A Biomimetic Approach for Selective Catalysis

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Aims for Selective Chemistry

Prevent waste-no toxicity

Atom Economy

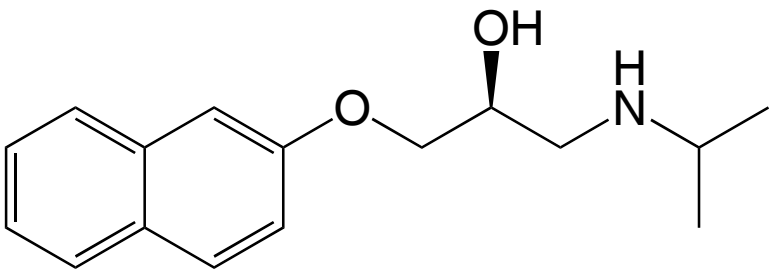
Minimize energy

Renewable starting materials

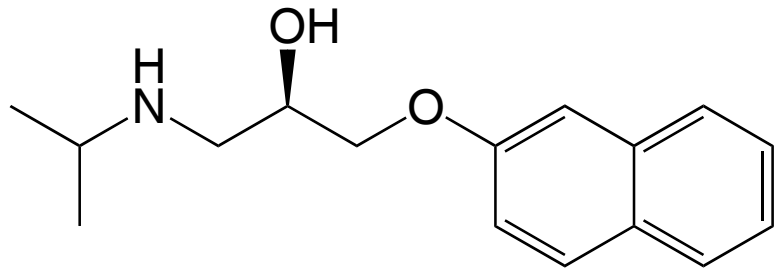
Catalytic reagents

High Stereocontrol

The construction of enantiomerically pure drugs is of immense importance



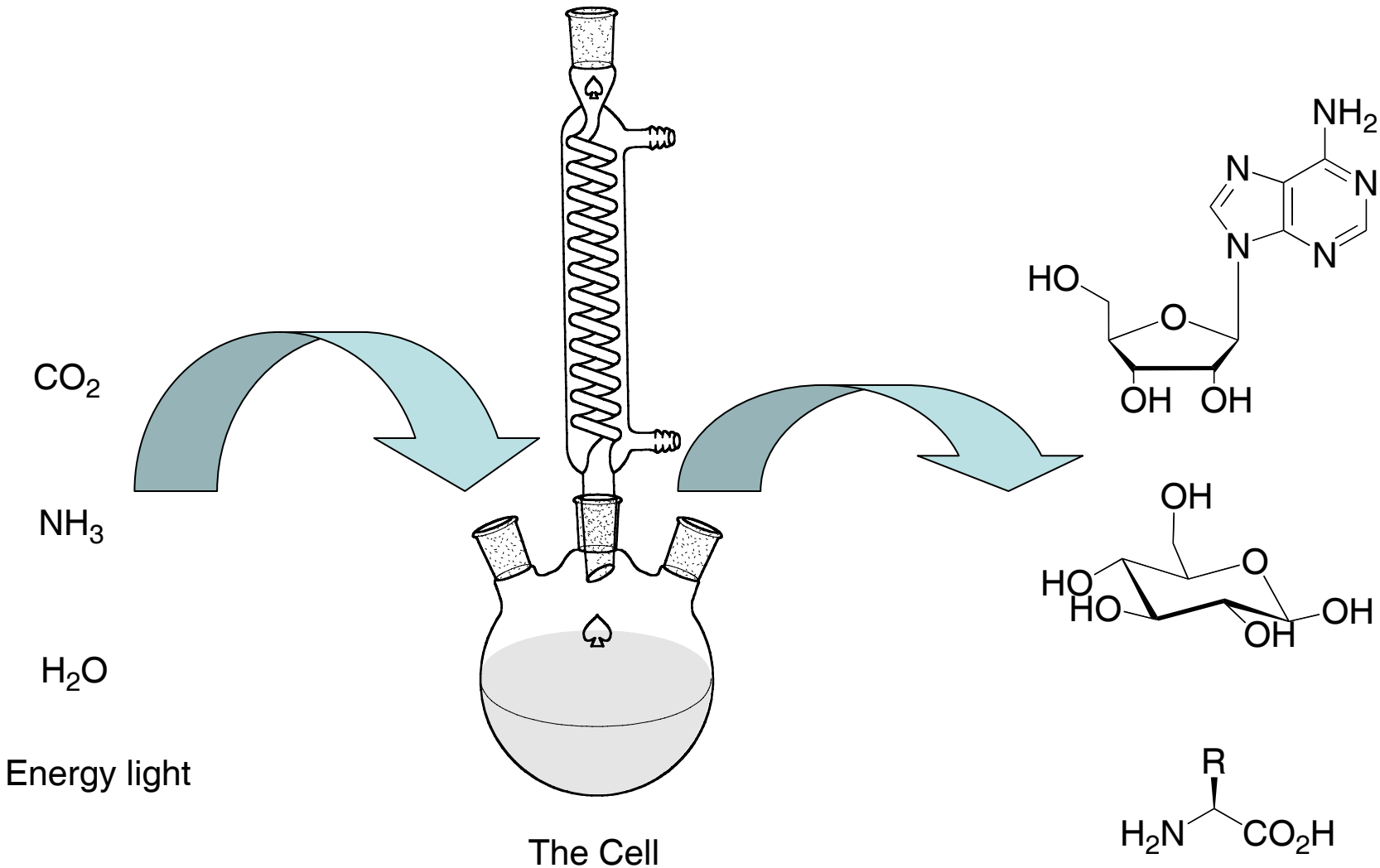
(*S*)-Enantiomer



(*R*)-Enantiomer

The (*S*)-enantiomer is active and the (*R*)-enantiomer is inactive.

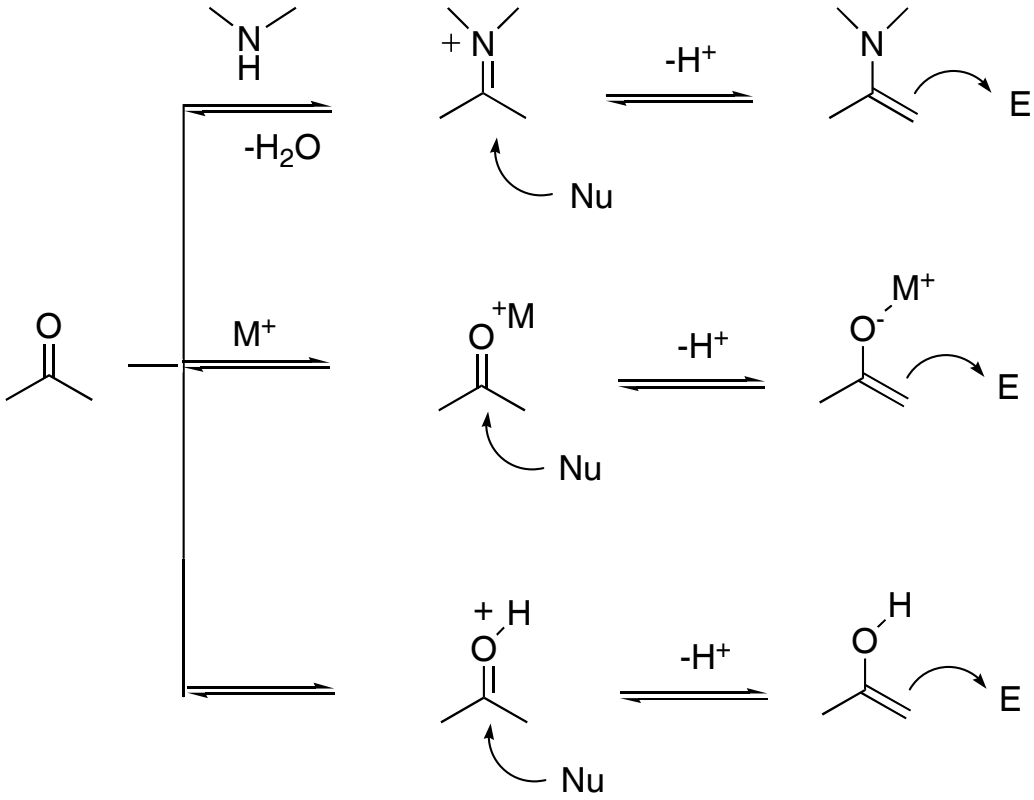
The Biosynthesis



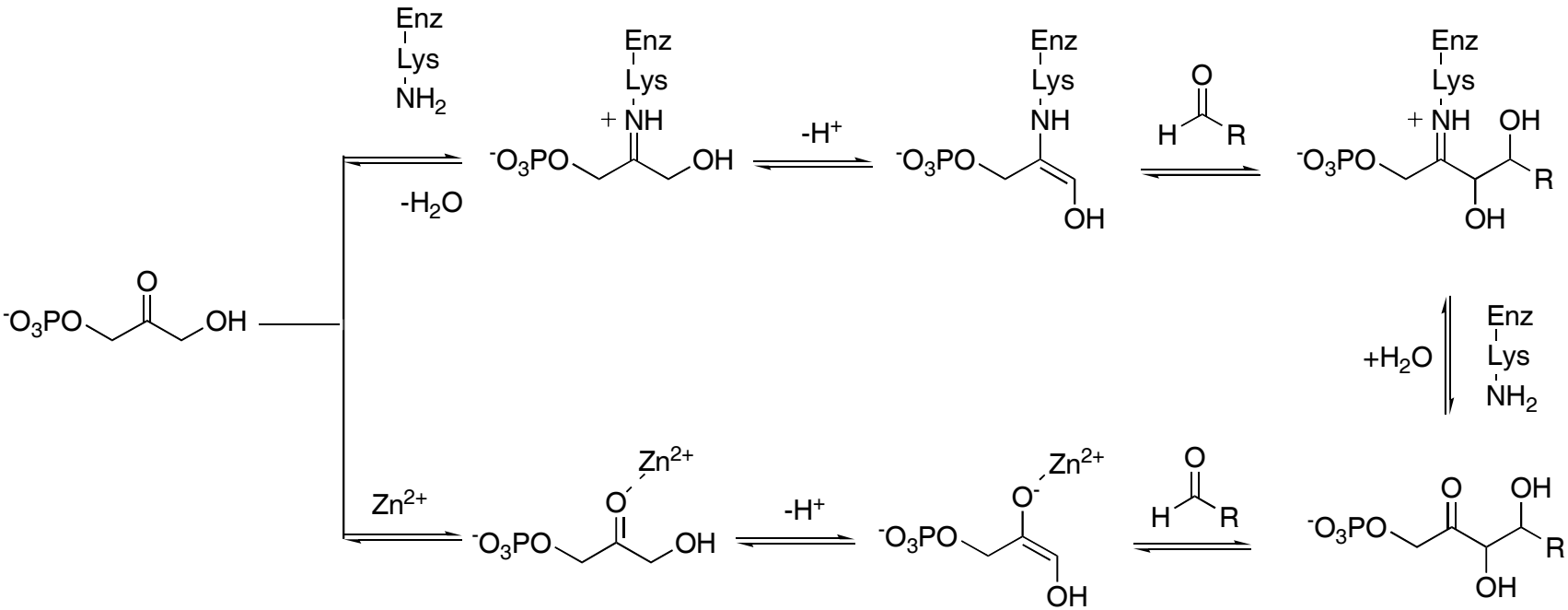
The Cell

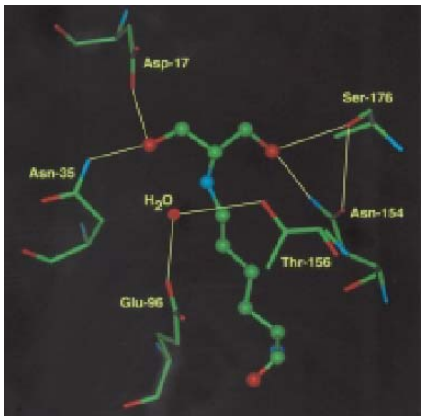
A Machinery and Factory with Enzymes as the Catalysts

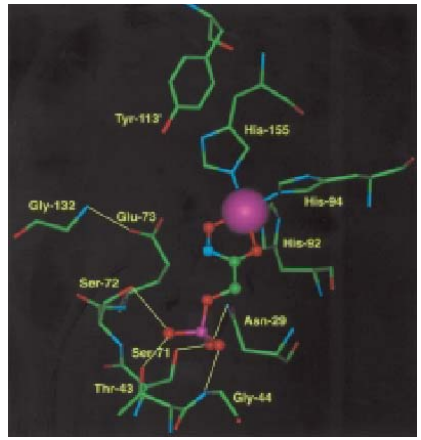
Activation of carbonyl compounds:



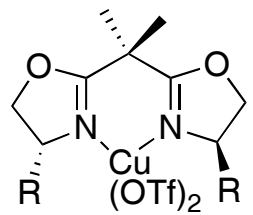
Enzyme catalysis:
Type 1 and Type 2 aldolase enzymes





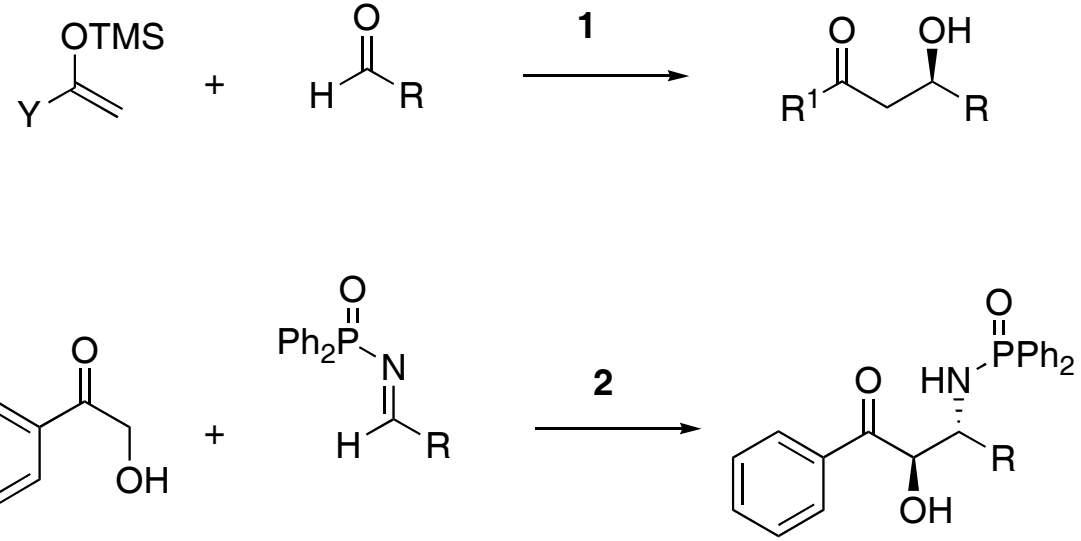


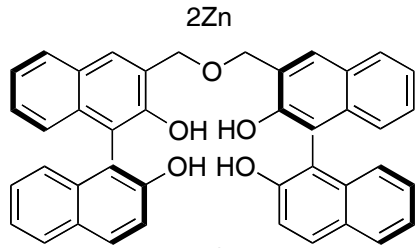
Chiral Organometallic Complexes:



1

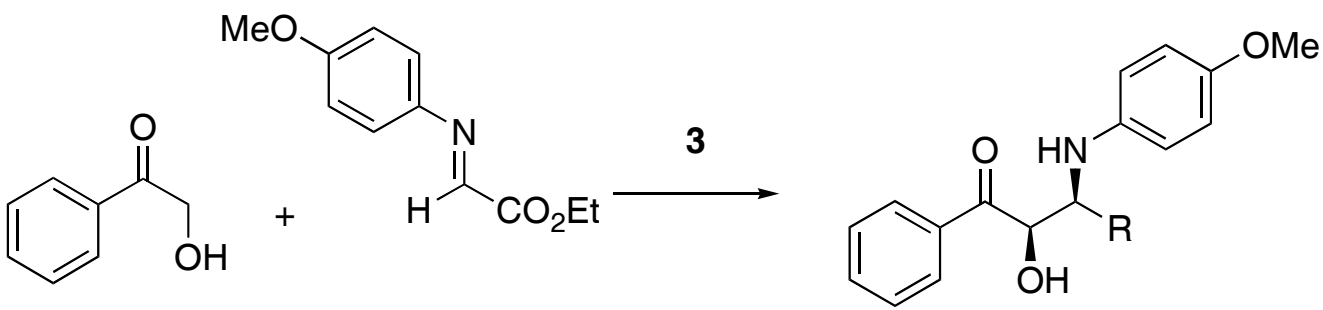
Evans, Jørgensen

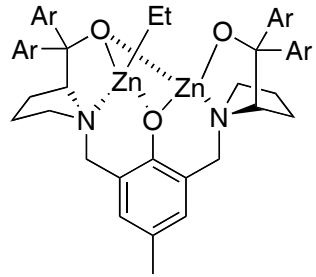




2

Shibasaki

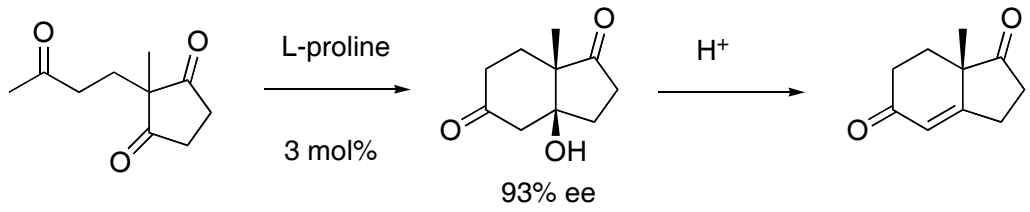




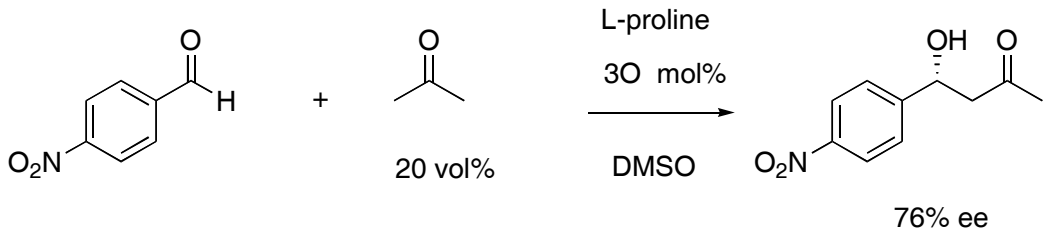
3

Trost

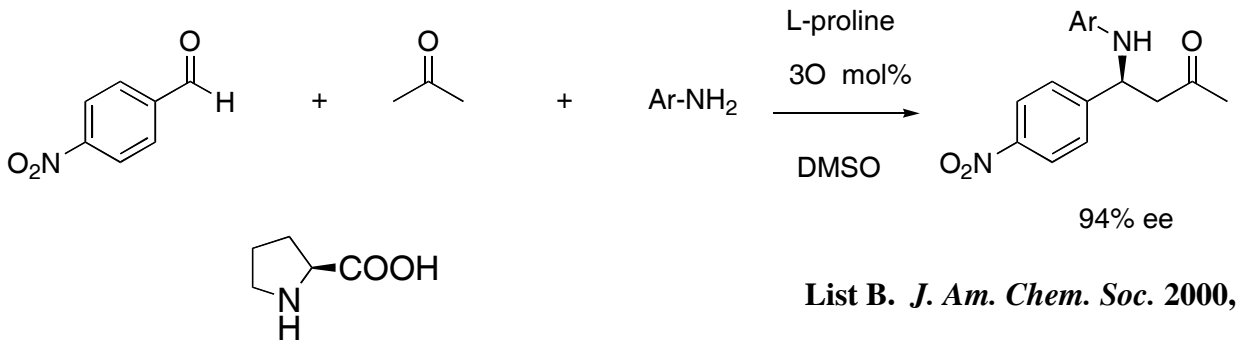
Enamine Catalysis:



Hajos Z. G. and Parrich, D. R. *J. Org. Chem.* 1974, *39*, 1615.
Eder, U. et al. *Angew. Chem. Int. Ed.* 1971, *10*, 496.

