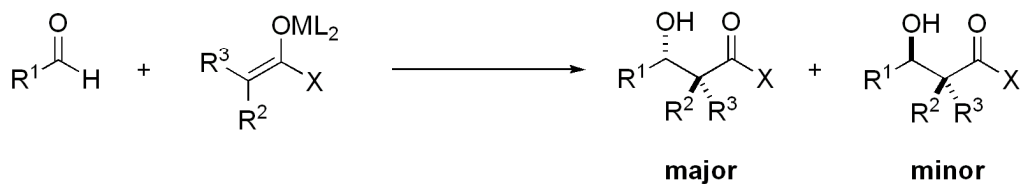


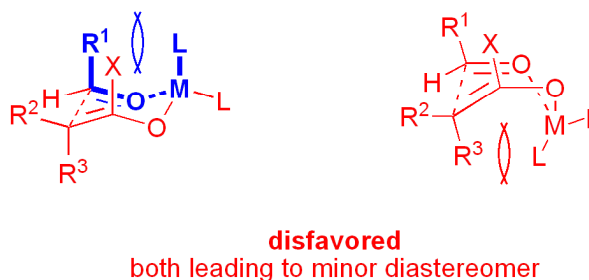
The Aldol Addition

1. Model

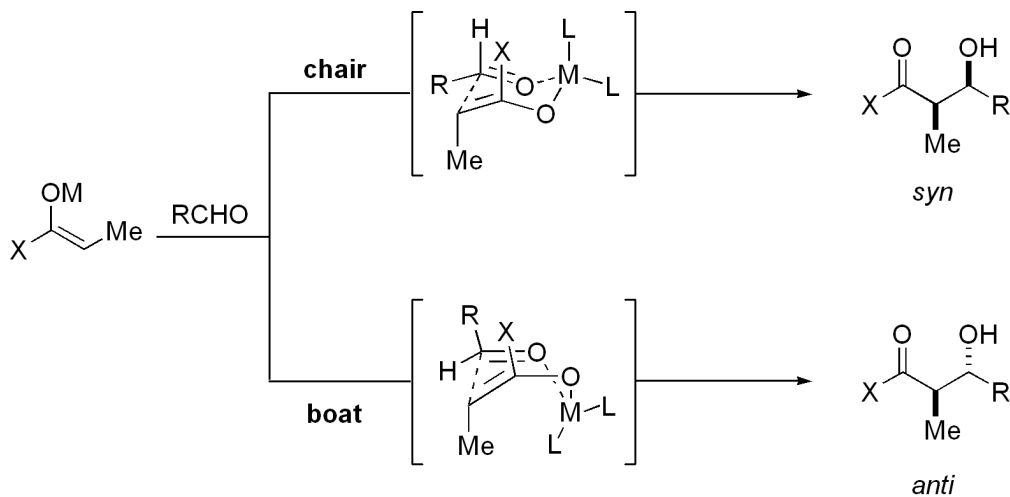
general model: Zimmerman-Traxler



closed, six-membered transition state



simple diastereoselection:

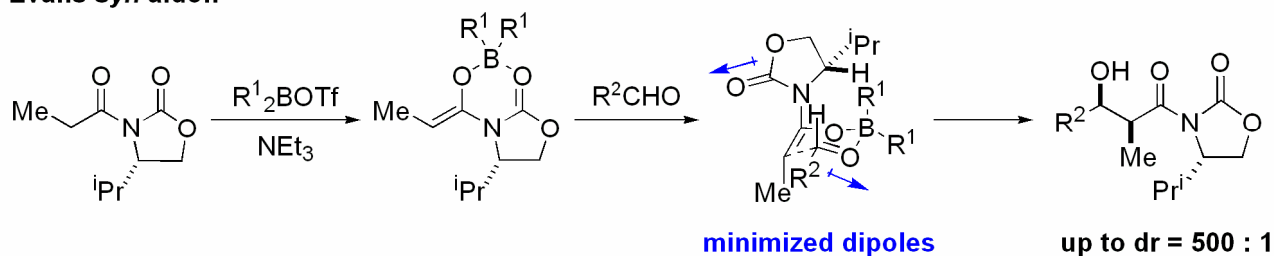


The Zimmerman-Traxler transition state, in which the reaction partners adopt a chair-like structure, is usually preferred. Some rare aldol reactions, however, proceed via a boat transition state.

2. Chiral Auxiliaries on Enolate

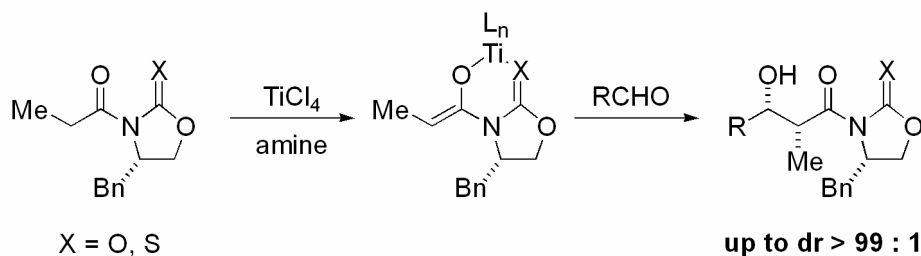
2.1 Evans Auxiliary

Evans *syn* aldol:



Evans *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Crimmins modification of Evans aldol:



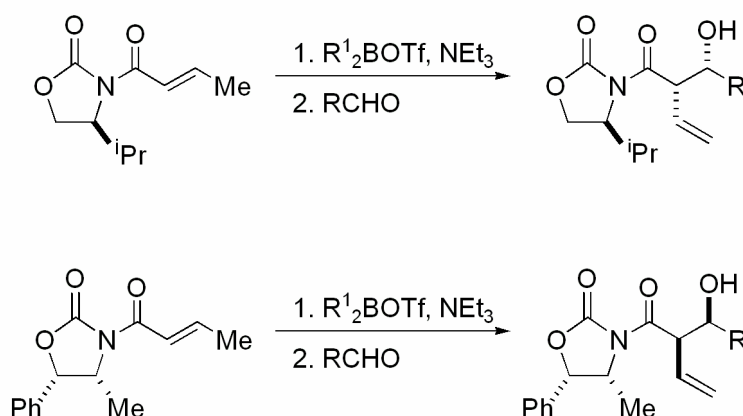
X = O, S

transition state:



Crimmins *J. Am. Chem. Soc.* **1997**, *119*, 7883.
J. Org. Chem. **2001**, *66*, 894.

