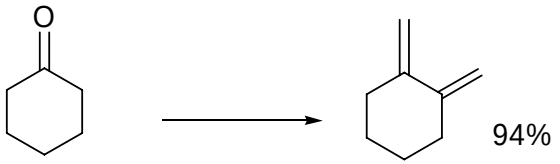
An anomalous reaction of Dimethyl Sulfoxonium Metylide



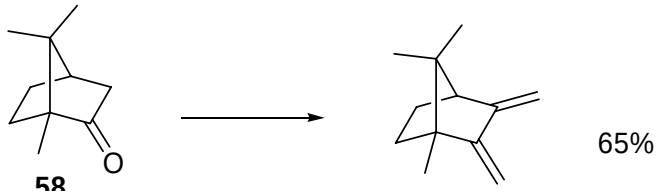
Alexander G.Yurchenko and Natalie N.Melnik Tetrahedron Letters, Vol.30, pp. 3653-3654, 1989

NEW REACTION WAS TESTED FOR THE NUMBER OF KETONES

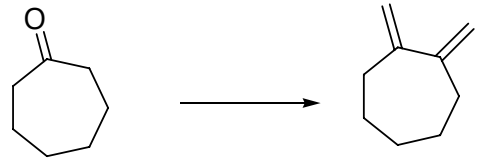




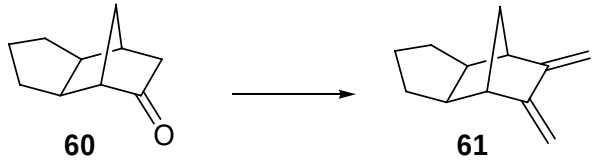
52 53 94%



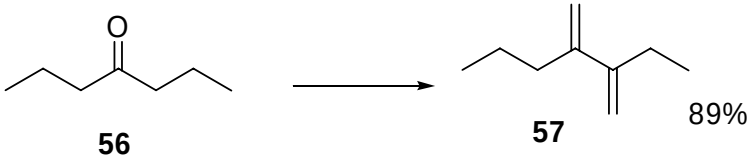
58 59 65%



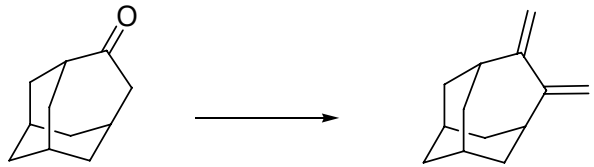
54 55 98%



60 61 92%



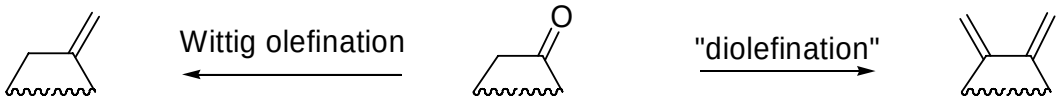
56 57 89%

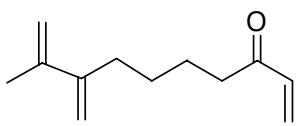


62 63 44%

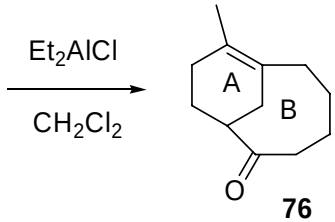
A.G.Yrchenko, A.B.Kyrij, I.R.Lihotvorik, N.N.Melnik ats all, Synthesis, 5 ,pp.393-394, 1991

POSSIBLE APPLICATIONS OF „DIOLEFINATION“ REACTION
EXAMPLE: THE SYNTHESYS OF TAXOL

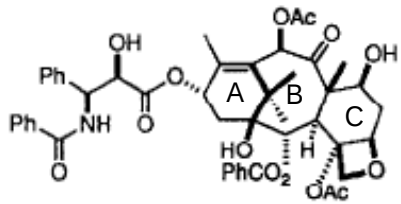




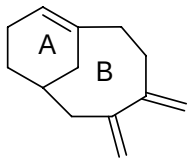
75



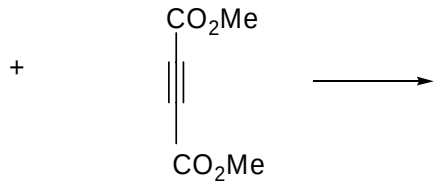
76



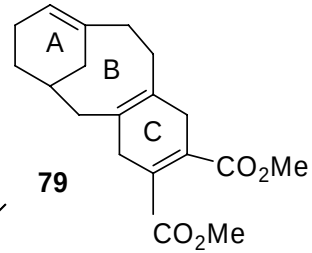
Taxol



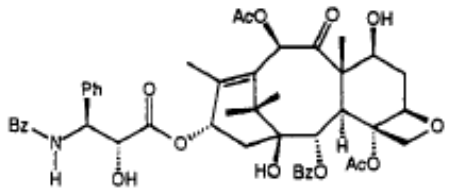
77



78



79

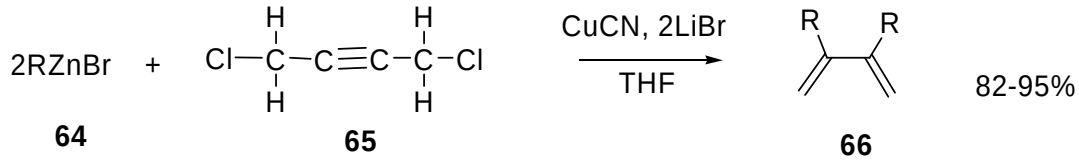


Taxol

Kenneth J.Shea andStiven T. Sakata, Tetrahedron Lett., 1992,.33, 4261-4264,

Zhaoyin Wang, S.E.Warder, H.Perrier, E.Grimm, M.A.Bernstein, J.Org.Chem., 1993, 58, 2931-2932.

