Chapter 6

Formation of Carbon-Carbon σ Bonds *via* Enolate Anions

6.1 – 1,3-Dicarbonyl and Related Compounds

- Relative p*Ka*
- Malonic Acid Esters
- β-Keto Esters

6.2 – Direct Alkylation of Simple Enolates

- Ester Enolates
- From Carboxylic Acids, Amines, and Nitriles
- Ketone Enolates

6.3 – Cyclization Reactions – Baldwin's Rules

- Intramolecular Aldol Reactions
- Intermolecular Alkylation of Enolates

6.1 – 1,3-Dicarbonyl and Related Compounds

KETONES

X=		
	H	(26.5)
	Ph	(19.8)
	SPh	(18.7)
	$COCH_3$	9 (13.3)
	SO_2Ph	(12.5)

19-20 (27.1)

(28.3)

(27.7)

(26.3)

ESTERS

24.5 (30.3)

(23.6)

(20.0)

11 (14.2)

13 (15.7)

SULFOXIDES

X=		
	H	(35.1)
	Ph	(29.0)
	SPh	(29.0)

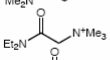
X=		
	H	(33)
	Ph	(27.2)
	SOPh	(18.2)

(24.5)

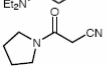
AMIDES

(26.6)

(25.9)



(24.9)



(17.2)

NITRILES

X=		
	H	(31.3)
	CH_3	(32.5)
	Ph	(21.9)
	COPh	(10.2)
	$CONR_2$	(17.1)
	CO_2Et	(13.1)
	CN	11 (11.1)
	OPh	(28.1)
	N^+Me_3	(20.6)
	SPh	(20.8)
	SO_2Ph	(12.0)

http://daecr1.harvard.edu/pdf/evans_pKa_table.pdf

Bordwell pKa data see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

6.1 – 1,3-Dicarbonyl and Related Compounds

Reviews:

Heathcock, C. H. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 133-238.

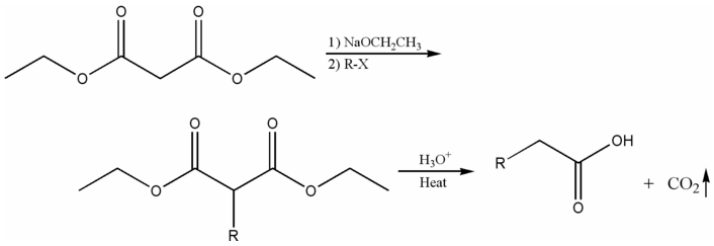
Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 239-275.

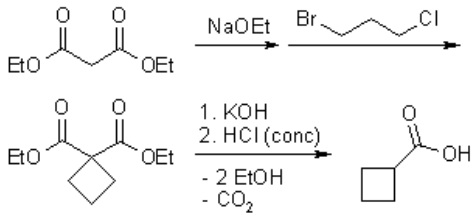
Paterson, I. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 301-319.

- The aldol reaction was discovered by Aleksandr Porfir'evich Borodin in 1872 where he first observed the formation of "aldol", 3-hydroxybutanal, from acetaldehyde under the influence of catalysts such as hydrochloric acid or zinc chloride.

6.1 – 1,3-Dicarbonyl and Related Compounds

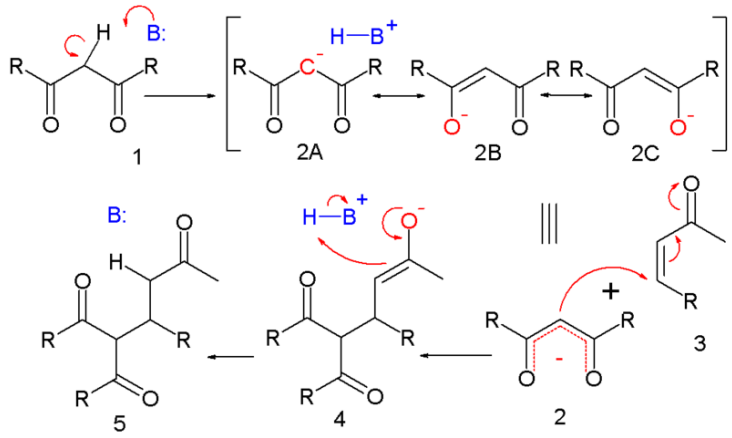
Malonic Ester Synthesis





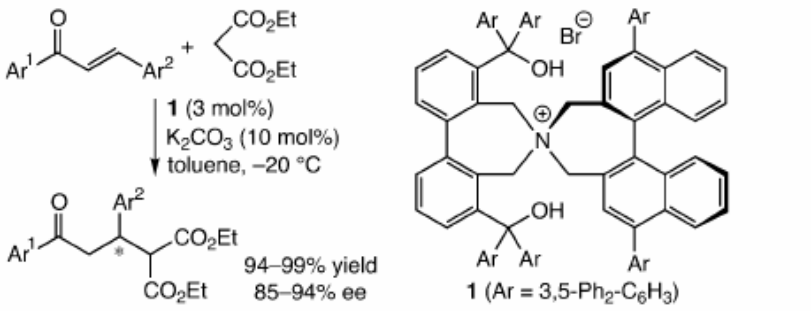
6.1 – 1,3-Dicarbonyl and Related Compounds

Michael Addition



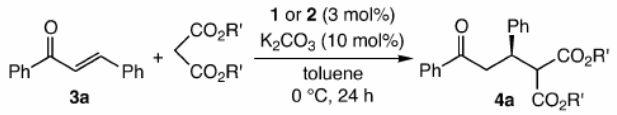
6.1 – 1,3-Dicarbonyl and Related Compounds

Michael Addition – use of chiral phase transfer reagents



T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.*, **2005**, *7*, 3195-3197.

6.1 – 1,3-Dicarbonyl and Related Compounds

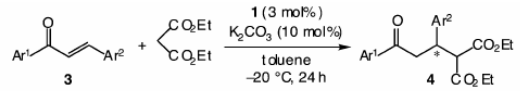


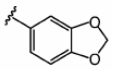
entry	catalyst	R′	% yield[b]	% ee[c] (configuration)[d]
1	**1**	Me	99	84
2	**1**	Et	99	86 (*R*)
3[e]	**1**	Et	99	90 (*R*)
4	**1**	Bn	99	61
5	**1**	*i*-Pr	99	74
6	**1**	*t*-Bu	nr[f]	
7	**2**	Et	98	15 (*R*)

[a] Unless otherwise specified, the reaction was conducted with 4 equiv of dialkyl malonate in the presence of 3 mol % of **1** or **2** and 10 mol % of K_2CO_3 in toluene at 0 °C for 24 h. [b] Isolated yield. [c] Enantiopurity of the Michael adduct **4a** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane−ethanol as a solvent. [d] Absolute configuration was determined by comparison of the optical rotation with the value previously reported.[11] [e] Performed at −20 °C. [f] No reaction.

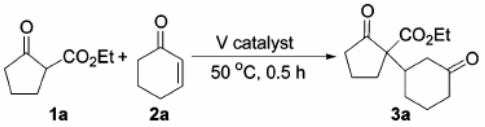
T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.*, **2005**, *7*, 3195-3197.

6.1 – 1,3-Dicarbonyl and Related Compounds



entry	enone **3** Ar[1]	Ar[2]	% yield[b]	% ee[c]	prod.
1[d]	Ph	2-Naphthyl	94	91	**4 b**
2	Ph	4-MeO-C_6H_4	99	87	**4 c**
3	Ph		99	89	**4 d**
4	Ph	4-Cl-C_6H_4	99	85	**4 e**
5[d]	4-Cl-C_6H_4	Ph	97	86	**4 f**
6[e]	Ph	2-Pyridyl	99	90	**4 g**
7	Ph	2-Furyl	99	86	**4 h**
8	Ph	2-Thienyl	99	94	**4 i**
9	2-Thienyl	Ph	99	94	**4 j**

6.1 – 1,3-Dicarbonyl and Related Compounds



1a 2a 3a

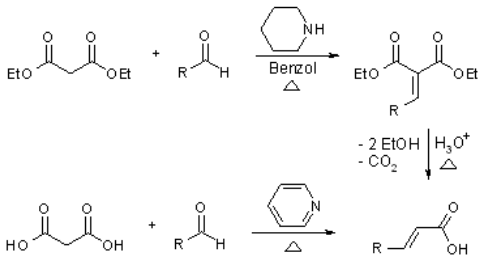
entry	catalyst[b]	solvent	convn (%)[c]	yield (%)[c]
1	VAp (800 °C)	water	>99	>99
2	VAp (600 °C)	water	20	18
3	VAp (400 °C)	water	11	10
4	VAp (200 °C)	water	2	2
5[d]	VAp (uncalcined)	water	38	36
6	VAp (800 °C)	neat	0	0
7	VAp (800 °C)	acetone	0	0
8	VAp (800 °C)	CH_3CN	0	0
9	VAp (800 °C)	EtOH	0	0
10	VAp (800 °C)	EtOAc	0	0
11	VAp (800 °C)	DMF	0	0
12	VAp (800 °C)	DMSO	0	0

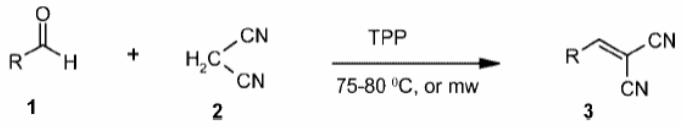
$Ca_9(HVO_4)(\overline{V}O_4)_5(OH)$

T. Hara, S. Kanai, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda,
J. Org. Chem., **2006**, *71*, 7455-7462.

6.1 – 1,3-Dicarbonyl and Related Compounds

Knoevenagel Condensation

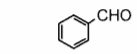
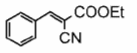
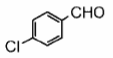
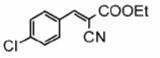
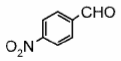
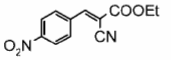
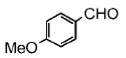
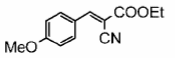


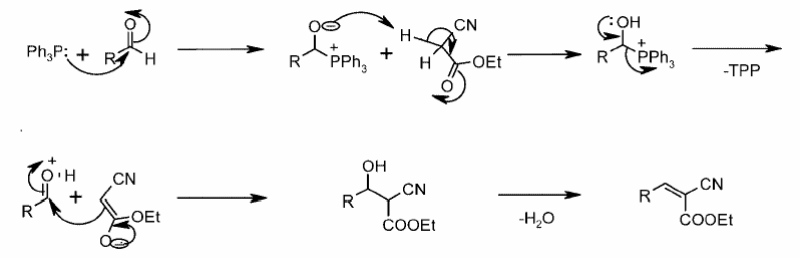


1 2 3

J. S. Yadav, B. S. S. Reddy, A. K. Basak, B. Visali, A. V. Narsaiah, K. Nagaiah,
Eur. J. Org. Chem., **2004**, 546-551.

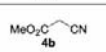
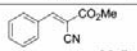
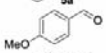
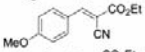
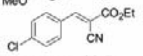
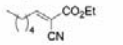
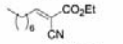
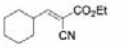
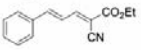
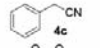
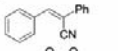
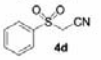
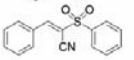
6.1 – 1,3-Dicarbonyl and Related Compounds

Entry	Aldehyde 1	Product[a] 3	Conversion (%)[b]	Conventional Time (h)	Conventional Yield (%)[c]	Microwave[d] Time (min)	Microwave[d] Yield (%)[c]
a			98	4.0	85	3	90
b			99	3.0	87	3	92
c			100	2.5	90	2	95
d			95	4.5	82	4	85



6.1 – 1,3-Dicarbonyl and Related Compounds

TABLE 3. Knoevenagel Condensation in Water Using VAp Catalyst[a]

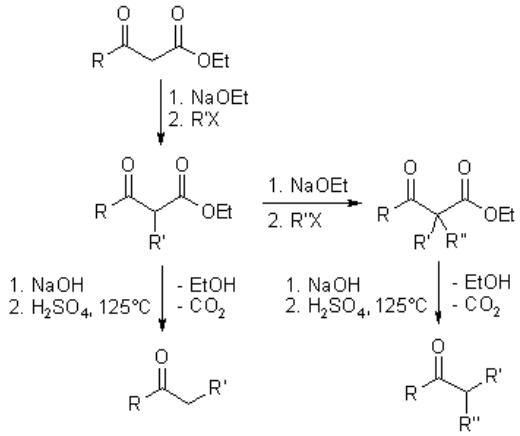
entry	donor	acceptor	time (h)	product	yield (%)[b]
1	 4b	 5a	1		>99
2	4a		3		98
3	4a		6		96
4	4a		4		95
5	4a		6		91
6	4a		3		99
7	4a		3		>99
8[c]	 4c	5a	12		89
9[d]	 4d	5a	2		90

[a] Donor (1.5 mmol), acceptor (1 mmol), water (5 mL), VAp (0.05 g), 50 °C. [b] Determined by GC using an internal standard method. [c] 110 °C. [d] THF (1 mL) was used as a cosolvent, 60 °C.

