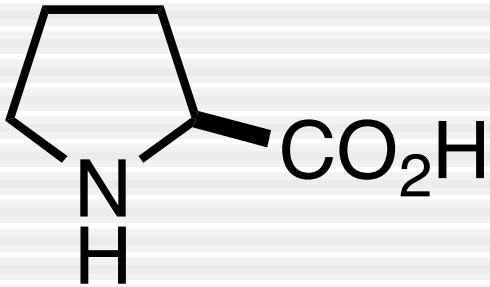
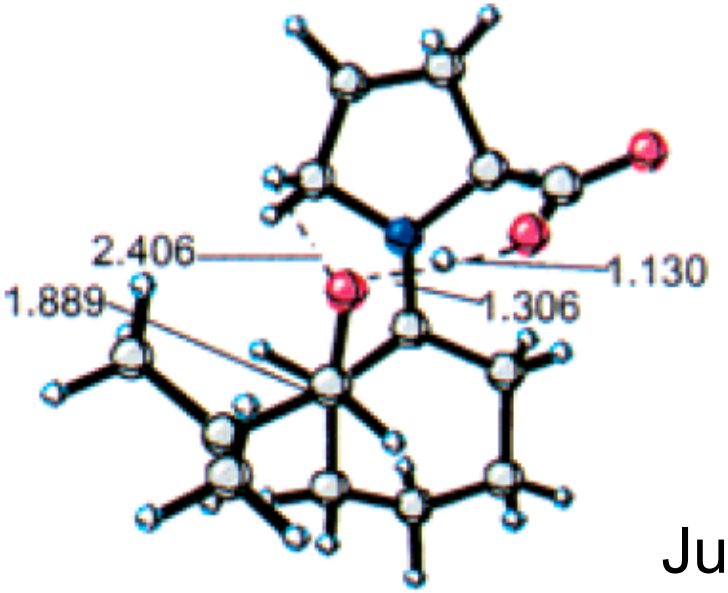
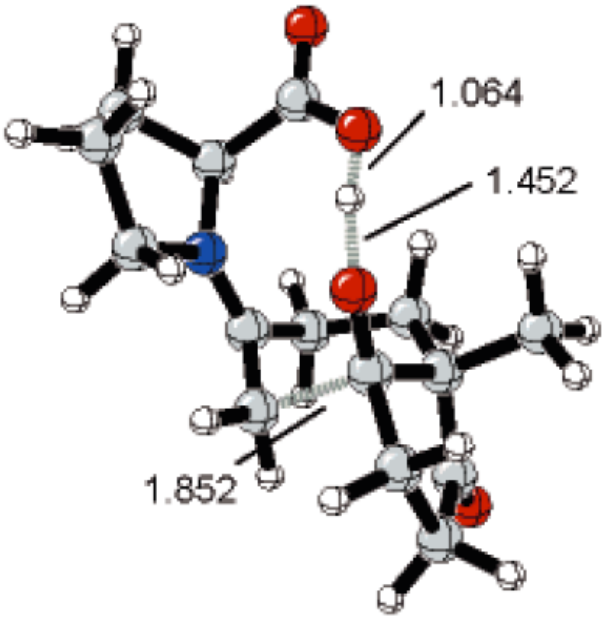
Mechanistic Studies of Proline-Catalyzed Reactions

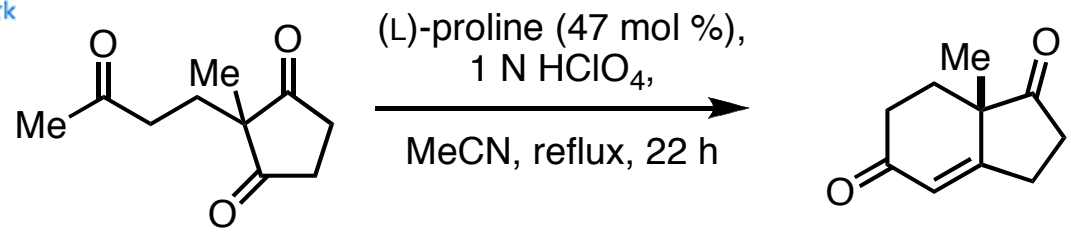




Jack Liu
July 25, 2006

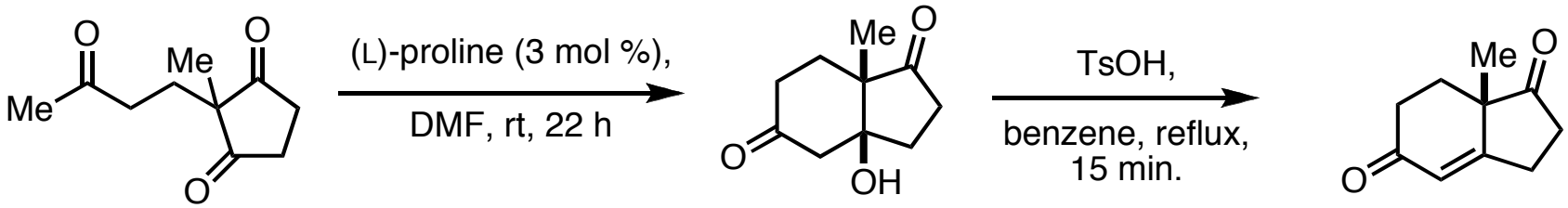


How It Got Started



87%, e.r. = 84/16

Eder, U.; Sauer, G.; Wiechert, R. German patent DE 2014757, 1971.
Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

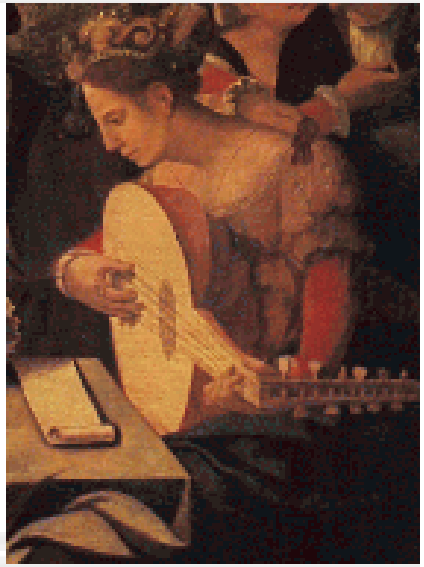


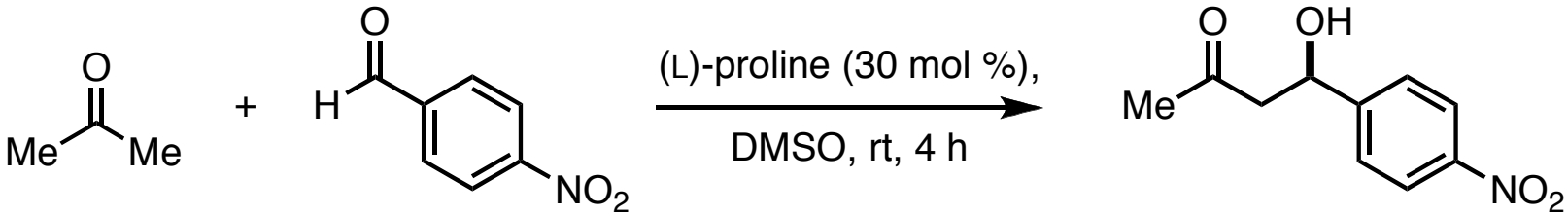
100%, e.r. = 93.4/6.6

92%, e.r. = 87.7/12.3

Hajos, Z. G.; Parrish, D. R. German patent DE 20102623, 1971.
Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

The Renaissance of Proline Catalysis

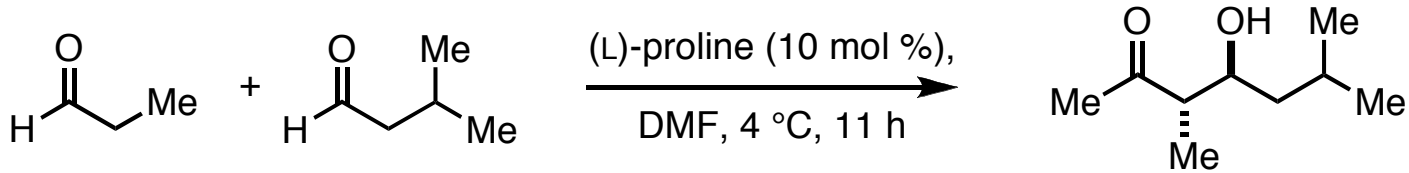




68%, 76% ee

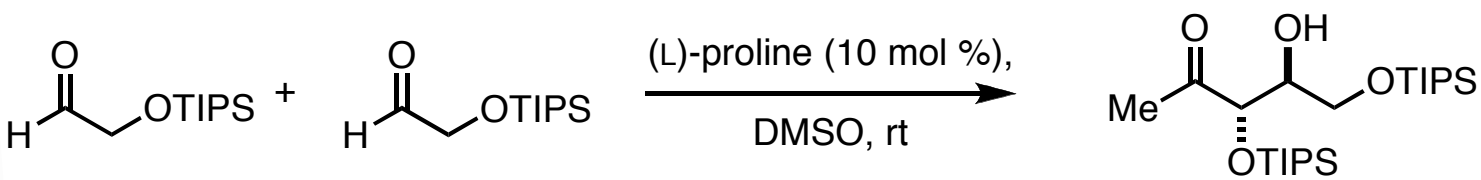
List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

Proline-Catalyzed Aldol with Aldehyde Donors

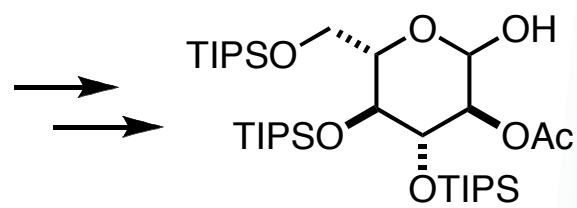


88%, anti/syn = 3/1, 97% ee

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



92%, anti/syn = 4/1, 95% ee

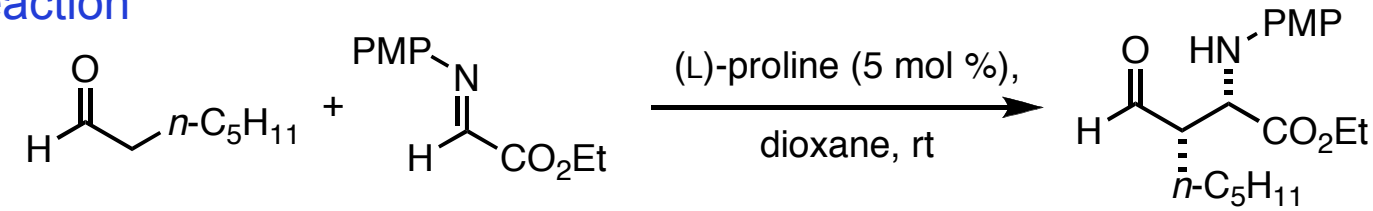


protected glucose

Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1753.

More Recent Developments

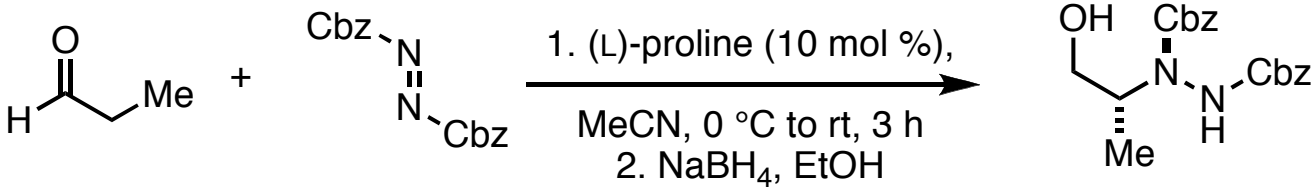
Mannich reaction



81%, syn/anti > 19/1, >99% ee

Córdova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F. III *J. Am. Chem. Soc.* **2002**, *124*, 1866.
Ketone donor: Barbas, C. F. III *et al. J. Am. Chem. Soc.* **2002**, *124*, 1842.

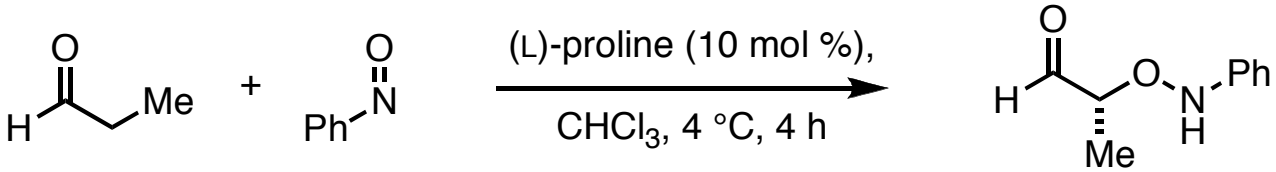
α-amination



97%, >95% ee

List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
Ketone donor: Jørgensen, K. A. *et al. J. Am. Chem. Soc.* **2002**, *124*, 6254.

α-aminoxylation



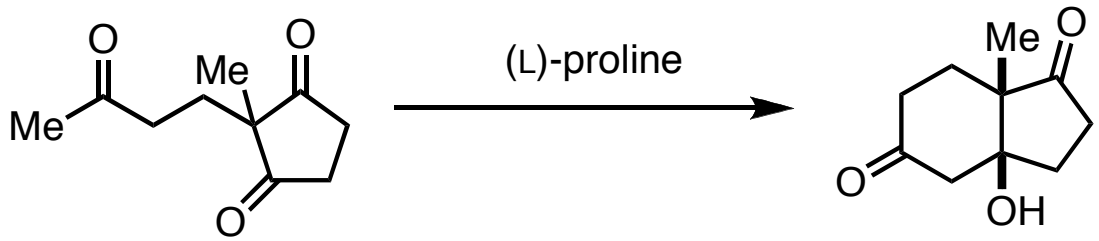
88%, 97% ee

Brown, S. P.; Bochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
Ketone donor: Córdova, A. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 1109.
Hayashi, Y. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

Mechanistic Studies of Proline-Catalyzed Reactions

- Proline-catalyzed aldol reaction
  - Mechanistic investigations
  - Computational studies
- Other related reactions
- Asymmetric amplification

Mechanistic Questions

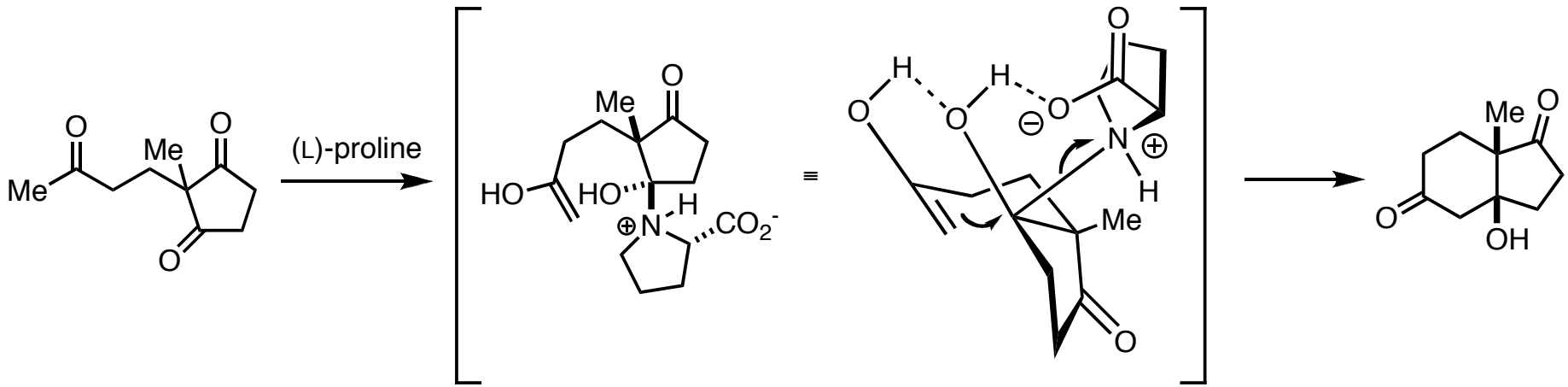


What is the intermediate?

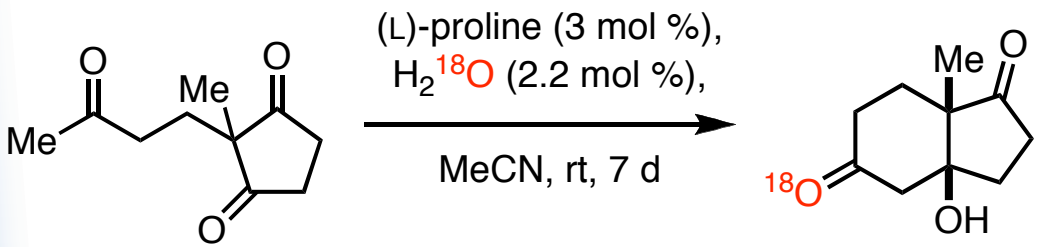
How does proline catalyze the C-C bond formation?

What is the origin of enantioselectivity?

