"Direct Asymmetric anti-Mannich Type Reactions Catalyzed by a Designed Amino Acid"

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Presented by: Zack Brown
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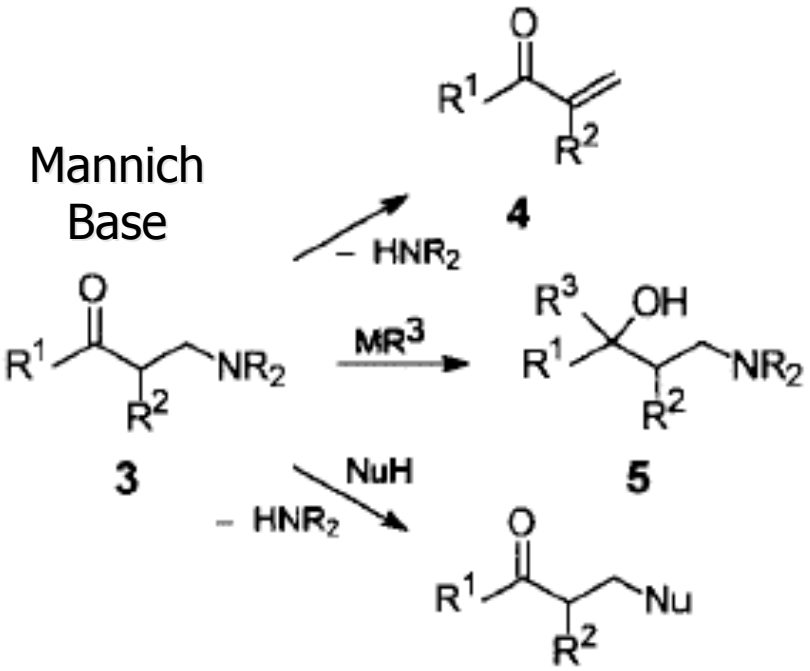
Mannich Reaction - Outline

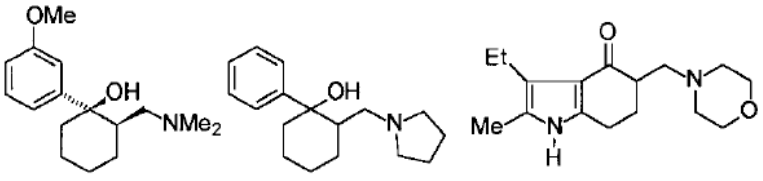
I. Current Implementations
II. Classic Mannich Mechanism
III. New Developments (Asymmetric)
    - Direct vs. Indirect
    - Proline Catalysis
IV. Current Work
    - Designed Amino Acid
V. Further Extensions

Implementations of the Mannich

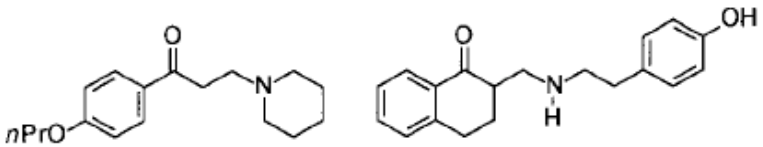
Derivatization



Pharmaceutical Examples



Tramadol Analgesic | Osnervan Antiparkinsonic | Moban Neuroleptic



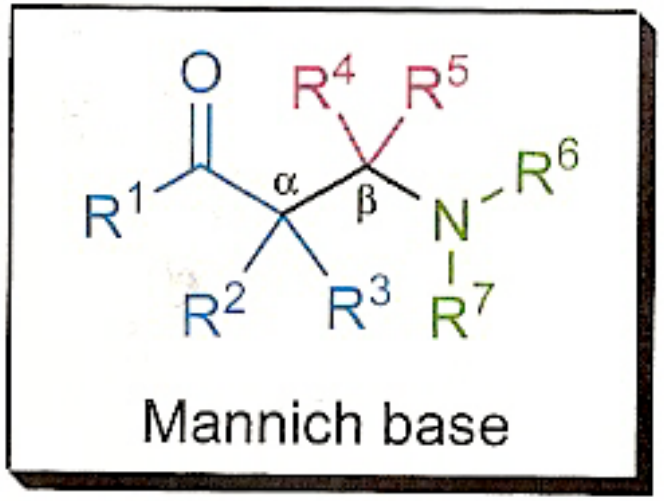
Falicain Anaesthetic | Be-2254 Antihypertensive

- 3->4: Formation of a Michael Acceptor
- 3->5: Addition of Organometallic
- 3->6: Sub. by a Nucleophile