T. Hara, S. Kanai, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *J. Org. Chem.*, **2006**, *71*, 7455-7462.

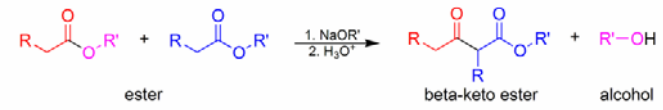
6.1 – 1,3-Dicarbonyl and Related Compounds

β-Keto Esters

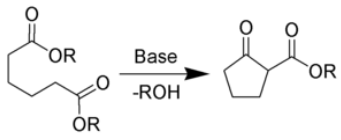


6.1 – 1,3-Dicarbonyl and Related Compounds

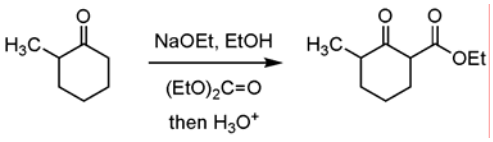
β-Keto Esters – *via* the Claisen Condensation



β-Keto Esters – *via* the Dieckman Condensation

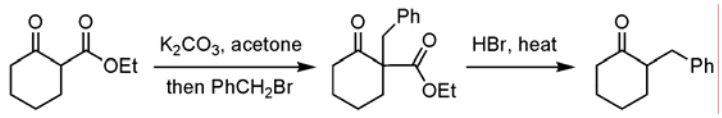


β-Keto Esters – *via* Acylation

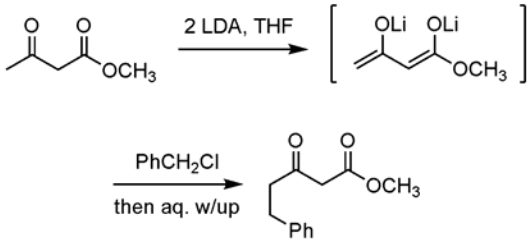


6.1 – 1,3-Dicarbonyl and Related Compounds

β-Keto Esters – Alkylation

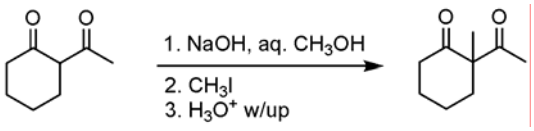


β-Keto Esters – Double Deprotonation

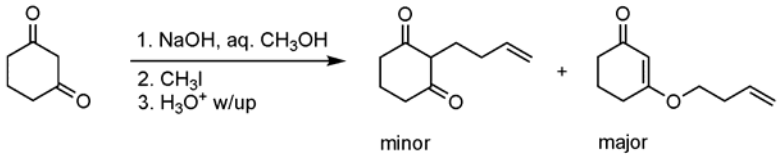


6.1 – 1,3-Dicarbonyl and Related Compounds

1,3-Diketones

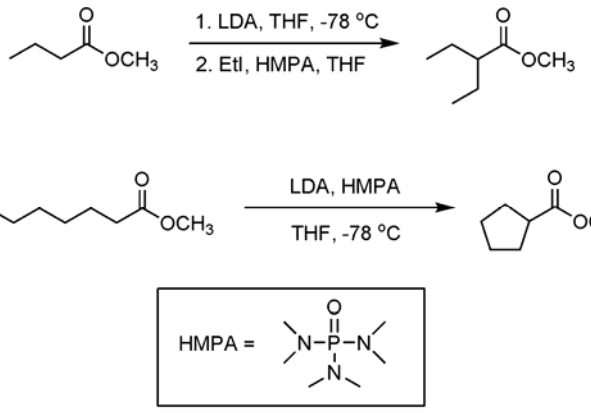


1,3-Diketones - Limitations



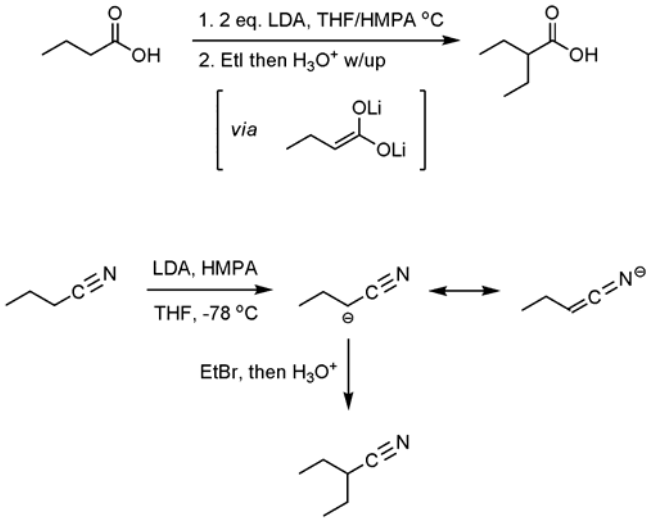
O-alkylation competes, outcome depends on amount of enol

6.2 – Direct Alkylation of Simple Enolates

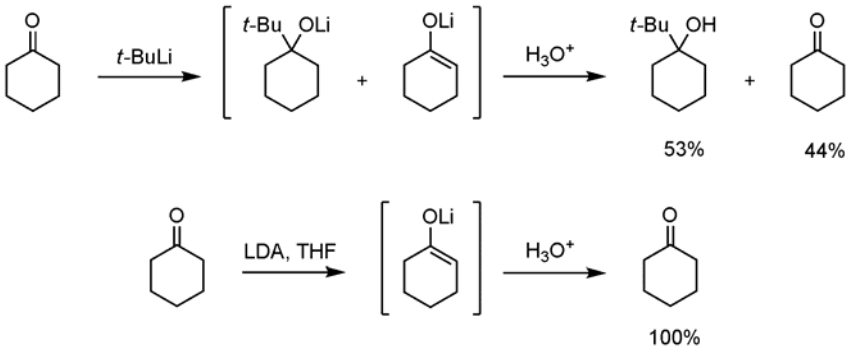


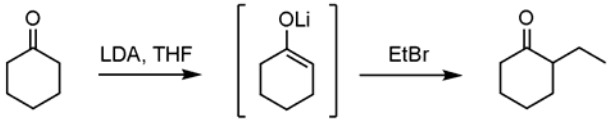
HMPA, and similar additives, break up Li aggregates

6.2 – Direct Alkylation of Simple Enolates

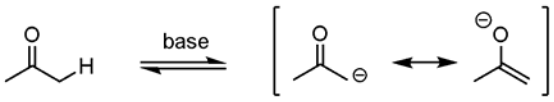


6.2 – Ketone Enolates





6.2 – Ketone Enolates



pK_a ~20 NaOEt EtOH pK_a~16

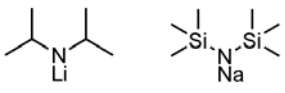
K ~10^{-4}

pKa ~20 LDA $(i\text{-Pr})_2$NH pKa~36

K ~10^{16}

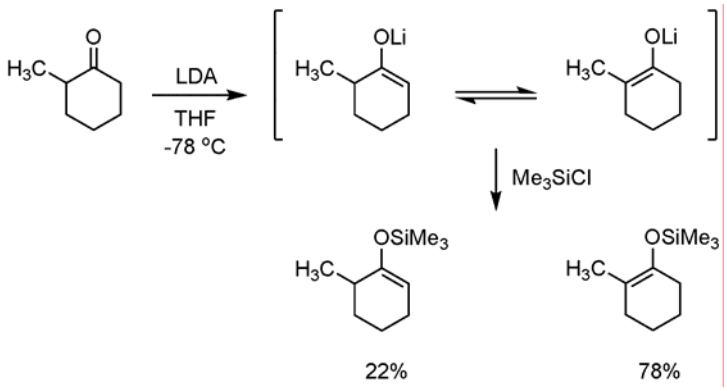
Typical bases used:

NaOEt ; $NaOCH_3$; KO*t*-Bu



6.2 – Ketone Enolates

Regioselective Enolate Formation

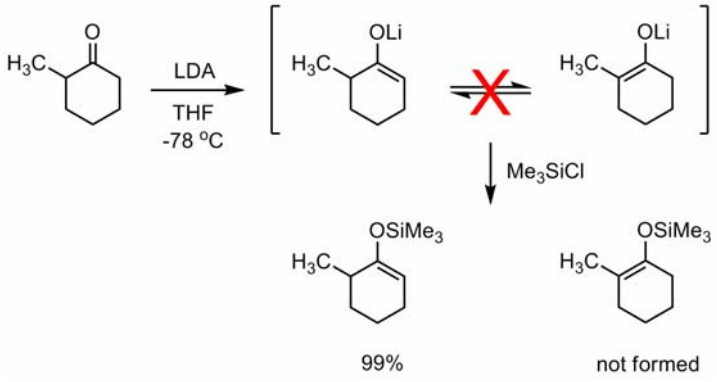


Using 1.02 equivalents of ketone to 1.0 equivalent of LDA, i.e. slight excess of ketone (weak base)

Also use of KH and BEt_3 gives thermodynamic enolate

6.2 – Ketone Enolates

Regioselective Enolate Formation

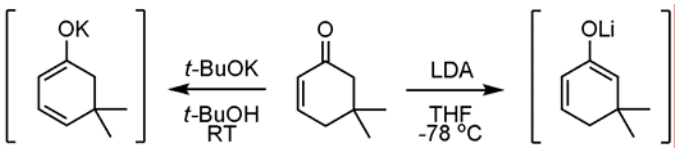


Using 1.0 equivalents of ketone to 1.05 equivalents of LDA, i.e. slight excess of the strong base

More accessible proton removed, no chance of equilibration

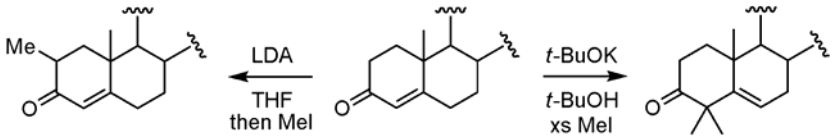
6.2 – Ketone Enolates

Deprotonation of Enones



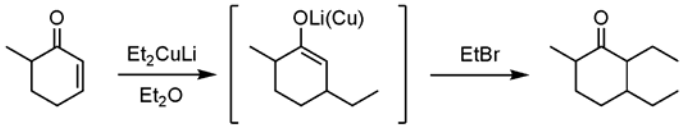
Conjugated
(more stable)

Cross-conjugated
(less stable)

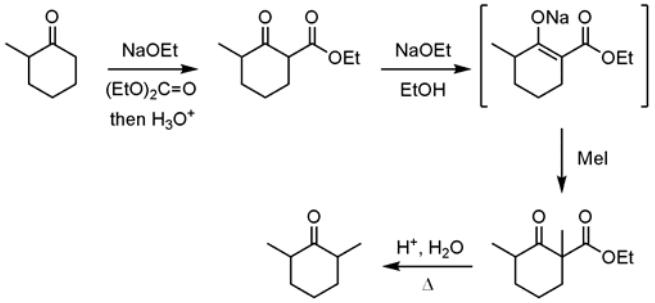


6.2 – Ketone Enolates

Enolates via Conjugate Addition



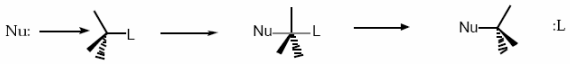
Use of Activating Groups



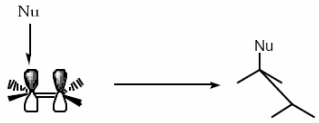
6.3 – Baldwin's Rules

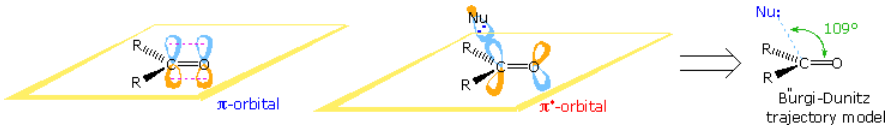
Approach Vector Analysis

- for an S_N2 displacement at a tetrahedral center, the approach vector of the entering nucleophile is 180° from the departing leaving group



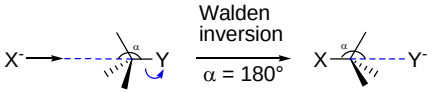
- for the addition of a nucleophile to an Sp2 center, the nucleophile approaches perpendicular to the π-system.



