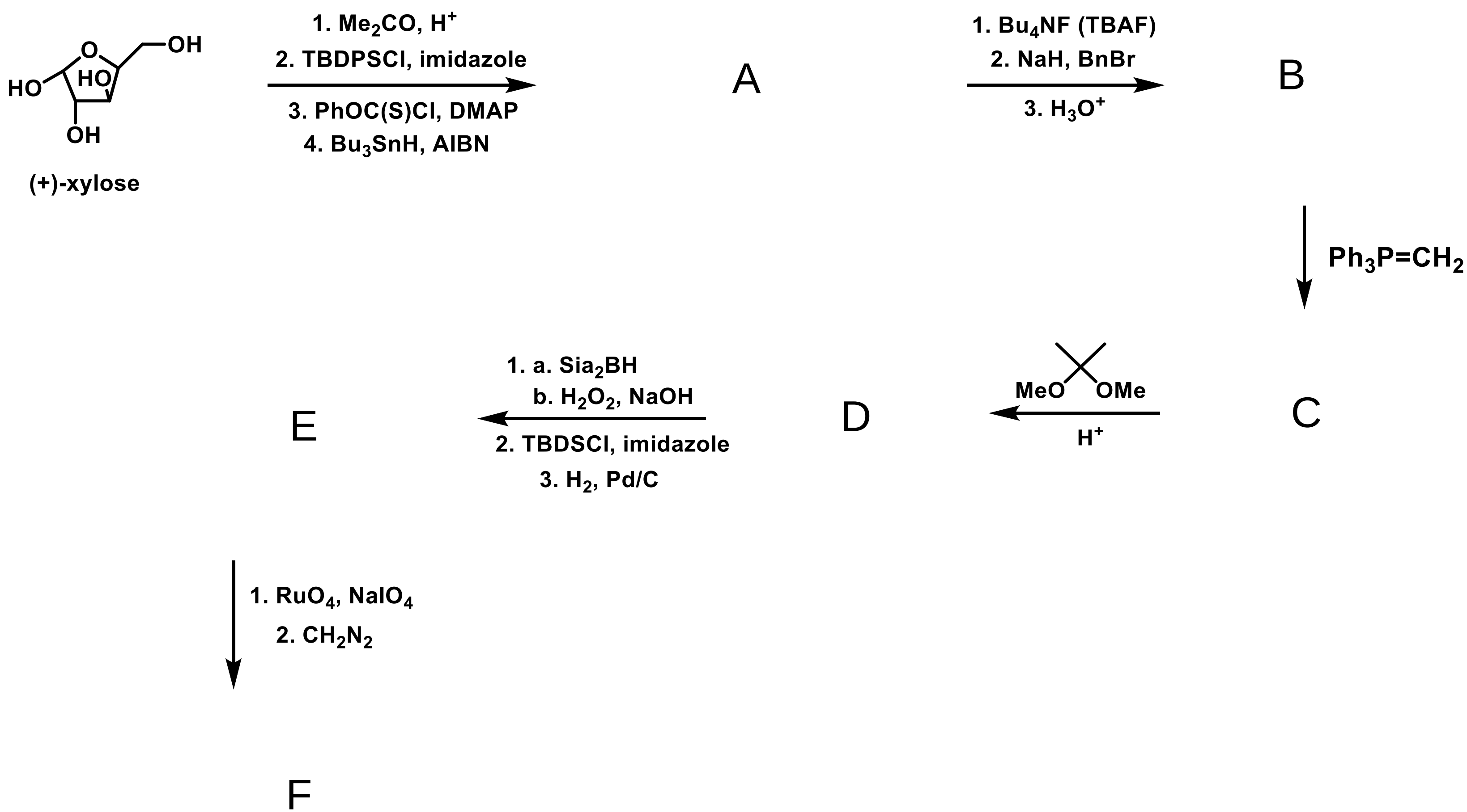
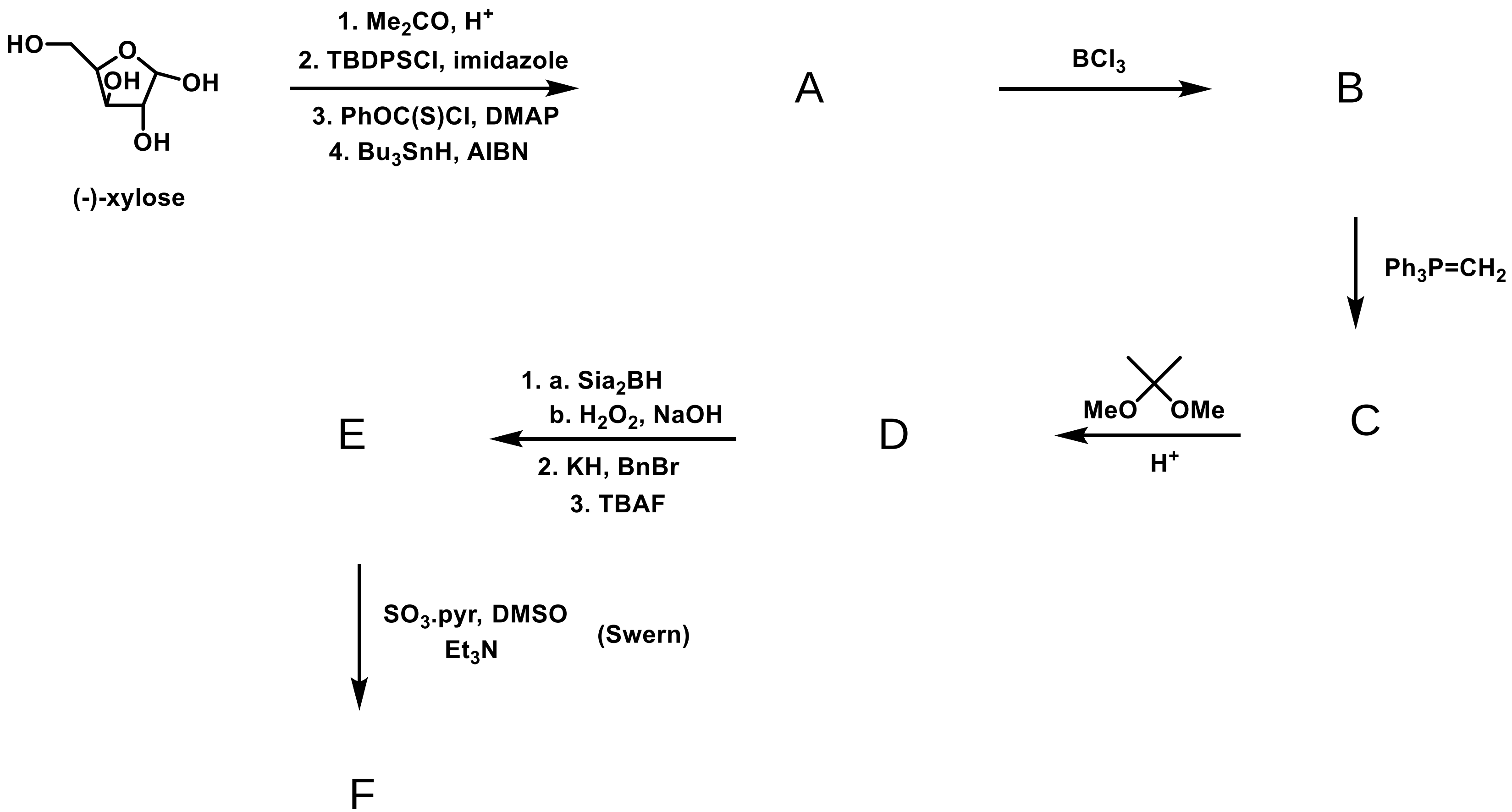
Organic synthesis

