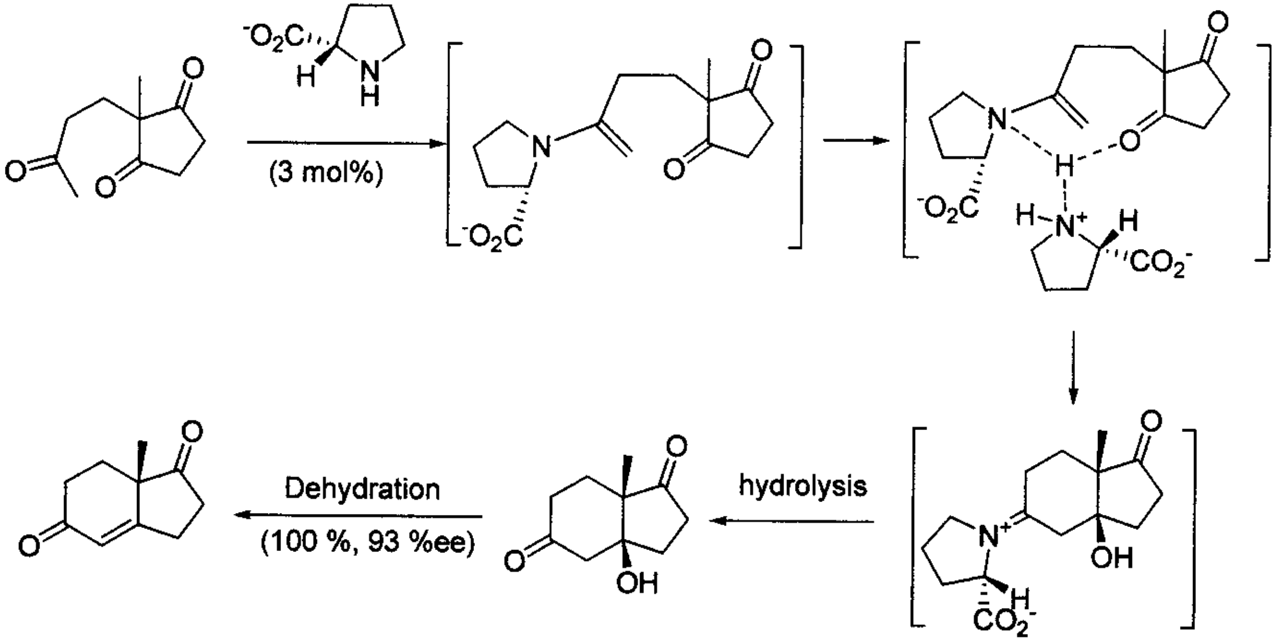
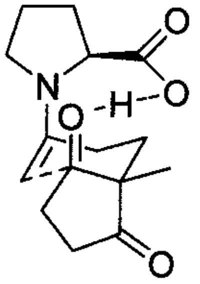
12-06-03
Gil Ma

Asymmetric Organocatalyst and Polymer-supported Organocatalyst

In **1971**, Eder, Sauer and Wiechert demonstrated that asymmetry could be induced in a Robinson-type annulation unsing a *meso*-triketone by simply adding a catalytic amount of D- or L-proline.

Eder, U; Sauer, G.; Wiechert, R. *ACIEE*. **1971**, *10*, 496-497.