Aldol on α,β -unsaturated imides:

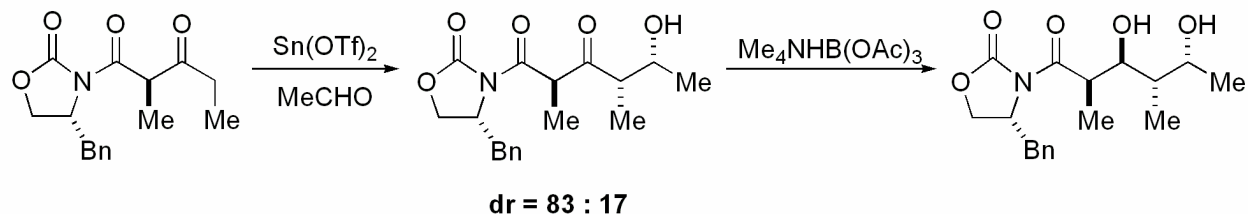
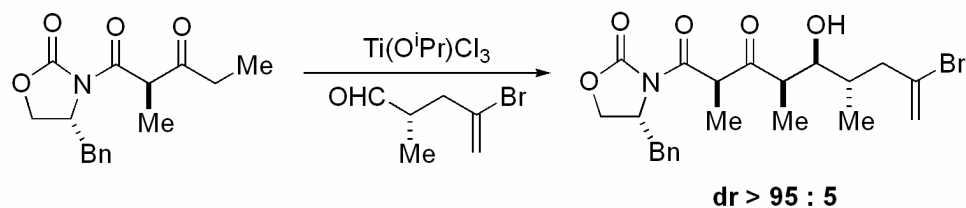


R	yield [%]
Me	82
Et	94
iPr	90
Ph	92

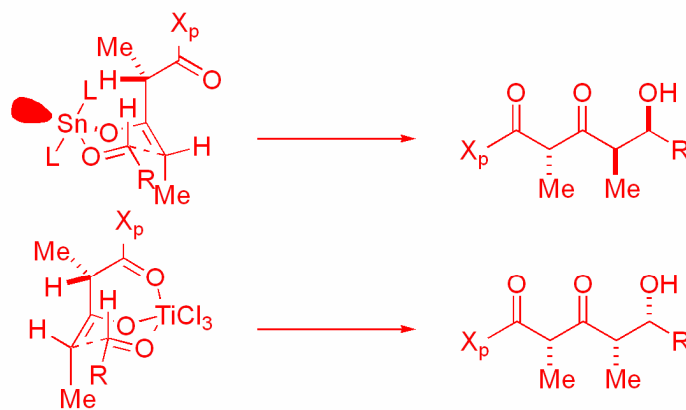
R	yield [%]
Et	94
iPr	90
Ph	92

Evans *Tetrahedron Lett.* **1986**, *27*, 4957.

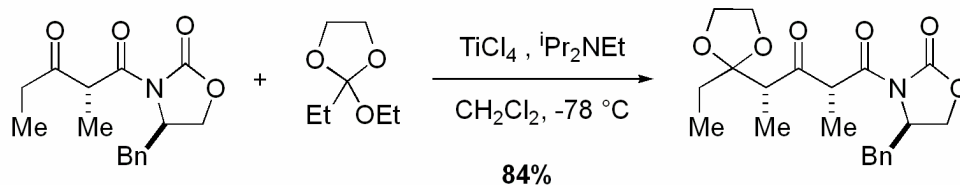
Use of enolates of dicarbonyl compounds derived from Evans auxiliary:

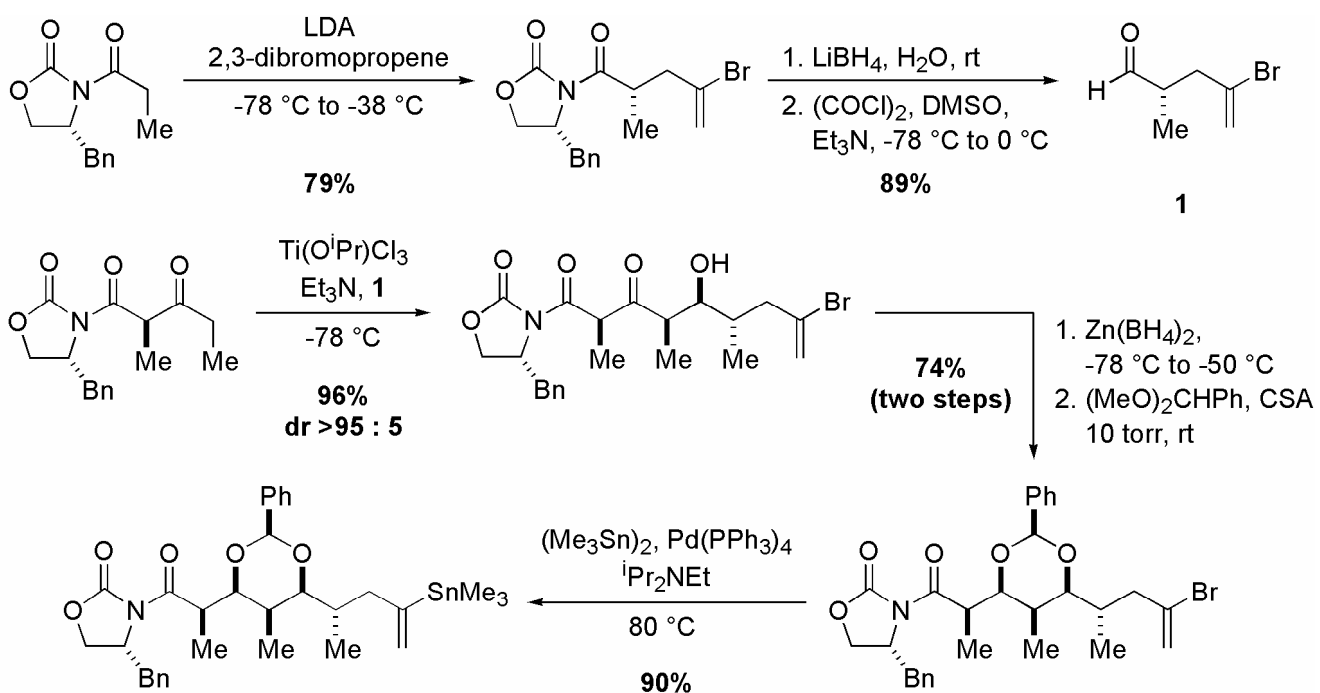


Proposed transition states:

Evans *J. Am. Chem. Soc.* **1990**, *112*, 866.