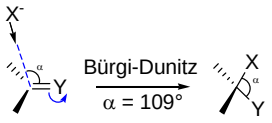


6.3 – Baldwin's Rules

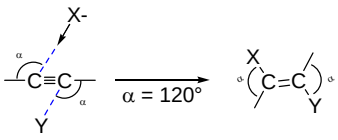
Favoured paths to transition states are:



Tetrahedral Systems



Trigonal Systems



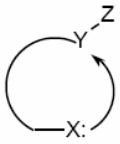
Digonal Systems

6.3 – Baldwin's Rules

Nomenclature

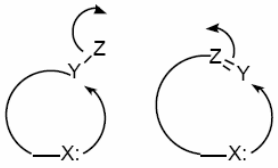
1. indicate ring size being formed
   - 3 membered ring = **3**
   - 4 membered ring = **4**
   - etc.

2. indicate geometry of electrophilic atom
   - if Y= Sp3 center; then **Tet** (tetrahedral)
   - if Y= Sp2 center; then **Trig** (trigonal)
   - if Y= Sp center; then **Dig** (digonal)



6.3 – Baldwin's Rules

3. indicate where displaced electrons end up
   - if the displaced electron pair ends up out side the ring being formed; then **Exo**
   - if the displaced electron pair ends up within the ring being formed; then **Endo**



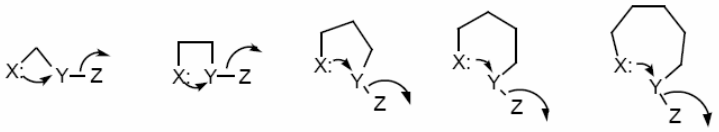
Exo Endo

4. Ring forming reaction is designated as **Favored** or **Disfavored**
   disfavored does not imply the reaction can't or won't occur- it only means the reaction is more difficult than favored reactions.

6.3 – Baldwin's Rules

Rules (Suggestions) for Ring Closure

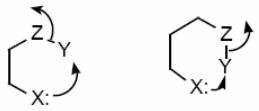
- All **Exo-Tet** reactions are *favored*



3- 4- 5- 6- 7-

----------Favored----------

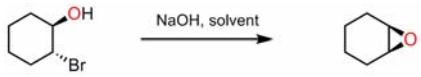
- **5-Endo-Tet** and **6-Endo-Tet** are *disfavored*

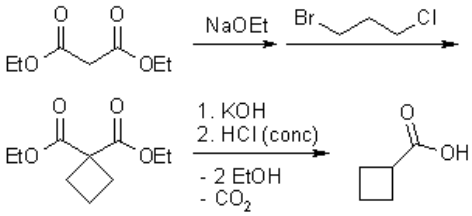


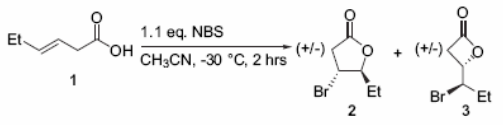
5- 6-

-----Disfavored-----

6.3 – Baldwin's Rules



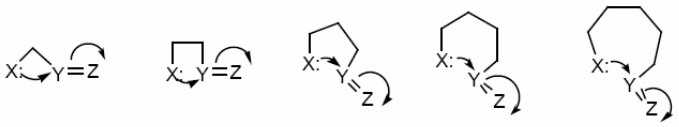




	2	3
no catalyst	2	1
5 mol % PhSeSePh	17	1
5 mol % PhSeBr	4	1
5 mol % PhSe(pthalimide)	2	1

6.3 – Baldwin's Rules

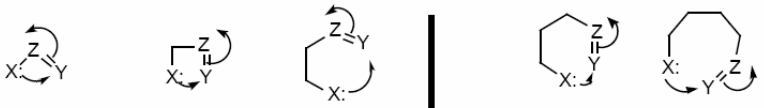
- All **Exo-Trig** reactions are *favored*



3- 4- 5- 6- 7-

----------Favored----------

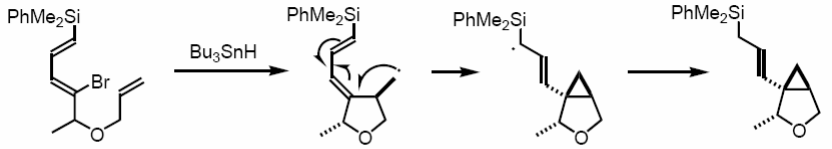
- **3-Endo-Trig**, **4-Endo-Trig** and **5-Endo-Trig** are *disfavored*; **6-Endo-Trig**, **7-Endo-Trig**, etc. are *favored*



3- 4- 5- 6- 7-

----------Disfavored---------- ------Favored------

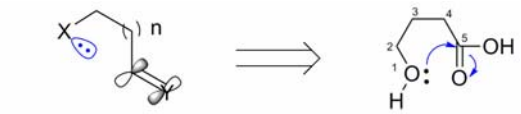
6.3 – Baldwin's Rules



Luh, T.Y. *et al J. Org. Chem.* **1993**, *58*, 5574

58%

Why are all exo-Trig cyclisations favoured?

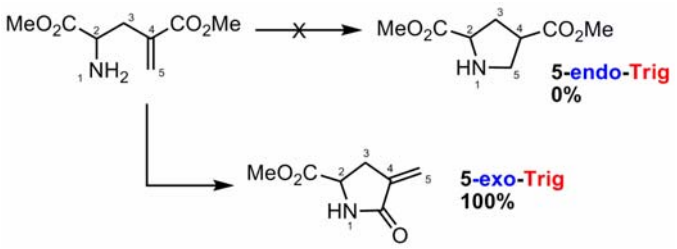


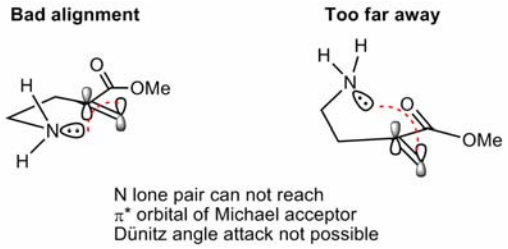
X lone pair
Overlap with C=Y π*
Attack at 109° angle possible

5-exo-Trig

6.3 – Baldwin's Rules

5-endo-Trig *versus* 5-exo-Trig

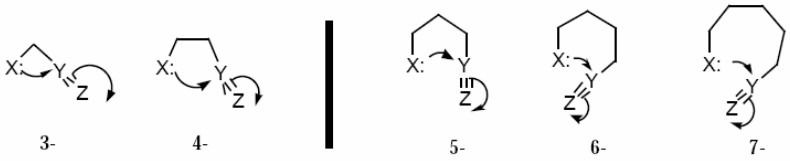




N lone pair can not reach
π* orbital of Michael acceptor
Dünitz angle attack not possible

6.3 – Baldwin's Rules

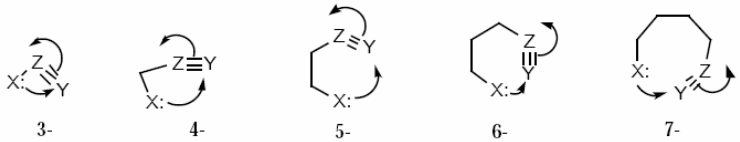
- 3-Exo-Dig and 4-Exo-Dig are *disfavored*; 5-Exo-Dig, 6-Exo-Dig, 7-Exo-Dig, etc. are *favored*



3- 4- 5- 6- 7-

------Disfavored----- ----------Favored----------

- All Endo-Dig are *favored*

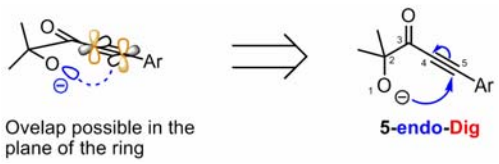


3- 4- 5- 6- 7-

----------Favored----------

6.3 – Baldwin's Rules

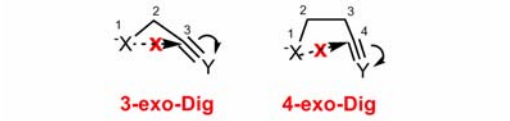
All endo-Dig cyclizations are favoured



Ovelap possible in the plane of the ring

5-endo-Dig

3- and 4-exo-Dig cyclisations are disfavoured

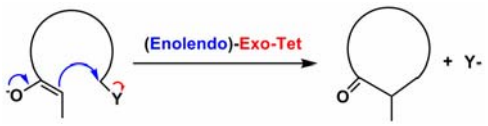


3-exo-Dig 4-exo-Dig

Nuclephile can not attack with the required 120° angle

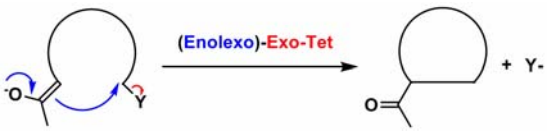
6.3 – Baldwin's Rules – Enolate Alkylation

Endocyclic alkylations



- 6- to 7- membered RC Favoured
- 3- to 5- membered RC Disfavoured

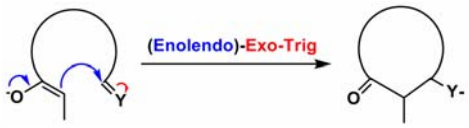
Exocyclic alkylations



- 3- to 7- membered RC Favoured

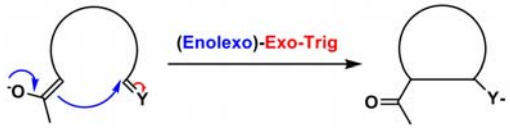
6.3 – Baldwin's Rules – Intramolecular Aldol

Endocyclic reactions



- 3- to 5- membered RC Disfavoured
- 6- to 7- membered RC Favoured

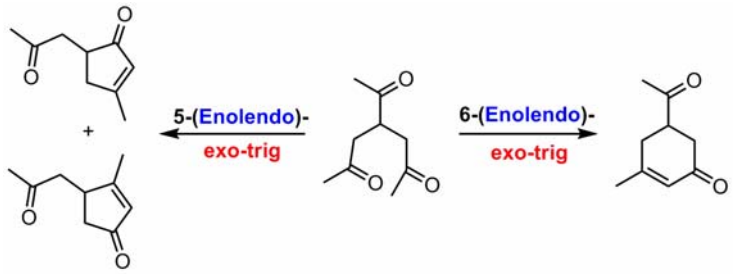
Exocyclic reactions



- 3- to 7- membered RC Favoured

6.3 – Baldwin's Rules - Enolates

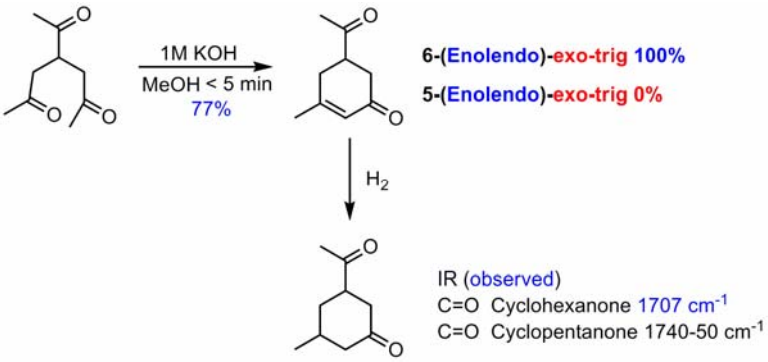
6-(enolendo)-exo-trig versus 5-(enolendo)-exo-trig



Statistics : 4 possibilities to form a 5-membered ring
2 possibilities to form a 6-membered ring

Thermodyn. : 6-membered ring would be predominant or exclusive

6.3 – Baldwin's Rules - Enolates

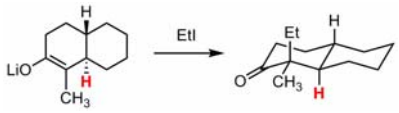


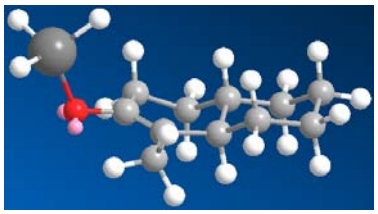
Formation of cyclohexanone totally dominates over even statistically preferred cyclopentanones production.

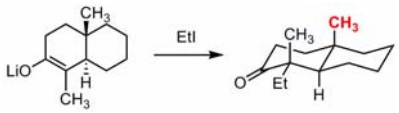
6.3 – Baldwin's Rules - Enolates

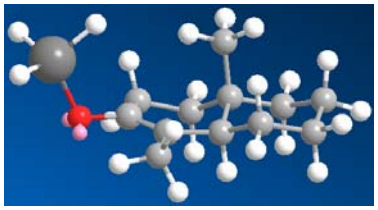
- Only give information about whether processes are favoured or disfavoured and not allowed and forbidden.
- Nucleophilic RC feasibility strongly depends on ring size, geometry of reacting atom and exo or endo nature of reaction.
- Structural modification can dramatically affect the cyclization mode.
- If favoured trajectory of attack valid, then reaction will follow the Baldwin's rules.

