

Enantioselective Organic Catalysis: Non-MacMillan Approaches

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8 November 2000

- I. Catalytic Antibodies and Multi-Peptide Catalysis
- II. Phase Transfer Catalysis
- III. Bifunctional Organic Catalysis
- IV. Phosphoramidate Catalysts
- V. Catalysis via Enamine Intermediates
- VI. Catalysts as Nucleophilic Triggers
- VII. Ketone Catalyzed Epoxidations
- VIII. Amine Catalyzed Epoxidations

Catalytic Antibodies and Multi-Peptide Catalysis

- Antibodies have been used to catalyze a range of specific transformations

Recent review, containing pertinent references: Hilvert, D., *Annu. Rev. Biochem.*, **2000**, *69*, 751.

Slightly older review: Hsieh-Wilson, L. C., Xiang, X., Schultz, P. G. *Acc. Chem. Res.*, **1996**, *29*, 164.

- Molecules consisting of multiple linked peptides have been used to catalyze a range of reactions, including azide conjugate additions, asymmetric acylations, the Strecker synthesis, epoxidations, and HCN additions. These reactions currently lack clear mechanistic understandings.

Relevant Articles:

Miller, S. J., *et al.*, *Angew. Chem. Int. Ed. Engl.*, **2000**, *39*, 3635.

Miller, S. J., *et al.*, *J. Am. Chem. Soc.*, **1999**, *121*, 11638.

Miller, S. J., *et al.*, *J. Org. Chem.*, **1998**, *63*, 6784.

Miller, S. J., *et al.*, *J. Am. Chem. Soc.*, **1998**, *120*, 1629.

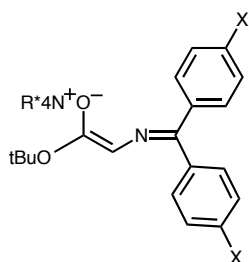
Lipton, M., *et al.*, *J. Am. Chem. Soc.*, **1996**, *118*, 4910.

Itsuno, S., *et al.*, *J. Org. Chem.*, **1990**, *55*, 6047.

Inoue, S., *et al.*, *J. Org. Chem.*, **1990**, *55*, 181.

Phase Transfer Catalysis: Support for Stereochemical Model

The intermediacy of a contact ion pair is supported by varying electronics of the enolate aryl substituents

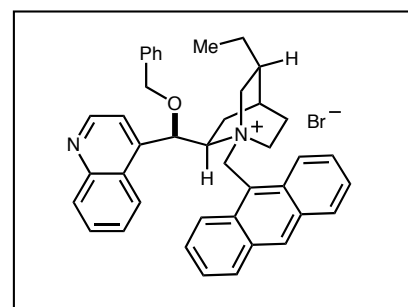
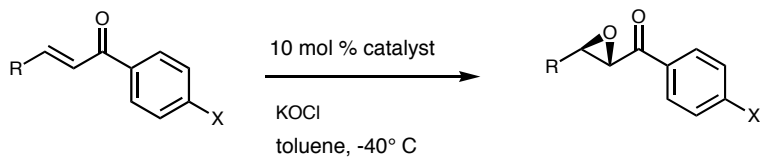


| X | H | tBu | OMe | NMe ₂ |
|------------|-----|-------|-------|------------------|
| σ_p | 0 | -0.15 | -0.28 | -0.63 |
| ee | 67% | 81% | 91% | 96% |

- As the value of σ becomes more negative, the aryl substituents become more electron-donating.
- As the aryl substituents become more electron donating, electron density on the enolate oxygen increases.
- More electron density on the enolate oxygen results in a tighter contact ion pair, bringing the substrate further into the chiral cavity, thereby accentuating the effect of the sterics in the cavity on bond formation \Rightarrow higher % ee

Corey, E. J., et al., *J. Am. Chem. Soc.*, **1998**, 120, 13000.

Phase Transfer Catalysis: Epoxidation of α,β -Unsaturated Ketones

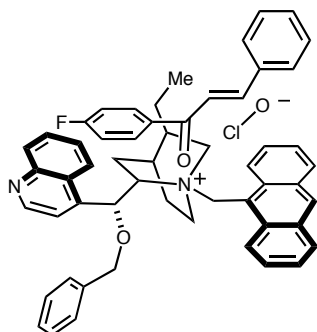
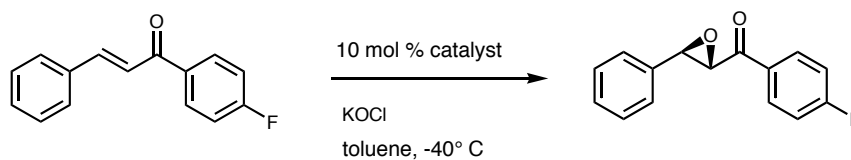


Cinchonine-derived catalyst

| R | X | % yield | % ee | R | X | % yield | % ee |
|--|----|---------|------|---|--|---------|------|
| C ₆ H ₅ | H | 96 | 93 | 4-CH ₃ -C ₆ H ₄ | H | 70 | 94 |
| C ₆ H ₅ | F | 93 | 98 | 4-Cl-C ₆ H ₄ | H | 94 | 92 |
| C ₆ H ₅ | Br | 92 | 93 | 4-Cl-C ₆ H ₄ | F | 94 | 98.5 |
| 4-NO ₂ -C ₆ H ₄ | H | 90 | 94 | 4-CH ₃ O-C ₆ H ₄ | H | 70 | 95 |
| 4-NO ₂ -C ₆ H ₄ | F | 97 | 95 | C ₆ H ₅ | C ₆ H ₅ O | 89 | 93 |
| n-C ₅ H ₁₁ | F | 90 | 91 | C ₆ H ₅ | 2,4-Br ₂ -C ₆ H ₃ O | 90 | 98 |
| cyclo-C ₆ H ₁₁ | H | 85 | 94 | β -naphthyl | H | 87 | 93 |
| cyclo-C ₆ H ₁₁ | F | 87 | 95 | | | | |

Corey, E. J., et al., *Org. Lett.*, **1999**, 1, 1287.

Phase Transfer Catalysis: Stereochemical Rationale for Epoxidation of α,β -Unsaturated Ketones



- Nucleophilic oxygen of ClO^- is proximate to β carbon of ketone
- 4-fluorophenyl group wedged between ethyl and quinoline substituents
- Carbonyl oxygen is placed close to N^+

Negative charge on O in TS is stabilized by proximate N^+



charge acceleration of nucleophilic attack

Corey, E. J., *et al.*, *Org. Lett.*, **1999**, 1, 1287.

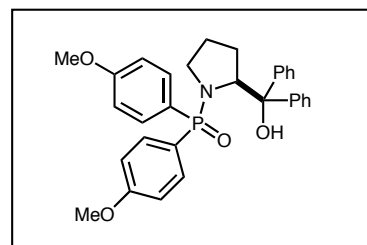
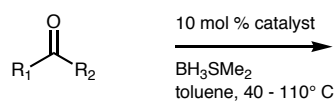
Cinchonidine-derived catalysts have been used in aldol and nitroaldol reactions: Corey, E. J., *et al.*, *Tetrahedron Lett.*, **1999**, 40, 3843.
Corey, E. J., *et al.*, *Angew. Chem. Int. Ed. Engl.*, **1999**, 38, 1931.

Conjugate additions of thiol have been reported: Wynberg, H., *J. Am. Chem. Soc.*, **1981**, 103, 417.