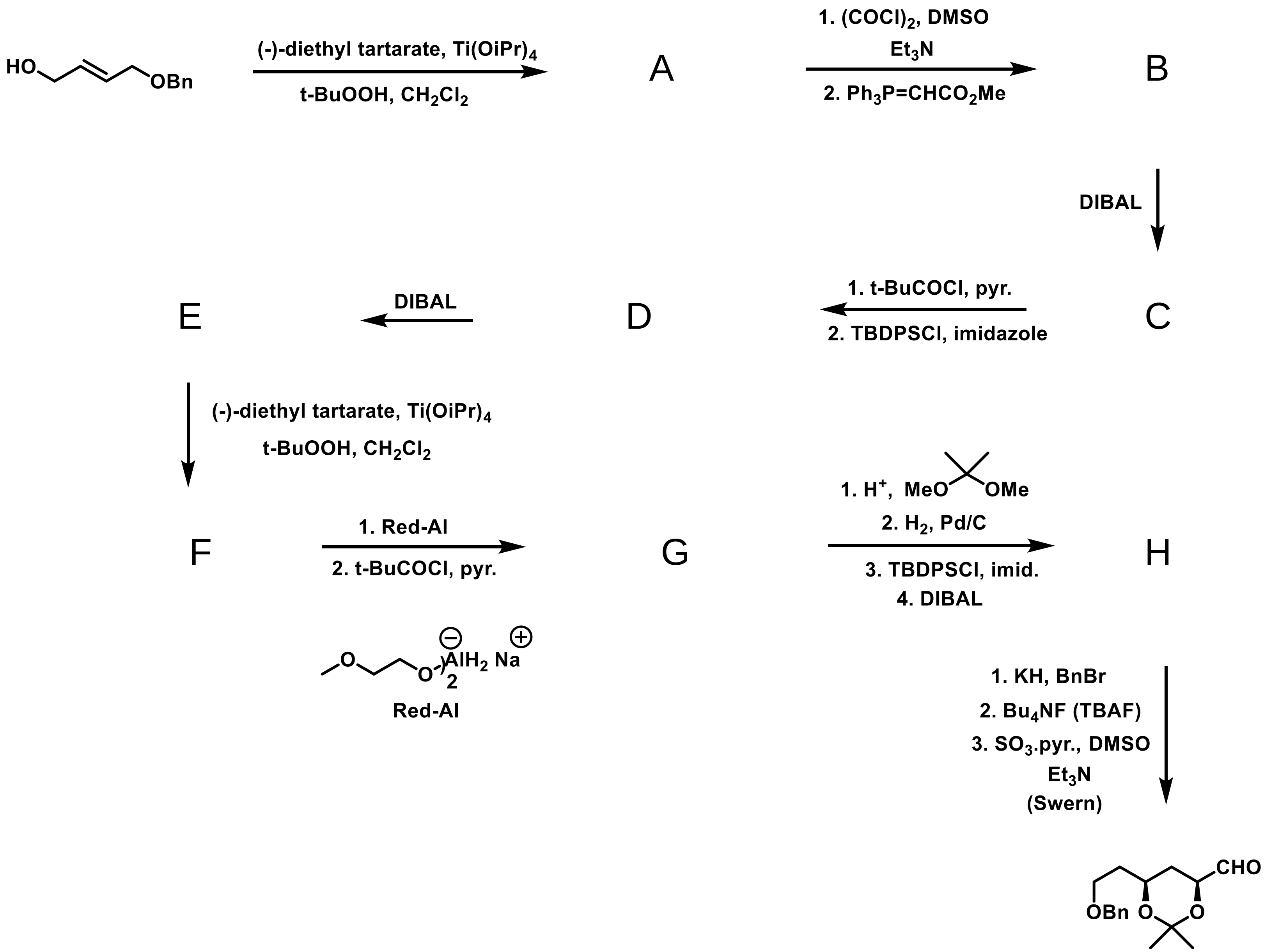
Kamil Paruch

Masaryk University, Brno

1. step: formation of 5-membered ring

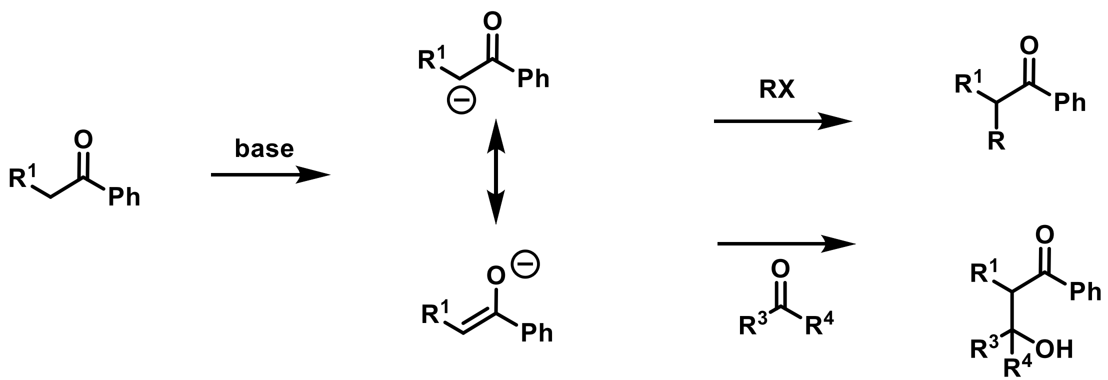



HO
O
OH
OH
OH
(-)-xylose
1. Me_2CO, H^+
2. TBDPSCl, imidazole
3. PhOC(S)Cl, DMAP
4. Bu_3SnH, AIBN
A
BCl_3
B
$Ph_3P{=}CH_2$
C
MeO OMe
H^+
D
1. a. Sia_2BH
b. H_2O_2, NaOH
2. KH, BnBr
3. TBAF
E
SO_3.pyr, DMSO
Et_3N
(Swern)
F

