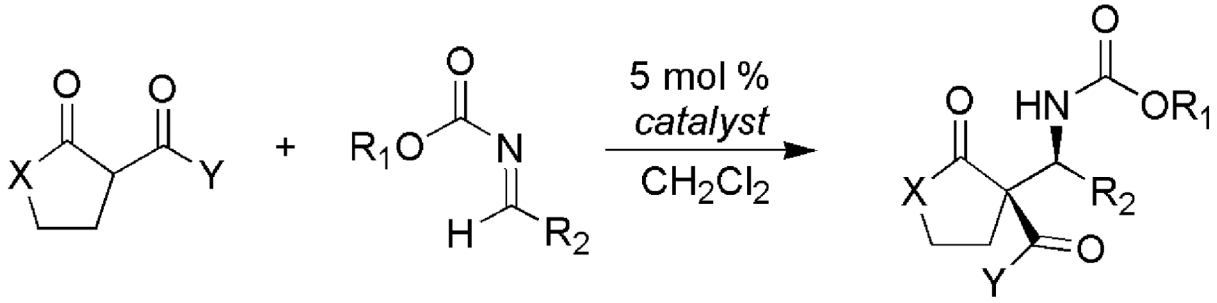
Highly Diastereoselective Asymmetric Mannich Reactions of 1,3-Dicarbonyls with Acyl Imines



Amal Ting, Sha Lou, and Scott E. Schaus

Org. Lett., **2006,** *8*, 2003-2006

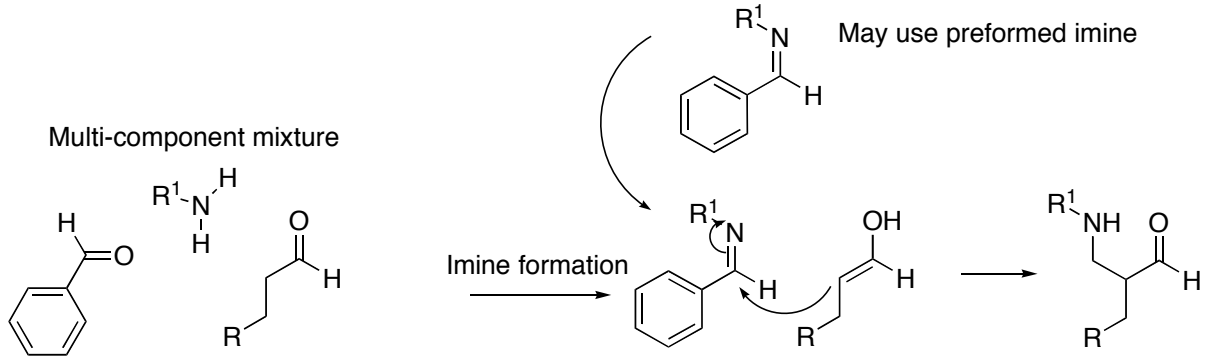
Presented by:

John Maciejewski

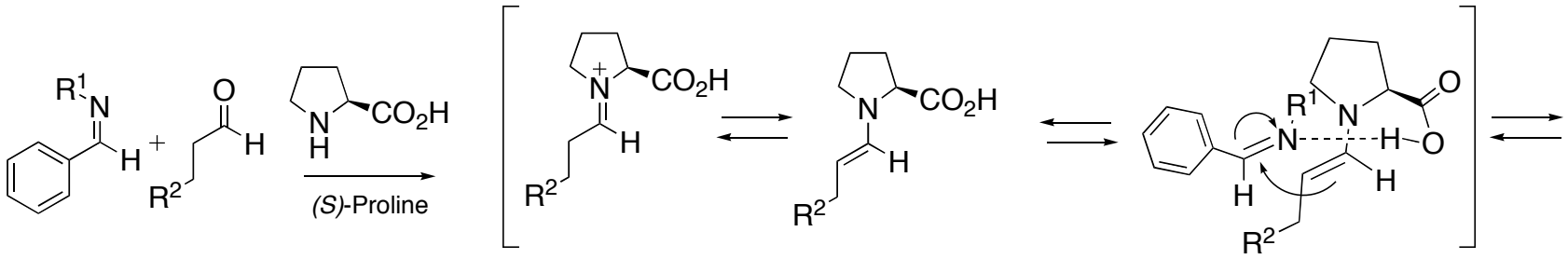
July 1, 2006

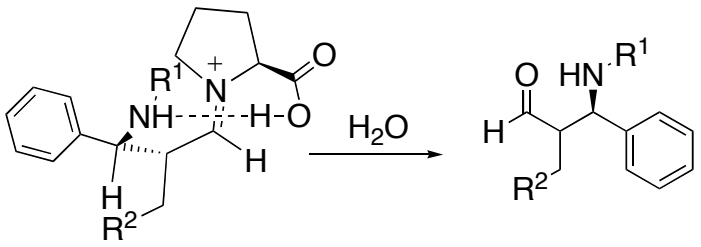
General Mannich Reaction

Racemic Mannich



Asymmetric Mannich





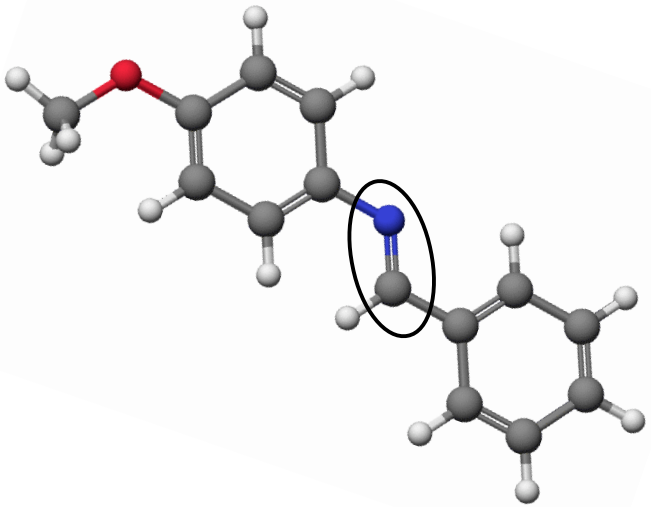
Modest diastereoselectivity with good enantioselectivities

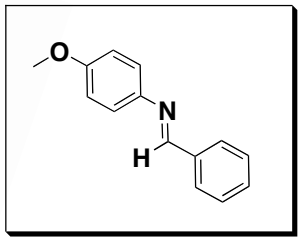
Reviews on Asymmetric Mannich reactions:

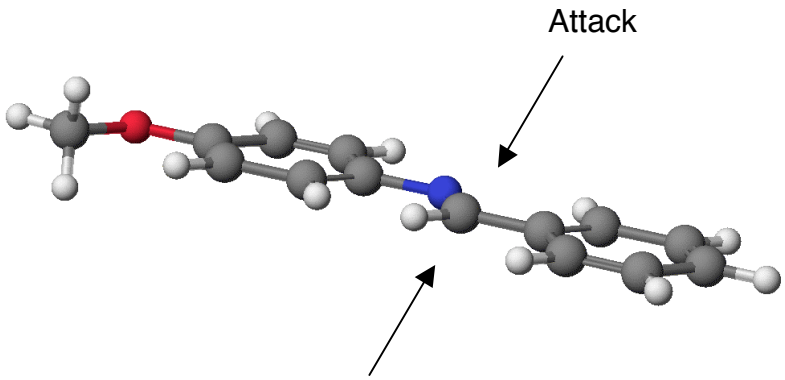
Risch *Angew. Chem., Int. Ed.* **1998,** *37,* 1044 - 1070

Dalko *Angew. Chem., Int. Ed.* **2004,** *43,* 5138 - 5175

Asymmetric Nucleophilic Addition to Imines







- Selective addition to pro-chiral face of imine continues to be studied extensively
- Chiral Proline derivatives have been used to invoke enantioselective addition to imines
- Other nucleophiles (ex. β-keto esters, β-diketones) require source of chirality for asymmetric addition to imines

Importance of asymmetric Mannich Reactions

- Ability to form quaternary carbon stereocenters
- Form valuable enantioenriched synthons
- Organocatalytic

Selected organocatalytic examples:

(S)-Proline - Parrish *J. Org. Chem.,* **1974,** *39,* 1615 - 1621

Modified prolines - Barbas *J. Am. Chem. Soc.,* **2006,** *128,* 1040-1041

Cinchona alkaloids - Schaus *J. Am. Chem. Soc.,* **2005,** *127,* 11256-11257

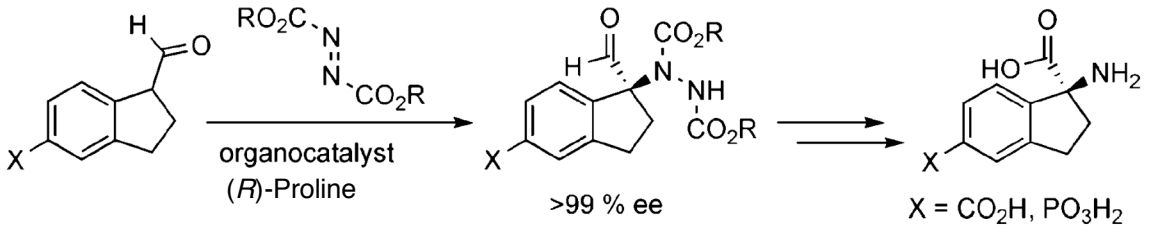
Organometallic Catalytic

Shibasaki - *Tet. Lett.* **1999,** *40*, 307-310

Mannich Reactions

Applications of asymmetric synthesis

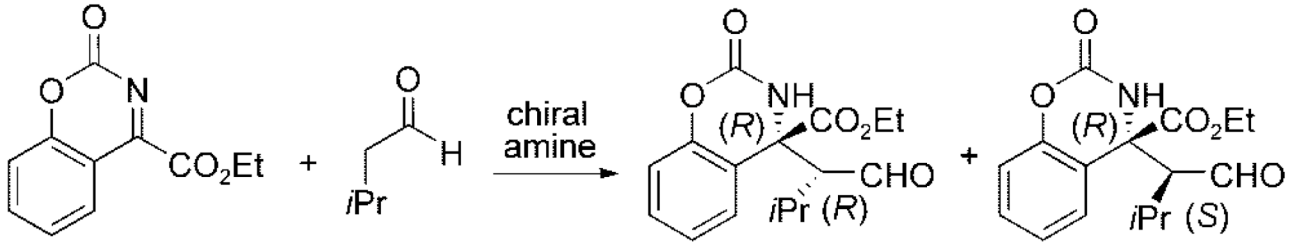
α-Amination



Barbas *Org. Lett.,* **2005,** *7,* 3885-3888

Compounds used to treat neurodegenerative diseases

Organocatalysis on ketimines

