

Stereoselective Synthesis of Multiple Stereocenters by Using a Double Aldol Reaction

Reporter: Jing Luo

Checker: Xian-Feng Cai

Date: 04/16/2013

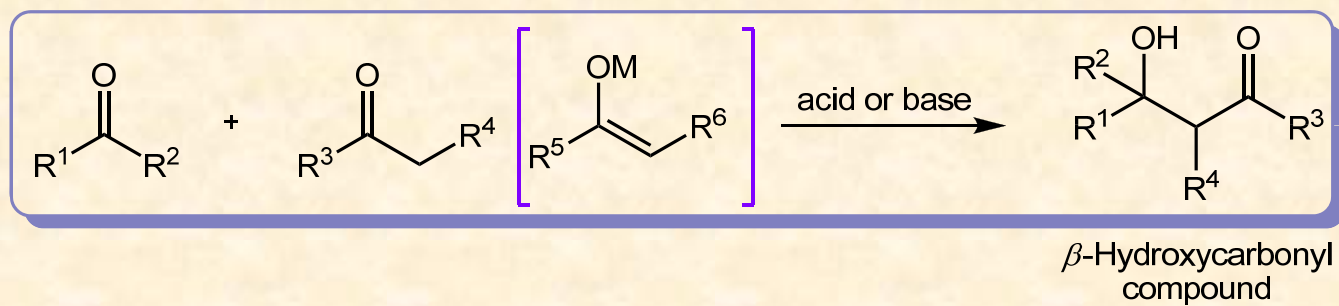
Nakajima. M. *et al.*
Angew. Chem. Int. Ed. **2013**, 52, 3461.

Contents

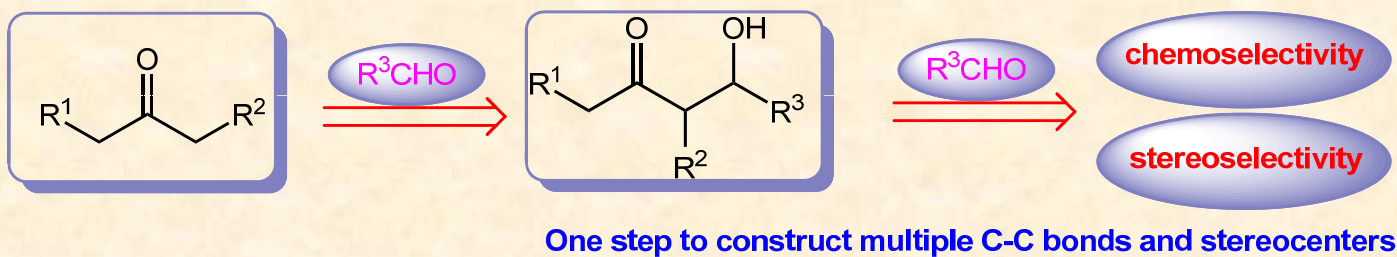
- ◆ Double aldol reaction
- ◆ Boron-mediated double aldol reaction of carboxylic esters
- ◆ Enantioselective double aldol reaction
- ◆ Summary