The First Mechanistic Proposal

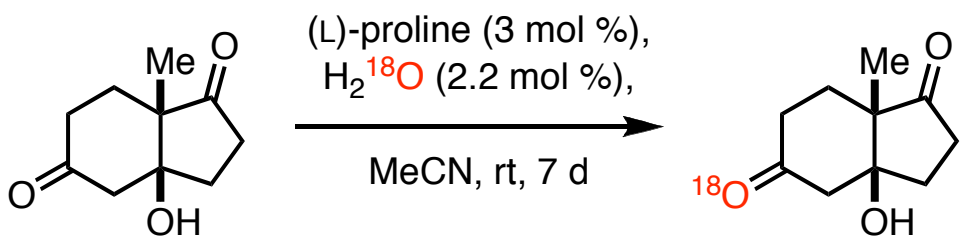


Supporting evidence: the Lack of ^{18}O incorporation



"Mass spectral analysis for ^{18}O-labeled CO_2 of the sample indicated 7.2% ^{18}O enrichment"

Control experiment:

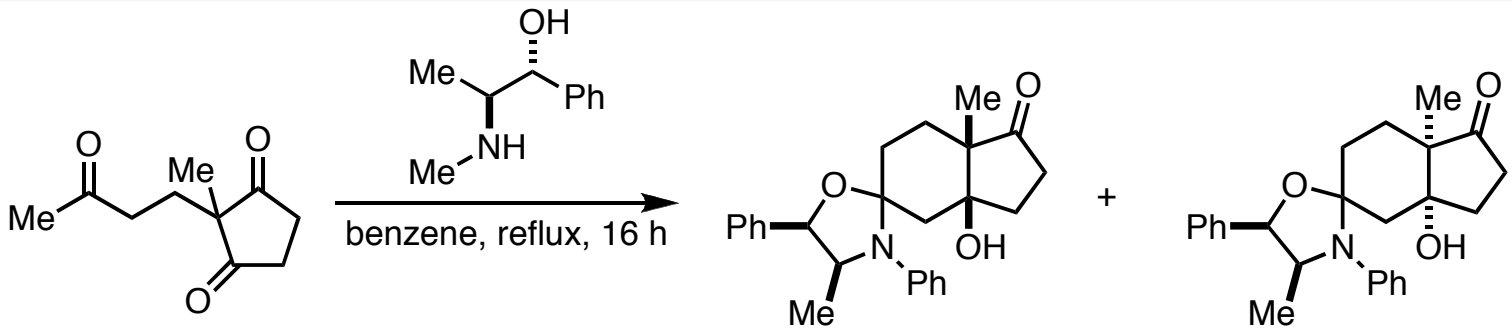


"Mass spectral analysis for ^{18}O-labeled CO_2 of the sample indicated 33.1% ^{18}O enrichment"

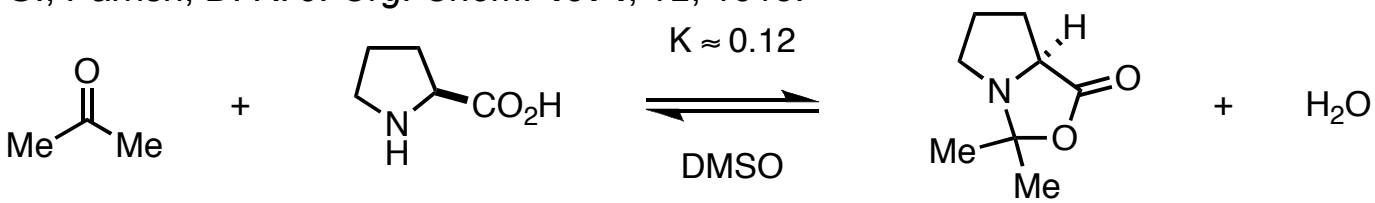
What do you think?

Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *12*, 1615.

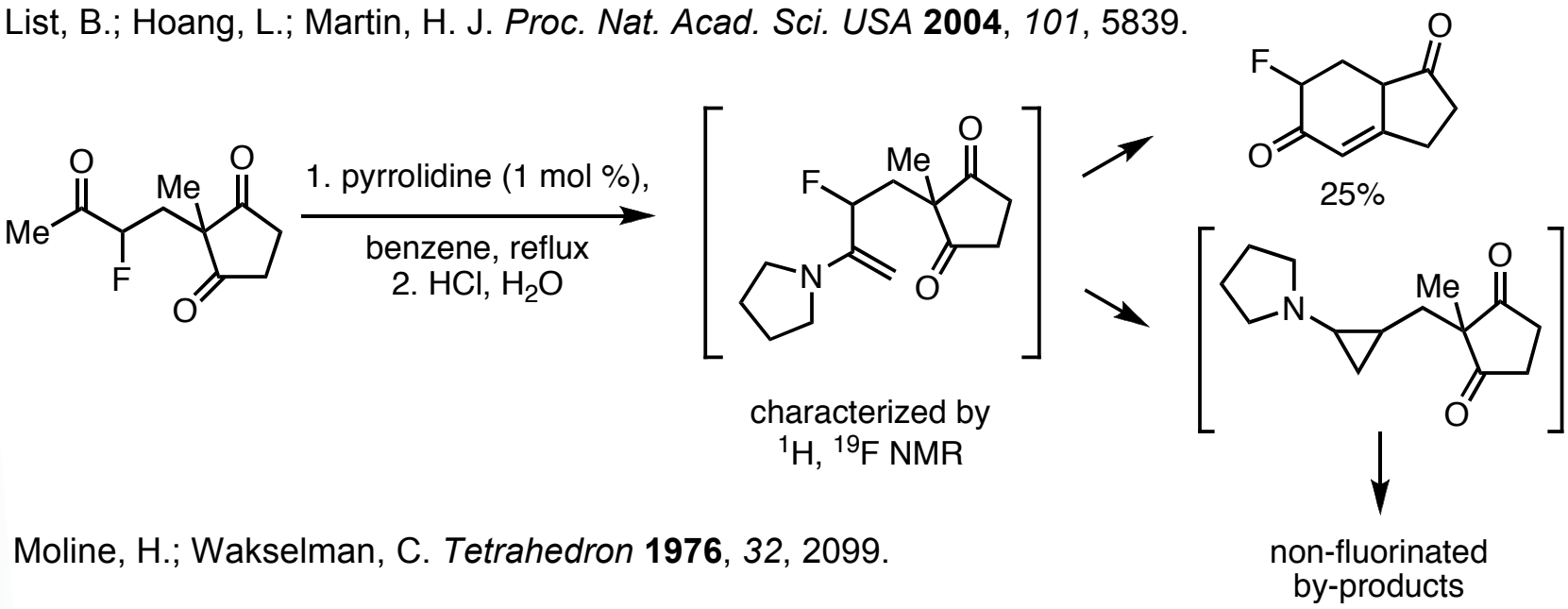
Evidence Favouring An Enamine Intermediate



Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *12*, 1615.

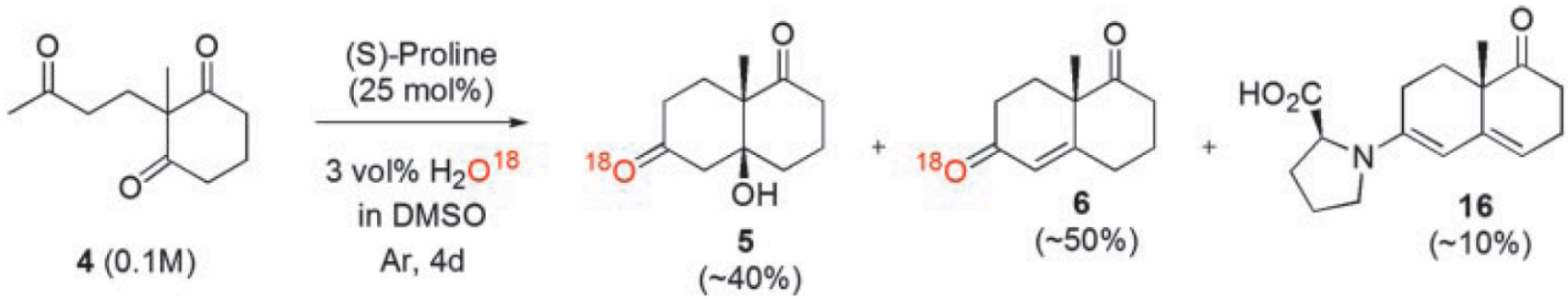


List, B.; Hoang, L.; Martin, H. J. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5839.



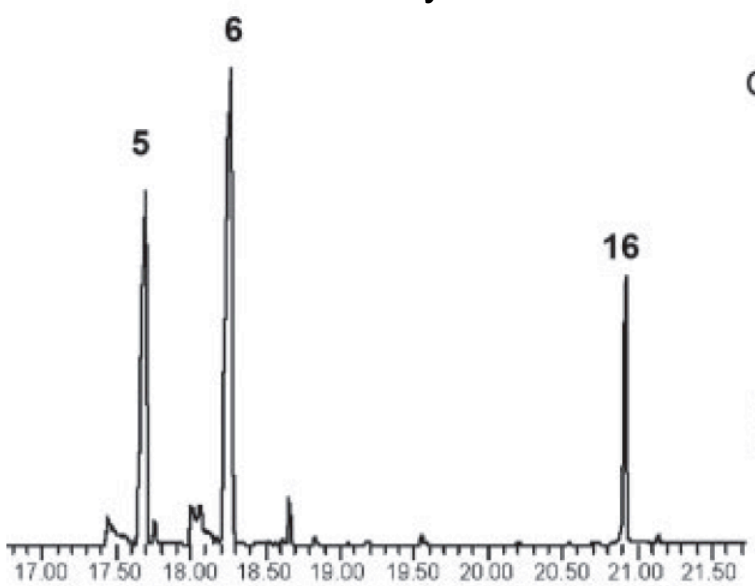
Moline, H.; Wakselman, C. *Tetrahedron* **1976**, *32*, 2099.

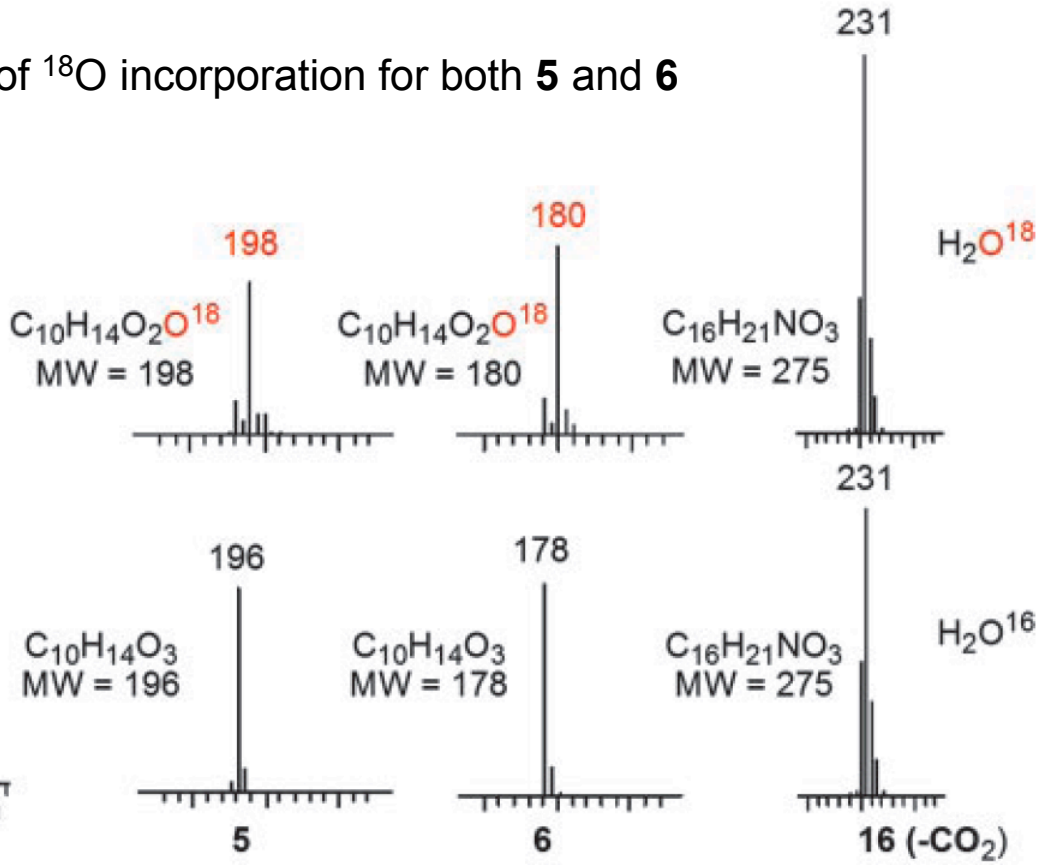
^{18}O–Incorporation Reexamined



>90% of ^{18}O incorporation for both **5** and **6**

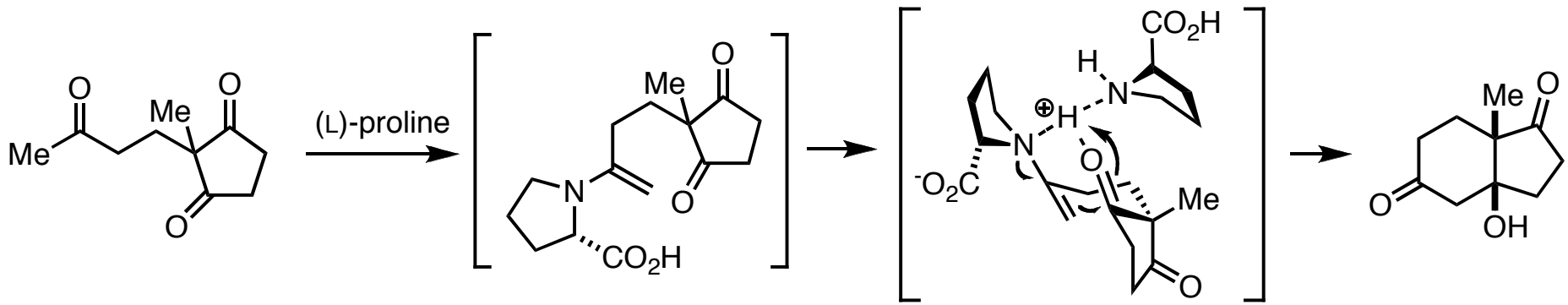
GC-MS trace of 4 day





List, B.; Hoang, L.; Martin, H. J. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5839.

The Dual Proline Model

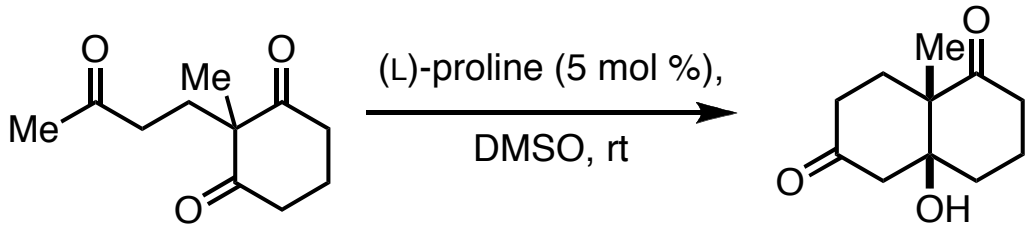


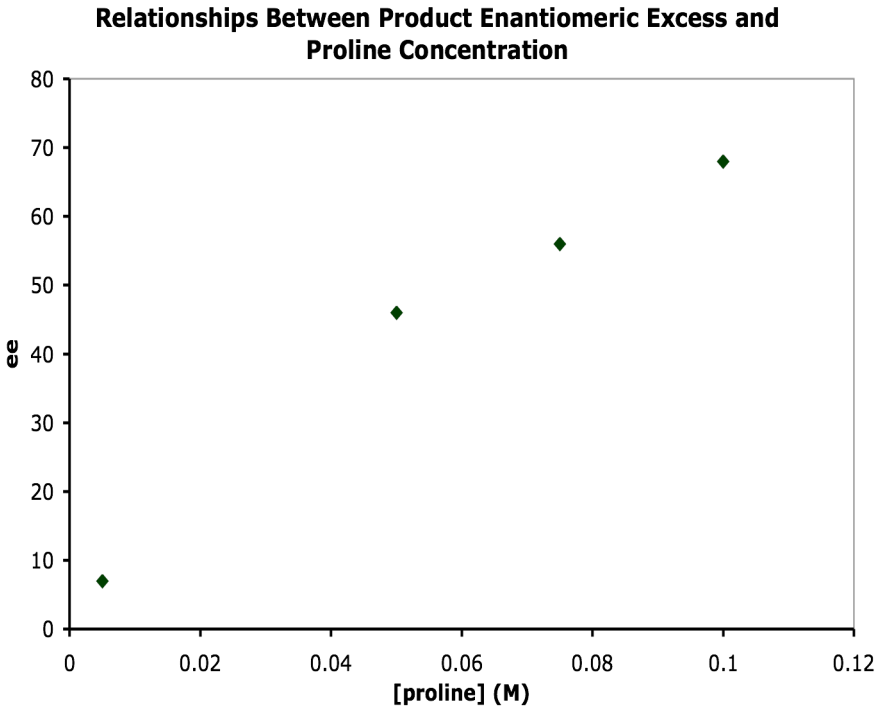
Supporting evidence: 1. Dilution effect

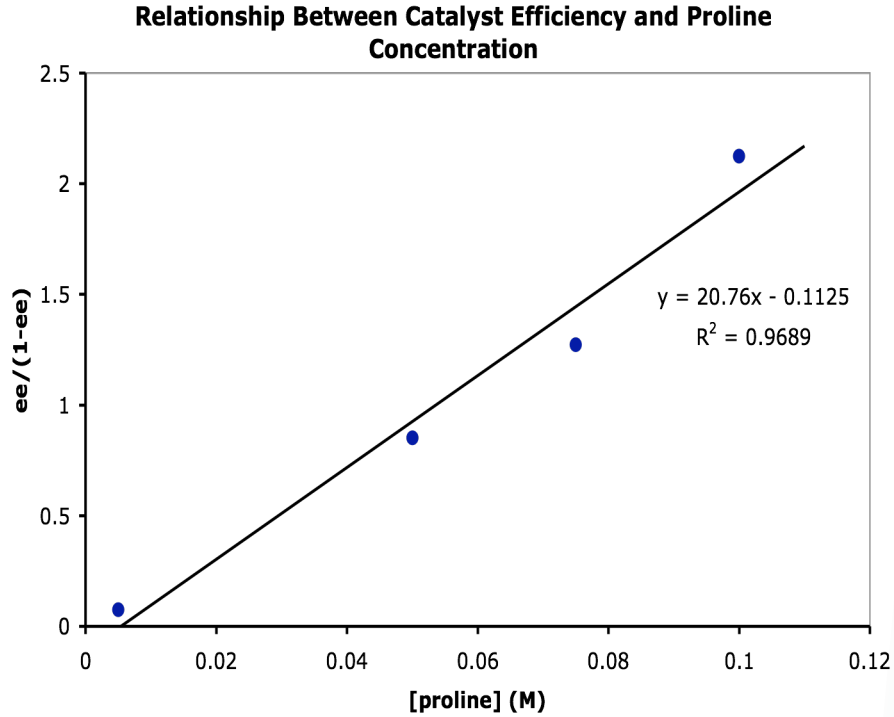
2. Non-linear effect of enantioselectivity

Agami, C.; Levisalle, J.; Puchot, C. *J. Chem. Soc., Chem. Comm.* **1985**, 441.
Agami, C.; Puchot, C. *J. Mol. Catal.* **1986**, *38*, 341.
Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1988**, 499.