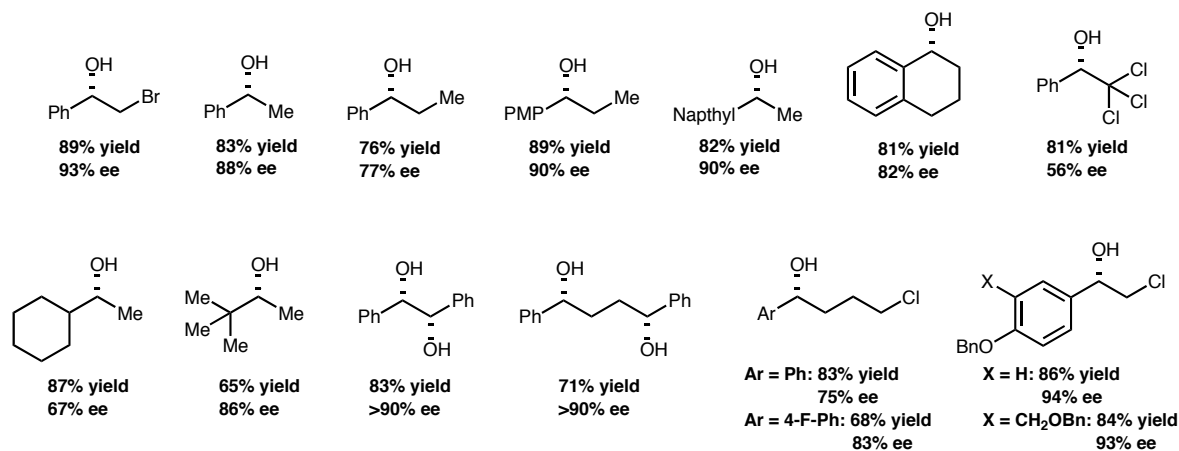
Analogous Michael reactions have been performed: Corey, E. J., *et al.*, *Org. Lett.*, **2000**, 2, 1097; Corey, E. J., *et al.*, *Tetrahedron Lett.*, **1998**, 39, 5347.

A Diels-Alder reaction has been reported: Kagan, H., *Tetrahedron Lett.*, **1989**, 30, 7403.

Bifunctional Enantioselective Organic Catalysts: Ketone Reduction

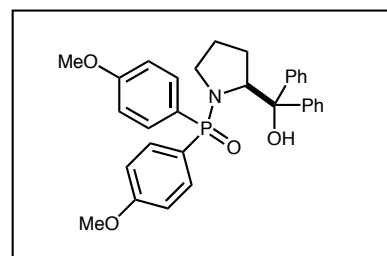
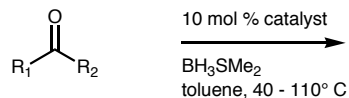


Phosphinamide catalyst

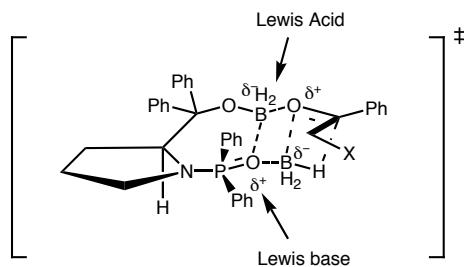


Wills, M., *et al.*, *J. Org. Chem.*, **1998**, 63, 6068.

Bifunctional Enantioselective Organic Catalysts: Stereochemical Rationale for Ketone Reduction



Phosphinamide catalyst



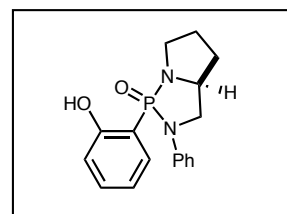
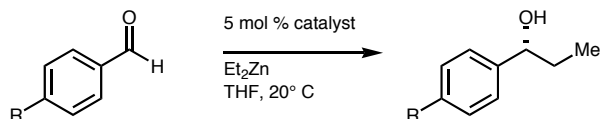
- High temperatures are required to facilitate catalyst turnover after reduction (to break the numerous B–O bonds)

- ^{11}B and ^{31}P NMR studies indicate no decomposition of catalyst

- Anhydrous conditions not required

Wills, M., et al., *J. Org. Chem.*, **1998**, 63, 6068.

Bifunctional Enantioselective Organic Catalysts: Diethyl Zinc Addition

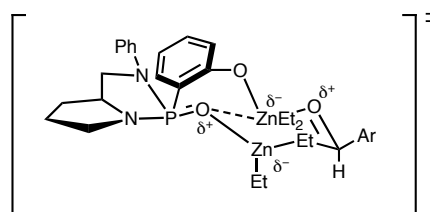


Diazaphospholidine catalyst

| R | % yield | % ee |
|------------------|---------|------|
| H | 98 | 73 |
| NMe ₂ | 98 | 71 |
| Cl | 84 | 86 |
| CN | 91 | >99 |

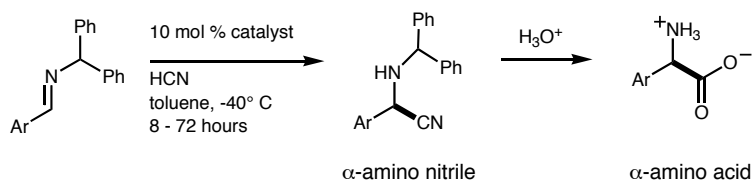
- Electron withdrawing substituents result in increase in enantioselectivity

Possible transition state

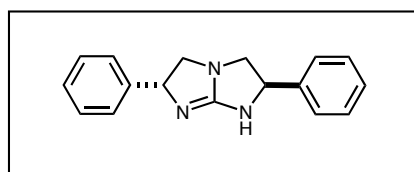


Buono, G., et al., *Tetrahedron Lett.*, **1998**, 39, 2961.

Bifunctional Enantioselective Organic Catalysts: Strecker Synthesis



| Ar | % yield | % ee |
|------------|---------|------|
| Ph | 96 | 86 |
| p-tolyl | 96 | 80 |
| 3,5-xylyl | 96 | 79 |
| o-tolyl | 88 | 50 |
| 4-tBu-Ph | 80 | 85 |
| 4-TBSO-Ph | 98 | 88 |
| 4-MeO-Ph | 99 | 84 |
| 4-F-Ph | 97 | 86 |
| 4-Cl-Ph | 88 | 81 |
| 1-naphthyl | 90 | 76 |

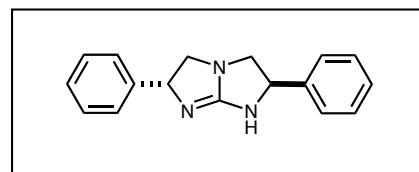
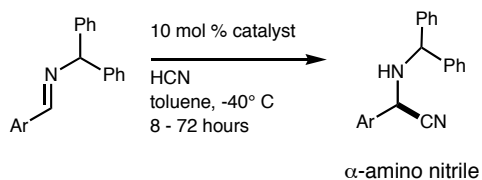


C_2 -symmetric Guanidine catalyst

- No background reaction below 10° C
- N-methyl derivative of catalyst is inactive

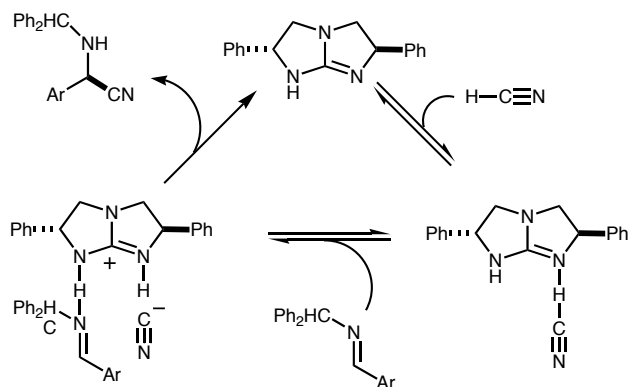
Corey, E.J., et al., *Organic Lett.*, **1999**, 1, 157.

Bifunctional Enantioselective Organic Catalysts: Mechanism and Stereochemical Rationale for Corey's Strecker Synthesis

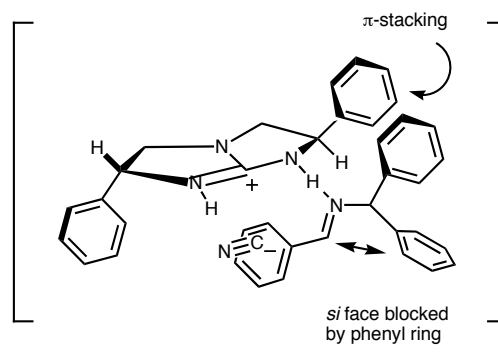


C_2 -symmetric Guanidine catalyst

■ Catalyst Cycle

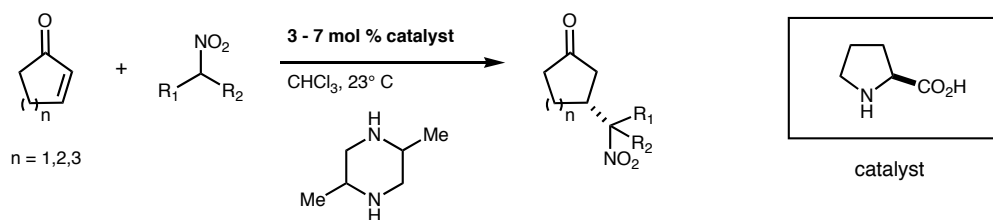


■ Pre-transition state assembly predicts outcome

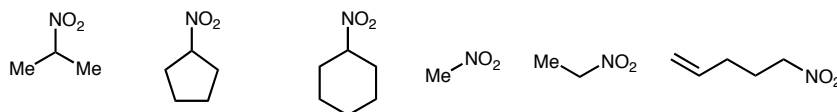


Corey, E.J., et al., *Organic Lett.*, **1999**, 1, 157.