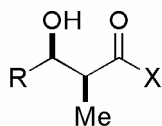
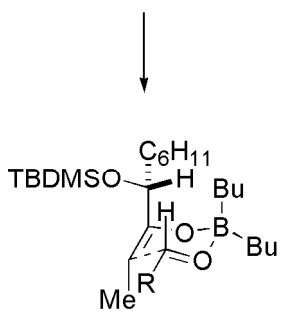
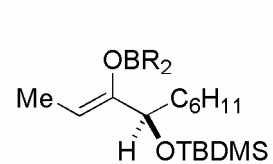
Examples:

Evans *Tetrahedron Lett.* **1993**, *34*, 2229.



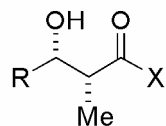
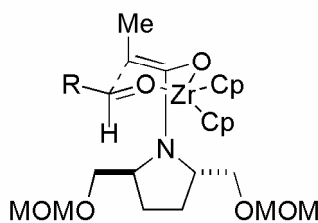
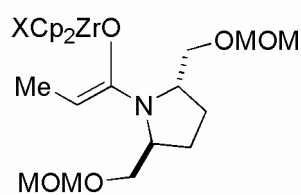
Evans *J. Am. Chem. Soc.* **1996**, *118*, 11323.

2.2. Other Auxiliaries



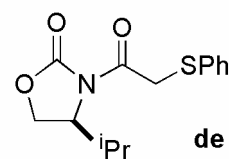
dr > 100 : 1

Masamune
J. Am. Chem. Soc. **1981**, *103*, 1566.



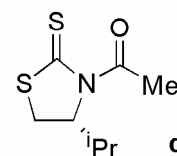
dr = 60-100 : 1

Yamaguchi
Tetrahedron Lett. **1985**, *26*, 5807.



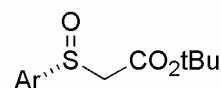
de = 85-99%

Evans
J. Am. Chem. Soc. **1981**, *103*, 2127.



de = 85-97%

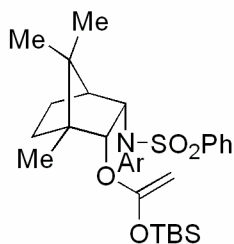
Nagao
J. Org. Chem. **1986**, *51*, 2391.



de = 84-91%

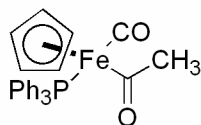
Solladie
Tetrahedron **1980**, *36*, 227.

Auxiliaries for acetate aldol reactions:

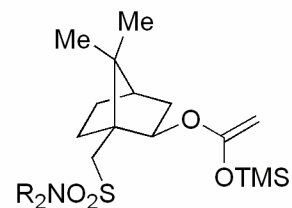


de = 86-90%

Helmchen
Angew. Chem. Int. Ed. Engl.
1985, 24, 874.

de = 90-99%
(Al enolate)

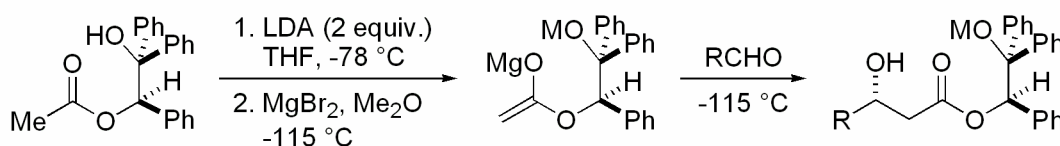
Davies
J. Organomet. Chem.
1985, 285, 213.



de = 84-92%

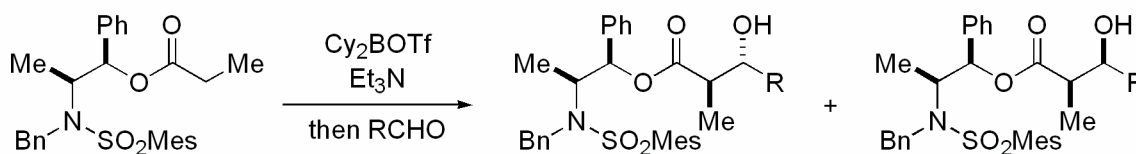
Oppolzer
Helv. Chim. Acta **1986**, 69, 1699.
Tetrahedron **1987**, 43, 1669.

remember: Evans auxiliary does not work for acetate aldols



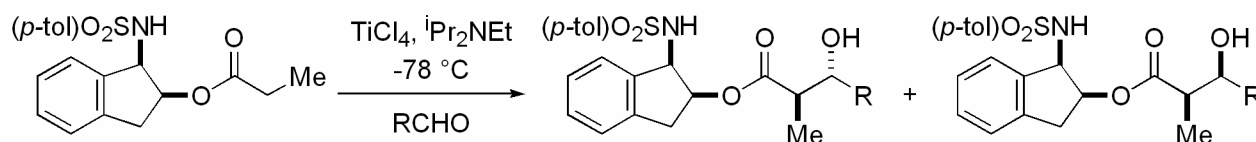
R	de [%]
Ph	94
ⁱ Pr	90
ⁿ Pr	84

Braun *Tetrahedron Lett.* **1984**, 25, 5031.
Tetrahedron Lett. **1987**, 28, 1385.