6.4 – Stereochemistry of Cyclic Ketone Alkylation



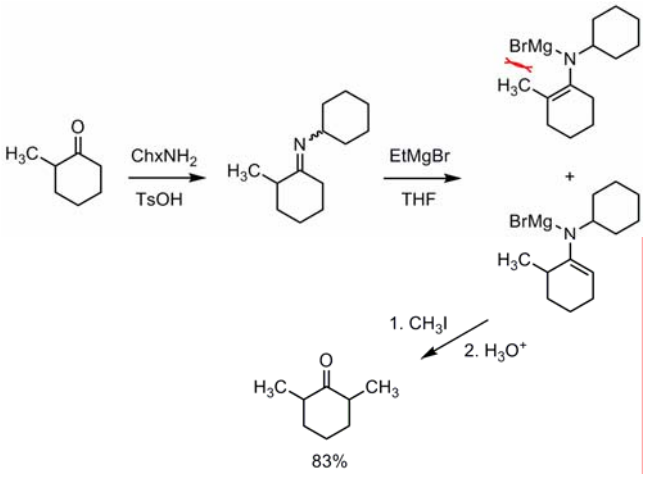






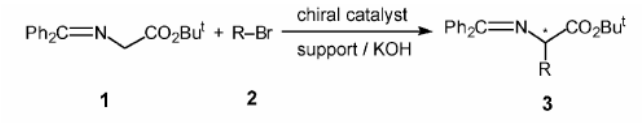
Local groups will have an obvious effect on the direction of approach of the electrophile

6.5 – Imine and Hydrazone Anions



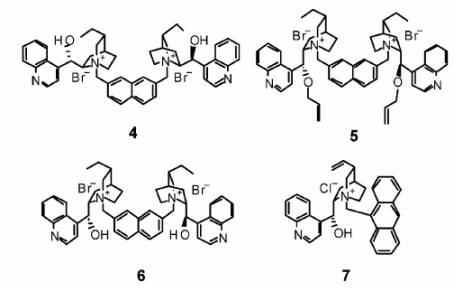
Often cleaner reactions than with aldehyde and ketone enolates due to no overalkylation

6.5 – Imine and Hydrazone Anions



1 2 3

H. Yu *et al*. *Tetrahedron* **2004**, *60*, 8405–8410

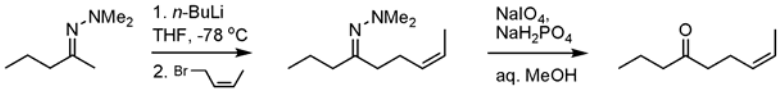


4 5 6 7

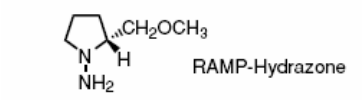
Entry	Catalyst	Support	Time (h)	Yield (%)	Ee (%) (Config.)
1	4	Kaolin	1.0	97	81 (*R*)
2	5	Kaolin	0.5	97	82 (*S*)
3	6	Kaolin	6.5	86	84 (*S*)
4	7	Kaolin	0.5	91	72 (*S*)
5	8[b]	Kaolin	5.0	91	86 (*R*)
6	5	Aluminium oxide	3.5	90	84 (*S*)
7	5	Montmorillonite K10	24	90	86 (*S*)
8	5	Celite	140	50	62 (*S*)

6.5 – Imine and Hydrazone Anions

Simple case -

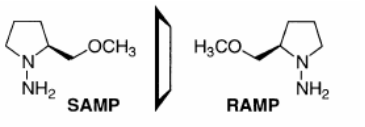


Enantioselective variants – SAMP/RAMP



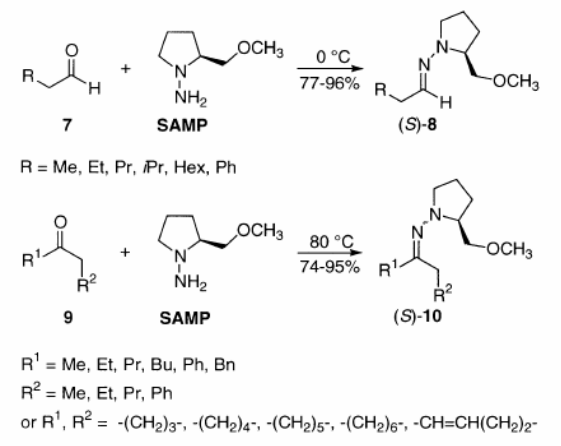
(*R*)-(+)-1-Amino-2-(methoxymethyl) pyrrolidine [RAMP-Hydrazone] $97.9/g (1 g)

(*S*)-(+)-1-Amino-2-(methoxymethyl) pyrrolidine [SAMP-Hydrazone] $46.1/g (1 g)



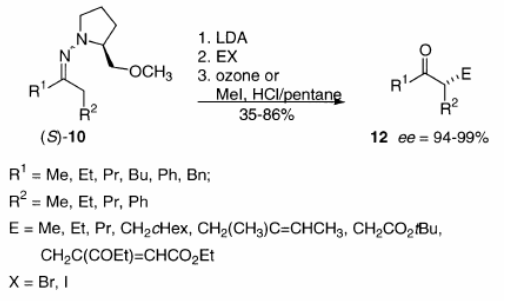
6.5 – Imine and Hydrazone Anions

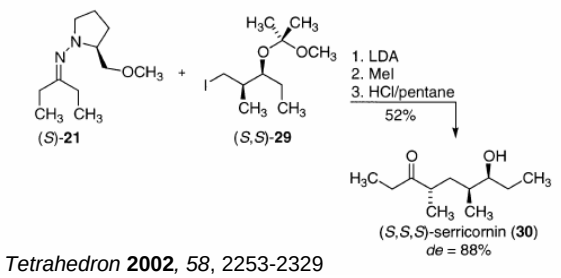
Formation of Hydrazones



Enders, D.; *et. al*. *Tetrahedron* **2002***, 58*, 2253-2329

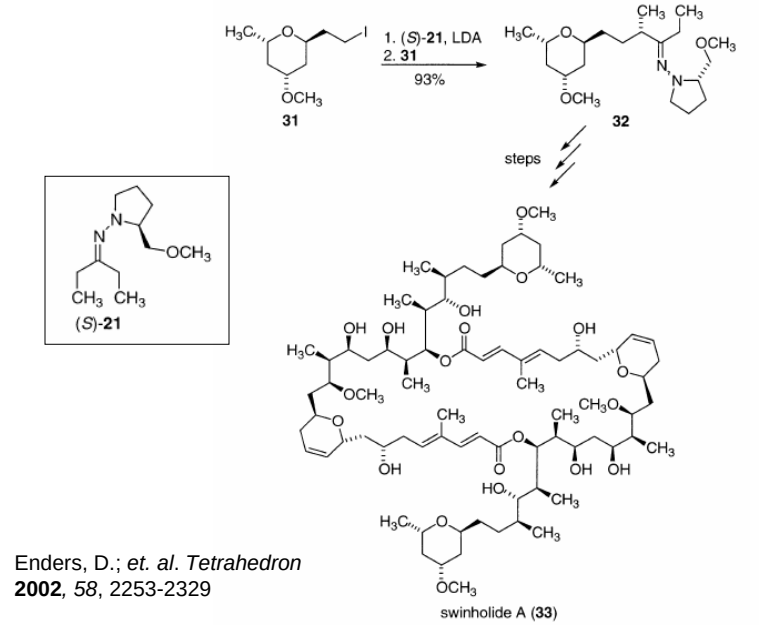
6.5 – Imine and Hydrazone Anions





Enders, D.; *et. al*. *Tetrahedron* **2002***, 58*, 2253-2329

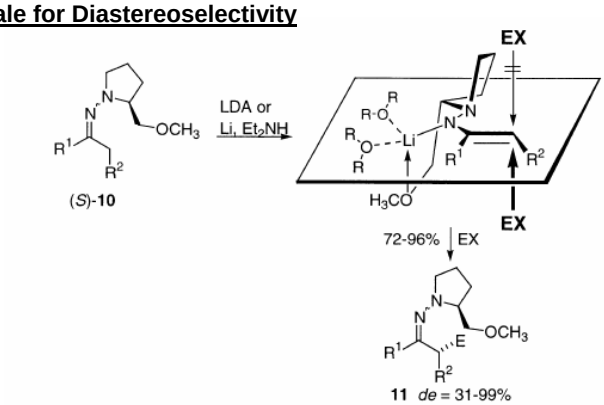
6.5 – Imine and Hydrazone Anions



Enders, D.; *et. al*. *Tetrahedron* **2002**, *58*, 2253-2329

6.5 – Imine and Hydrazone Anions

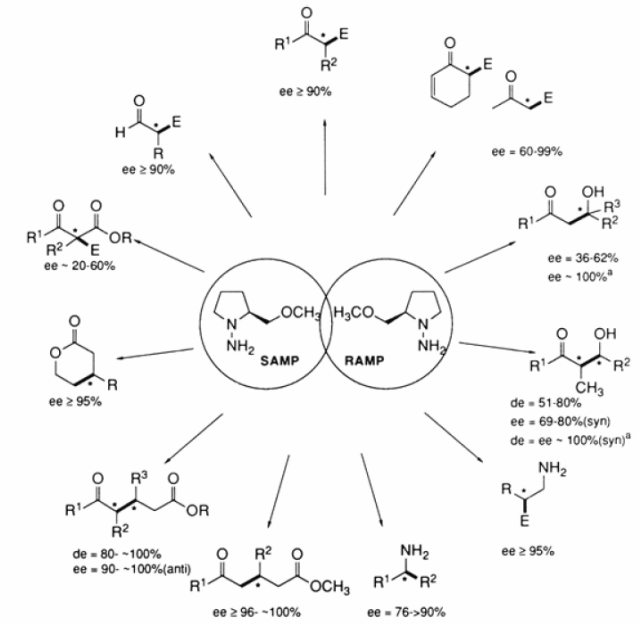
Rationale for Diastereoselectivity



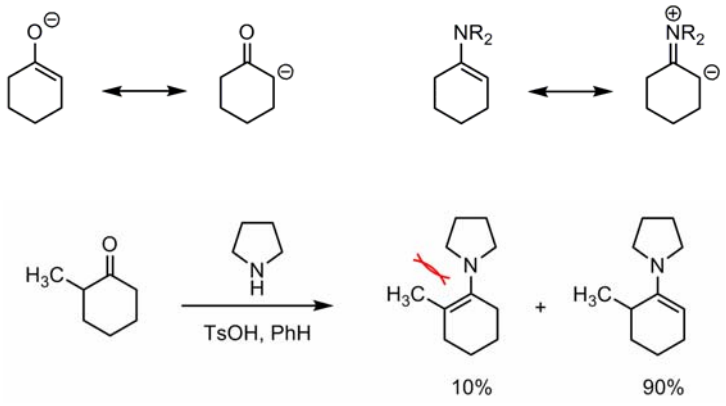
R^1 = H, Me, Et, Pr; R^2 = Me, Et, Pr, *i*Pr, Hex, Ph
and R^1, R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH=CH(CH_2)_2-$
R = Et, $-(CH_2)_4-$
E = Me, Et, Pr, Bn, allyl
X = Br, I

Enders, D.; *et. al*. *Tetrahedron* **2002**, *58*, 2253-2329

6.5 – Imine and Hydrazone Anions

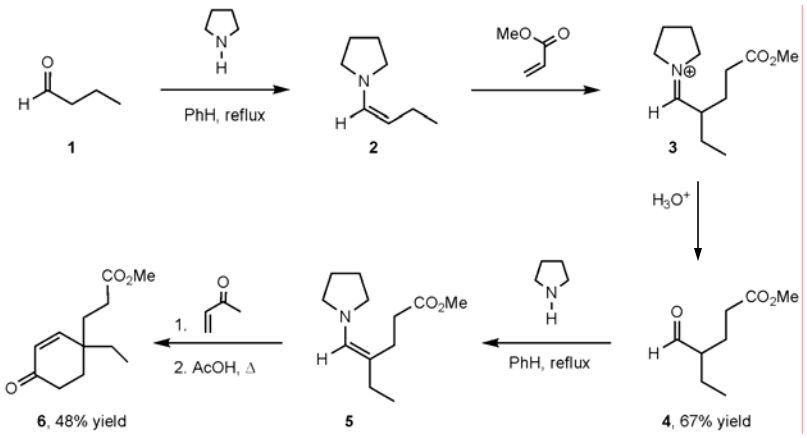


6.6 – Enamines



Work well with reactive electrophiles and give mainly *C*-alkylation products

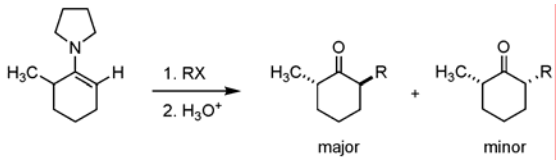
6.6 – Enamines

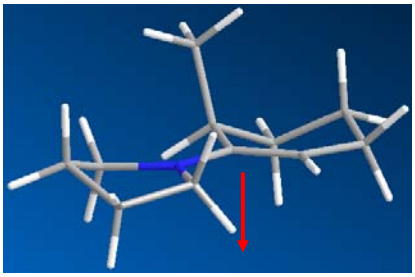


Total synthesis of Aspidospermine

G. Stork and J.E. Dolfini, *J. Am. Chem. Soc.* **1963**, *85*, 2872

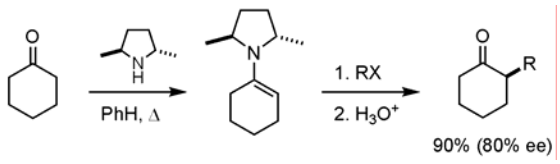
6.6 – Enamines

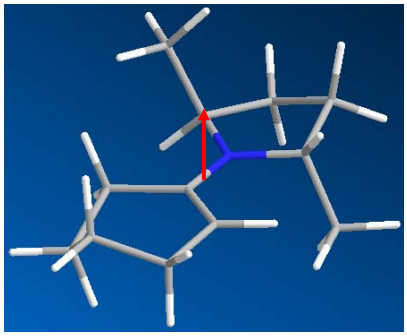




Preferred conformation of enamine avoids interaction between pyrrolidine ring and CH_3 group; alkylation from below