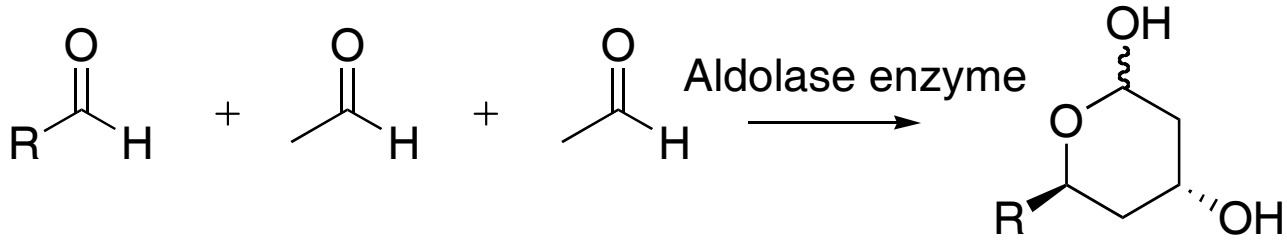


List B. et al. *J. Am. Chem. Soc.* 2000, *122*, 2395.

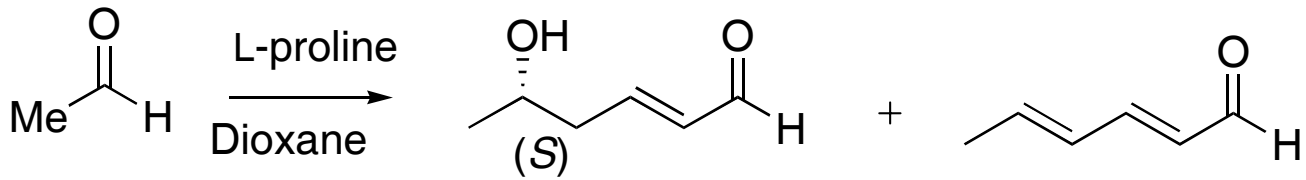


List B. *J. Am. Chem. Soc.* 2000, *122*, 9336..

One-step asymmetric synthesis of 5-hydroxy-(2E)-hexenal.



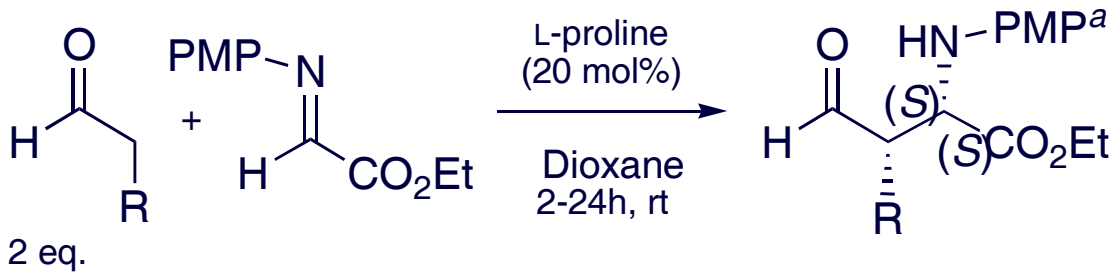
Gijsen, H. and Wong, C.-H. *J. Am. Chem. Soc.* 1994,*116*, 8422.



82% ee

Córdova, A et al. *J. Org. Chem.* 2002

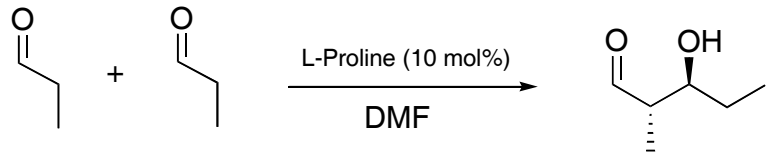
Amino acid-catalyzed asymmetric synthesis of amino acid derivatives.



57-81% yield, up to >19:1 dr and 93->99% ee

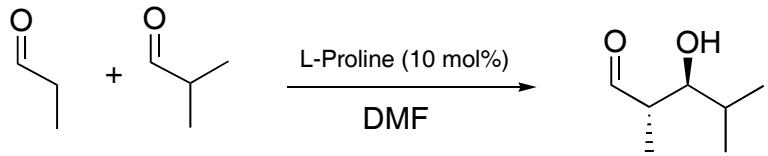
Córdova, A. et al. *J. Am. Chem. Soc.* 2002, *124*, 1866

L-Proline Catalyzed Cross-Aldol Reactions of Aldehydes



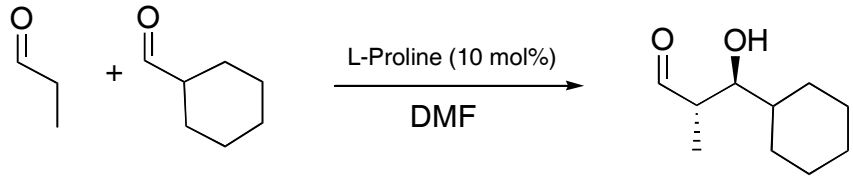
anti

dr = 4:1, ee = 99%



anti

dr = 24:1, ee = >99%

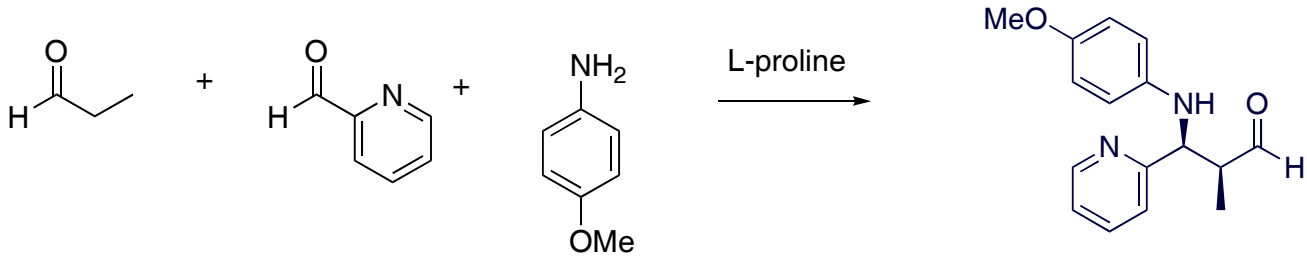


anti

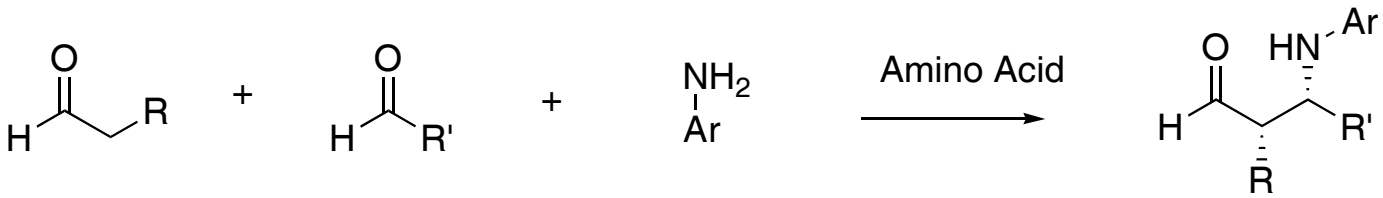
dr = 14:1, ee = 99%

Northrup & MacMillan *J. Am. Chem. Soc* 2002

One-pot three-component direct catalytic asymmetric Mannich reactions.



