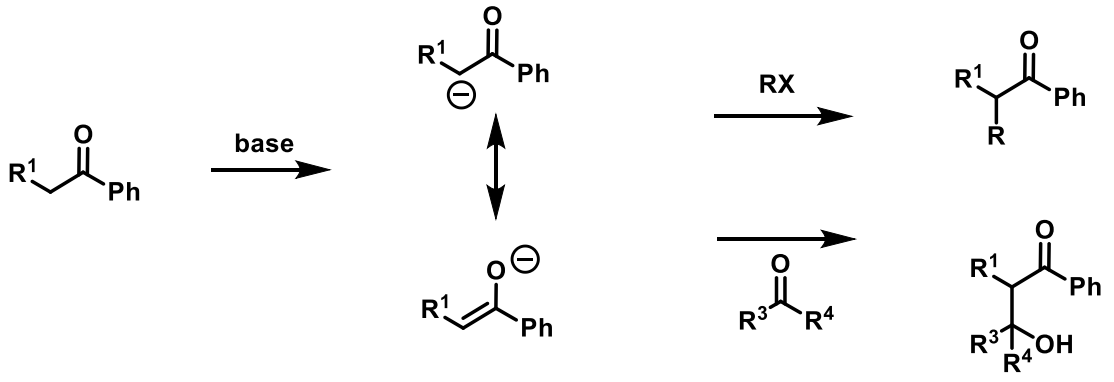
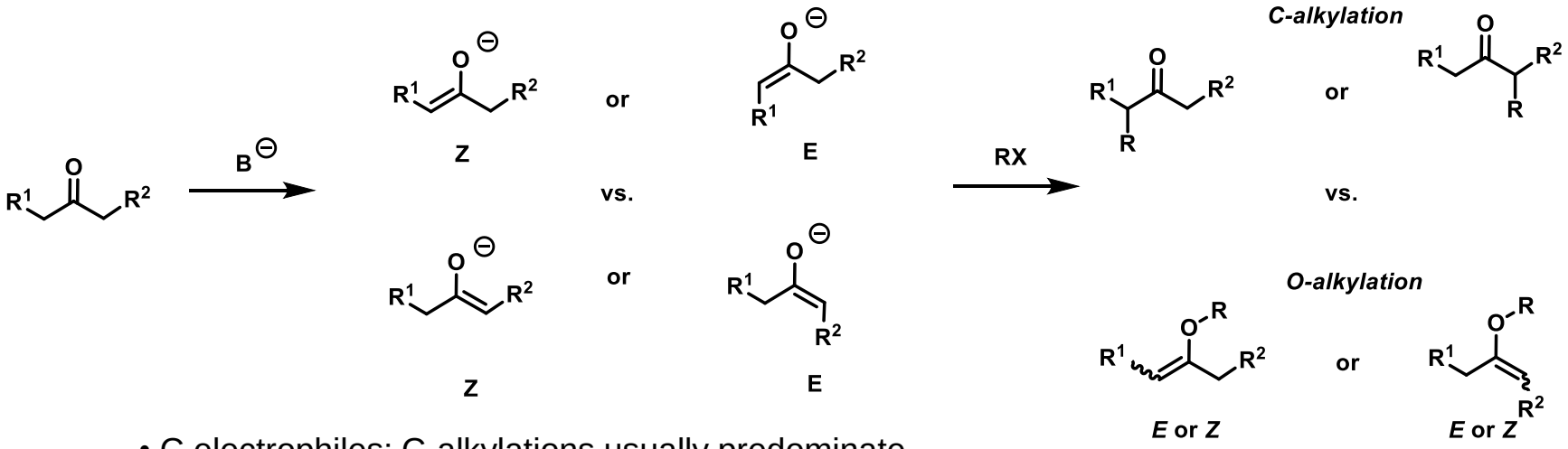
Organic synthesis

Kamil Paruch

Masaryk University, Brno

Enolates: preparation, structure, reactivity





- C electrophiles: C-alkylations usually predominate
- O alkylations: very reactive (hard) electrophile (e.g. ROTf); K^+ a Na^+ enolates

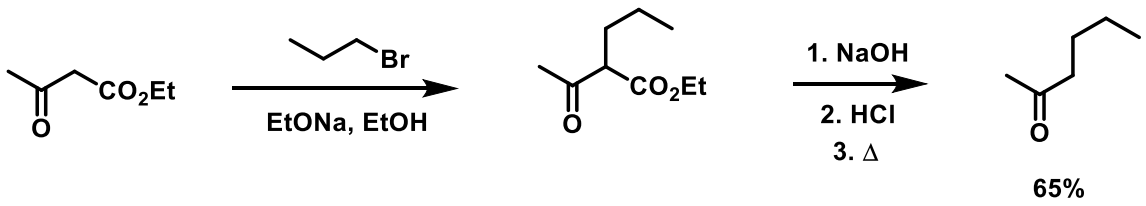
ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS

KYSELINA	pK_a	pK_{DMSO}	BÁZE	pK_a (KONJUG.KYSELINY)	pK_{DMSO}
$O_2NCH_2NO_2$	3,6		$MeCO_2^-$	4,2	11,6
$MeCOCH_2NO_2$	5,1				
$PhCH_2NO_2$		12,2			
$MeCH_2NO_2$	8,6				
$MeCOCH_2COMe$	9,0				
$PhCOCH_2COMe$	9,6		PhO^-	9,9	16,4
CH_3NO_2	10,2	17,2			
$MeCOCH_2CO_2Et$	10,7		Et_3N	10,7	
$MeCOCH(Me)COMe$	11,0		Et_2NH	11,0	
$NCCH_2CN$	11,2	11,1			
$CH_2(SO_2Et)_2$	12,2	14,4			
$CH_2(CO_2Et)_2$	12,7				
Cyklopentadien	15,0				
$PhSCH_2COMe$		18,7			
$PhCH_2COMe$		19,8	MeO^-	15,5	29,0

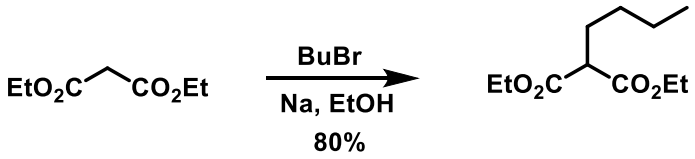
ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS

KYSELINA	pK_a	pK_{DMSO}	BÁZE	pK_a (KONJUG.KYSELINY)	pK_{DMSO}
$EtCH(CO_2Et)_2$	15,0		HO^-	15,7	31,4
$PhSCH_2CN$		20,8			
$PhCH_2CN$		21,9			
$(PhCH_2)_2SO_2$		23,9	EtO^-	15,9	29,8
$PhCOCH_3$	15,8	24,7	Me_3CO^-	19,0	32,2
CH_3COCH_3	20,0	26,5			
$MeCH_2COCH_2Me$		27,1			
Fluoren	20,5	22,6			
$PhSO_2CH_3$		29,0			
CH_3CN	25	31,3			
Ph_3CH	33,0	30,6	NH_2^-	35,0	41
$PhCH_3$		42	$MeSOCH_2^-$	35,0	35,1
CH_4		55	Et_2N^-	36,0	

acetoacetate synthesis

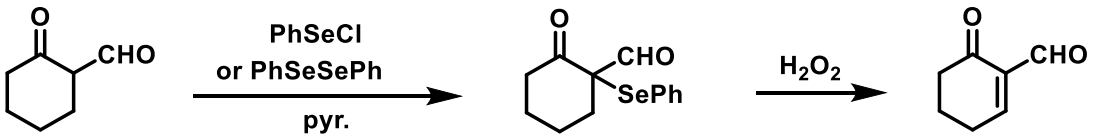


malonic ester synthesis



selenation of carbonyl compounds

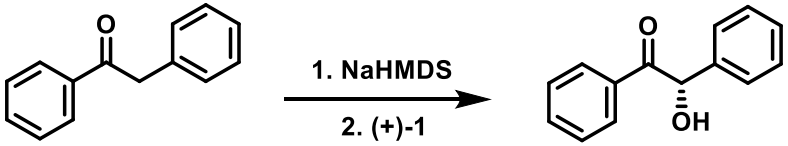
- preparation of α,β-unsaturated carbonyl compounds



oxidation of enolates

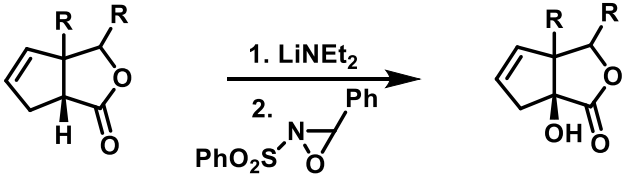
J. Am. Chem. Soc. 1974, *96*, 5944.

MoOPh : MoO_5+pyr.+HMPA



J. Am. Chem. Soc. 1990, *112*, 6679.

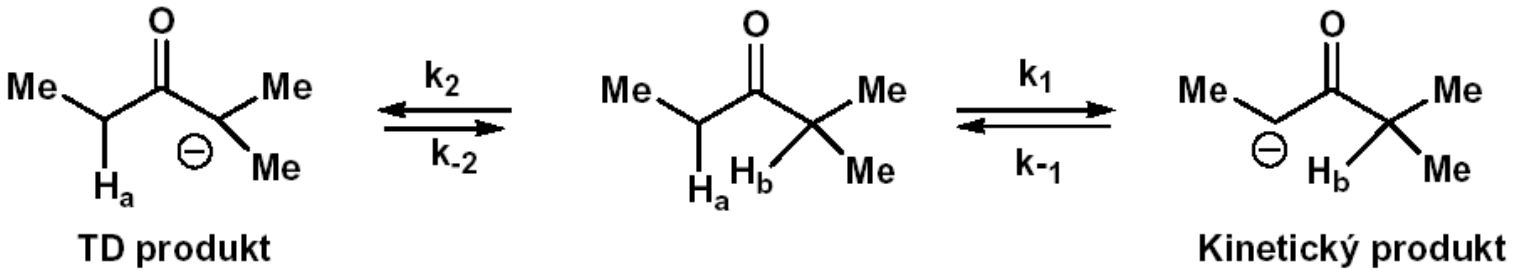
(+)-1
(camphorsulfonyl)oxaziridine



(Davis' oxaziridine)

J. Am. Chem. Soc. 1988, *110*, 649.

ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS
KINETIC VS. THERMODYNAMIC ENOLATE