Bifunctional Enantioselective Organic Catalysts: Conjugate Addition



nucleophile

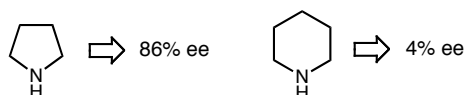


30 - 88% yield

71 - 93% ee

1:1 dr where relevant

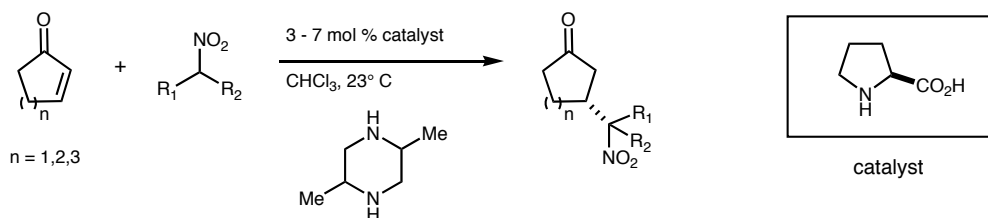
- $n = 2$ (cyclohexenone) affords best ee
- Numerous basic additives tried: basicity and structure have large effect on ee



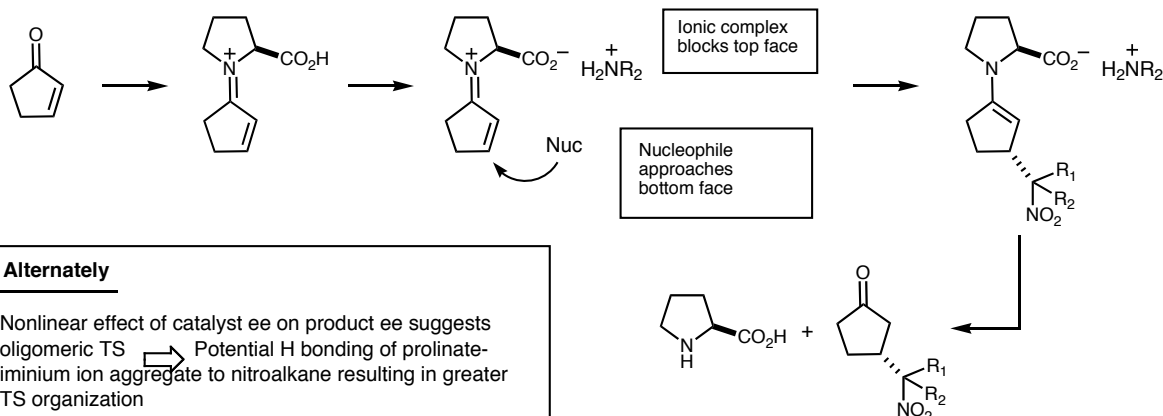
- This work is an extension of Yamaguchi's work using Rubidium prolinates:
 Yamaguchi, M., *et al.*, *Tetrahedron*, **1997**, *53*, 11223.

Hanessian, S., *et al.*, *Organic Lett.*, **2000**, *2*, 2975.

Bifunctional Enantioselective Organic Catalysts: Possible Mechanism of Conjugate Addition



- Possible iminium ion intermediate

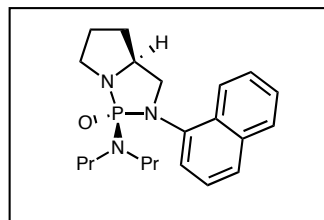
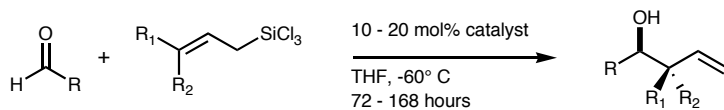


Alternately

Nonlinear effect of catalyst ee on product ee suggests oligomeric TS \Rightarrow Potential H bonding of prolinates-iminium ion aggregate to nitroalkane resulting in greater TS organization

Hanessian, S., *et al.*, *Organic Lett.*, **2000**, *2*, 2975.

Enantioselective Catalysis by Phosphoramides: Aldehyde Allylation



catalyst

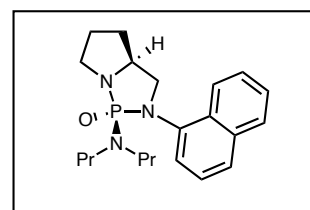
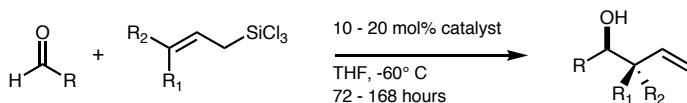
| R | R ₁ | R ₂ | % yield | <i>syn:anti</i> | % ee |
|------------------------------------|----------------|----------------|---------|-----------------|------|
| C ₆ H ₅ | H | H | 83 | -- | 88 |
| 2-MeC ₆ H ₄ | H | H | 86 | -- | 81 |
| C ₆ H ₅ | Me | H | 80 | 98:2 | 77 |
| C ₆ H ₅ | H | Me | 90 | 2:98 | 83 |
| 2-MeC ₆ H ₄ | Me | H | 78 | >99:1 | 83 |
| 4-tBuC ₆ H ₄ | Me | H | 72 | 95:5 | 82 |

- Unlike Lewis acid catalyzed addition of crotylsilanes and crotylstannanes, this reaction allows access to both *syn* and *anti* homoallylic alcohols

Iseki, K., *et al.*, *Tetrahedron*, **1997**, *53*, 3513.

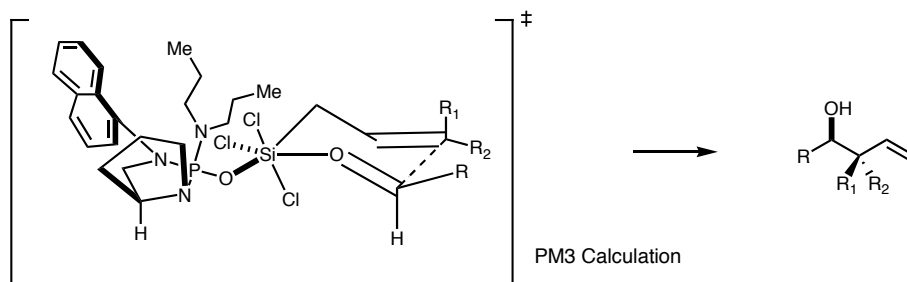
For a review of Phosphorus reagents in enantioselective catalysis, see: Buono, G., *et al.*, *Synlett*, **1999**, 377.

Enantioselective Catalysis by Phosphoramides: Mechanism of Aldehyde Allylation



catalyst

- Chair-like transition state accounts for observed diastereo- and enantioselectivity

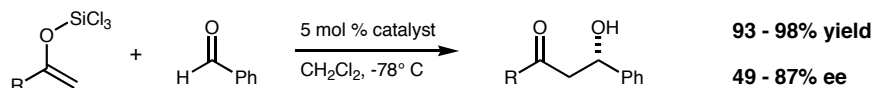


- Hexacoordinate silicate proposed
- Larger N(alkyl)₂ of phosphoramidate leads to higher ee's

Iseki, K., *et al.*, *Tetrahedron*, **1997**, *53*, 3513.