82% yield, dr > 19:1, >99% ee



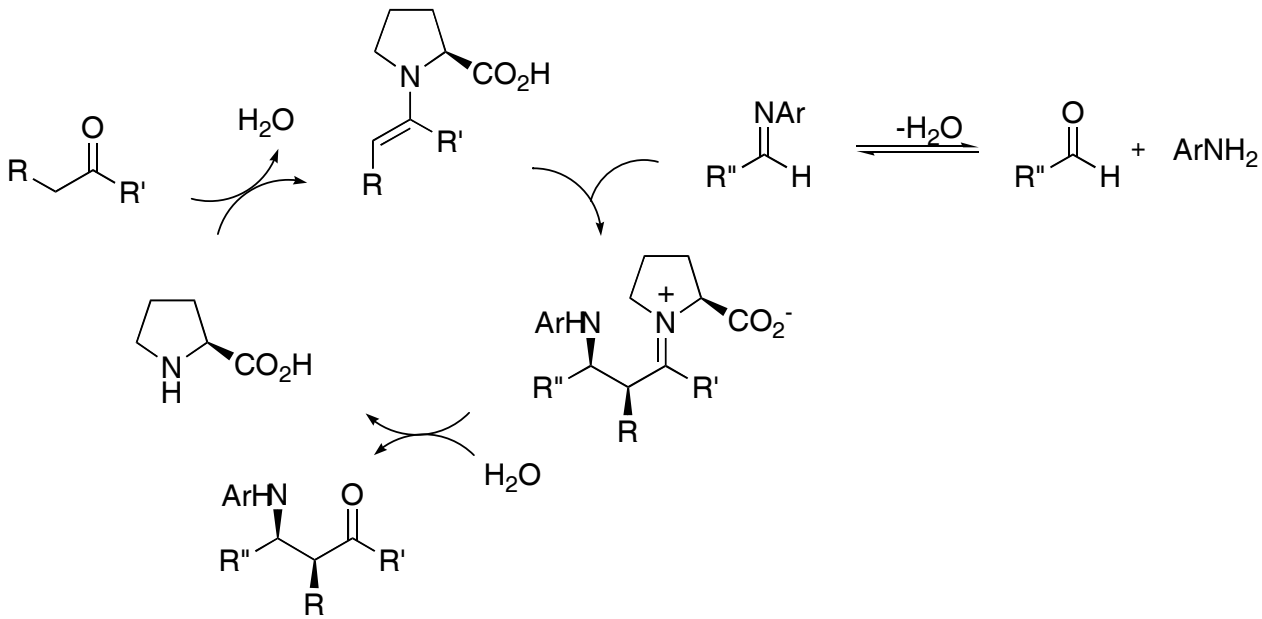
Yield up to 99%, >99% ee

R = Me, Alkyl; R' = Ar, Et, Alkyl, COOEt

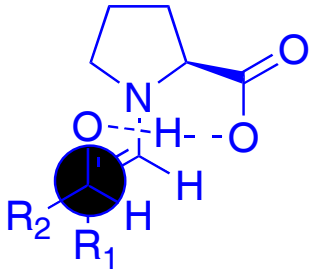
Córdova, A. ***Synlett*** **2003**

Córdova, A. *Chem. Eur. J.* **2004**

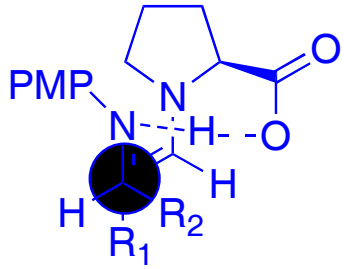
Mechanism


R
O
R'
H2O
N
CO2H
R'
R
NAr
R"
H
-H2O
O
R"
H
+
ArNH2
+
N
CO2-
ArHN
R"
R'
R
N
H
CO2H
H2O
ArHN
O
R"
R'
R

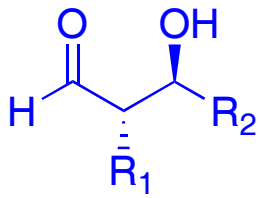
Plausible Transition States

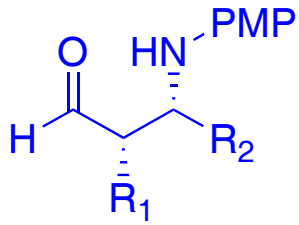


I

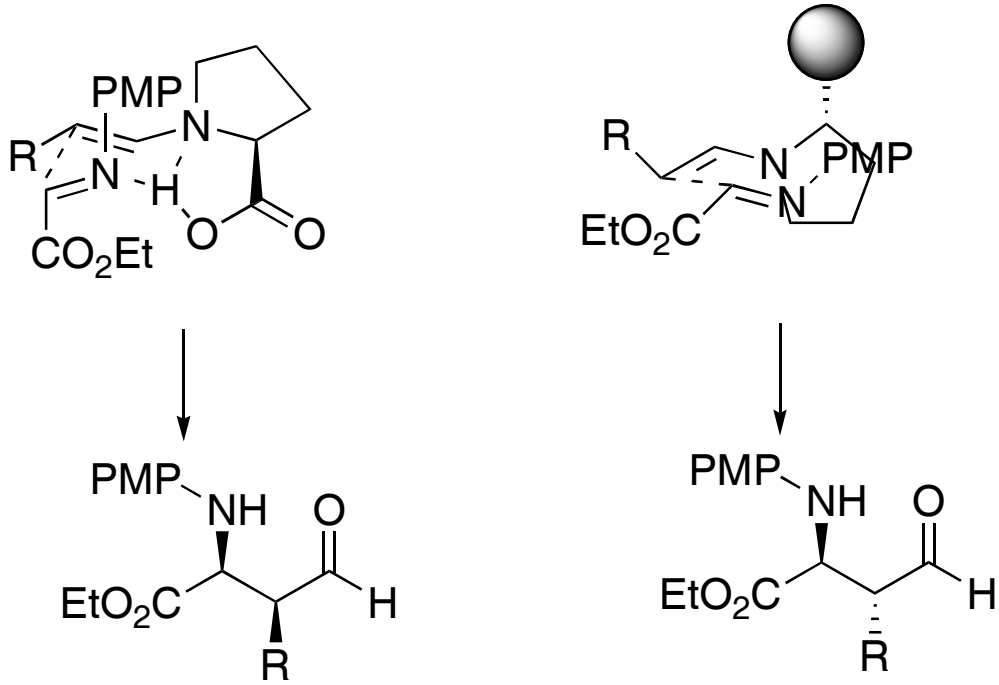


II

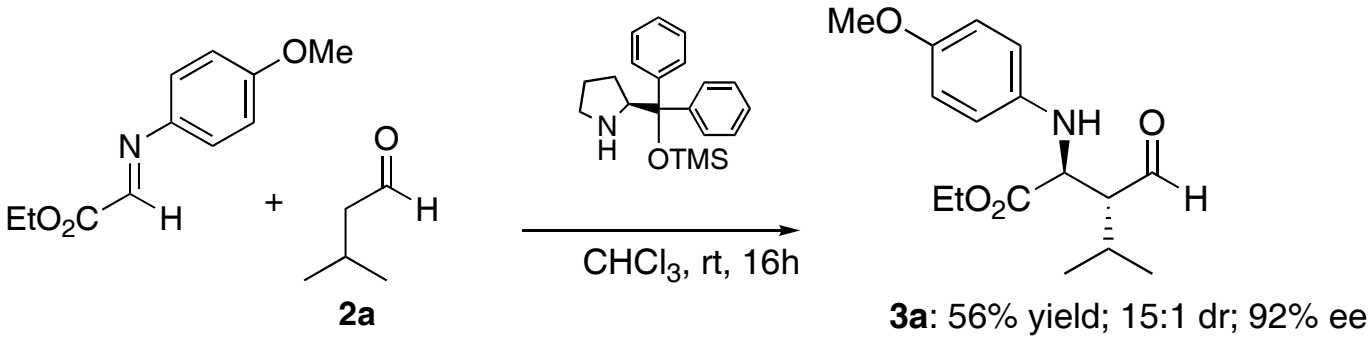


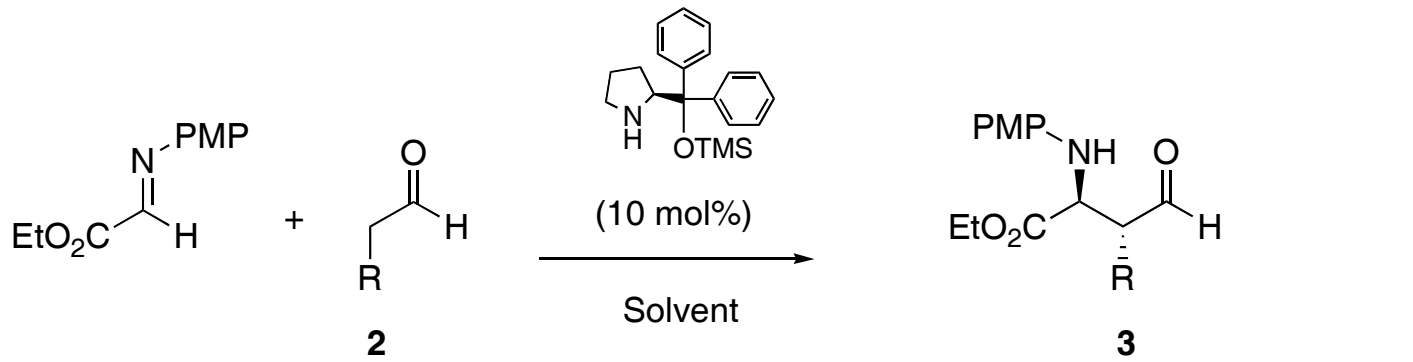


Development of *anti*-selective Mannich-type reactions



Highly *anti*-selective Mannich-type reactions





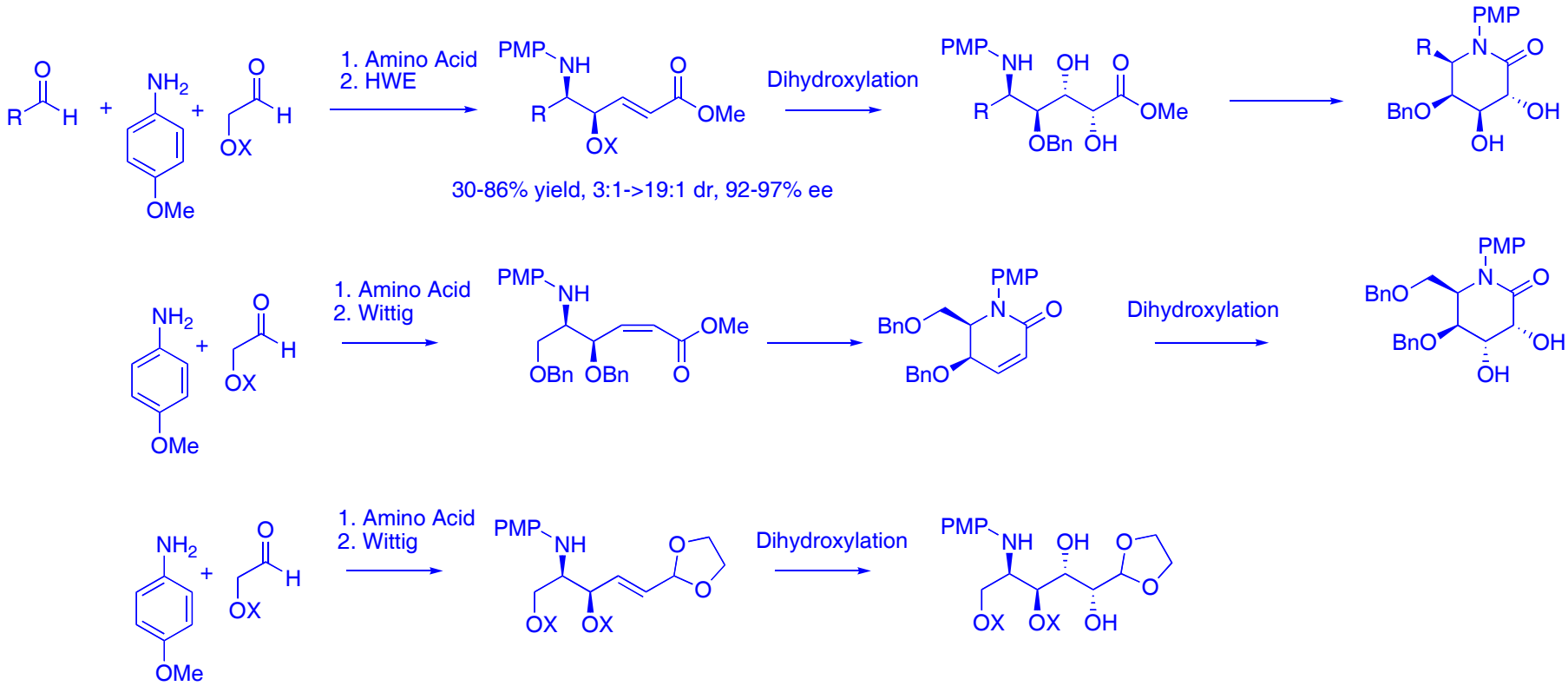
R = R, CH_2OR

45-68% yield, 14.1->19:1 dr, 97-99% ee

Jørgensen and co-worckers *J. Am. Chem. Soc.*

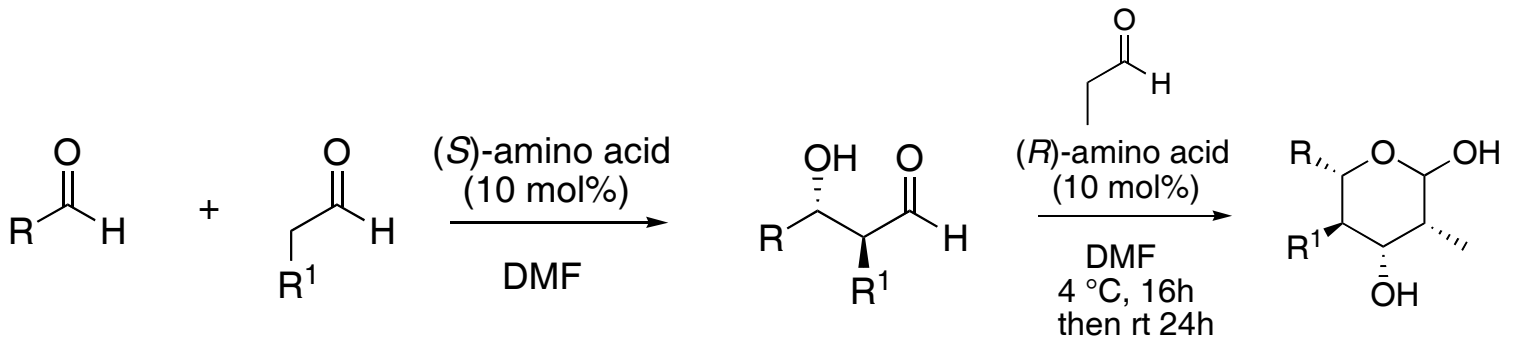
Ibrahem, I. et al. *Chem. Commun.*

A short route to aza-sugars



Liao et al. Chem Commun. 2006, 7023.

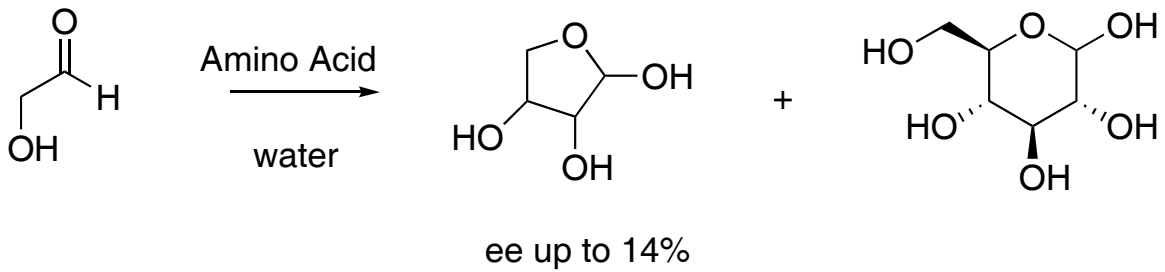
Biomimetic Sugar Synthesis



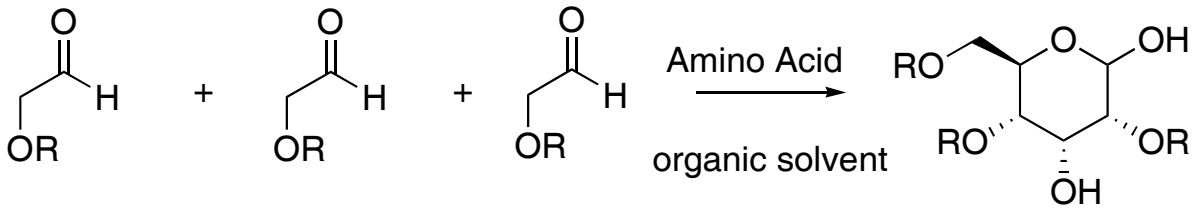
up to >19:1 dr and
>98% ee

Casas et al. Angew. Chem. Int. Ed. **2005**

Natural amino acids catalyze the asymmetric neogenesis of sugars



ee up to 14%

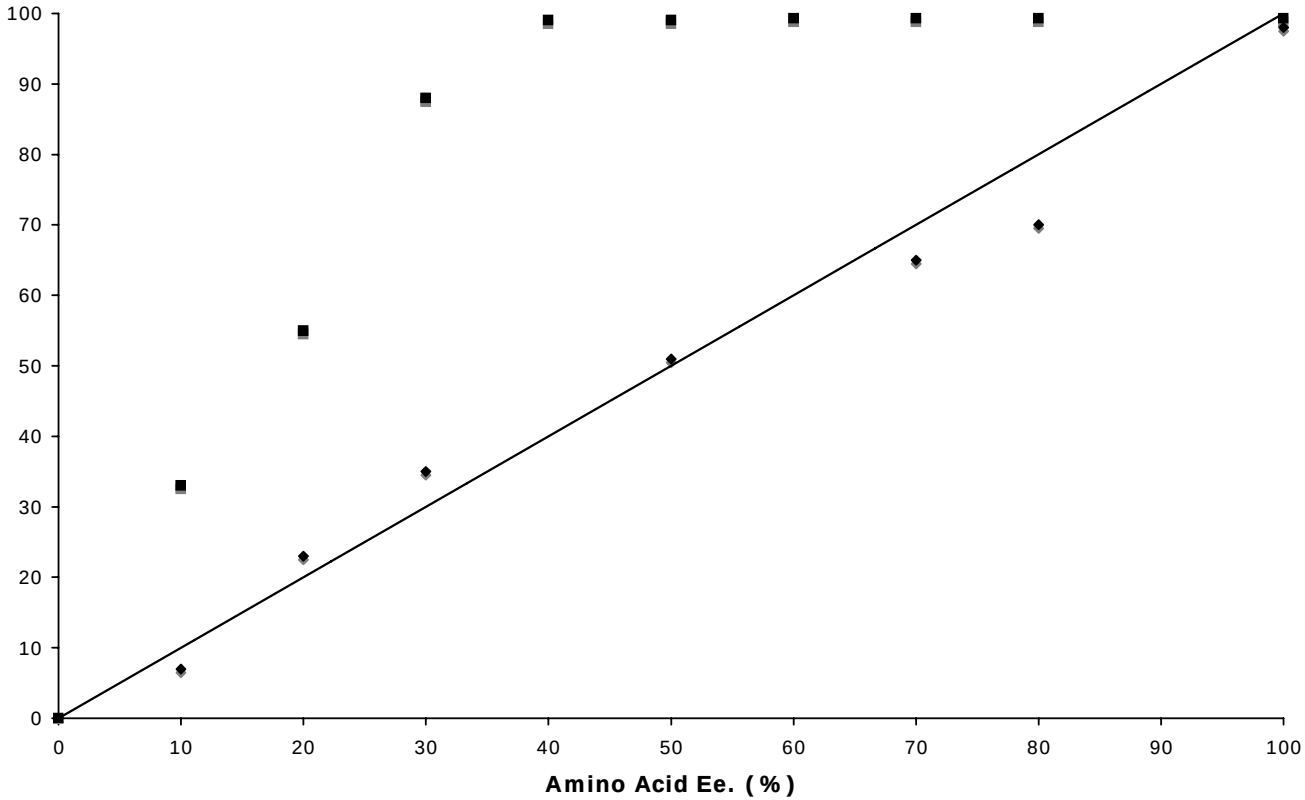


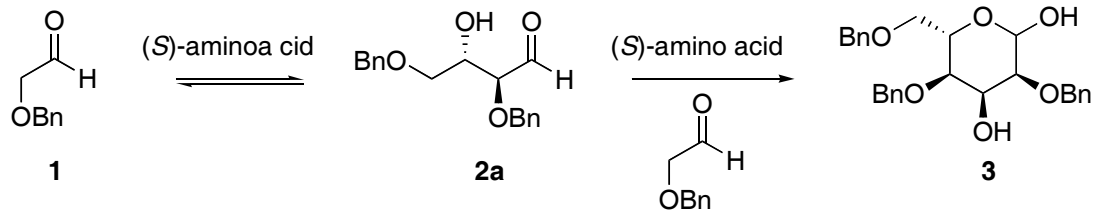
R = Bn

up to >99% ee

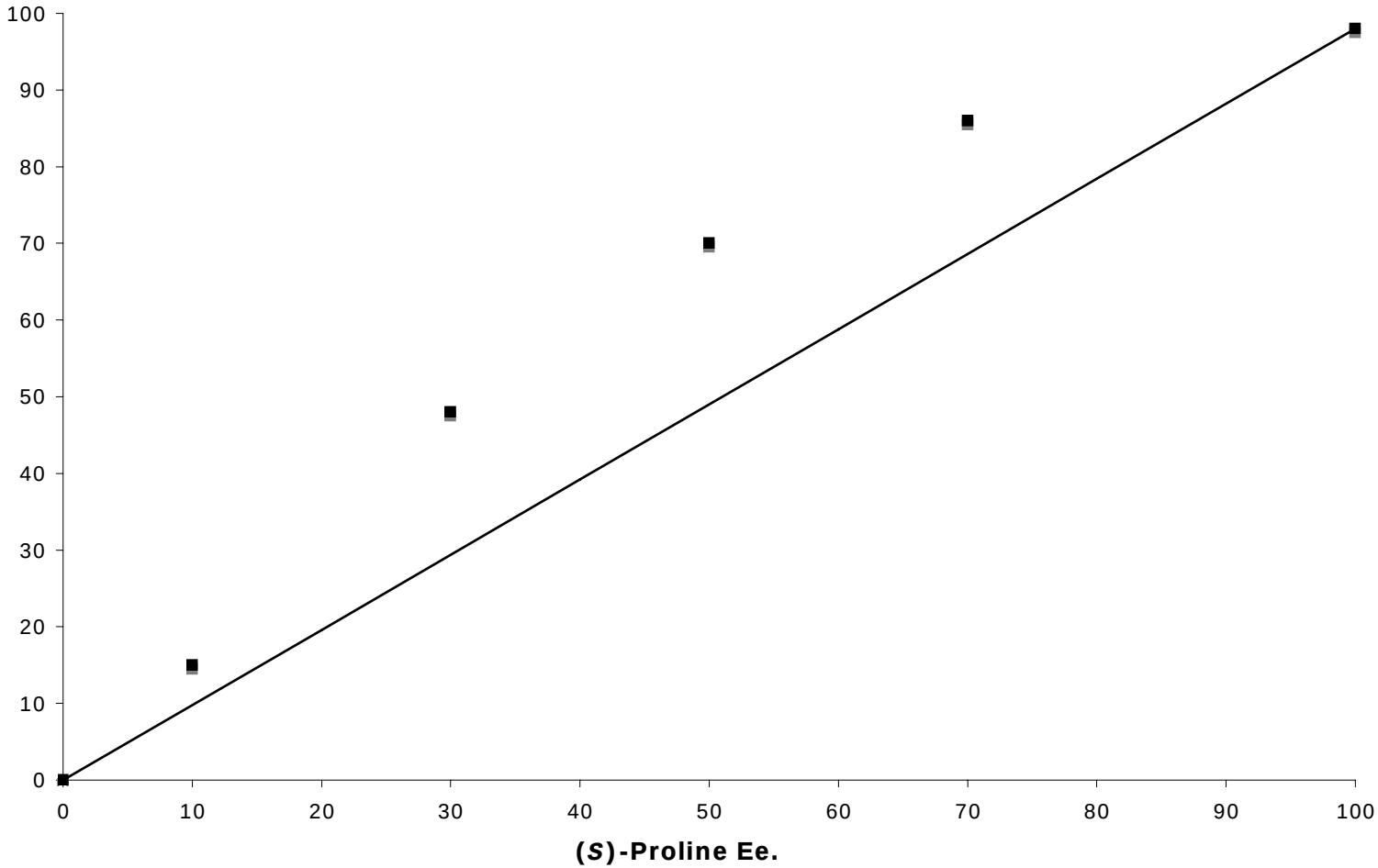
Casas, J. et al. *Angew. Chem. Int. Ed.* 2005, 44, 1343.
Córdova, A. et al. *Chem Eur. J.* 2005, *11*, 4772.

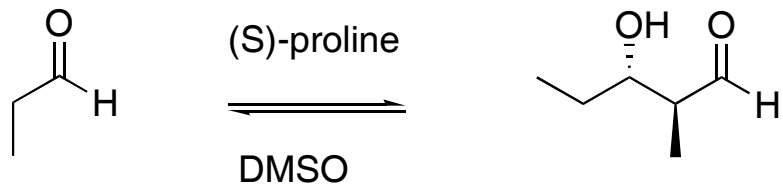
Evolution of homochirality?

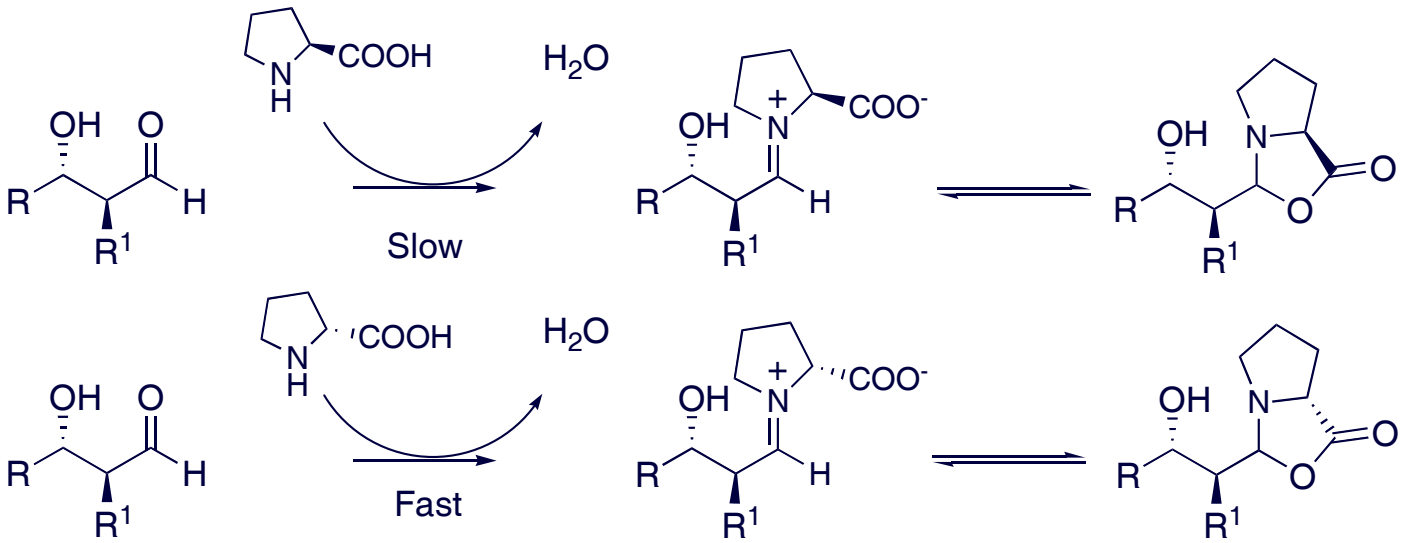




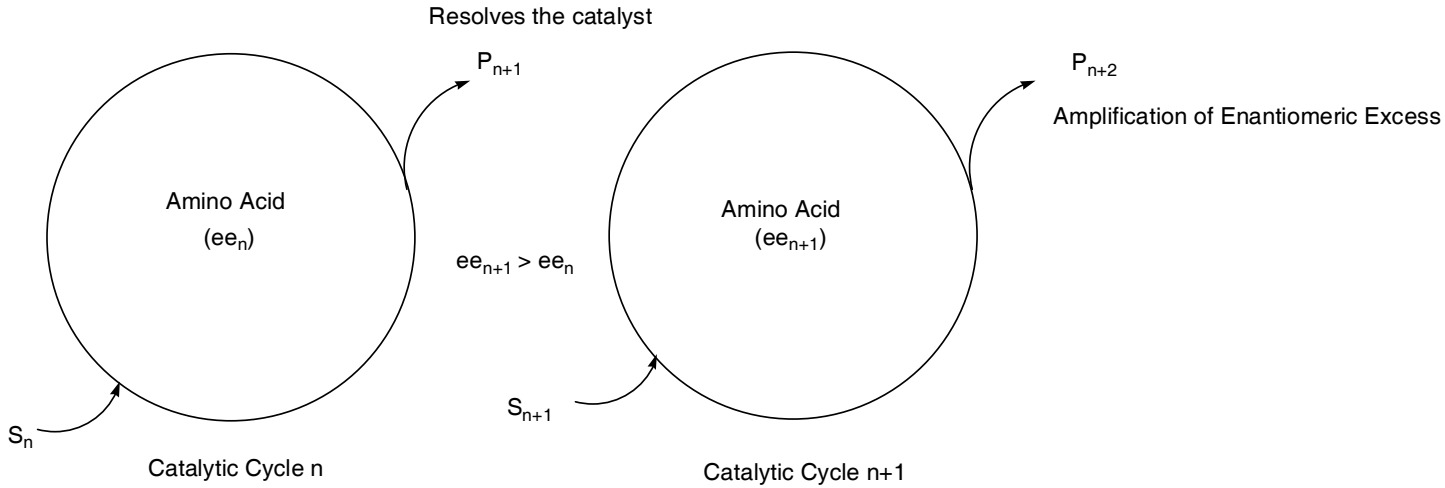
Córdova et al. Chem Commun, 2005, 2047


100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
(S)-Proline Ee.