Double aldol reaction

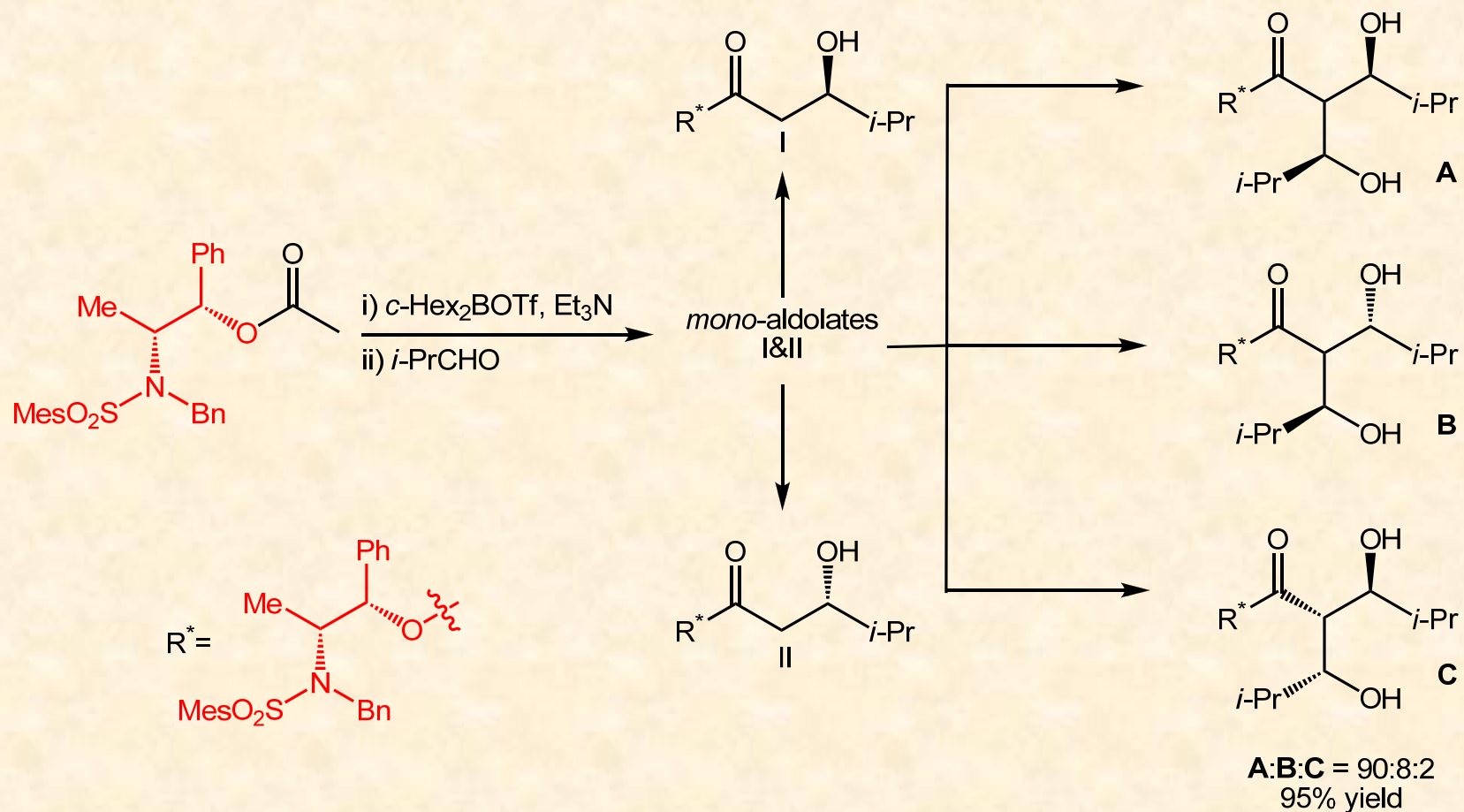
Aldol reaction :



Double aldol reaction:

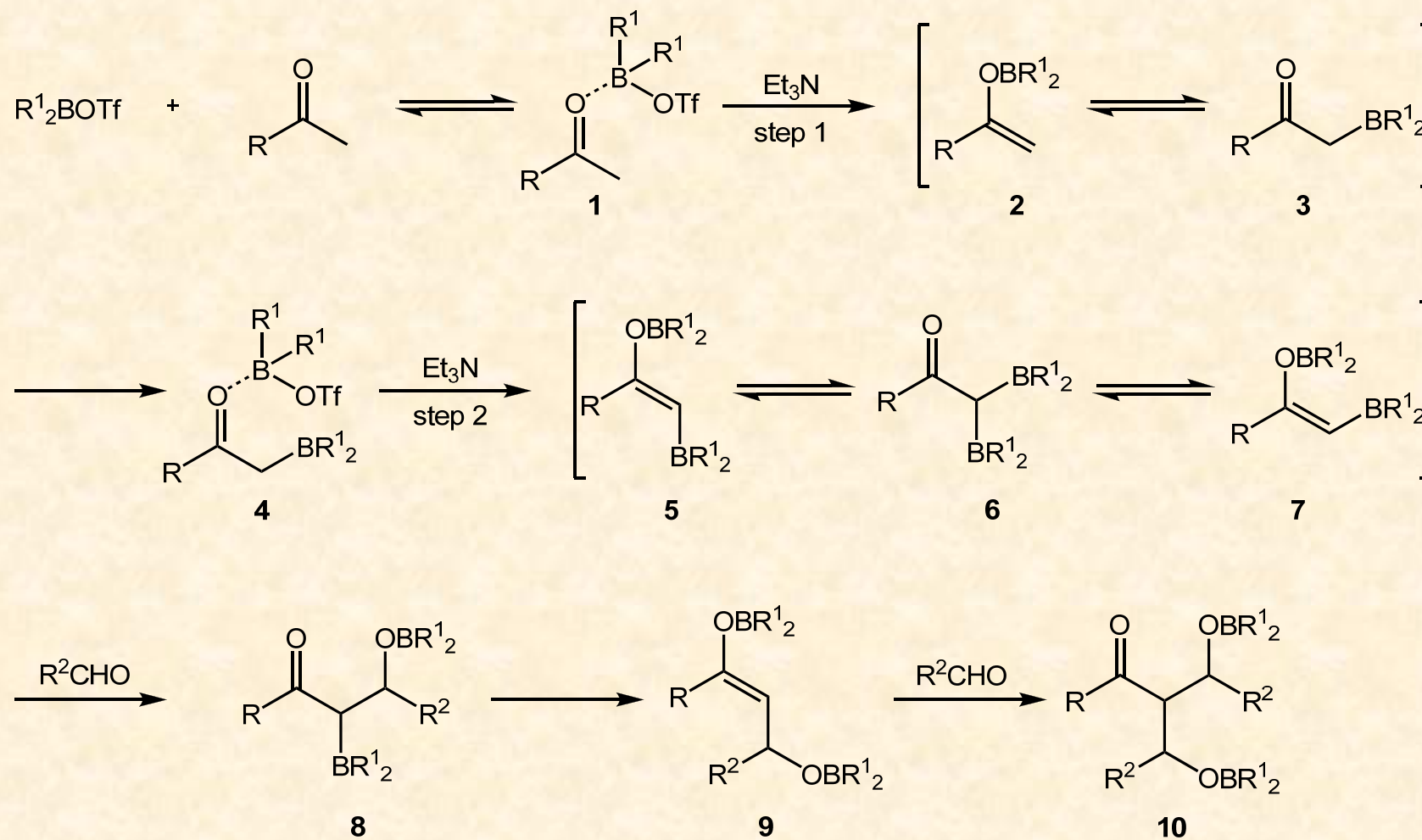


Boron-mediated double aldol reaction

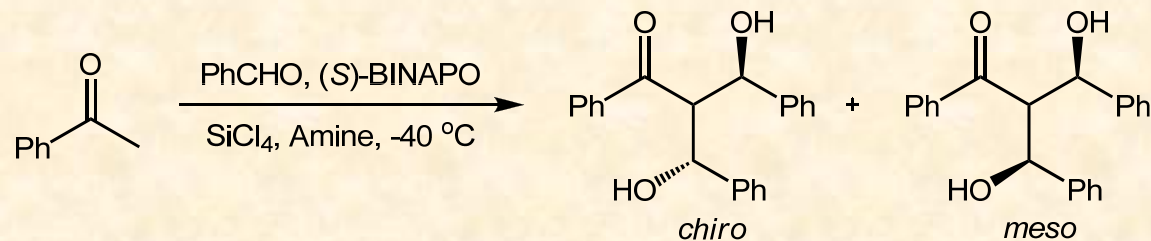


Mes = 2,4,6-trimethylphenyl

Proposed mechanism



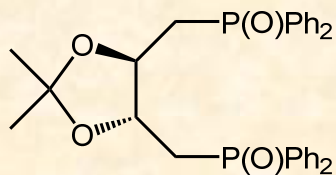
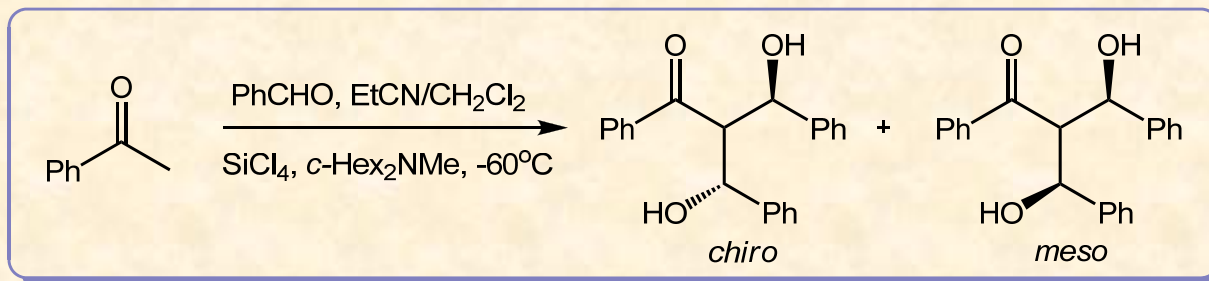
Enantioselective double aldol reaction



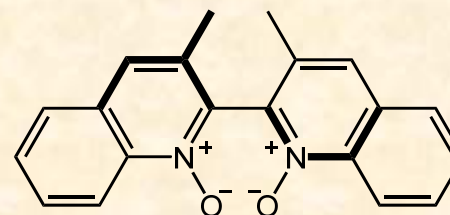
Entry	Solvent	Amine	Yield [%]	d.r.	Ee [%] (<i>chiro</i>)
1	CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	90	81:19	60
2	EtCN	<i>i</i> -Pr ₂ NEt	12	73:27	70
3	EtCN/CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	82	77:23	62
4	EtCN/CH ₂ Cl ₂	Pempidine	72	77:23	64
5	EtCN/CH ₂ Cl ₂	<i>c</i> -Hex ₂ NMe	95	79:21	61
6^a	EtCN/CH₂Cl₂	<i>c</i>-Hex₂NMe	86	78:22	70