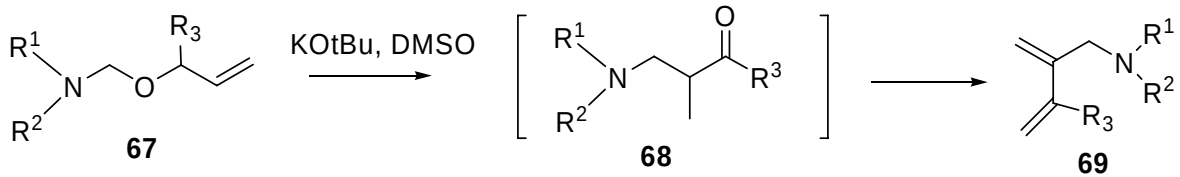
EXISTING METHODS FOR PREPARATION OF TERMINAL DIENES ARE DIFFICULT



64 **65** **66**

R : $-(CH_2)_7CH_3$, $-(CH_2)_6Cl$, $-(CH_2)_3CO_2Et$, $-(CH_2)_3CN$, -Bz, -Ph

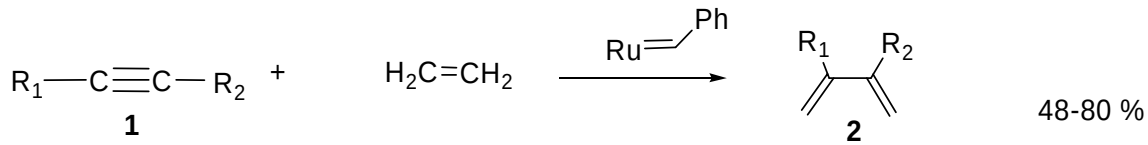
Lishan Zhu and Reuben D.Rieke, Tetrahedron Lett., V.32, pp.2865, 1991



67 **68** **69**

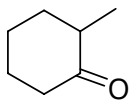
R_1, R_2 : C_2H_5 , $-(CH_2)_5$ -, $CH(CH_3)_2$; R_3 : H, CH_3

T. Arenz, H. Frrauenrath, Angew. Chem. 102, 929, 1990

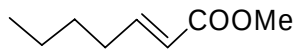


1 **2**

R_1 : OAc, Et, OBz,

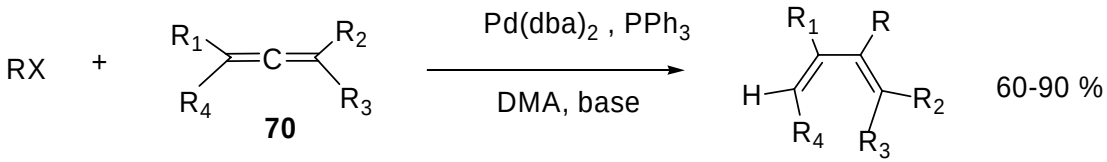


R_2 : OAc, OBz,



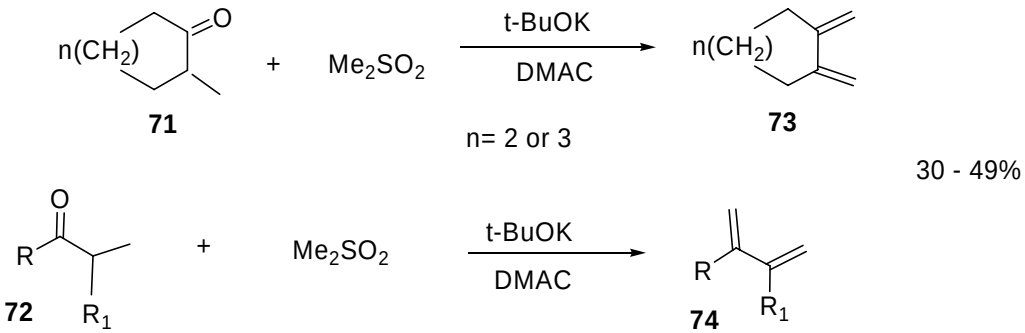
Atsushi Kinoshita, Norikazu Sskakibara, and Miwako Mori, J.Am.Chem.Soc, 119,12388, 1997

STILL DIFFICULT



R_1, R_2, R_3, R_4 : -CH_3, -Ph, cyclohexane; X. Hal; R: -$PhCOCH_3$, -PhCl, -$PhNO_2$, -PhCN, -OCH_3, -PhBr