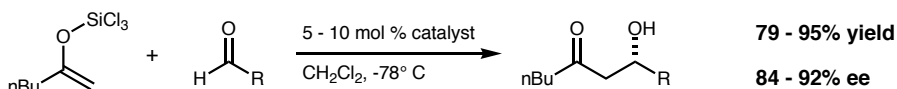
Enantioselective Catalysis by Phosphoramides: Acetate Aldol Reaction

■ Variation in the trichlorosilyl enol ether component



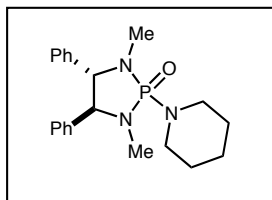
R = Me, nBu, iBu, iPr, tBu, Ph, CH₂OSiMe₃tBu

■ Variation in the aldehyde component



R = cinnamyl, α -methylcinnamyl, naphthyl, 4-phenyl-phenyl, cyclohexyl, tBu

The catalyst

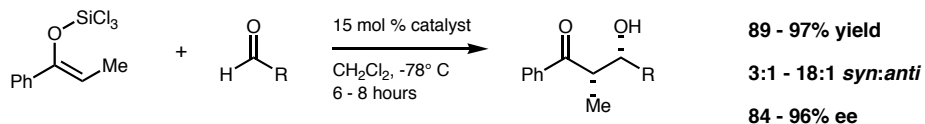


- Trichlorosilyl enol ethers are prepared from the corresponding trimethylsilyl enol ethers by treatment with SiCl₄ and catalytic Hg(OAc)₂

Denmark, S. E., *et al.*, *J. Org. Chem.*, **1998**, 63, 918.

Enantioselective Catalysis by Phosphoramides: Syn and Anti Aldol Reactions

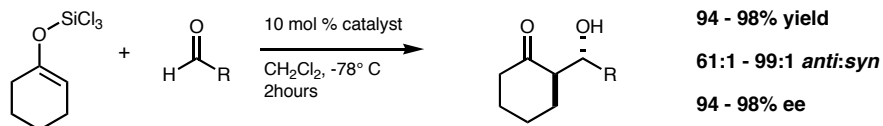
■ Propionate aldol with various aldehydes



R = cinnamyl, naphthyl, phenyl, tolyl, crotyl

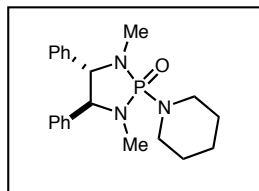
The uncatalyzed reaction at 0° C is slightly anti selective (2:1)

■ Enforced E-enol silane aldol reaction: *anti* selective



R = cinnamyl, α -methylcinnamyl, naphthyl, phenyl

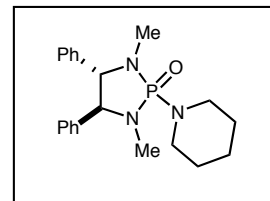
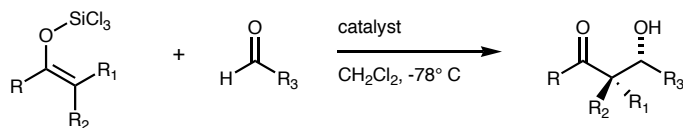
The uncatalyzed reaction at 0° C is very syn selective (5:1 - 49:1)



The catalyst

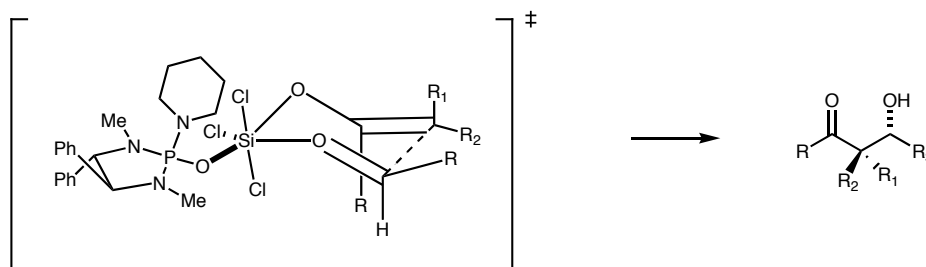
Denmark, S. E., *et al.*, *J. Am. Chem. Soc.*, **1996**, 118, 7404.
Denmark, S. E., *et al.*, *J. Am. Chem. Soc.*, **1997**, 119, 2333.

Enantioselective Catalysis by Phosphoramides: Mechanism of the Aldol Reactions



The catalyst

- Chair-like transition state accounts for observed diastereo- and enantioselectivities

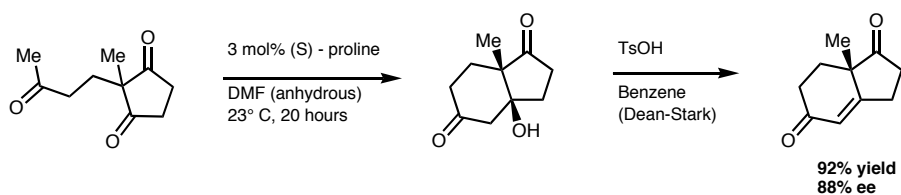


Hexacoordinate silicate proposed

Iseki, K., et al., *Tetrahedron*, **1997**, 53, 3513.

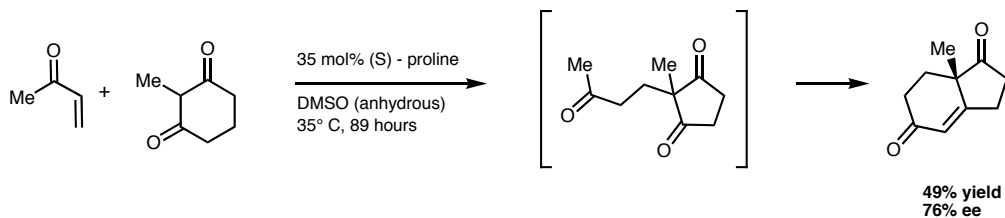
Catalysis Involving Enamine Intermediates: Robinson Annulation

- Initial report: Hajos



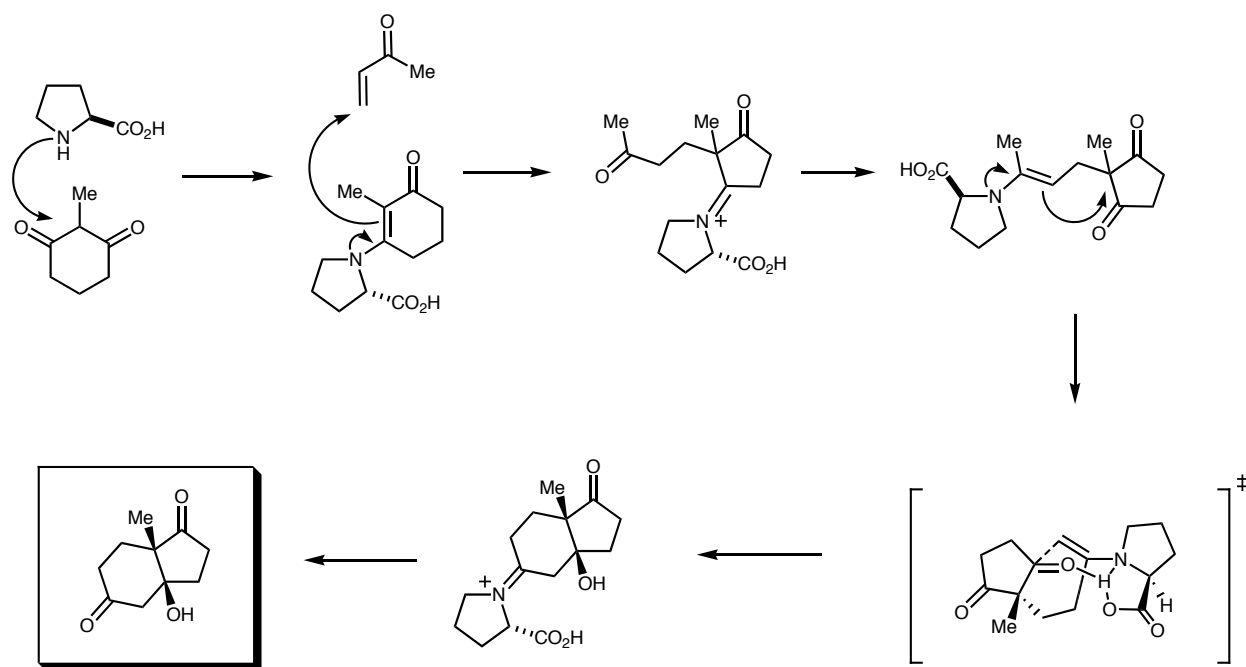
Hajos, Z. G., *J. Org. Chem.*, **1974**, 39, 1615.

- Extension to one-pot annulation: Barbas



Barbas III, C. F., *Tetrahedron Lett.*, **2000**, 41, 6951.