[a] -60 °C

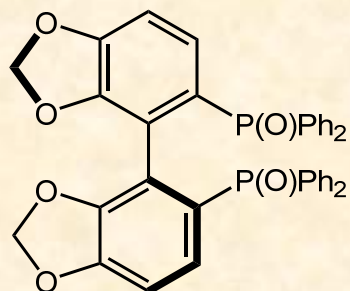
Enantioselective double aldol reaction



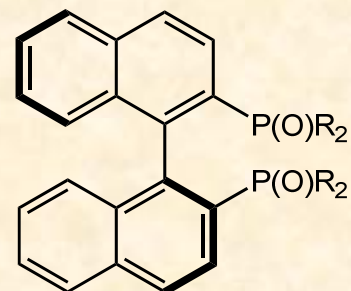
(*R,R*)-DIOPO
68% yield, 36% ee, 68:32 d.r.



(*R*)-BQNO
21% yield, -29% ee, 69:31 d.r.

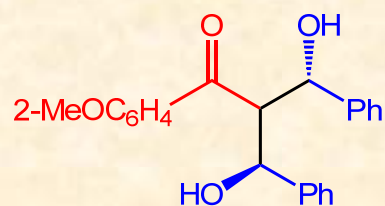
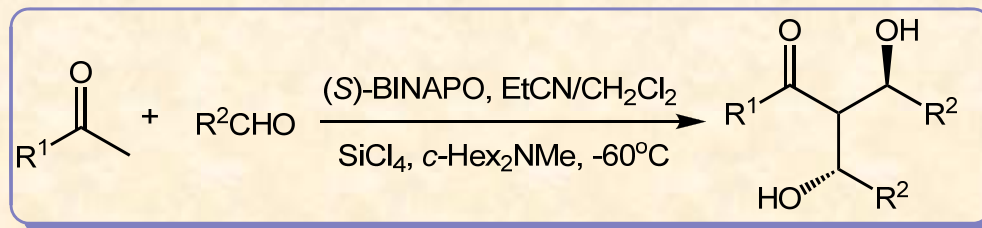


(*S*)-SEGPHOSO
93% yield, 63% ee, 79:21 d.r.

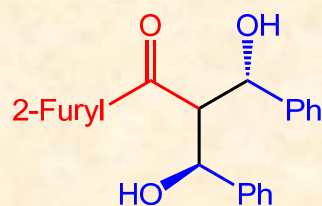


R = 4-Tolyl; (*S*)-toI-BINAPO
88% yield, 70% ee, 76:24 d.r.
R = Ph; (*S*)-BINAPO
86% yield, 70% ee, 78:22 d.r.

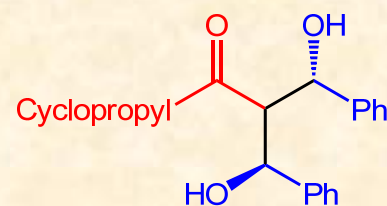
Substrate scope



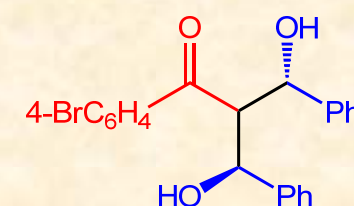
d.r. 90:10 (56% ee)



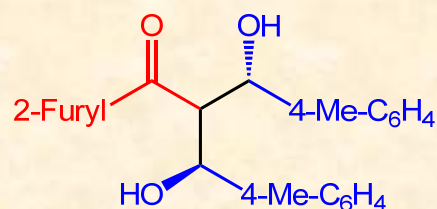
d.r. 86:14 (91% ee)



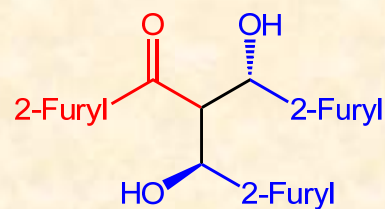
d.r. 98:2 (93% ee)



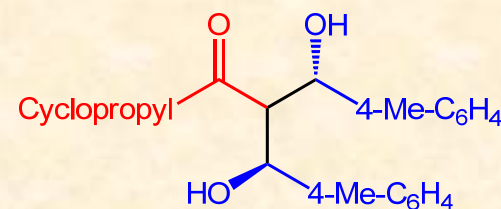
d.r. 77:23 (75% ee)



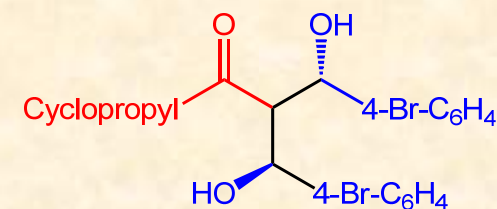
d.r. 86:14 (90% ee)



d.r. 92:8 (97% ee)