6.6 – Enamines – Stereoselective Alkylation

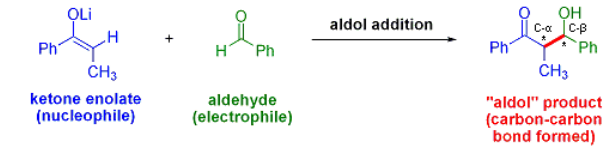


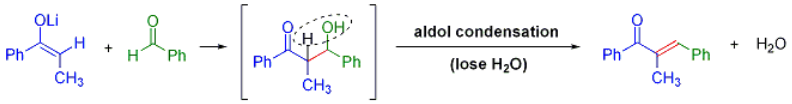


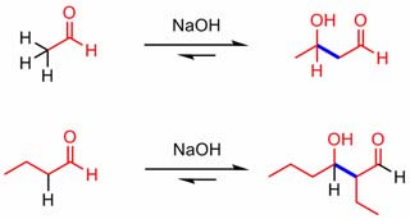
C2 symmetric pyrrolidine biases the system such that electrophile attacks preferably from one face

6.7 – The Aldol Reaction – Intermolecular Cases

a typical aldol reaction

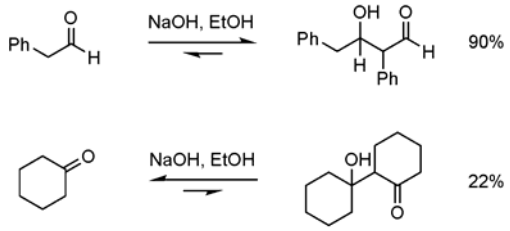




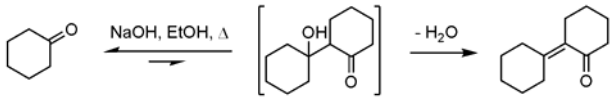


ald-ol

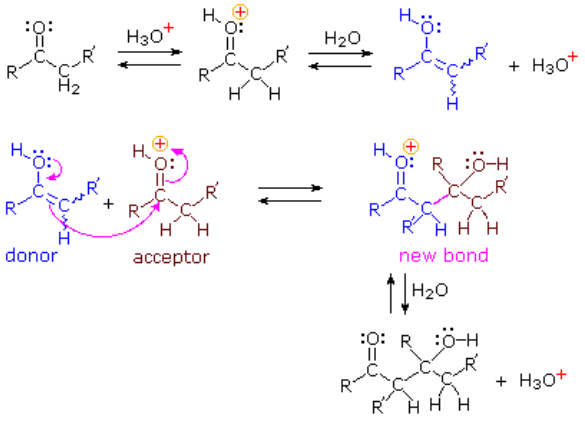
6.7 – The Aldol Reaction – Position of the Equilibrium



- These reactions are reversible (base used) and will give mixtures based on relative thermodynamic stabilities
- Aldehydes are more reactive than ketones and there is less strain in the aldol products (H vs. R group)
- Ketone aldols sent to completion by heating and loss of H_2O:

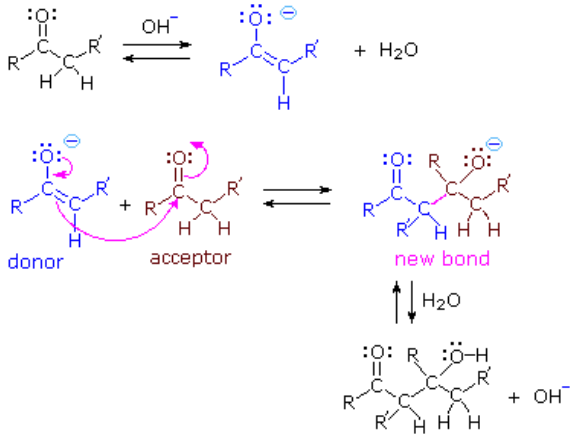


6.7 – The Aldol Reaction - Catalysis



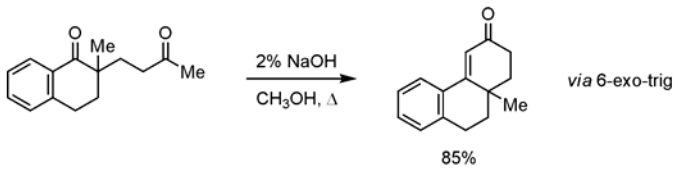
***Via* the enol** – acid also catalyzes keto-enol tautomerism and often will catalyze loss of H_2O to give the α,β-unsaturated product

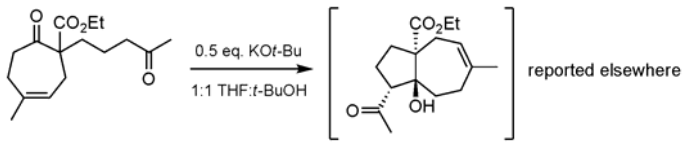
6.7 – The Aldol Reaction - Catalysis



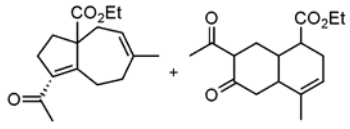
***Via* the enolate** – deprotonation of enol or keto form generates the enolate and basic conditions will often catalyze loss of H_2O to give the α,β-unsaturated product

6.7 – The Aldol Reaction – Intramolecular Cases

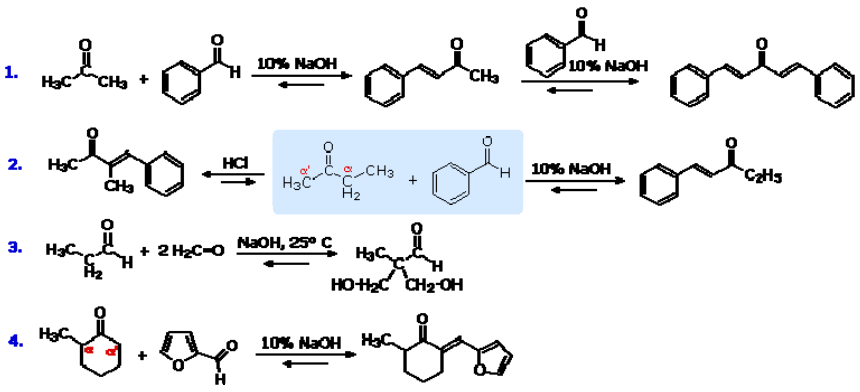




Chiu *et. al*. *Tetrahedron Lett*. **1998**, *39*, 9229-9232



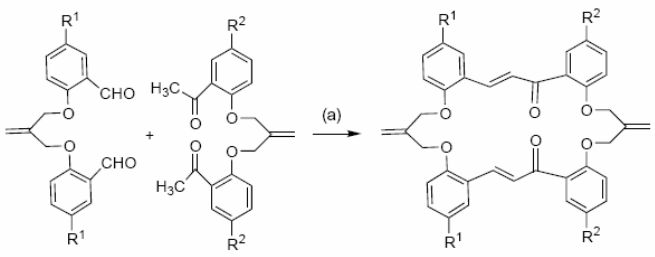
6.7 – Mixed (Crossed) Aldol Reactions



ArCHO + ketone is known as the **Claisen-Schmidt** reaction

One substrate is non-enolizable to avoid mixtures of enolates/products

6.7 – Mixed (Crossed) Aldol Reactions



1 2 3

1a. R^1 = H
1b. R^1 = Cl
1c. R^1 = CH_3

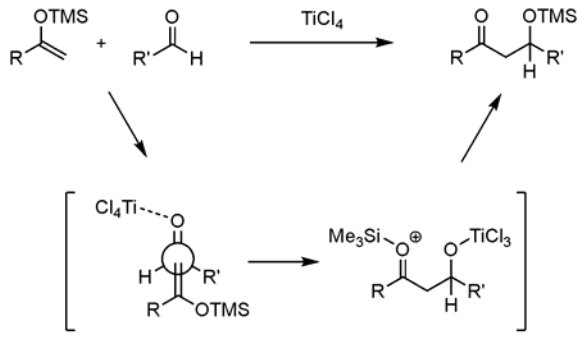
2a. R^2 = H
2b. R^2 = OMe
2c. R^2 = CH_3

(a) t-BuOK (10mol%), r.t., 16h, THF

1a + 2a = **3a** (41%)
1a + 2b = **3b** (28%)
1a + 2c = **3c** (33%)
1b + 2a = **3d** (26%)
1c + 2a = **3e** (39%)

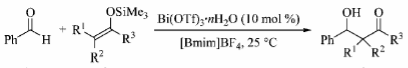
Hiratani; *et. al*. *Tetrahedron Lett.* **2001**, *42*, 8351-8355

6.7 – Mixed (Crossed) Aldol Reactions – Mukaiyama



Other Lewis acids – $SnCl_4$, $TiCl_4$, $InCl_3$, $BF_3.OEt_2$

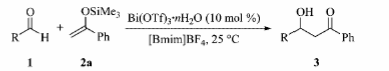
6.7 – Mukaiyama in Ionic Liquids



1a **2** **3**

Entry	Silyl enolate **2**	*t* [h]	Product **3**	Yield of product **3** [%][b]
1		5	**3a**	92[c]
2		8	**3b**	83[d]
3		23	**3c**	77
4		6	**3d**	56[e]
5		22	**3e**	63[c,e]
6		23	**3f**	81[e,f]
7		21	**3g**	56
8		19	**3h**	64[g]

[a] Conditions: benzaldehyde (**1a**) (1.0 equiv.), silyl enolate (2 equiv.), $Bi(OTf)_3{\cdot}nH_2O$ (0.10 equiv.), concentration = 2 M. [b] Isolated yield. [c] Including TMS-protected aldol product. [d] A 50:50 mixture of *syn*/*anti* stereoisomers was obtained. [e] 4 equiv. of silyl enol ether were used. [f] A 55:45 mixture of *syn*/*anti* stereoisomers was obtained. [g] A 61:39 mixture of *syn*/*anti* stereoisomers



1 **2a** **3**

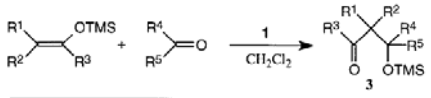
Entry	Aldehyde **1**	*t* [h]	Product **3**	Yield of product **3** (%)[b]
1		6	**3i**	79
2		40	**3j**	58
3		27	**3k**	87
4		23	**3l**	89
5		26	**3m**	47
6		7	**3n**	51
7		40	**3o**	48

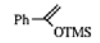
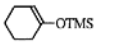
[a] Conditions: aldehyde (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane (**2a**) (2 equiv.), $Bi(OTf)_3{\cdot}nH_2O$ (0.10 equiv.), concentration = 2 M. [b] Isolated yield.

Ollevier, T.; *et. al*. *Eur. J. Org. Chem.* **2005**, 4971-4973

6.7 – Mixed (Crossed) Aldol Reactions – Mukaiyama

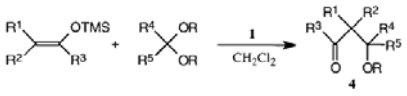
Table 1. $Bi(OTf)_3$ (**1**)-Catalyzed Aldol Reactions with Ketones and Aldehydes.