Classic Mannich Reaction

Multi-Component Condensation

- Nonenolizable Carbonyl (usually Aldehyde)
- Amine (1° or 2°)
- Enolizable carbonyl
- Acid (Usual) or Base Catalyzed
- Product: β-Amino Carbonyl Derivatives

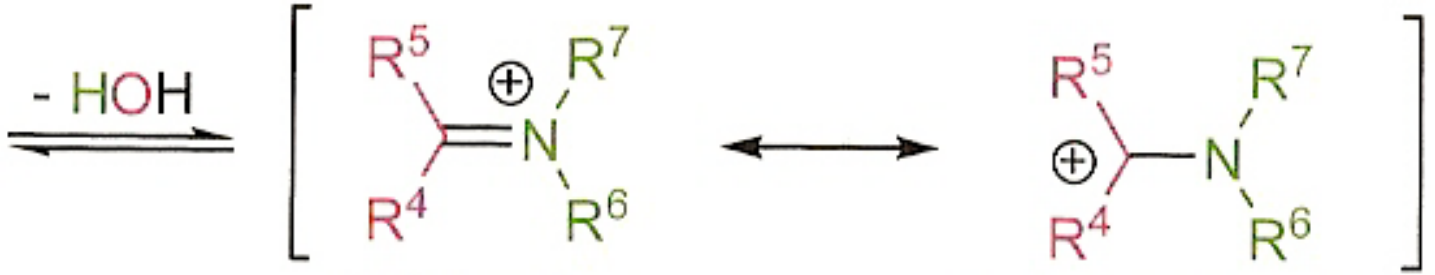


Mannich base

Mannich Reaction: Mechanism

Formation of the reactive iminium ion under acidic conditions:

hemiaminal

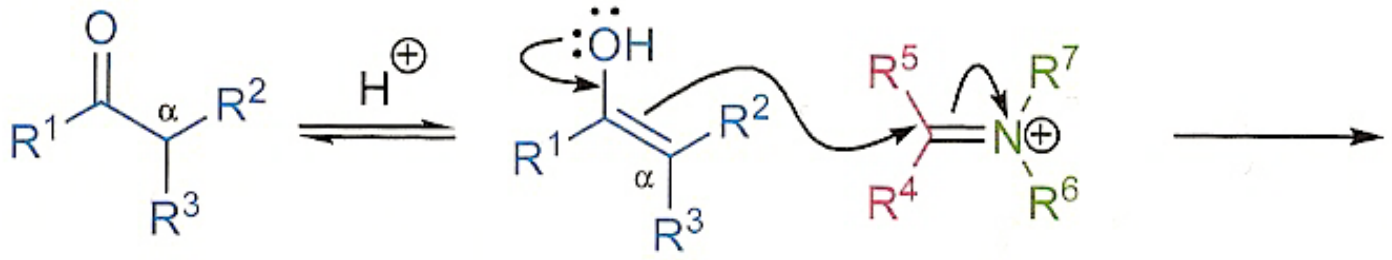


iminium ion

aminocarbenium ion

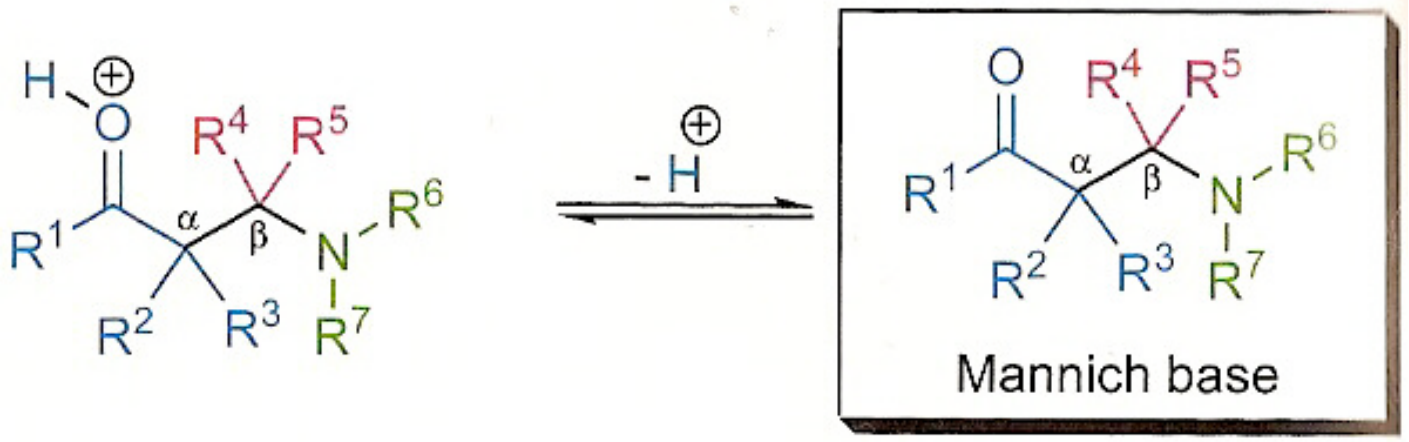
Mannich Reaction: Mechanism

Alkylation of the enolized carbonyl compound:

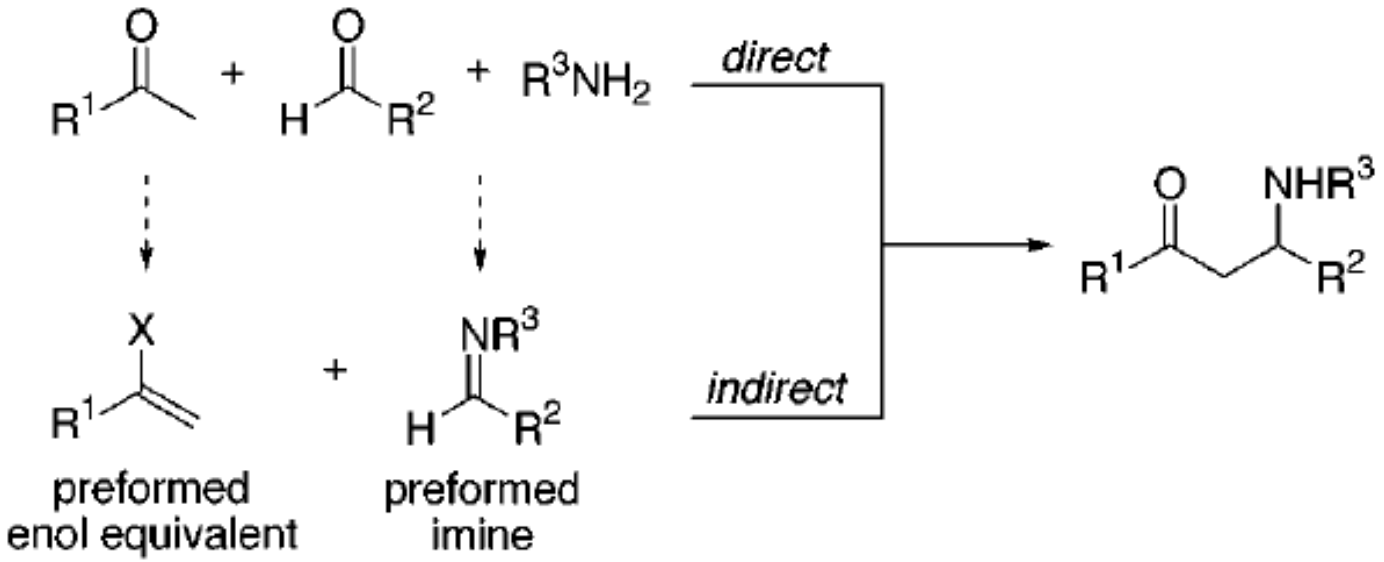


enolizable carbonyl compound

enolized carbonyl compound



Mannich Reaction: Direct vs. Indirect



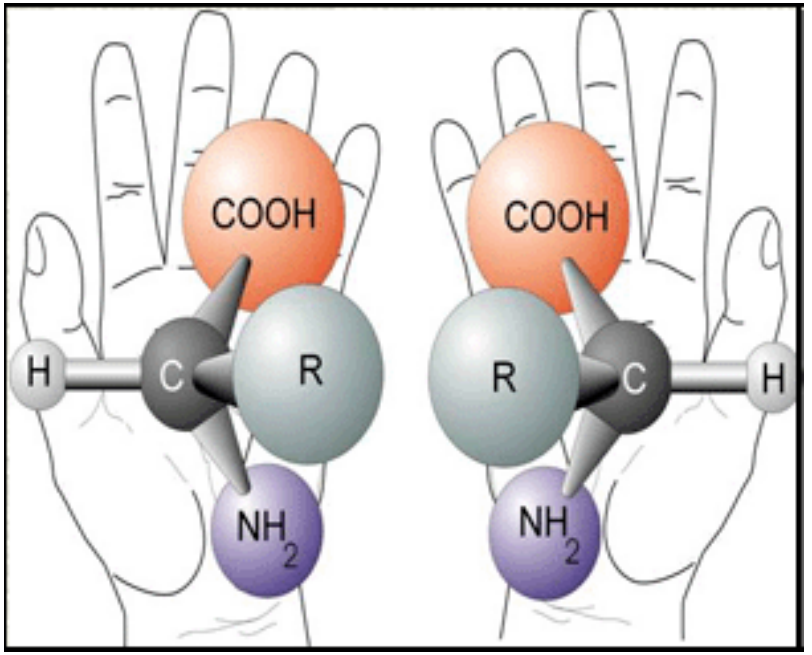
Direct:
- Components in Equilibrium
- Limitations of Substrates