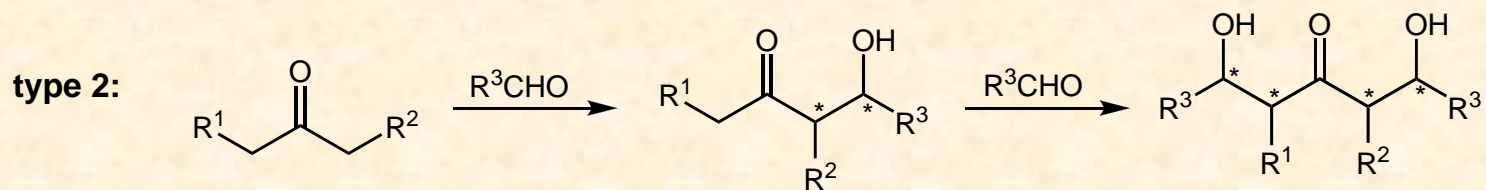
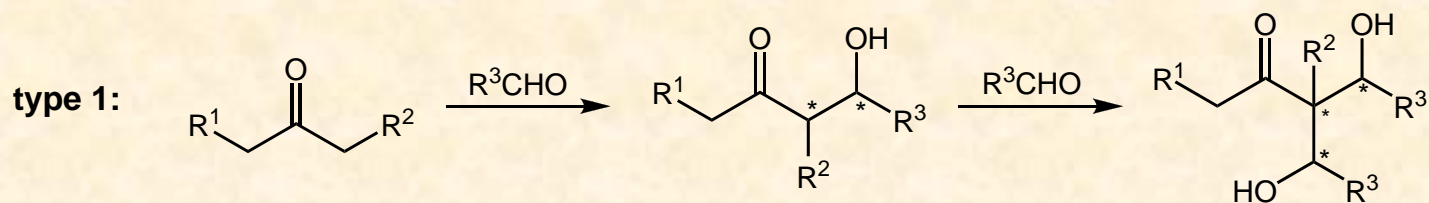


d.r. 97:3 (91% ee)

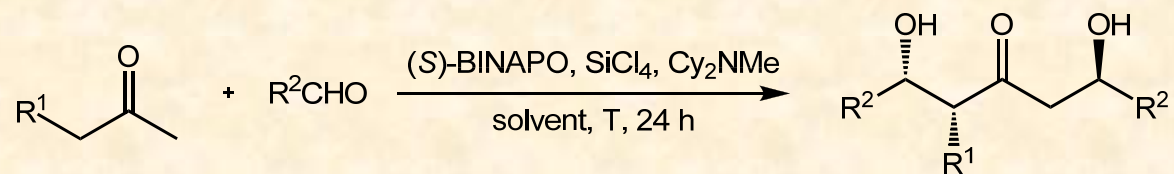


d.r. 97:3 (90% ee)

Two types of aldol reaction modes

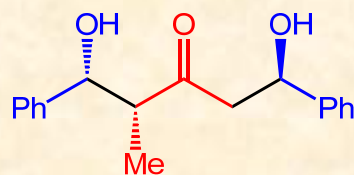
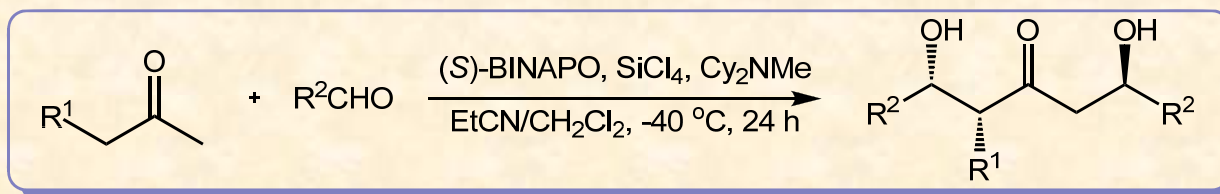


Linear-type double aldol reaction

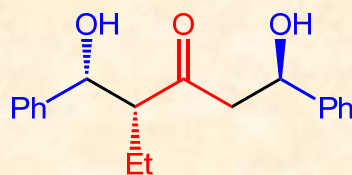


Entry	Solvent	T [°C]	Yield [%]	d.r.	ee [%]
1	CH ₂ Cl ₂	-60	65	90:10	93
2	CH ₂ Cl ₂	-60	71	91:9	95
3	CH ₂ Cl ₂	-60	73	91:9	94
4	CH ₂ Cl ₂	-40	80	90:10	86
5	EtCN	-40	28	89:11	97
6	EtCN/CH ₂ Cl ₂ (1:1)	-40	86	90:10	91