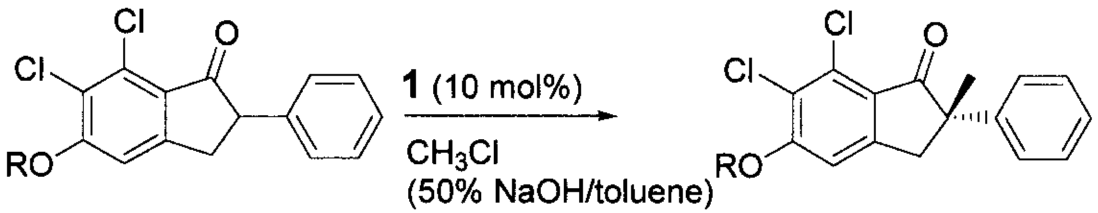


Houk

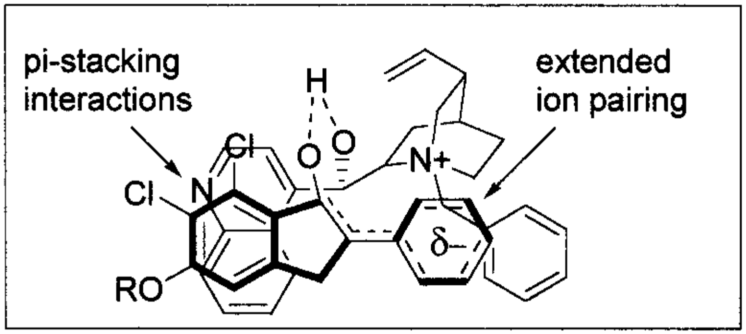
Cinchoninium-based Catalysts and Asymmetric Phase Transfer Catalysis (PTC)

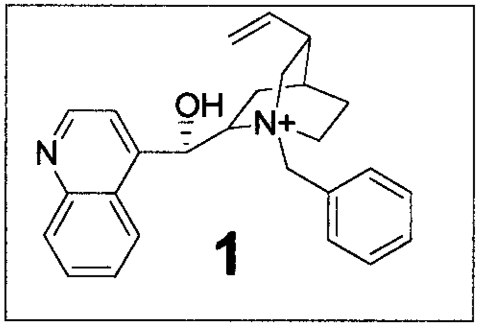
- In 1984 at Merck, substituted 2-phenyl-1-indanone was enantioselectively alklyalted in the presence of catalytic amounts of substituted *N*-benzylcinchoninium halides under PTC conditions (50%NaOH/toluene).

Dolling, U. H.; Davis, P.; Grabowski, E. J. *JACS*, **1984**, *106*, 446.



95 %, 92 %ee





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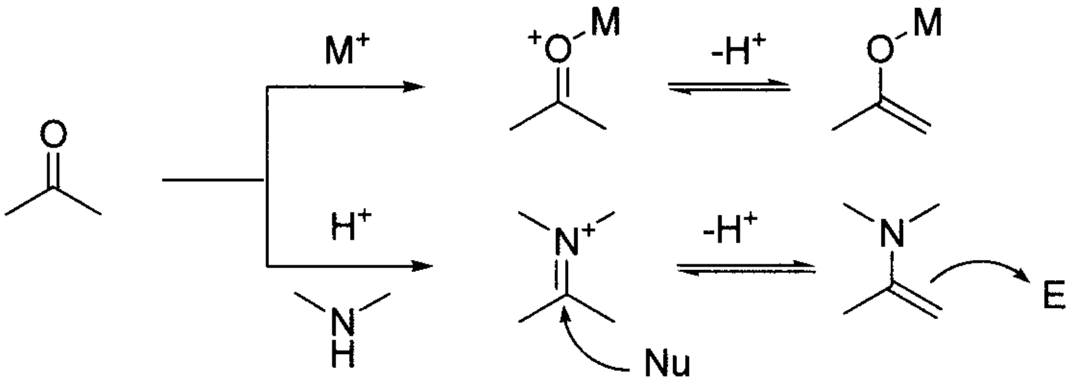
Contents and reference.

- 1. introduction
- 2. Examples of asymmetric organocatalysis.
- 3. Polymer-supported organocatalysts.

- Review.
  1. Enationselective Organocatalysis; Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3726.
  2. Polymer-Supported Organic Catalysits; Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.
  3. Amino acids and peptides as asymmetric organocatalysts; Jarvo, E. R.; Miller, S. J. *Tetrahedron*, **2002**, *58*, 2481.
  4. Proline-catalyzed asymmetric reactions; List, B. *Tetrahedron*, **2002**, *58*, 5573.