unusual *anti*-selective aldols:

up to dr > 99 : 1

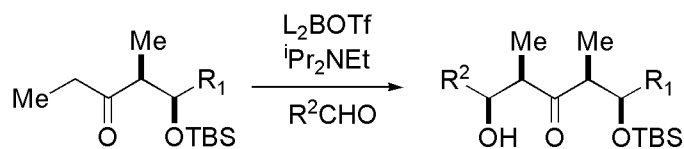
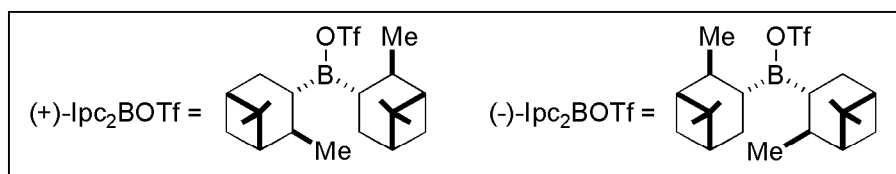
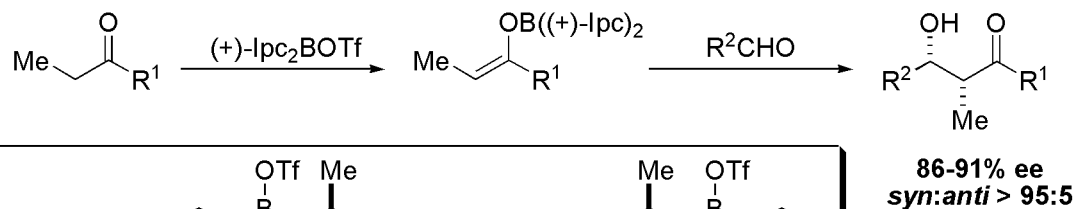
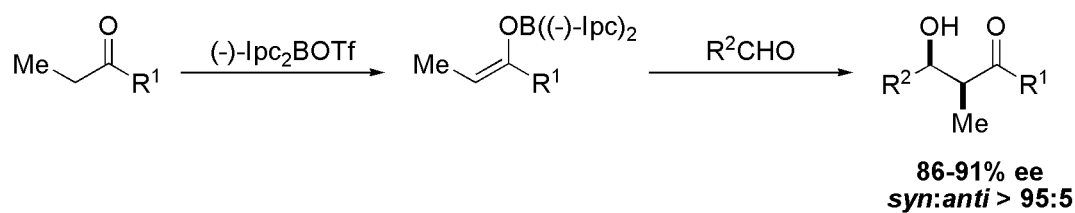
Masamune *J. Am. Chem. Soc.* **1997**, 119, 2586.



up to dr > 99 : 1

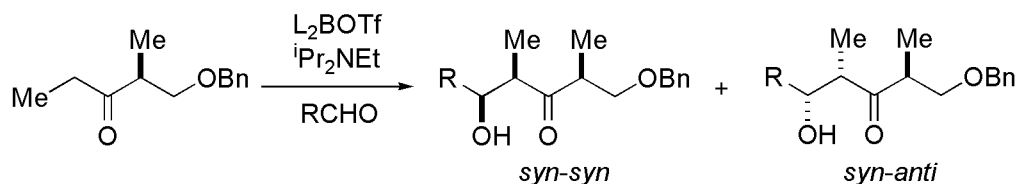
Ghosh *J. Am. Chem. Soc.* **1996**, 118, 2527.

2.3. Chiral Boron Reagents



L	de [%]
Bu	26-68
9-BBN	66-70
(-)-Ipc	44
(+)-Ipc	82-88

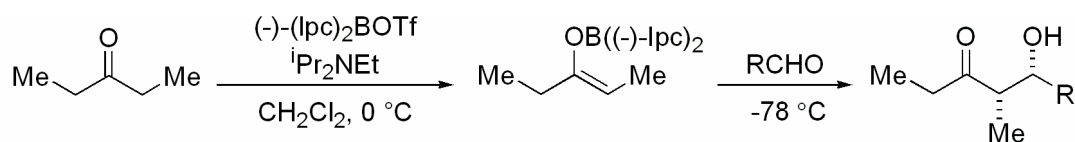
Paterson *Tetrahedron Lett.* **1987**, 28, 1229.



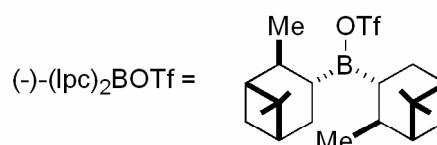
R	L	de [%] ^a
2-furanyl	Bu	68 (<i>anti</i>)
	9-BBN	50 (<i>anti</i>)
	(-)-Ipc	80 (<i>syn-syn</i>)
	(+)-Ipc	84 (<i>syn-anti</i>)
CH ₂ =CMe	Bu	88 (<i>anti</i>)
	(+)-Ipc	86 (<i>syn-syn</i>)
	(-)-Ipc	86 (<i>syn-anti</i>)
MeCH=CH	(-)-Ipc	84 (<i>syn-anti</i>)
	Me	84 (<i>syn-anti</i>)

^a *anti* refers to the combined de of both *anti* aldol products

Paterson *Tetrahedron Lett.* **1988**, 29, 585.



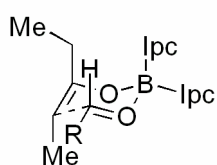
R	syn : anti	ee [% , syn]
Me	97 : 3	82
ⁿ Pr	97 : 3	80
ⁱ Pr	96 : 4	66
MeCH=CH	90 : 10	68
CH ₂ =CMe	95 : 5	90



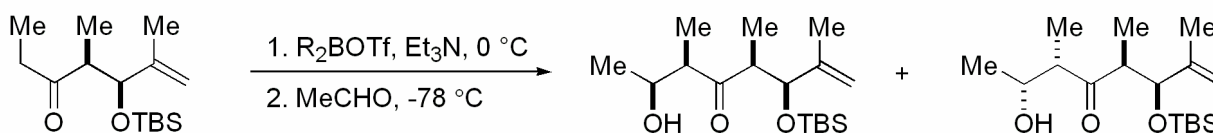
Paterson *Tetrahedron Lett.* **1986**, 27, 4787.
Tetrahedron Lett. **1987**, 28, 1229.

see also: Seebach *Helv. Chim. Acta* **1986**, 69, 604.

transition state:



External chiral centers can lead to double asymmetric induction and products with increased selectivities.