Dilution Effect



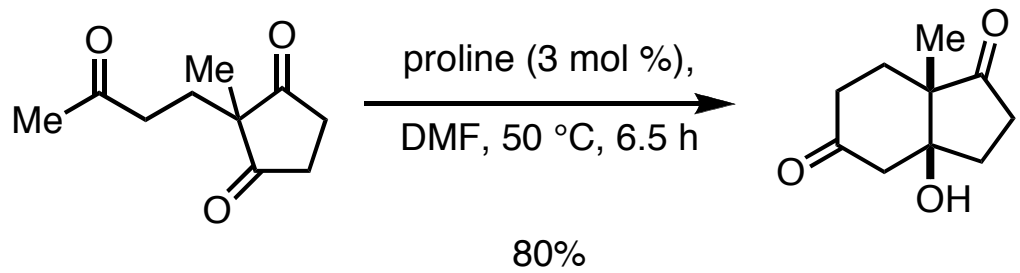




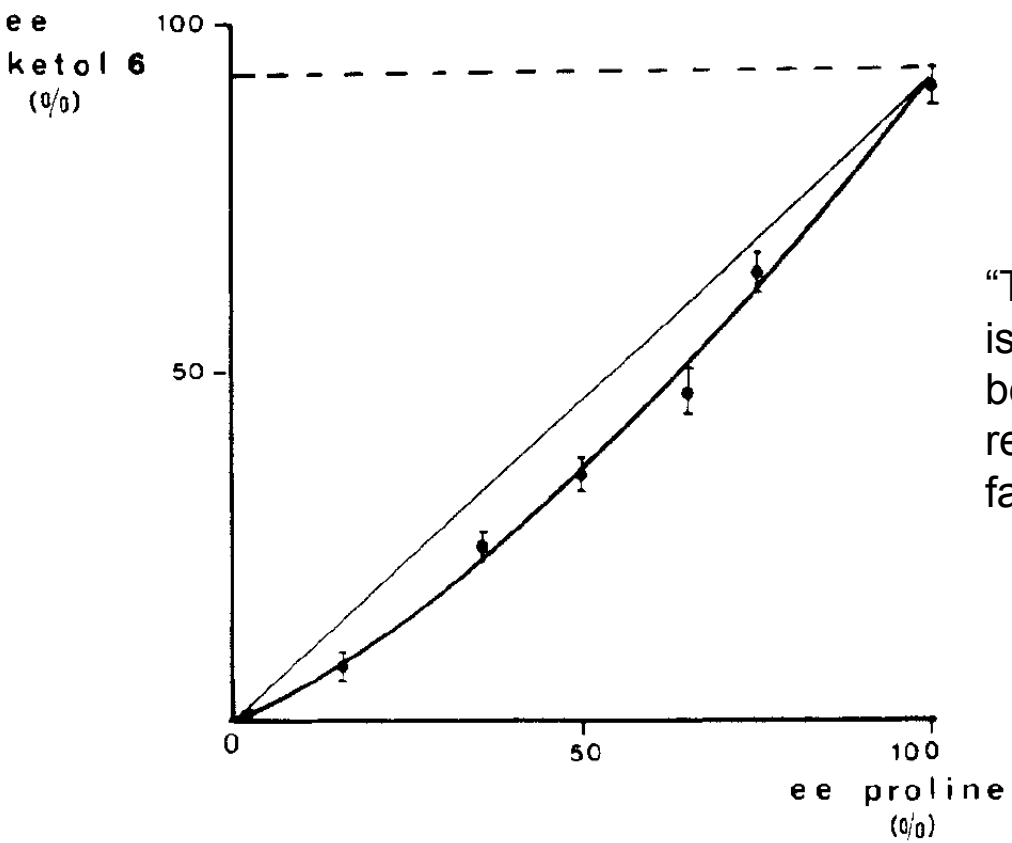
"ee values were determined from the specific totation of the enantiomerically pure ketol."

Agami, C.; Levisalle, J.; Puchot, C. *J. Chem. Soc., Chem. Comm.* **1985**, 441.

Non-Linear Effect



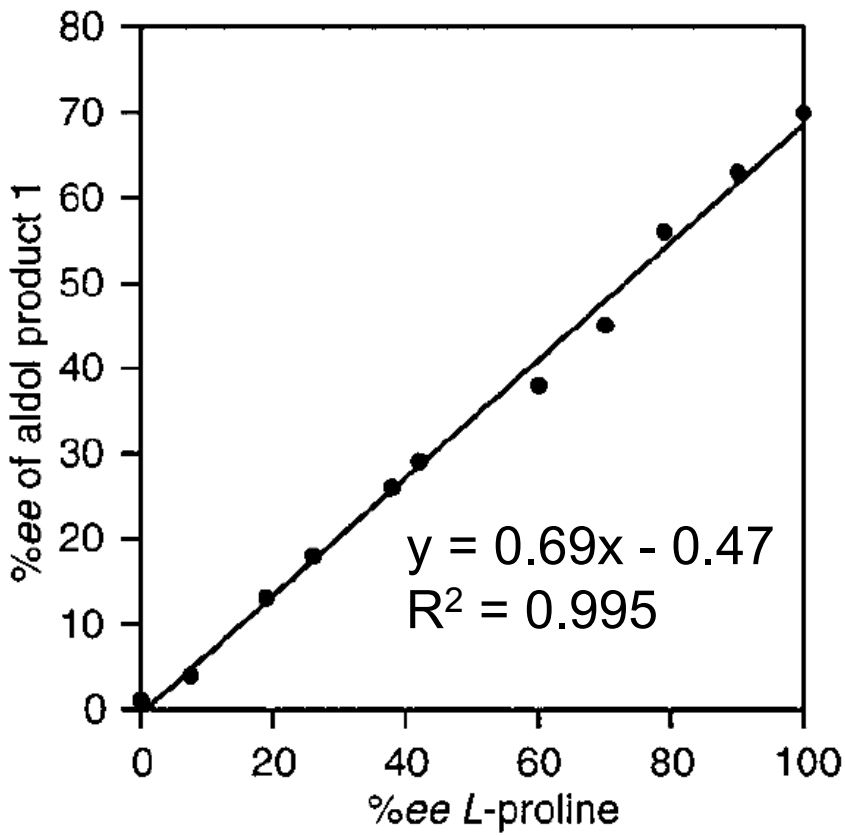
1.0 M in DMF



"The kinetic process of this catalytic reaction is complicated to such extent that it would not be wise to draw any definite conclusion as regards to homo or heterochiral nature of the favored diastereomeric transition state."

Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

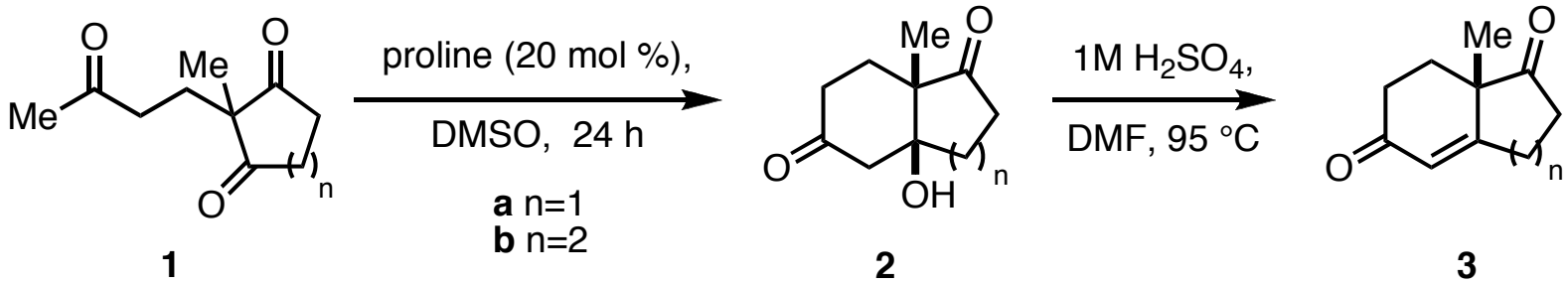
The Absence of Non-Linear Effect



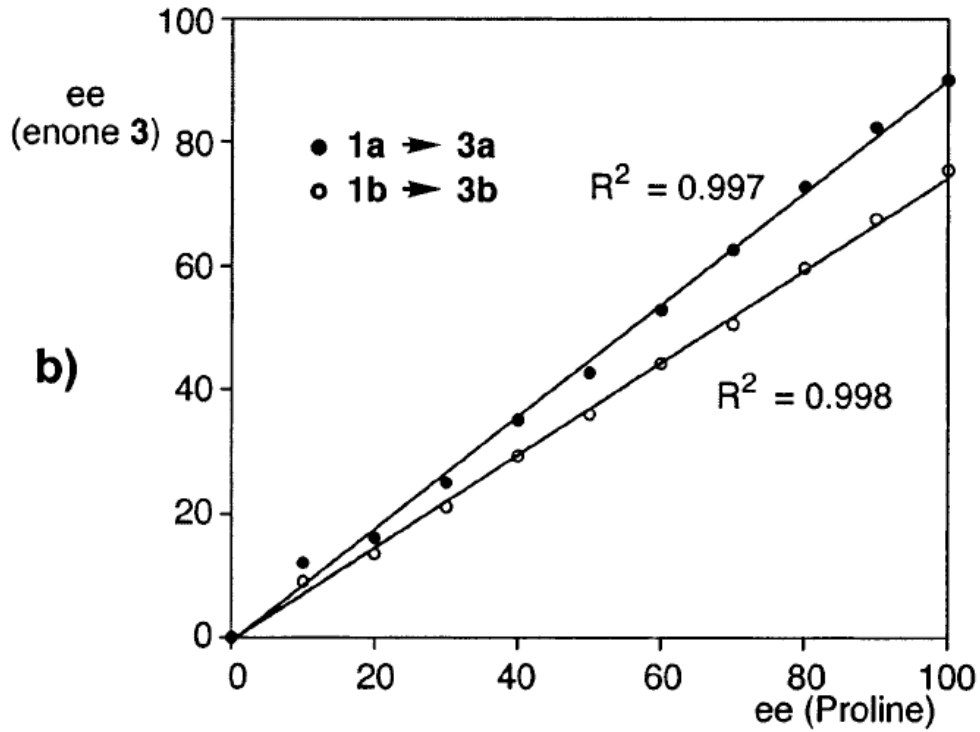
ee determined by chiral HPLC

Sakthivel, K.; Notz, W.; Bui, Tommy, Barbas, C. F. III *J. Am. Chem. Soc.* **2001**, *123*, 5260.

The Absence of Non-Linear Effect



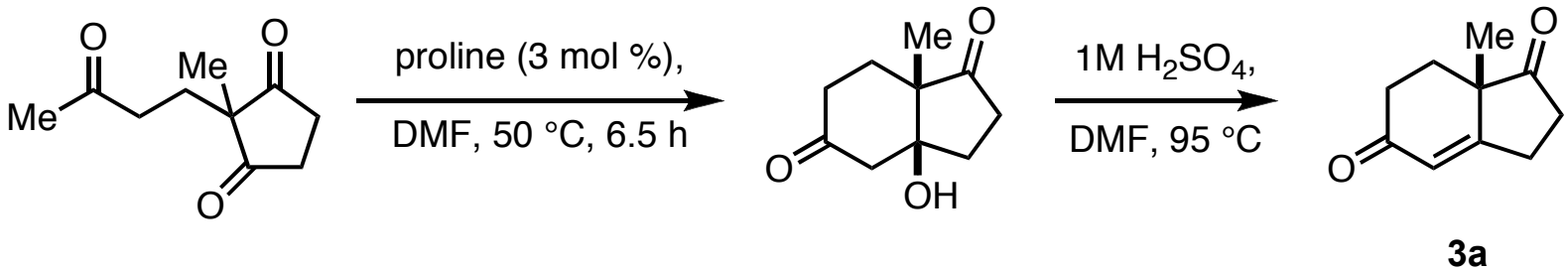
0.1 M in DMSO



ee determined by chiral HPLC

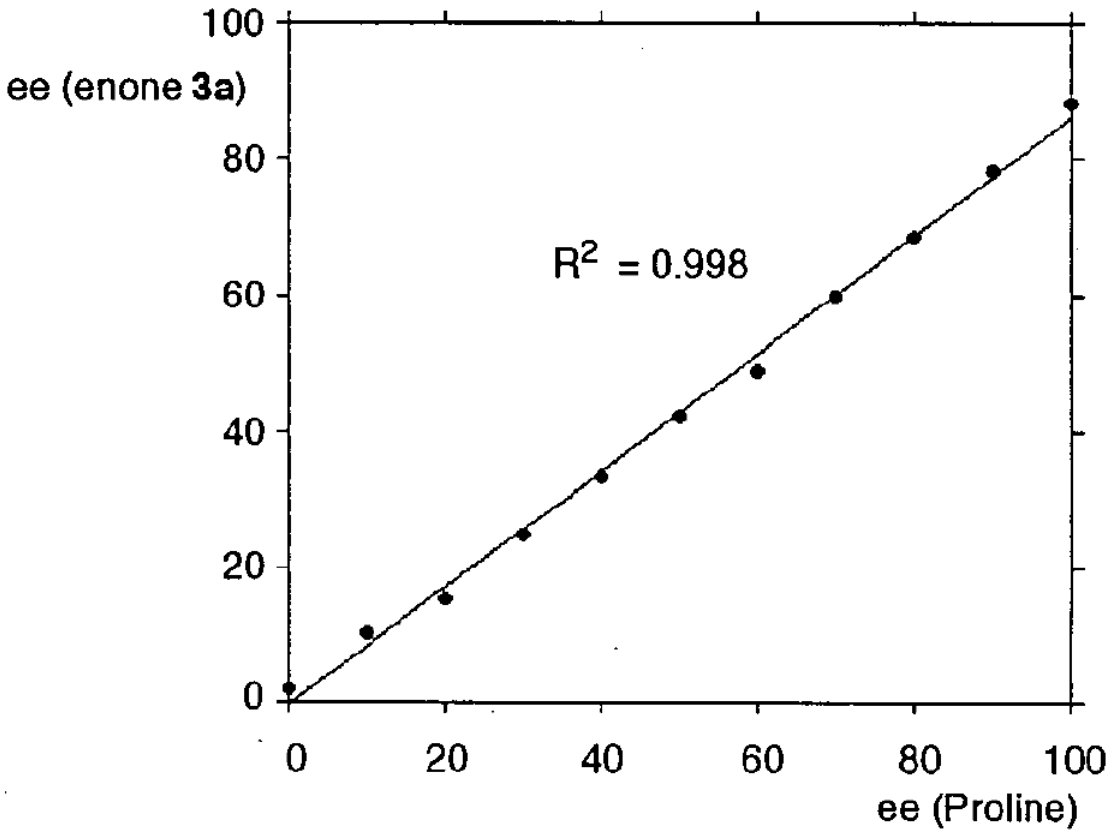
Hoang, L.; Bahnmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

