Back to Sugars: “Enzymatic” Synthesis

Zhensheng Ding

Nov. 04

Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305,* 1752

Northrup, A. B. and MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002,** *124,* 6798 - 6799

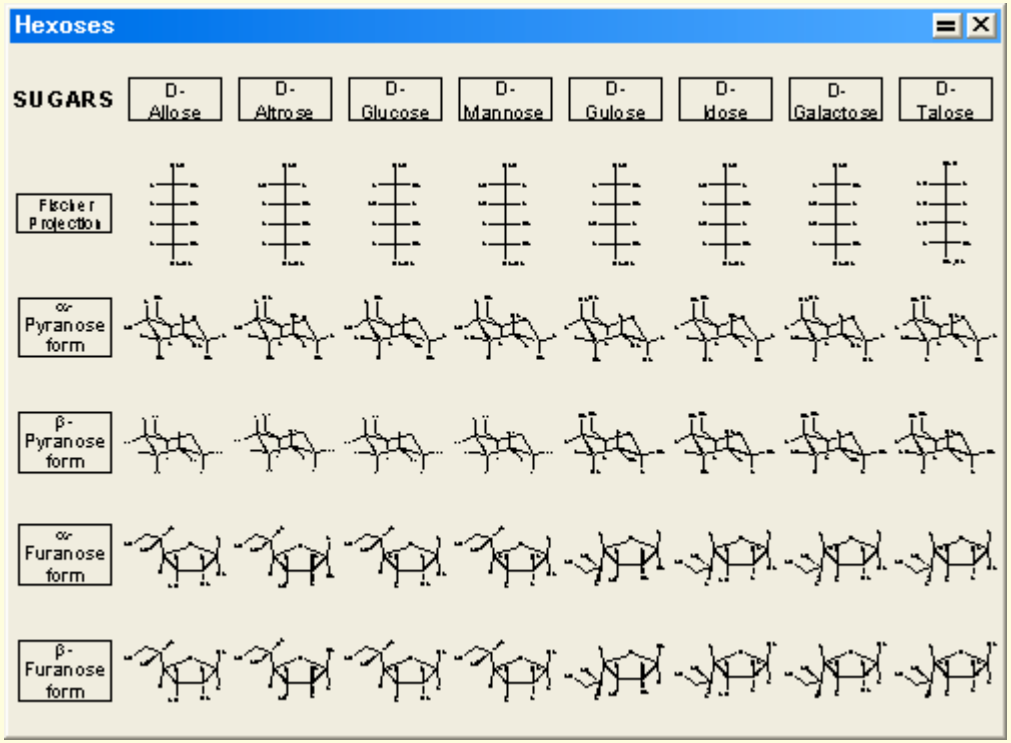
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed. Engl.* 2004, *43*, 2152

List, B. *Tetrahedron* **2002,** *58*, 5573

Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed , L. A.; Sharpless, K. B. *Science* **1983**, *220,* 949

List, B. ; Lerner, R. A. and Barbas III, C. F. *J. Am. Chem. Soc.,* **2002,** *122*, 2395 -2396

Introduction to Hexoses

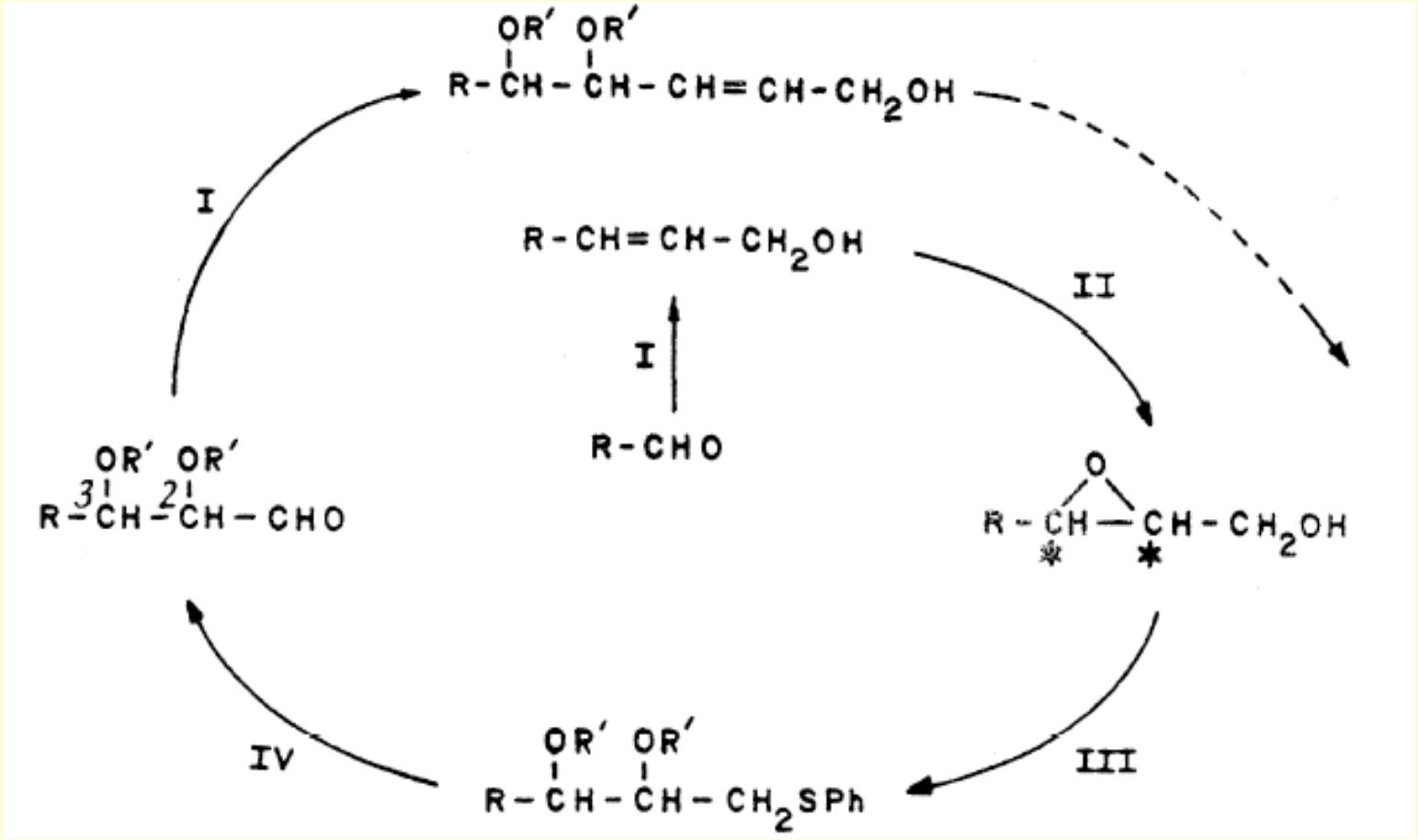


- Play vital roles in biological process
  - signal transduction, cognition, immune response
- Synthetically challengeable to chemistry
  - 4 stereocenters with 5 similar hydroxyl groups

Common Methods toward Sugars

- Sharpless's reiterative two-carbon extension cycle
  - Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed , L. A.; Sharpless, K. B. *Science* **1983**, *220,* 949
  - Takeuchi, M; Taniguchi, T; Ogasawara, K. *Synthesis* **1999,** *1999, 341*
- Hetero-Diels-Alder reactions
  - Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985,** *107*, 7761
  - Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793
  - Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett.* **1994**, *1994,* 509
  - Bataille, C. *et al.*, *J. Org. Chem.* **2002,** *67*, 8054
- Iterative syn-Glycolate aldol strategy
  - Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Synlett.* **2002**, *2002,* 1637

