Ward, D.E; Jheengut, V.; Akinnusi, O.T. "Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution," *Organic Letters* 2005, ASAP.

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Current Literature

February 26, 2005

Wipf Group

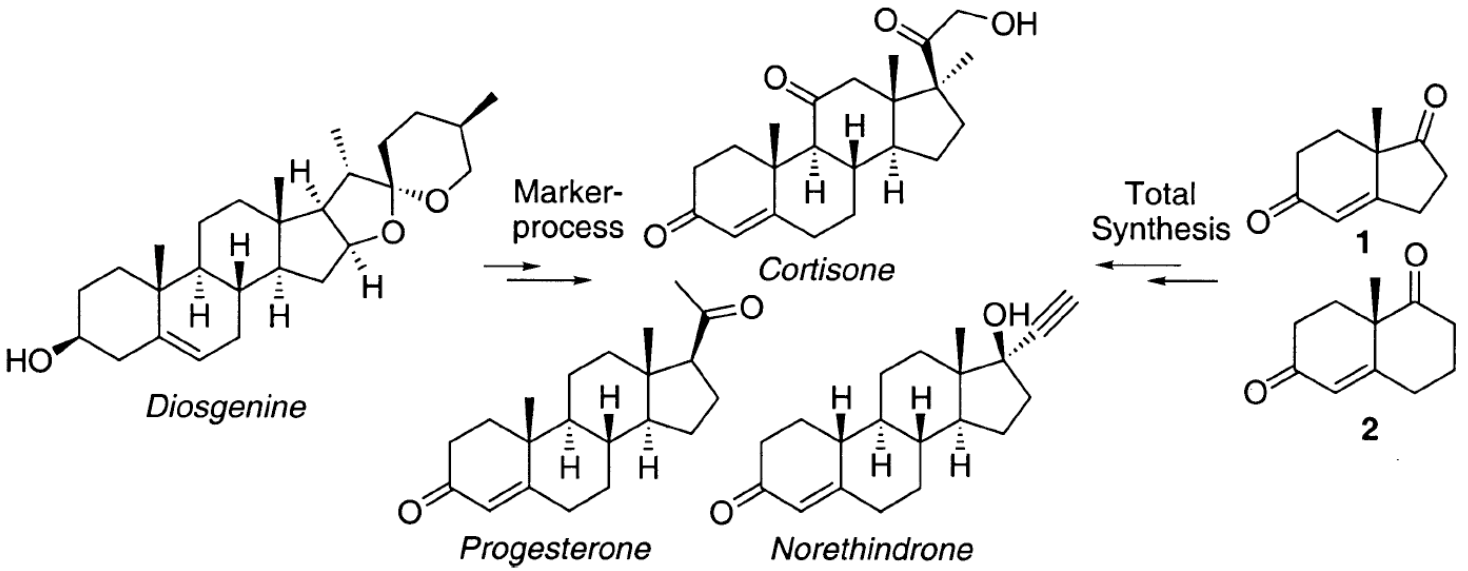
Outline

- Introduction to Proline-Catalyzed Aldol Reactions
- Previous Intermolecular Proline-Catalyzed Aldol Reactions
- Mechanistic Viewpoint
- Novelty of Current Literature
- Critiques

$$$ - The Driving Force - $$$

List, B. *Tetrahedron* **2002**, *58*, 5573-5590.

- **1960's era** - Emphasis on efficient and economic steroid syntheses driven by commercial success of contraceptive agents
- **1969** - 7.5 million American women were on "the pill"
- Potentially active steroids such as cortisone
- *Marker process* - most efficient large-scale synthesis of steroids at the time
  - ➢ Used Diosgenine, a potentially rare plant steroid isolated from Mexican wild yams



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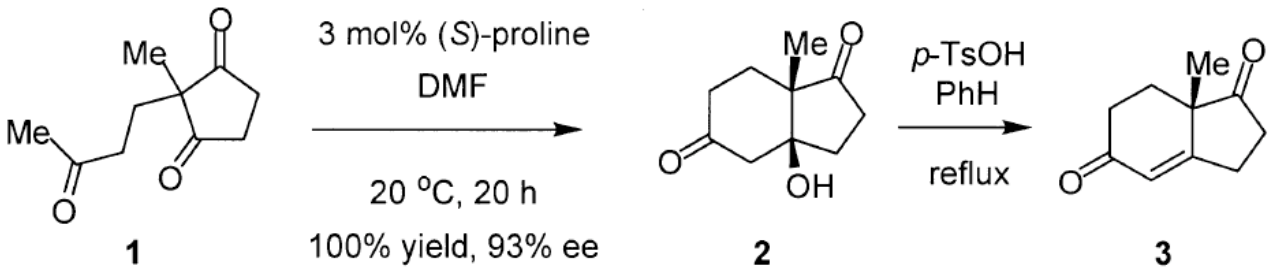
Early 1970's Work