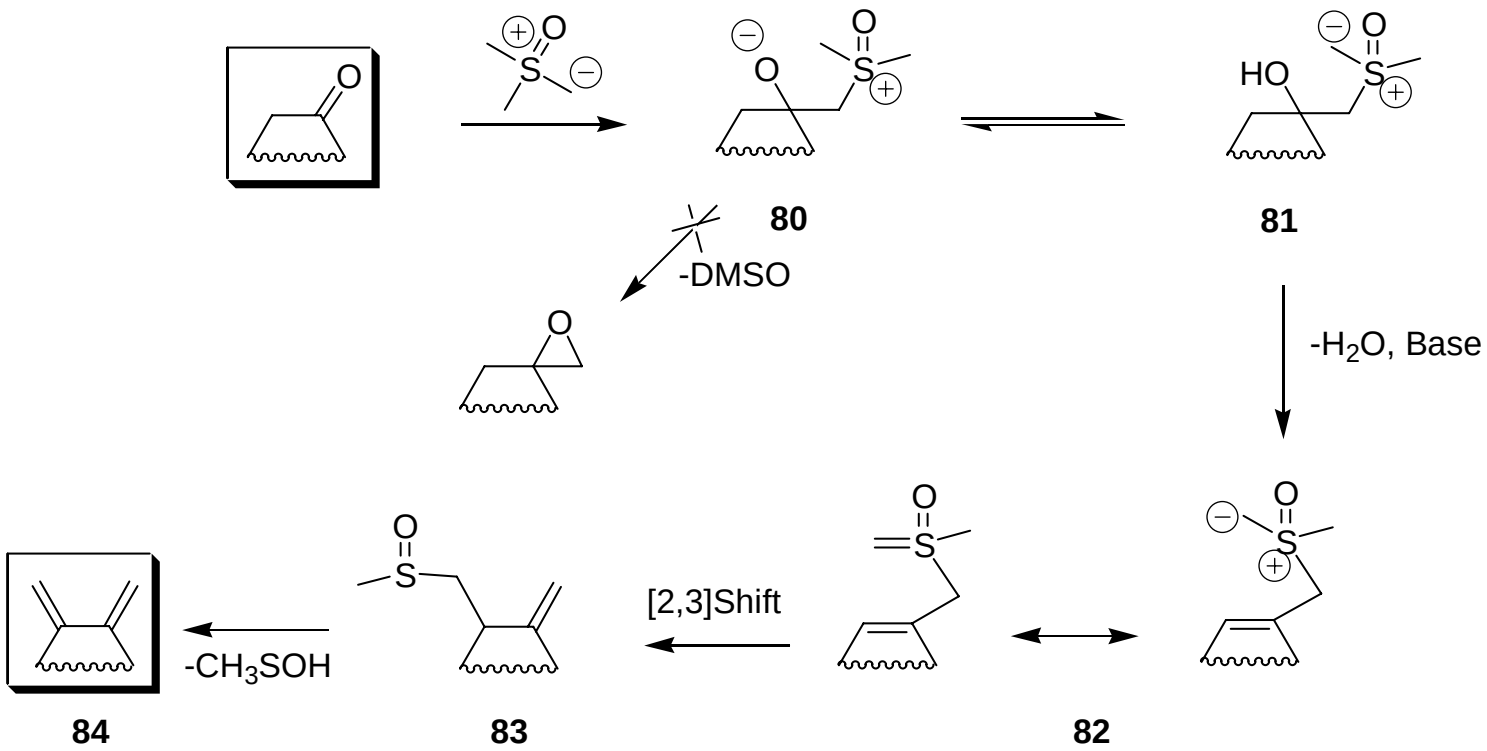
Hao-Ming Chang and Chien-Hong Cheng, J.Org.Chem., 65, 1767, 2000



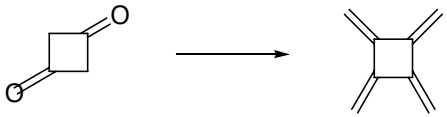
R, R_1 : H, CH_3, Alk

Michael E. Garst, Lloyd J.Dolby and all, J.Org.Chem., 71,553, 2006

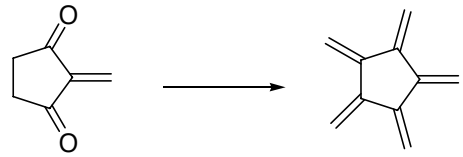
The mechanism proposed for the „diolefination“ reaction