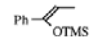
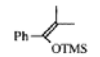
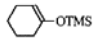


Entry	Silyl enol ether	Electrophile R^4R^5CO	Conditions[a] [h, °C]	Product (yield %)[b]
1		PhCHO	0.5, -70	**3a** (92)
2		FuCHO	2, -70	**3b** (91)
3		^{n}PrCHO	5, RT	**3c** (74)
4		PhCOMe	5, 0	**3d** (55)
5		MeCOMe	2, 0	**3e** (65)
6		PhCHO	0.5, -70	**3f** (95)[c]
7		FuCHO	1, -70	**3g** (95)[d]

[a] In every case 1 mol % of **1** tetrahydrate was used as catalyst except for entries 3 and 4 where 5 mol % was used; Fu : 2-furyl;
[b] Yields in isolated products; [c] *Syn*/*anti* = 55/45; [d] *Syn*/*anti* = 33/67.

Table 2. $Bi(OTf)_3$ (**1**)-Catalyzed Aldol-type Reactions with Acetals.

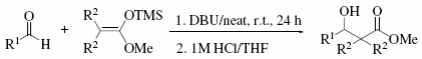


Entry	Silyl enol ether	Electrophile R^4R^5CO	Conditions[a] [min, °C]	Product (yield %)[b]
1		$PhCH(OMe)_2$	15, -70	**4a** (82)
2		$PhMeC(OMe)_2$	15, -70	**4b** (84)
3		$^nPrCH(OMe)_2$	60, -70	**4c** (92)
4		$MeCH(OEt)_2$	120, -70	**4d** (81)
5		$PhCH(OMe)_2$	15, -70	**4e** (90)[c]
6		$PhCH(OMe)_2$	30, -70	**4f** (92)
7		$PhCH(OMe)_2$	20, -70	**4g** (90)[d]
8		$Me_2C(OMe)_2$	60, -70	**4h** (85)
9		$HC(OMe)_3$	20, -70	**4i** (88)
10		$Ph(CH_2)_2CH(OMe)_2$	240, -30	**4j** (89)

Dubac, J.; *et. al*. *Synlett* **1998**, 1249-1251

6.7 – Mixed (Crossed) Aldol Reactions – Mukaiyama

No solvent

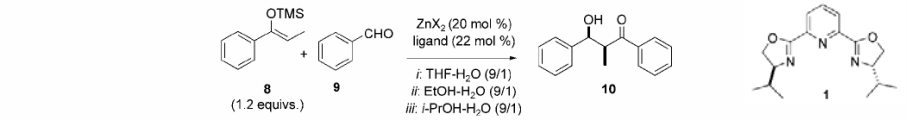


Entry	R^1	R^2	Product	Yield (%)[b]
1	$2\text{-}NO_2C_6H_4$	CH_3	**1a**	67
2	$2\text{-}NO_2C_6H_4$	H	**1b**	60[c]
3	$4\text{-}ClC_6H_4$	CH_3	**1c**	73
4	$4\text{-}ClC_6H_4$	H	**1d**	60
5	C_6H_5	CH_3	**1e**	77
6	C_6H_5	H	**1f**	51
7	$4\text{-}MeC_6H_4$	CH_3	**1g**	79
8	$4\text{-}MeC_6H_4$	H	**1h**	55
9	$2\text{-}OMeC_6H_4$	CH_3	**1i**	68
10	$2\text{-}OMeC_6H_4$	H	**1j**	33
11	$C_6H_5CH{=}CH$	CH_3	**1k**	83
12	$C_6H_5CH{=}CH$	H	**1l**	65
13	$3\text{-}C_5H_4N$	CH_3	**1m**	63[d]
14	$3\text{-}C_5H_4N$	H	**1n**	79[d]
15	$n\text{-}C_8H_{17}$	CH_3	**1o**	58
16	$n\text{-}C_8H_{17}$	H	**1p**	64

[a] The reactions were carried out at room temperature for 24 h using aldehydes (1 mmol), ketene silyl acetals (2 mmol), DBU (0.2 mmol).
[b] Isolated yield.
[c] An aldol condensation product was obtained in 22% yield.
[d] Including TMS protected aldol product.

Ji, S.-J.; *et. al*. *Tetrahedron Lett.* **2005**, *46*, 507-508

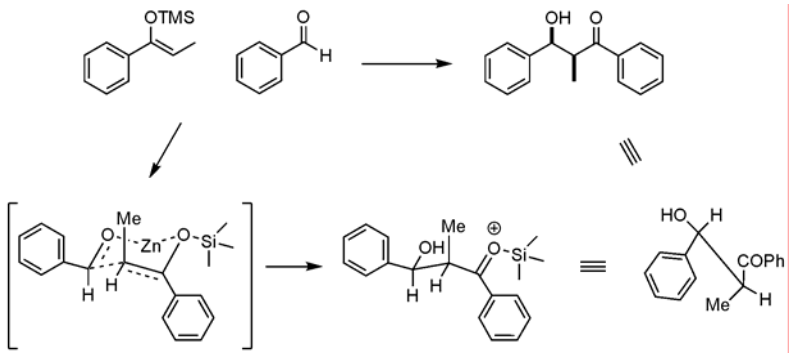
6.7 – Asymmetric Mukaiyama aldol

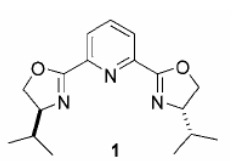


Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Yield[a] (*syn/anti*)	Ee[c] *syn*
a) ligand and anion effects						
1	**A1**	*i*	0	10	73 (9/1)	53 (*S,S*)[12]
2	**B1**	*i*	0–rt	20	14	10
3	**C1**	*i*	0–rt	20	trace	–
4	**D1**	*i*	0	20	53	50
5	**A2**	*i*	0	10	82	–24
6	**A3**	*i*	0	96	56	–13
7	**A4**	*i*	0	20	67	–3
8	**A5**	*i*	0	20	59	0
9	**A6**	*i*	0–rt	40	25	0
10	**A7**	*ii*	0	20	58	–27
b) solvent and temperature effects						
11	**A1**	*ii*	0	10	80 (9/1)	39
12	**A1**	*ii*	–10	48	97[b]	62
13	**A1**	*i*+*ii* (2:1)	–10	48	66[b]	73
14	**A1**	*iii*	–10	48	30	65
15	**A1**	*ii*	–20	72	88 (95/5)	69
16	**A1**	*ii*	–20	24	93 (95/5)[b]	69
17	**A1**	*i*+*ii* (1:1)	–20	72	43 (95/5)	75
18	**A1**	*i*+*ii* (2:1)	–20	72	34 (96/6)	77
19	**A1**	*i*+*ii* (1:1)	–25	48	**86** (96/4)[b]	**75**
20	**A1**[d]	*i*+*ii* (1:1)	–25	48	88 (93/7)[b]	72

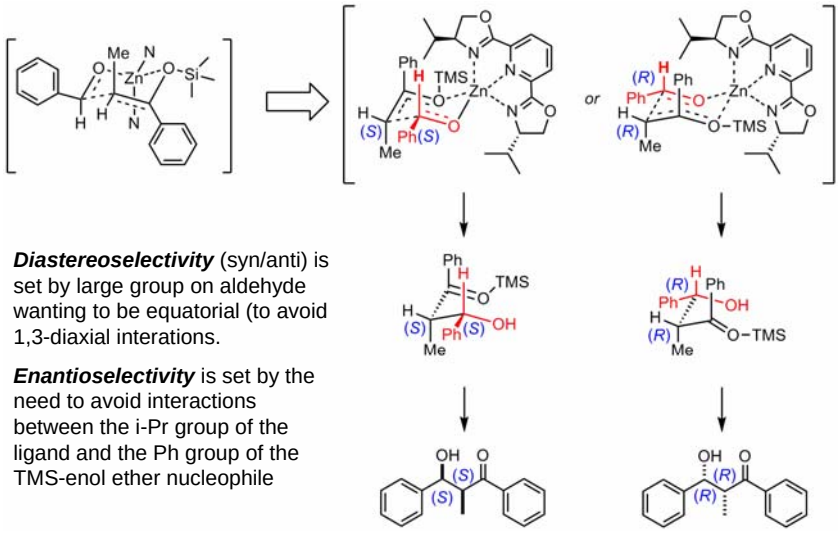
Mlynarski, J. and Jankowska, J.; *Adv. Synth. Catal.* **2005**, *347*, 521-525

6.7 – Asymmetric Mukaiyama aldol





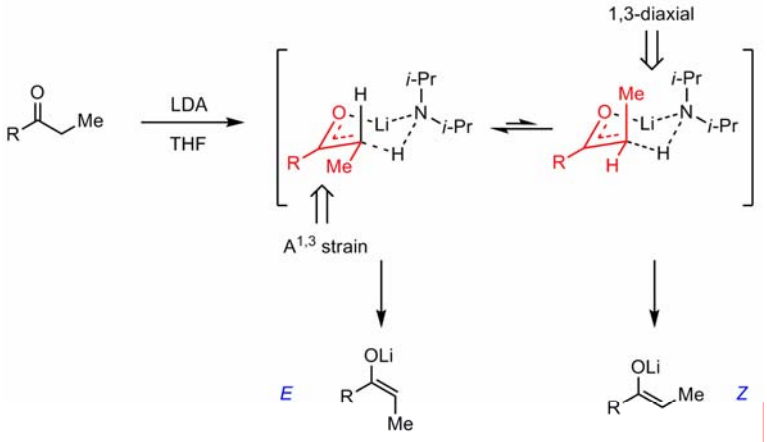
6.7 – Asymmetric Mukaiyama aldol



Diastereoselectivity (syn/anti) is set by large group on aldehyde wanting to be equatorial (to avoid 1,3-diaxial interations.

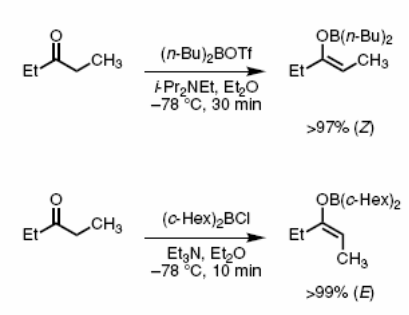
Enantioselectivity is set by the need to avoid interactions between the i-Pr group of the ligand and the Ph group of the TMS-enol ether nucleophile

6.7 – E/Z Enolates



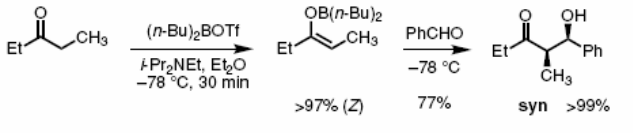
R	(*E*)-(*O*)-enolate (%)	(*Z*)-(*O*)-enolate (%)
OMe	95	5
Et	70	30
i-Pr	44	56
t-Bu	~0	100

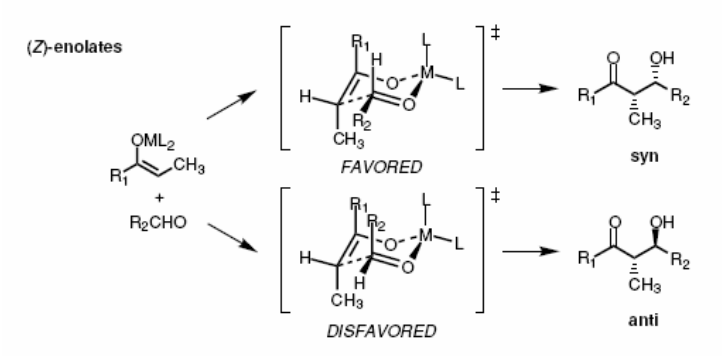
6.7 – Aldol Reactions Using Boron Enolates



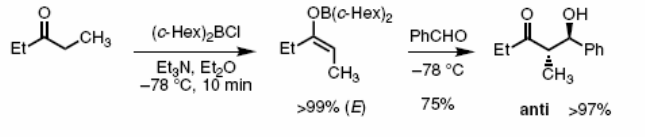
- Dialkylboron triflates typically afford (*Z*)-boron enolates, with little sensitivity toward the amine used or the steric requirements of the alkyl groups on the boron reagent.
- In the case of dialkylboron chlorides the geometry of the the product enolates is much more sensitive to variations in the amine and the alkyl groups on boron.
- The combination of $(c\text{-Hex})_2BCl$ and Et_3N provides the (*E*)-boron enolate preferentially.