Jarvo, E.R.; Miller, S.J. *Tetrahedron* **2002**, *58*, 2481-2495.
Dalko, P.I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.

- First proline-catalyzed enantioselective aldol reaction
  - Hajos-Parrish-Eder-Sauer-Wiechert Reaction
    - Hajos and Parrish at Hoffmann-LaRoche - isolated intermediate **2**
    - Wiechert and co-workers at Schering AG - reported conversion to **3**



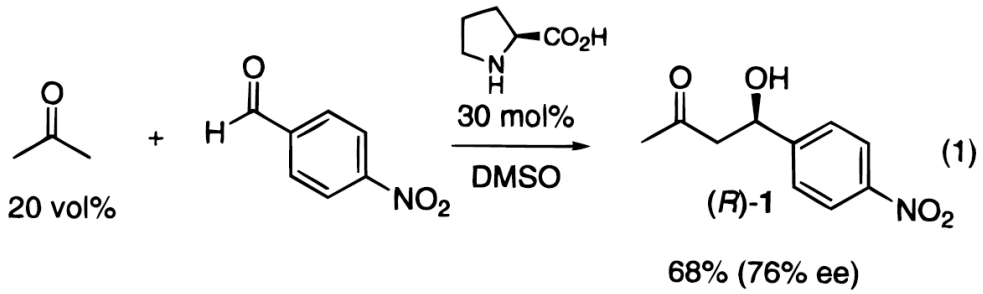
1 **2** **3**

- Only naturally-occurring amino acid with a secondary amine functionality - acts as a nucleophile
- Carboxylic acid functions as a Brønsted acid
- Bi-functional catalyst

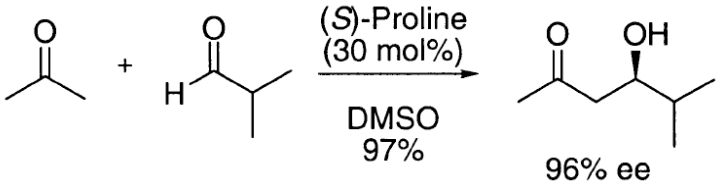
Two Decades Later

List, B.; Lerner, R.A.; Barbas, C.F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

- First proline-catalyzed enantioselective *direct* intermolecular aldol reaction



- Screened variety of cyclic and acyclic amino acid analogs
  - ➢ Proline proved most effective
- Aryl aldehydes gave moderate to high yield's and *ee*'s

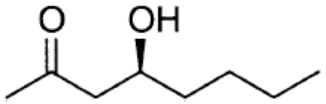
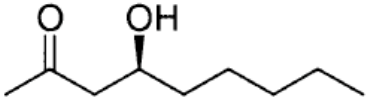
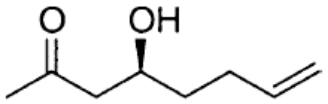
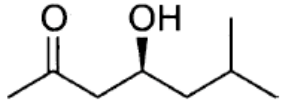
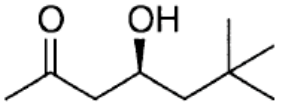


Substrate Scope

List, B. *Tetrahedron* **2002**, *58*, 5573-5590.