Asymmetric organometalcatalysis, Enzyme and Organocatalysis.

- Organocatalysis display characteristic and mechanistic similarities to known bioorganic catalysis and are often referred to as enzyme mimics.



ketoacid decarboxylases

class I aldolases

- Enzymes are more than highly evolved catalysts, but organic molecules promote the reactions as simple reagents, which possess a wider substrate scope and can be used in a variety of organic solvents.
- Many organocatalysts are ligands in organometal chemistry.
- Complement each other.

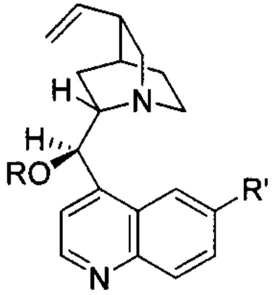
What and why organocatalysis ?

- Asymmetric organocatalysis, in which a chiral *organic (metal free)* molecules catalyze an enantioselective transformation, such as phase transfer catalysis, kinetic resolutions and a variety of asymmetric syntheses in substoichiometric quantity.

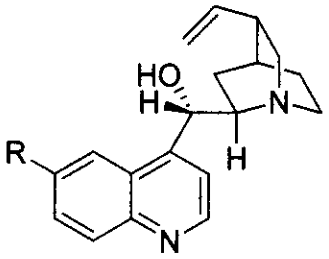
- Advantage under metal-free condition; the possibility of
  - i. working in wet solvents and under an aerobic atmosphere.
  - ii. simpler preparation, more stable, less expensive
  - iii. avoid the contamination of the organic product by a (possibly toxic) metal and the toxic waste. (often more environmentally friendly)
  - iv. more readily amenable to anchor on a support for recovery and recycling.
  - v. promising adaptability to high-throughput screening and process chemistry.

What type of Catalyst ?

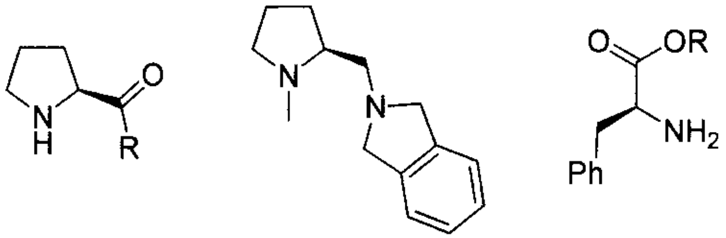
- 1. derived from Natural products and derivatives;
  cinchono alkaloid, proline, ephedrine,
  amino acids…
  readily available, inexpensive and easily derivatized.
  already studied as ligand in organometal chemistry.
  in some cases, enantiomeric counterpart is available.