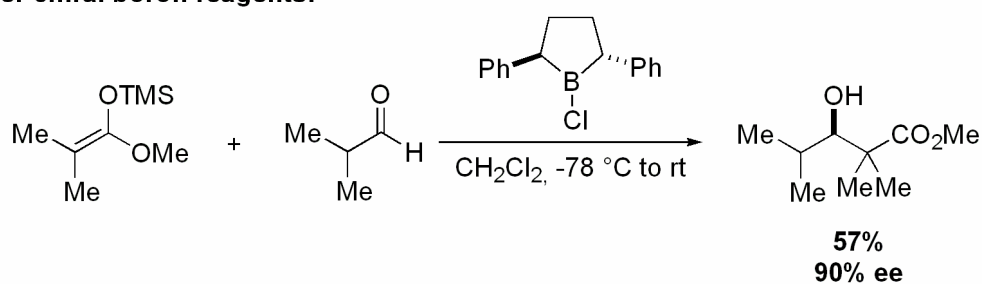


R ₂ BOTf	enolate	syn : anti	dr
9-BBN-OTf	91 : 9	90 : 10	92 : 8
(+)-(<i>lpc</i>)₂BOTf	97 : 3	96 : 4	98 : 2
(-)-(<i>lpc</i>)₂BOTf	97 : 3	96 : 4	75 : 25

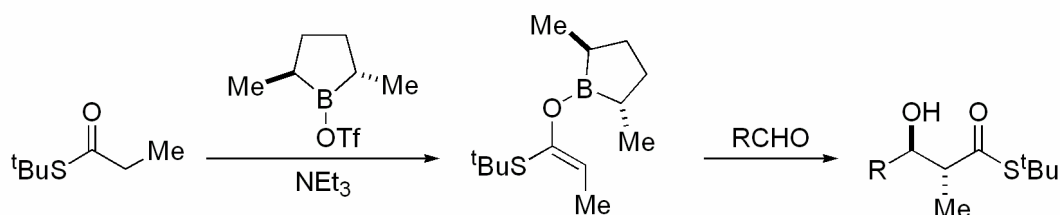
matched case

mismatched case

Other chiral boron reagents:

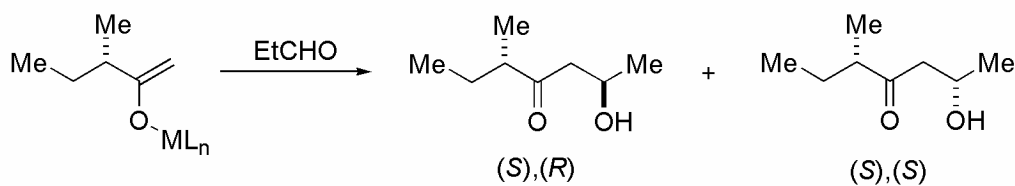


Reetz *Tetrahedron Lett.* **1986**, 27, 4721.



Masamune.

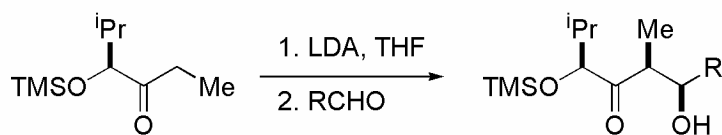
3. Aldol Reactions of Chiral Ketones and Aldehydes



ML _n	solvent	(S),(R) : (S),(S)
Li	THF	57 : 43
Bu ₂ B	Et ₂ O	57 : 43
Bu ₂ B	CH ₂ Cl ₂	63 : 37
Bu ₂ B	pentane	64 : 36

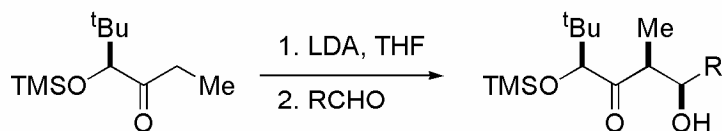
Seebach *Liebigs Ann. Chem.* **1976**, 1357.

Evans *Tetrahedron Lett.* **1980**, 21, 4675.



R	de [%]
CH ₂ =CH	6
Ph	34
iPr	48

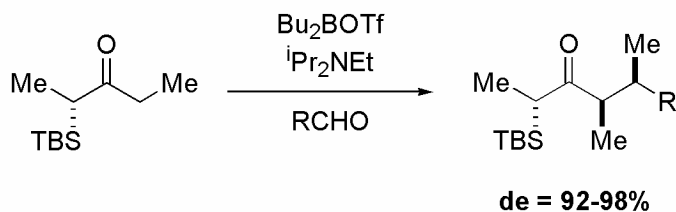
Heathcock. In *Asymmetric Synthesis*; Morrison Ed.; Academic Press: Orlando, **1984**; vol. 3, p. 111.