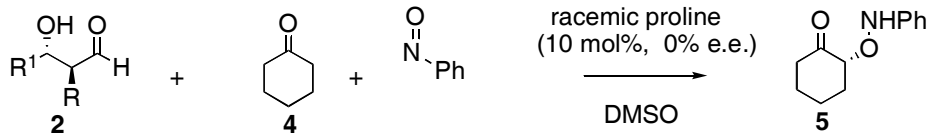

O
H
(S)-proline
DMSO
OH
O
H

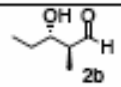
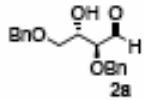
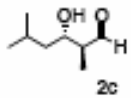
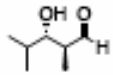
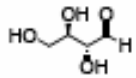
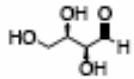
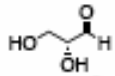

OH
O
R
H
R1
N
H
COOH
H2O
Slow
+
N
COO-
OH
R
H
R1
N
O
O
R
R1
OH
O
R
H
R1
N
H
COOH
H2O
Fast
+
N
COO-
OH
R
H
R1
N
O
O
R
R1

Alternative model to autocatalysis

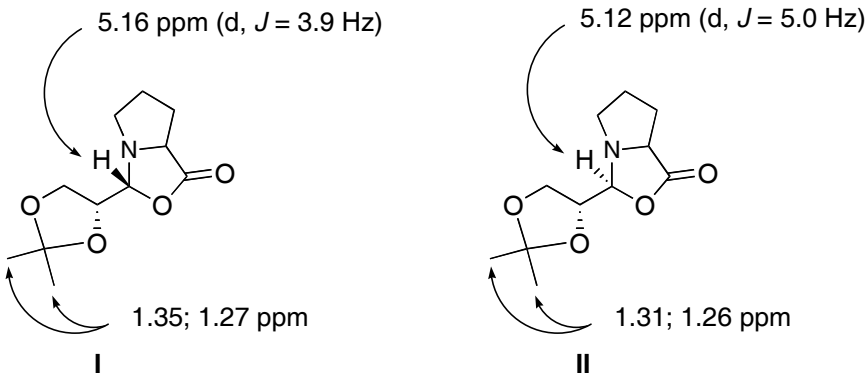


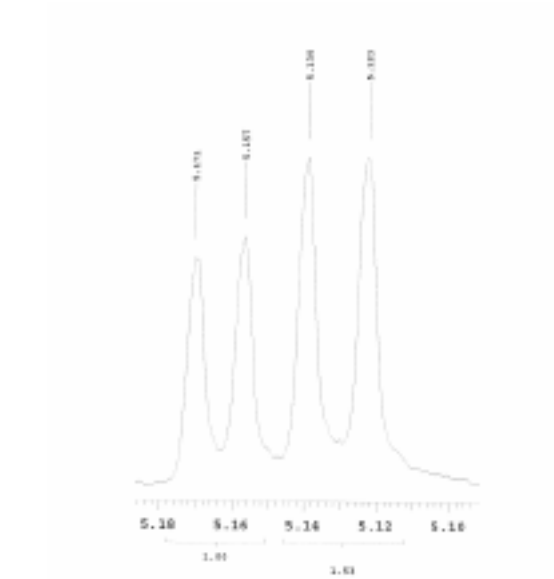
Córdova et al.Chem. Eur. J., 2006,12, 5446..



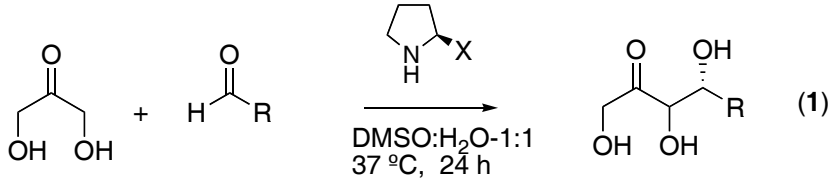
Entry	Sugar	Dr[a]	Ee (%)[b]	Product	Yield (%)[c]	Ee (%)[d]
1	 2b	4:1	98	**5**	57	27
2	**2b**	4:1	98	**5**	51[e]	66[e]
3	 2a	4:1	99	**5**	26	5
4	 2c	4:1	>99	**5**	48	10
5	 2d	>19:1	>99	**5**	55	27
6	 *ent*-2e	>19:1	>99	**5**	45[f]	-5
7	 *ent*-2f	>19:1	>99	**5**	24[f]	-2
8	 2g		>98	**5**	47	7

Formation of oxazolidinones



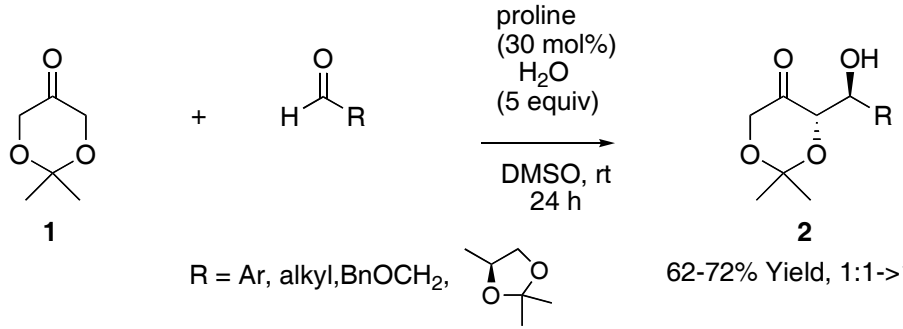


Proline-catalyzed de novo synthesis of C-4 to C-6 ketoses

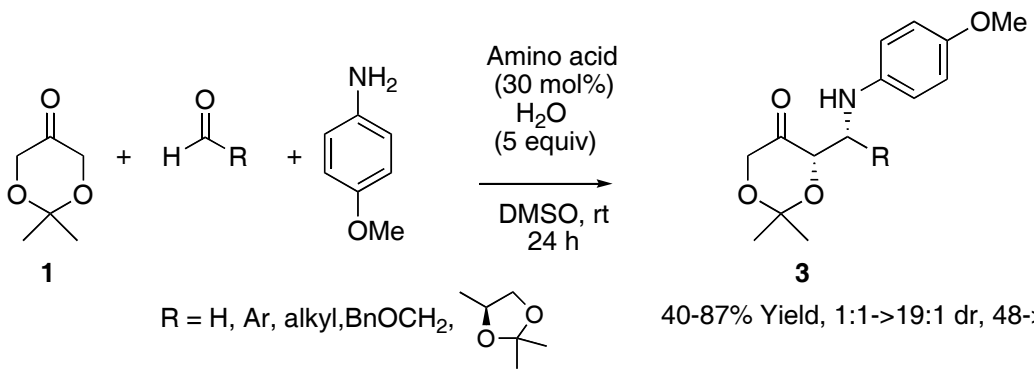


20-95% yield, <10% ee

Córdova, A. et al. *Chem Commun.* 2002



62-72% Yield, 1:1->19:1 dr, 93-98% ee

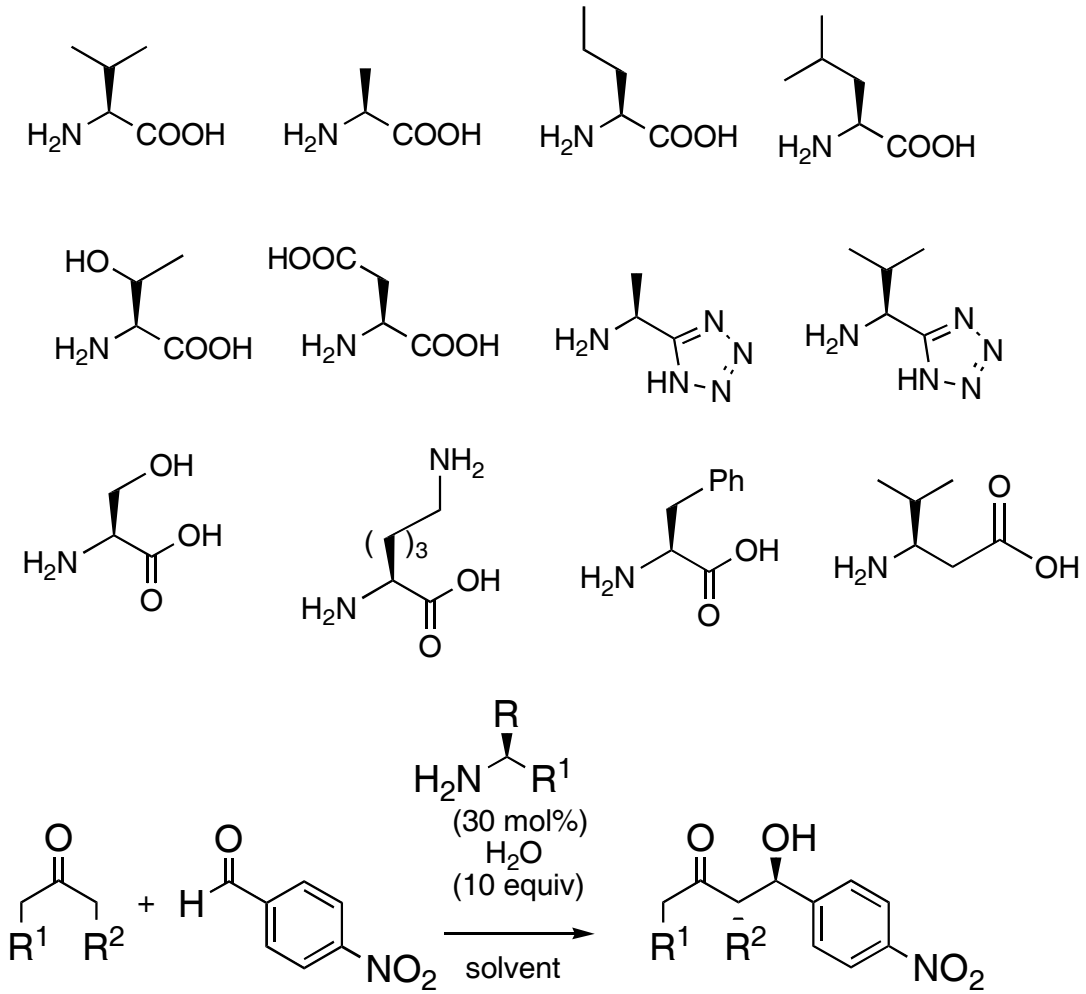


40-87% Yield, 1:1->19:1 dr, 48->99% ee

Enders, Barbas and Westermann

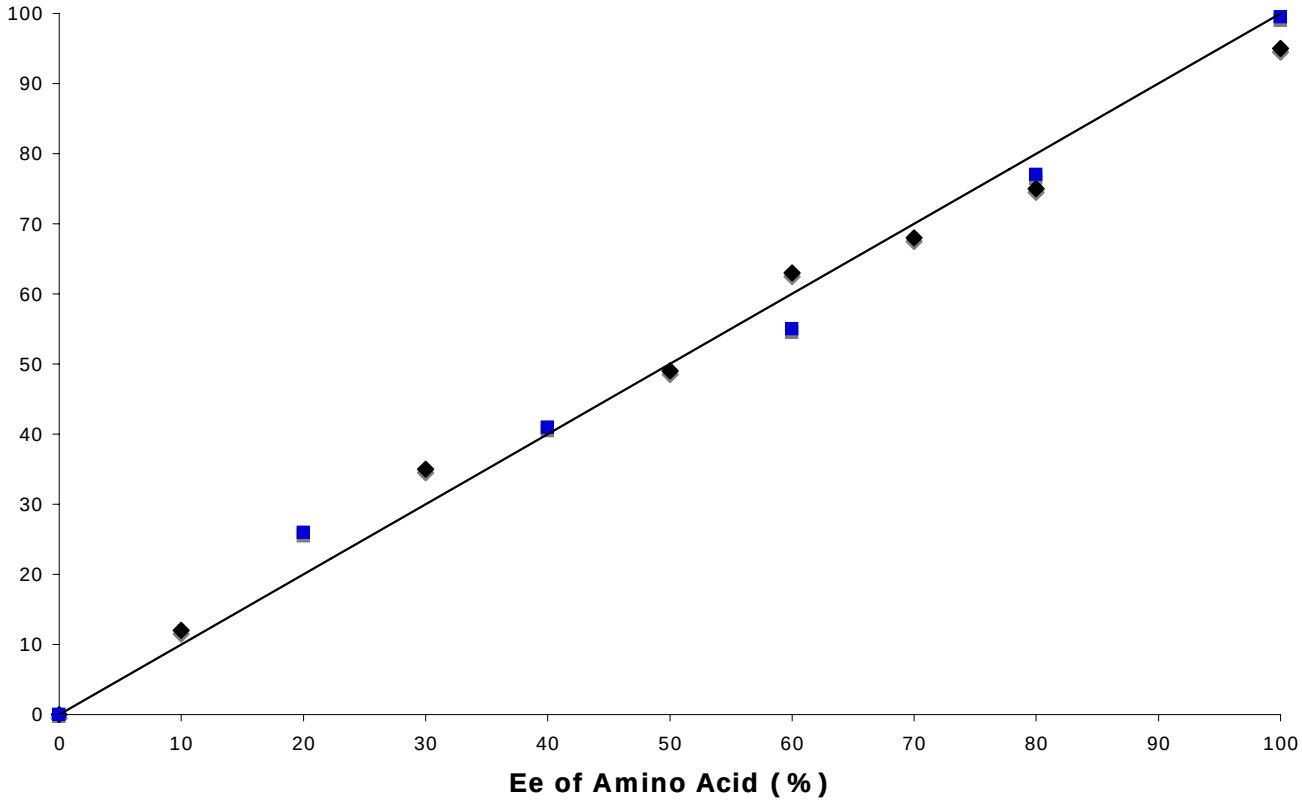
Ibrahem, I. et al. *Tetrahedron Lett* 2005

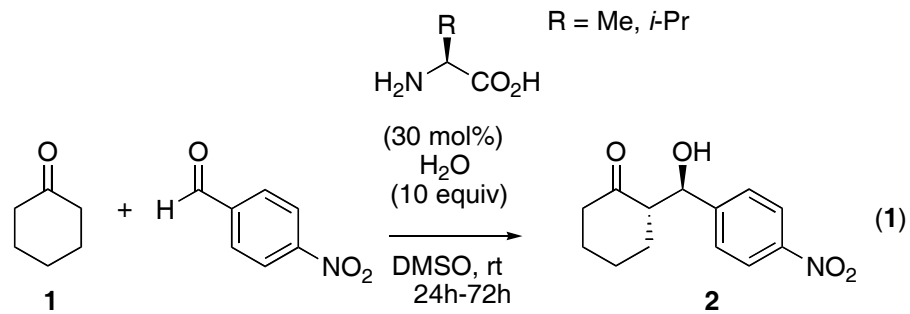
Biomimetic Asymmetric Catalysis



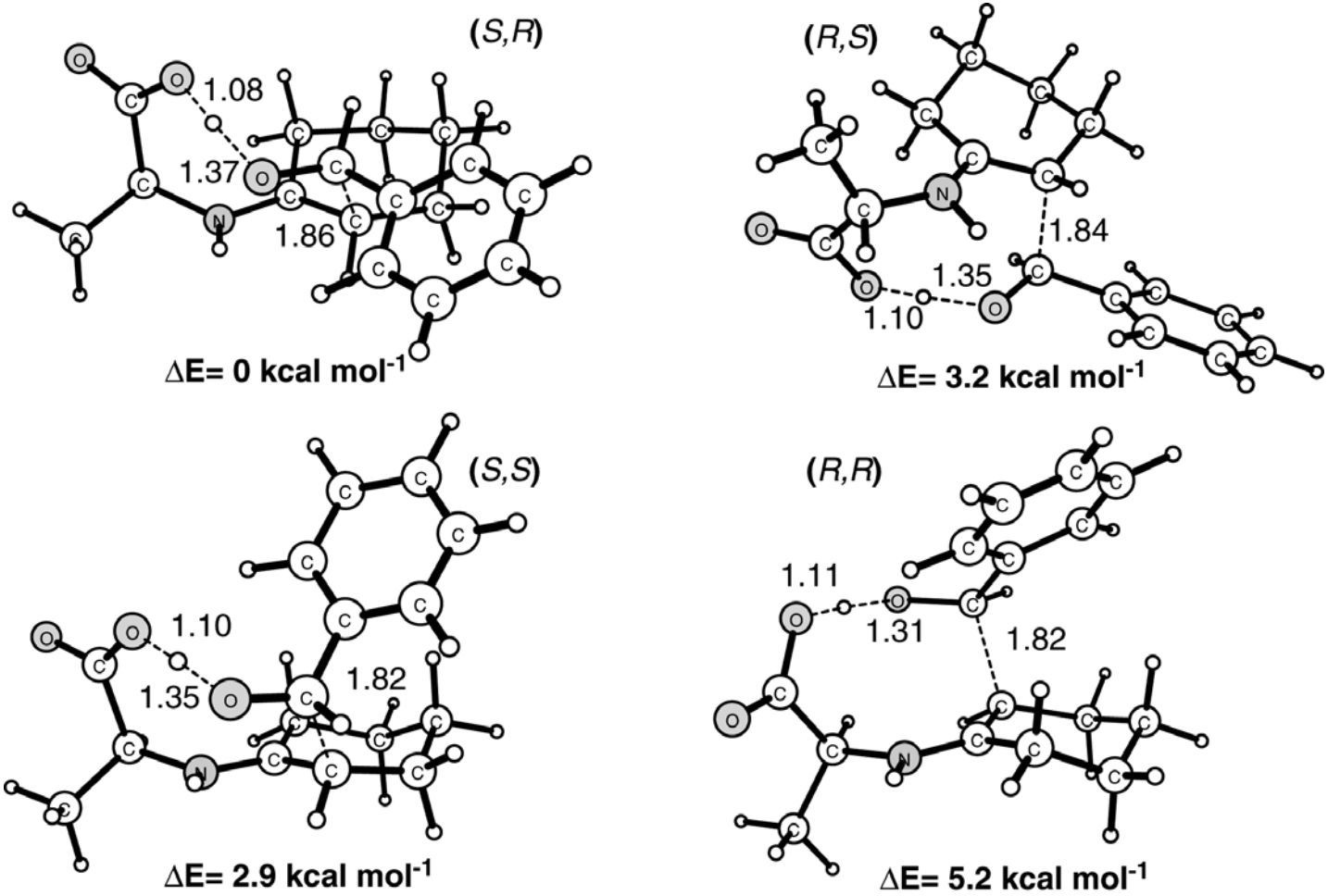
up to 95% yield and >99% ee

Córdova et al. Chem Commun, 2005, 3586.; Zou et. Al. *Chem Commun*, 2005, 4946.; Bassan et al. *Angew. Chem. Int*. Ed. 2005, *44*, 7028