The Absence of Non-Linear Effect



1.0 M in DMF

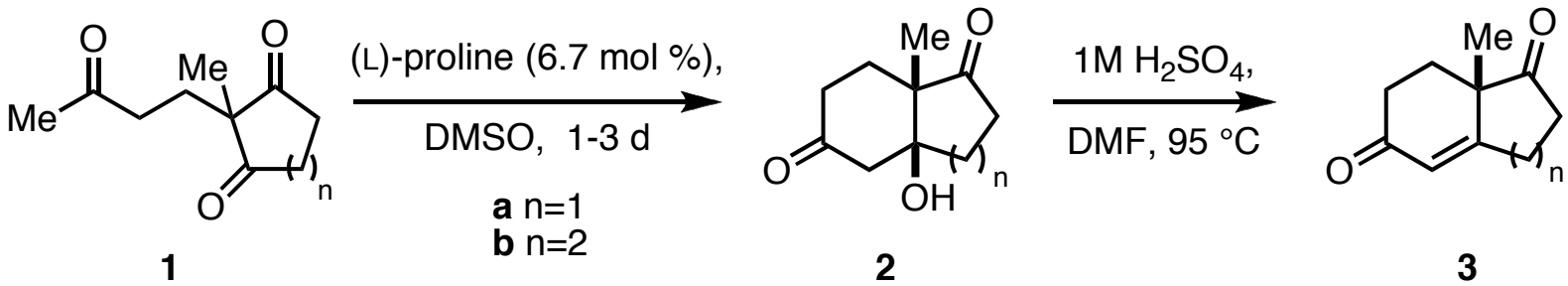
Agami's experiments repeated

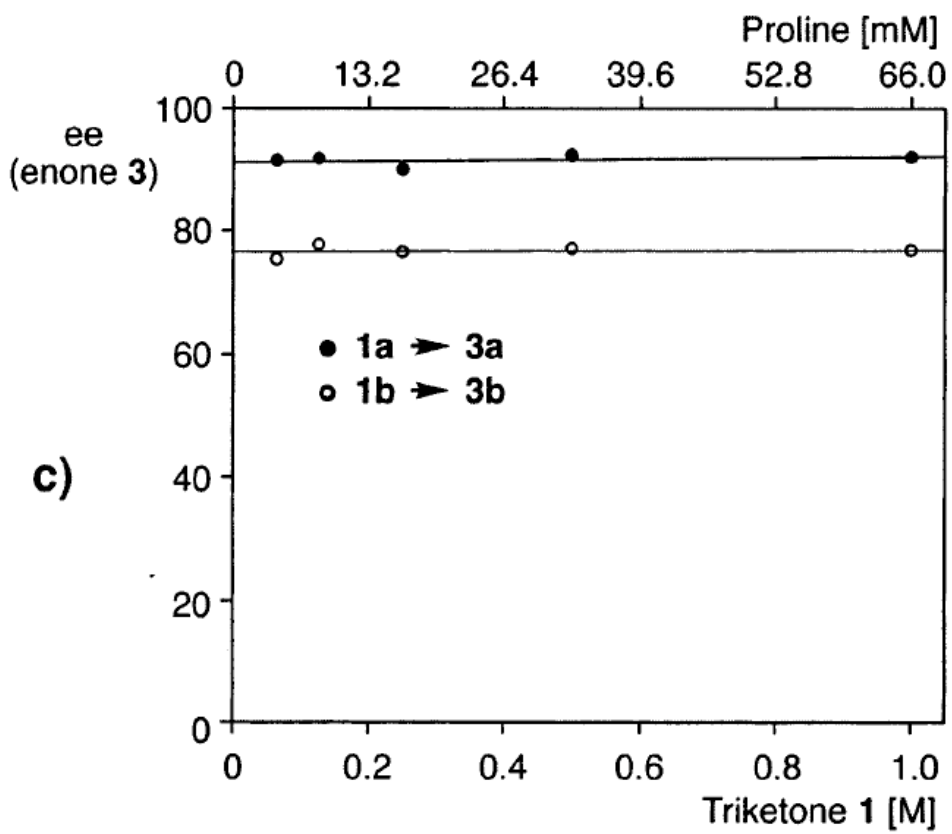


ee determined by chiral HPLC

Hoang, L.; Bahnmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. SI.

The Absence of Dilution Effect

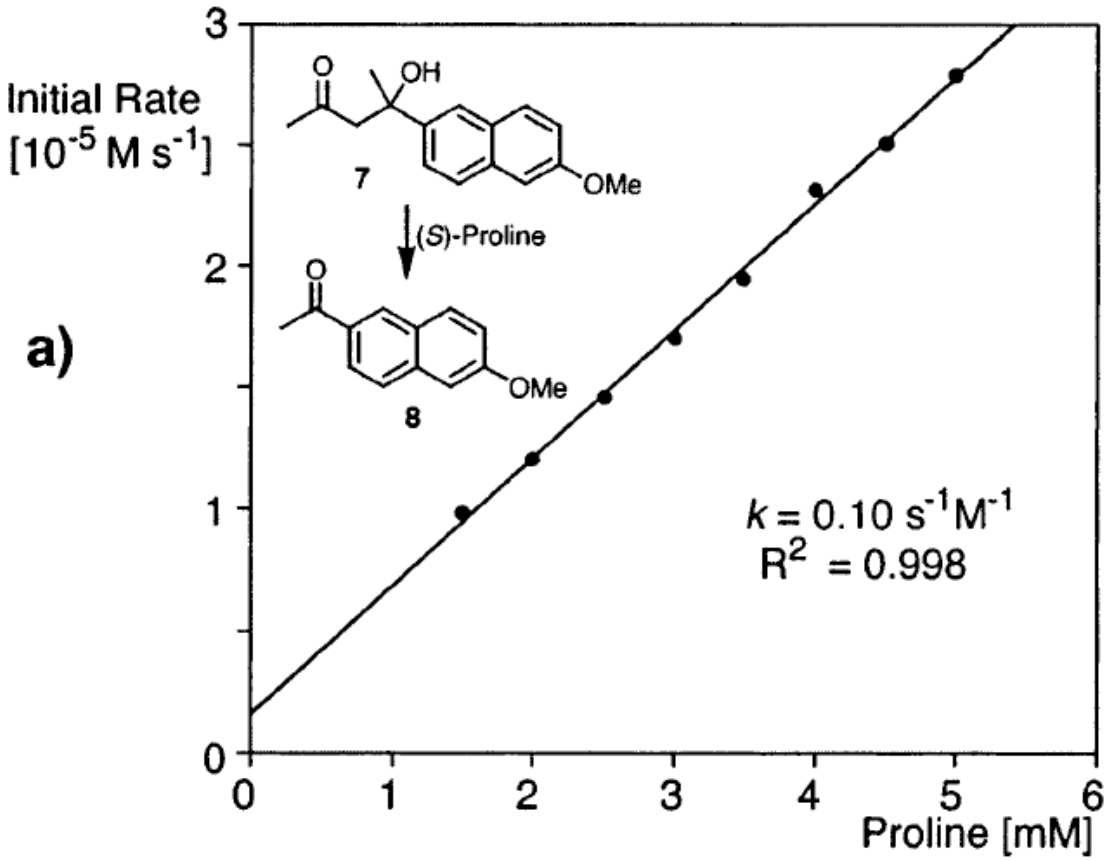




ee determined by chiral HPLC

Hoang, L.; Bahnmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

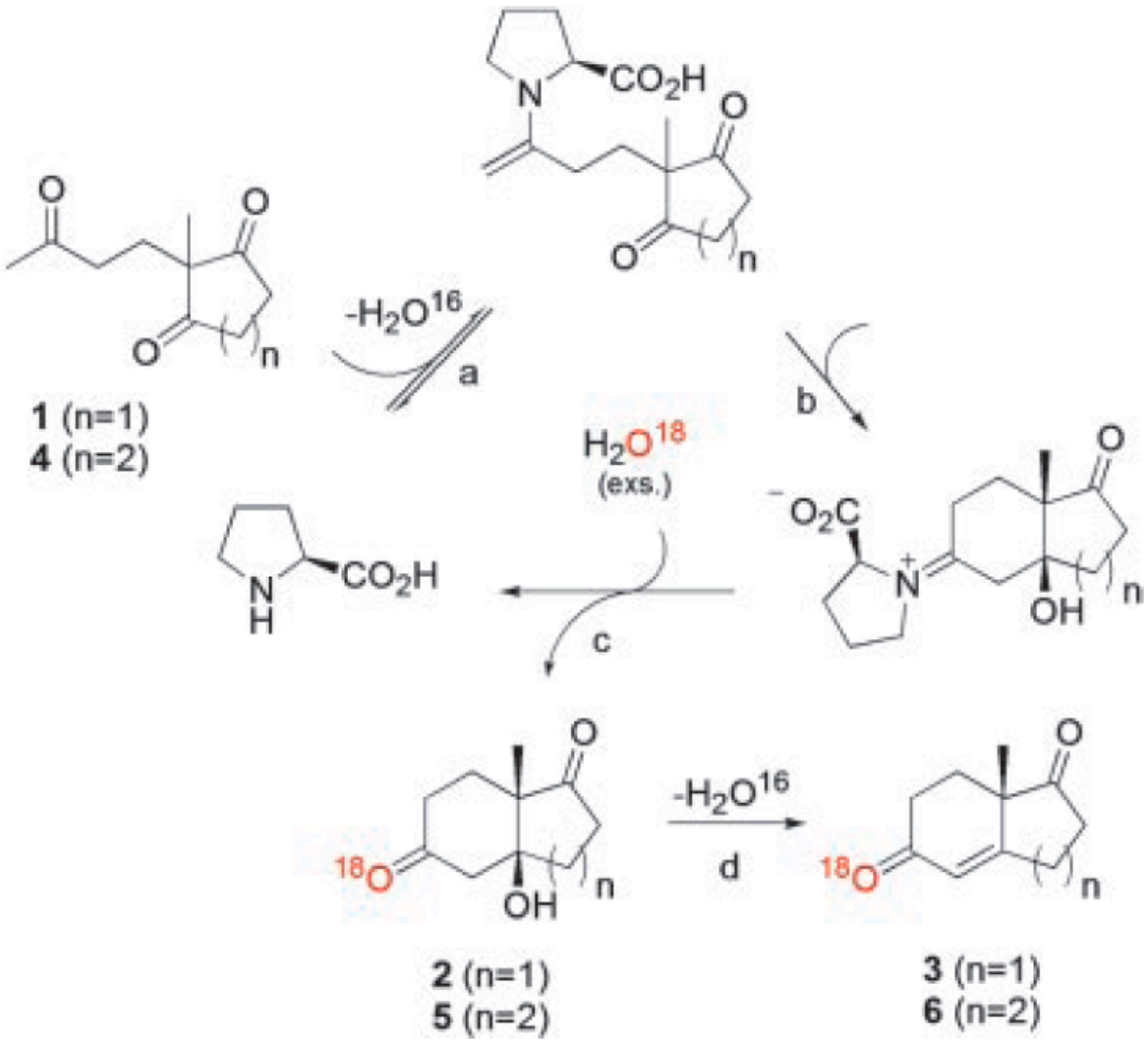
Kinetic Order of Proline in Retro-Aldol



The rate of retro-aldol was found to be first order in proline

Hoang, L.; Bahnmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

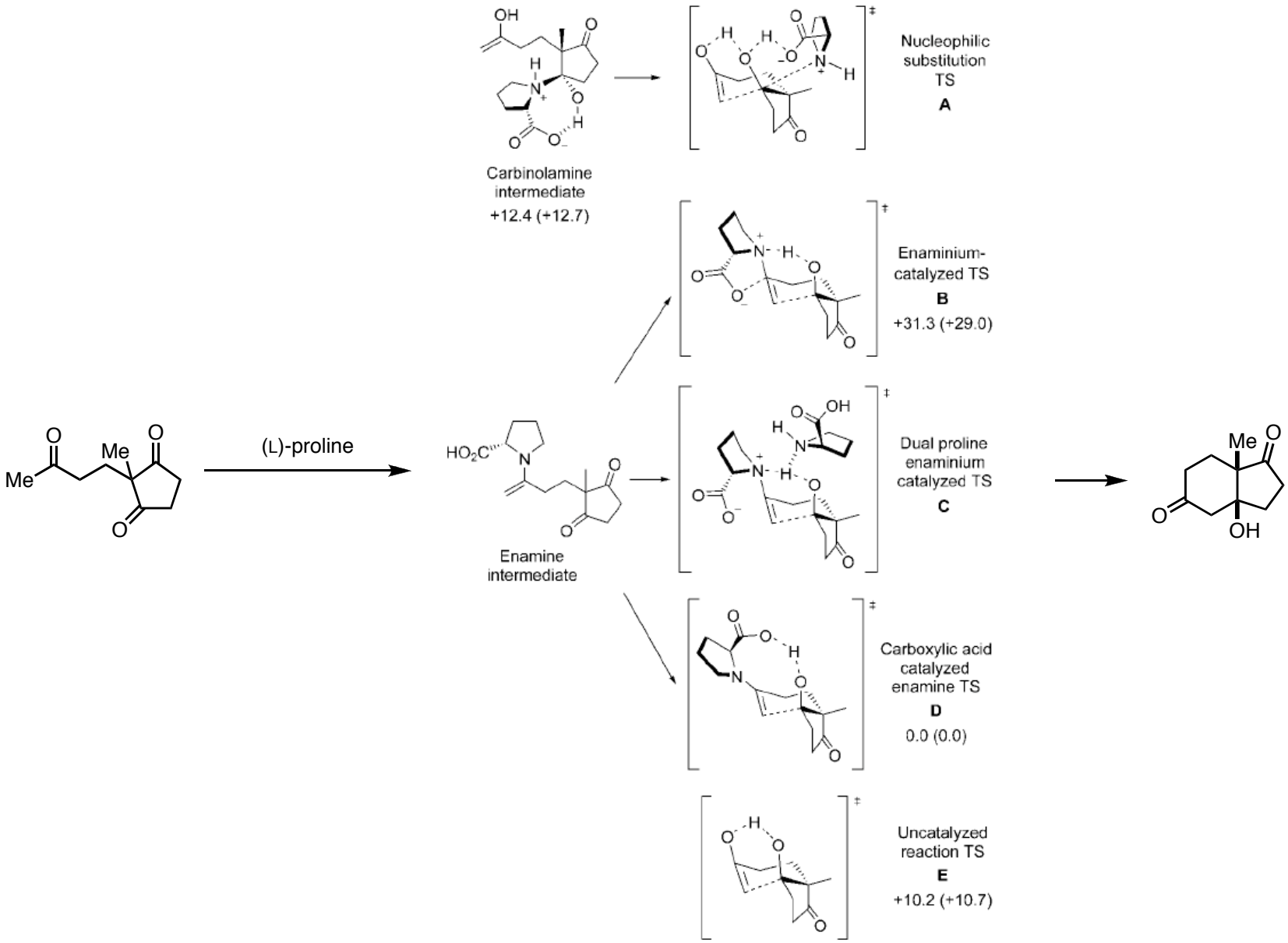
Currently Accepted Mechanistic Picture



List, B.; Hoang, L.; Martin, H. J. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5839.

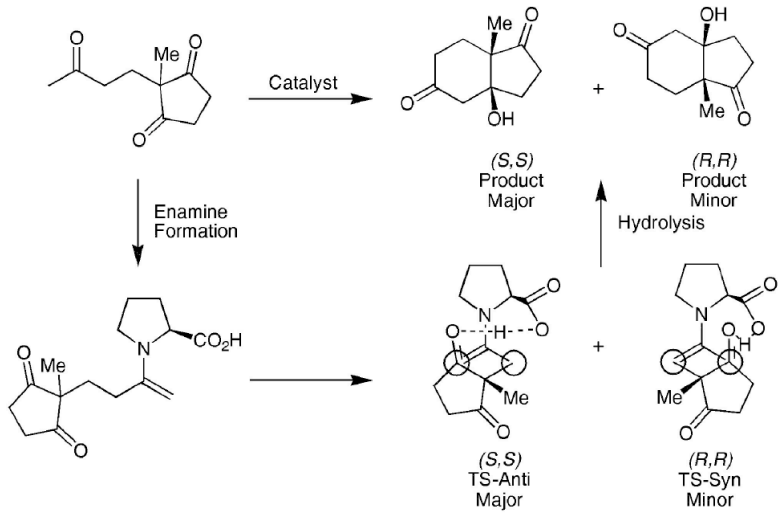
Time for a Quick Break

What is the Nature of the Aldolization Transition State?

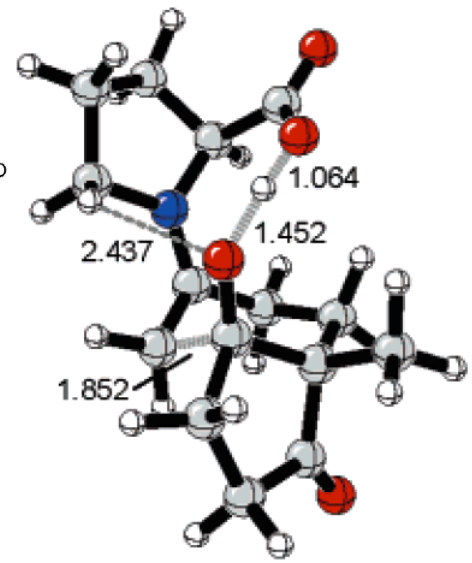


Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 5766.