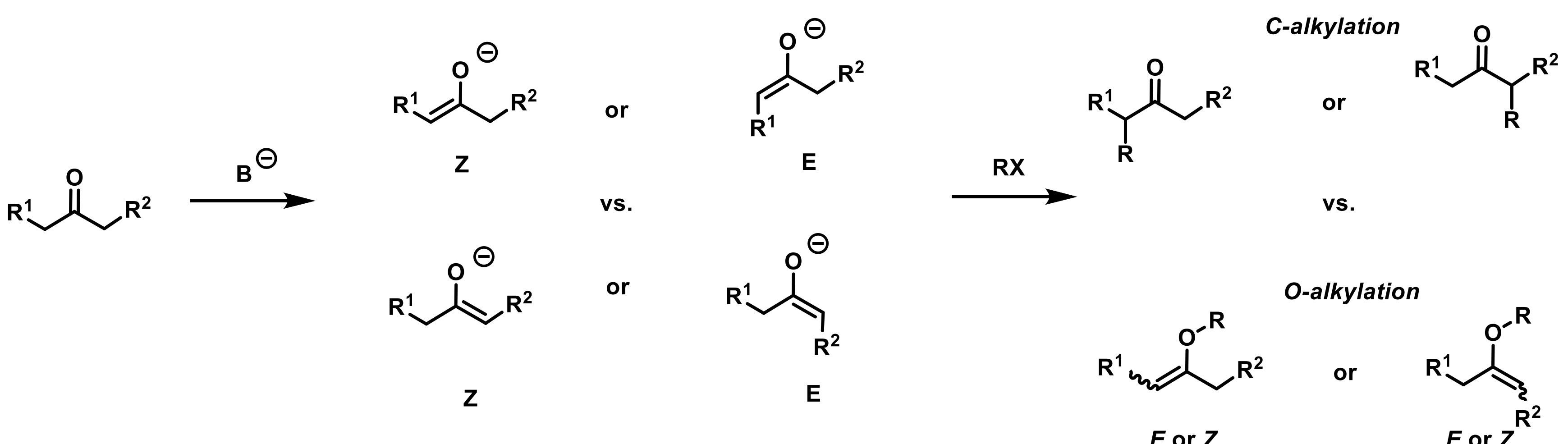


HO
OBn
(-)-diethyl tartarate, Ti(OiPr)4
t-BuOOH, CH2Cl2
A
1. (COCl)2, DMSO
Et3N
2. Ph3P=CHCO2Me
B
DIBAL
C
1. t-BuCOCl, pyr.
2. TBDPSCl, imidazole
D
DIBAL
E
(-)-diethyl tartarate, Ti(OiPr)4
t-BuOOH, CH2Cl2
F
1. Red-Al
2. t-BuCOCl, pyr.
G
1. H+, MeO OMe
2. H2, Pd/C
3. TBDPSCl, imid.
4. DIBAL
H
AlH2 Na
Red-Al
1. KH, BnBr
2. Bu4NF (TBAF)
3. SO3.pyr., DMSO
Et3N
(Swern)
CHO
OBn O O

Enolates: preparation, structure, reactivity



C-C bonds



• C electrophiles: C-alkylations usually predominate

• O alkylations: very reactive (hard) electrophile (e.g. ROTf); K^+ a Na^+ enolates

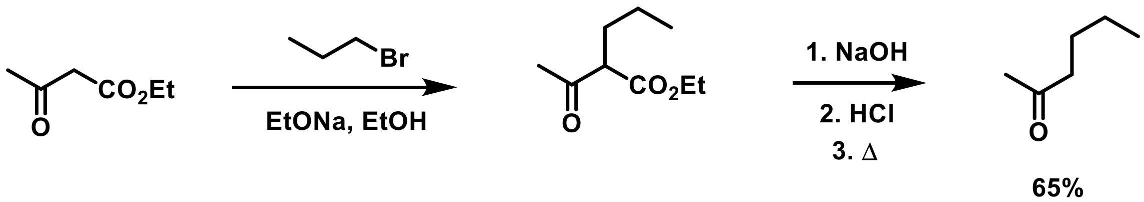
ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS

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

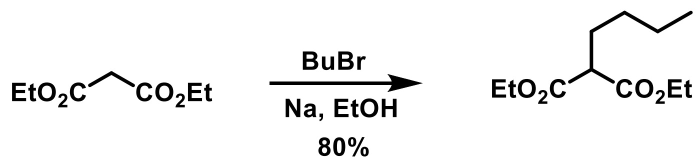
ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS

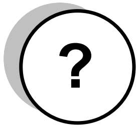
KYSELINA	pK_a	pK_{DMSO}	BÁZE	pK_a (KONJUG.KYSELINY)	pK_{DMSO}
$EtCH(CO_2Et)_2$	15,0		HO^-	15,7	31,4
$PhSCH_2CN$		20,8			
$PhCH_2CN$		21,9			
$(PhCH_2)_2SO_2$		23,9	EtO^-	15,9	29,8
$PhCOCH_3$	15,8	24,7	Me_3CO^-	19,0	32,2
CH_3COCH_3	20,0	26,5			
$MeCH_2COCH_2Me$		27,1			
Fluoren	20,5	22,6			
$PhSO_2CH_3$		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	

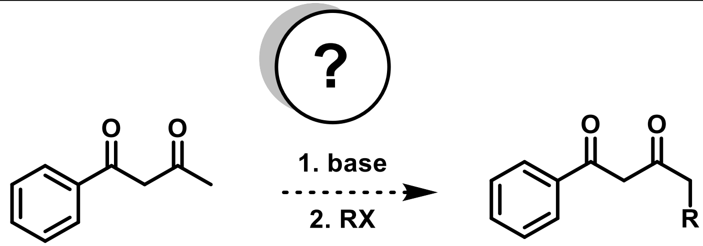
acetoacetate synthesis

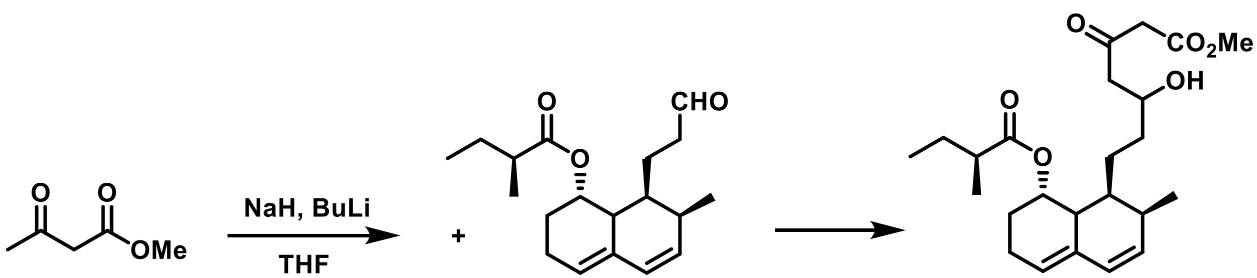


malonic ester synthesis





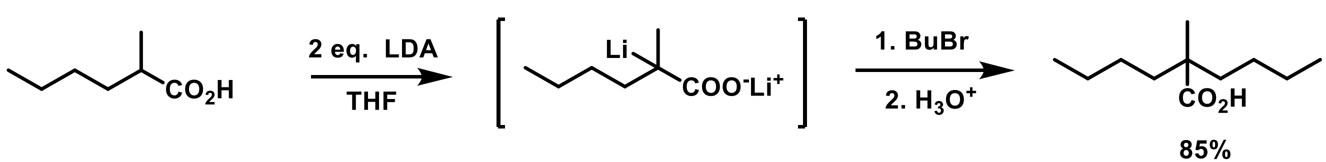




J. Am. Chem. Soc. **1981**, *103*, 6538.

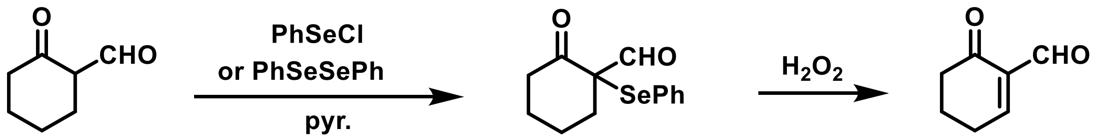
„superbase“: BuLi + t-BuOK

similarly:

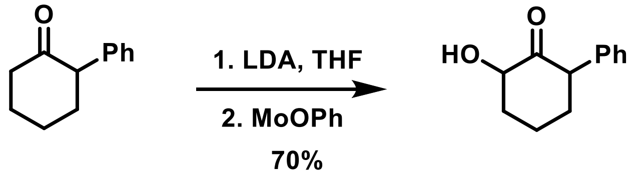


selenation of carbonyl compounds

- preparation of α,β-unsaturated carbonyl compounds

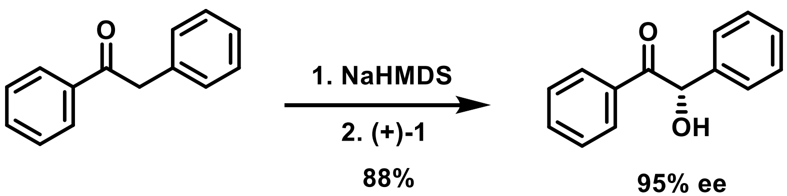


oxidation of enolates



MoOPh : MoO_5+pyr.+HMPA

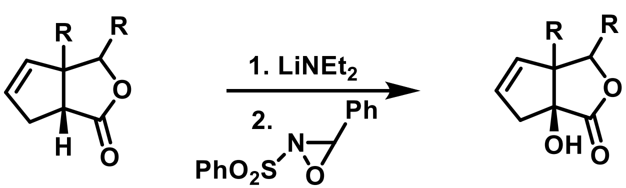
J. Am. Chem. Soc. **1974**, *96*, 5944.



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

(+)-1
(camphorsulfonyl)oxaziridine

?

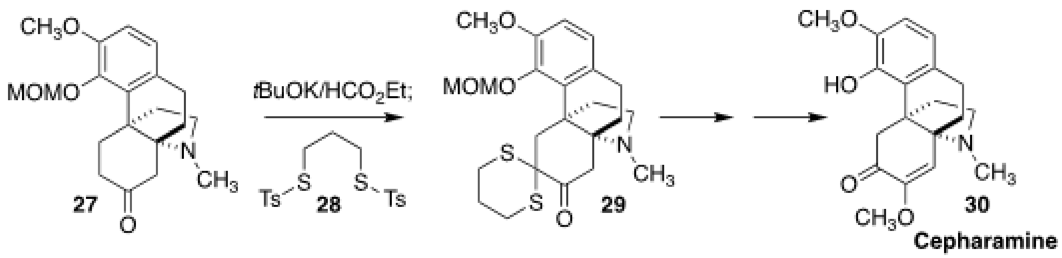


(Davis' oxaziridine)

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

enols/enolates

formal oxidation of α-position of carbonyl compounds

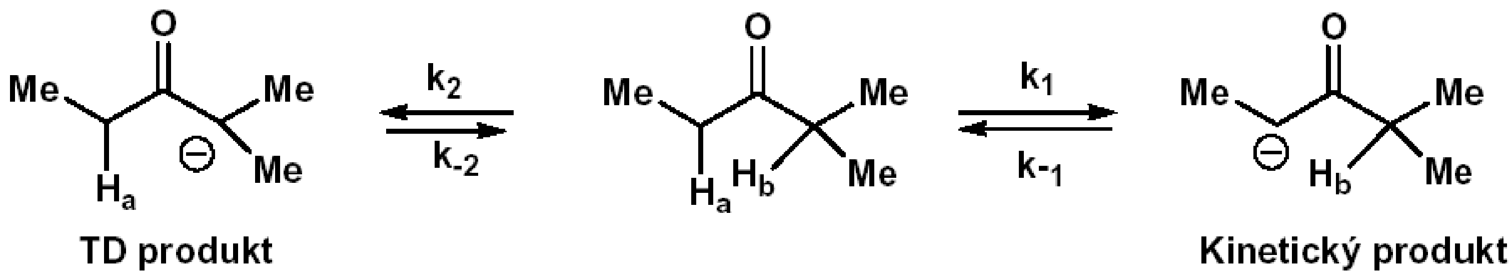


(leaving group: toluene sulfinate)

Nature Commun. **2021**, *12*, 36.

(*J. Org. Chem.* **1971**, *36*, 1137.)

ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS
KINETIC VS. THERMODYNAMIC ENOLATE



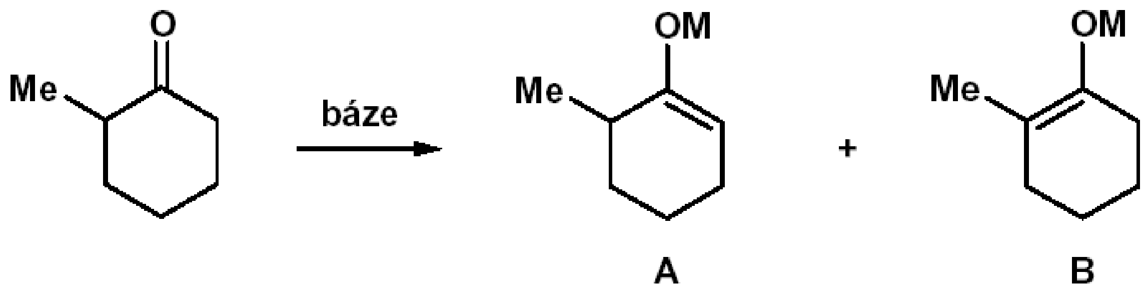
Formation of *kinetic* product ($k_1 > k_2$; $k_1 >> k_{-1}$) is typically observed under these conditions:

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

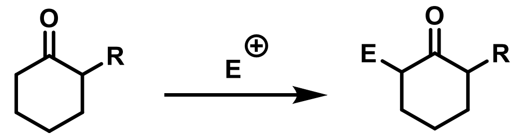
Formation of *thermodynamic* product ($k_1 \sim k_{-1}$) is typically observed under these conditions:

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

ACIDOBASIC PROPERTIES OF CARBONYL COMPOUNDS
KINETIC VS. THERMODYNAMIC ENOLATE

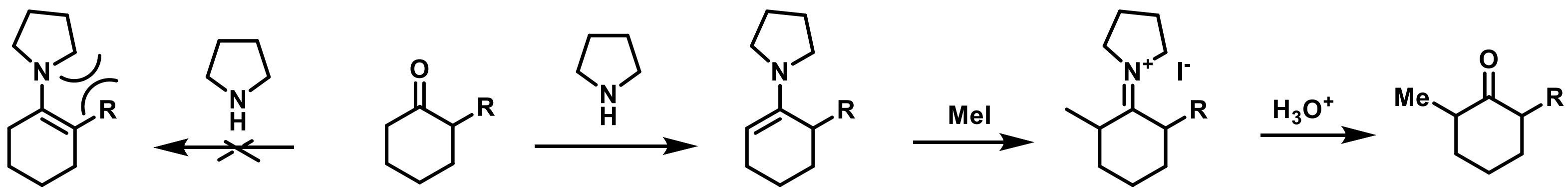


Báze (teplota ve °C)	Podmínky	Poměr A/B
$LiN(i\text{-}C_3H_7)_2$ (0)	Kinetické	99 : 1
$KN(SiMe_3)_2$ (-78)	Kinetické	95 : 5
Ph_3CLi (-78)	Kinetické	90 : 10
Ph_3CK	Kinetické	67 : 33
Ph_3CLi	Termodynamické	10 : 90
NaH	Termodynamické	26 : 74
Ph_3CK	Termodynamické	38 : 62



enamines

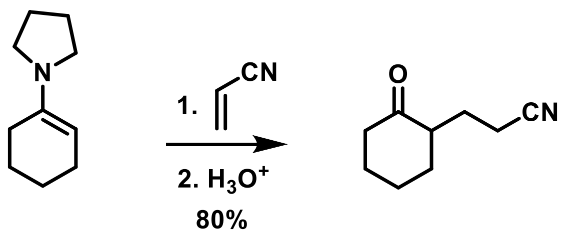
• "nitrogenous enolates"; some can be isolated



planar geometry

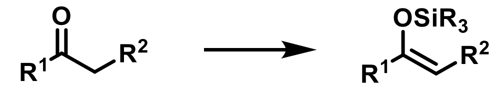
➢ formation of kinetic isomer

• enamines react well with C-electrophiles

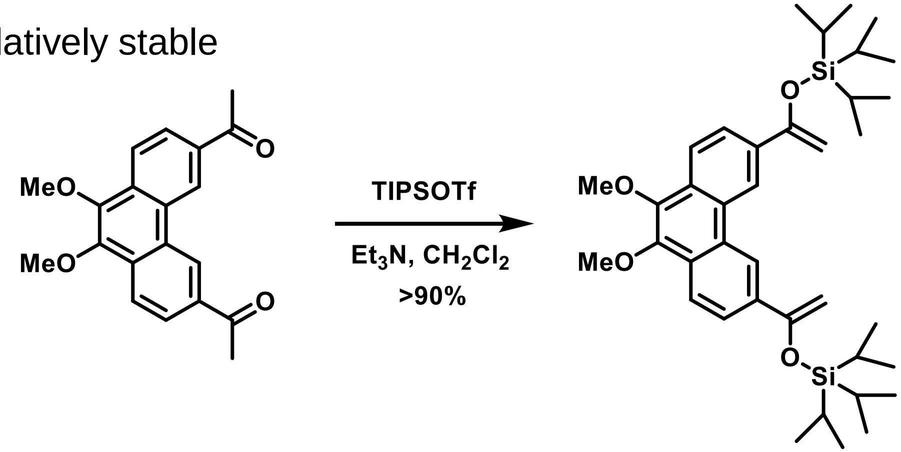


Tetrahedron **1958**, *3*, 314.

silyl enol ethers

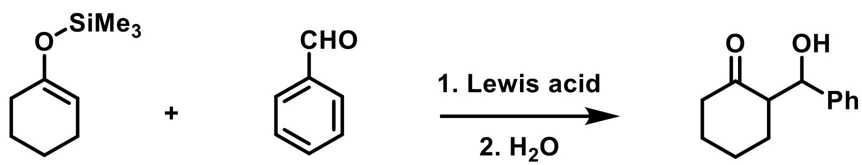


- formation of Si-O bond; irreversible
- silyl enol ethers are relatively stable



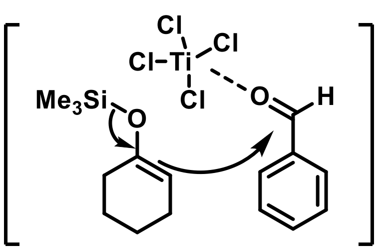
J. Org. Chem. **2000**, *65*, 7602.

Mukaiyama (aldol) reaction



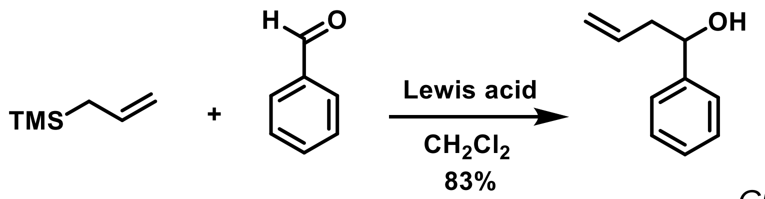
J. Am. Chem. Soc. **1974**, *96*, 7503.

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



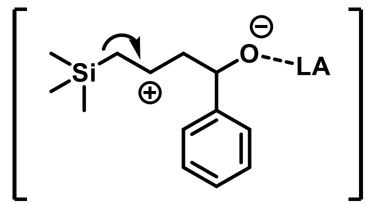
Sakurai allylation

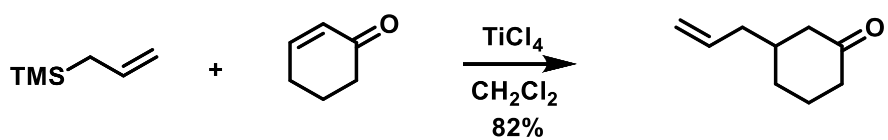
- quite universal, mild conditions (cf. addition of organometalic reagents)



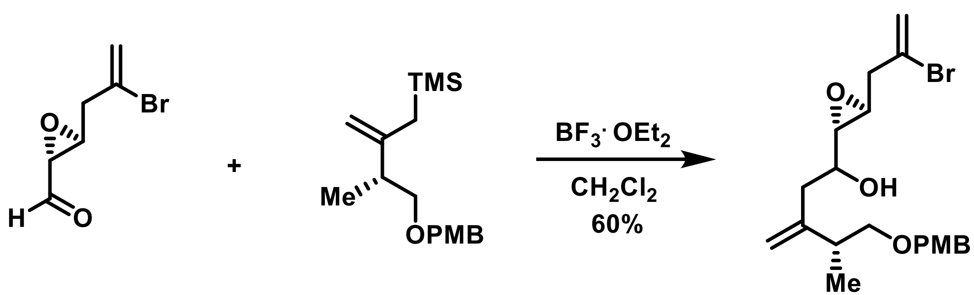
Chem. Lett. **1985**, 977.

10 000 more nucleophilic than propene





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

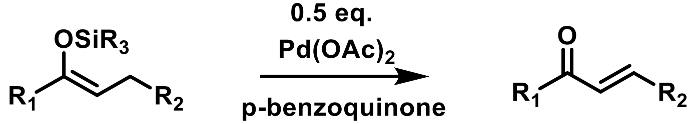


Org. Lett. **2000**, *2*, 945.