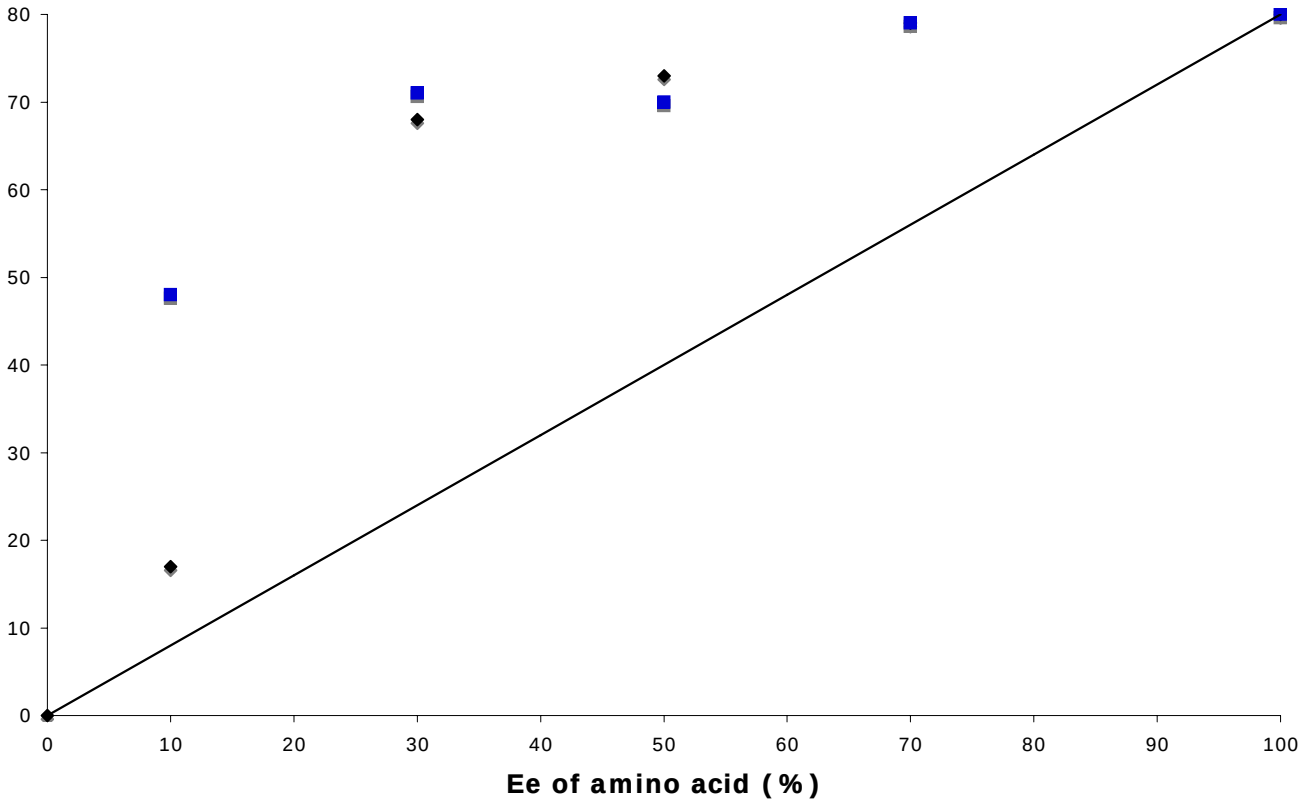

100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Ee of Amino Acid (%)

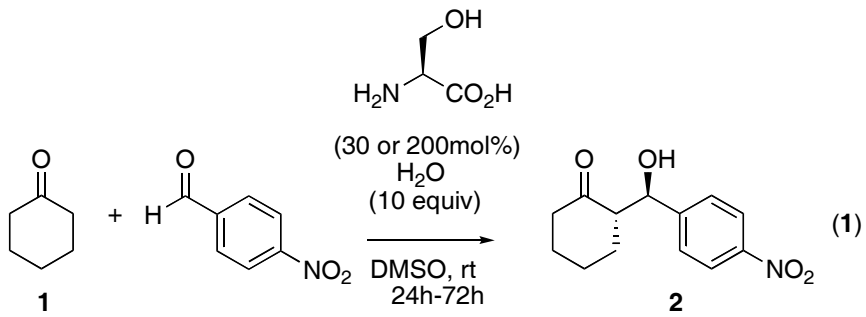

R
H2N
CO2H
R = Me, i-Pr
O
+
H
O
NO2
(30 mol%)
H2O
(10 equiv)
DMSO, rt
24h-72h
O
OH
NO2
1
2
(1)

Origins of stereoselectivity for the acyclic amino acid catalyzed aldol reactions



Bassan, A et al. ***Angew. Chem.*** **2005,** ***44*****, 7028.**

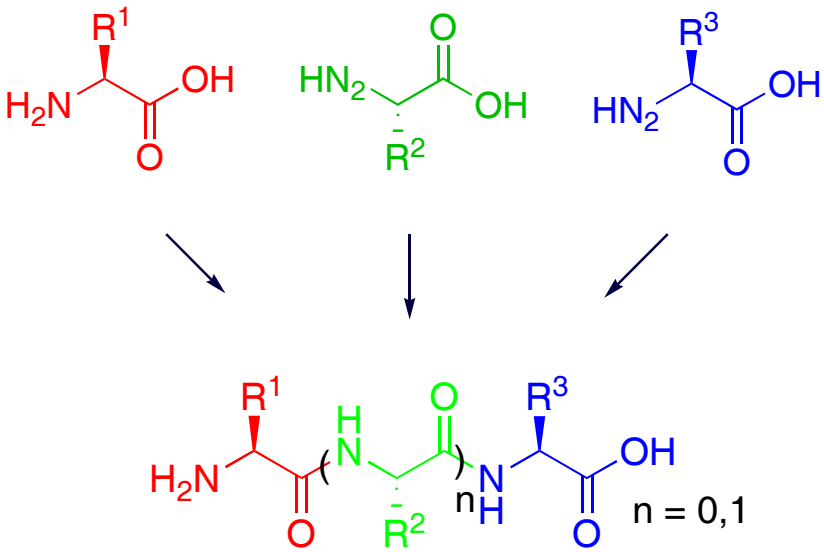


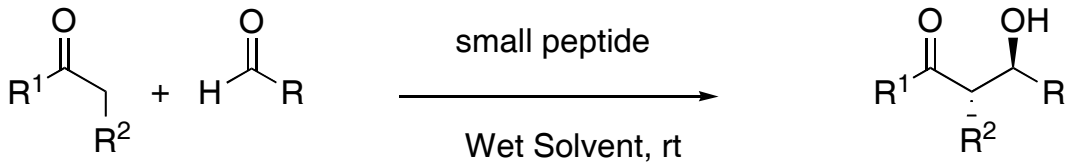


Córdova et al. Chem Eur. J., 2006.

Blackmond and co-workers, Nature 2006

Small modular peptides as catalysts for the asymmetric aldol reaction

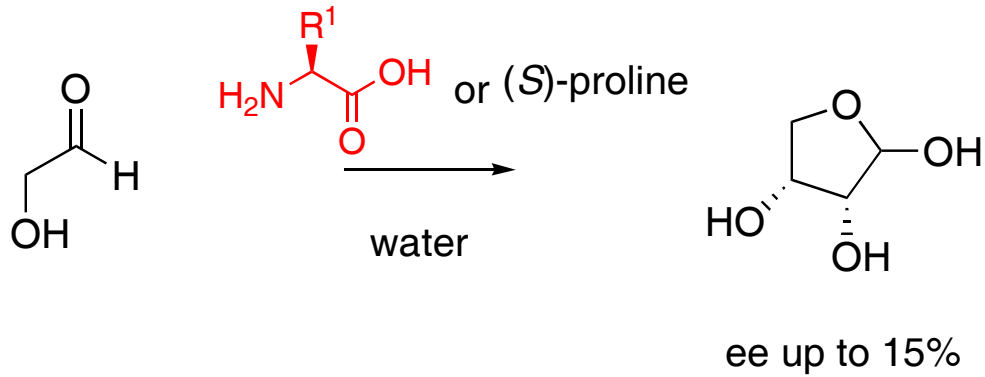




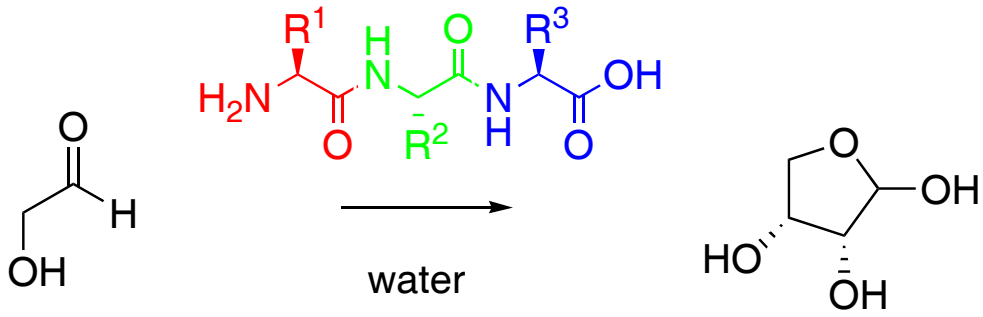
up to 90% yield, up to 10:1 dr and 99% ee

Zou, W. et al. *Chem. Commun.*2005 4946.
Diedzic P. Et al. *Org. Biomol. Chem.* 2006, *149*

Small peptides can achieve high stereoselectivity in water.

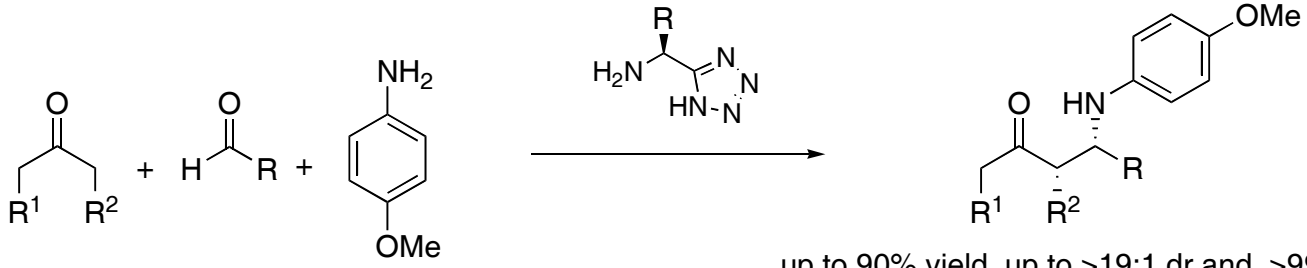


ee up to 15%

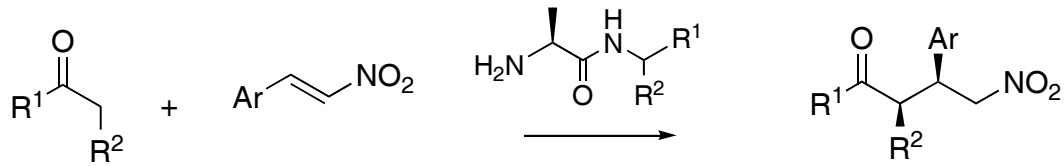


ee up to 88%

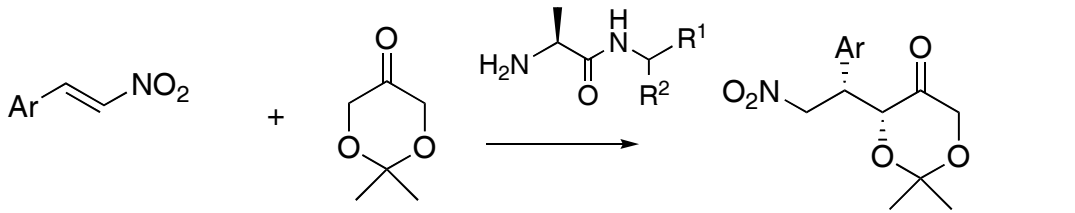
Córdova et al. Chem Eur. J., 2006. Zou, W. et al. *Chem. Commun.*2005.



up to 90% yield, up to >19:1 dr and >99% ee



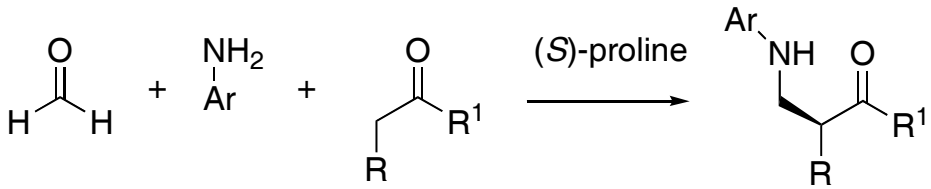
62-90% yield, up to >34:1 dr and >99% ee



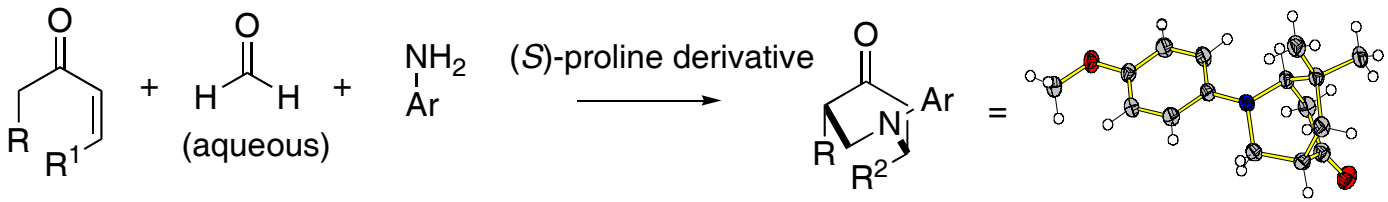
up to >34:1 dr and 99% ee

Xu et al. Chem Commun, 2006; Xu et. Al. *Adv. Synth. Cat*, 2006;
Ibrahem et al. *Chem. Eur. J*. 2005

Catalytic Asymmetric α-aminomethylation of ketones and aza-Diels Alder reactions



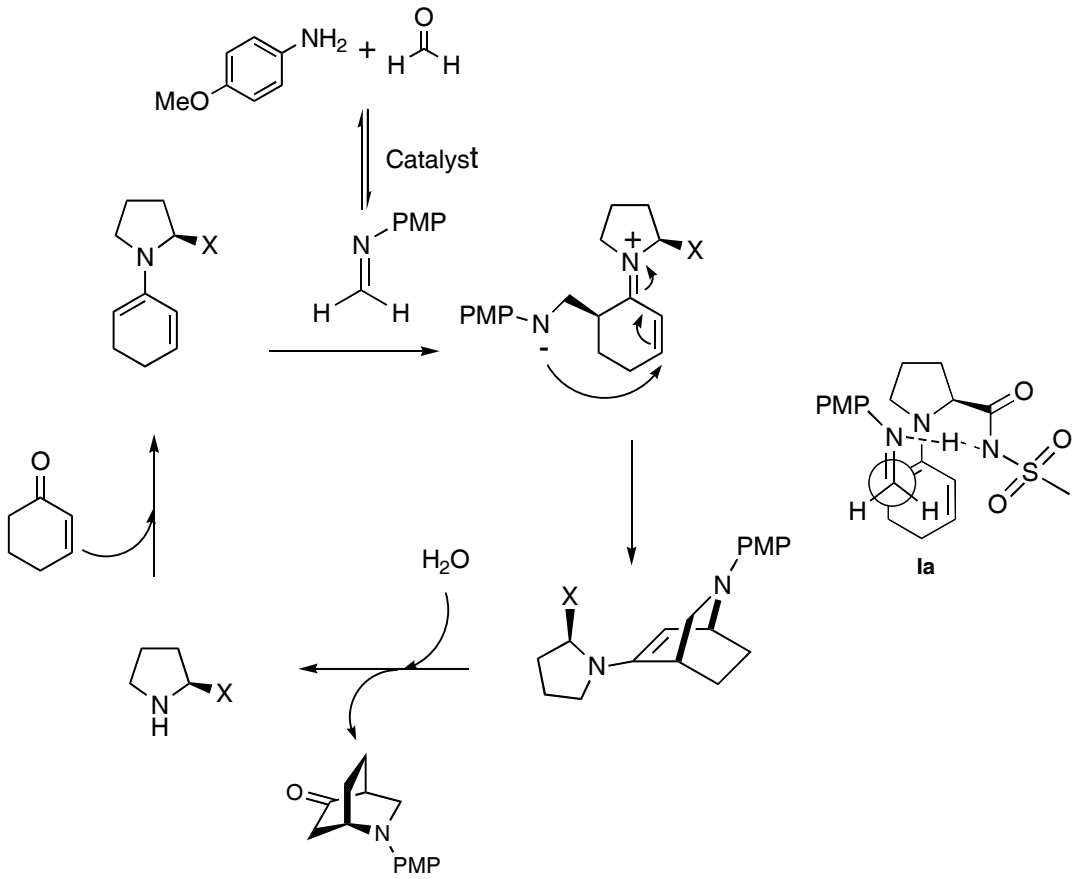
up to >99% ee



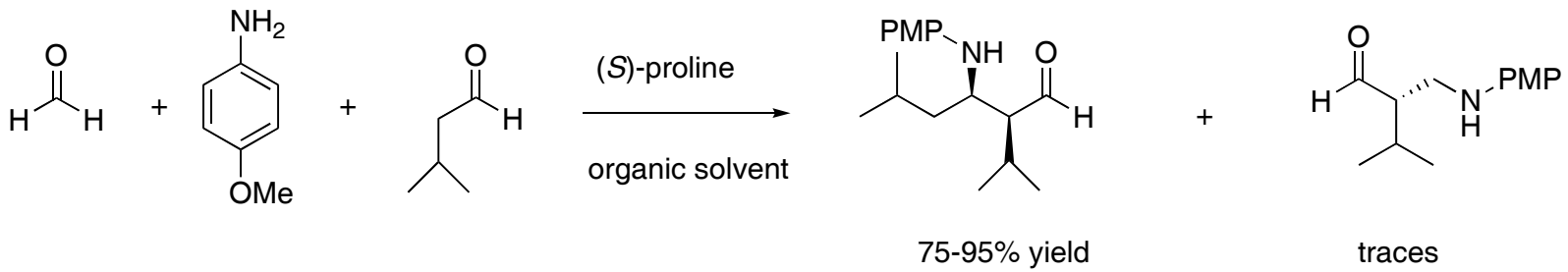
up to 90% yield, up to >99% ee

Ibrahem et al. Angew. Chem. Int. Ed. 2004, *43*, 6528.; Sundén et al. *Angew. Chem. Int*. Ed. 2005, *44*, 4877.