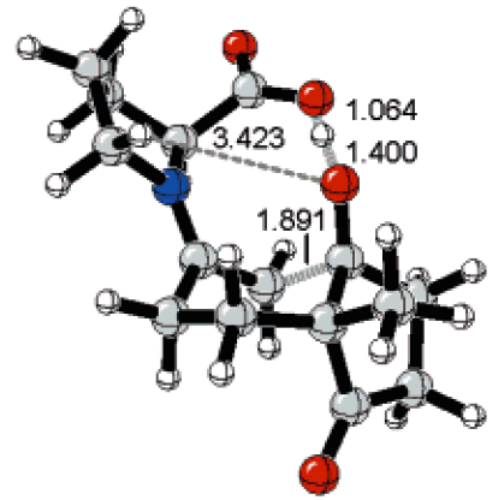
A Closer Look at the Aldolization Transition State



(*S*,*S*)-4
E_{rel} = 0.0 kcal/mol
(E_{act} = 10.5 kcal/mol)

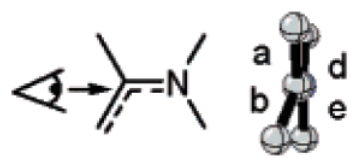


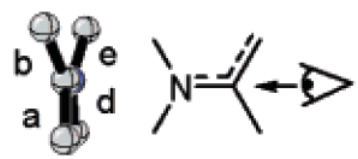
(*R*,*R*)-4
E_{rel} = 3.3 kcal/mol



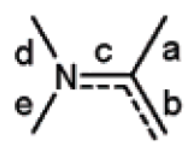
- Both transition states chair-like
- C=C, C=O bonds are synclinal
- Anti-enamine more stable
- Carboxylic acid of proline very important
- O-H···O distance very short for **(*R*,*R*)-4**
- Enamine of **(*R*,*R*)-4** less planar
- H on C5 of proline may also stabilize the developing negative charge of carbonyl

ω_1 = 0°
ω_2 = -19°
ω_3 = 162°
ω_4 = 180°
ϕ = -84°

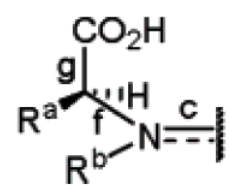




ω_1 = 2°
ω_2 = 31°
ω_3 = -162°
ω_4 = -164°
ϕ = -91°



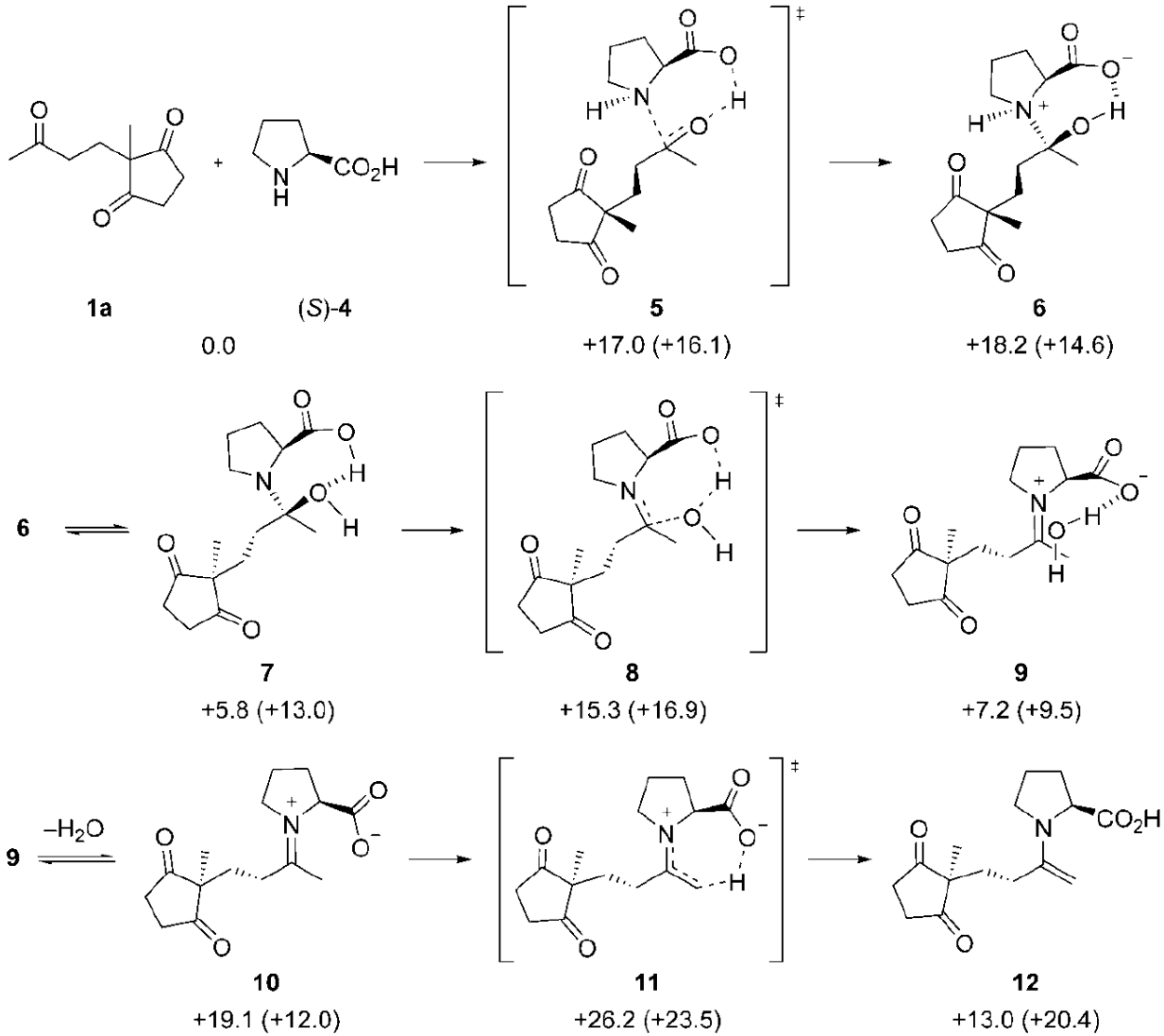
ω_1 = <acd
ω_2 = <bce
ω_3 = <bcd
ω_4 = <ace



ϕ = <gfc

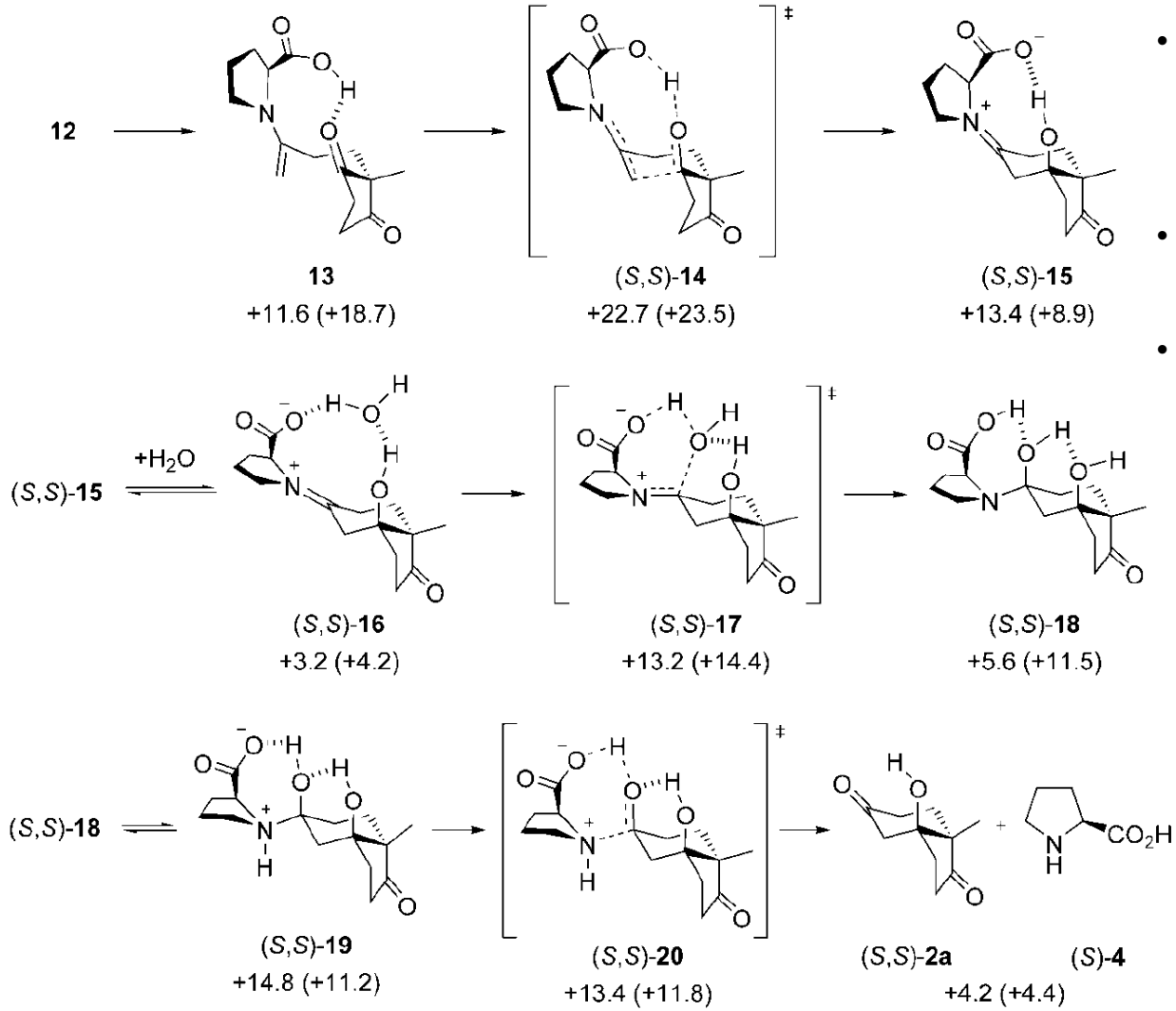
Bahnmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.
Cheong, P. H.-Y.; Houk, K. N.; Warrier, J. S.; Hanessian, S. *Adv. Syn. Catal.* **2004**, *346*, 1111.
Cheong, P. H.-Y.; Houk, K. N. *Synthesis* **2005**, 1533.
Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294.

Energy Profile of Proline-Catalyzed Cyclization



Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 5766.
Similar calculation of proline-catalyzed intermolecular aldol: Boyd, R. J. *et al. J. Phys. Chem. A* **2002**, *106*, 5155.

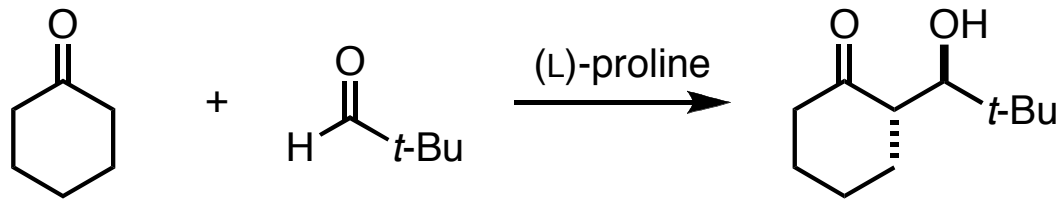
Energy Profile of Proline-Catalyzed Cyclization



- Rate determining steps:
  - Iminium-enamine tautomerization
  - aldolization
- Stereochemistry determining step: aldolization
- The energy profiles of intra- and intermolecular reaction similar

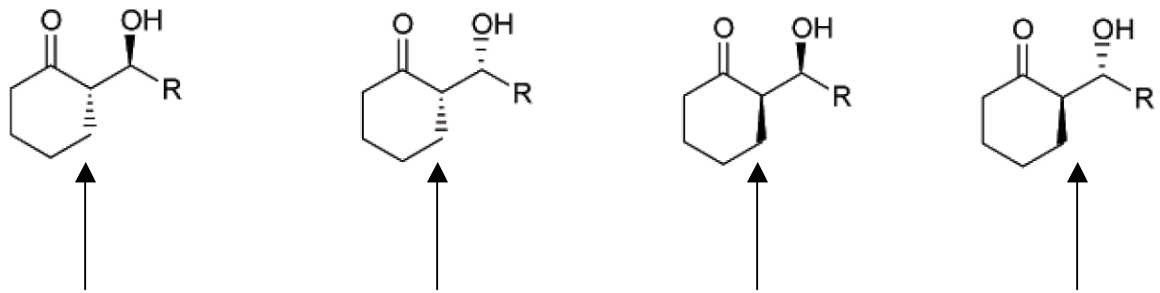
Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 5766.

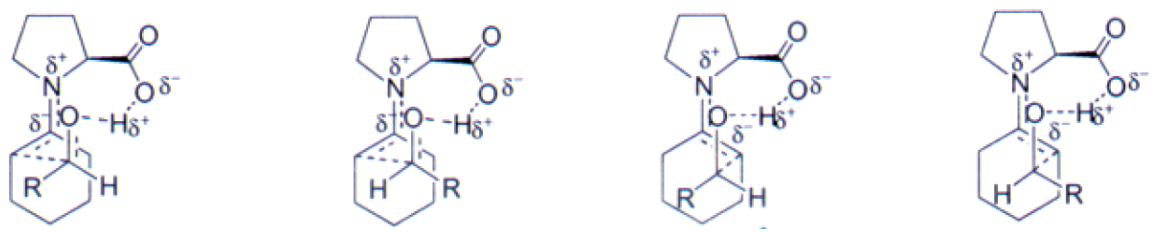
Origin of Enantioselectivity for the Intermolecular Reactions

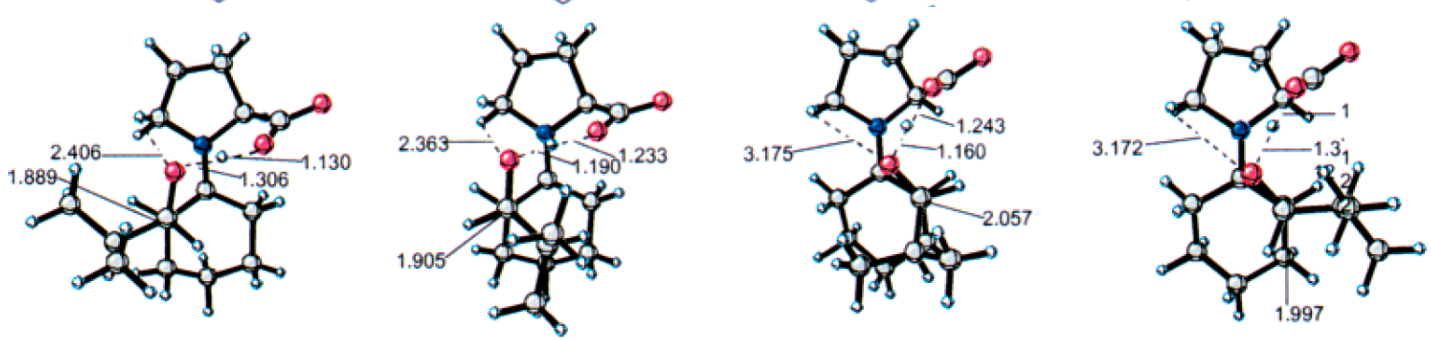


Re-face attack on aldehyde most favourable

R = *t*-Bu





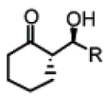
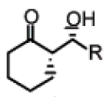
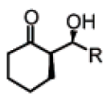
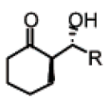


TS-6a	TS-6b	TS-6c	TS-6d
ΔH_{298} = 0.0 kcal/mol	ΔH_{298} = 6.7 kcal/mol	ΔH_{298} = 7.8 kcal/mol	ΔH_{298} = 4.6 kcal/mol

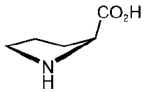
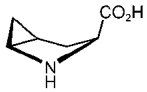
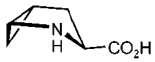
Bahnmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *123*, 2475.

How accurate/inaccurate are the Calculations?

Intermolecular aldol reactions

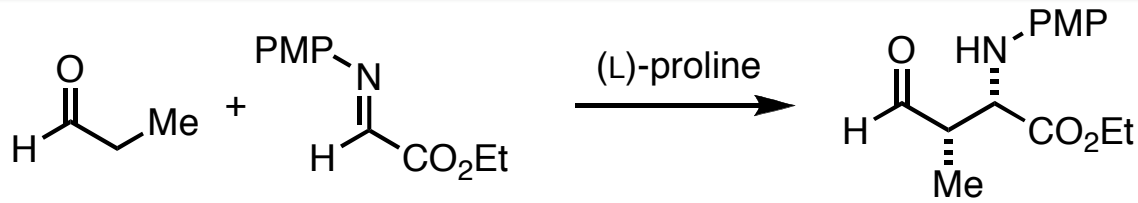
	R = Ph		R = *i*-Pr	
	Predicted	Experiment	Predicted	Experiment
 *anti*-2	50-80% (ΔH_{298} = 0.0)	45-47% ΔG_{exp} = 0.0	≥99% (ΔH_{298} = 0.0)	97-100% ΔG_{exp} = 0.0
 *syn*-2	20-50% (ΔH_{298} = 0.4 ± 0.4)	43-45% ΔG_{exp} = 0.03 ± 0.05	<1% (ΔH_{298} = 6.7 ± 0.4)	<1% ΔG_{exp} > 4.1 ± 0.03
 ent-*syn*-2	<1% (ΔH_{298} = 3.6 ± 0.4)	5-7% ΔG_{exp} = 1.2 ± 0.05	<1% (ΔH_{298} = 7.8 ± 0.4)	<1% ΔG_{exp} > 4.1 ± 0.03
 ent-*anti*-2	1-4% (ΔH_{298} = 2.3 ± 0.4)	3-5% ΔG_{exp} = 1.4 ± 0.05	<1% (ΔH_{298} = 4.6 ± 0.4)	0-3% ΔG_{exp} = 2.5 ± 0.03

Hajos-Parrish-Eder-Sauer-Wiechert cyclization

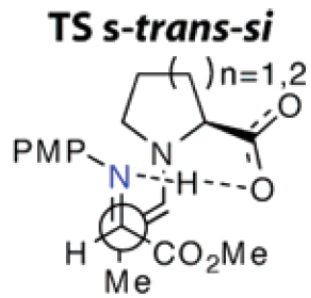
Entry	Catalyst	Experiment ($\Delta G^{\ddagger}$)	Calculated ($\Delta H^{\ddagger}$)
1		2.1	2.2
2		1.9	2.1
3		1.4	1.3

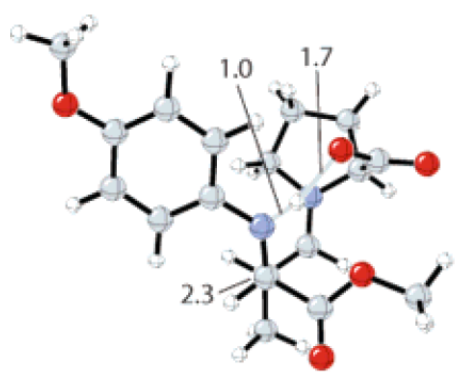
Cheong, P. H.-Y.; Houk, K. N.; Warrier, J. S.; Hanessian, S. *Adv. Syn. Catal.* **2004**, *346*, 1111.
Bahnmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *123*, 2475.