Indirect:
- Assign Chemical Roles
- Additional Steps

Mannich Reaction: New Twists

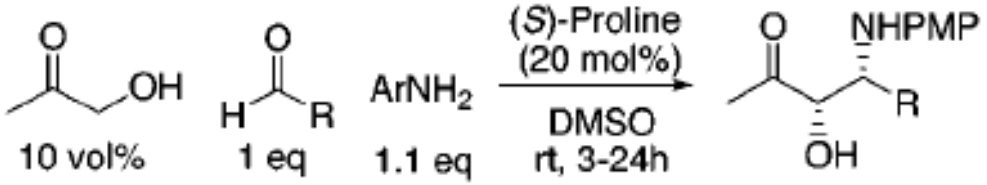
Enantioselective Catalysis

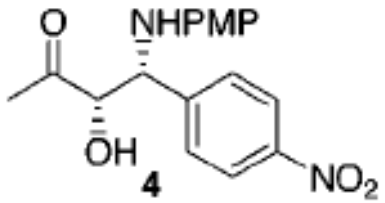
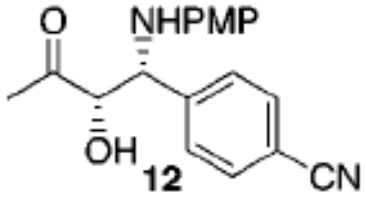
- Preformed Imine and Enols with Metals
- Transition Metals
- Proline