Domino Mannich/Michael reaction pathway

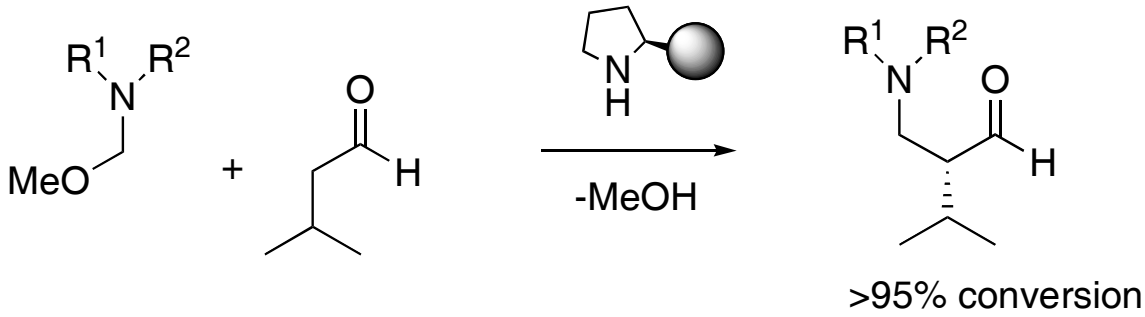


Direct catalytic α-aminomethylation of aldehydes

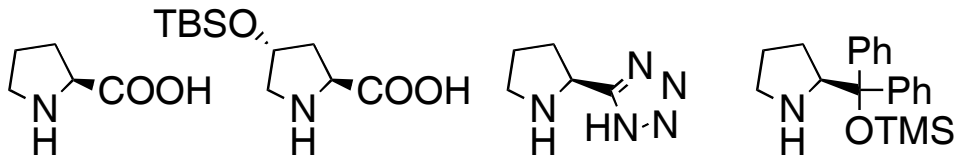


Ibrahem et al. Tetrahedron. 2005

Screened a series of catalysts and aminomethyl ethers.

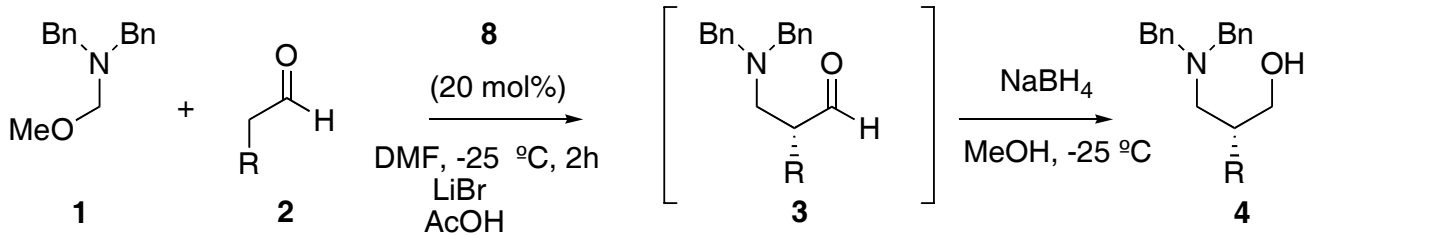


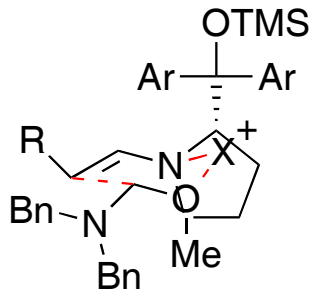
>95% conversion



(-66% ee) (-55% ee) (-18% ee) (96% ee)

Catalytic enantioselective α-aminomethylation of aldehydes





Gellman et al. J. Am. Chem. Soc. 2006

Ibrahem et al. Chem Eur. J. 2006

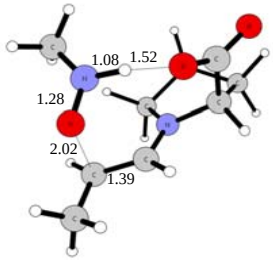
Amino Acid-Catalyzed Direct Catalytic Enantioselective α-Aminooxylation of Carbonyl Compounds

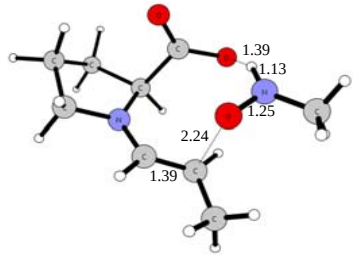
R = H or R'

up to 99% yield, >99% ee

Yamamoto, Zhong, Macmillan and Hayashi

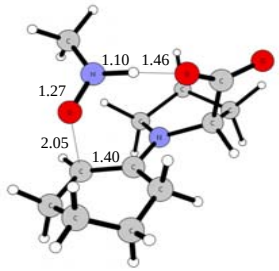
Bøgevig, A. et al. ***Angew. Chem. Int. Ed.*** **2004,** ***43*****, 1109 .**
Córdova, A. *Chem. Eur. J.* **2004.** *124*, 3673.

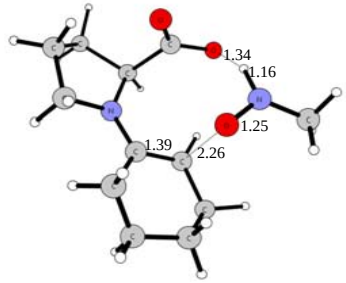




ΔΔG = 6.6 kcal/mol

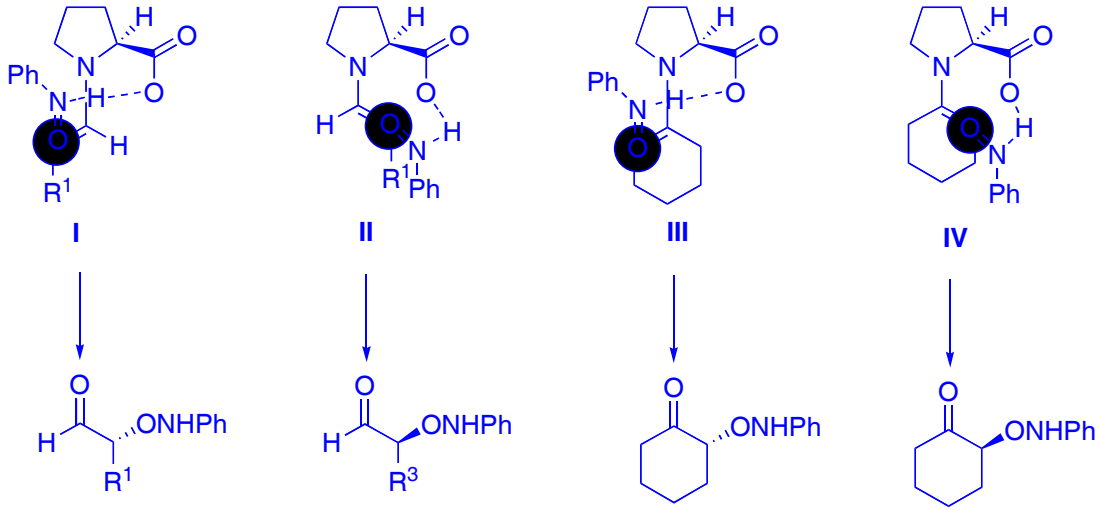
TS-I **TS-II**





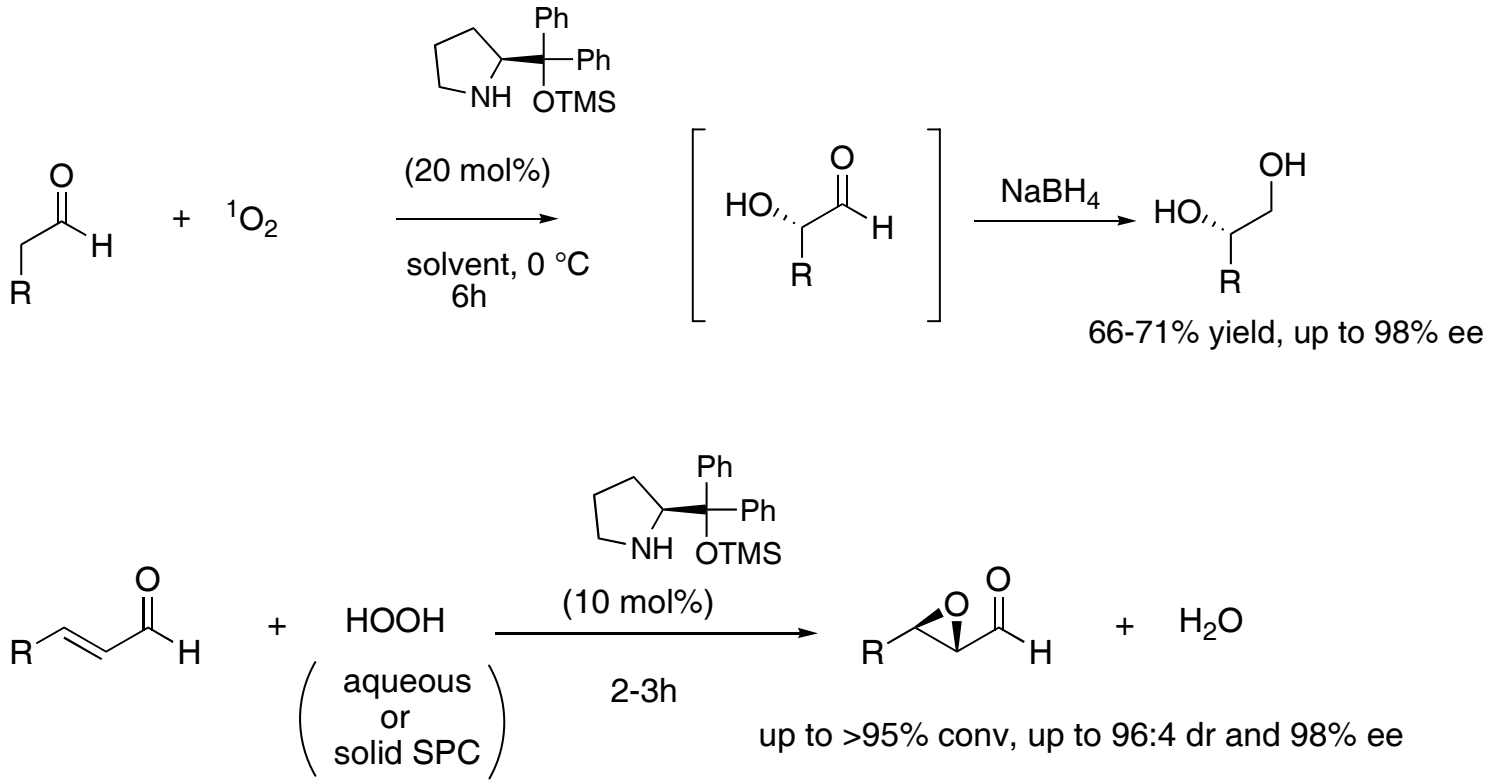
ΔΔG = 7.2 kcal/mol

TS-III **TS-IV**



F. Himo

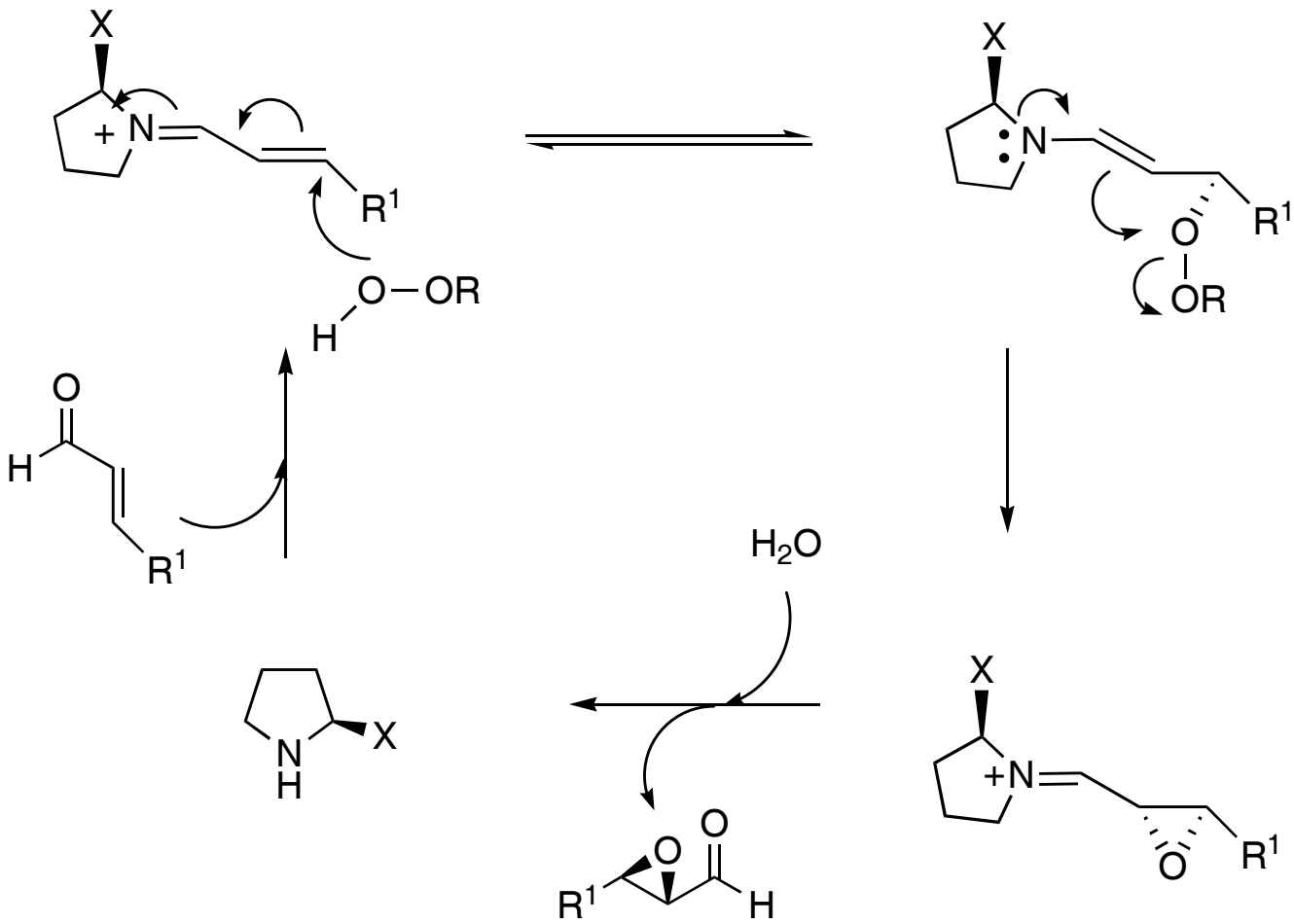
Catalytic “Green” Asymmetric Oxidations



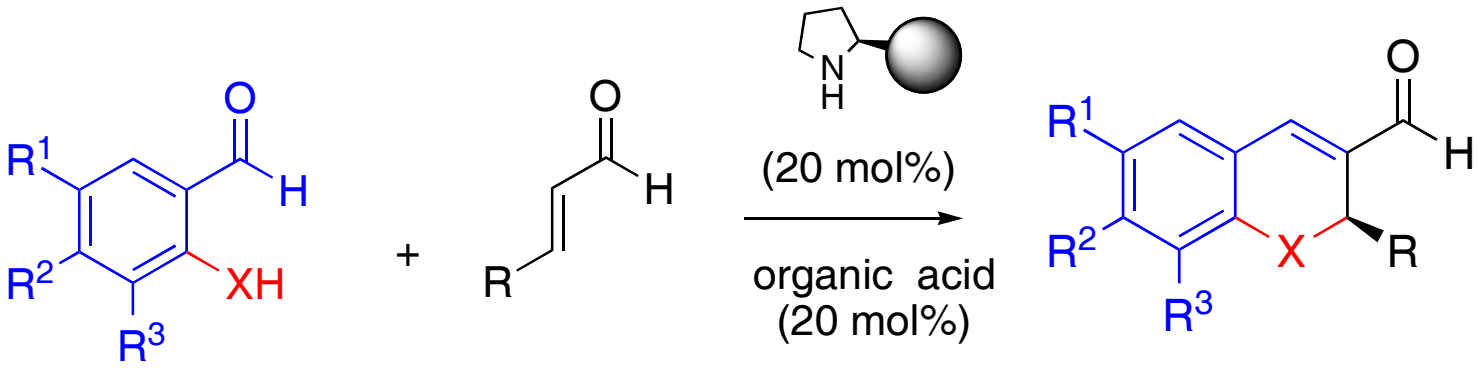
Ibrahem et al. J. Am. Chem. Soc. 2004.; Súnden et al. *Angew. Chem. Int*. Ed. 2004.