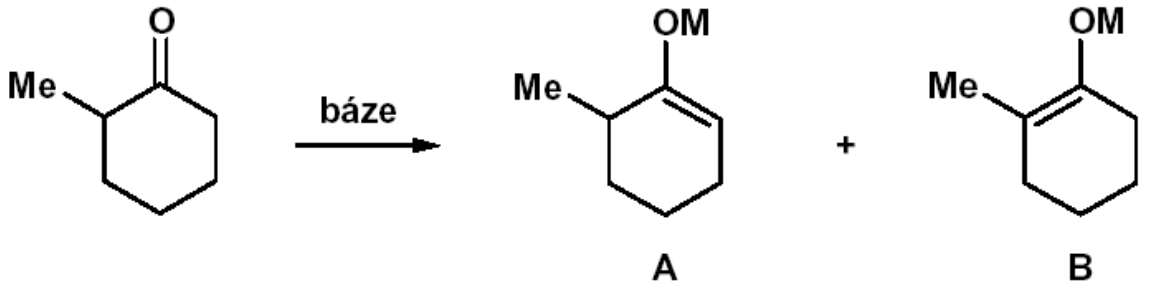
Formation of *kinetic* product ($k_1 > k_2$; $k_1 >> k_{-1}$) is typically observed under these conditions:

- aprotic solvent;
- strong non-nucleophilic base;
- low temperature;
- short reaction time (equilibrium not established).

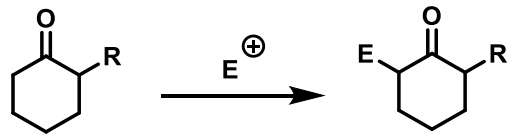
Formation of *thermodynamic* product ($k_1 \sim k_{-1}$) is typically observed under these conditions:

- protic solvent (deprotonation-reprotonation);
- weaker bases;
- higher temperature;
- longer reaction time (sufficient for establishing equilibrium).

ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS
KINETIC VERSUS THERMODYNAMIC PRODUCT

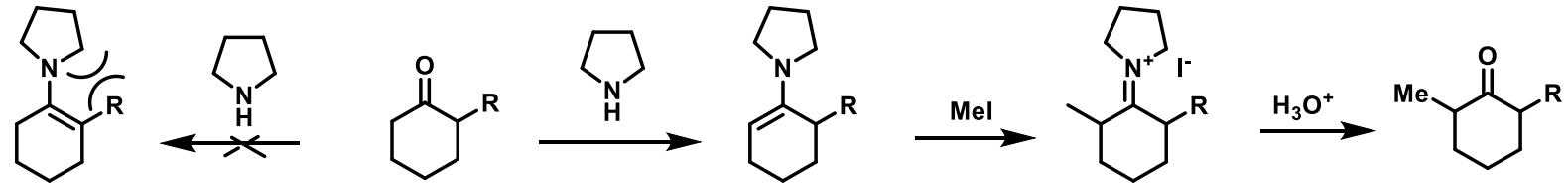


Báze (teplota ve °C)	Podmínky	Poměr A/B
$LiN(i\text{-}C_3H_7)_2$ (0)	Kinetické	99 : 1
$KN(SiMe_3)_2$ (-78)	Kinetické	95 : 5
Ph_3CLi (-78)	Kinetické	90 : 10
Ph_3CK	Kinetické	67 : 33
Ph_3CLi	Termodynamické	10 : 90
NaH	Termodynamické	26 : 74
Ph_3CK	Termodynamické	38 : 62



enamines

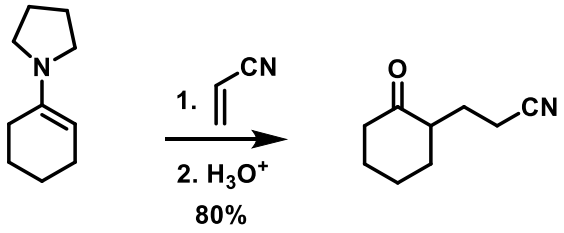
• “nitrogenous enolates“; some can be isolated



planar geometry

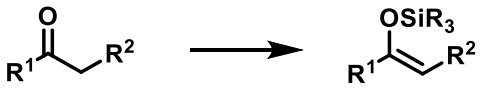
- formation of kinetic isomer

• enamines react well with C-electrophiles

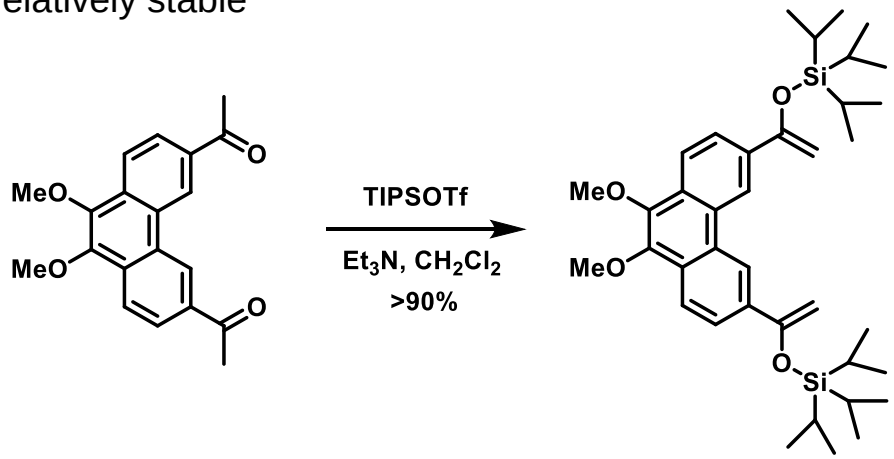


Tetrahedron 1958, *3*, 314.