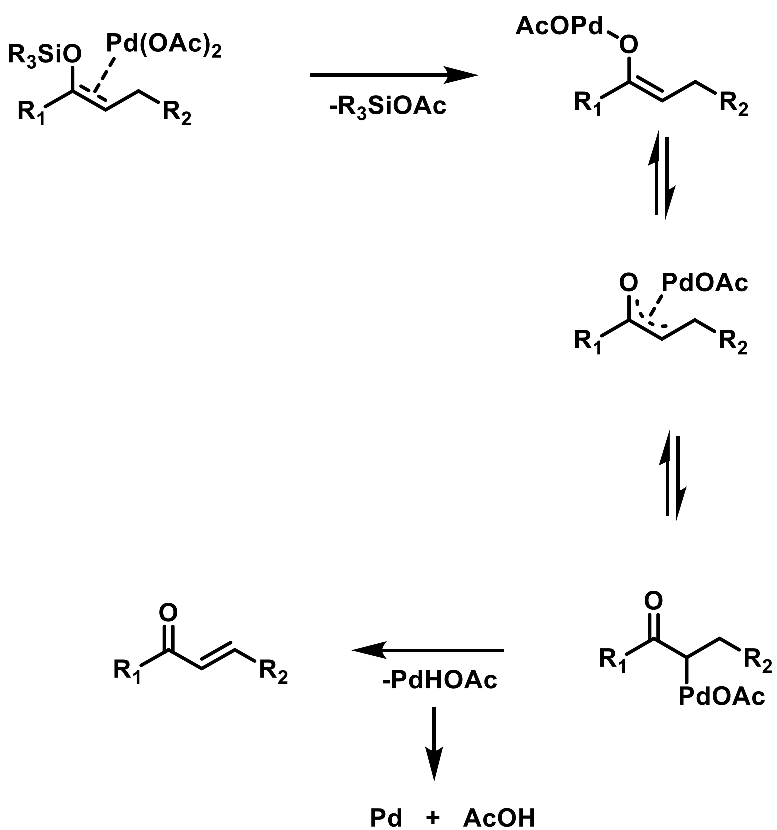
Saegusa oxidation

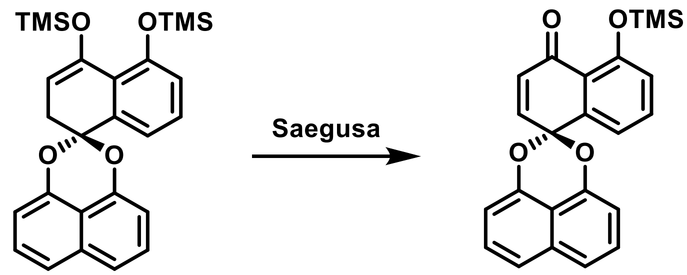
recent review: *Organic Reactions* **98**.

• very mild conditions



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

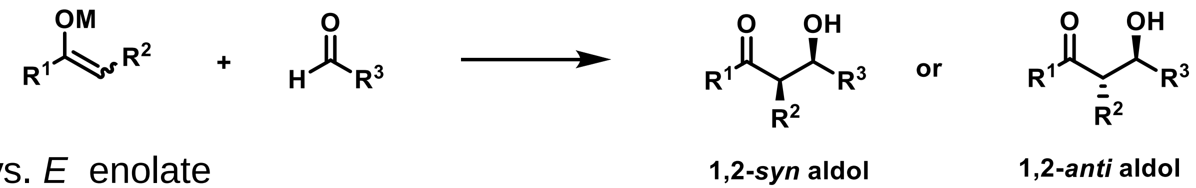




J. Org. Chem. **2002**, *67*, 2735.

enols/enolates

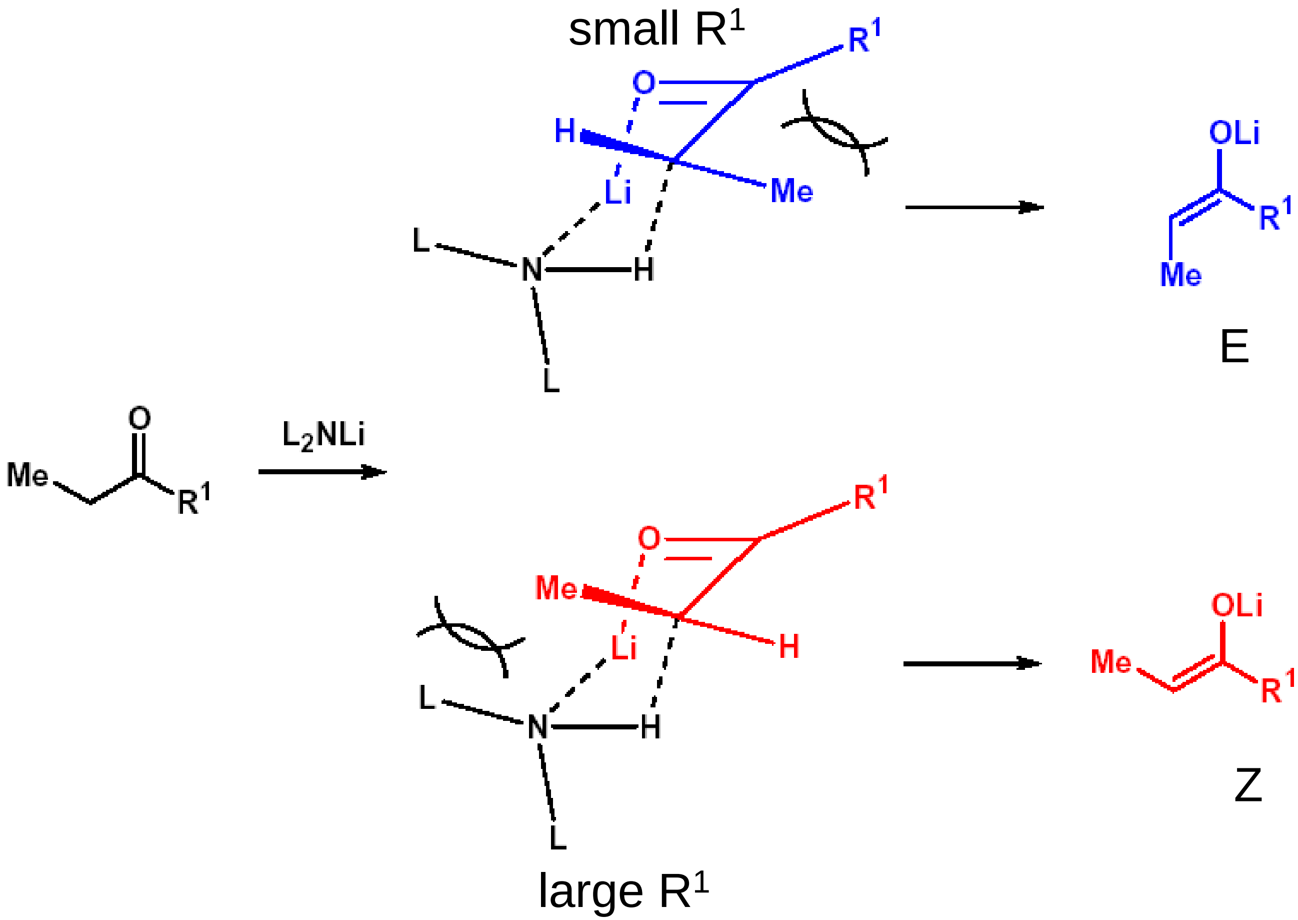
Aldol reaction: 2 new stereogenic centers can be created