Jørgensen and co-workers J. Am. Chem. Soc. 2005

A Highly Selective Catalytic Cycle



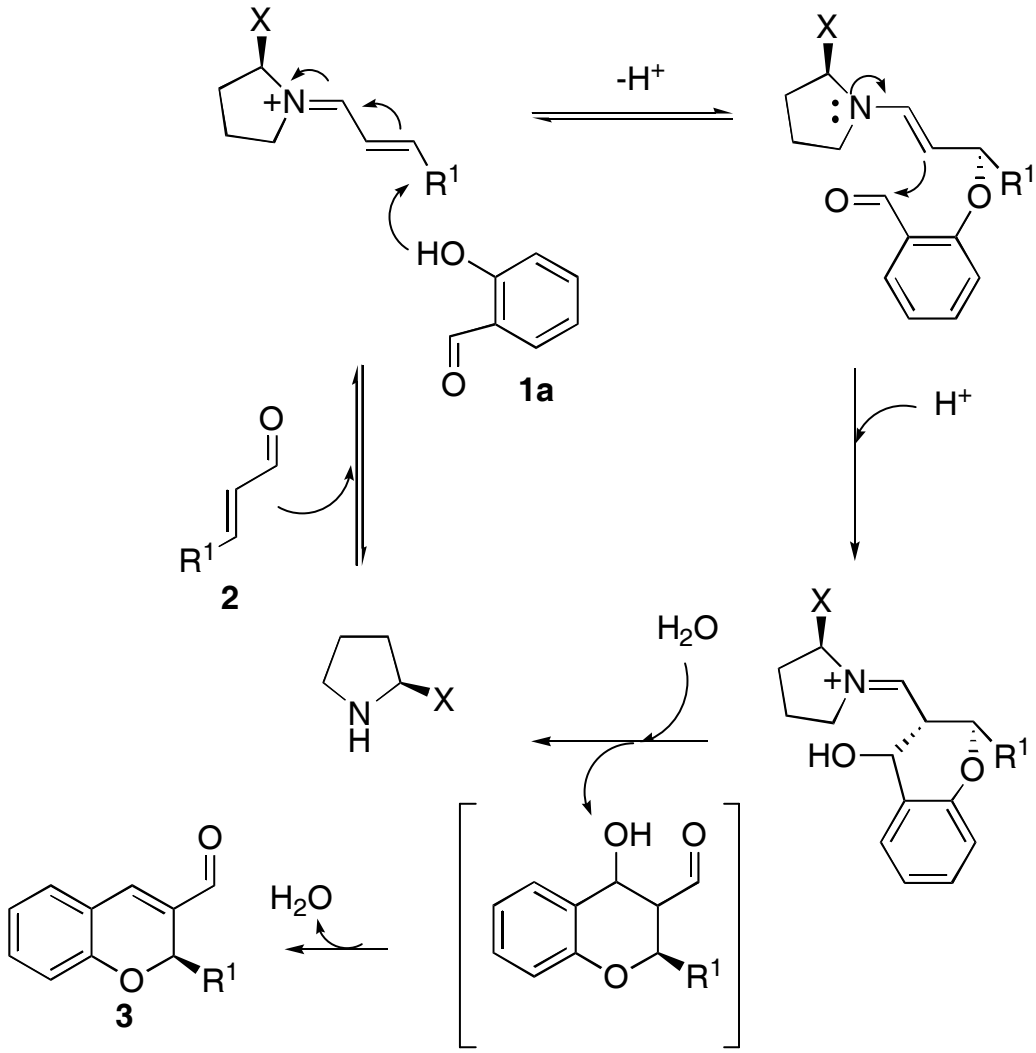
Catalytic asymmetric domino reactions: Synthesis of pharmaceutically valuable compounds

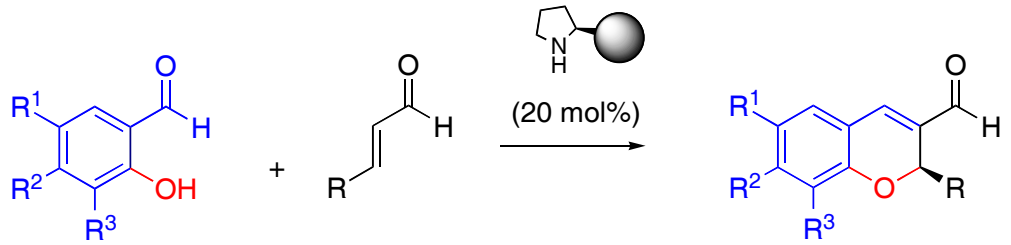


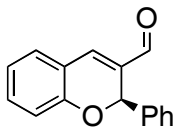
R^1, R^2, R^3 = H or OMe; X = O, S

US Patent. Application 2006

The mechanism of the catalytic asymmetric domino reaction

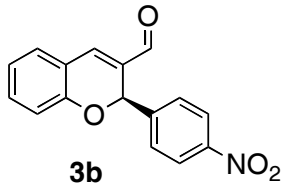






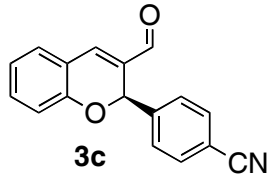
3a

89%, 89% ee



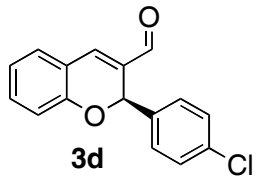
3b

52%, 94% ee



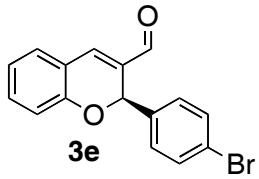
3c

72%, 90% ee



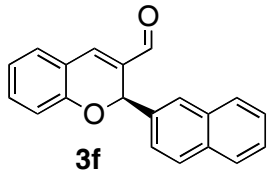
3d

59%, 83%ee



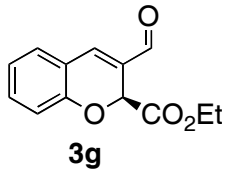
3e

51%, 84% ee



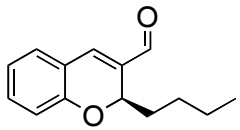
3f

52%, 84% ee



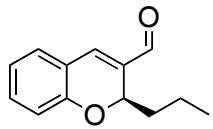
3g

70%, 96% ee



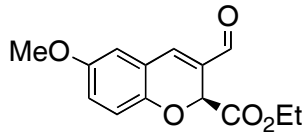
3h

67%, 87% ee



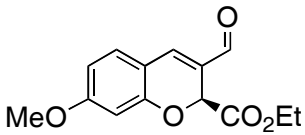
3i

57%, 87% ee



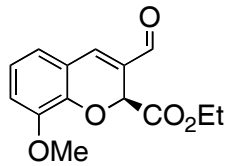
3j

92%, 93% ee



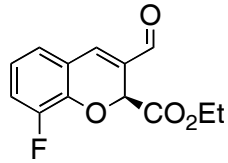
3k

52%, 92% ee



3l

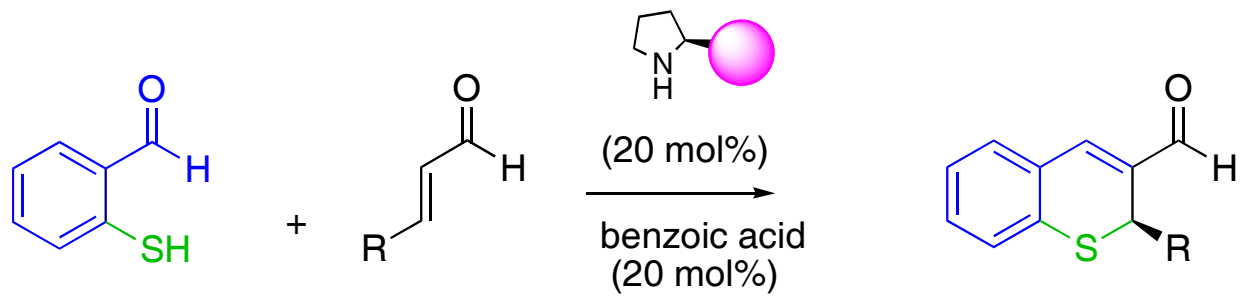
68%, 95% ee

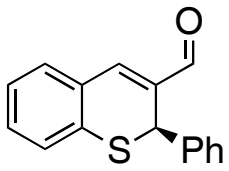


3m

72%, 97% ee

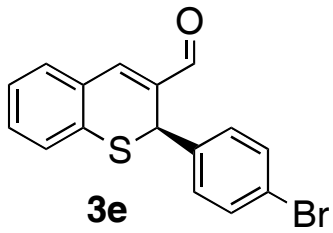
Sundén et al. Chem Eur. J. 2006





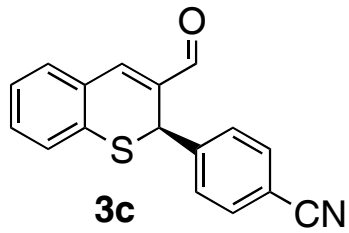
3a

74%, 98% ee



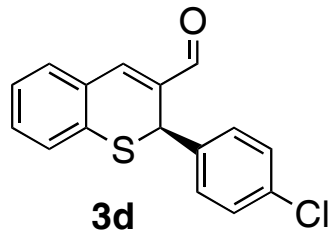
3e

93%, 98% ee



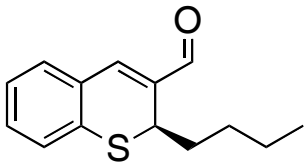
3c

80%, 98% ee



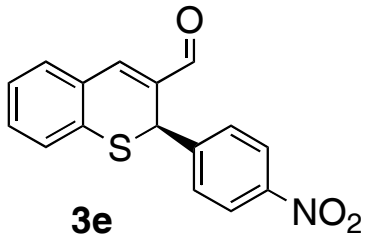
3d

53%, 96%ee



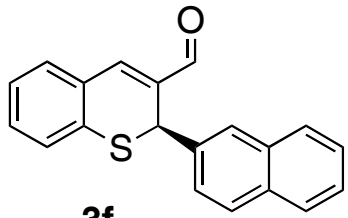
3h

70%, 96% ee



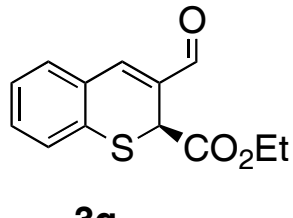
3e

93%, 98% ee



3f

68%, 94% ee

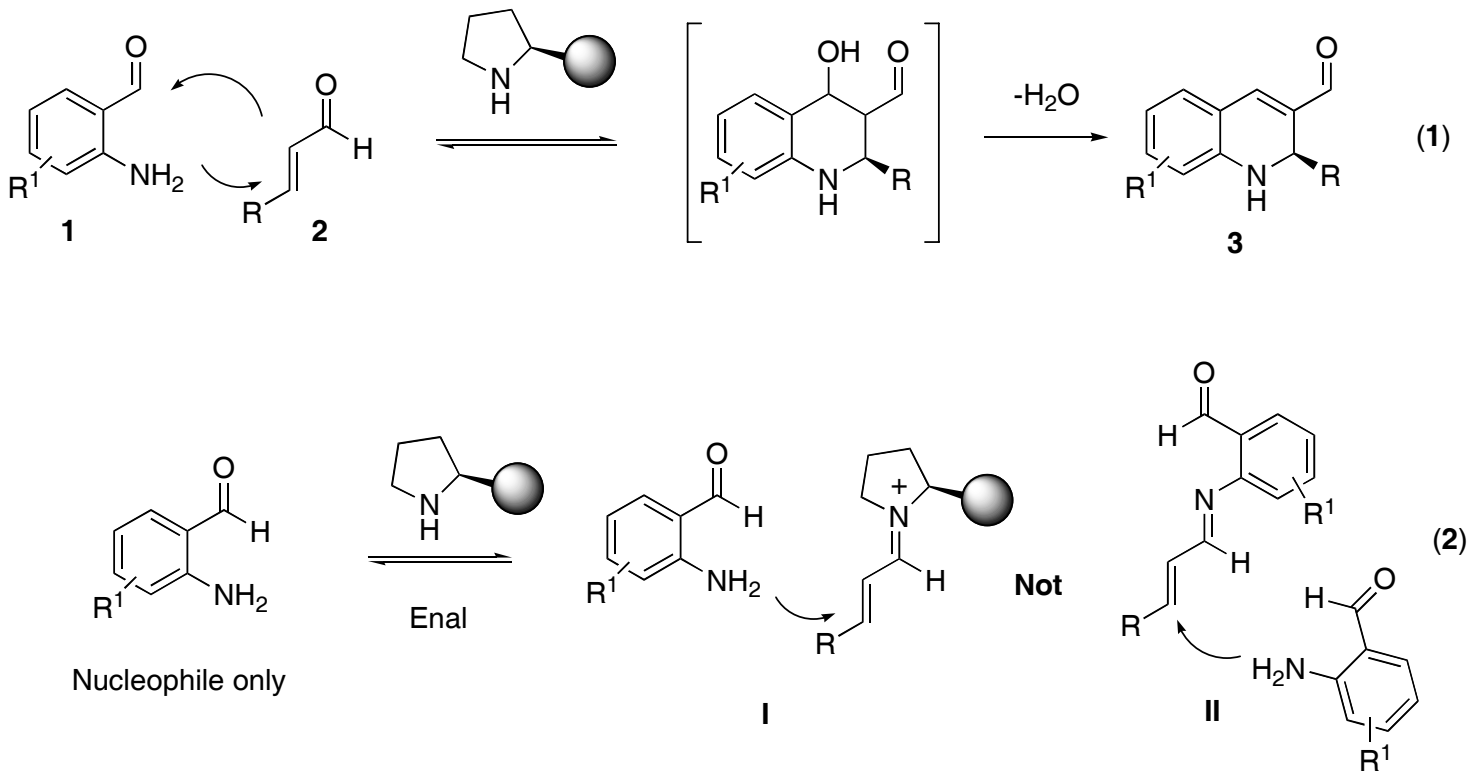


3g

61%, 91% ee

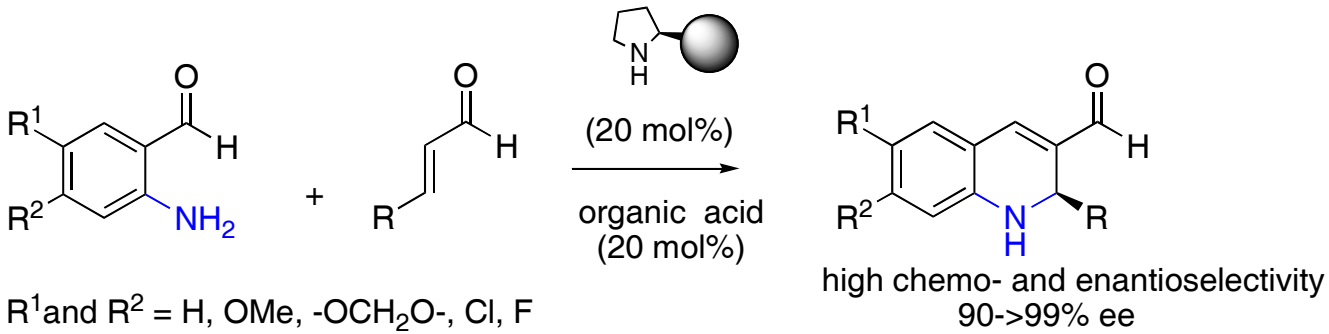
Rios et al. 2006

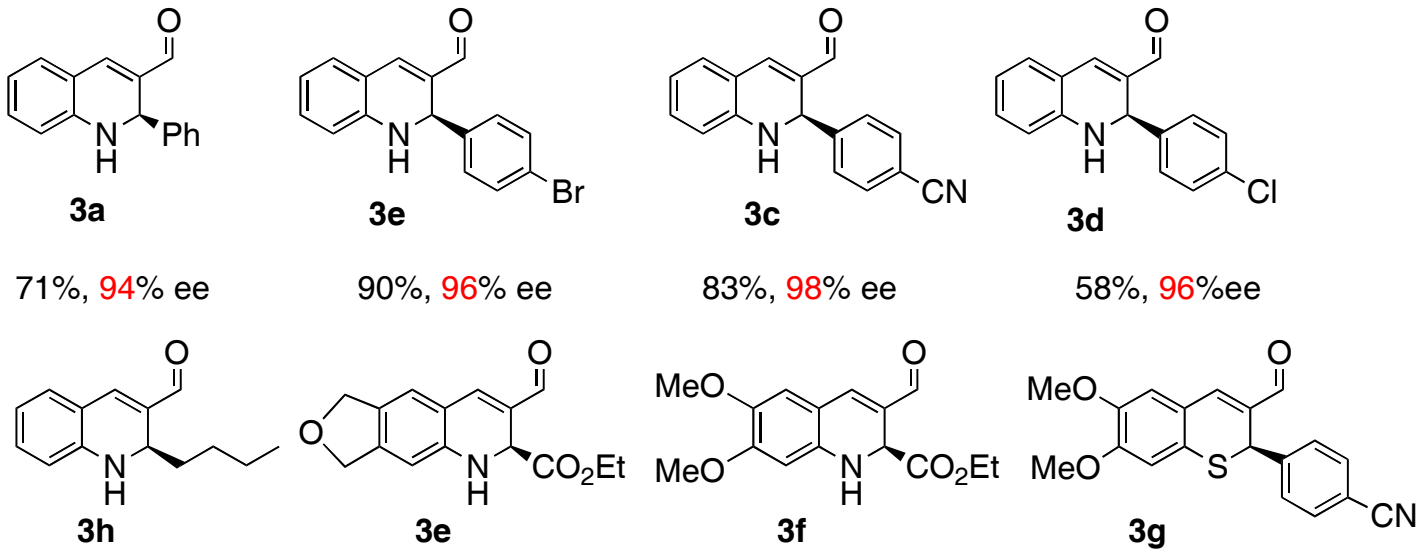
Catalytic asymmetric synthesis of dihydroquinolidines