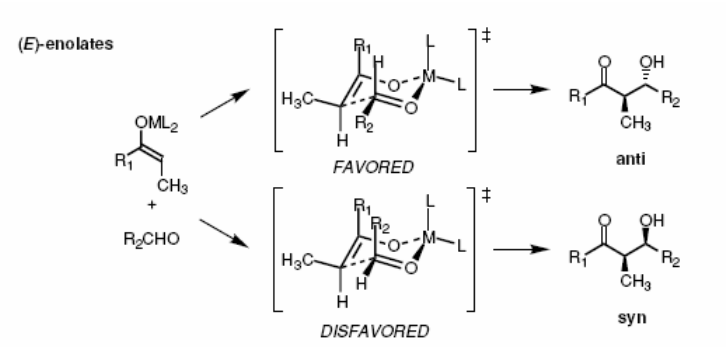
6.7 – Zimmerman-Traxler TS for aldol





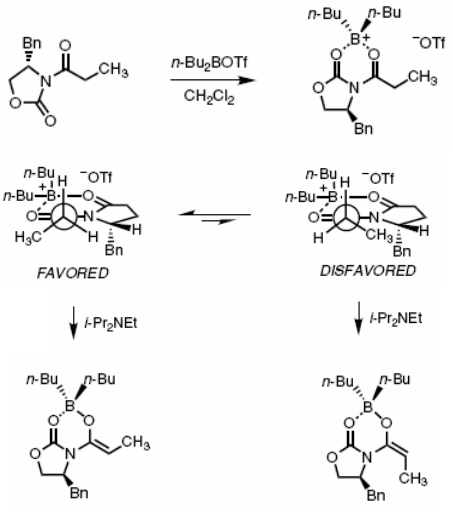
6.7 – Zimmerman-Traxler TS for aldol



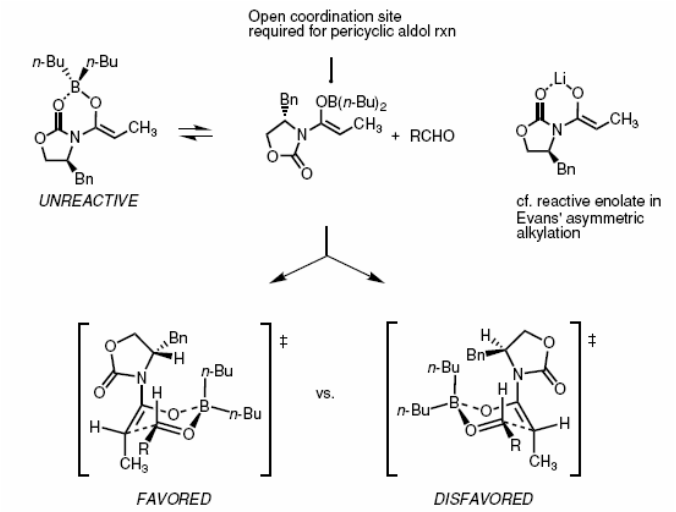


6.7 – Evans Asymmetric Aldol Reaction – Chiral Auxiliaries

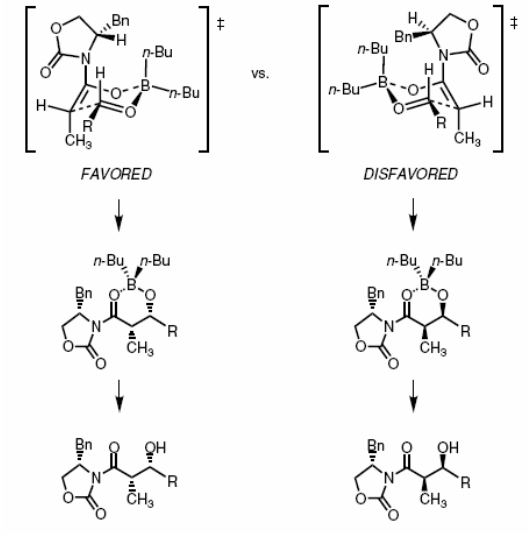
(*Z*)-Selective Preparation of Boron Enolates from Evans' Acyl Oxazolidinones (Imides)



6.7 – Evans Asymmetric Aldol Reaction – Chiral Auxiliaries

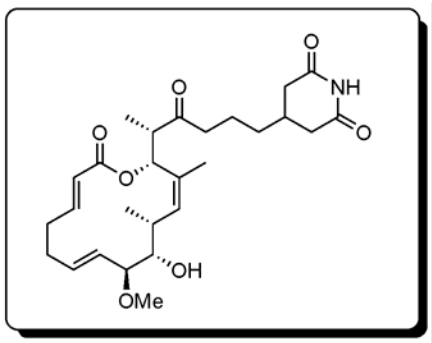


6.7 – Evans Asymmetric Aldol Reaction – Chiral Auxiliaries



Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

6.7 – Evans Asymmetric Aldol Reaction – Migrastatin

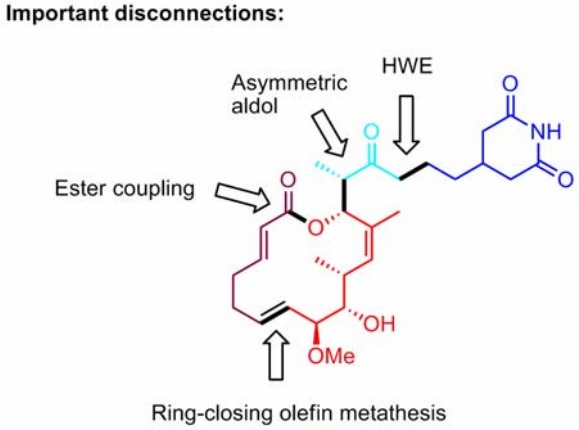


Migrastatin

Migrastatin - Gaul, C.; Njardarson, J.T.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2003**, *125*, 6042-6043.

6.7 – Evans Asymmetric Aldol Reaction – Migrastatin

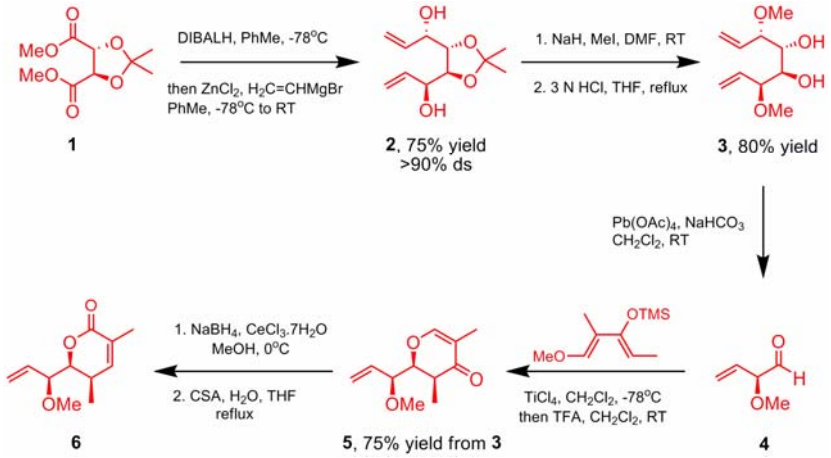
Important disconnections:



Ring-closing olefin metathesis

6.7 – Evans Asymmetric Aldol Reaction – Migrastatin

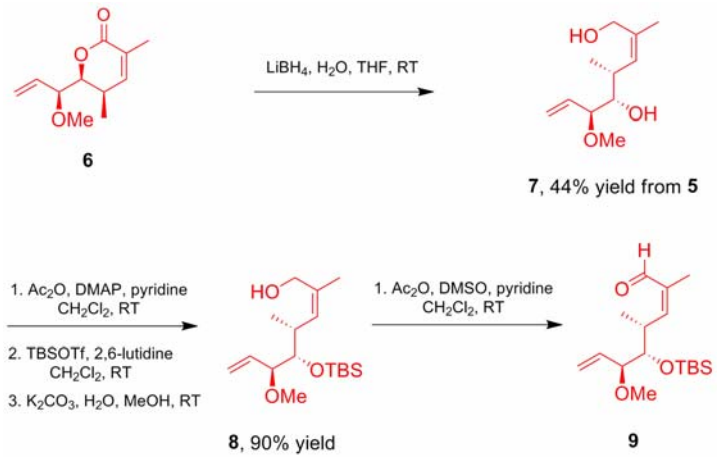
Southern (red) portion of Migrastatin



1 | **2**, 75% yield, >90% ds | **3**, 80% yield | **4** | **5**, 75% yield from **3** | **6**

6.7 – Evans Asymmetric Aldol Reaction – Migrastatin

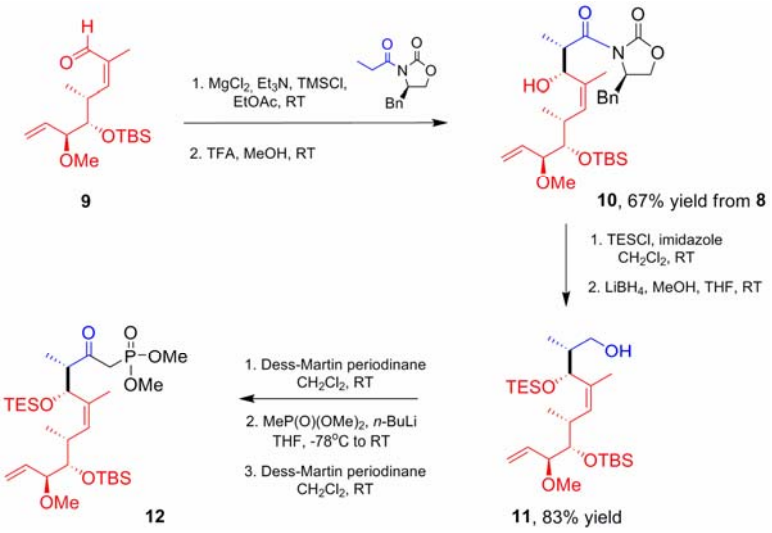
Finishing the required aldehyde



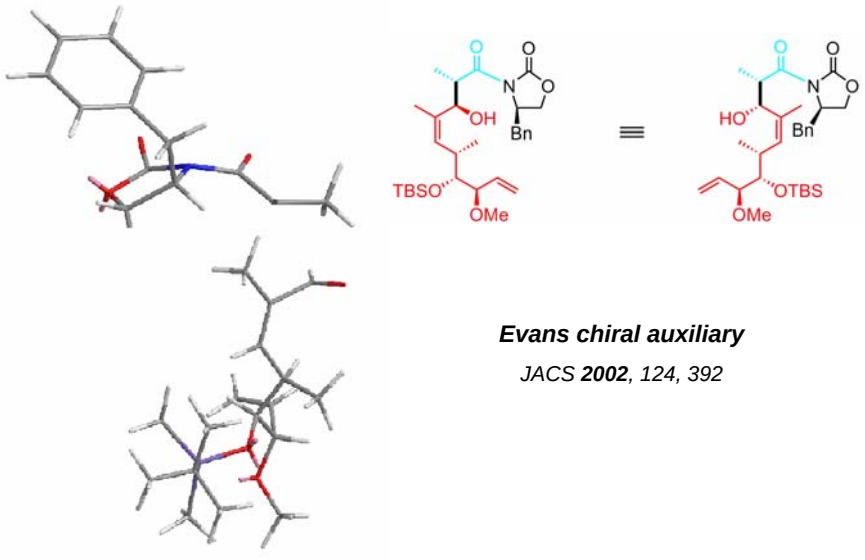
6 | **7**, 44% yield from **5** | **8**, 90% yield | **9**

6.7 – Evans Asymmetric Aldol Reaction – Migrastatin

Evans chiral auxiliary – asymmetric aldol



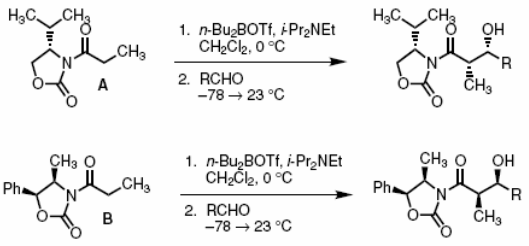
6.7 – Evans Asymmetric Aldol Reaction – Migrastatin



Evans chiral auxiliary

JACS ***2002****, 124, 392*

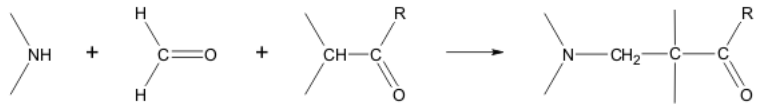
6.7 – Evans Asymmetric Aldol Reaction

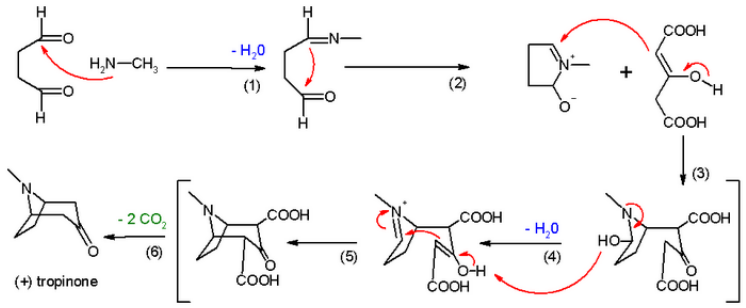


imide	aldehyde	diastereomeric[a] ratio	yield
A	$(CH_3)_2CHCHO$	497:1	78
B	$(CH_3)_2CHCHO$	<1:500	91
A	n-C_4H_9CHO	141:1	75
B	n-C_4H_9CHO	<1:500	95
A	C_6H_5CHO	>500:1	88
B	C_6H_5CHO	<1:500	89

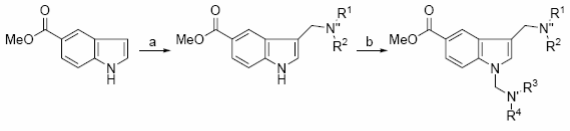
[a]Ratio of major syn product to minor syn product.