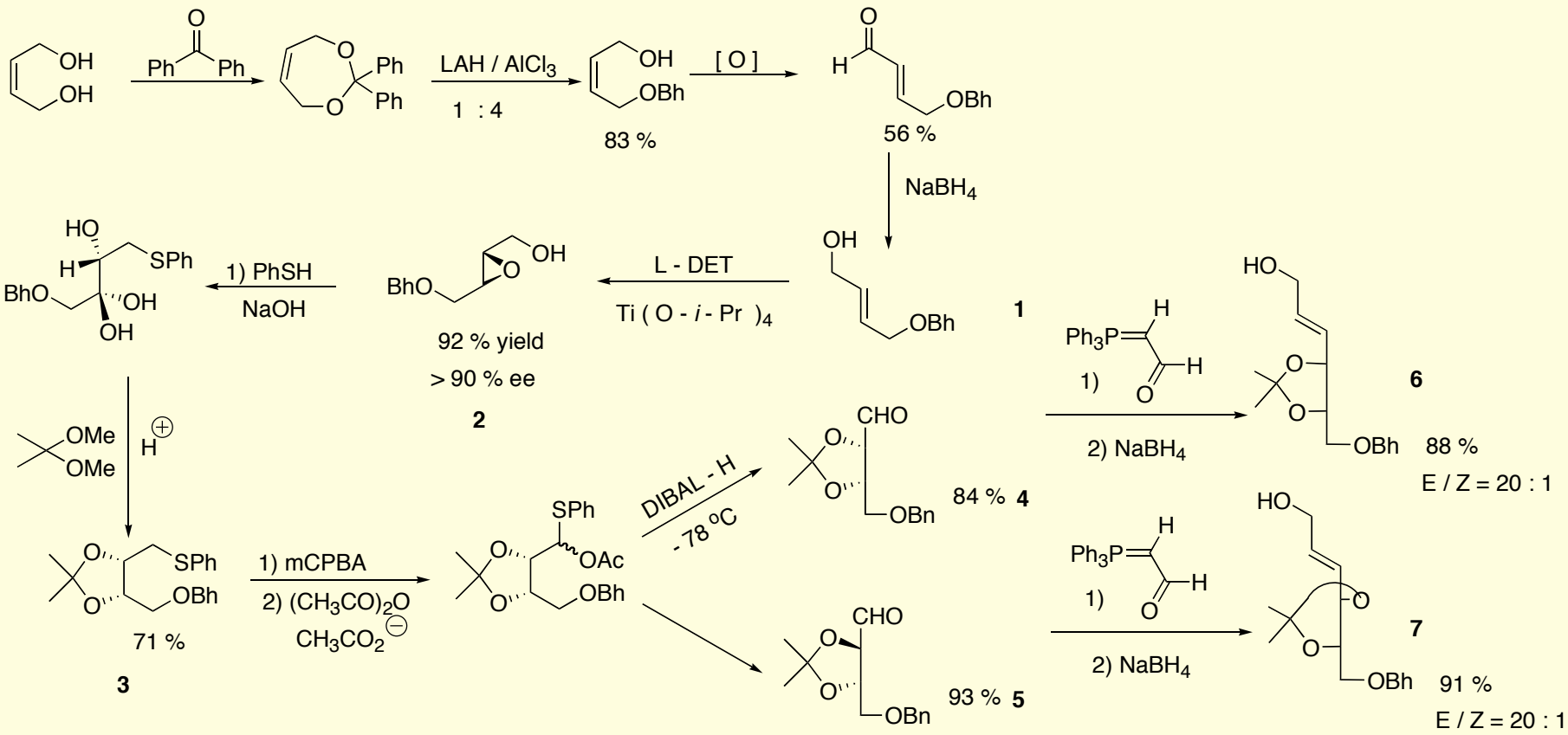
Sharpless's Two-carbon Extension Cycle: the Idea



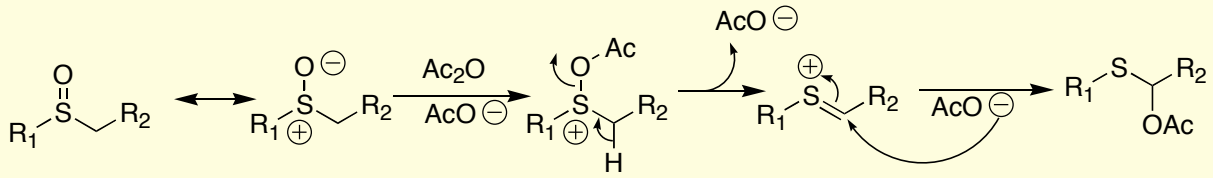
Key step: Sharpless asymmetric epoxidation

Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed , L. A.; Sharpless, K. B. *Science* **1983**, *220,* 949

Completion of the 1st Cycle



Pummerer rearrangement



Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed , L. A.; Sharpless, K. B. *Science* **1983**, *220,* 949

Completion of the 2nd Cycle to 8 Hexoses

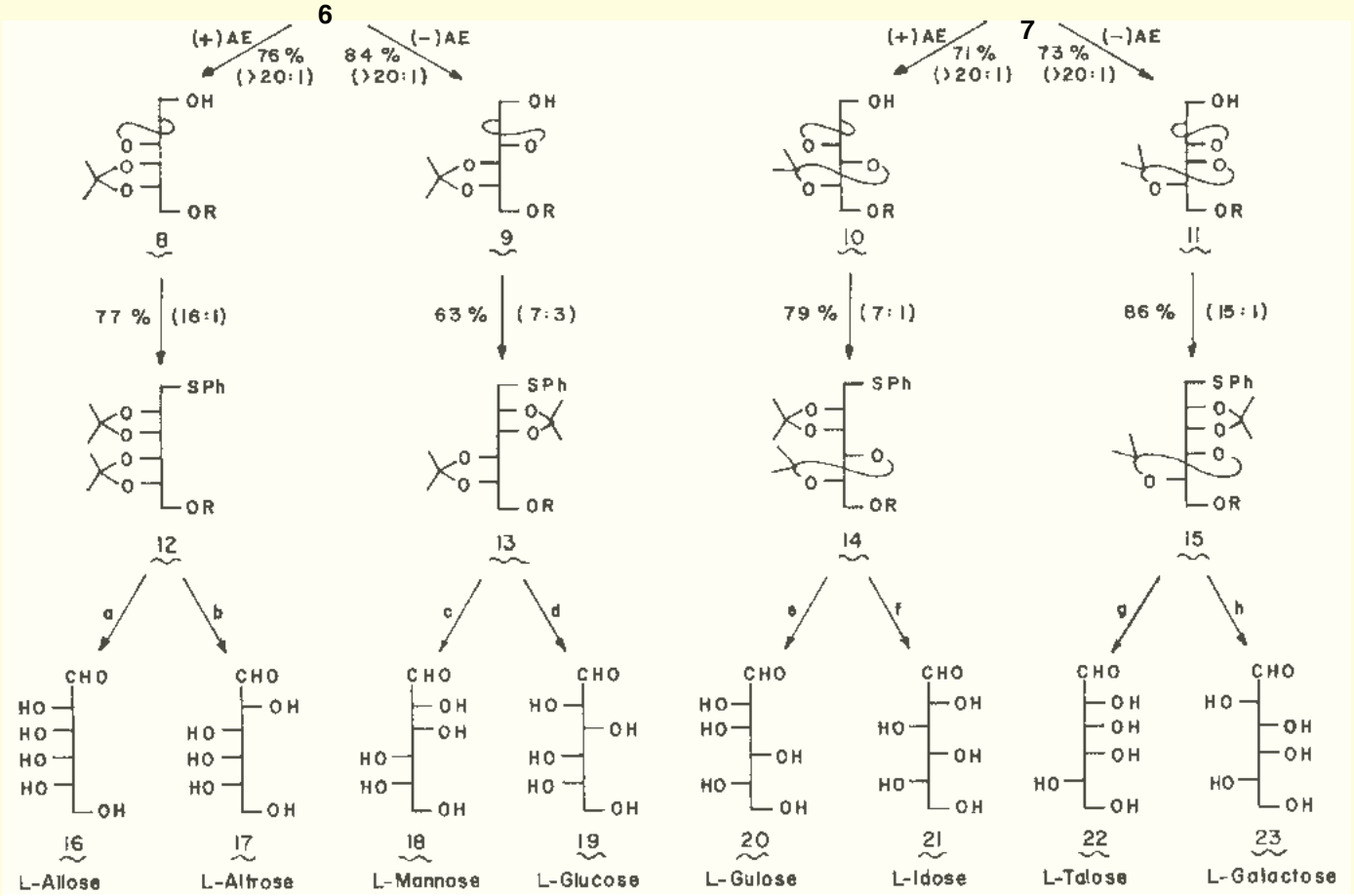
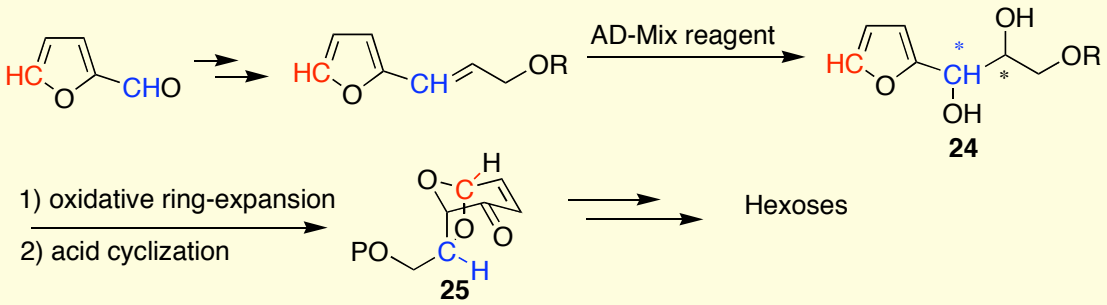