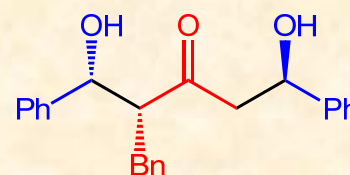
Substrate scope



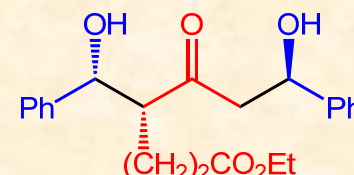
d.r. 90:10 (91% ee)



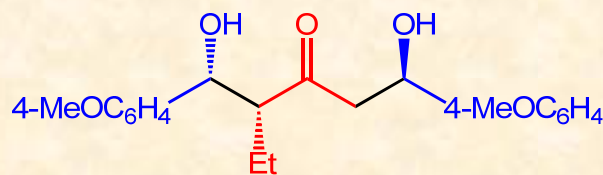
d.r. 90:10 (95% ee)



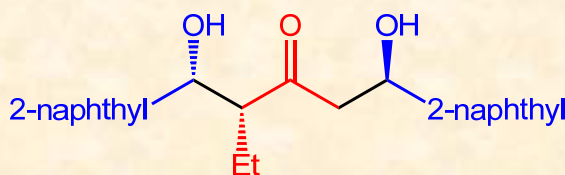
d.r. 89:11 (79% ee)



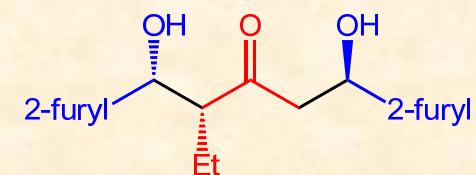
d.r. 89:11 (94% ee)



d.r. 92:8 (98% ee)