silyl enol ethers

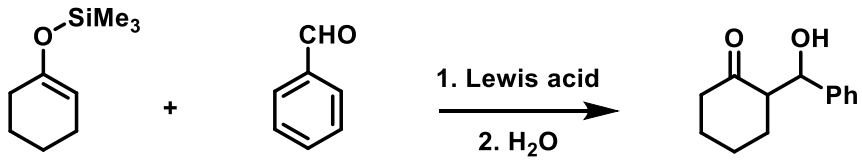


- formation of Si-O bond; irreversible
- silyl enol ethers are relatively stable



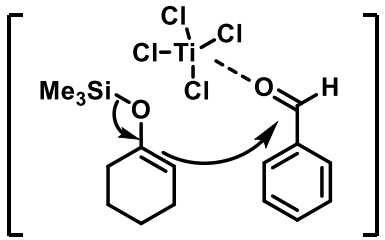
J. Org. Chem. 2000, *65*, 7602.

Mukaiyama (aldol) reaction



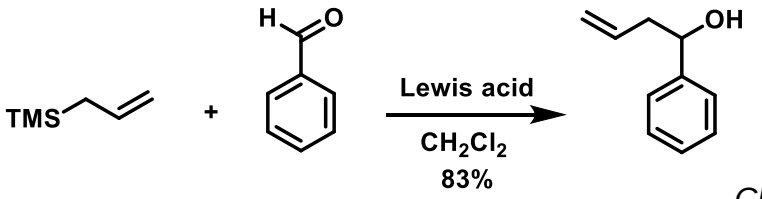
L. A. : $TiCl_4$, $SnCl_4$, $BF_3.OEt_2$

J. Am. Chem. Soc. 1974, *96*, 7503.



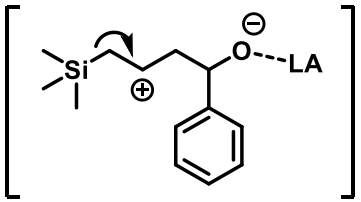
Sakurai allylation

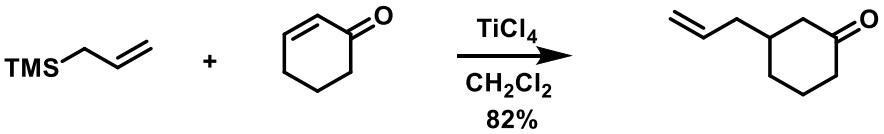
- quite universal, mild conditions (cf. addition of organometalic reagents)



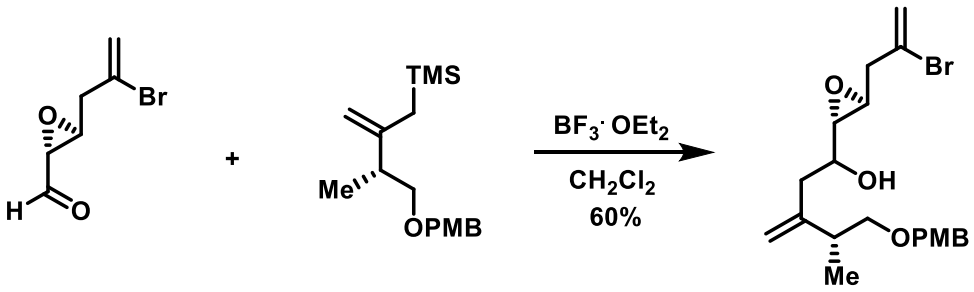
Chem. Lett. 1985, 977.

10 000 more nucleophilic than propene





J. Am. Chem. Soc. 1977, *99*, 1673.

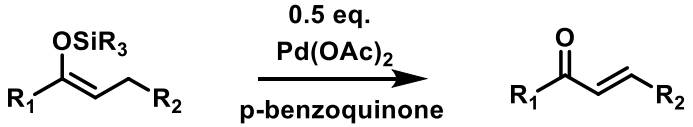


Org. Lett. 2000, *2*, 945.

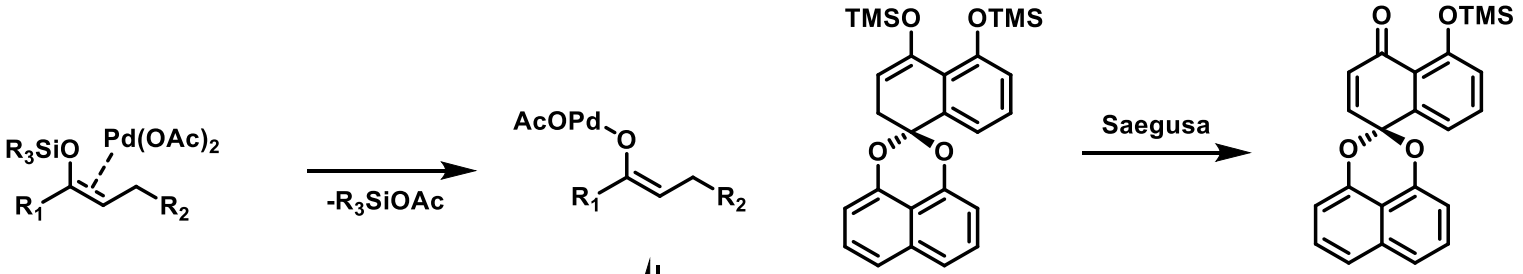
Saegusa oxidation

recent review: *Organic Reactions* **98**.