Source: http://web99.arc.nasa.gov/~astrochm/aachiral.html

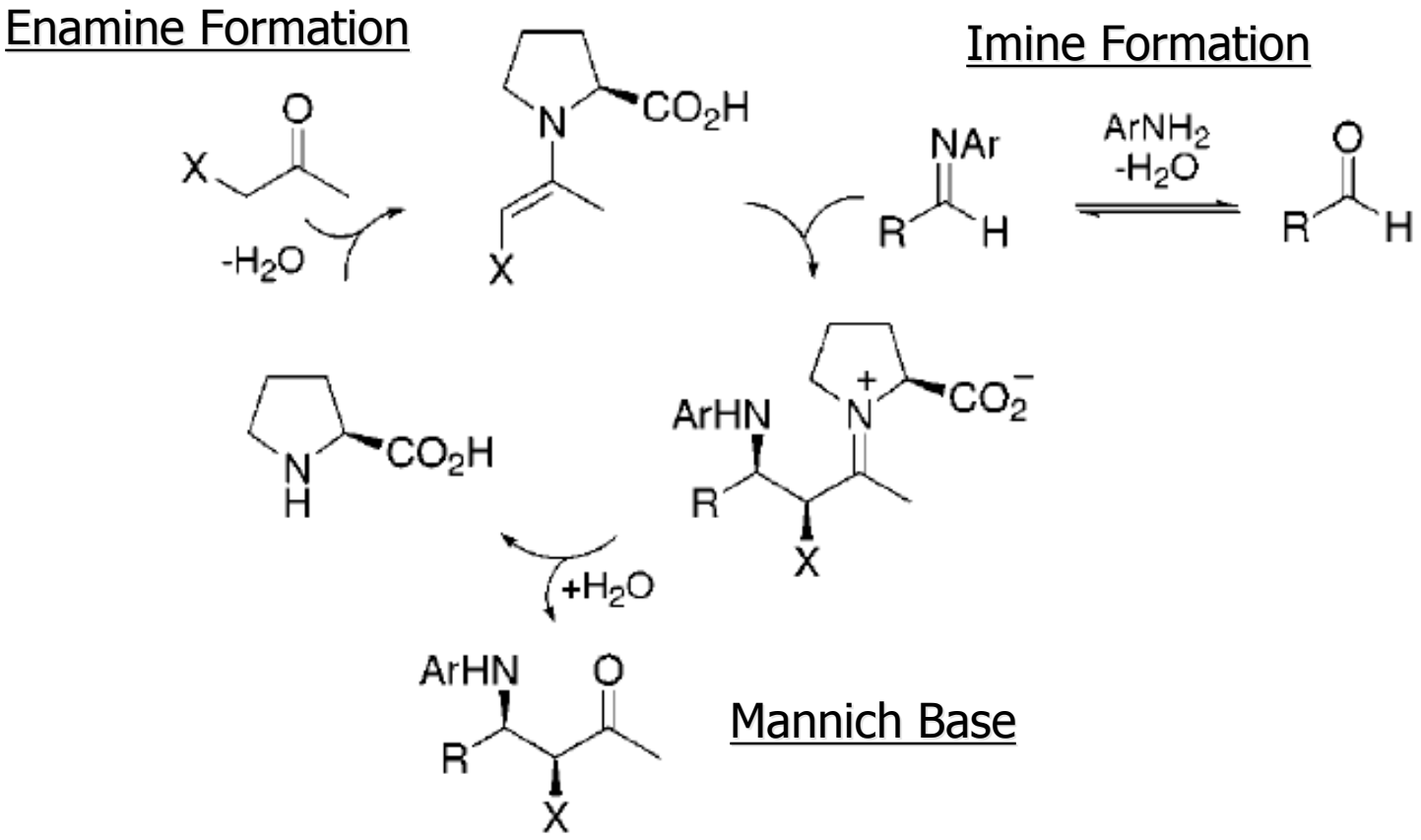
Mannich Reaction: Proline



Entry	Product	Yield %	dr	ee %
1	 **4**	92	20:1	>99
2	 **12**	88	15:1	99
3	 **13**	90	15:1	98

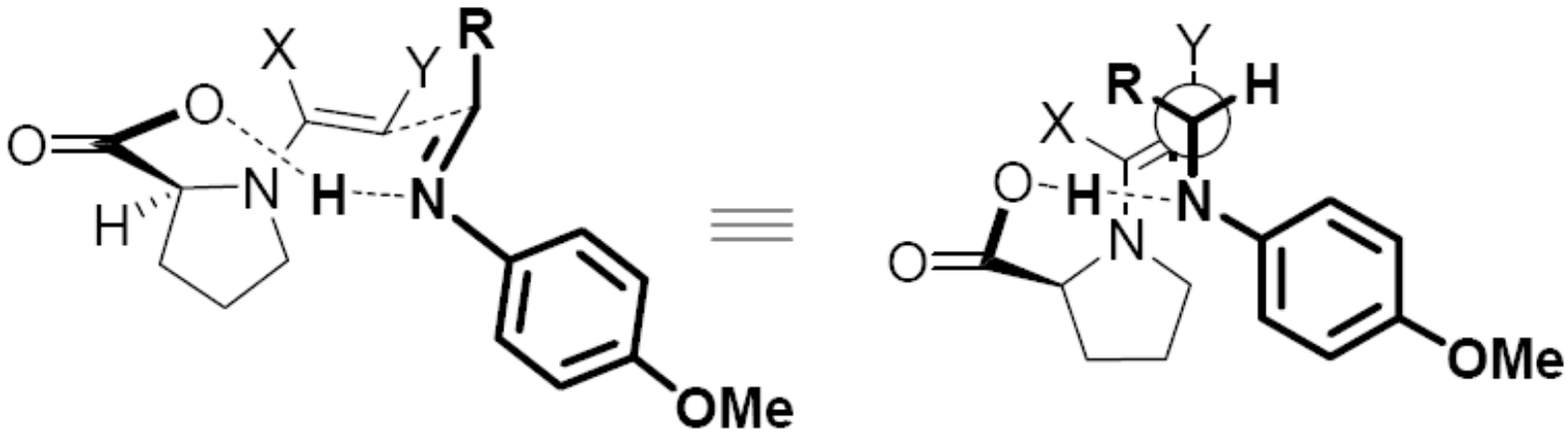
- Excellent dr's and ee's
- Exclusive syn diastereomer
- Other substrates tested