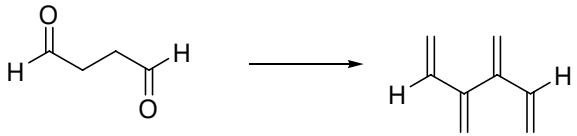
OUR TARGETS



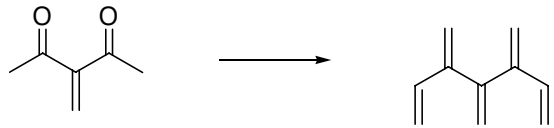
85



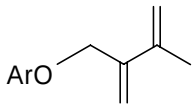
86



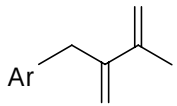
87



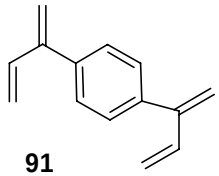
88



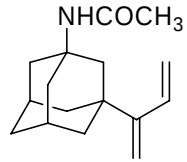
89



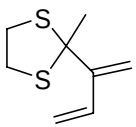
90



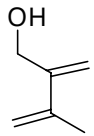
91



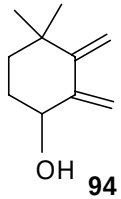
96



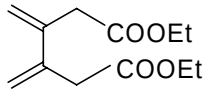
92



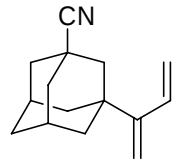
93



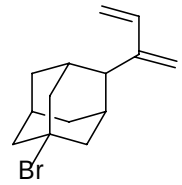
94



95

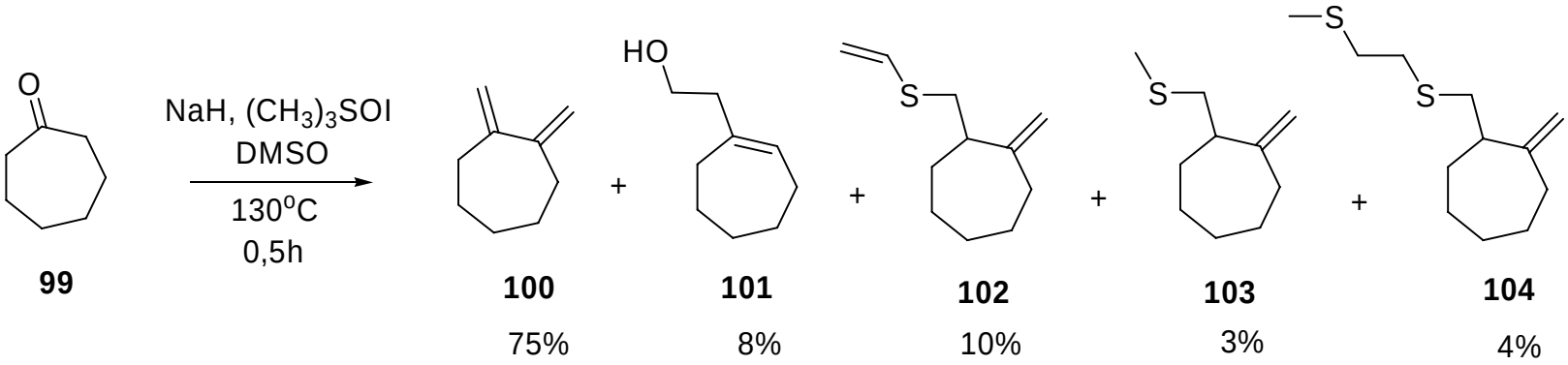


97



98

MANY BY- PRODUCTS FORM



99

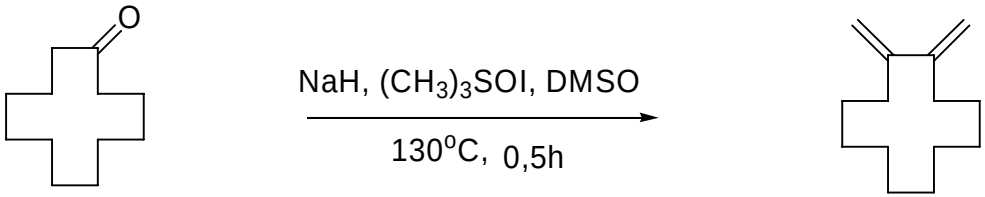
100 75%

101 8%

102 10%

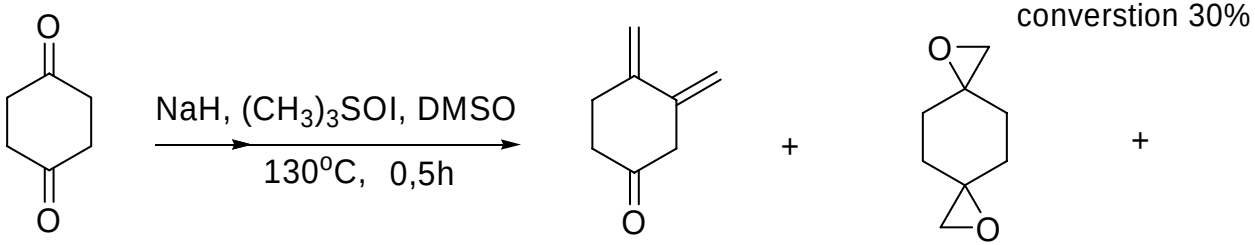
103 3%

104 4%



105

106



converstion 30%

107

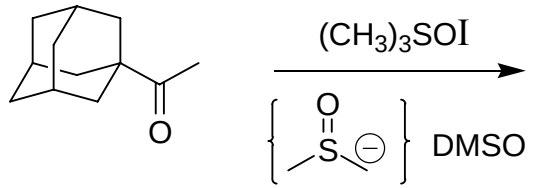
25%

40%

35%

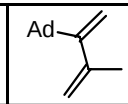
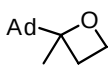
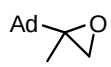
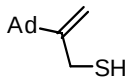
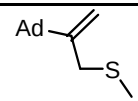
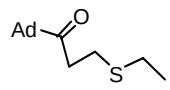
Conclusion : OPTIMISATION IS NEEDED

FIRST OPTIMIZATION RESULTS : (reaction in DMSO)