Catalysis Involving Enamine Intermediates: Mechanism of the Robinson Annulation



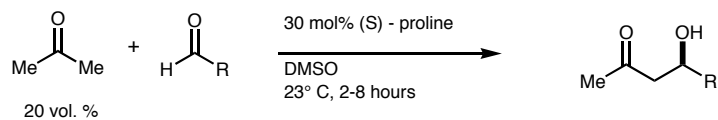
■ Chair-like transition state accounts for observed stereochemistry

Agami, C., *et al.*, *Tetrahedron*, **1984**, *40*, 1031.

Hajos, Z. G., *J. Org. Chem.*, **1974**, *39*, 1615.

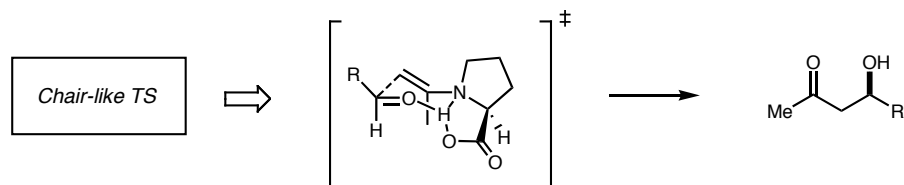
List, B., *et al.*, *J. Am. Chem. Soc.*, **2000**, *122*, 2395.

Catalysis Involving Enamine Intermediates: Acetate Aldol Reaction



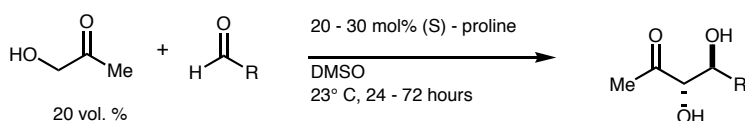
| R | % yield | % ee | R | % yield | % ee |
|---|---------|------|---|---------|------|
| | 68 | 76 | | 97 | 96 |
| | 62 | 60 | | 94 | 69 |
| | 74 | 65 | | 54 | 77 |

■ Enamine intermediate is proposed, in analogy to the Robinson annulation



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

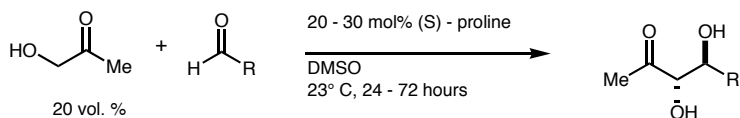
Catalysis Involving Enamine Intermediates: Anti Aldol Reaction



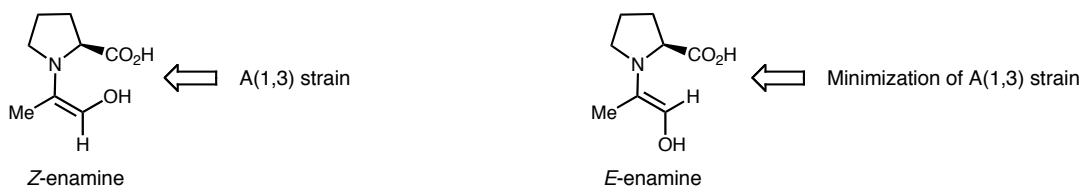
| R | % yield | anti:syn | % ee | R | % yield | anti:syn | % ee |
|---|---------|----------|------|---|---------|----------|------|
| | 60 | >20:1 | >99 | | 62 | >20:1 | >99 |
| | 38 | 1.7:1 | >97 | | 95 | 1.5:1 | 67 |
| | 40 | 2:1 | >97 | | 51 | >20:1 | >95 |

List, B., et al., *J. Am. Chem. Soc.*, **2000**, *122*, 7386.

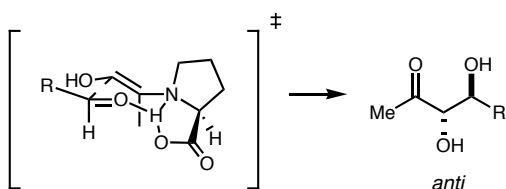
Catalysis Involving Enamine Intermediates: Mechanistic Aspects of the Anti Aldol Reaction



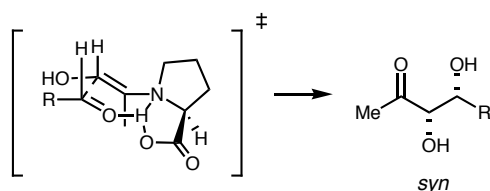
■ *E*-enamine geometry due to minimization of A(1,3) strain



■ Chair-like transition state is proposed

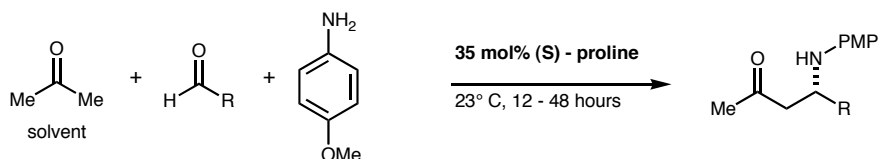


■ Boat-like transition state explains origin of *syn* isomer for less hindered and α -oxygenated aldehydes



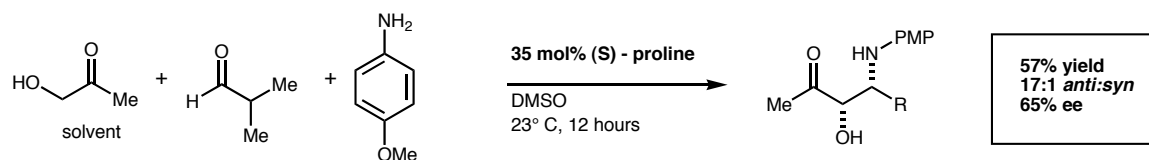
List, B., et al., *J. Am. Chem. Soc.*, **2000**, *122*, 7386.

Catalysis Involving Enamine Intermediates: Mannich Reaction



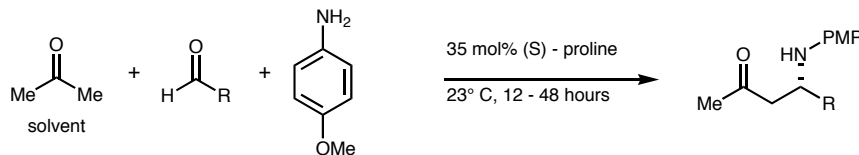
| R | % yield | % ee | R | % yield | % ee |
|---|---------|------|---|---------|------|
| | 50 | 94 | | 56 | 70 |
| | 35 | 96 | | 90 | 93 |
| | 82 | 75 | | 74 | 73 |

- Hydroxy acetone can be used in place of acetone



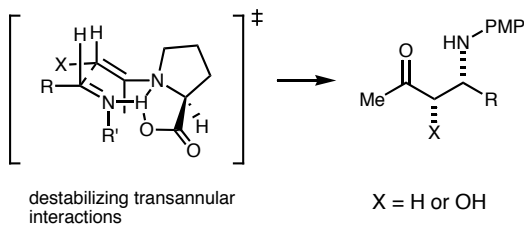
List, B. *J. Am. Chem. Soc.*, **2000**, 122, 9336.

Catalysis Involving Enamine Intermediates: Mechanistic Aspects of the Mannich Reaction

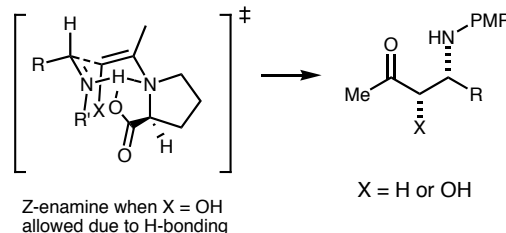


- Two potential transition states proposed

boat-like TS

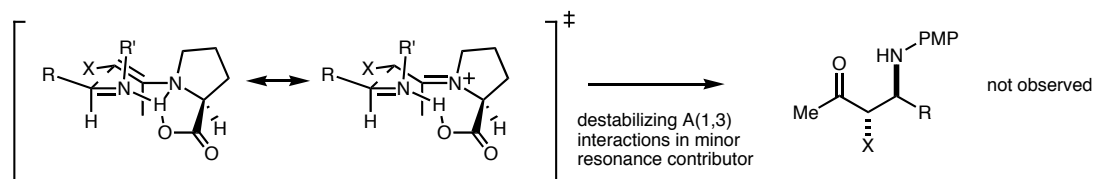


chair-like TS



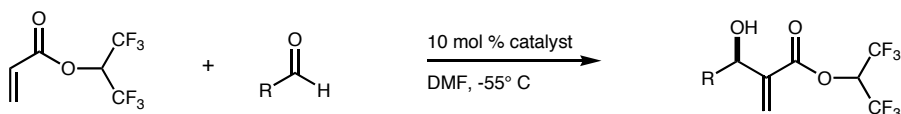
- Opposite sense of stereoselection observed compared to proline-catalyzed aldol reactions

Chair-like TS of aldol reaction disfavored

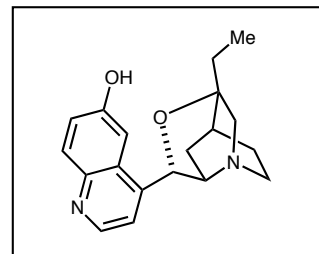


List, B. *J. Am. Chem. Soc.*, **2000**, 122, 9336.