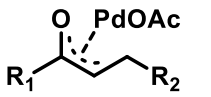
- very mild conditions

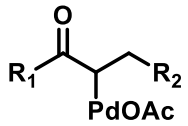


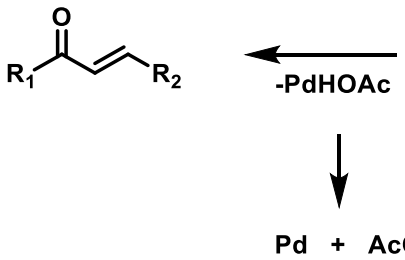
J. Org. Chem. 1978, *43*, 1011.



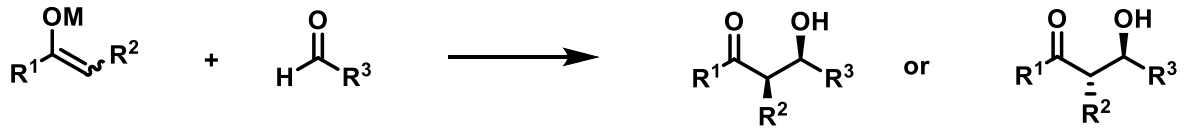
J. Org. Chem. 2002, *67*, 2735.







Aldol reaction: 2 new stereogenic centers can be created

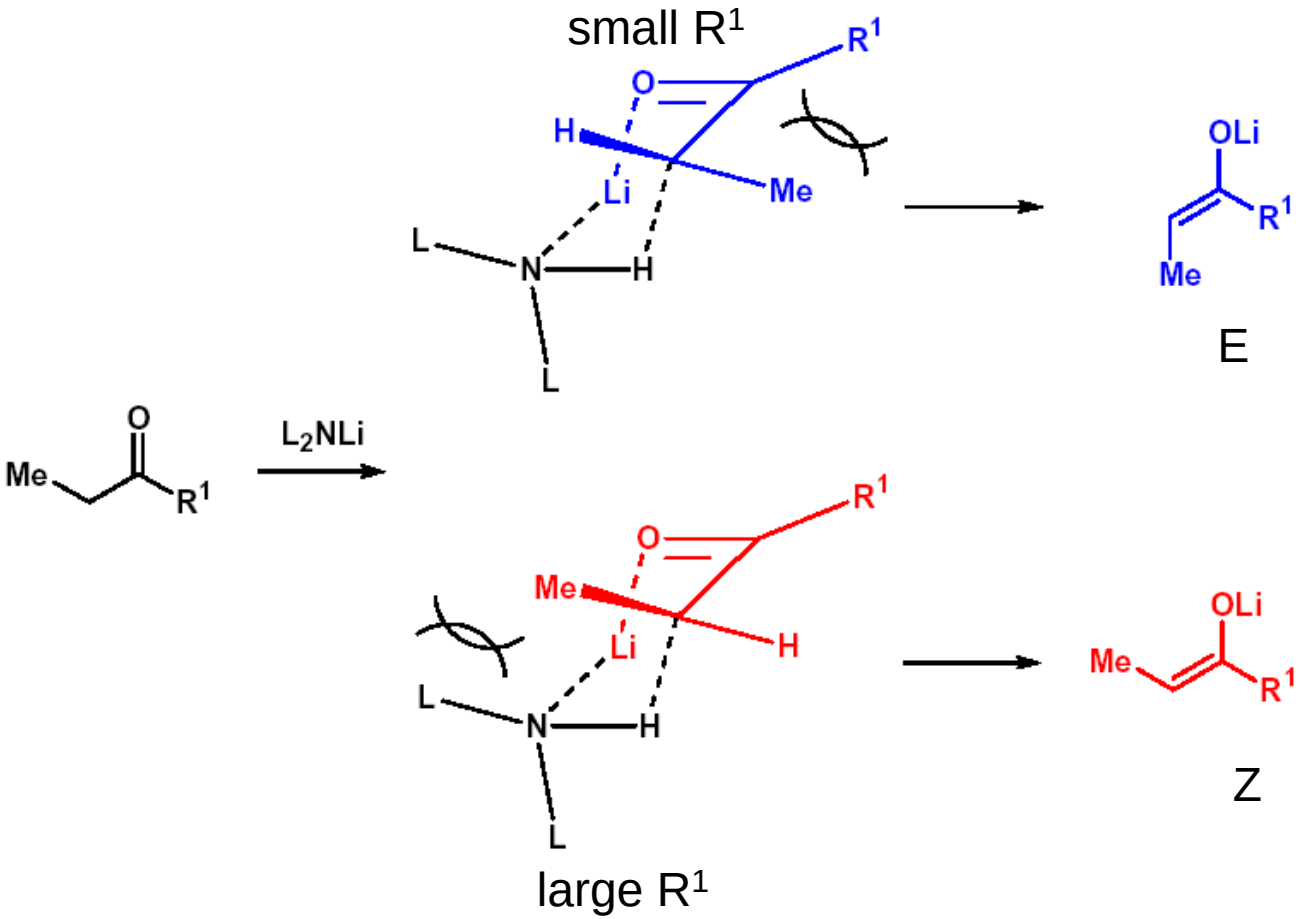


Z vs. *E* enolate

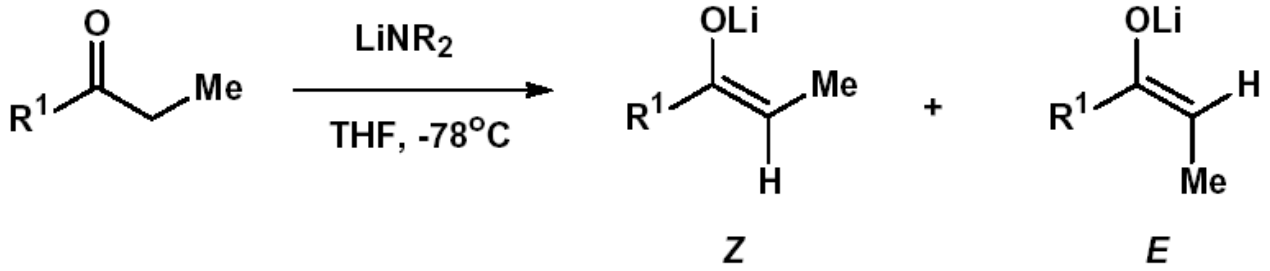
1,2-*syn* aldol **1,2-*anti* aldol**

- sterochemistry of products depends on the configuration of the starting enolates

GEOMETRY OF ENOLATES - IRELAND MODEL

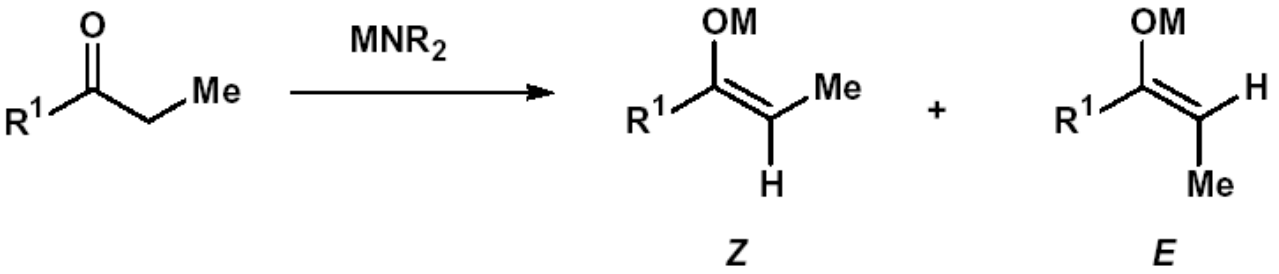