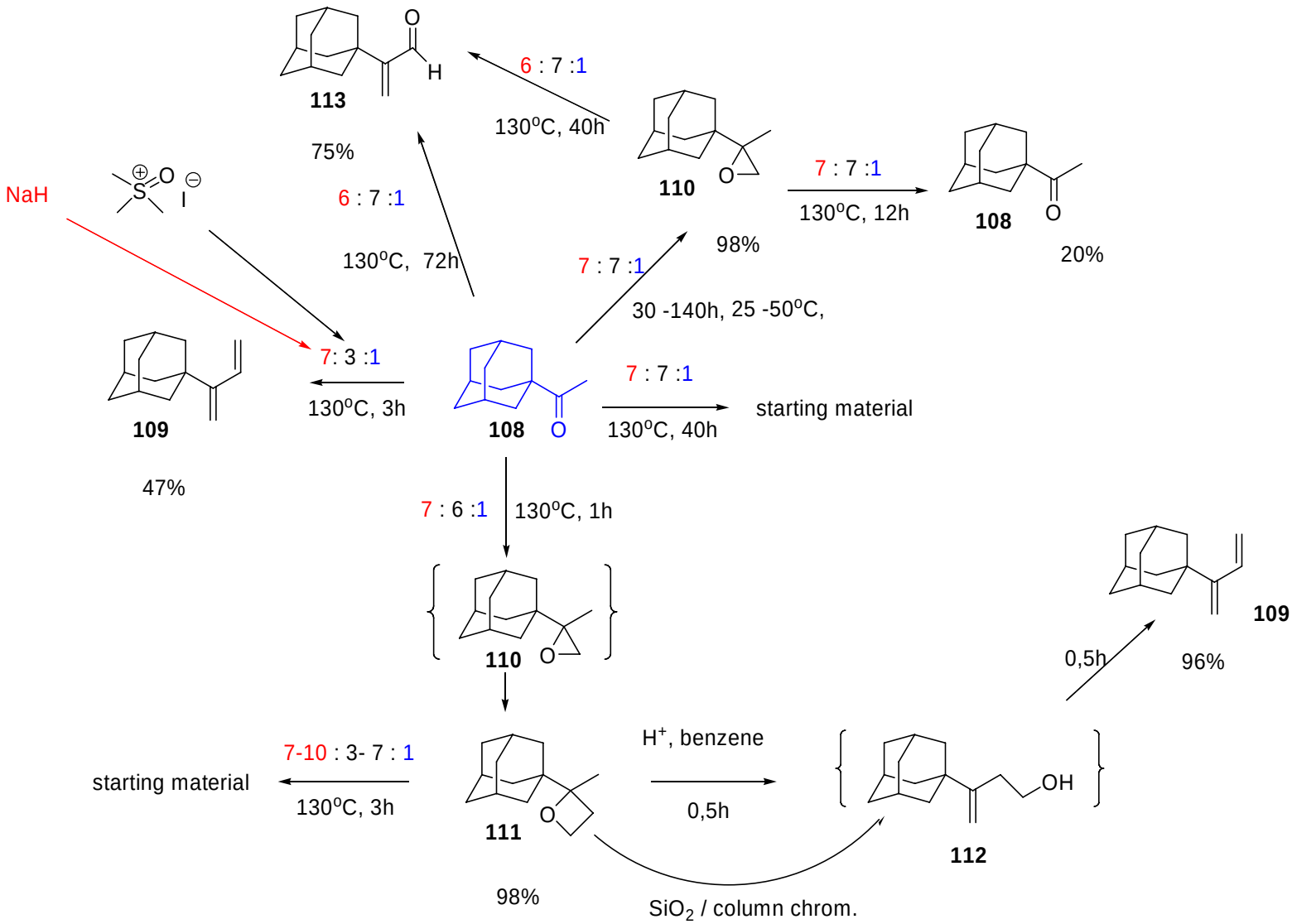
Optimization of the reaction :