Mechanism of the Proline Reaction



TS of the Proline Reaction

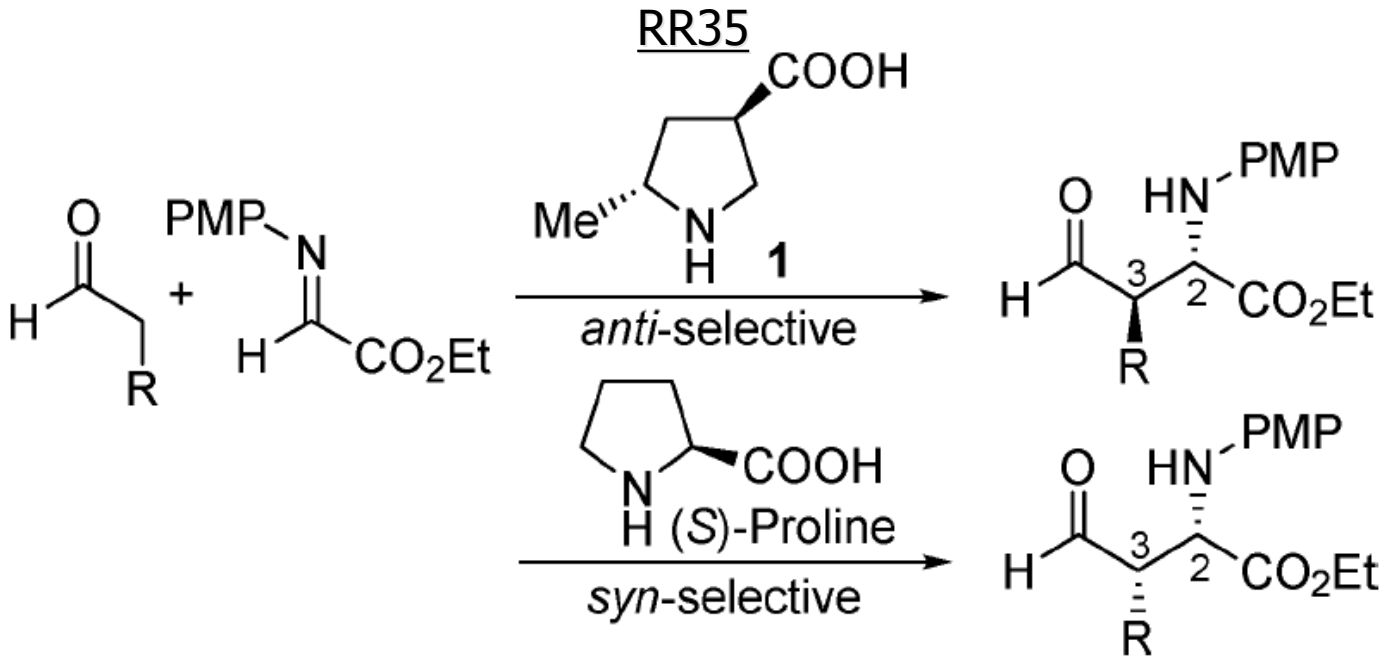
- Formation of the (E)-Aldimine
- Cyclic TS creates syn stereoselectivity through addition to Si face of Aldimine
- (R)-Proline give syn enantiomer