A Brief Look at Proline-Catalyzed Mannich Reaction



Transition state giving rise to the major product

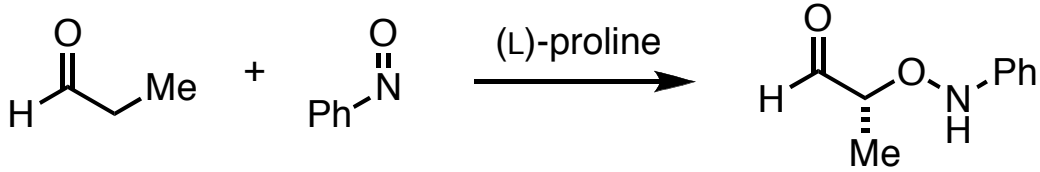


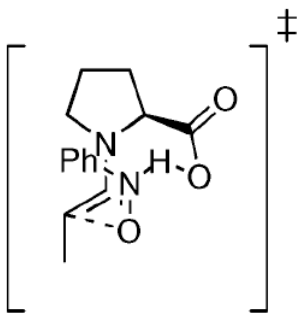


TS-(*S,S*)-4
$\Delta G = 0.0$

Cheong, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F. III *Org. Lett.* **2006**, *8*, 811.

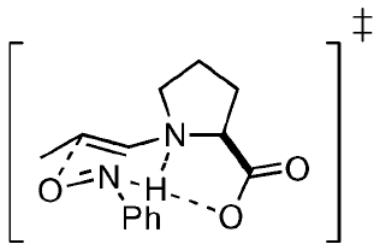
A Brief Look at Proline-Catalyzed α-Aminoxylation





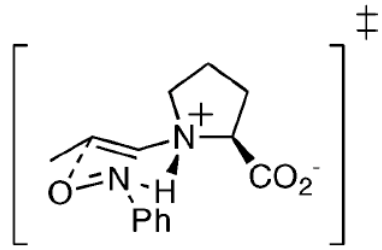
4a

Hayashi model



4b

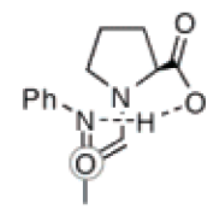
Zhong model

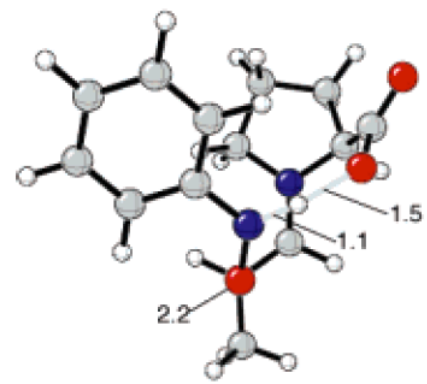


4c

MacMillan model

Transition state giving rise to the major product



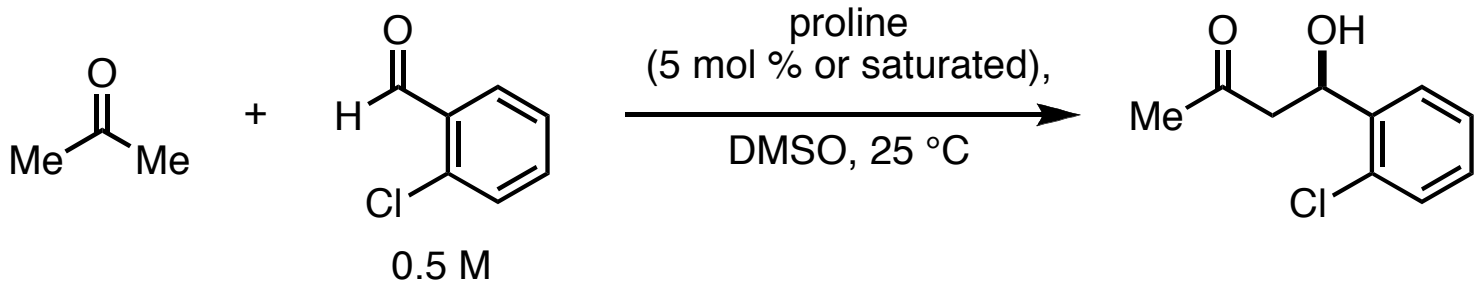


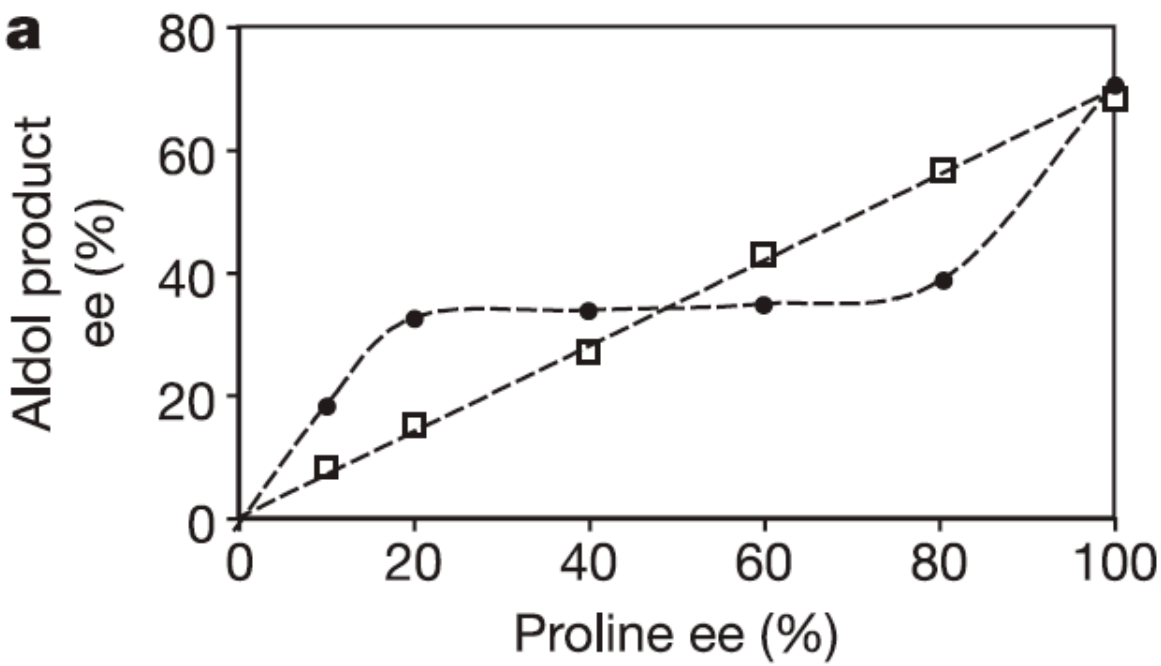
***(R)*-O-Anti-8**
$\Delta H^{\ddagger}$ = 4.8 (0.0)
$\Delta G_{solv}^{\ddagger}$ = 22.2 (0.0)

- Enamine reacts with monomeric Ph-NO
- Regioselectivity depends on the basicity of the heteroatom
- Transition states correspond to **4b** and **4c** cannot be located

Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912.

An Interesting Twist—Non-Linear Effect Revisited



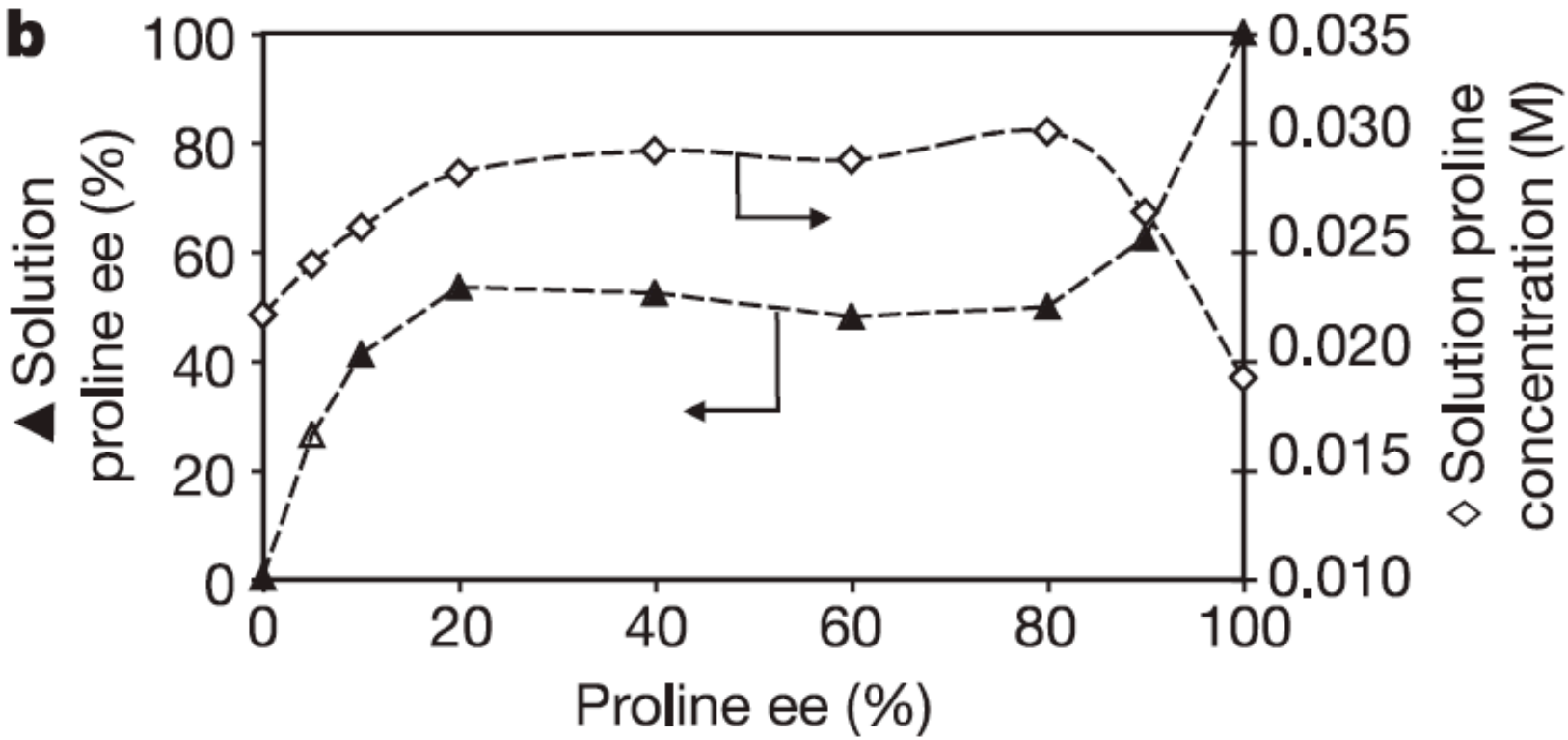


□: [proline] = 0.025 M
●: total [proline] = 0.1 M

When the solvent is saturated with proline, a non-linear effect is observed.

Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H. Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

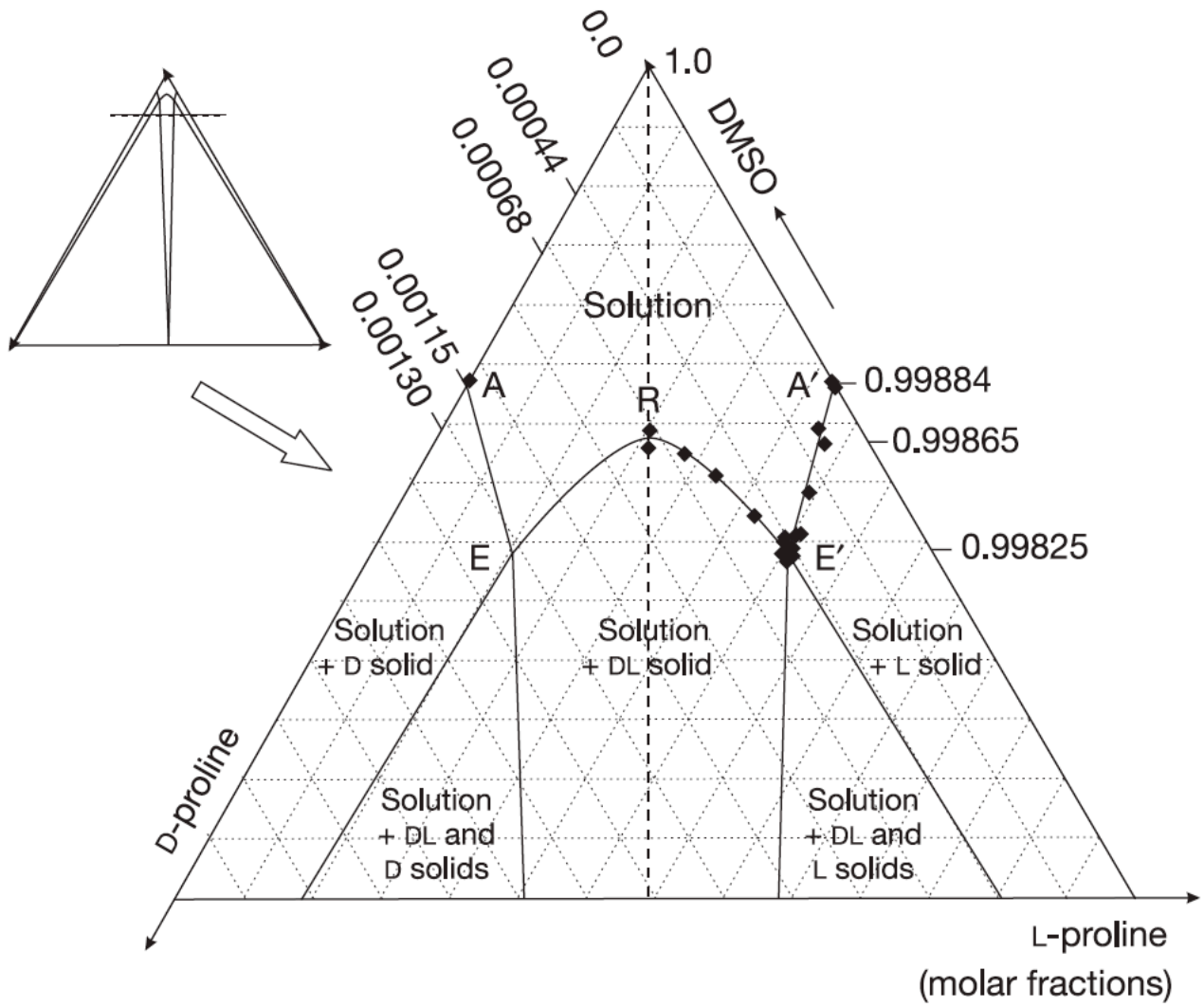
Asymmetric Amplification by Dissolution



- All experiment carried out in DMSO with 0.8 wt% H_2O at 25 ºC.
- Concentration of dissolved proline and enantiomeric composition determined by chiral HPLC.
- Total proline concentration: 0.1 M.

Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H. Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

Ternary Phase Diagram of (L)-, (D)-Proline, and DMSO



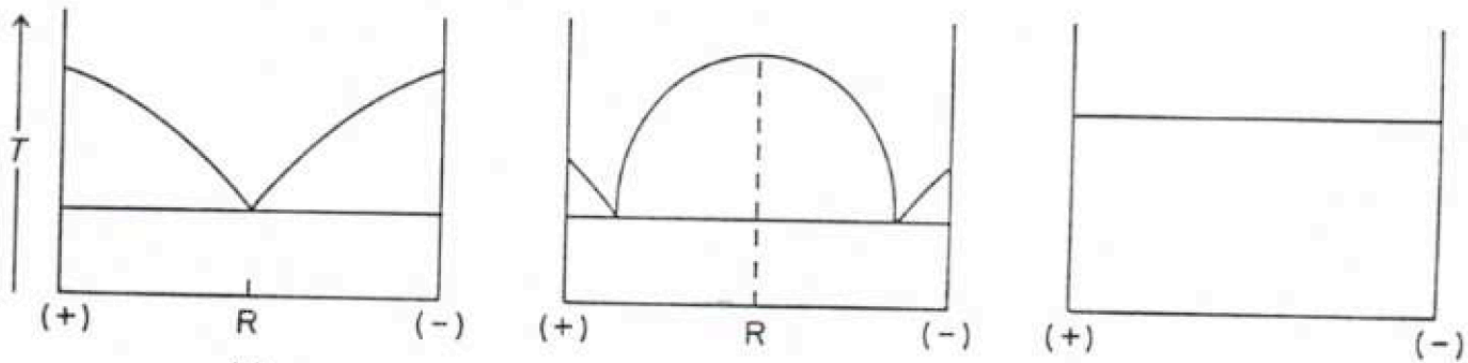
Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H. Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

Some Important Definitions

- Racemic Compound
  - IUPAC: A crystalline racemate in which the two enantiomers are present in equal amounts in a well defined arrangement within the lattice of a homogeneous crystalline addition compound.
  - Eliel: A racemate in which the two enantiomers form a crystalline compound. The unit cell contains equal numbers of enantiomeric molecules.
- Conglomerate
  - IUPAC: An equimolar mechanical mixture of crystals each one of which contains only one of the two enantiomers present in a racemate.
  - Eliel: An equimolar mechanical mixture of crystals that form a eutectic of two enantiomers.
- Solid Solution
  - IUPAC: A crystal containing a second constituent which fits into and is distributed in the lattice of the host crystal.
  - Eliel: Two enantiomers are miscible in the solid state.