R	de [%]
Ph	50
PhCH ₂	74
Ph ₂ CH	> 80
iPr	50
tBu	> 90

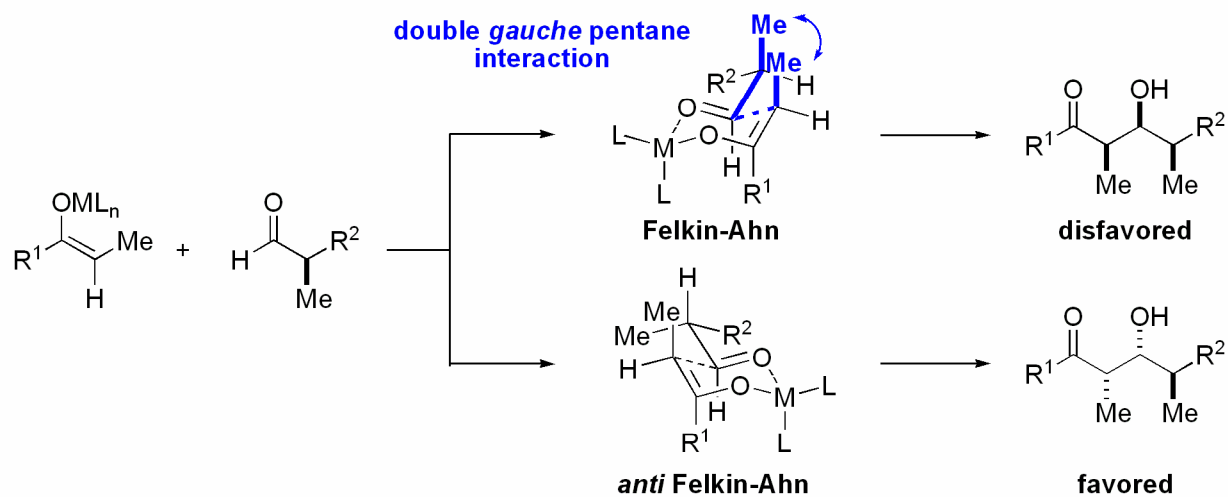
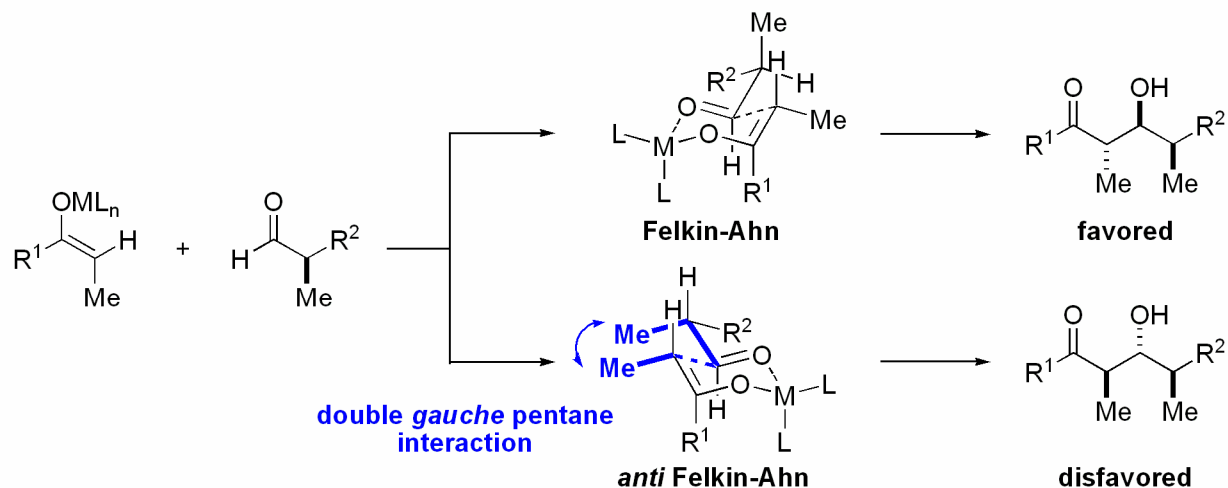
Heathcock *J. Am. Chem. Soc.* **1979**, 101, 7077.