6.7 – Mannich Reaction





6.7 – Mannich Reaction



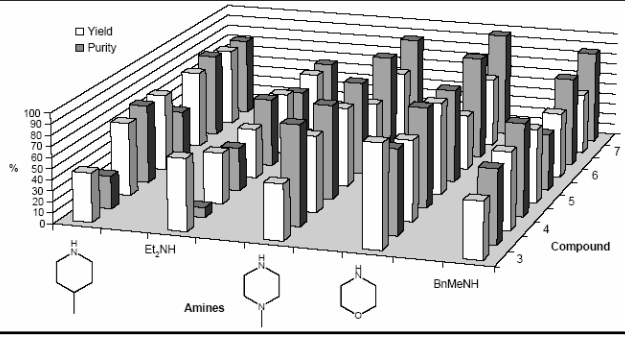
1 — 8–31

2 $R^1R^2N''H$=pyrrolidine, 77%
3 $R^1R^2N''H$=4-methylpiperidine, 93%
4 $R^1R^2N''H$=diethylamine, 78%
5 $R^1R^2N''H$=4-methylpiperazine, 45%
6 $R^1R^2N''H$=morpholine, 57%
7 $R^1R^2N''H$=benzylmethylamine, 66%

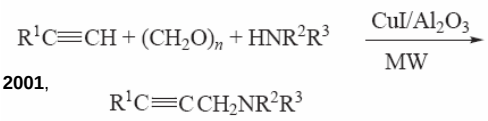
C. Lindquist et al. *Tetrahedron*, **2006**, *62*, 3439-3445

Scheme 1. (a) $R^1R^2N^0H$ (1.2 equiv), HCHO (1.2 equiv), room temperature, 18 h; (b) $R^3R^4N'H$ (1.5 equiv), HCHO (1.5 equiv), room temperature, 48 h.

Table 1. Yields and purity of library compounds[a]

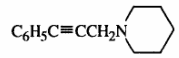
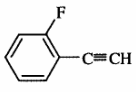
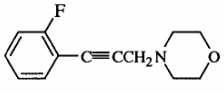
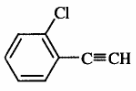
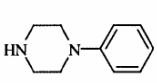
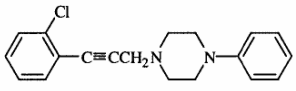


6.7 – Mannich Reaction

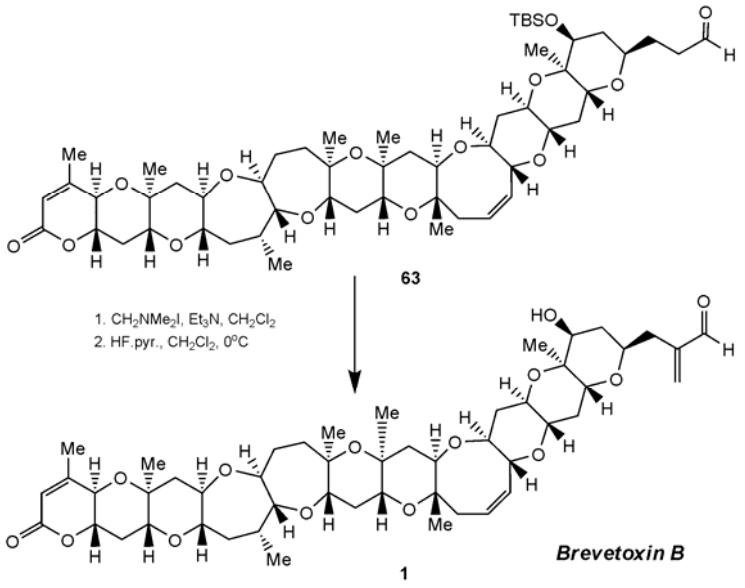


G. Kabalka et al. *Synlett*, **2001**, 676-678

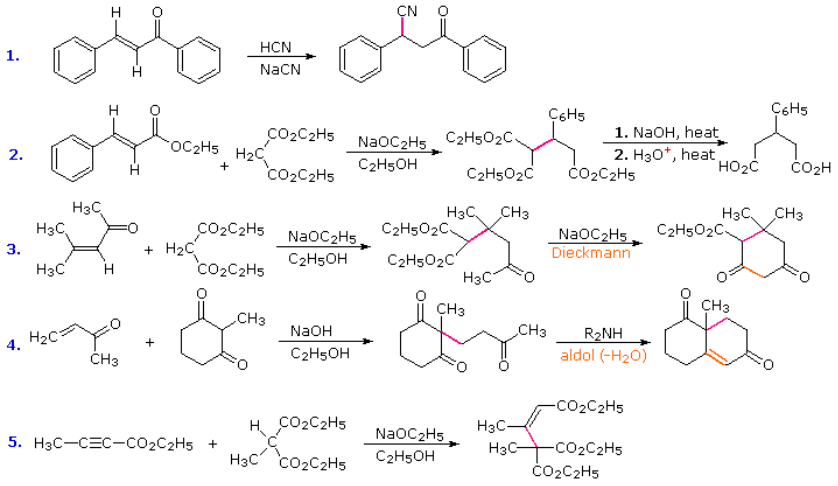
No solvent!

Entry	Alkyne	Amine	Product	Yield(%)[1]
1	$CH_3(CH_2)_7C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$(C_6H_5CH_2)_2NCH_2C{\equiv}C(CH_2)_7CH_3$	90
2	$CH_3(CH_2)_5C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$(C_6H_5CH_2)_2NCH_2C{\equiv}C(CH_2)_5CH_3$	86
3	*p*-$CH_3C_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$(C_6H_5CH_2)_2NCH_2C{\equiv}CC_6H_4CH_3$-*p*	80
4	$C_6H_5C{\equiv}CH$			77
5				63
6				81

6.7 – Mannich Reaction

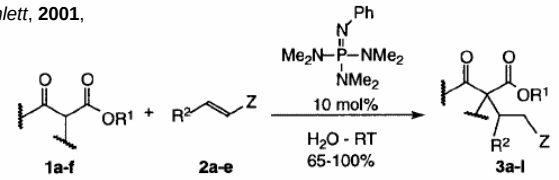


6.7 – Michael Addition



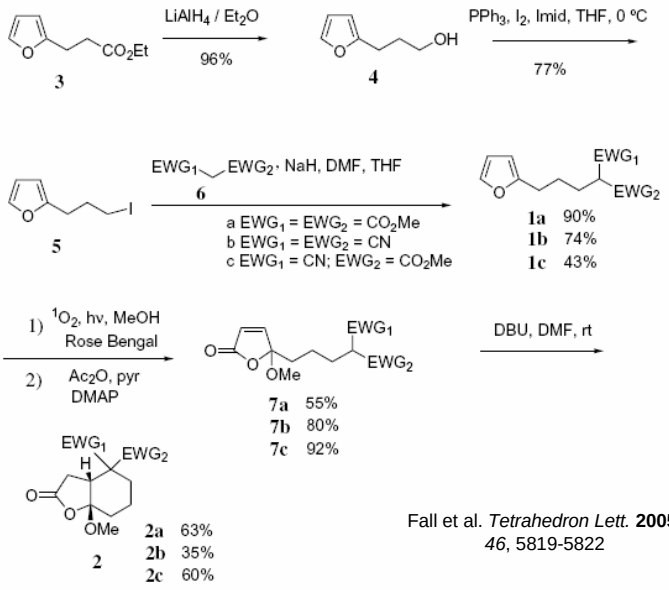
6.7 – Michael Addition in Water

Rodriquez et al. *Synlett*, **2001**, 715-717



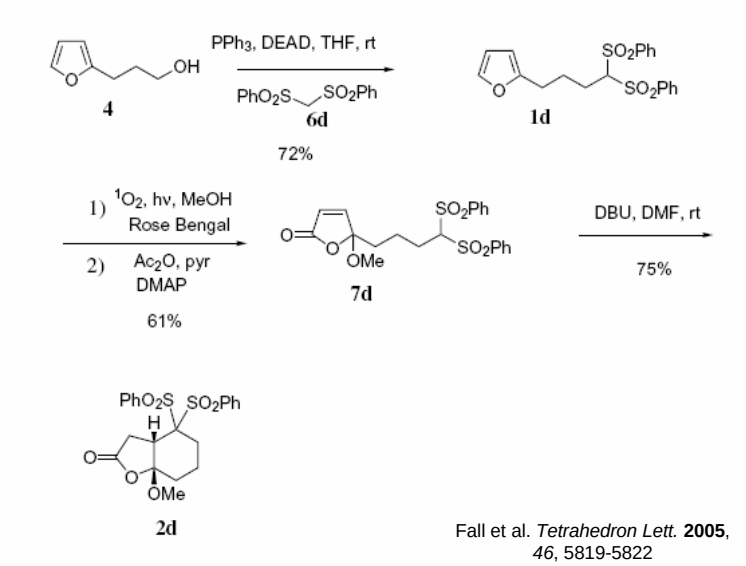
Entry	Ketoester	Acceptor R^2 / Z	Time [t/h]	Product	Yield [%][a]
1	**1a**	**2a**: R^2 = H, Z = COMe	24	**3a**	75
2	**1a**	**2b**: R^2 = H, Z = CHO	24	**3b**	72
3	**1b**	**2a**: R^2 = H, Z = COMe	24	**3c**	>99
4	**1c**	**2a**: R^2 = H, Z = COMe	22	**3d**	>99
5	**1c**	**2b**: R^2 = H, Z = CHO	24	**3e**	90

6.7 – Michael Addition - Intramolecular



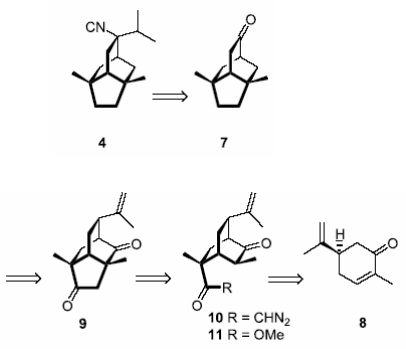
Fall et al. *Tetrahedron Lett.* **2005**, *46*, 5819-5822

6.7 – Michael Addition - Intramolecular



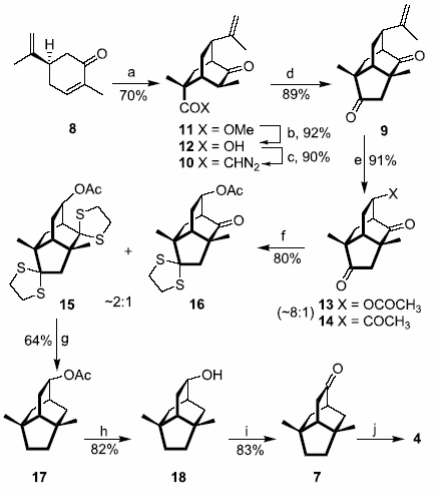
Fall et al. *Tetrahedron Lett.* **2005**, *46*, 5819-5822

6.7 – Michael Addition - Intramolecular



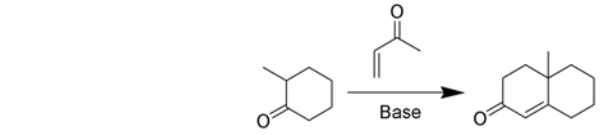
Intermolecular Michael addition followed by intramolecular Michael addition

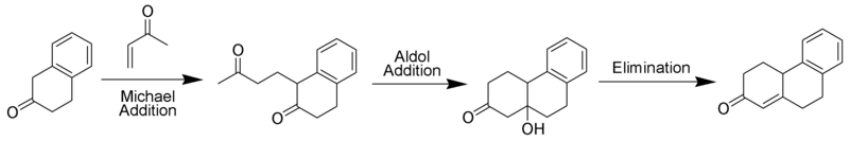
Srikrishna et al. *Tetrahedron* **2005**, *61*, 8855-8859



Scheme 2. (a) $LiN(TMS)_2$, CH_2=C(Me)COOMe, hexane; (b) NaOH, MeOH–H_2O, reflux; (c) (i) $(COCl)_2$, C_6H_6; (ii) CH_2N_2, Et_2O; (d) $Rh_2(OAc)_4$, CH_2Cl_2; (e) O_3/O_2, MeOH–CH_2Cl_2, −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux; (f) $(CH_2SH)_2$, I_2, $CHCl_3$; (g) Raney Ni, EtOH, reflux; (h) K_2CO_3, MeOH; (i) PCC, silica gel, CH_2Cl_2; (j) Ref. 4.

6.7 – Robinson Annulation





Wichterle variant