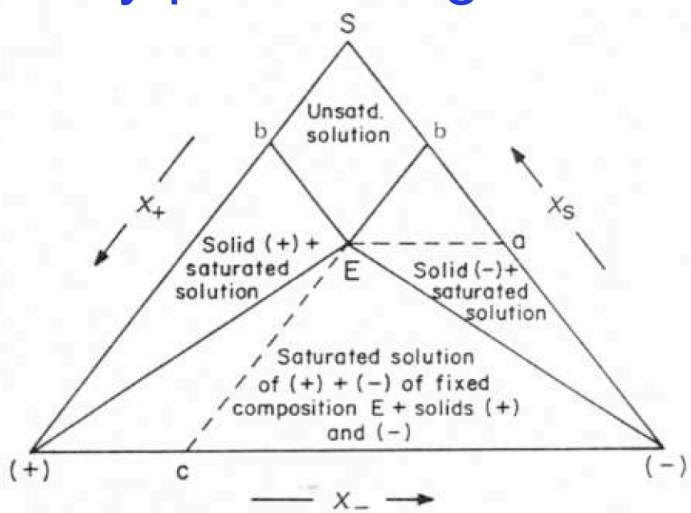
More on Phase Diagrams

Binary phase diagrams

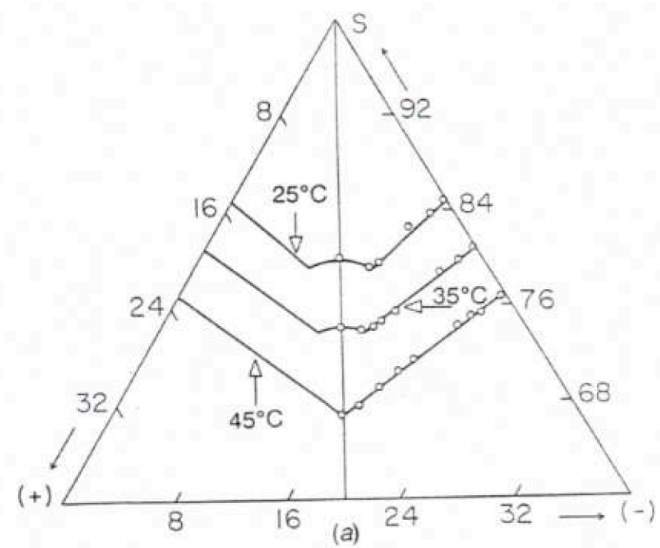


conglomerate racemic compounds solid solution

Ternary phase diagrams



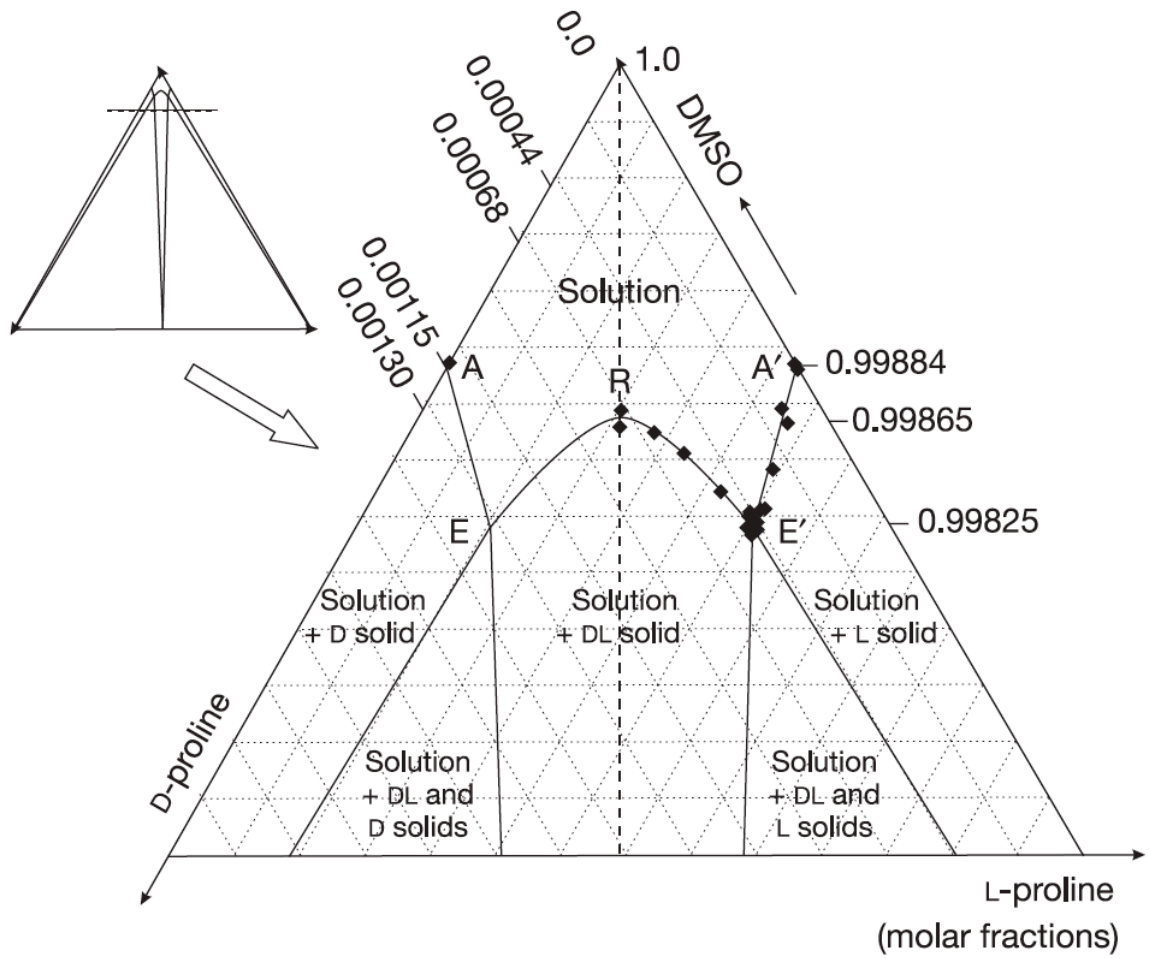
conglomerate



Temperature dependence of the solubility of histidine·HCl in water

Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*. New York: Wiley. 1994.

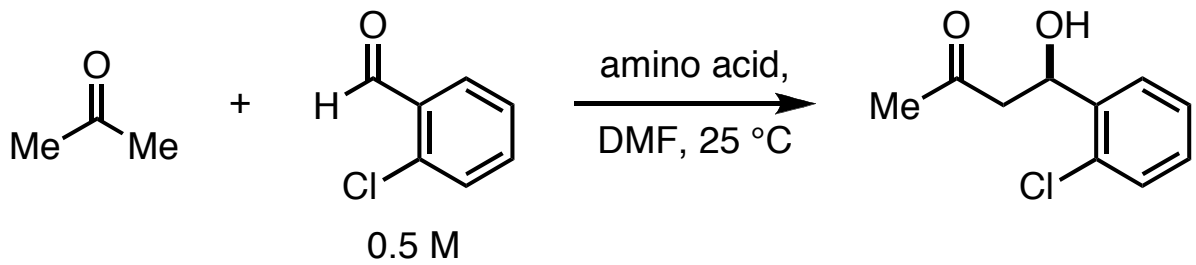
Ternary Phase Diagram of (L)-, (D)-Proline, and DMSO

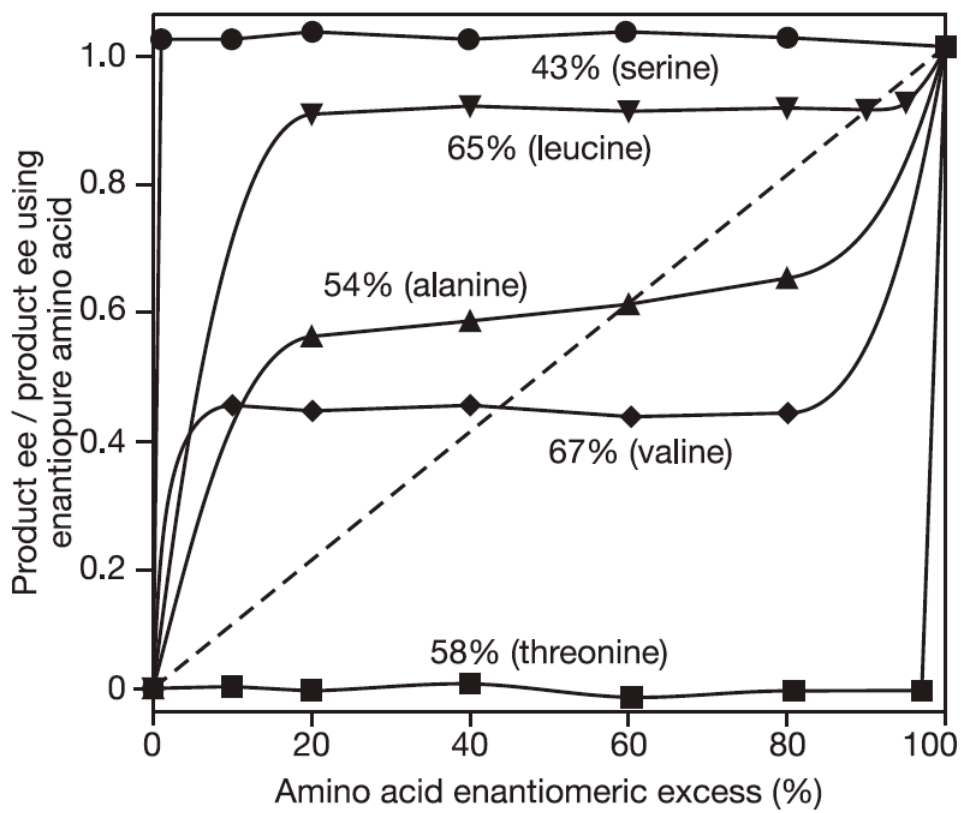


What would happen if an unsaturated solution of (L)-proline/(D)-proline = 4/1 is concentrated isothermally?

Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H. Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

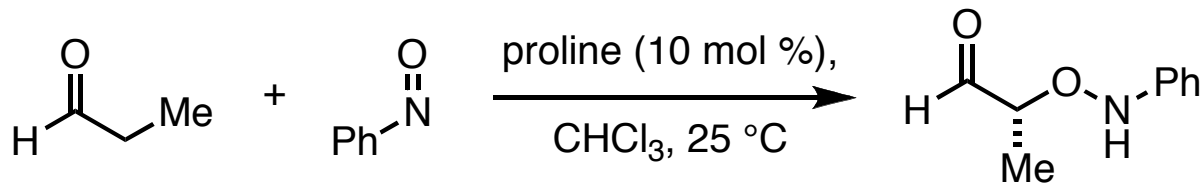
What About Other Amino Acids?



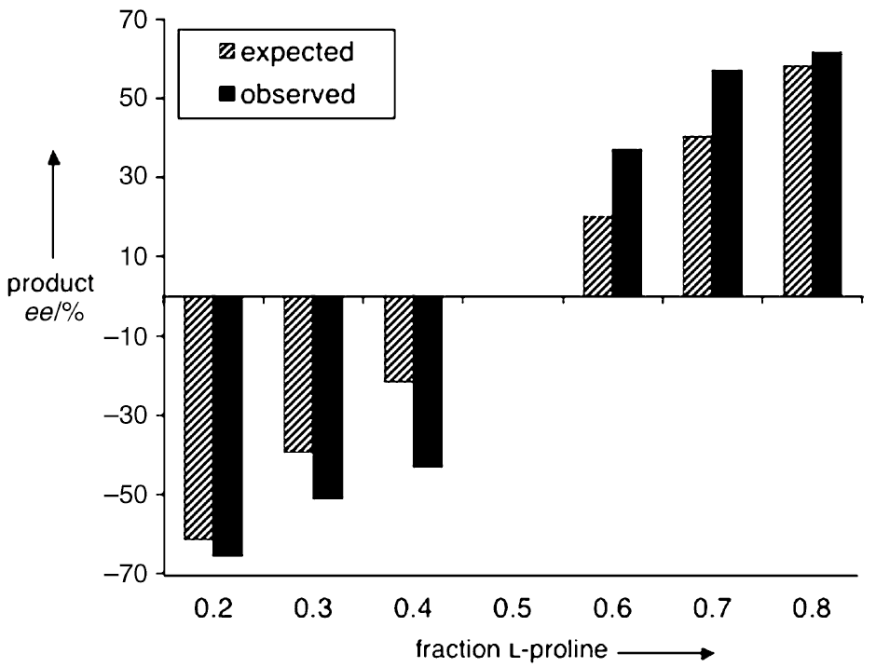


Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H. Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

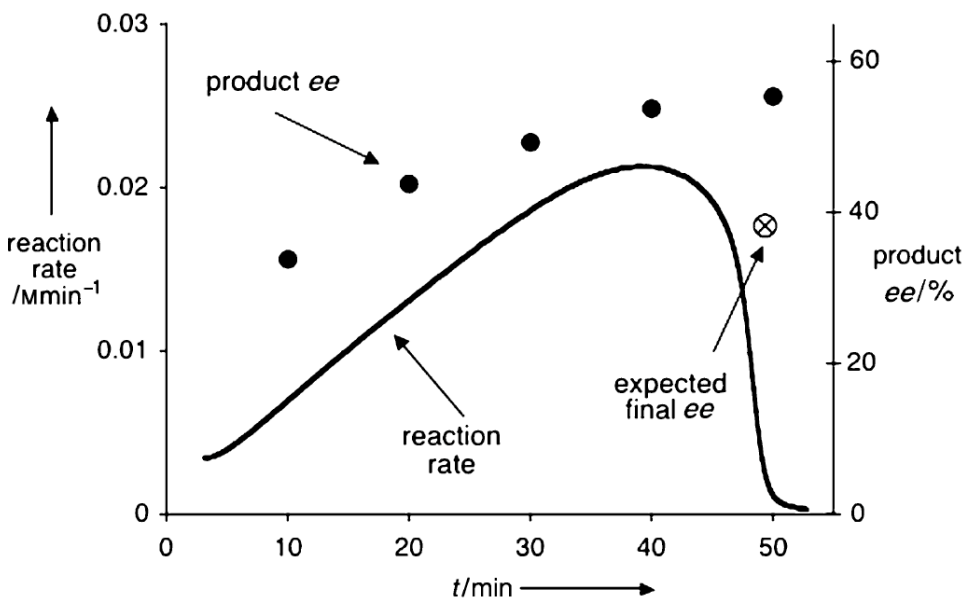
Asymmetric Amplification by Catalyst Improvement



The non-linear effect observed.

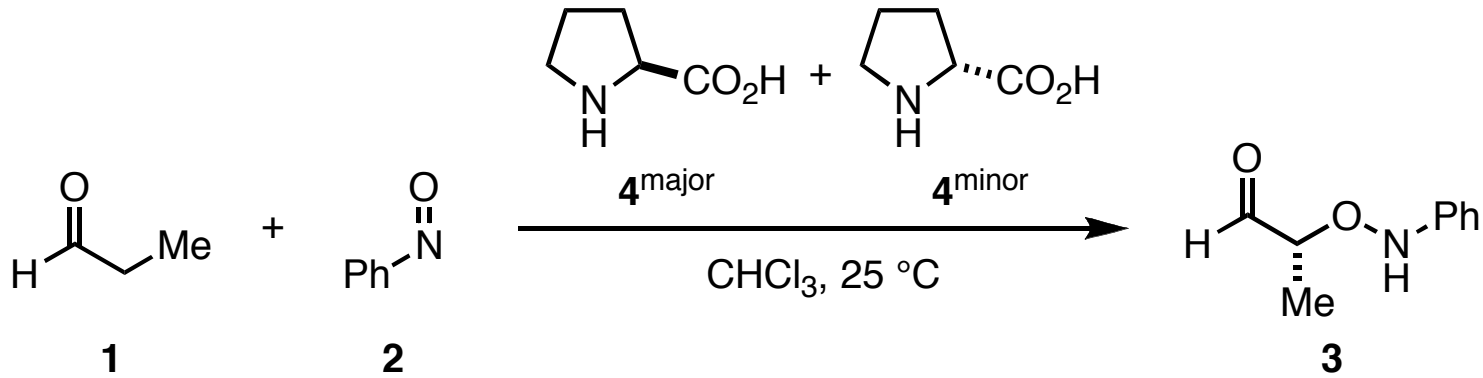


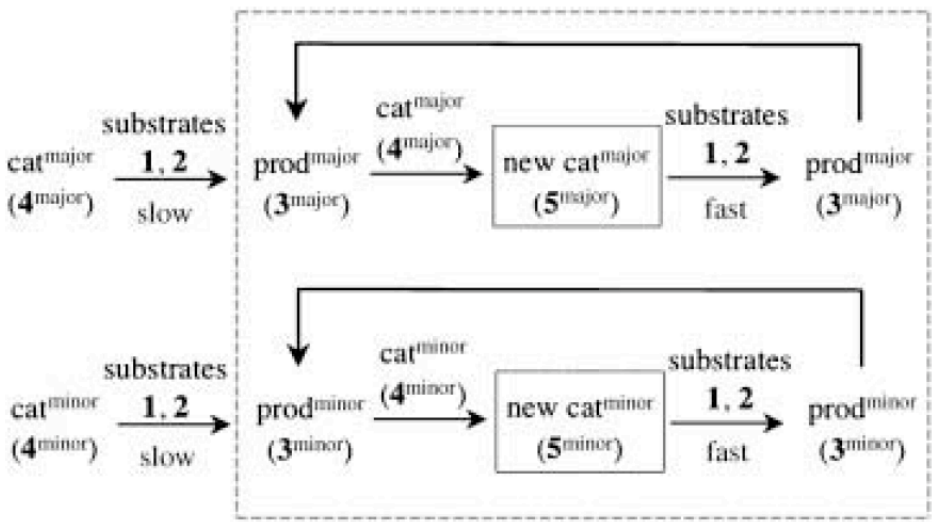
The progress of reaction catalyzed by (L)-proline with 40% ee.