Tabl.2

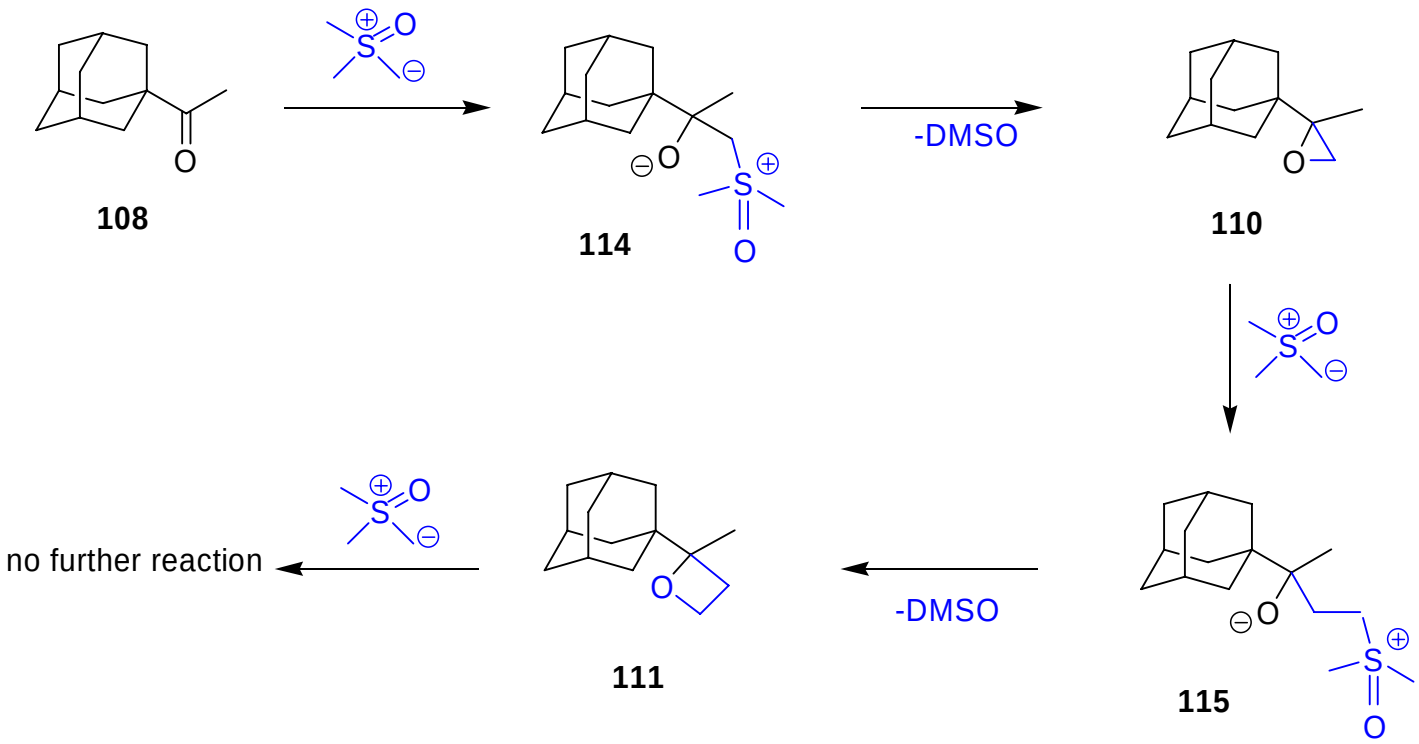
Parameters: T = 130 ? 140 °C , 3 h			Reaction mixture [%]										
NaH, mol	$(CH_3)_3S(O)I$ mol	Keton, mol					M= 204					
7	**2.5**	**1**	**4**	**47**	**5**		**3**		**3**	**5**	**15**	**10**
7	3	1	3	45	7		15			10	20	
7	4	1	2	30	17		10	6		7	29	
7	5	1		14	4	6	6	69			3	
7	**6**	**1**		**2**				**98**				
7	**7**	**1**	**100**									
7*	**7**	**1**							**100**			
9	5	1	3	25	10		10	35			20	
9	3	1	8	47		12	6			2	3	22
8	3	1	3	45	4		25			1	20	2
10	3	1	15	45	2	5	30				10	
15*	**3**	**1**	**3**	**3**						**9**	**36**	**49**
3.5**	3	1	15	5					80			