J. Org. Chem. **1981**, 46, 2290.

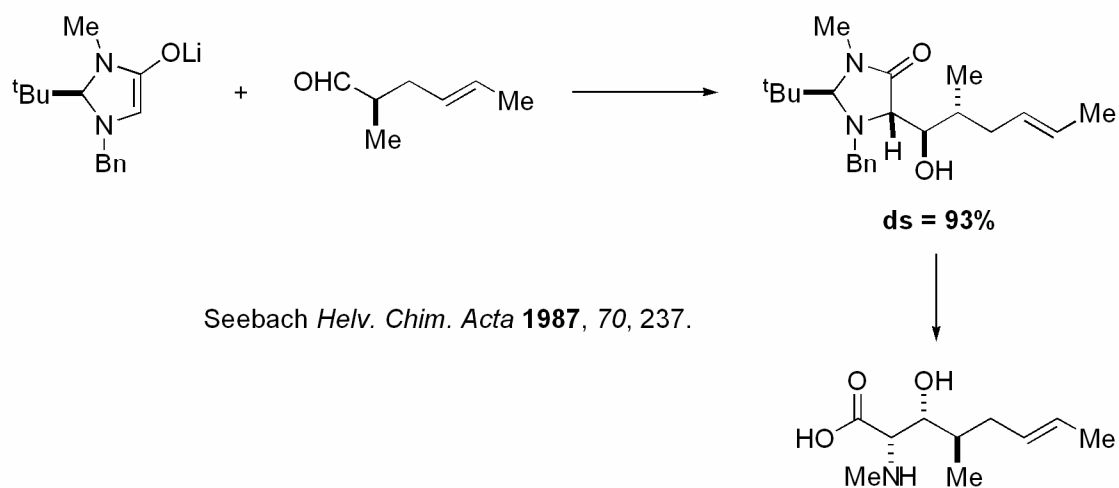


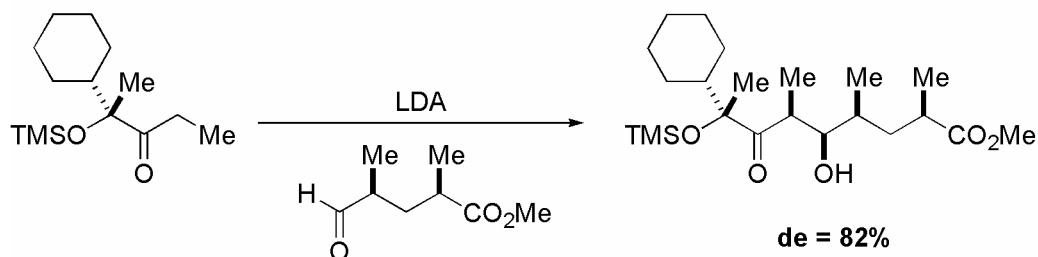
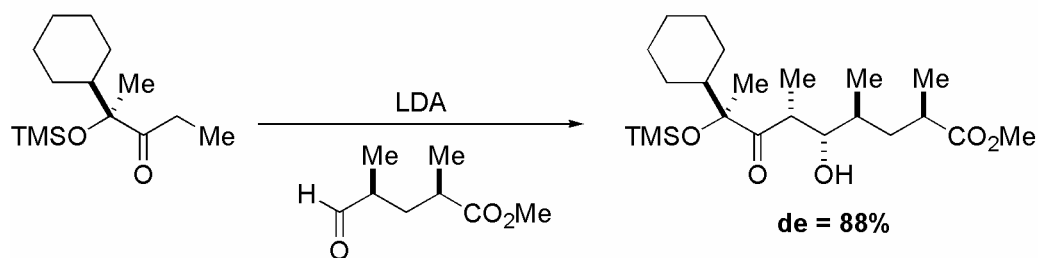
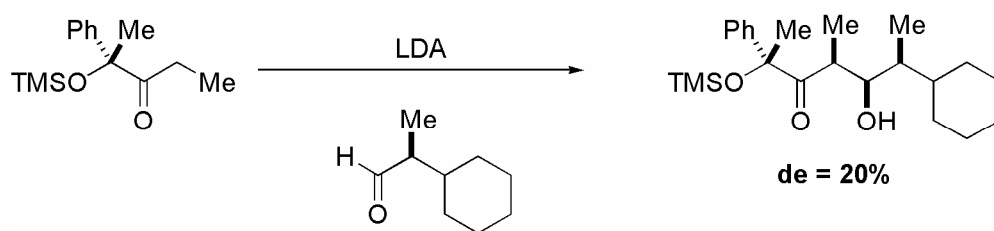
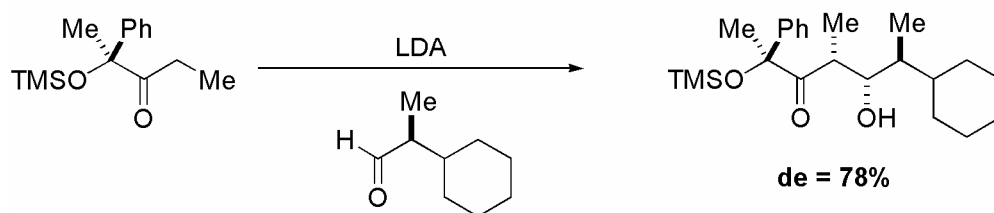
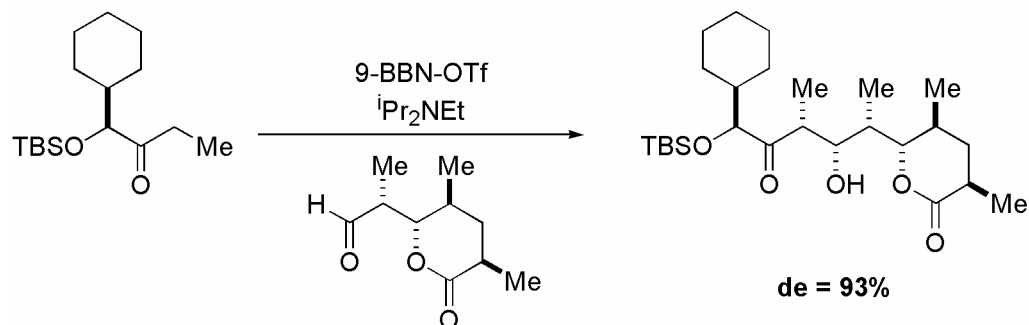
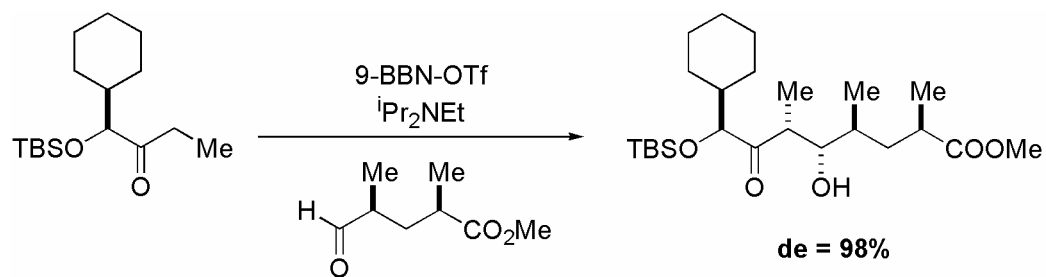
Enders *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 581.

Aldol and chiral aldehydes:

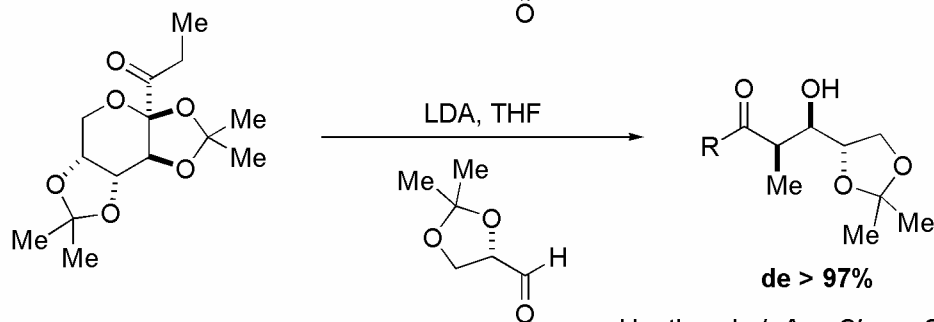
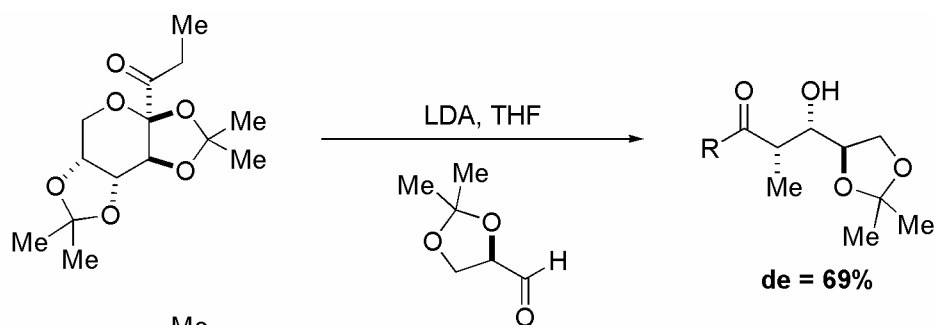