GEOMETRY OF ENOLATES - EFFECT OF BASE



BÁZE	R_1=Et (*Z* : *E*)	R_1=cyklohexyl (*Z* : *E*)
$LiN(i\text{-}Pr)_2$	30 : 70	61 : 39
$LiN(SiMe_3)_2$	70 : 30	85 : 15
$LiN(SiEt_3)_2$	99 : 1	96 : 4
$LiN(SiMe_2Ph)_2$	100 : 0	100 : 0

GEOMETRY OF ENOLATES – EFFECT OF SUBSTITUENT

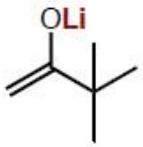


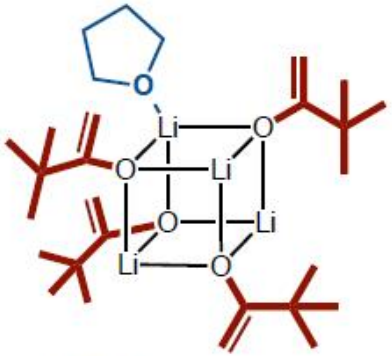
Z *E*

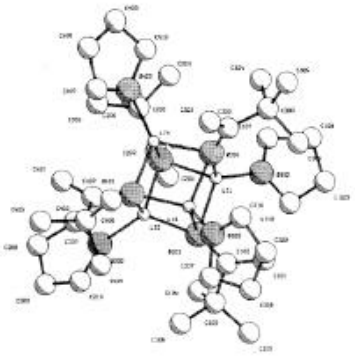
BÁZE (rozpouštědlo)	R^1	*Z*/*E* poměr
LDA (THF)	OMe, O*t*-Bu	5 : 95
LDA (THF)	S*t*-Bu	5 : 95
LDA (THF)	Et	23 : 77
LDA (THF)	*i*-Pr	100 : 0
LDA (THF)	*t*-Bu	60 : 40
LDA (THF)	Ph	100 : 0
LDA (THF)	NEt_2	100 : 0
s-BuLi (THF)	NEt_2	75 : 25