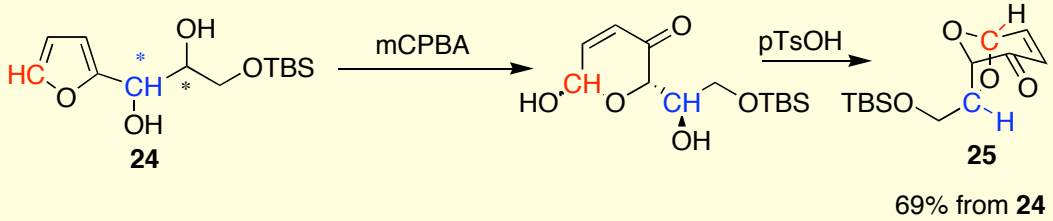
Fig. 2. Synthesis of L-hexoses. For a, c, e, and g, 1 = Pummerer reaction, 2 = Dibal, 3 = deprotection. a: 1 (90 percent), 2 (81 percent), 3 (90 percent). c: 1 (90 percent), 2 (95 percent), 3 (90 percent). e: 1 (87 percent), 2 (81 percent), 3 (84 percent). g: 1 (71 percent), 2 (77 percent), 3 (61 percent). For b, d, f, and h: 1 = Pummerer reaction, 2 = potassium carbonate and methanol, 3 = deprotection. b: 1 (90 percent), 2 (48 percent), 3 [see (*11*)]. d: 1 (90 percent), 2 (60 percent), 3 (20 percent). f: 1 (87 percent), 2 (66 percent), 3 (85 percent). h: 1 (71 percent), 2 (41 percent), 3 (27 percent).

Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed , L. A.; Sharpless, K. B. *Science* **1983**, *220,* 949

Modifications to Sharpless's Strategy



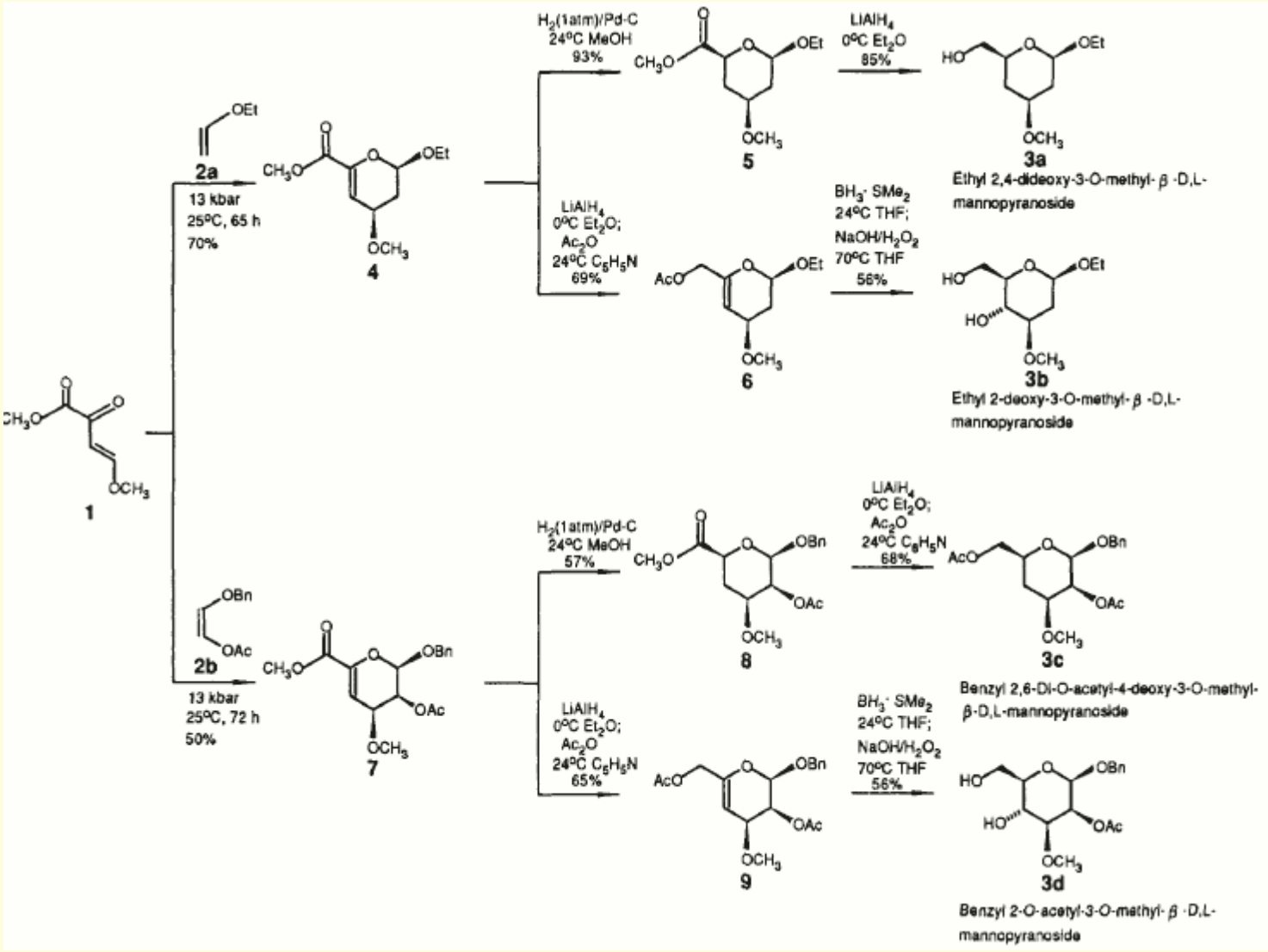
The key step:



69% from **24**

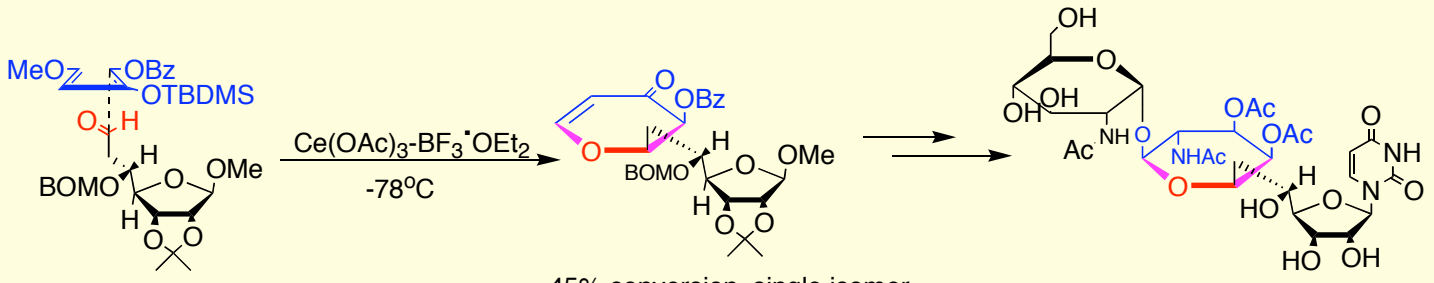
Takeuchi, M; Taniguchi, T; Ogasawara, K. *Synthesis* **1999,** *1999, 341*