* t = 25 °C, 140 h, ** t = 130 °C, 1h

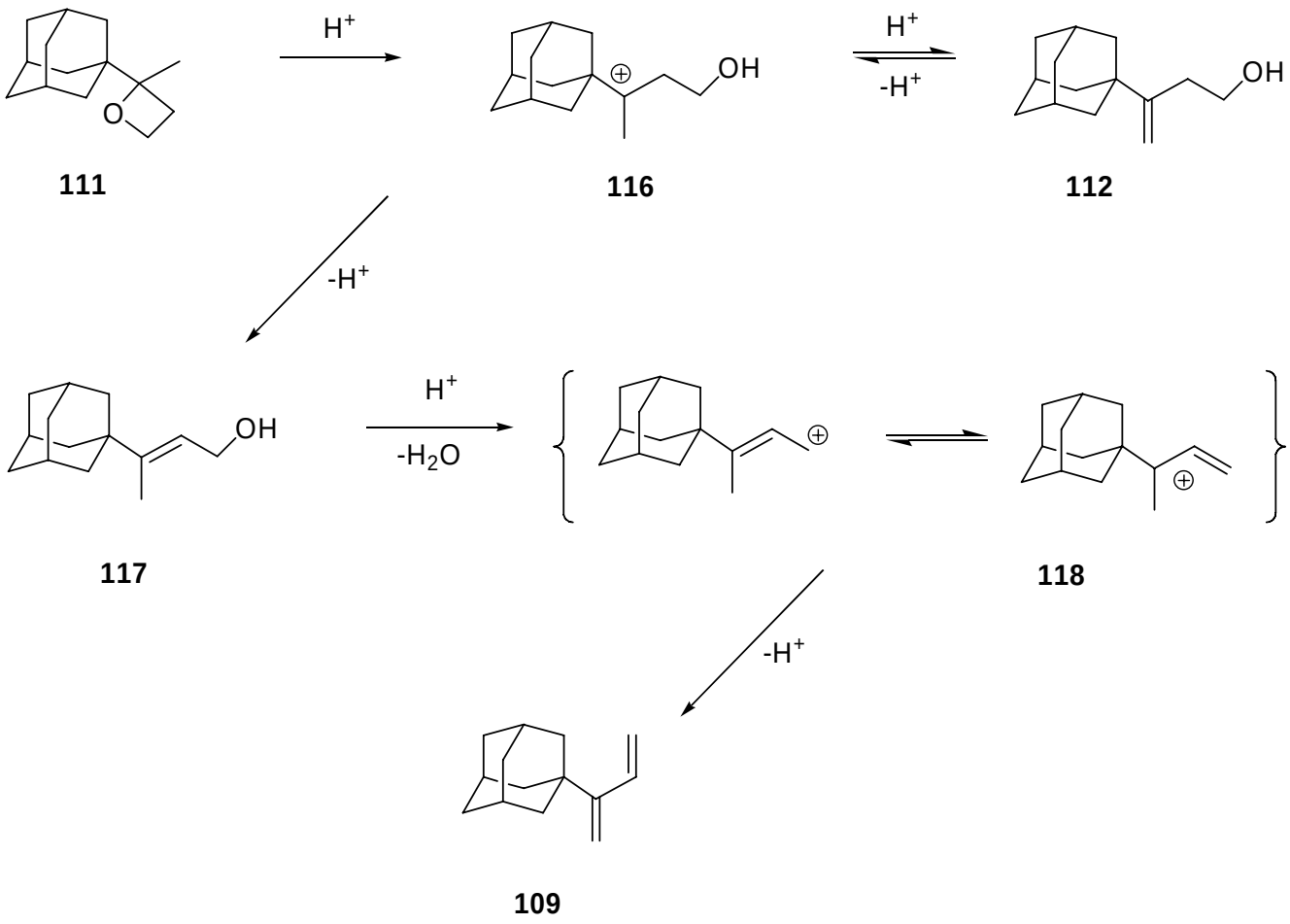
REACTION RESULTS STRONGLY DEPEND ON THE RATIO OF THE REACTANTS



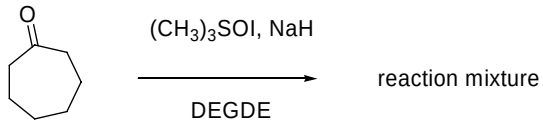
OXETANE IS NOT THE INTERMEDIATE IN THE DIOLEFINATION REACTION



The acid - catalyzed transformation of the oxetane

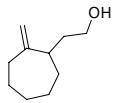
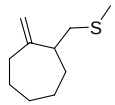
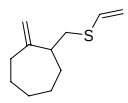
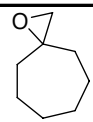