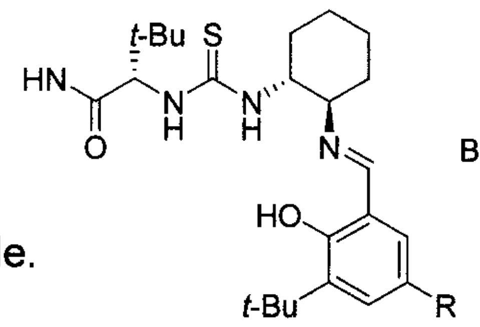
quinine

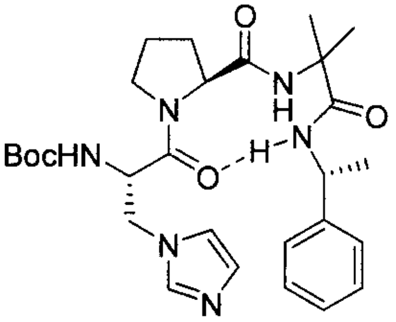


quinidine

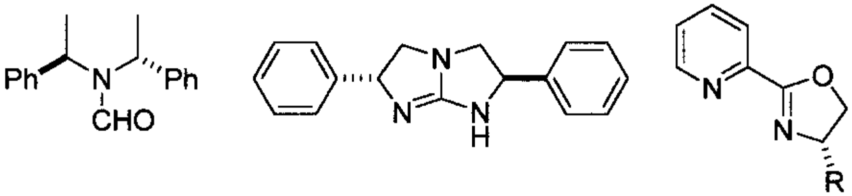


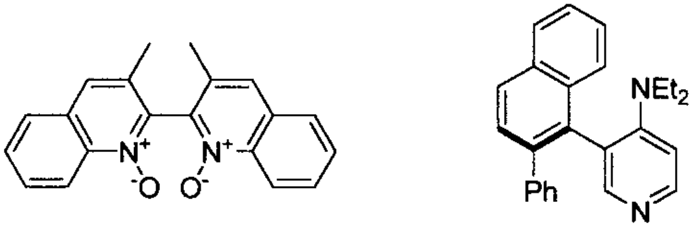
- 2. peptide – Dimer, oligomer, polymer
  peptide-like enzyme mimic.
  easy preparation.
  opposite enantiomer or epimer are available.
  combinatorial chemistry.

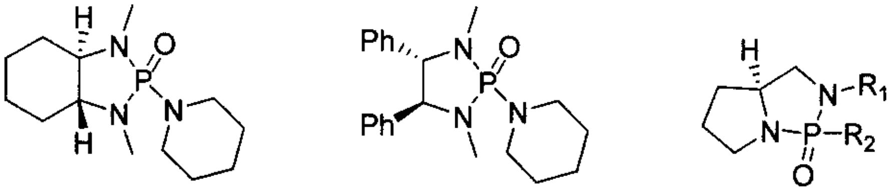




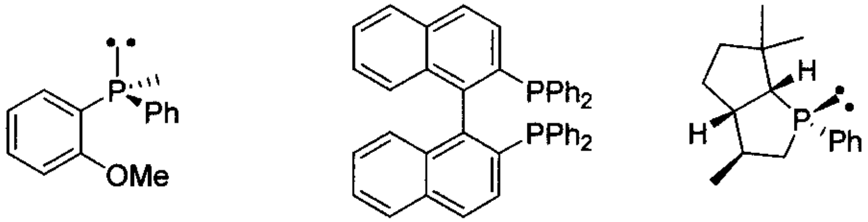
- 3. synthetic molecules with N, P, O, S.....;
  phosphoramides, phosphanes, urea, thiourea, *N*-oxide, sulfoxides, heterocycles.
  both enantiomers are readily available than natural molecules.
  most originate from ligand chemistry.
  diverse functionality.