- Unbranched aldehydes = poor yields and *ee*'s
- DMSO gave homo-aldol addition, homo-aldehyde condensation, and cross-coupled elimination
- Acetone or acetone/chloroform with 10-20 mol% proline:

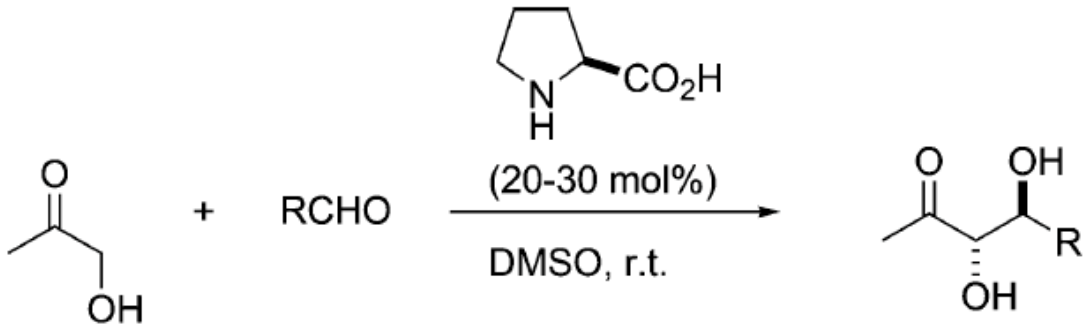
Table 3. Proline-catalyzed direct asymmetric aldol reactions using α-unbranched aldehydes as acceptor

Product	Yield (%)	ee (%)
	31	67
	35	73
	34	72
	34	73
	22	36

Substrate Scope

Palomo, C.; Oiarbide, M.; García, J.M. *Chem. Soc. Rev.* **2004**, *33*, 65-75.

- Acetone and hydroxyacetone suitable keto-functionality



aldehyde	yield, %[a]	d.r.	ee,%
$cC_6H_{11}CHO$	60	>20:1	>99
$(CH_3)_2CHCHO$	62	>20:1	>99
Ph(Me)CHCHO	51	>20:1	>95
2-Cl-PhCHO	95	1.5:1	67
$(CH_3)_3CCH_2CHO$	38	1.7:1	>97

[a]Isolated yield after column chromatography.

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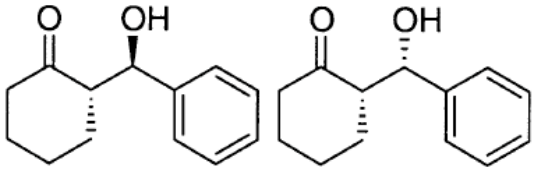
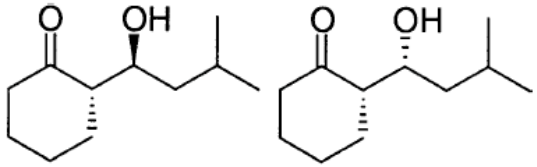
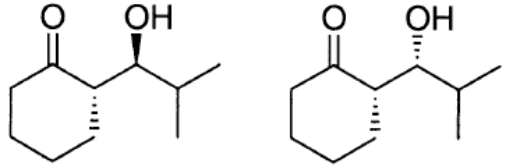
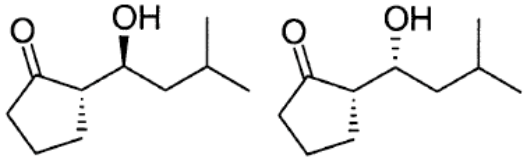
Substrate Scope

- Large excess of ketone moiety necessary for reactions to proceed
- Self-condensation of the aldehyde or ketone donors when acceptors react slowly
- Narrow substrate scope

Table 4. The proline-catalyzed intermolecular aldol reaction using cyclic ketones as donors

Product	Yield (%)	dr
 *anti* (85% ee) *syn* (76% ee)	85	1:1
 *anti* (86% ee) *syn* (89% ee)	41	7:1
 *anti* (97% ee) *syn* (not detected)	68	>20:1
 *anti* (95% ee) *syn* (20% ee)	77	2.5:1