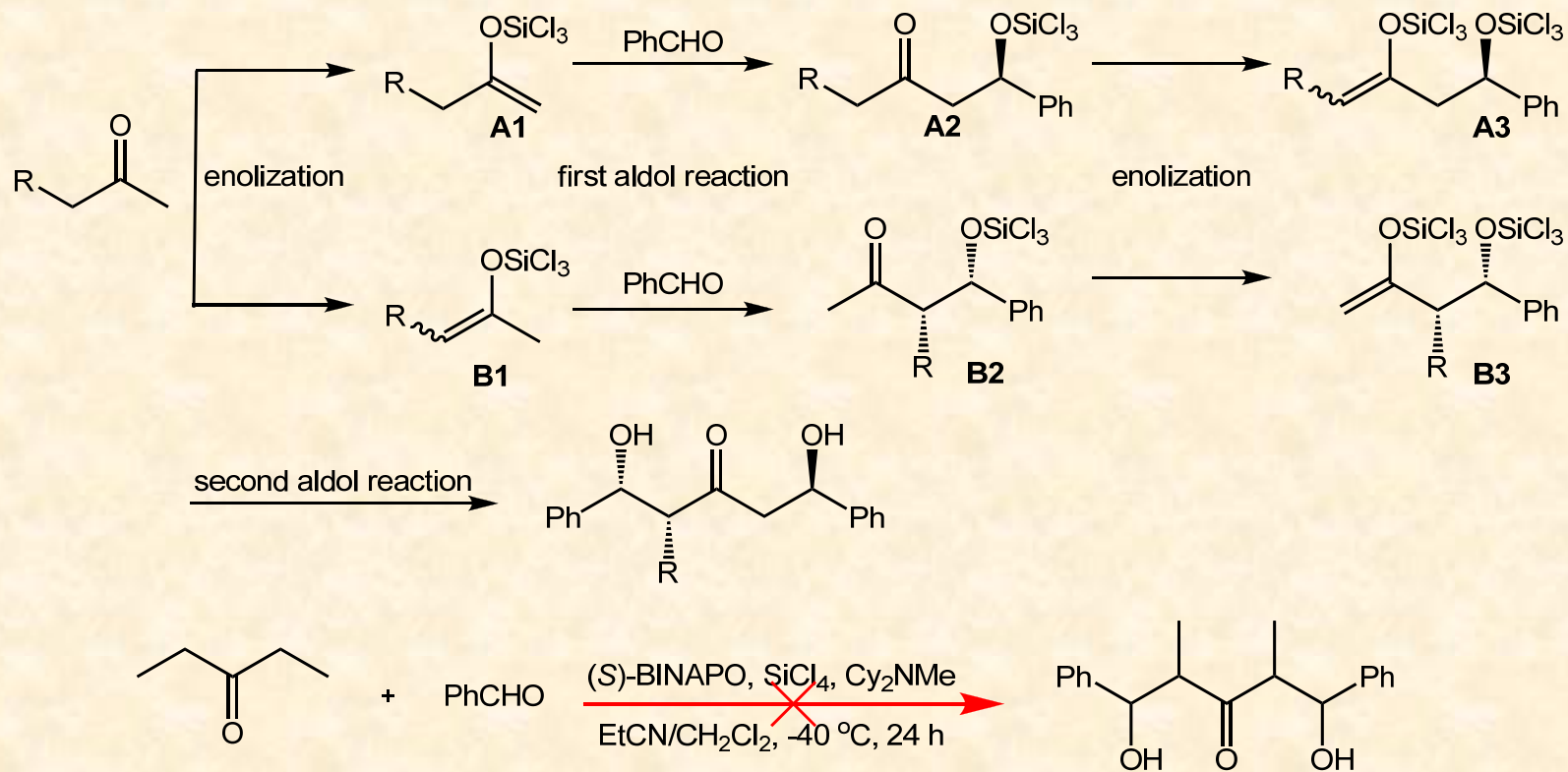


d.r. 90:10 (93% ee)



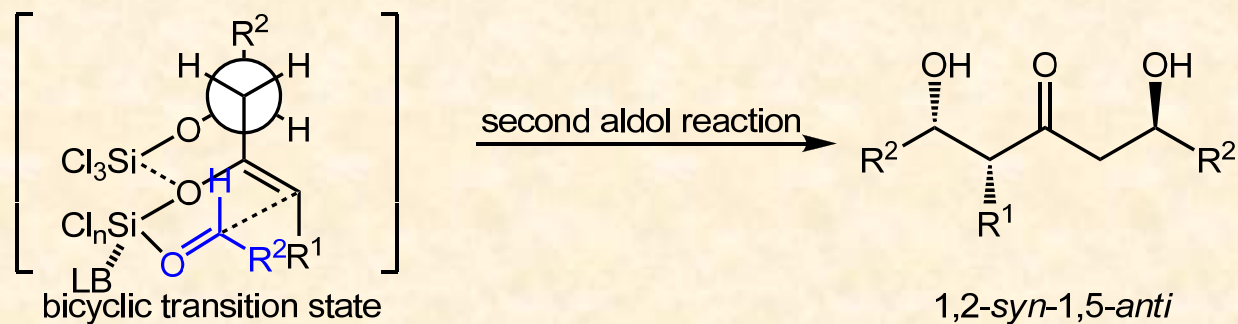
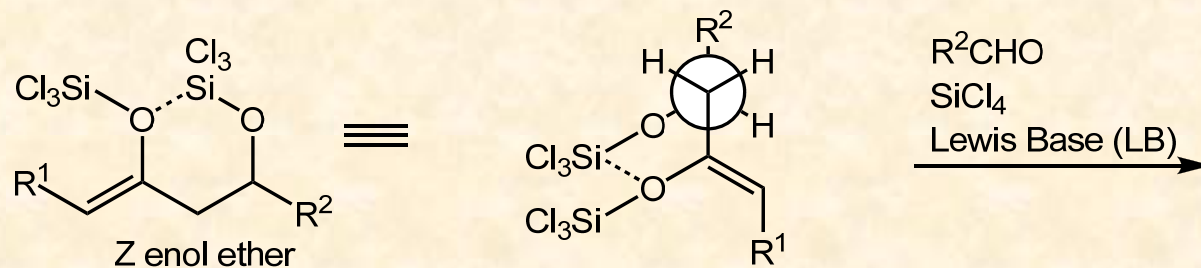
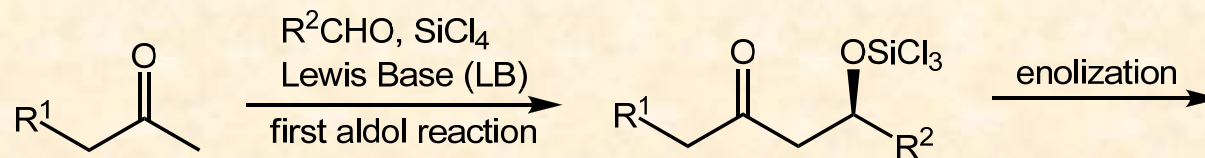
d.r. 90:10 (88% ee)