Boger's Hetero-Diels-Alder Reactions toward Hexoses



Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793

Other Hetero-Diels-Alder Reactions toward Hexoses

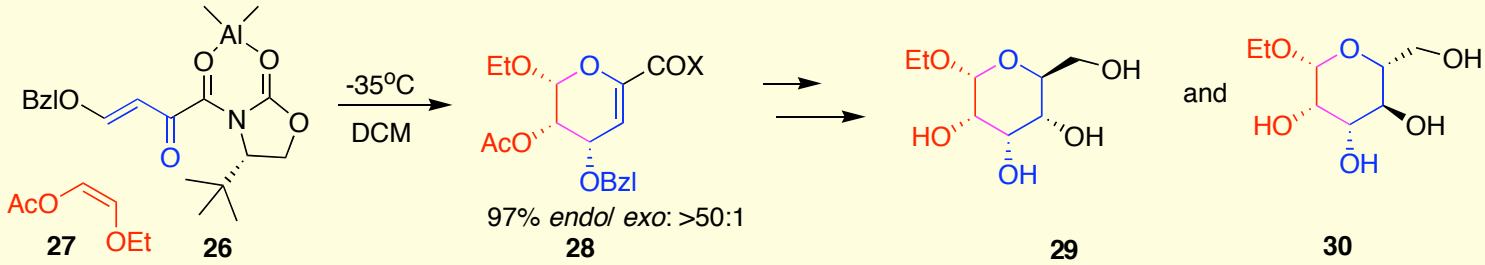


45% conversion, single isomer

Tunicamycins

35 **36** **37**

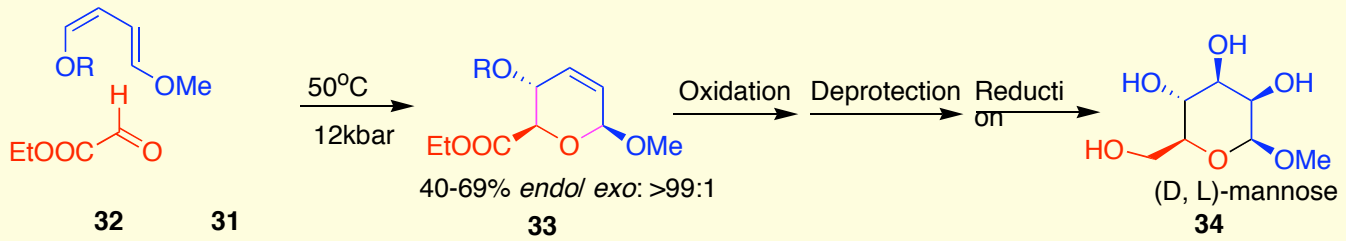
Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985,** *107*, 7761



97% *endo*/ *exo*: >50:1

27 **26** **28** **29** **30**

Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett.* **1994**, *1994,* 509



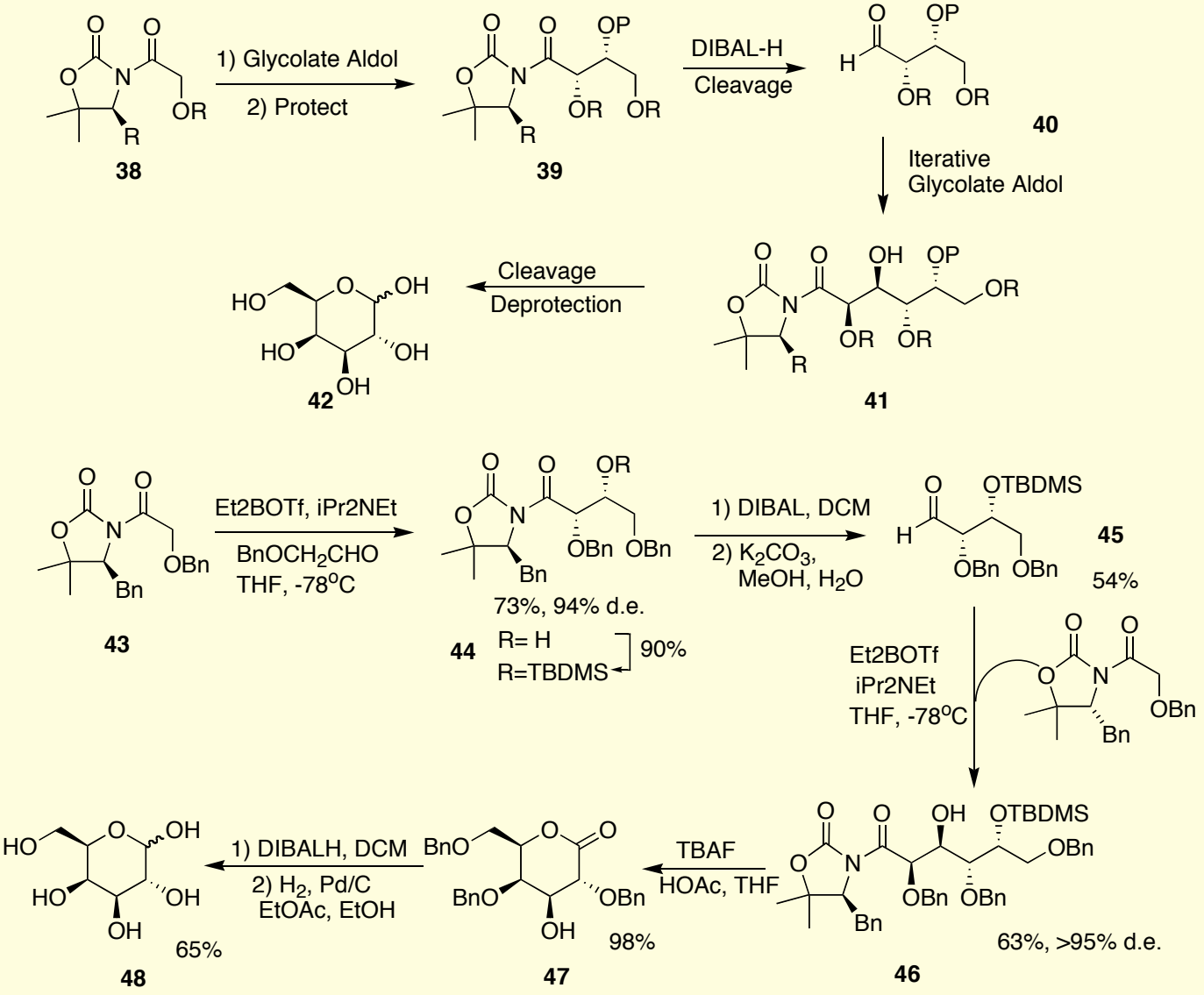
40-69% *endo*/ *exo*: >99:1

(D, L)-mannose

32 **31** **33** **34**

Bataille, C. *et al.*, *J. Org. Chem.* **2002,** *67*, 8054

Iterative *syn*-Glycolate Aldol Strategy



Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Synlett.* **2002**, *2002,* 1637

Disadvantages and Advantages of the Old Methods

Disadvantages:

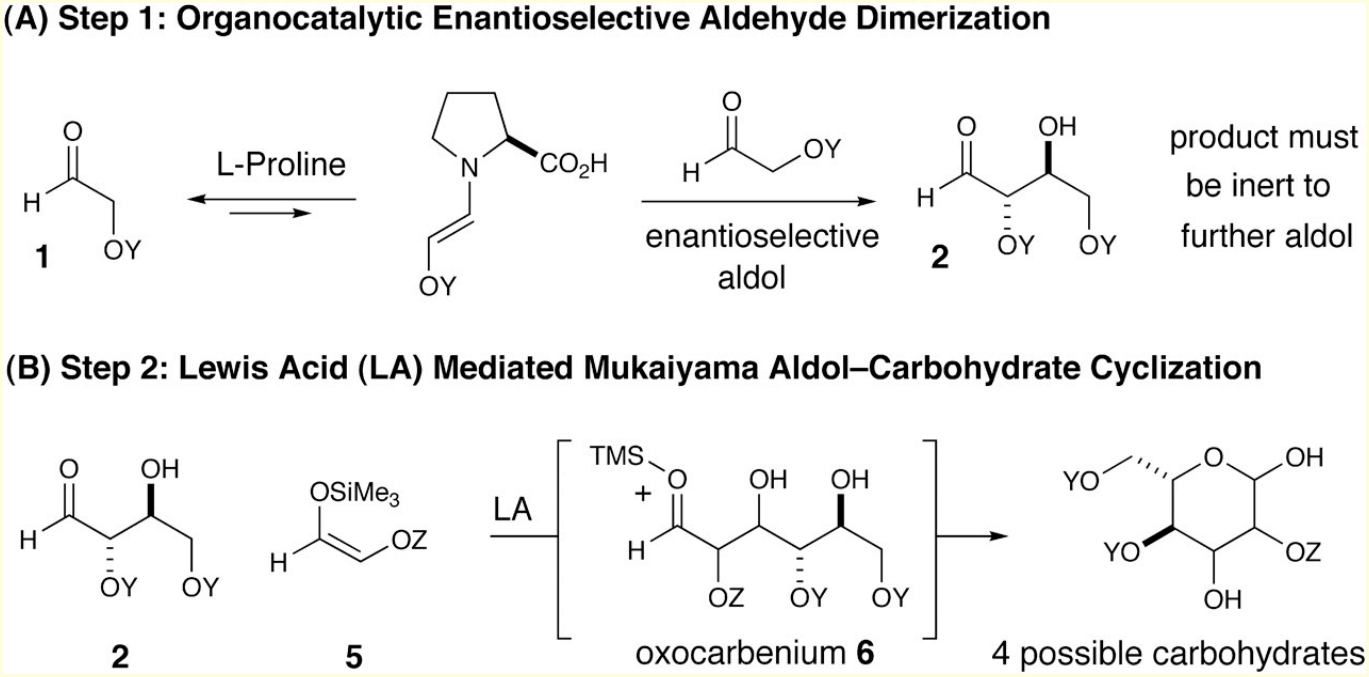
- Require protection-group manipulations
- Need for iterative oxidation-state adjustment
- Long synthetic pathways

Advantages:

- Hexoses can be independently derivatized
- Hydroxyl groups of hexoses are protected
- Hydroxyl groups of hexoses are chemically discriminated
- Ready to couple with other sugars to produce polysaccharides and other derivatives

Can hexoses be synthesized more efficiently by such de novo methods?