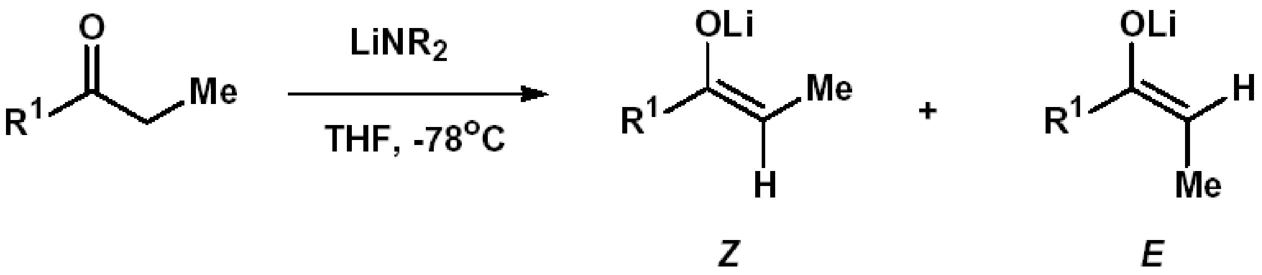
Z vs. *E* enolate

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

GEOMETRY OF ENOLATES - IRELAND MODEL



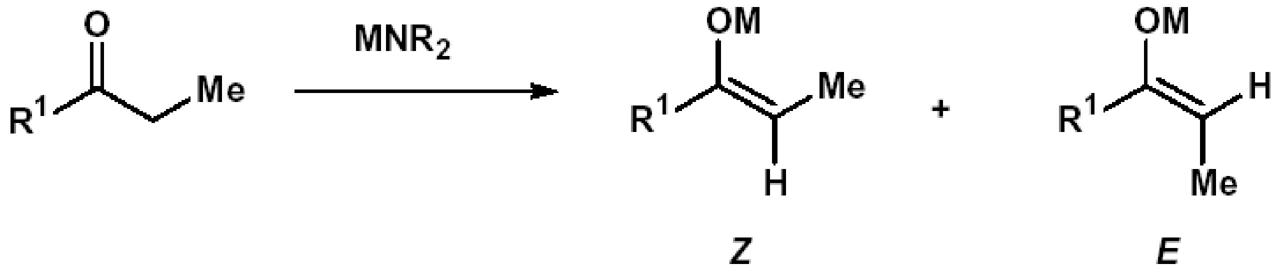
GEOMETRY OF ENOLATES - EFFECT OF BASE



BÁZE	R_1=Et (*Z* : *E*)	R_1=cyklohexyl (*Z* : *E*)
LiN(*i*-Pr)$_2$	30 : 70	61 : 39
LiN(SiMe$_3$)$_2$	70 : 30	85 : 15
LiN(SiEt$_3$)$_2$	99 : 1	96 : 4
LiN(SiMe$_2$Ph)$_2$	100 : 0	100 : 0

enols/enolates

GEOMETRY OF ENOLATES – EFFECT OF SUBSTITUENT

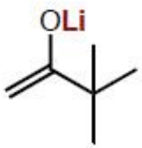


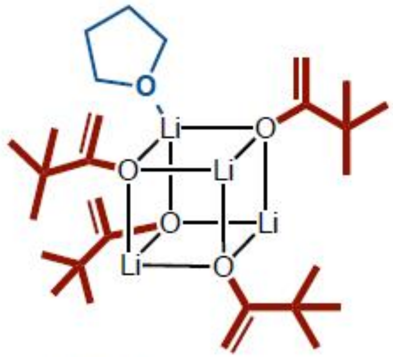
BÁZE (rozpouštědlo)	R^1	*Z*/*E* poměr
LDA (THF)	OMe, O*t*-Bu	5 : 95
LDA (THF)	S*t*-Bu	5 : 95
LDA (THF)	Et	23 : 77
LDA (THF)	*i*-Pr	100 : 0
LDA (THF)	*t*-Bu	60 : 40
LDA (THF)	Ph	100 : 0
LDA (THF)	NEt_2	100 : 0
s-BuLi (THF)	NEt_2	75 : 25