Source: www.scs.uiuc.edu/chem/gradprogram/chem435/fall05/Hoyt_Mirth.pdf

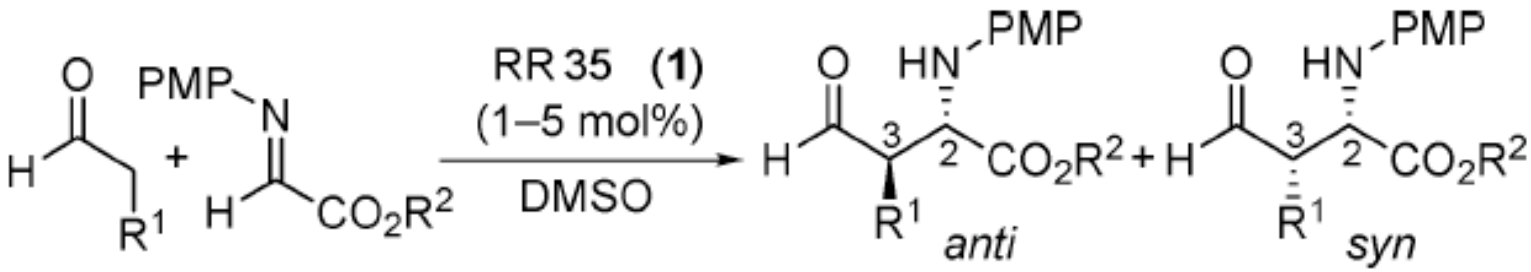
A Designed Catalyst

- Derivative of Proline offers Anti Diastereomers



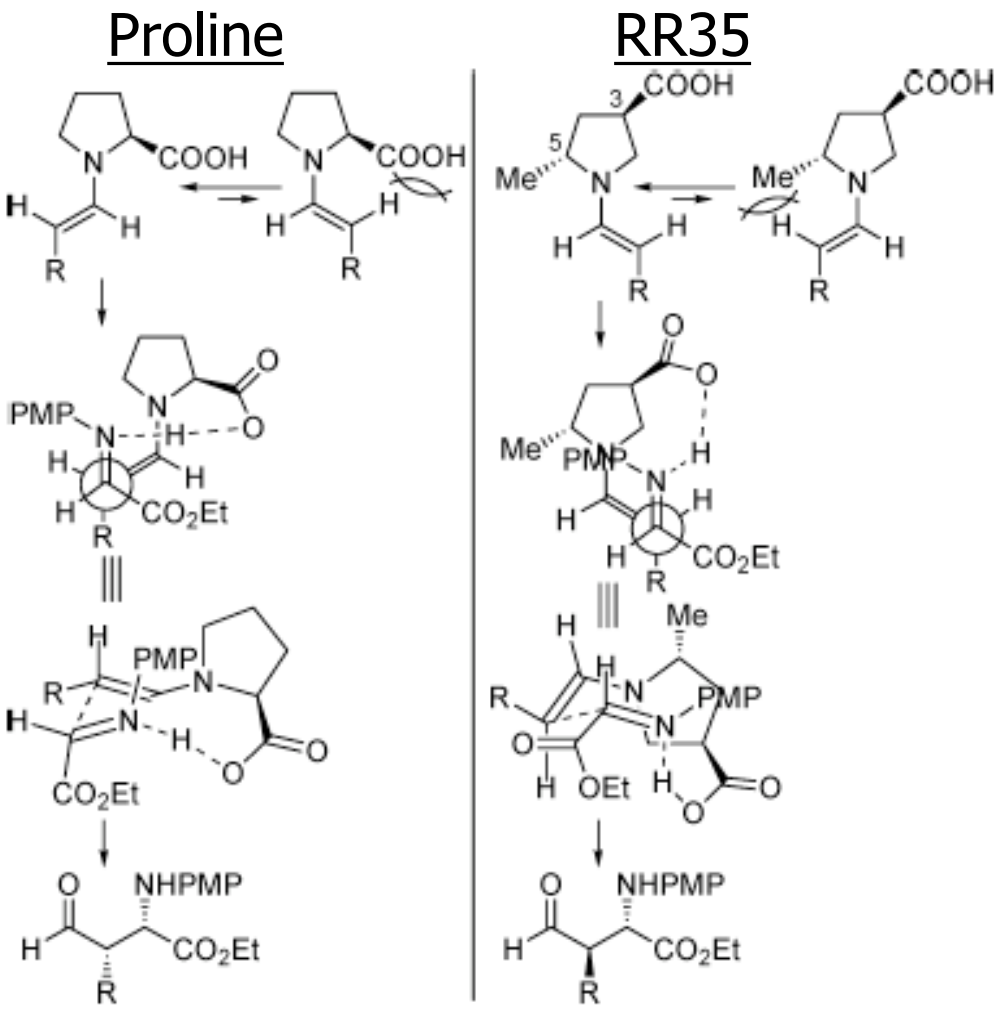
RR35 = (3R,5R)-5-methyl-3-pyrrolidinecarboxylic acid