DMSO IS NOT NEEDED FOR STERICALLY UNHENDERED KETONES



Optimisation of the reaction in the Diglym

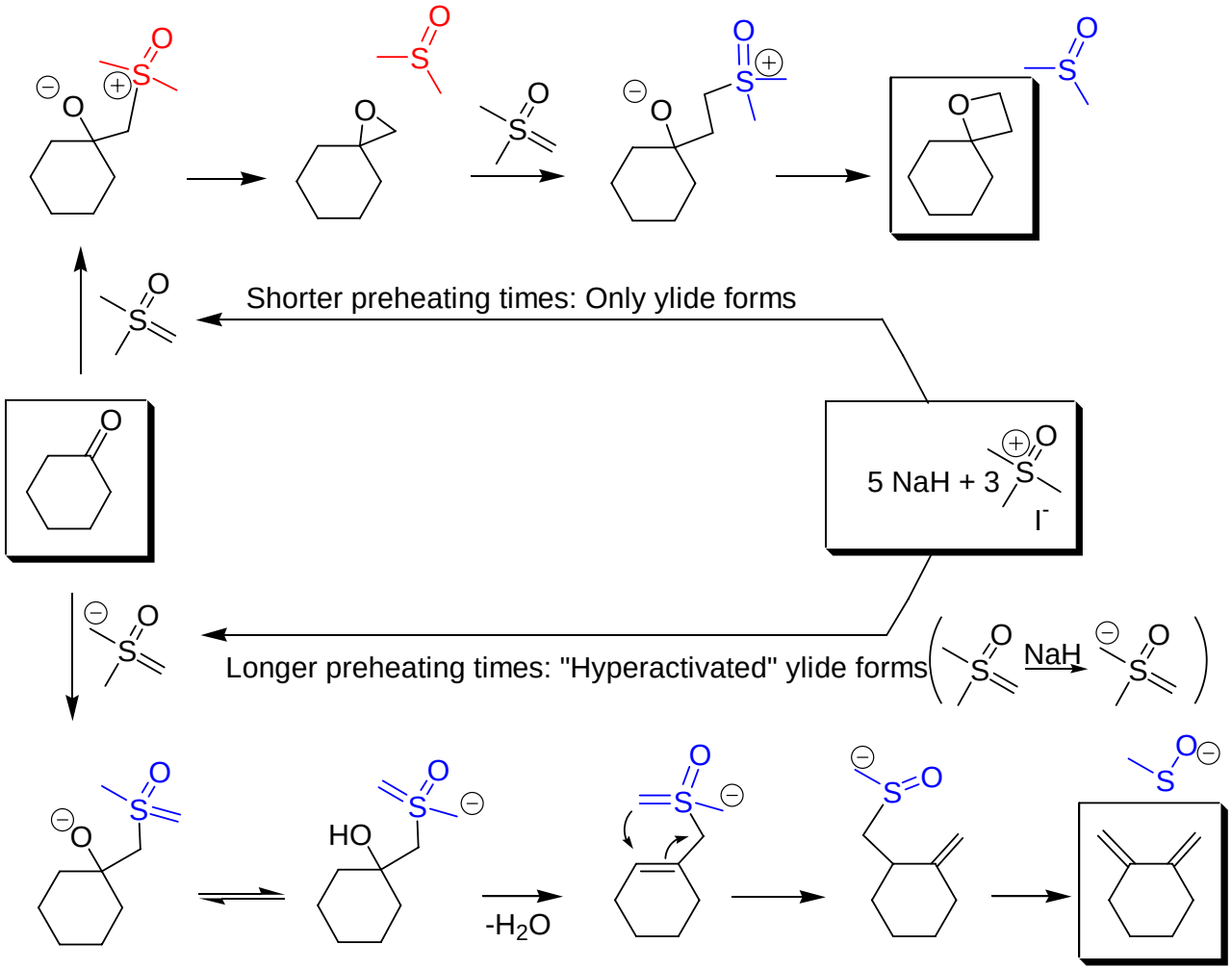
Tabl3

130–140 °C, 0.5 h				Reaction mixture (%), from GC/MS								
NaH, mol	$(CH_3)_3SOI$ mol	Keton, mol	DMSO, mol							M=136	M=202	others
12	3	1	9	9.5						56	29.5	5
7	3	1	14	40			10	30		15		5
5	3	1	85	60		10	10	15				5
7	3	1	1	82						7.5	10.5	
5[a]	**3**	**1**	**0**	**5**	**95**							
5[b]	3	1	0	25	75							
5[c]	3	1	0	68	32							
5[d]	**3**	**1**	**0**	**95**	**5**							
2,2	1,1	1	0	15,5	12				58			14,5

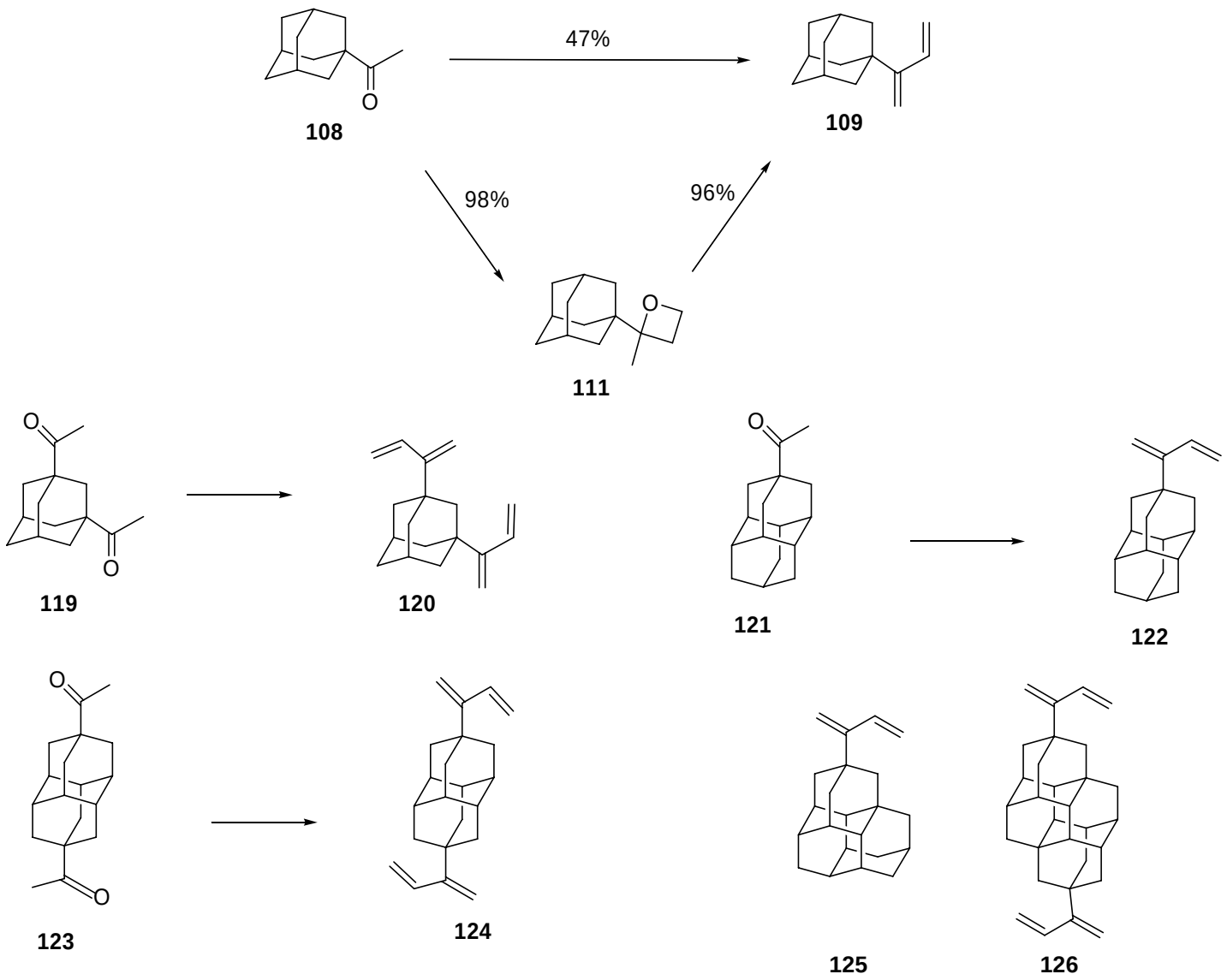
[a] Mixing NaH + Salt at room, FAST heating to 140 °C, and adding ketone
[b] Mixing NaH + Salt at room, FAST heating to 130 °C and adding ketone
[c] Mixing NaH + Salt at room, FAST heating to 90 °C, raising to 140 °C and adding ketone
[d] Mixing NaH + Salt then SLOW heating to 140 °C and adding ketone

PREHEATING TIME IS IMPORTANT : HYPERACTIVATED YLIDE FORMS?

Scheme, which explains why preheating time (NaH+Salt) is decisive



FURTHER APPLICATIONS



Possible applications of cage dienes