Possible reaction routes



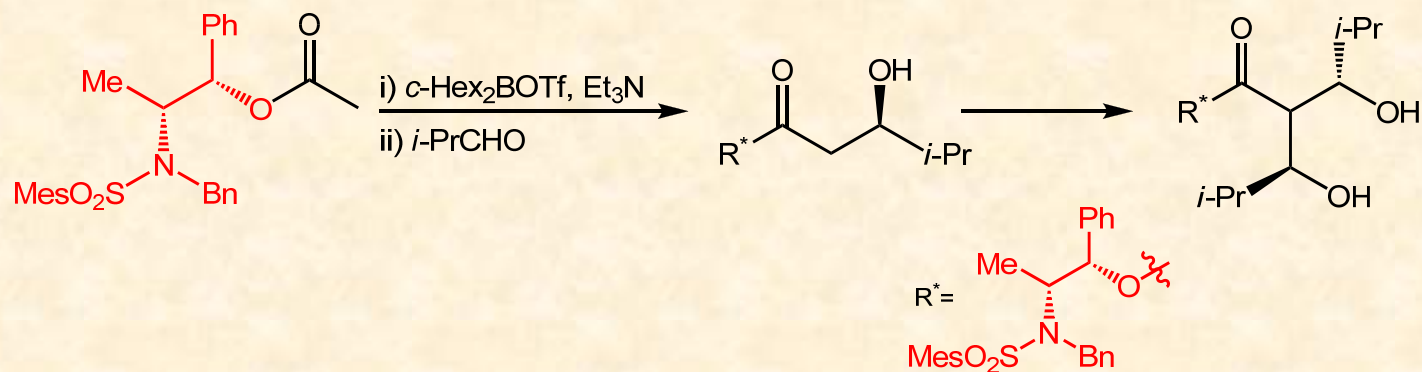
This investigation result indicated the aldolate **A** for the first aldol reaction

Proposed mechanism

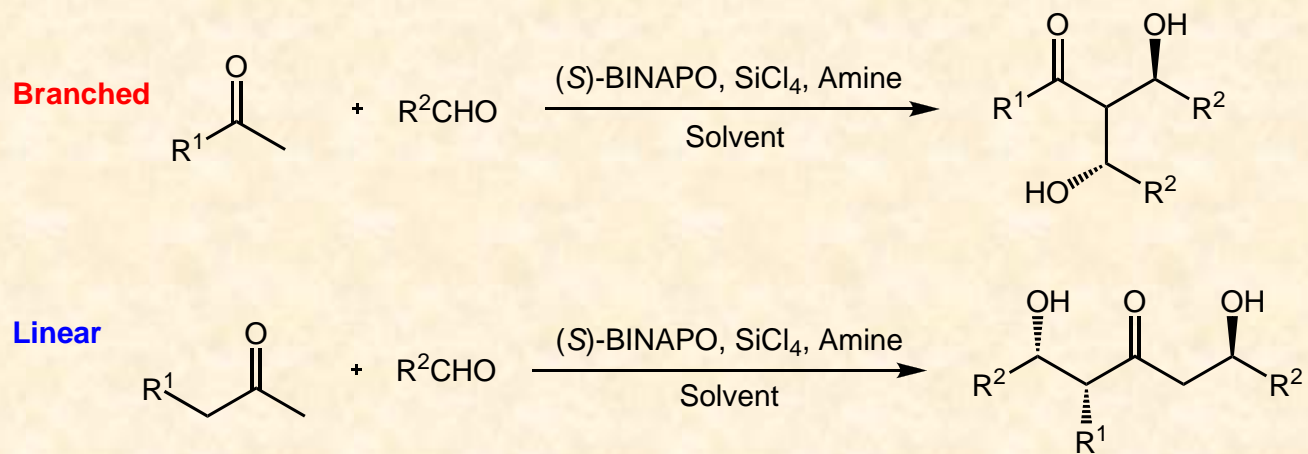


Summary

Boron-mediated double aldol reaction



Enantioselective double aldol reaction



Asymmetric multicomponent reactions have attracted much attention in organic synthesis because they both simplify synthetic processes and permit the construction of multiple chiral centers in a single operation. **Although several asymmetric aldol reactions have been developed, Relatively few examples of sequential aldol reactions which lead to the formation of multiple carbon-carbon bonds with chiral centers are available.** Among the various sequential aldol reactions, double aldol reactions involving one aldol donor and two aldol acceptors have two types of reaction modes. **a) two aldol reactions may occur at a single α -position on an aldol donor to give a branched double aldol adduct with three contiguous stereogenic centers;** b) a reaction at both α -positions of a carbonyl group in an aldol donor provides a linear double aldol adduct having a 1,5-dihydroxy group with at most four chiral centers in a single operation.

In summary, we demonstrated a novel enantioselective double aldol reaction of an alkyl methyl ketone and two aldehydes using a chiral phosphine oxide as an organo-catalyst. **The present reaction allows ready access to the 1,2-*syn*-1,5-*anti*-1,5-dihydroxy-3-pentanones with high stereoselectivity in a single operation.** Investigations focused on achieving higher reactivity and selectivity for double aldol reaction are in progress.