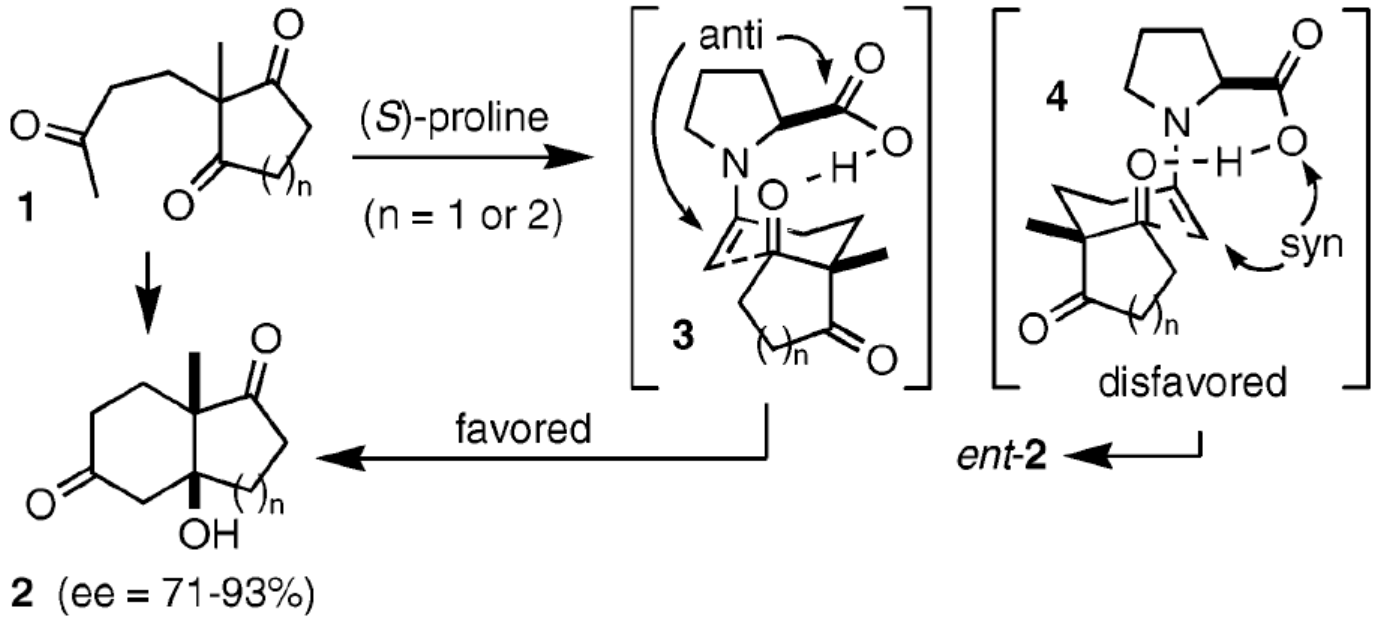
Mechanistic Viewpoint

Allemann, C.; Gordillo, R. Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* **2004**, *37*, 558-569.
Bahmanyar, S. Houk, K.N. *J. Am. Chem. Soc.* **2001**, *123*, 12911-12912.

- *Enantiotopic* group selectivity

  1) *Anti*-orientation of enamine more stable

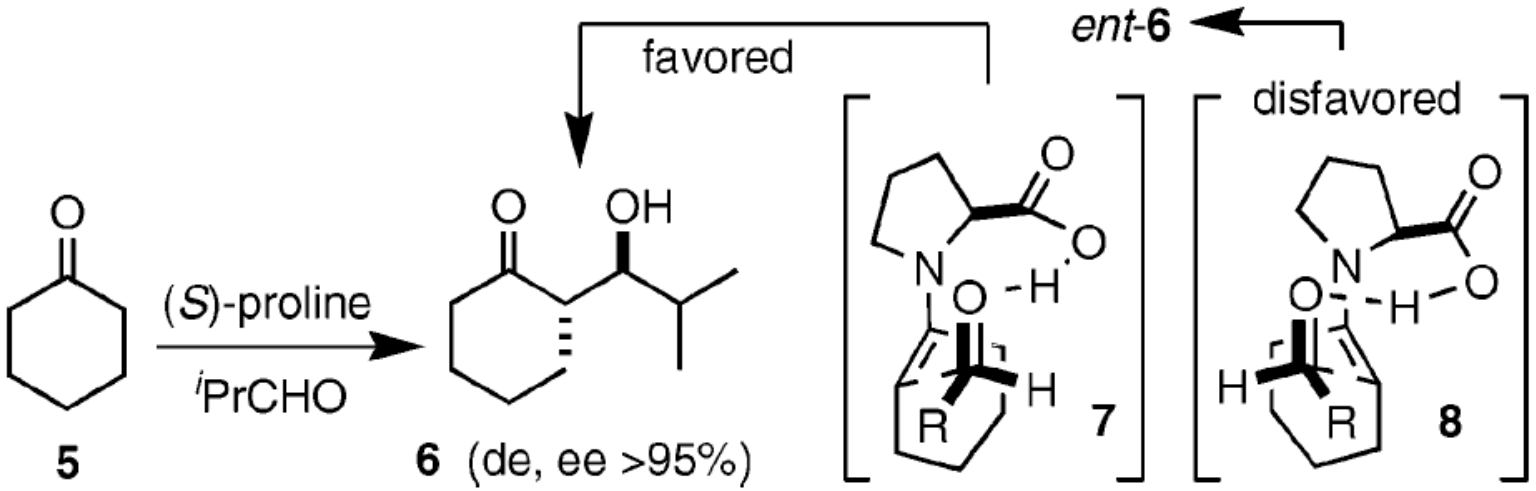
  2) Addition *trans* to the quaternary methyl group preferred