Performance of the Catalyst



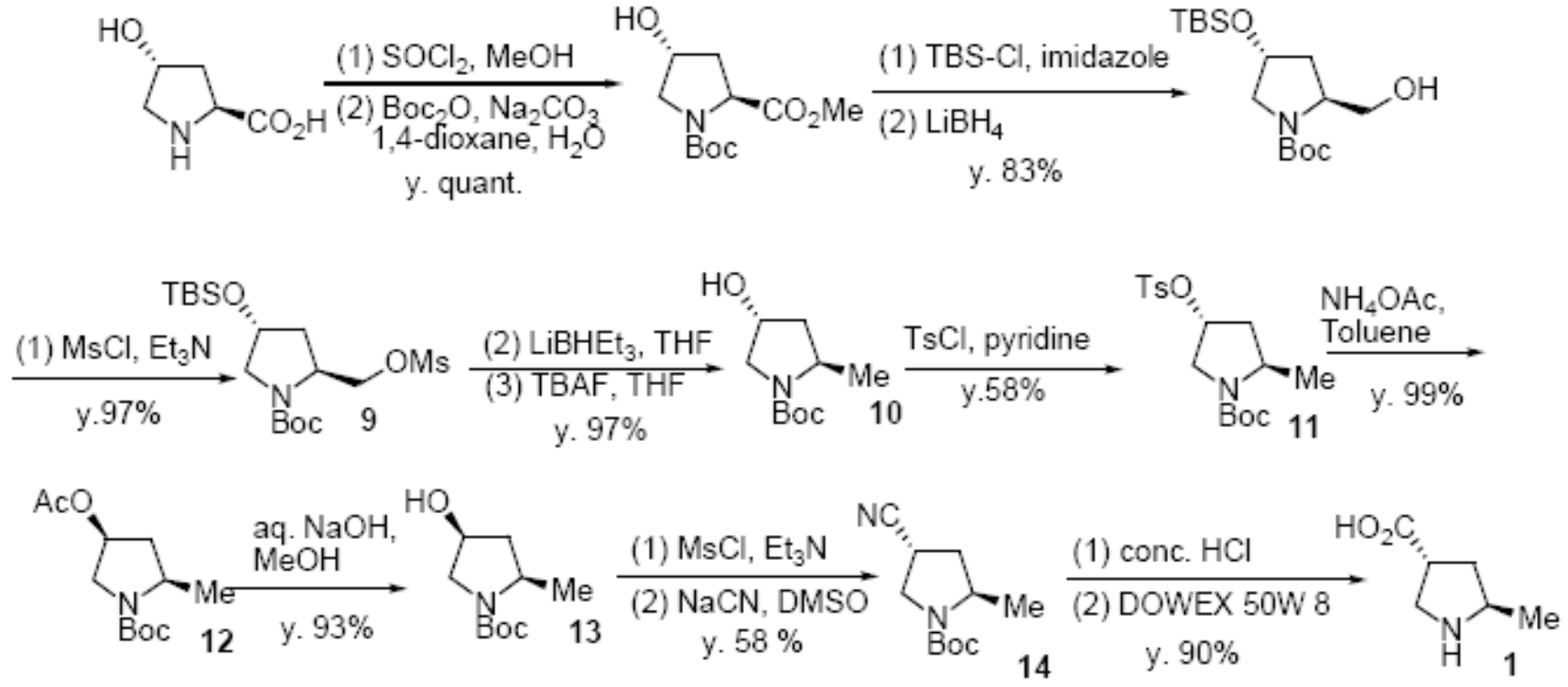
entry	R^1	R^2	time (h)	product	yield (%)	dr[b] *anti:syn*	ee[c] (%)
1[d]	Me	Me	-	—	—	95:5	98
2	Me	Et	1	**2**	70	94:6	>99[e]
3	*i*-Pr	Et	3	**3**	85	98:2	99
4	*n*-Bu	Et	0.5	**4**	54	97:3	99
5[f,g]	*n*-Bu	Et	1	**4**	71	97:3	99
6[f,h]	*n*-Bu	Et	2	**4**	57	97:3	>99

Anti-Selective Mechanism



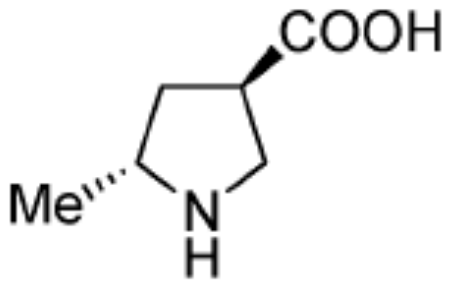
- s-trans conformation of enamine
- Placement of methyl group

Synthesis of the Catalyst

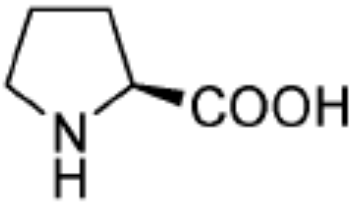


Future of the Asymmetric Mannich

- Applications and Extensions of this Paper



- Rational Design of Organocatalysts



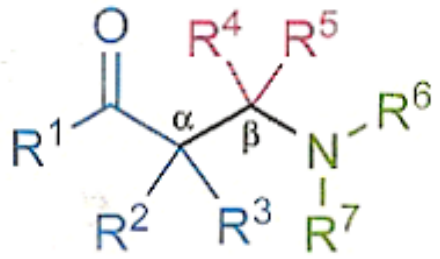
Conclusion

I. Classic Mannich

II. State of the Art

III. Current Work

IV. Further Extensions



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