The Idea: L-Proline Catalyzed Cross Aldol Reactions



- Both steps are not practically proved
- Product of step 1 must be inert to further aldol

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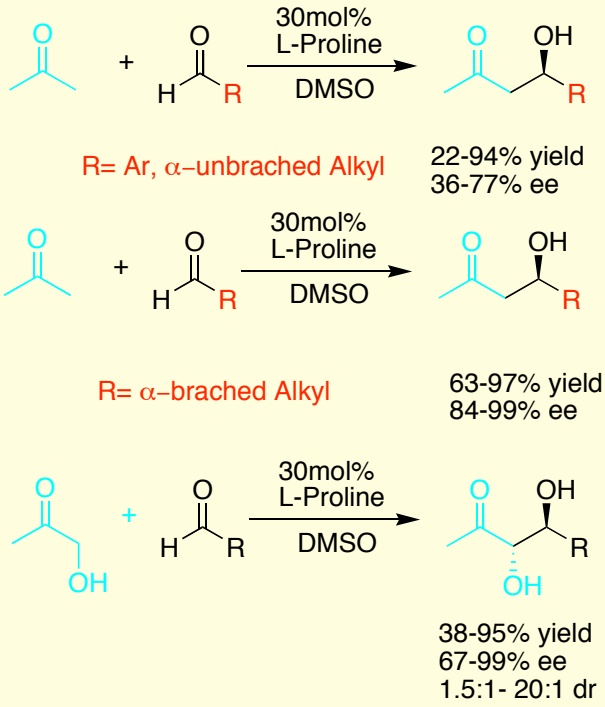
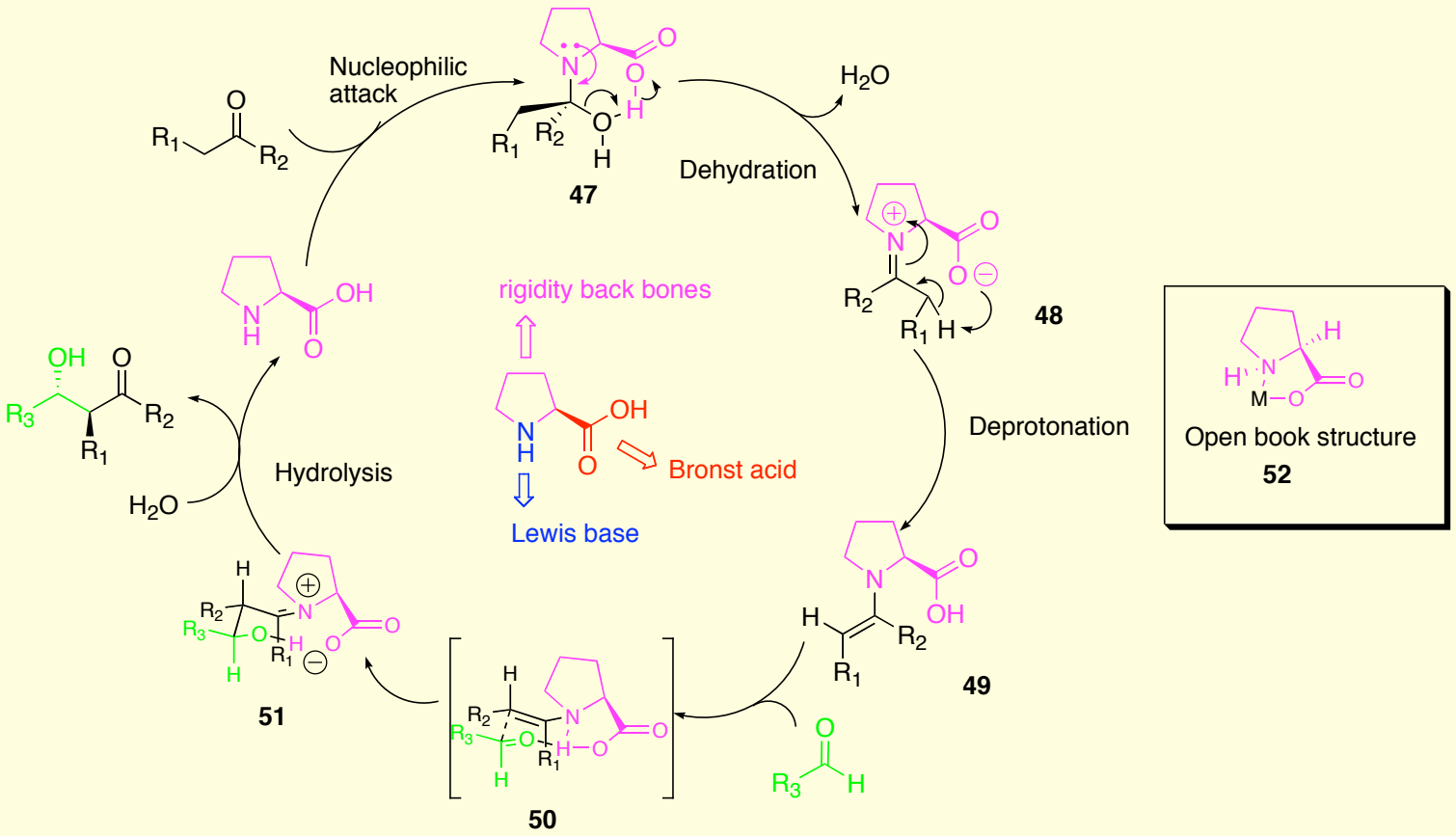
First Proline-catalyzed Direct Asymmetric Aldol Reactions - Breakthrough



- Not require the pregeneration of enolates or enolate equivalents
- Stereoselectivity is usually good
- Nucleophilic partners are acetone and a-hydroxyl acetone
- Stereoselectivity is substrate-sensitive with a-brached alkyl aldehydes give better e.e.s.

List, B. *Tetrahedron* **2002,** *58*, 5573
List, B. ; Lerner, R. A. and Barbas III, C. F. *J. Am. Chem. Soc.*, **2002,** *122*, 2395 -2396

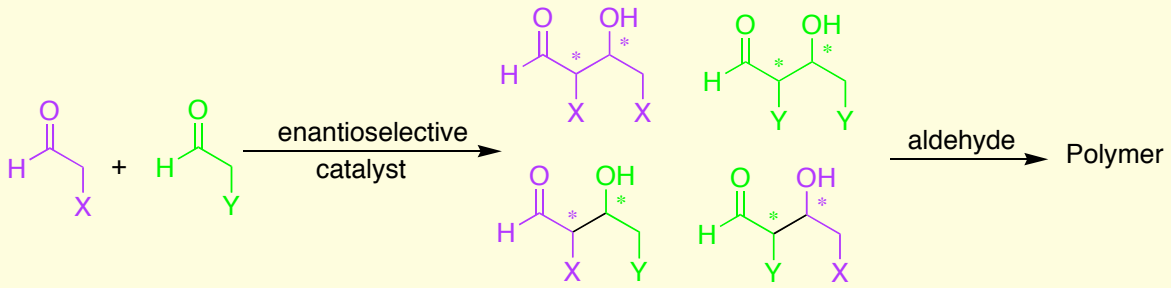
Features of Proline as Catalyst



1) Bifunctional catalyst with increase lewis basicity and rigid back bones
2) Nontoxic, inexpensive, readily available in both enantiomeric forms
3) No prior modification of carbonyls
4) Water soluble
5) No metal required

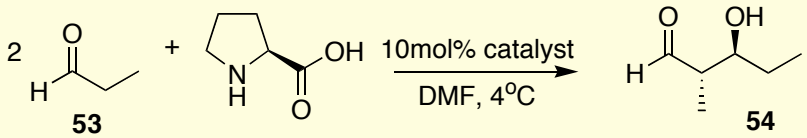
List, B. *Tetrahedron* **2002,** *58*, 5573
List, B. ; Lerner, R. A. and Barbas III, C. F. *J. Am. Chem. Soc.*, **2002,** *122*, 2395 -2396

Direct Enantioselective Cross-Aldol of Aldehydes — Elusive Transformations



- Nonequivalent aldehydes must selectively partition into two discrete components - nucleophilic donor and electrophilic acceptor
- The propensity of aldehydes to polymerize

Can proline be used for direct enantioselective cross-aldol reaction of aldehydes?