Mechanistic Viewpoint

Bahmanyar, S.; Houk, K.N.; Martin, H.J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

- Intermolecular is comparable to intramolecular T.S. structures
- Enamine addition to the *re* face of the aldehyde
- *Two chiral components* - reinforce or counteract the face selectivity resulting in stereodifferentiation and/or kinetic resolution



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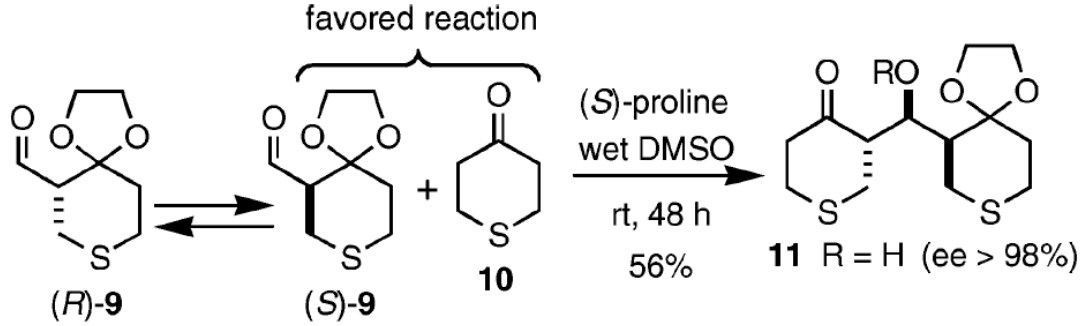
Crux of the Publication

Ward, D.E.; Jheengut, V.; Akinnusi, O.T. *Org. Lett.* **2005**, ASAP.

- "We speculated that these reactions might show significant enantiotopic group selectivity and double stereodifferentiation if the aldehyde possessed sufficient diastereoface selectivity."
- Ward's success with aldol reactions in the past:
  - Stereoselective two-step metal-catalyzed aldol reactions with **9** and **10**
  - Aldehyde **9** shows exclusive Felkin diastereoface selectivity
- *First attempt* - single diastereomer in 33% yield, ca. 50% *ee*



Reaction Optimization

- Concentration of aldehyde **9**
- Equivalents of thiopyranone **10**
- Equivalents of water
- Solvent (DMSO vs. DMF)
- Reaction time

Optimized conditions:
56% yield, >98% *ee*

Table 1. Proline-Catalyzed Aldol Reactions of **9** with **10**[a]

entry	[**9**](M)	**10** (equiv)	solvent (equiv of H_2O)	time (days)	yield[b] (%)	$[\alpha]_D$[c]
1	1	3	DMSO	2	33	−22
2	1	3	DMF	2	18	−19
3	1	3	DMF (2)	2	17	−29
4	1	3	DMSO (2)	2	39	−31
5	0.5	3	DMSO (2)	2	19	*d*
6	2	3	DMSO (2)	2	47	−20
7	1	3	DMSO (4)	2	32	−39
8	1	3	DMSO (8)	2	36	−43
9	1	3	DMSO (16)	2	19	−44
10	1	6	DMSO (8)	2	52	−46
11	1	12	DMSO (8)	2	52	−41
12	1	6	DMSO (8)	4	48	−46
13	1	6	DMSO (8)	8	47	−39
14[e]	1	6	DMSO (8)	2	38	−47
15[f]	1	6	DMSO (8)	2	37	−47
16[g]	**1**	**6**	**DMSO (8)**	**2**	**56**	**−47**[h]

[a] Reactions at room temperature with 50 mg of **9** and 0.5 equiv of (*S*)-proline. [b] Isolated yield of **11**. [c] At ambient temperature (ca. 23°C); c = 1.0, $CHCl_3$; $[\alpha]_D$(max) for **11** = −47. [d] Not determined. [e] 0.25 equiv of (*S*)-proline. [f] 1.0 equiv of (*S*)-proline. [g] 1.0 g of **9**. [h] This sample was shown to be >98% ee by ^{1}H NMR of the derived **12** in the presence of (+)-Eu(hfc)$_3$.