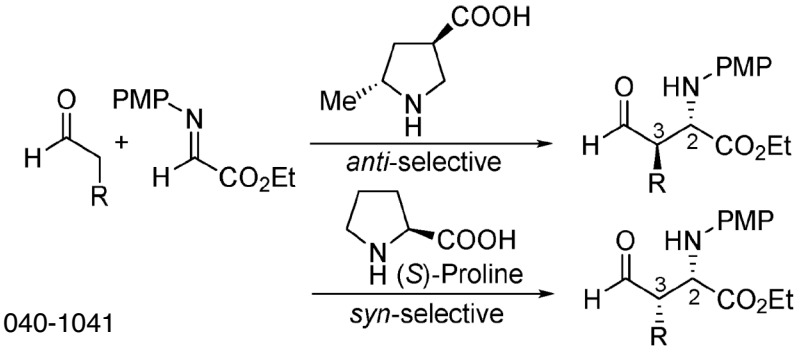


Jørgensen *Angew. Chem., Int. Ed.,* **2004,** *43,* 4476-4478

Used L-proline -derived catalysts to obtain selectivity

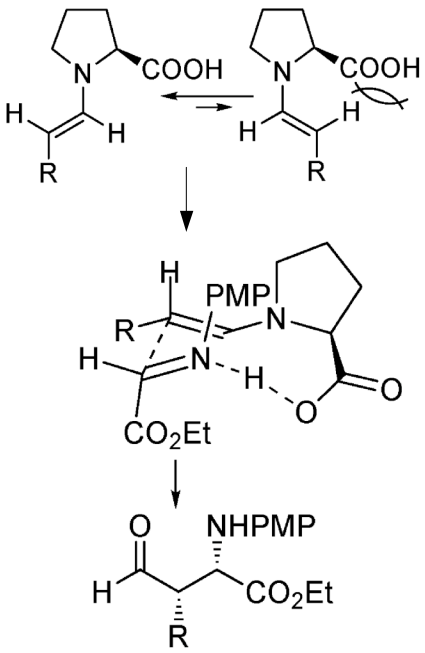
Mannich Reactions

Applications of asymmetric synthesis

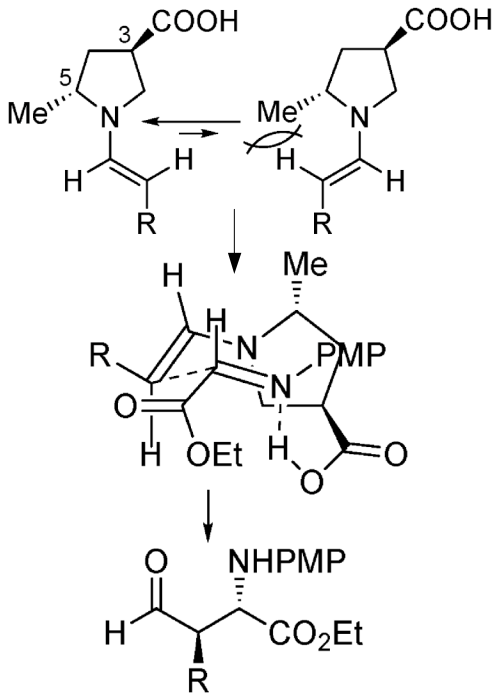


Barbas *J. Am. Chem. Soc.,* **2006,** *128,* 1040-1041

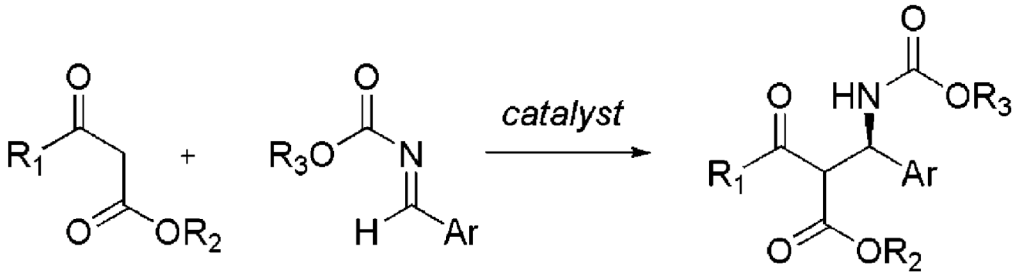
Syn-pathway



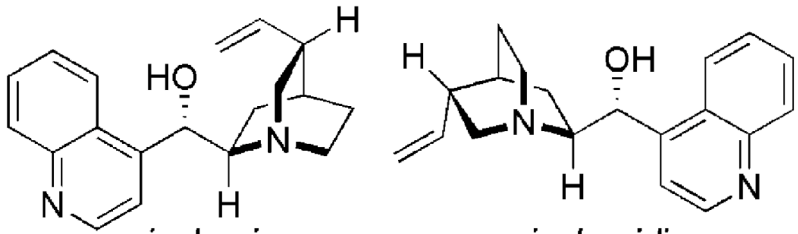
Anti-pathway



Mannich Reaction Using Chiral Lewis Bases



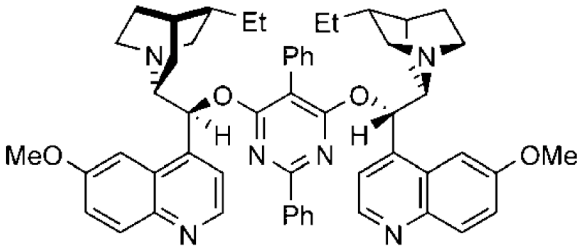
Modest diastereoselectivity with good enantioselectivities