4. Double Diastereoselection

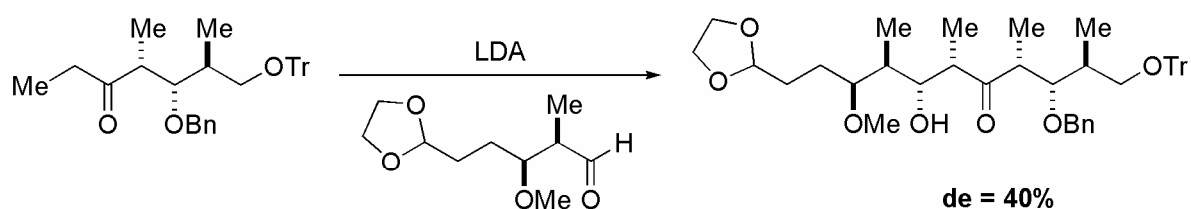




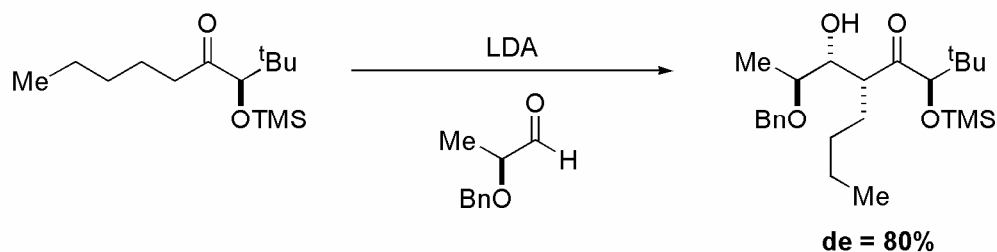
Masamune *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557.



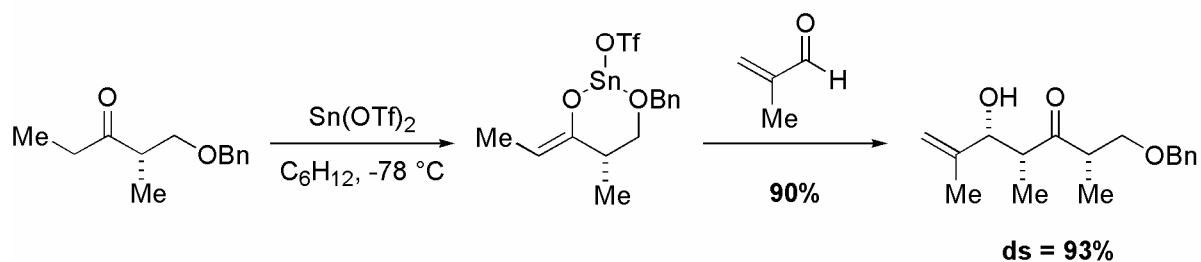
Heathcock *J. Am. Chem. Soc.* **1979**, *101*, 7076.
J. Org. Chem. **1981**, *46*, 1296.



Hanessian *J. Am. Chem. Soc.* **1982**, *104*, 1441.



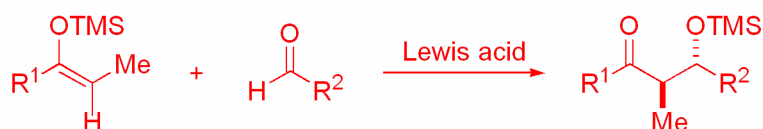
Heathcock *J. Org. Chem.* **1981**, *46*, 2290.



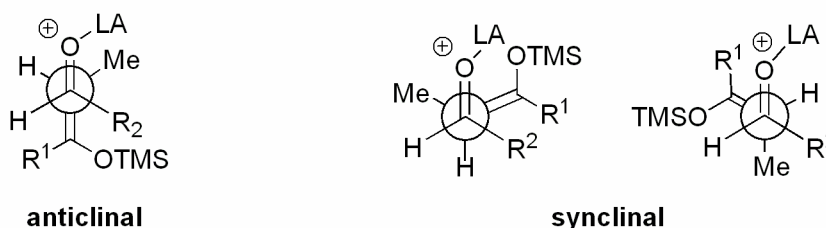
Paterson *J. Am. Chem. Soc.* **1994**, *116*, 11287.

5. Other Aldol Types

Mukaiyama aldol:

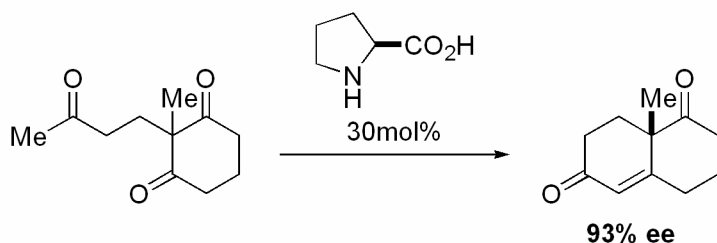


reaction proceeds via open transition states:

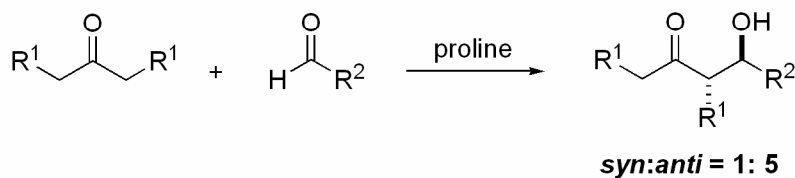


For Mukaiyama aldols, *anti* products are usually observed, not depending on the enolate geometry. Transition state analysis is complicated as both anticlinal and synclinal arrangements have to be considered.

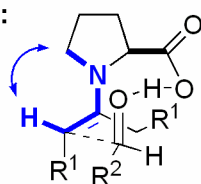
aldol via enamines: first example



more general reaction:



proposed transition state:



$A_{1,3}$ interactions minimized in enamine