Kinetic Resolution

Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327.

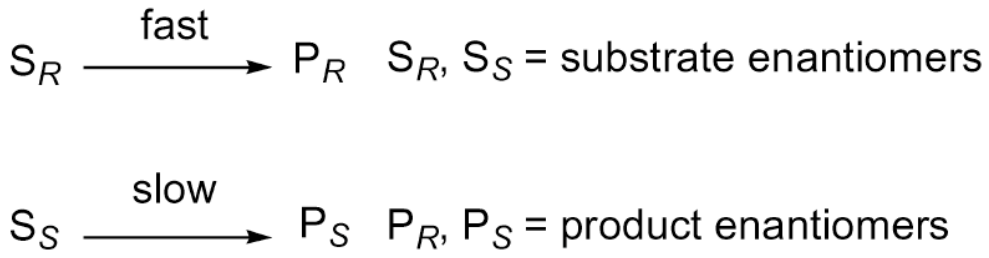


Figure 1. Classical kinetic resolution.

- DKR combines classical kinetic resolution with an *in situ* equilibration or racemization of the starting substrate
- Theoretical quantitative yield of one enantiomer

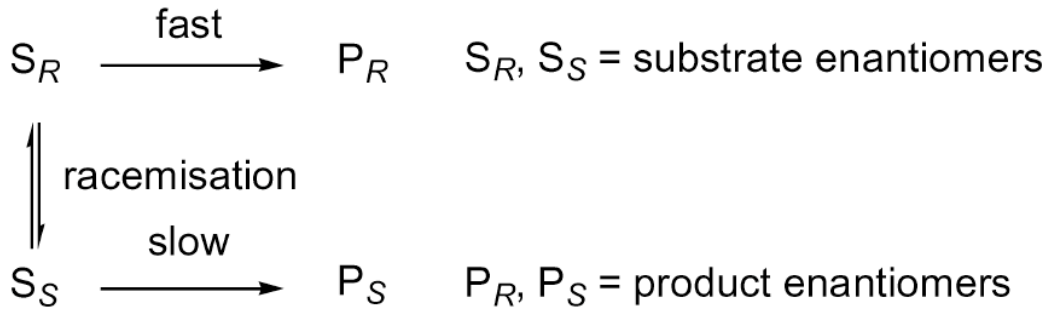
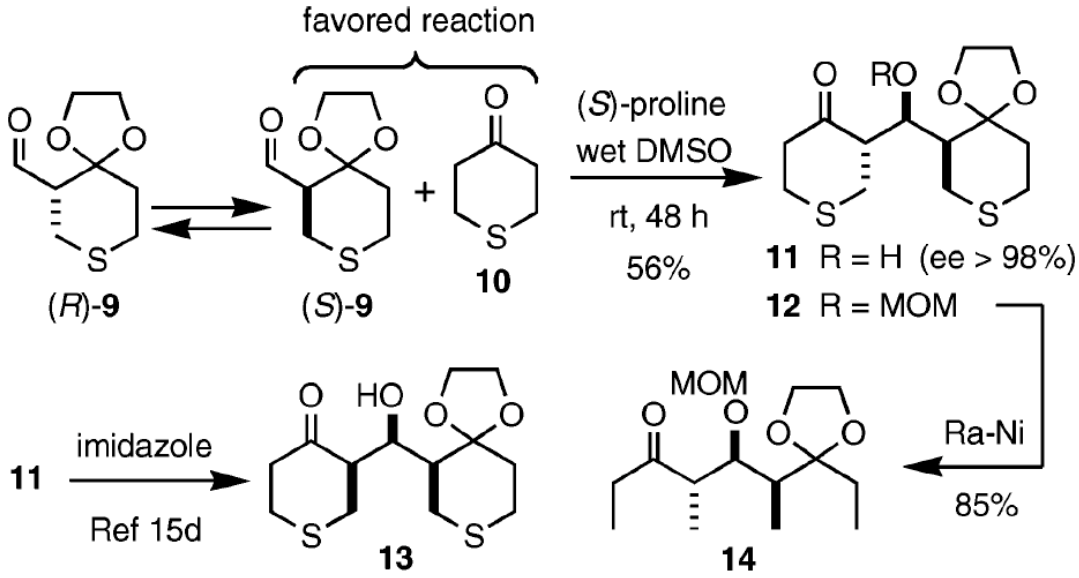


Figure 2. Dynamic kinetic resolution.