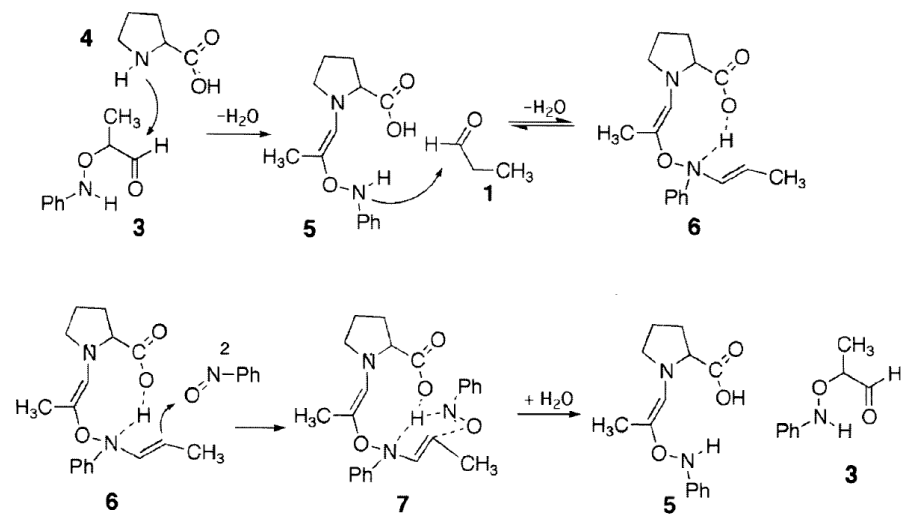


Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317.

Proposed Mechanistic Scheme



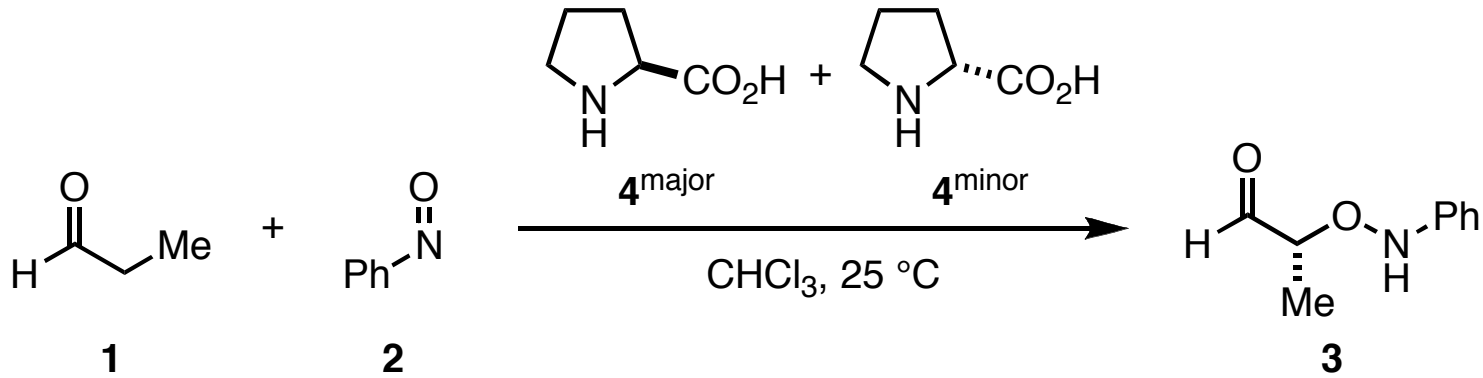


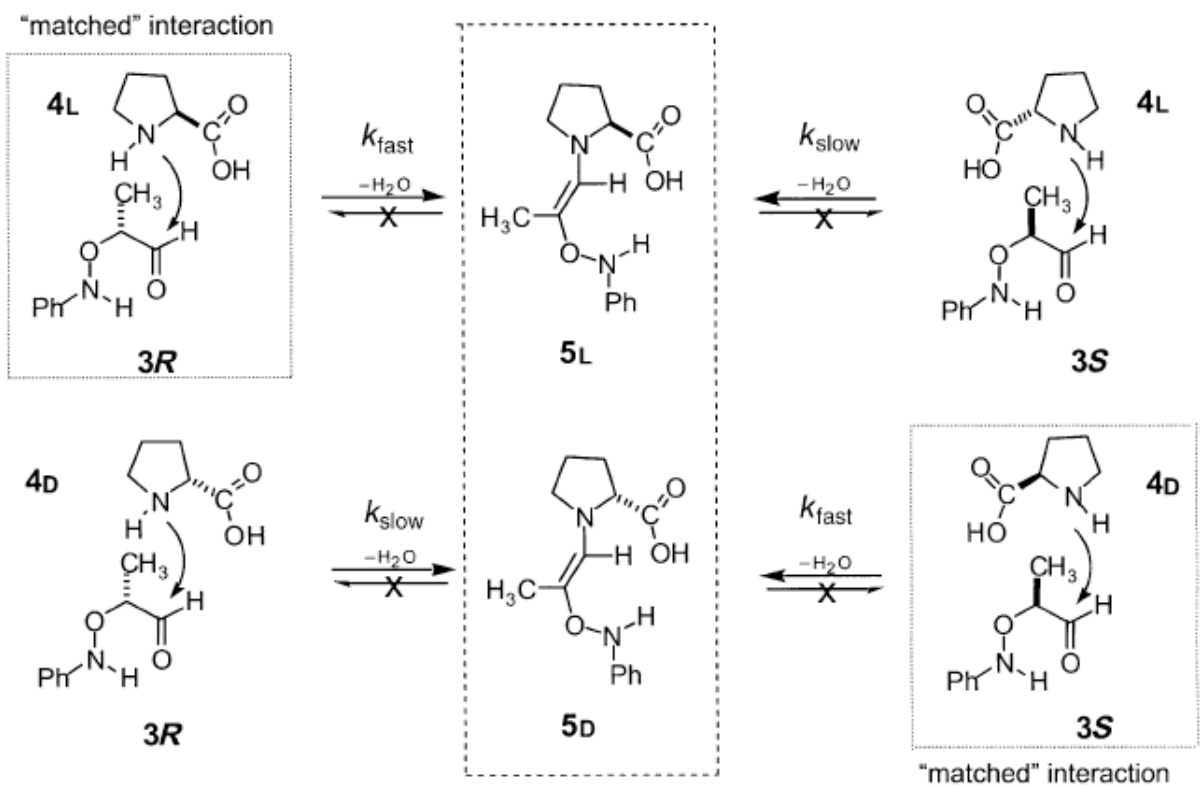


5 is more kinetically competent than proline as a catalyst

Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317.

“Kinetic Resolution” of Proline





Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317.

Summary

- Proline-catalyzed aldol reaction proceeds via enamine intermediate
- Only one proline is involved at the C-C bond formation
- Evidence for above conclusions:
  - ^{18}O incorporation
  - Absence of dilution effect
  - Absence of non-linear effect
  - Kinetics of retro-aldol
  - DFT computation
- Rate determining steps:
  - Iminium-enamine tautomerization
  - C-C bond formation
- The carboxylic acid functionality of proline very important in asymmetric induction of:
  - Aldol reaction
  - Mannich reaction
  - α-Aminoxylation
- Modes of asymmetric amplification in proline-catalyzed reations
  - Dissolution
  - Catalyst improvement

Kinetic Assumptions of Dilution Effect

Assuming:

1. Bi-molecular enantioselective process only produces *S* product.
2. The rate of non-enantioselective process is first order in proline.

i.e.,

$rate^{E} = k^{E}[proline]^{2}[s.m.]$

$rate^{NE} = k^{NE}[proline][s.m.]$

Thus,

$rate^{E}/rate^{NE} = k[proline]$

Also,

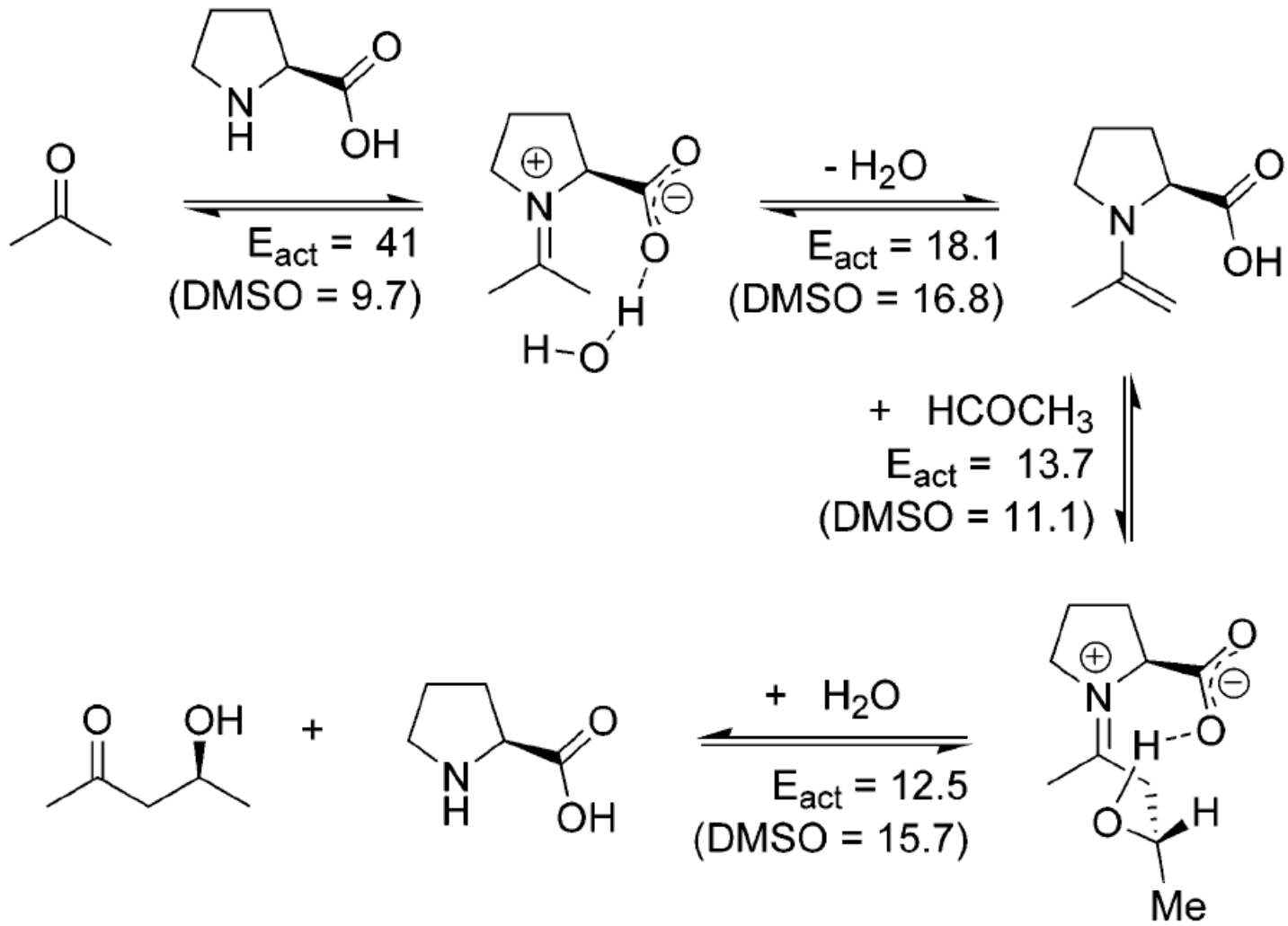
$$
\begin{aligned}
rate^{E}/rate^{NE} &= ([S]-[R])/2[R] \\
&= ([S]-[R])/\{([R]+[S])-([S]-[R])\} \\
&= ([S]-[R])/\{1-([S]-[R])\} \\
&= ee/(1-ee)
\end{aligned}
$$

Therefore,

$rate^{E}/rate^{NE} = k[proline] = ee/(1-ee)$

back

Energy Profile of Proline-Catalyzed Intermolecular Aldol Reaction



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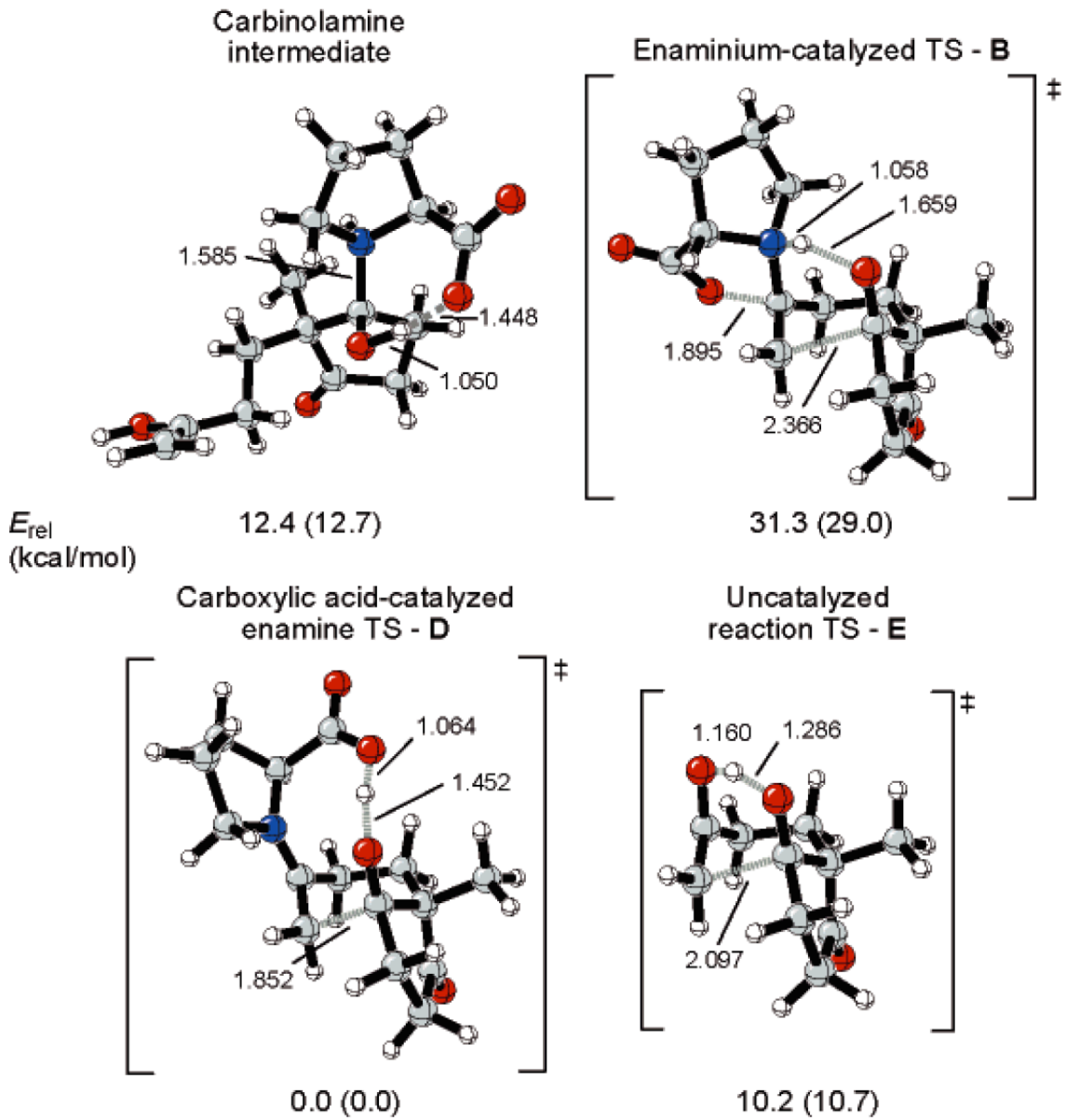
Calculated Structures of Different Transition States



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