cinchonine **1**

cinchonidine **2**

Schaus *J. Am. Chem. Soc.,* **2005,** *127,* 11256-11257



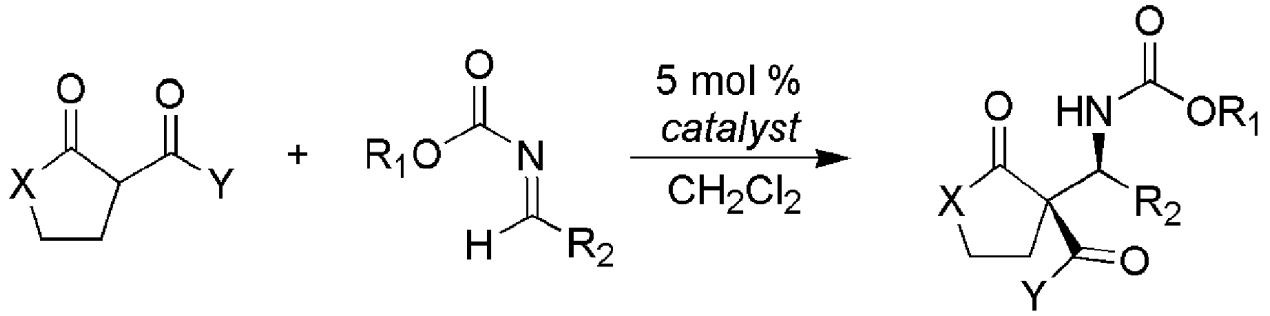
$(DHQD)_2PYR$

Poulsen *Angew. Chem., Int. Ed.* **2005,** *44,* 2896 - 2899

Used modified cinchona alkaloid as organocatalyst in Mannich reaction

Mannich Reactions Using Cinchona Alkaloids

Improved selectivity in cyclic systems



X = CH_2, Y = OCH_3
X = CH_2, Y = OCH_2CH_3
X = CH_2, Y = CH_3
X = O, Y = CH_3

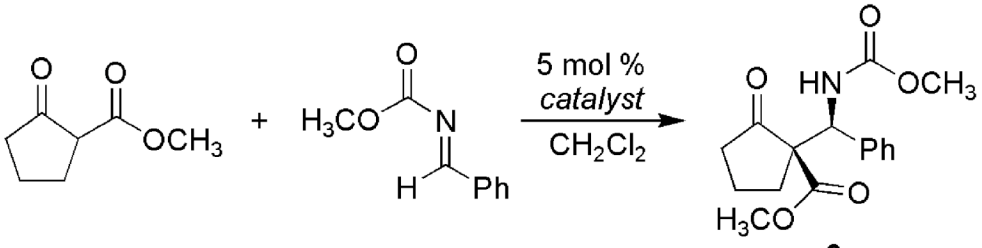
R_1 = CH_3, $CH_2CH{=}CH_2$
R_2 = Ar, (*E*)-$CH{=}CH_2Ar$

90-98% yield
90-99% de
90-99% ee

Expanded scope to cyclic 1,3-dicarbonyl compounds

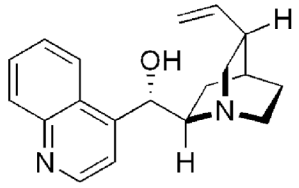
- Improved isolated yields
- Observed improved diastereo- and enantioselectivity
- Demonstrates potential for applications in organic synthesis

Screening of Chiral Lewis Bases

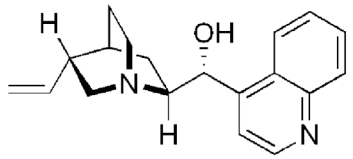


6a **7a** **9**

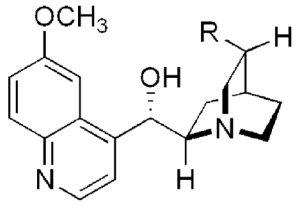
entry	catalyst	yield (%)[b]	de (%)[c]	ee (%)[c]
1	cinchonine **1**	96	93	90
2	cinchonidine **2**	96	94	−88
3	quinidine **3**	96	95	18
4	dihydroquinidine **4**	94	94	88
5	quinine **5**	95	94	−10