Examination of the Results

- Reaction proceeds under kinetic control with dynamic kinetic resolution
  - (-)-**11** re-isolated in >85% yield and >90% *ee* after exposure to (*S*)- and (*R*)-proline (48h, wet DMSO)
  - (±)-**9** recovered from the reaction
  - (*S*)-**9** readily racemizes under the reaction conditions



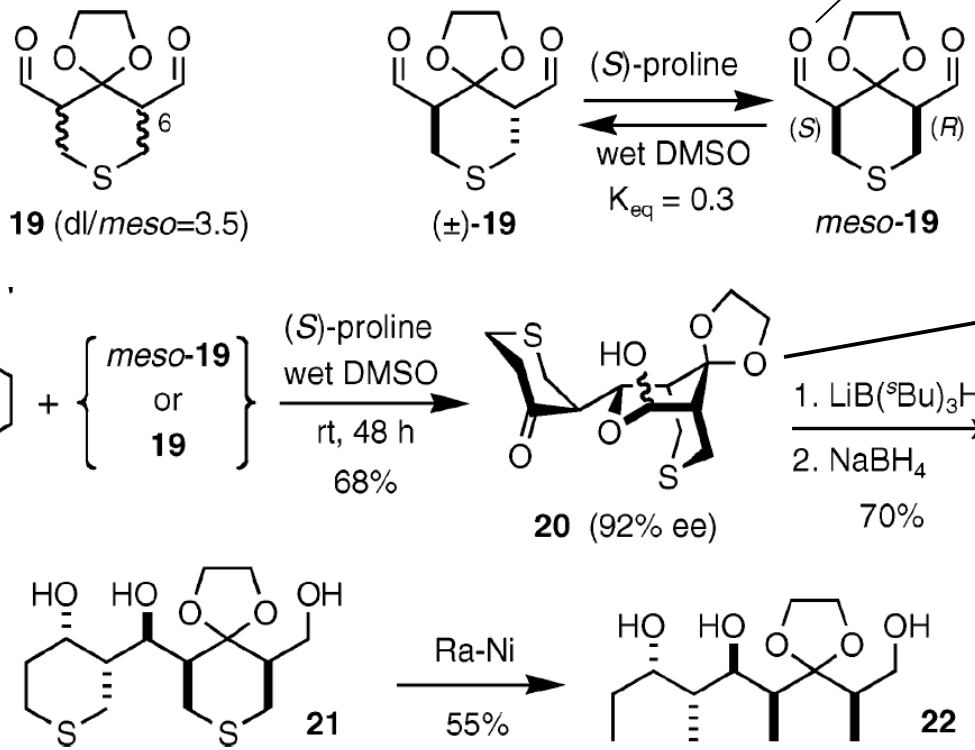
- Ability to obtain *anti-syn* or *syn-syn* stereotriads

Desymmetrization

Preferential reaction with (*S*,*S*)-**19** followed by rapid isomerization and hemiacetal formation

OR

Preferential reaction with (*S*)-aldehyde group of *meso*-**19** forms **20** selectively



Selective formation of **20** (3.5:1 mixture of anomers)

Critiques

- Highlights
  - No modified carbonyls or metals required (proline is inexpensive)
  - Insensitive, room temperature reactions
  - Water soluble catalyst/ease of purification
  - Only modest levels of enantiotopic group selectivity observed in past proline-catalyzed aldol reactions with chiral aldehyde acceptors
  - Examples of DKR and isomerization of aldehydes in past proline-catalyzed intermolecular aldol reactions only gave modest levels of stereoselectivity
  - Simultaneously generate four stereogenic centers (tetrapropionate synthon)
- Lowlights
  - Excess of ketone moiety
  - A "matched" reaction *only* needs:
    - Consistent addition to the aldehyde *re* face imposed by the (*S*)-proline
    - High Felkin diastereoface selectivity in the aldehydes
- Future Work
  - Continue to discover more suitable substrates
  - Extend methodology to dialdehydes and diketones