- enolates often form clusters

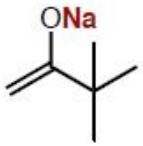
• Lithium enolate

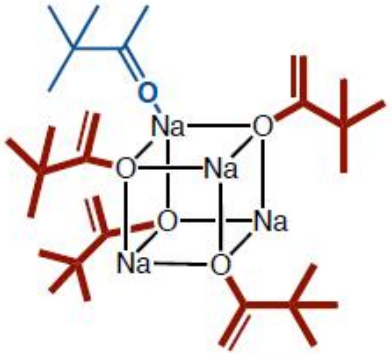


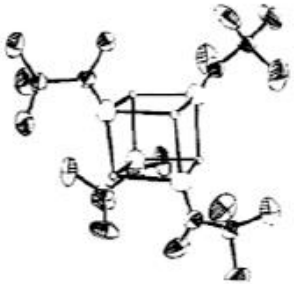


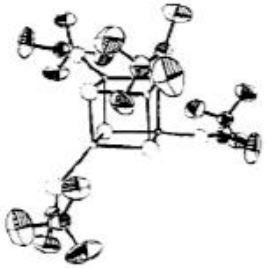


• Sodium enolate

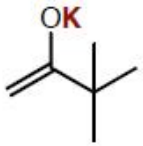


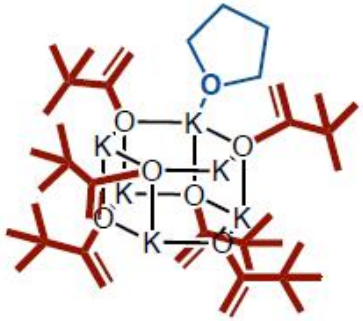


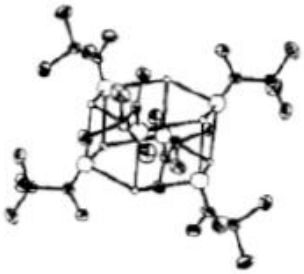


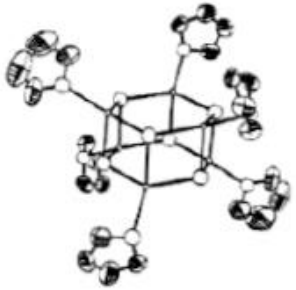


• Potassium enolate





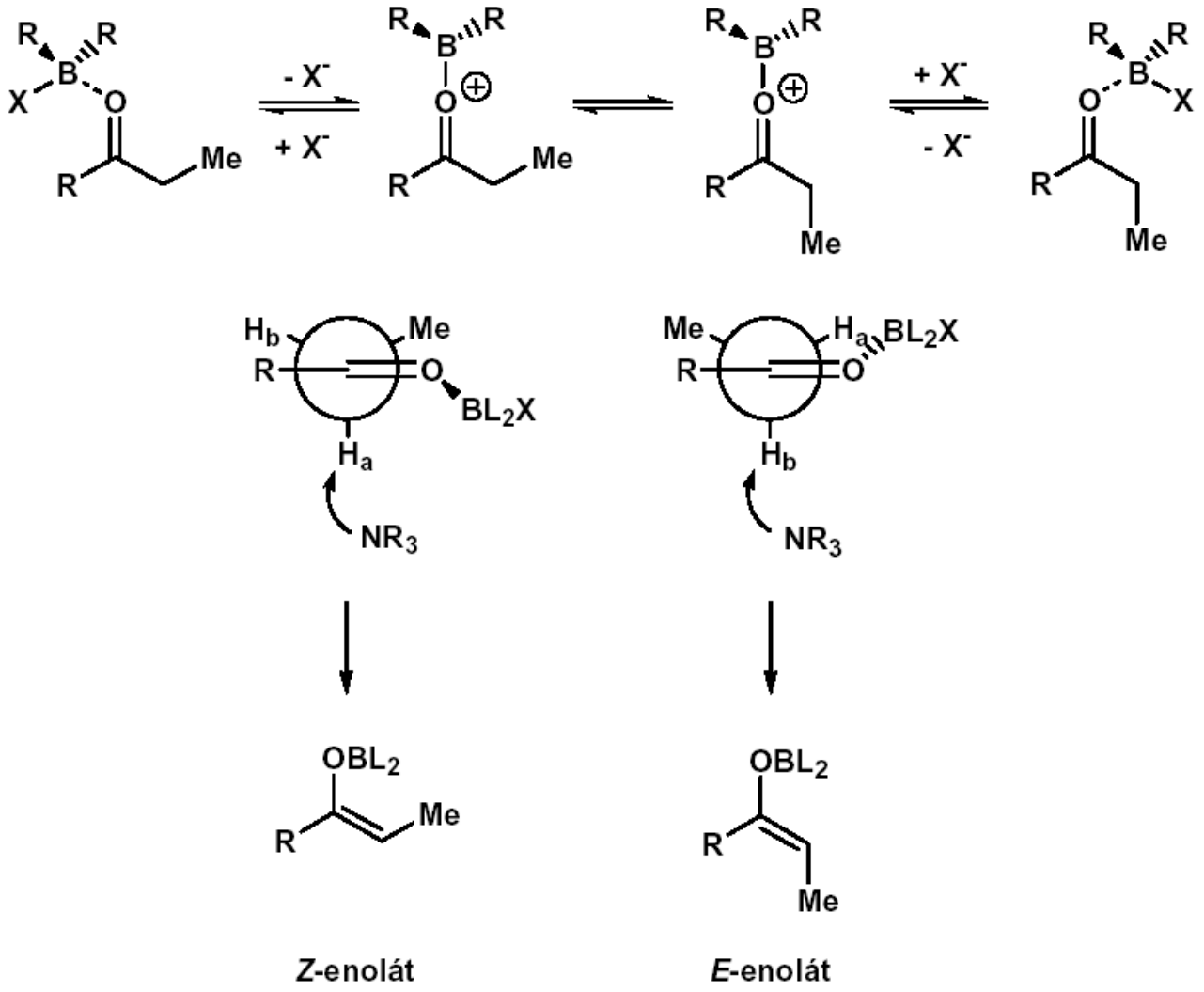




J. Am. Chem. Soc. 1986, *108*, 462.