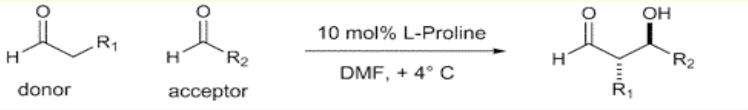


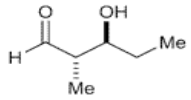
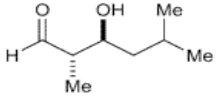
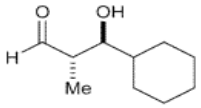
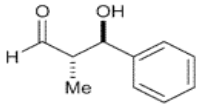
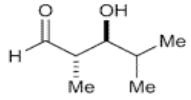
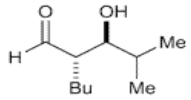
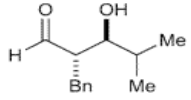
53 **54**

80% yield, 4:1 *anti*: *syn, 99%ee*

Northrup, A. B. and MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002,** *124,* 6798 - 6799

First Proline-catalyzed Direct Asymmetric Cross-Aldol Reactions of Aldehydes



entry	R_1	R_2	Product	% yield[a]	*anti:syn*[b]	% ee[c,d]
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6[e]	*n*-Bu	*i*-Pr		80	24:1	98
7[e]	Bn	*i*-Pr		75	19:1	91

a) Good yields with excellent ees

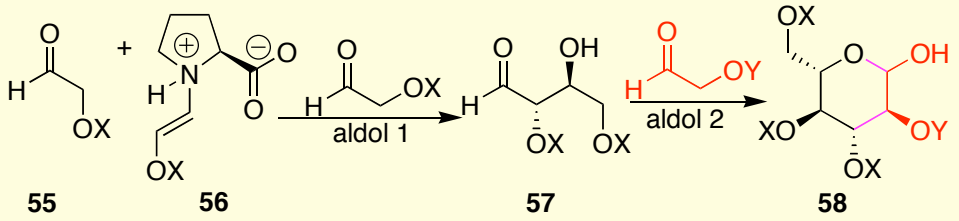
b) Tolerate a large range of substrates

c) Aldehyde donors must be added slowly

d) Lower catalyst loadings and shorter reaction time compared with ketone substrates

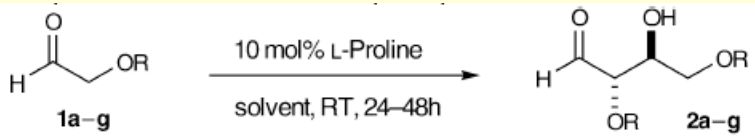
e) Scalable

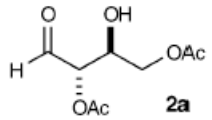
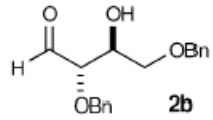
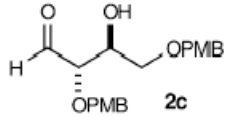
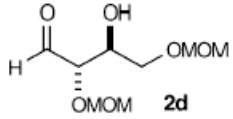
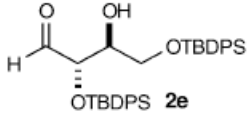
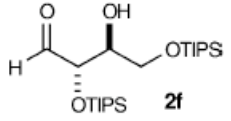
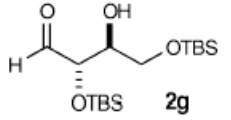
For sugar synthesis: a-oxyaldehydes as substrates:



Northrup, A. B. and MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002,** *124,* 6798 - 6799

Step 1 toward Sugar: Direct Asymmetric Aldol Reactions of Oxyaldehydes

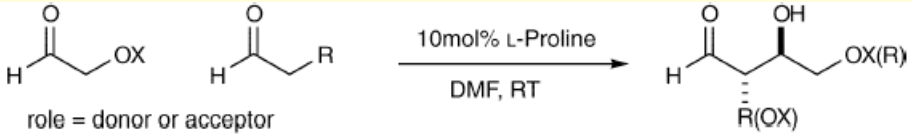


Entry	Product	Solvent	Yield [%]	*anti*:*syn*	*ee* [%][a],[b]
1	 **2a**	DMF	0	–	–
2	 **2b**	DMF	73	4:1	98
3	 **2c**	DMF	64	4:1	97
4	 **2d**	DMF	42	4:1	96
5	 **2e**	DMF/dioxane	61	9:1	96[c]
6	 **2f**	DMSO	92	4:1	95
7	 **2g**	dioxane	62	3:1	88[c]

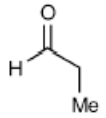
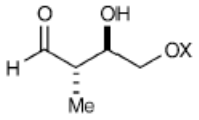
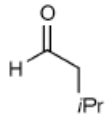
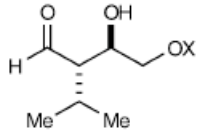
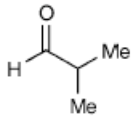
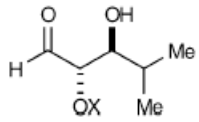
1) Greatly affected by electronic nature of oxyaldehydes
2) Bulky aldehydes with a-silyloxy group can work
3) Products are protected forms of naturally occurring sugar erythrose
4) Products are nonreactive in aldol union

Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed. Engl.* 2004, *43*, 2152

Direct Asymmetric Aldol Reactions of Oxyaldehydes with Alkyl Aldehydes



role = donor or acceptor

Entry	Aldehyde α-alkyl	Aldehyde OX	Product	Yield [%]	*anti*:*syn*	*ee* [%][a],[b]
1		OTIPS acceptor		75	4:1	99
2	donor	OTBDPS acceptor		84	5:1	99[c]
3		OTIPS acceptor		54	4:1	99
4	donor	OBn acceptor		64	4:1	94
5		OTIPS donor		43	8:1	99
6	acceptor	OBn donor		33	7:1	96

[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral HPLC. [c] Determined by Mosher ester analysis.

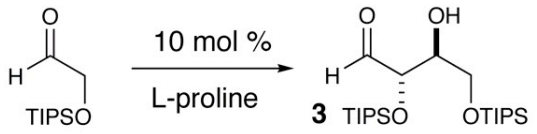
Glycoaldehydes:

1) Electrophile when a-methylene exists
2) Nuceophile when carbonyl is next to a-methine group

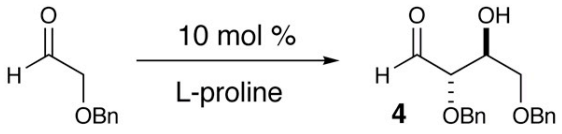
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed. Engl.* 2004, *43*, 2152