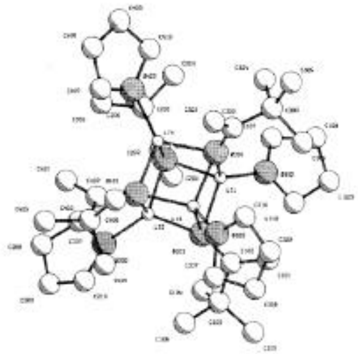
enols/enolates

- enolates often form clusters

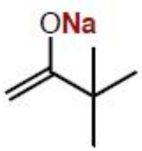
• Lithium enolate

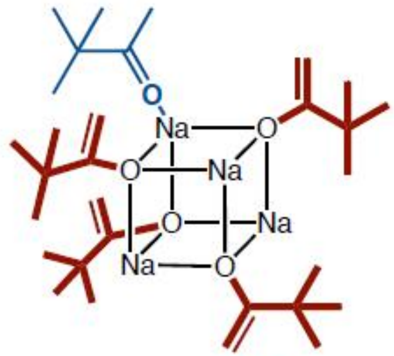


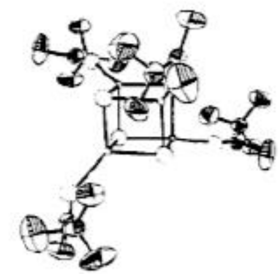




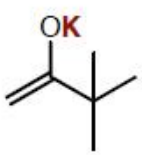
• Sodium enolate

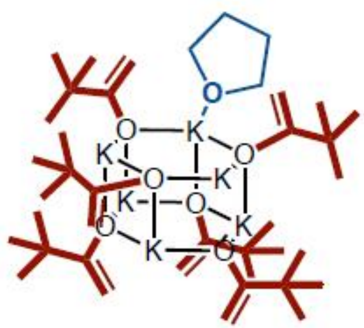


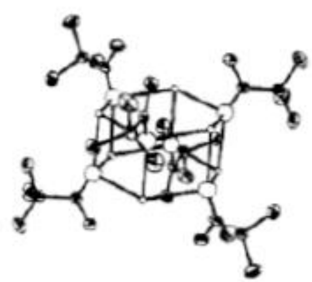


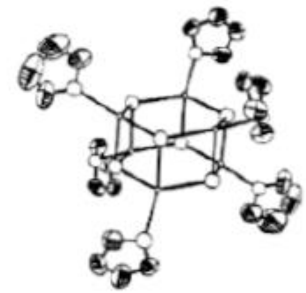


• Potassium enolate







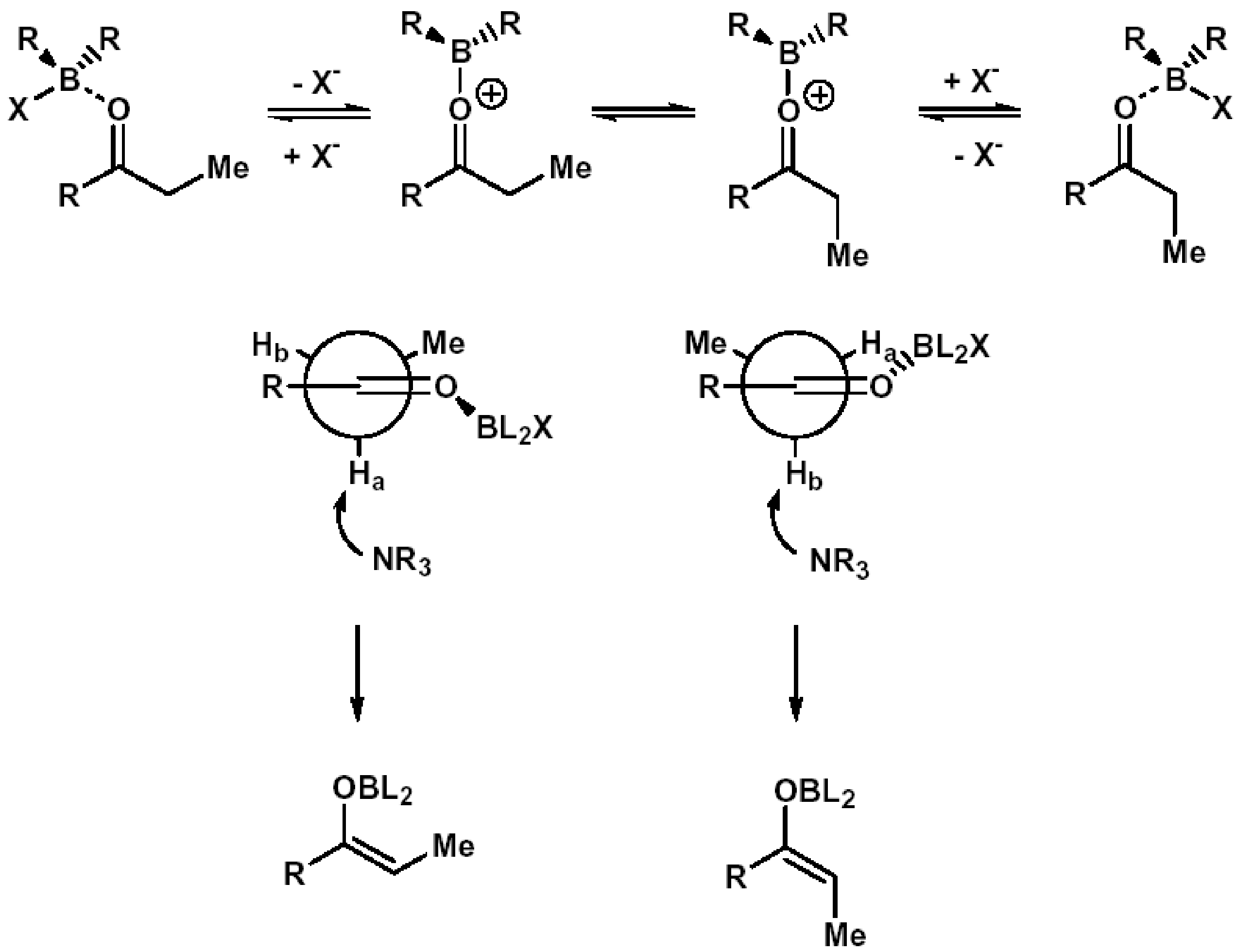


J. Am. Chem. Soc. **1986**, *108*, 462.

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

enols/enolates

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

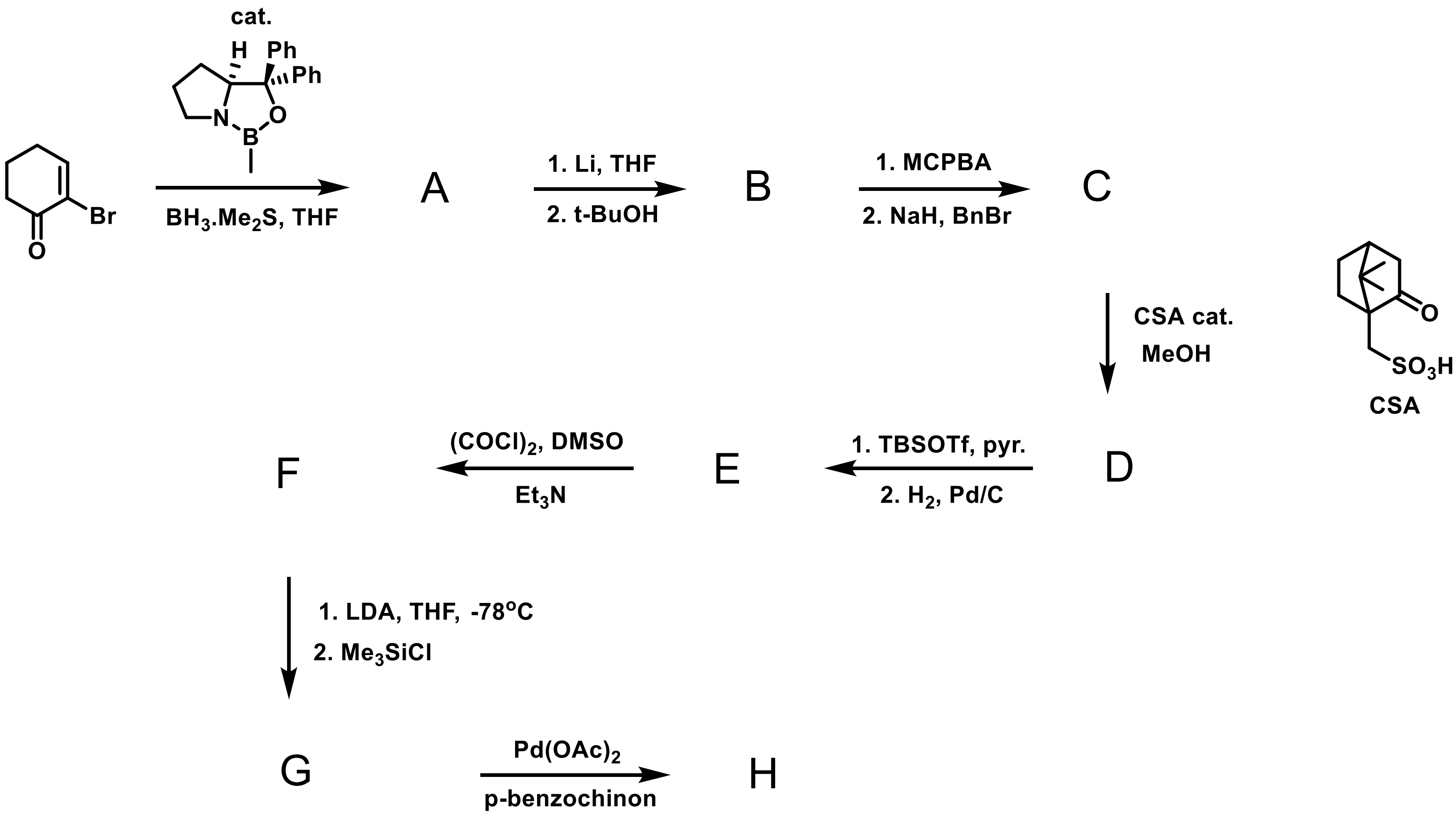


Z-enolát

E-enolát

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
O
B
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