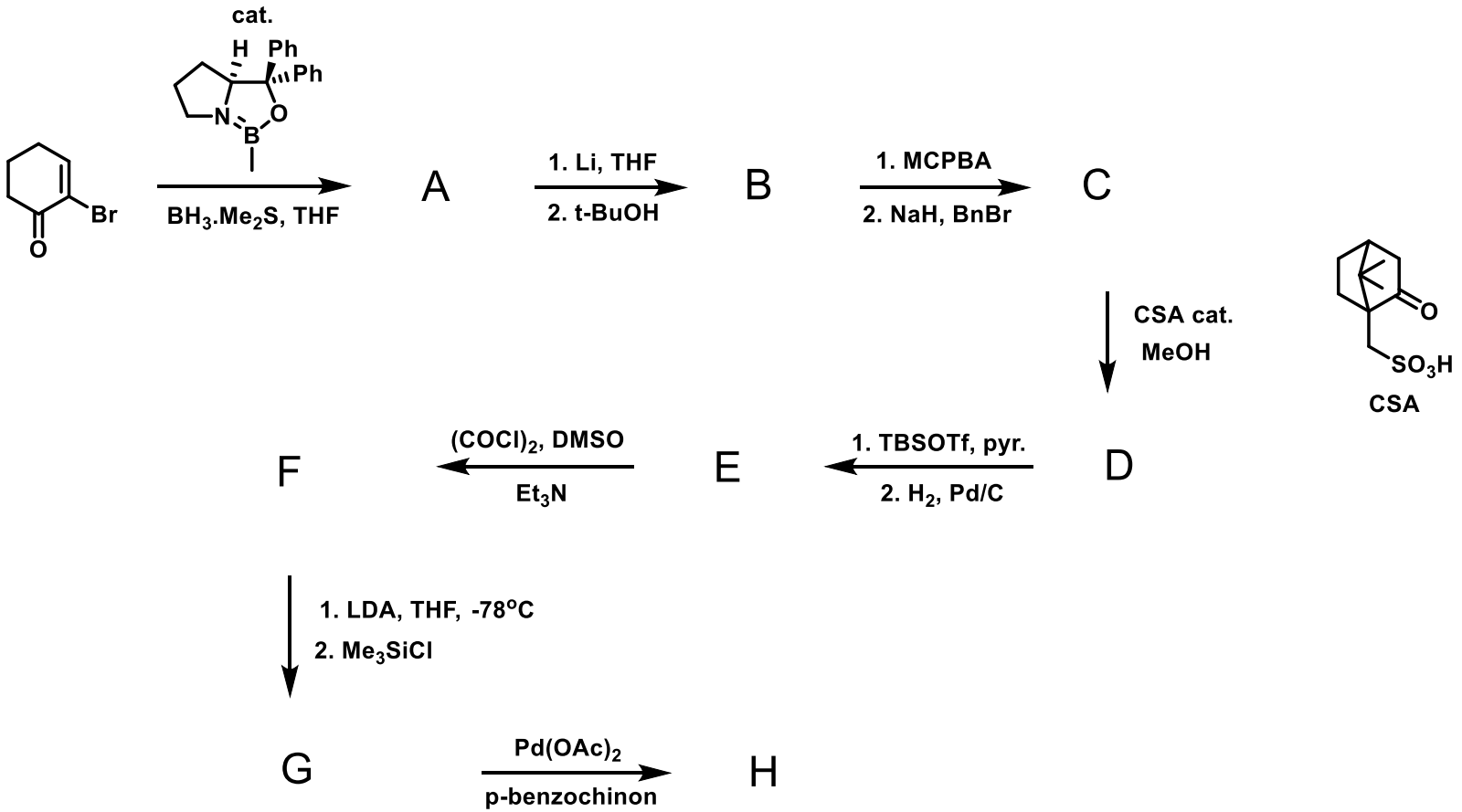
Helv. Chim. Acta 1981, *64*, 2617.

SELECTIVE FORMATION OF *E* OR *Z* ENOL BORINATES



R_2BCl with large alkyls (e.g. cyclohexyl) + small base (Et_3N) -> *E* enolates

R_2BOTf with small alkyls (e.g. n-butyl) + large base (DIPEA) -> *Z* enolates


cat.
H
Ph
Ph
N
B
O
Br
O
BH3.Me2S, THF
A
1. Li, THF
2. t-BuOH
B
1. MCPBA
2. NaH, BnBr
C
CSA cat.
MeOH
O
SO3H
CSA
D
1. TBSOTf, pyr.
2. H2, Pd/C
E
(COCl)2, DMSO
Et3N
F
1. LDA, THF, -78°C
2. Me3SiCl
G
Pd(OAc)2
p-benzochinon
H