Catalyst as Nucleophilic Trigger: Baylis-Hillman Reaction



| R | time (hours) | % yield | % ee |
|---|--------------|---------|------|
| p-NO ₂ Ph | 1 | 58 | 91 |
| Ph | 48 | 57 | 95 |
| cinnamyl | 72 | 50 | 92 |
| Et | 4 | 40 | 97 |
| (CH ₃) ₂ CHCH ₂ | 4 | 51 | 99 |
| (CH ₃) ₂ CH | 16 | 36 | 99 |
| cyclohexyl | 72 | 31 | 99 |
| tBu | 72 | NR | -- |

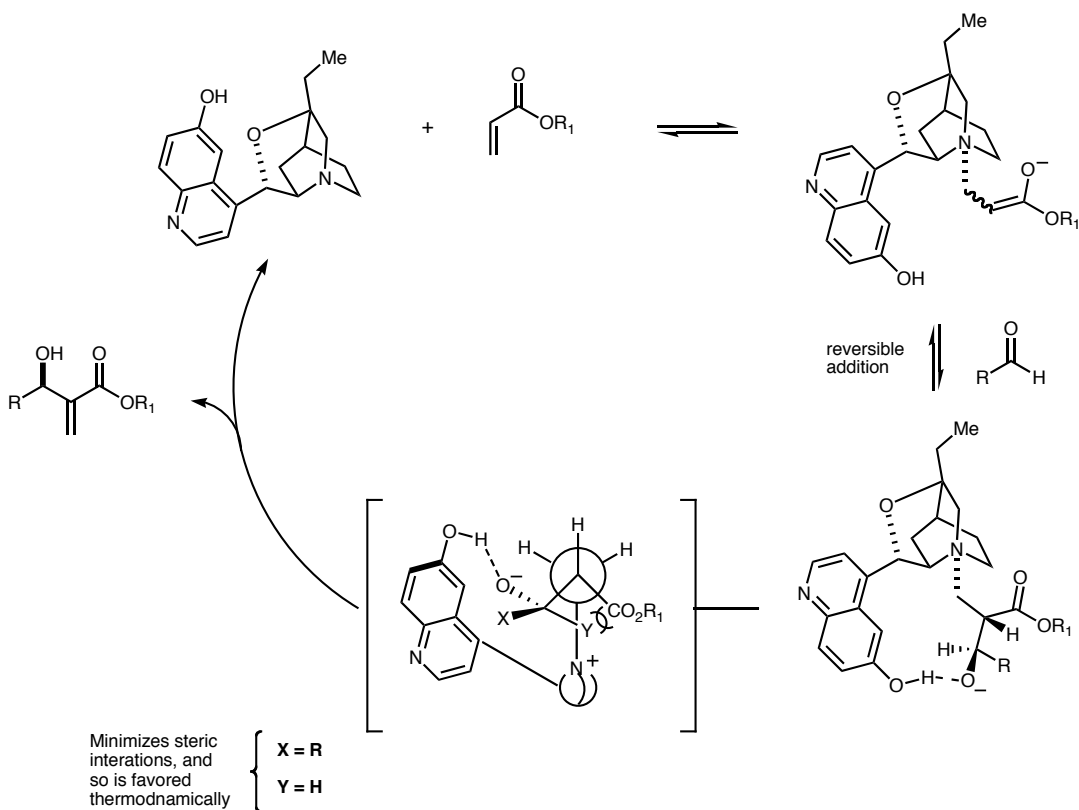


Quinidine-derived catalyst

■ Me ester is less reactive, requiring higher temperatures, resulting in lower ee's

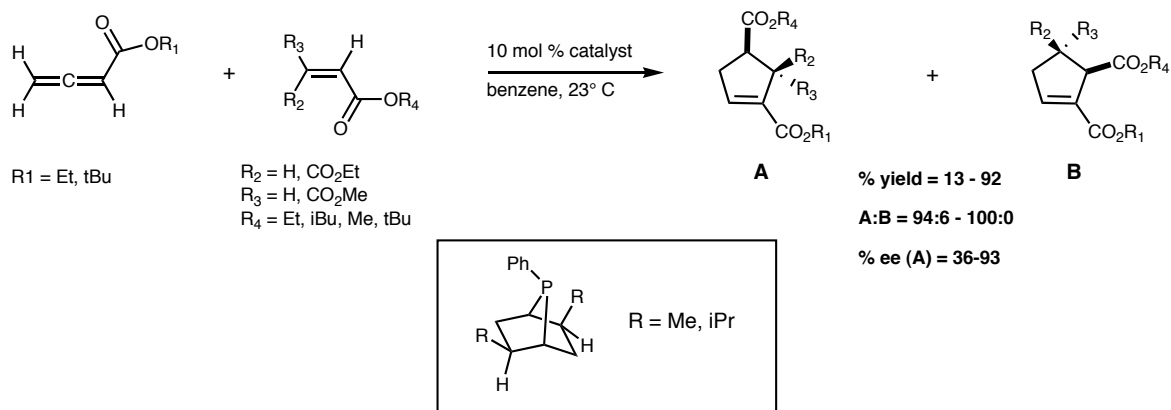
Hatakeyama, S., *et al.*, *J. Am. Chem. Soc.*, **1999**, 121, 10219.

Catalyst as Nucleophilic Trigger: Mechanism of the Baylis-Hillman Reaction

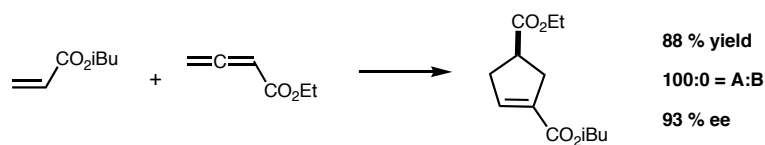


Hatakeyama, S., *et al.*, *J. Am. Chem. Soc.*, **1999**, 121, 10219.

Catalyst as Nucleophilic Trigger: [3+2] Cycloaddition



■ Best case:

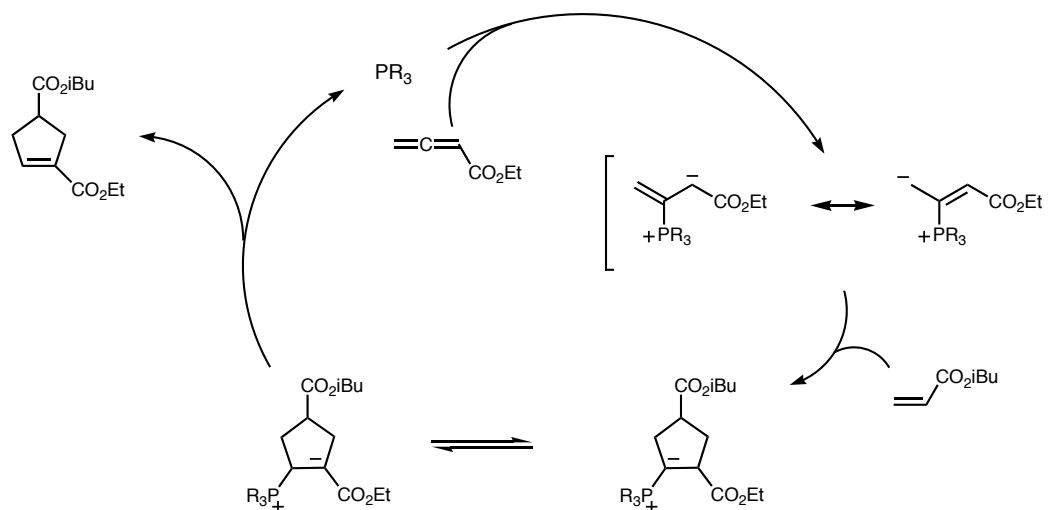


■ Size of R₄ alters enantioselectivity

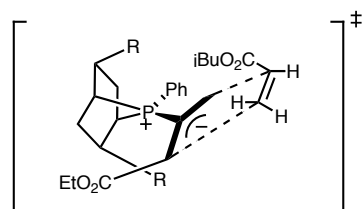
■ Rigid catalyst structure is important for enantioselectivity

Zhang, X., et al., *J. Am. Chem. Soc.*, **1997**, 119, 3836.