Step 2 toward Sugar: Metal Catalyzed Carbohydrate Construction

Step 1 Results: Organocatalytic Enantioselective α-Oxyaldehyde Dimerization

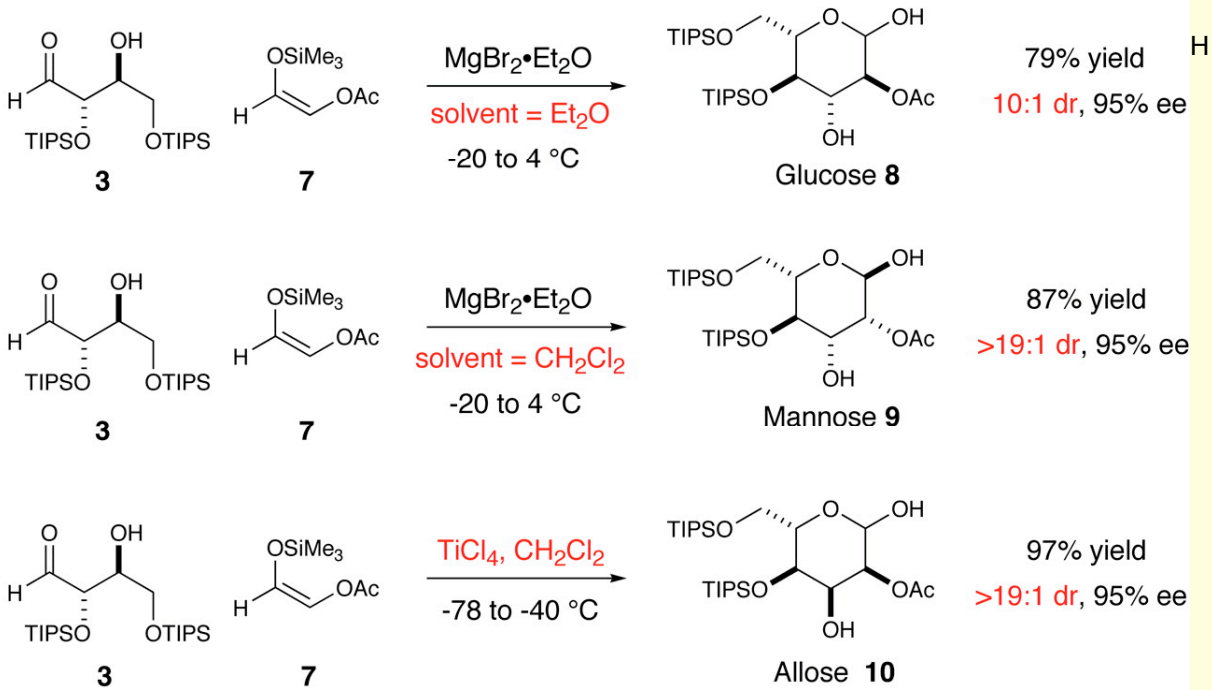


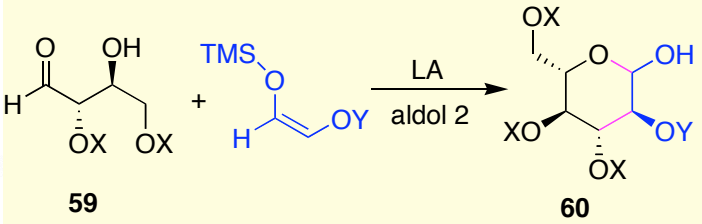
92% yield 4:1 (*anti*:*syn*) 95% ee (*anti*)



78% yield 4:1 (*anti*:*syn*) 98% ee (*anti*)

Step 2 Results: Metal Catalyzed Carbohydrate Construction

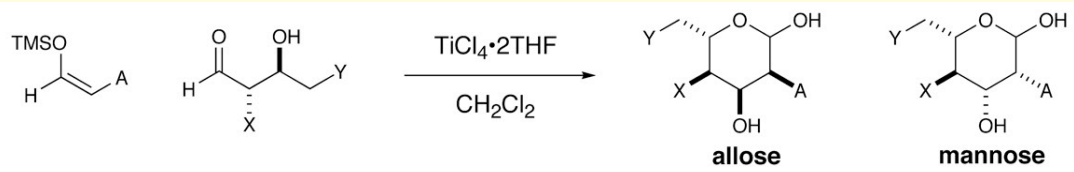


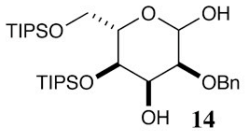
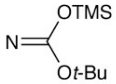
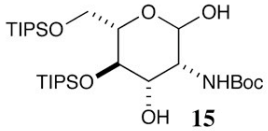
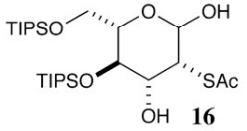
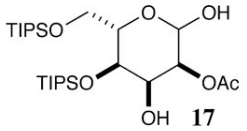
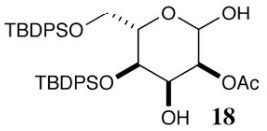
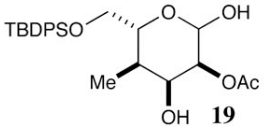


Effects of solvent and LA

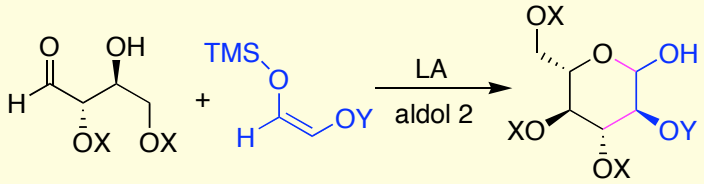
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305,* 1752

Structural Variation: A Lot Sugars!



Entry	A	X	Y	Major isomer	Temp (°C)	% yield	dr	%ee
1	OBn	OTIPS	OTIPS	 **14**	–30	83	>19:1	95
2		OTIPS	OTIPS	 **15**	–40	74	10:1 (mannose)	95
3	SAc	OTIPS	OTIPS	 **16**	–20	71	19:1 (mannose)	95
4	OAc	OTIPS	OTIPS	 **17**	–40	96	>19:1	95
5	OAc	OTBDPS	OTBDPS	 **18**	–20	86	>19:1	96
6	OAc	Me	OTBDPS	 **19**	–30	68	>19:1	99

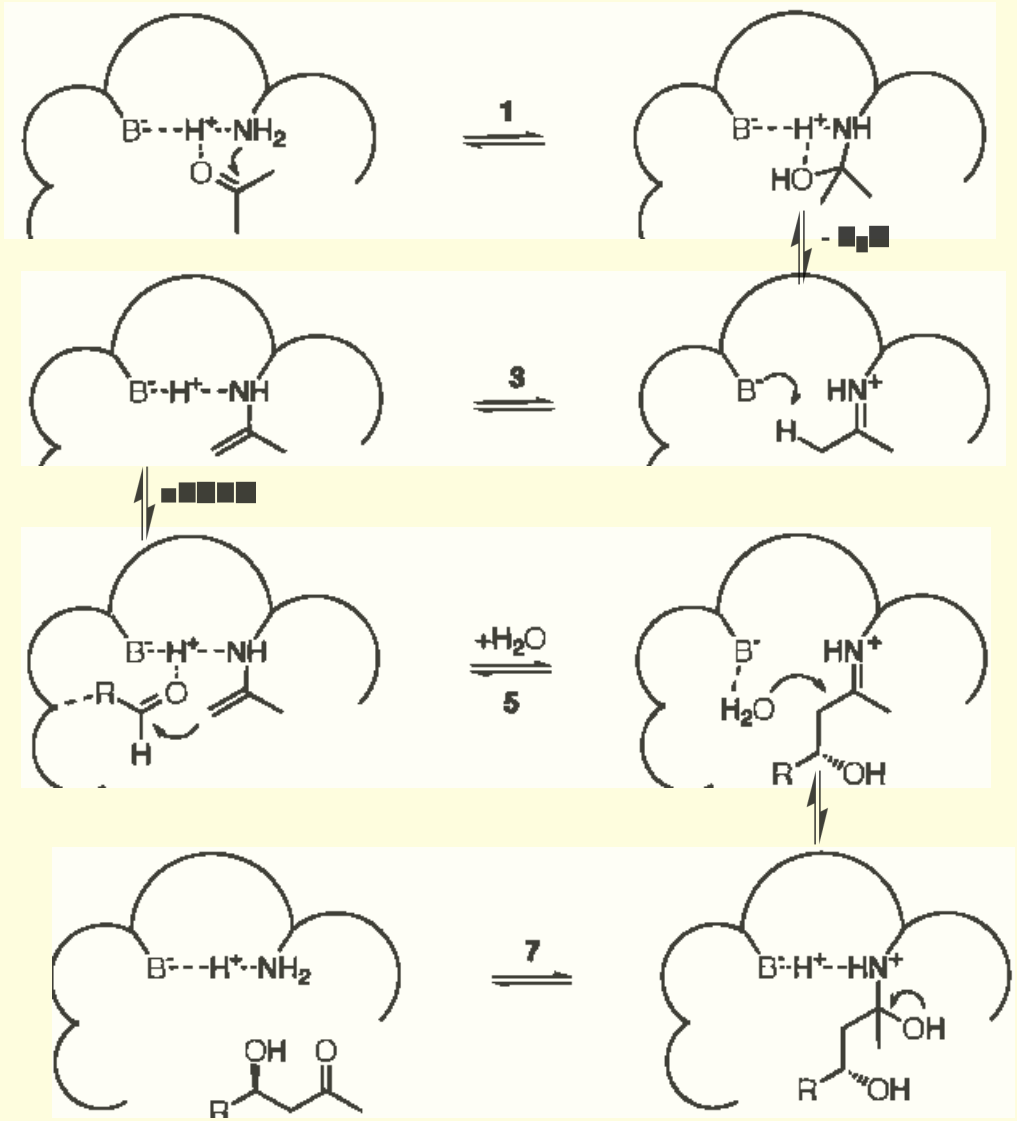
1) Quick construct polysaccharides
2) Broad diversification of subs. at C4 & C6 of sugars
3) Unnatural sugar synthesis with heteroatoms



Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305,* 1752

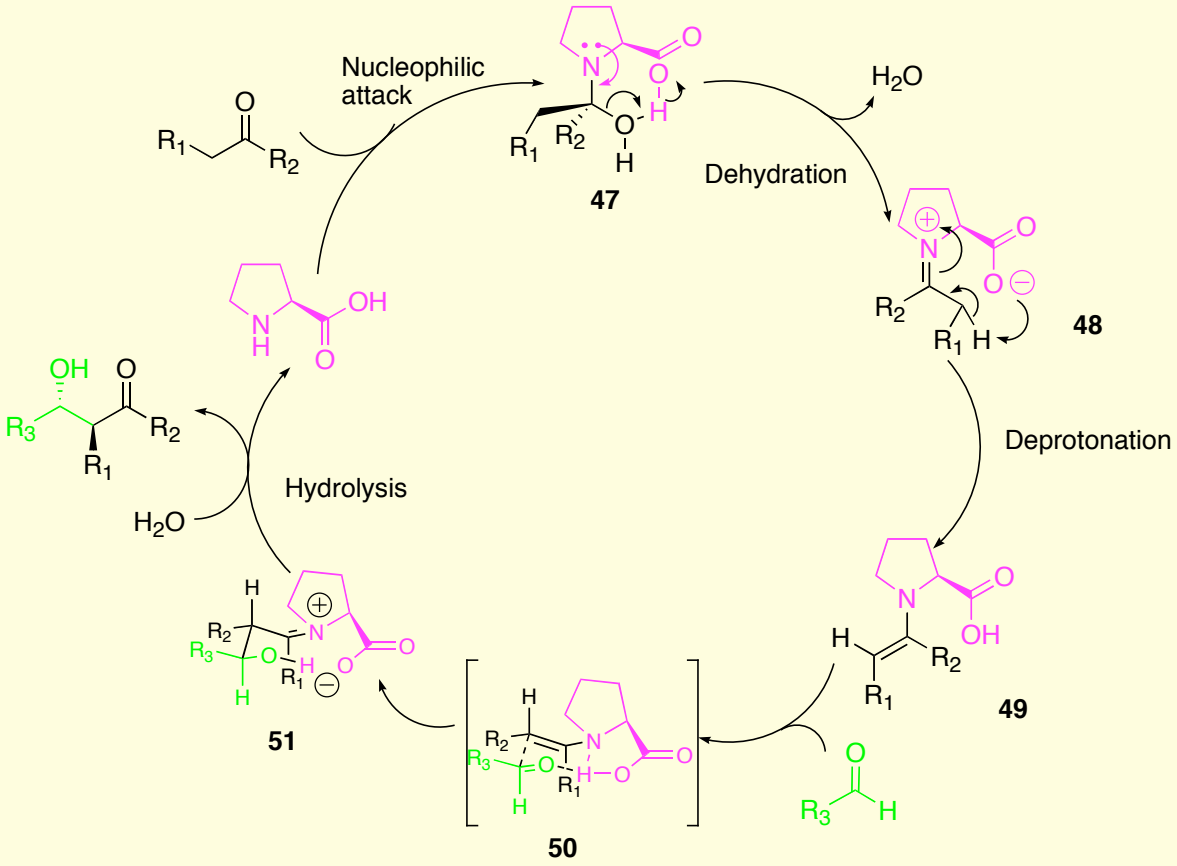
A Little Extension: Enzyme Catalyzed Aldol Reaction −Aldolase I and Aldolase II

1) Aldolase I utilize an enamine based mechanism
2) Aldolase II uses zinc cofactor
3) How Aldolase I works?



Hoffmann, T.; Barbas III, C. F. et al *J. Am Chem. Soc.* **1998**, *120,* 2768

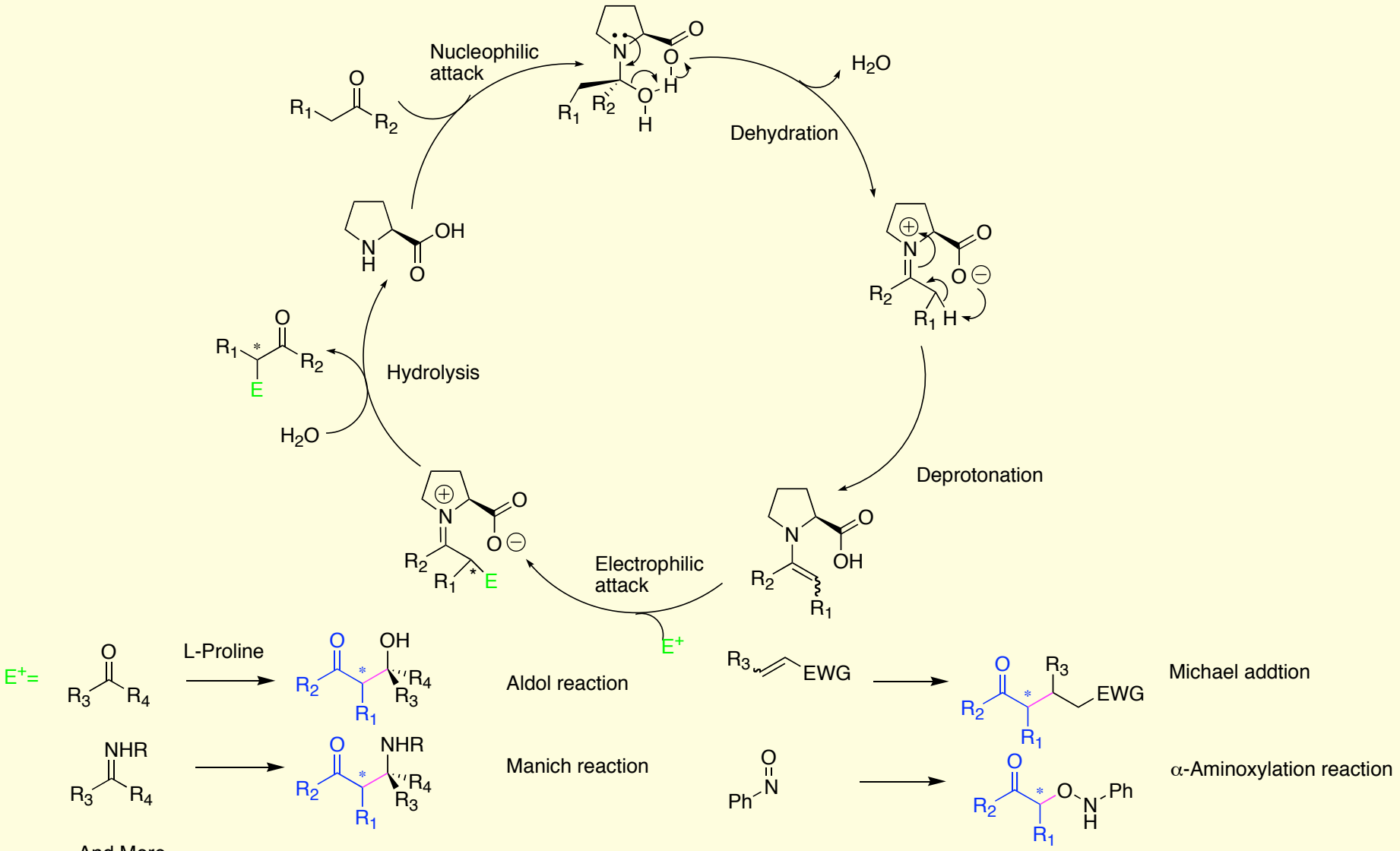
A Little Extension: Proline, An Aldolase I mimics



Proline, the simplest enzyme
—E. N. Jacobsen

Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, 298, 1904

Proline- A Universal Enzyme?



List, B. *Tetrahedron* **2002,** *58*, 5573

Merino, P.; Tejero, T. *Angew. Chem. Int. Ed. Engl.* 2004, *43*, 2995

Summary

- The strategy for the synthesis of differentially protected hexoses provides rapid enantioselective access to key building blocks in saccharide and polysaccharide synthesis.
- The approach efficiently yields isotopic and functional variants of the hexoses that have not been readily accessible for pharmaceutical study.
- Proline is a bifunctional catalyst that is efficient for many transformations