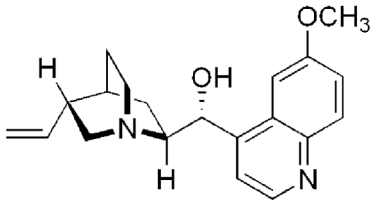
cinchonine **1**



cinchonidine **2**



R = $CH{=}CH_2$, *quinidine* **3**
R = CH_2CH_3, *dihydroquinidine* **4**



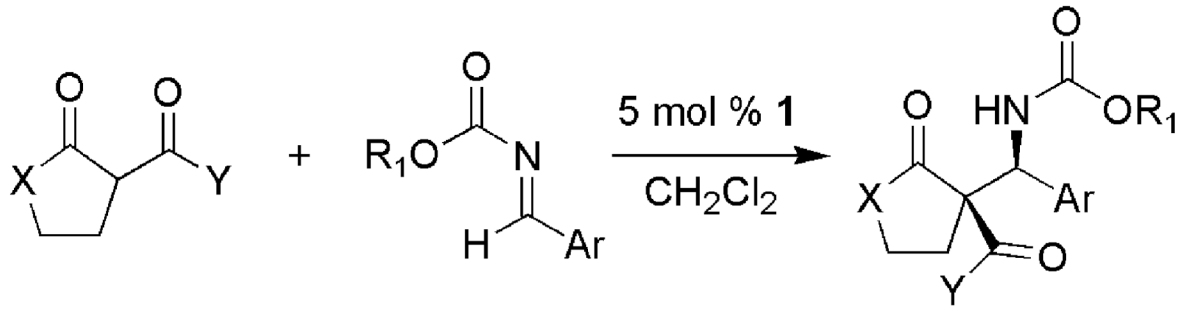
quinine **5**

Cinchona alkaloids were screened in asymmetric Mannich reaction

- Afford products in high yield and in high diastereo- and enantiomeric excess

Substrate Scope Using Cinchonine (1)

Addition of β-keto esters, β-keto lactones, and β-diketones to benzylidene carbamates



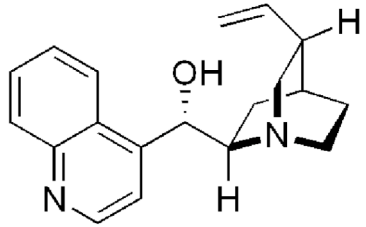
6a: X = CH_2, Y = OCH_3
6b: X = CH_2, Y = OCH_2CH_3
6c: X = CH_2, Y = CH_3
6d: X = O, Y = CH_3

7a-d: R_1 = CH_3
8a-b: R_1 = allyl

10-15

Cinchonine was established to be an effective catalyst for asymmetric synthesis

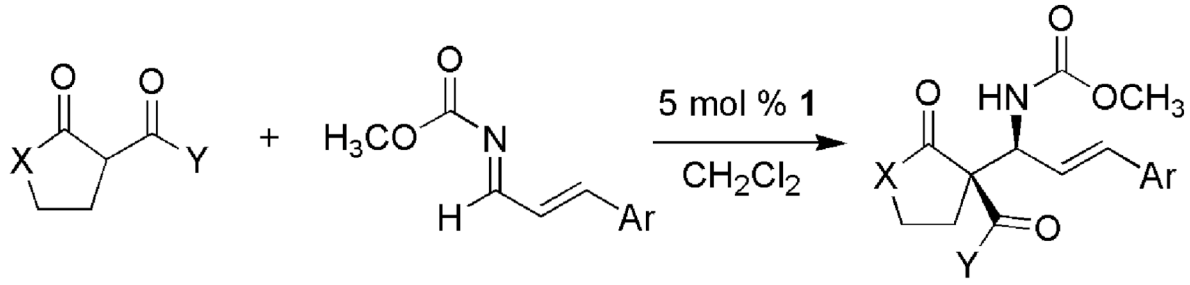
Yield (%) range	de (%) range	ee (%) range
78 - 98	38 - 99	90 - 99



cinchonine **1**

Substrate Scope Using Cinchonine (1)

Addition of β-keto esters, β-keto lactones, and β-diketones to aryl-propenyl acyl imines