Catalyst as Nucleophilic Trigger: Mechanism of [3+2] Cycloaddition



■ Concerted bond rearrangement

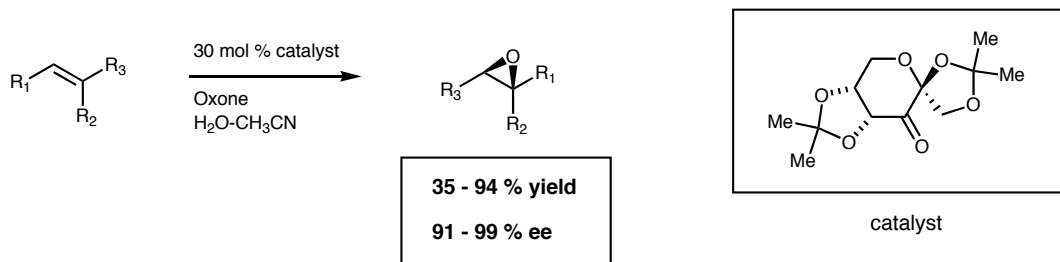


■ Concerted mechanism supported by preservation of olefin geometry

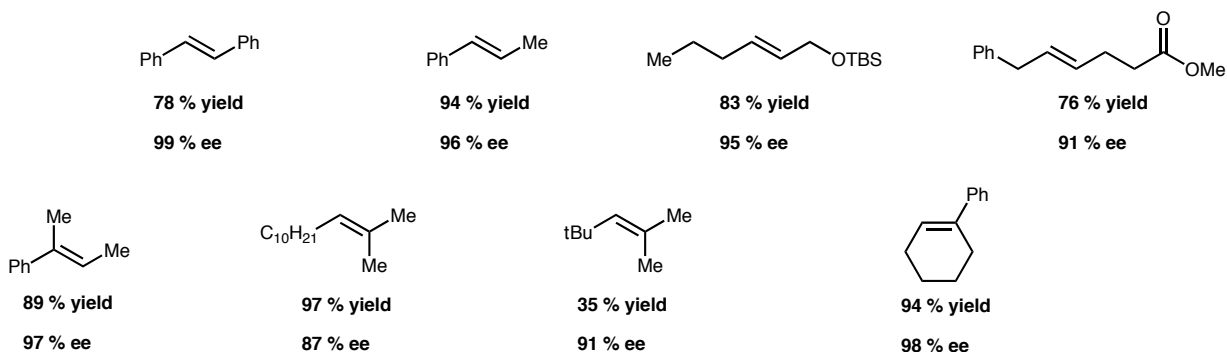
■ Achiral version of this reaction reported by Xiyan Lu: *J. Org. Chem.*, **1995**, 60, 2908.

Zhang, X., et al., *J. Am. Chem. Soc.*, **1997**, 119, 3836.

Chiral Ketone Catalyzed Alkene Epoxidation: Initial Report from Shi

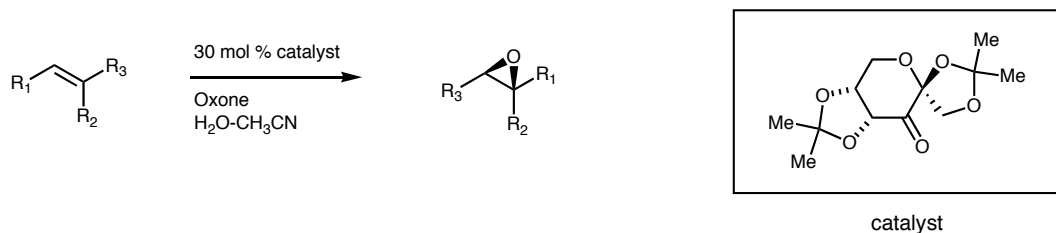


- Reaction tolerates alkyl, aryl, heteroatom-containing substituents
- Catalyst works well with *trans* disubstituted olefins and trisubstituted olefins
- Representative examples:

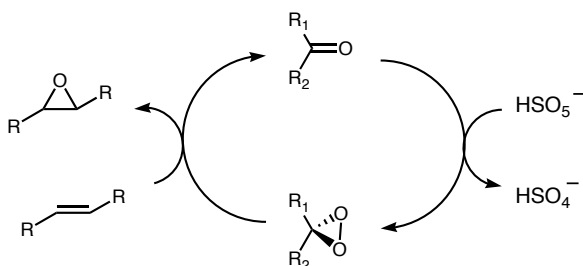


Shi, Y., et al., *J. Am. Chem. Soc.*, **1997**, 119, 11224.

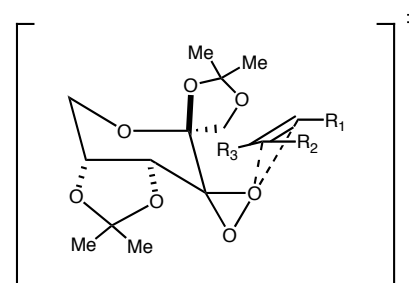
Chiral Ketone Catalyzed Alkene Epoxidation: Mechanism of the Shi Epoxidation



■ Catalytic Cycle



■ Proposed spiro TS



Shi, Y., et al., *J. Am. Chem. Soc.*, **1997**, 119, 11224.

Catalyst system also works for conjugated dienes: *J. Org. Chem.*, **1998**, 63, 2948.

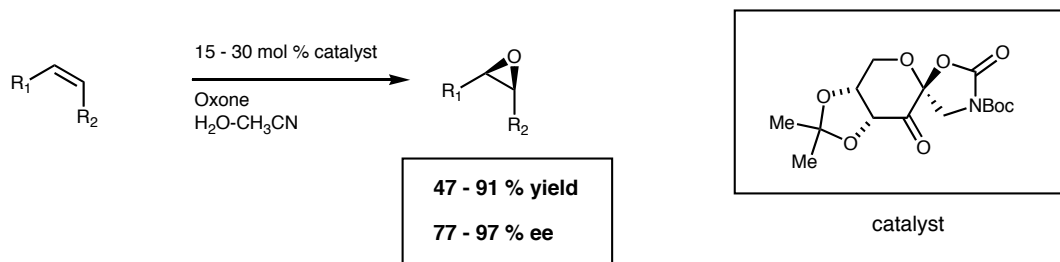
hydroxy alkenes: *J. Org. Chem.*, **1998**, 63, 3099.

conjugated enynes: *J. Org. Chem.*, **1999**, 64, 7646.

2,2-disubstituted vinylsilanes: *J. Org. Chem.*, **1999**, 64, 7675.

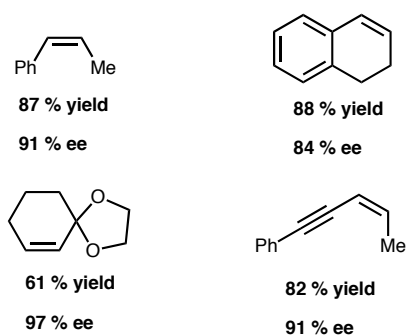
kinetic resolution of racemic cyclic olefins: hydroxy alkenes: *J. Am. Chem. Soc.*, **1999**, 121, 7718.