Chemoselectivity issues

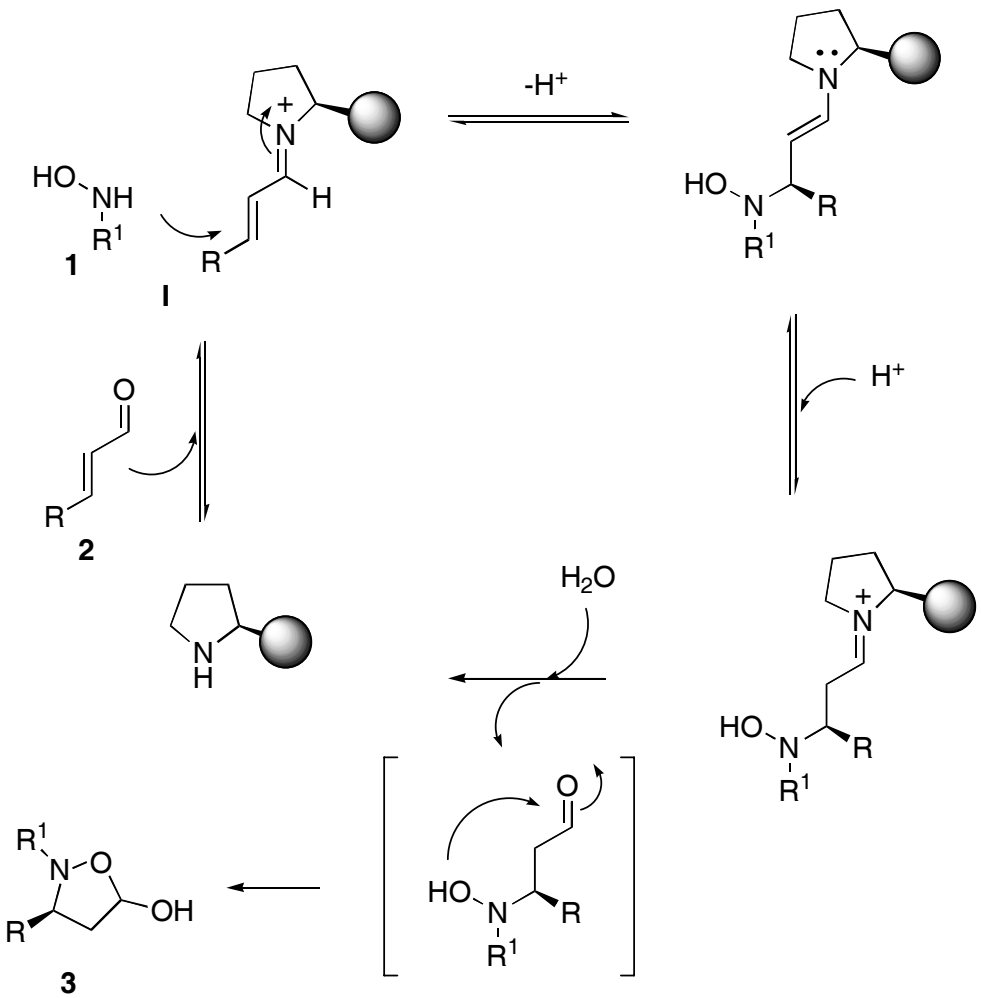
Sundén et al. 2006



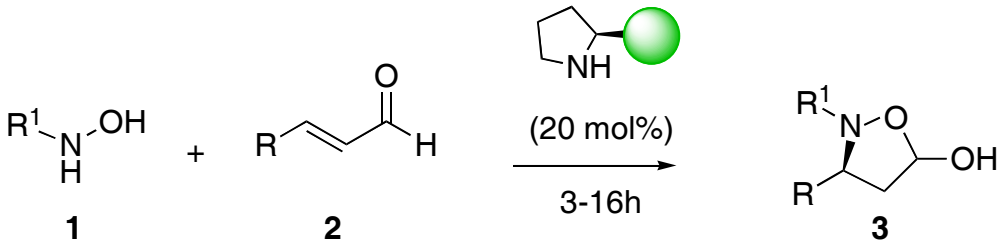


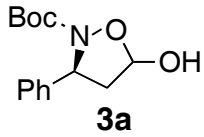
Sundén et al. 2006

Catalytic asymmetric synthesis of 5-hydroxyisoxazolidines



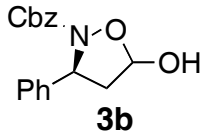
US Patent. Application 2006





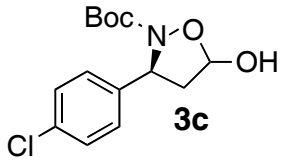
3a

80%, 99% ee



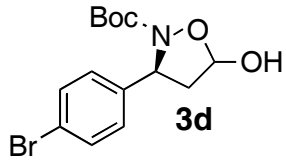
3b

94%, 99% ee



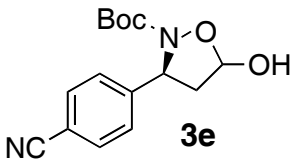
3c

89%, 90% ee



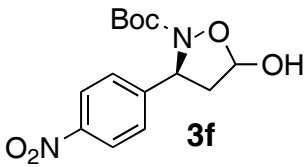
3d

80%, 97% ee



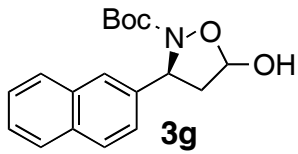
3e

90%, 97% ee



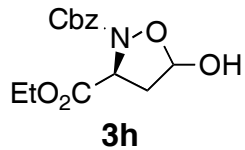
3f

75%, 98% ee



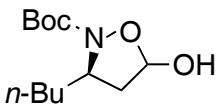
3g

77%, 95% ee



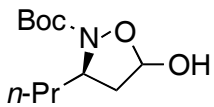
3h

85%, 97% ee



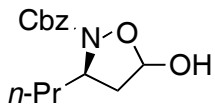
3i

94%, 91% ee



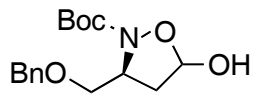
3j

93%, 91% ee



3k

92%, 95% ee

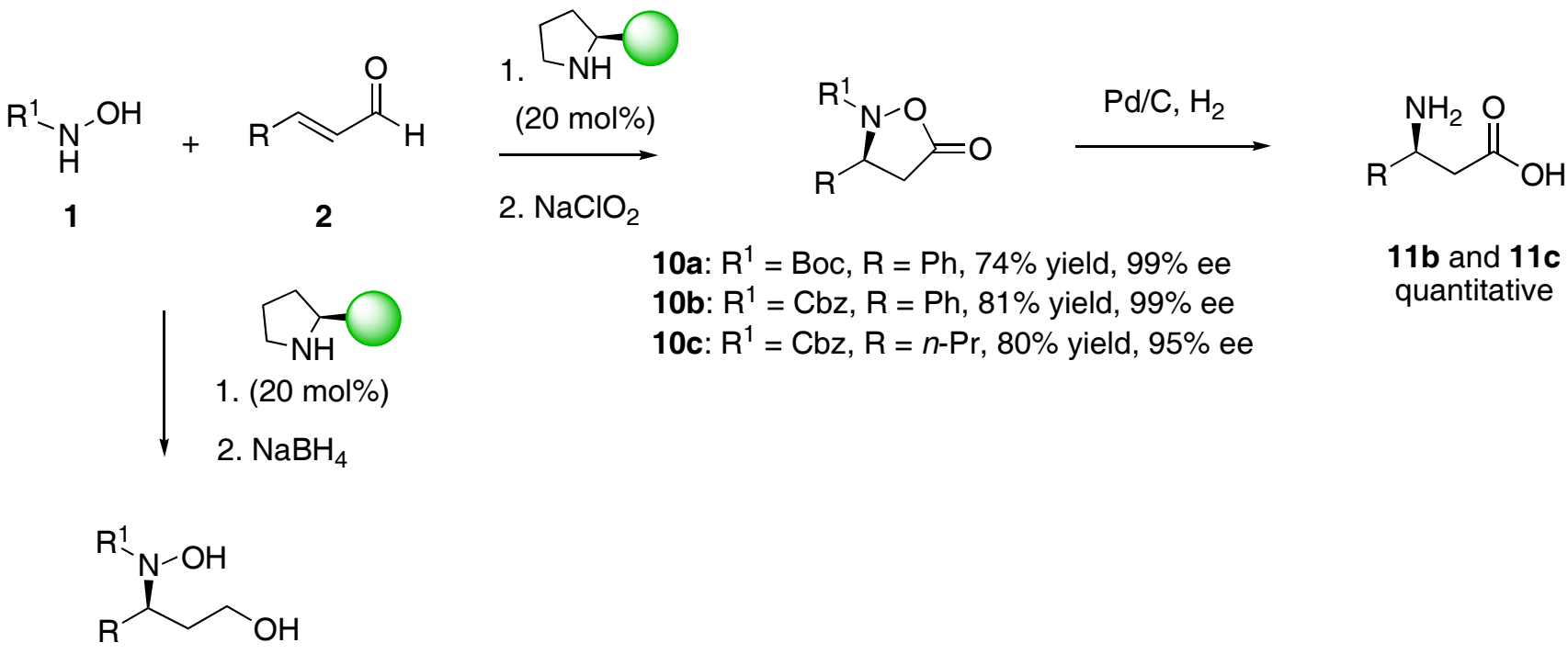


3k

86%, 98% ee

Ibrahem et al. 2006

Two-step synthesis of β-amino acids

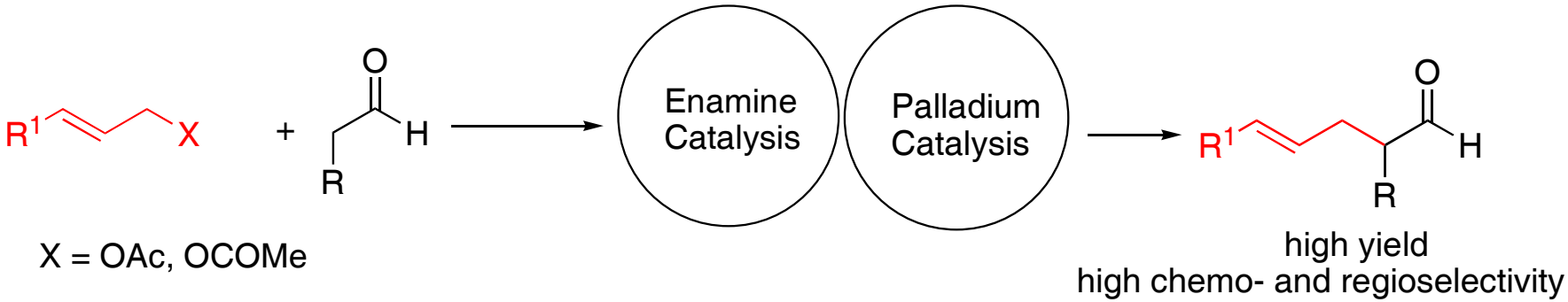


10a: R^1 = Boc, R = Ph, 74% yield, 99% ee
10b: R^1 = Cbz, R = Ph, 81% yield, 99% ee
10c: R^1 = Cbz, R = *n*-Pr, 80% yield, 95% ee

11b and **11c**
quantitative

12a: R^1 = Boc, R = Ph, 87% yield, 99% ee

One-pot catalytic asymmetric transition metal- and organocatalysis

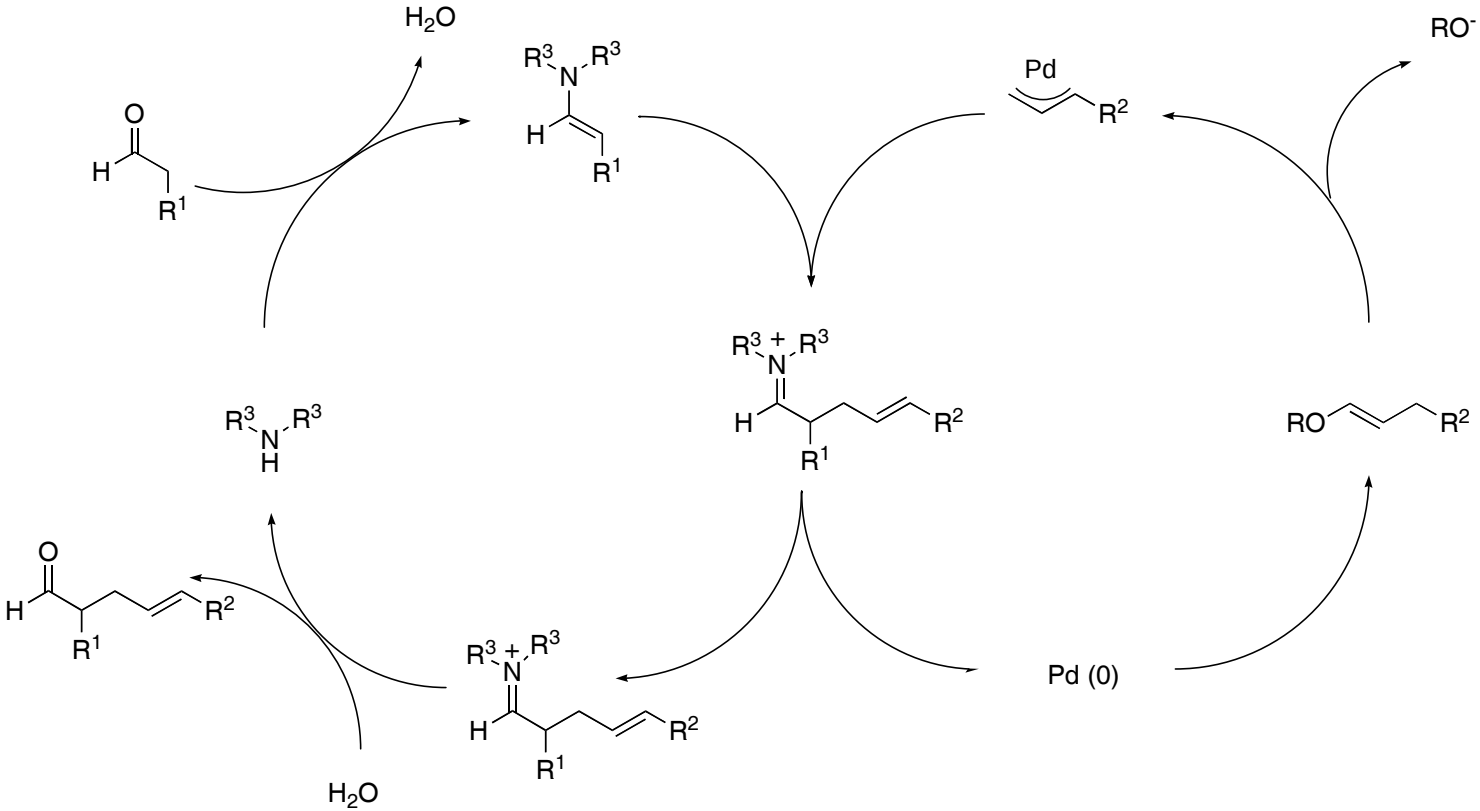


X = OAc, OCOMe

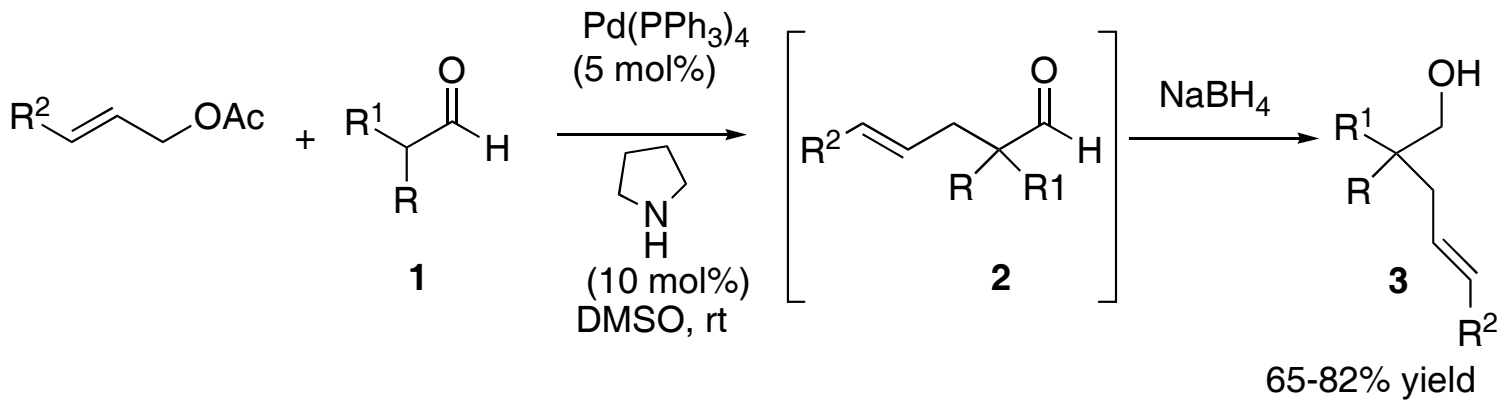
high yield
high chemo- and regioselectivity

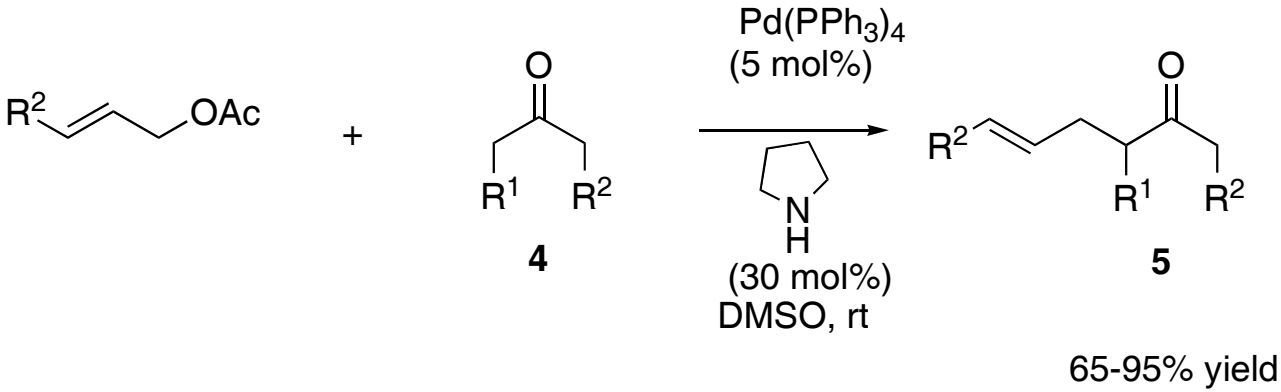
Ibrahem and Córdova Angew. Chem. Int. Ed. 2006, *45*, 1952.

Mechanism


H2O
RO-
Pd
R2
R3 R3
N
H
R1
O
H
R1
R3 + R3
N
H
R2
R1
R3 R3
N
H
RO
R2
O
H
R1
R2
R3 + R3
N
H
R2
R1
Pd (0)
H2O

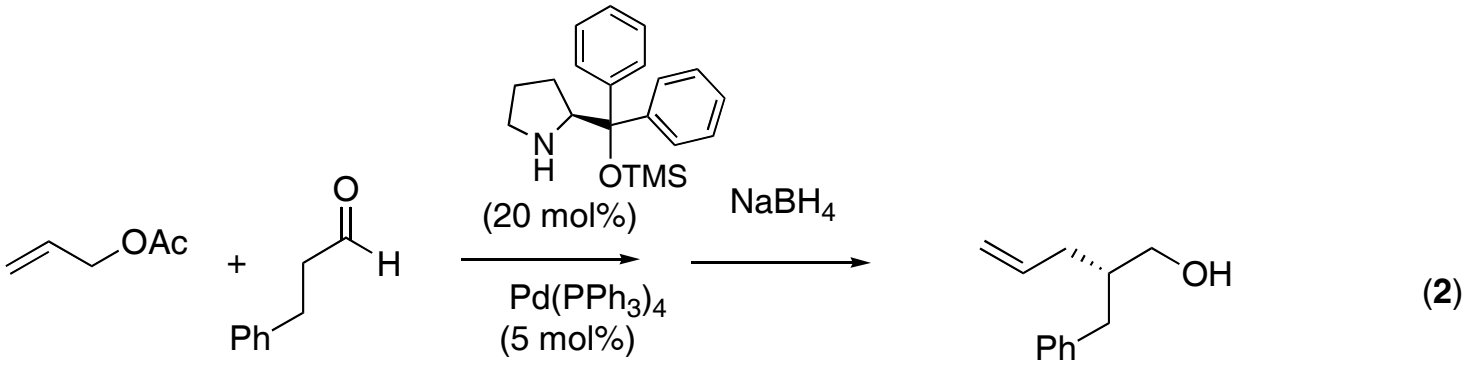
Works for aldehydes and cyclic ketones





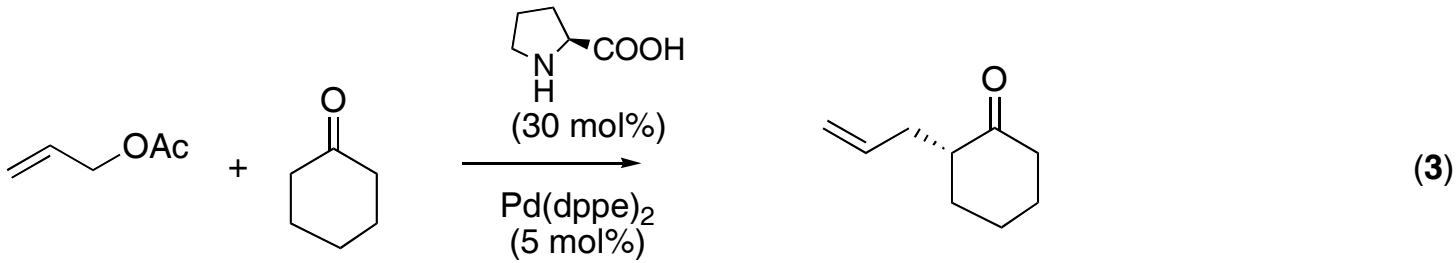
Excellent Regioselectivity

Direct catalytic asymmetric α-allylation



3a: 25% yield, 74% ee

(**2**)



5a: 20% yield, 60% ee

(**3**)

Summary

- Biomimetic selective catalysis can be non-toxic and therefore suitable for industrial applications
- It is highly stereoselective and converts simple starting materials to valuable compounds
- It prevents generation of waste and is environmentally benign.
- Amino acid catalysis may hold the clues for the origins of homochirality
- It will be an important tool for the future of chemical synthesis

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Prof. Fahmi Himo
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