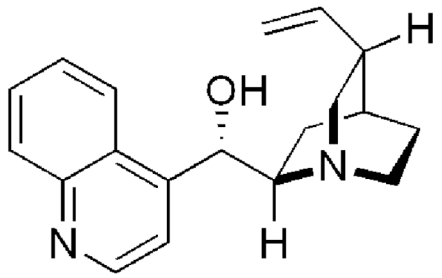


6a: X = CH_2, Y = OCH_3
6b: X = CH_2, Y = OCH_2CH_3
6c: X = CH_2, Y = CH_3
6d: X = O, Y = CH_3

17a-b

20, 21

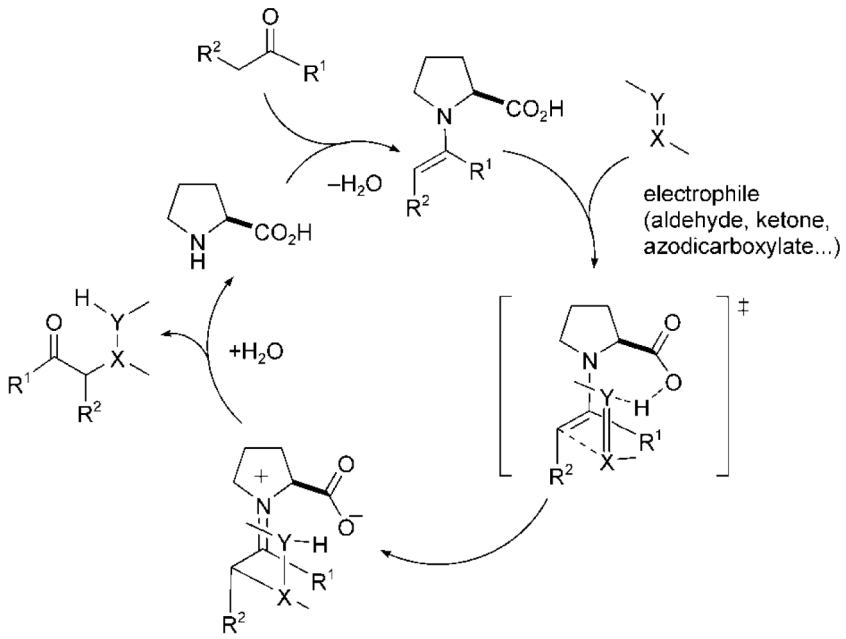
Yield (%) range	**de (%) range**	**ee (%) range**
88 - 98	38 - 99	93 - 99



cinchonine **1**

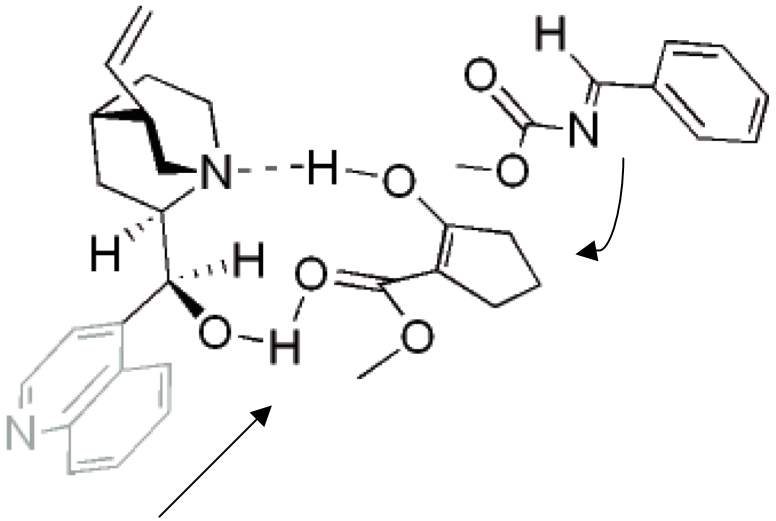
Transition States

Using molecular modeling to probe origin of selectivity in Cinchona-catalyzed Mannich reactions*



P. Dalko *Angew. Chem., Int. Ed.,* **2004,** *43,* 5138 - 5175

Imine approaches *re*-face of Cinchona-bound enolate



si-Face of enolate partially blocked by quinoline moiety

*Calculations performed using MMFF (Merck Molecular Force Field) to determine lowest-energy conformer of enol (above).

Summary & Next Directions

- *Cinchona alkaloids catalyze Mannich reactions to form highly diastereo- and enantioenriched products*

- *Using organocatalysts to facilitate highly diastereo- and enantioselective addition will continue to make this versatile reaction attractive*

- *Apply this methodology towards six-membered ring-containing β-keto esters and β-diketones*