Chiral Ketone Catalyzed Alkene Epoxidation: *cis* Olefins with Shi's Catalyst

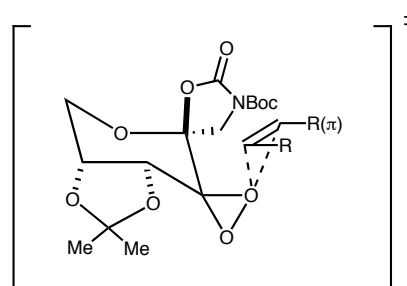


- Reaction tolerates cyclic and acyclic alkenes
- Reaction requires either R₁ or R₂ have π-electrons or a heteroatom

Representative examples:

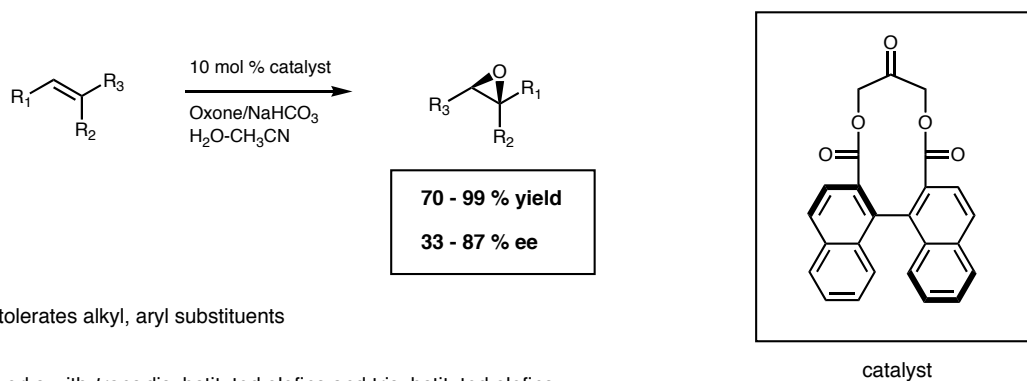


Proposed spiro TS



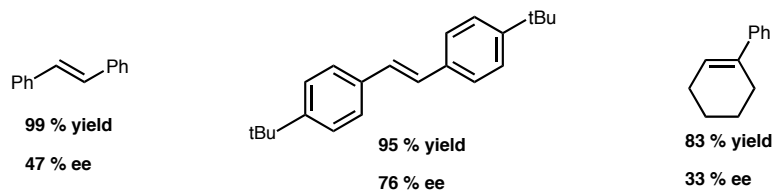
Shi, Y., et al., *J. Am. Chem. Soc.*, **2000**, ASAP.

Chiral Ketone Catalyzed Alkene Epoxidation: Initial Report from Yang



- Reaction tolerates alkyl, aryl substituents
- Catalyst works with *trans* disubstituted olefins and trisubstituted olefins

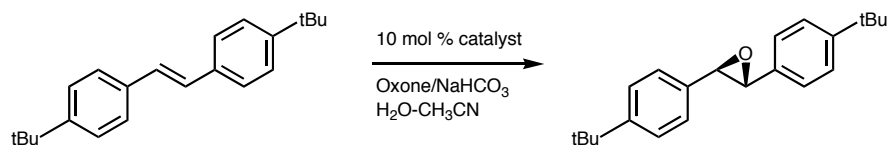
Representative examples:



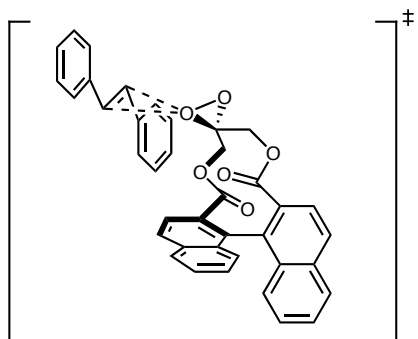
Yang, D., et al., *J. Am. Chem. Soc.*, **1998**, *120*, 5943.

Chiral Ketone Catalyzed Alkene Epoxidation: Developments by Yang

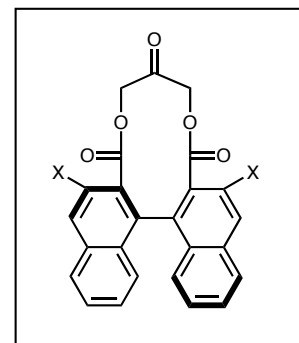
- Modifications to catalyst increase ee of stilbene reactions



- Stereochemical Rationale for Yang Epoxidation (Macromodel)



| X | % ee |
|----|------|
| | 90 |
| Cl | 91 |
| Br | 95 |

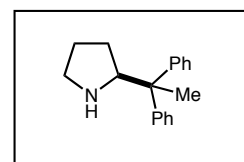
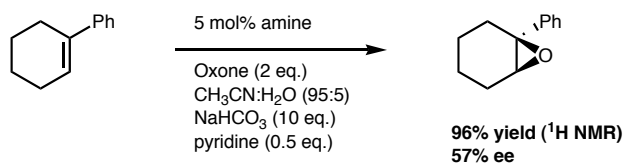


catalyst

Yang, D., *et al.*, *J. Am. Chem. Soc.*, **1998**, *120*, 5943.

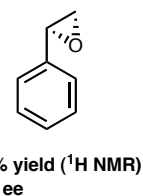
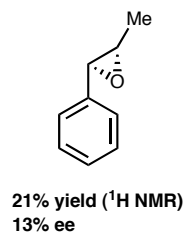
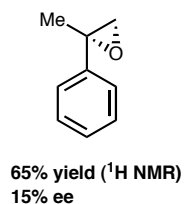
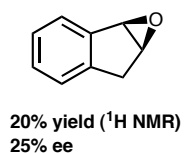
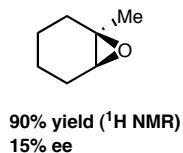
- More ketone catalyzed epoxidation: Denmark, *et al.*, *J. Org. Chem.*, **1997**, *62*, 8288.
Armstrong, A., *et al.*, *Chem. Commun.*, **1998**, 621.

Amine Catalyzed Alkene Epoxidation



Amine Catalyst

- The hit parade:

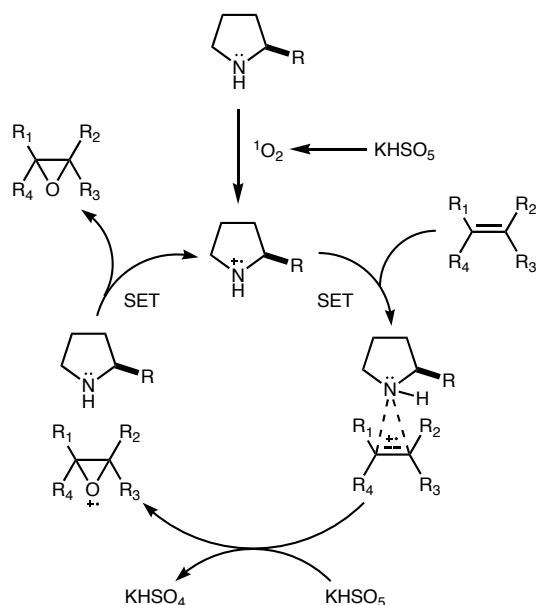


- Stilbenes and disubstituted aliphatic alkenes do not react

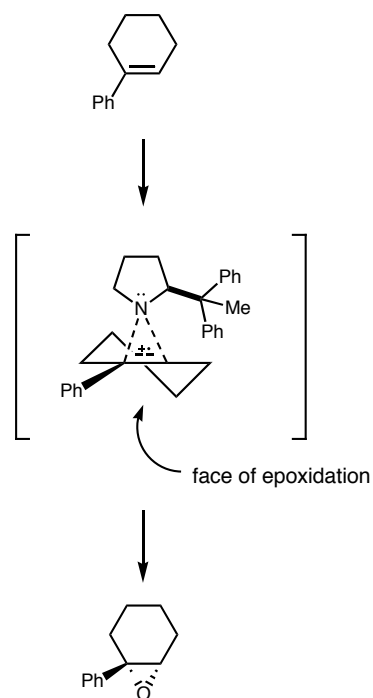
Adamo, M. F., *et al.*, *J. Am. Chem. Soc.*, **2000**, *122*, 8317.

Radical Cation Intermediates: Amine Catalyzed Alkene Epoxidation

Proposed catalytic cycle for the alkene epoxidation



Rationale for Observed Stereochemical Outcome



Adamo, M. F., *et al.*, *J. Am. Chem. Soc.*, **2000**, 122, 8317.

In Conclusion

- Many reactions are catalyzed enantioselectively by organic molecules.
- These reactions can be grouped by the mode of catalysis, deriving from the fact that numerous, quite different approaches to organic catalysis have been developed.
- Despite much success, often the organocatalyzed reactions lack generality (low yields, low ee's, and/or poor substrate scope).
- As well, the *modes of catalysis* often lack generality -- rarely has a catalyst system been applied successfully to several different reactions.
- Consequently, vast room for improvement remains; these examples may act as food for thought.