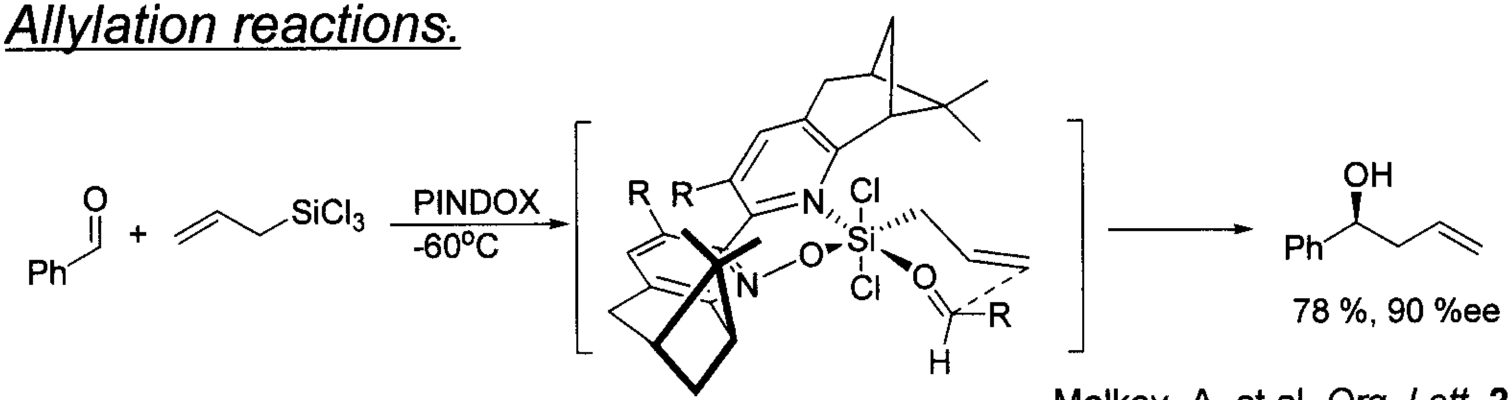


Phosphoramides

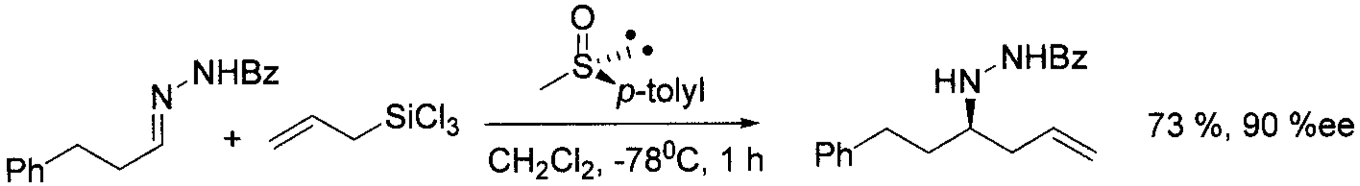


Phosphanes

Allylation reactions.



Malkov, A. et al. *Org. Lett.* **2002**, *4*, 1047.



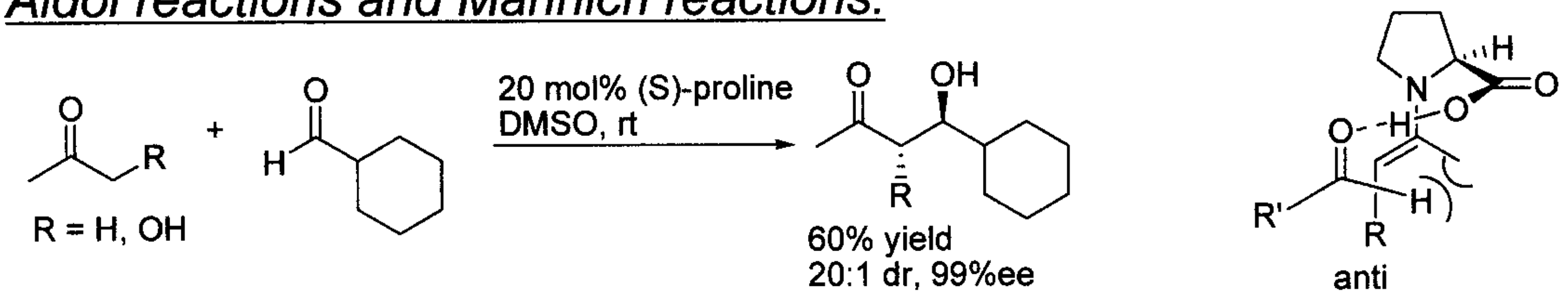
Kobayashi, S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 6610.

- Chiral Lewis bases such as phosphoramide, formamide, urea, oxazolidine, and amine *N*-oxide, have been used in enantioselective allylation.
- Formation of a tightly bound chiral complex between catalyst and silicon compound. In TS, octahedral hexacoordinated silicon center was formed.
- Tethered bis-phosphoramide results in better ee than monomer.
- The best ee (92 %ee, 10 mol% cat) with bisquinoline N,N'-dioxide.

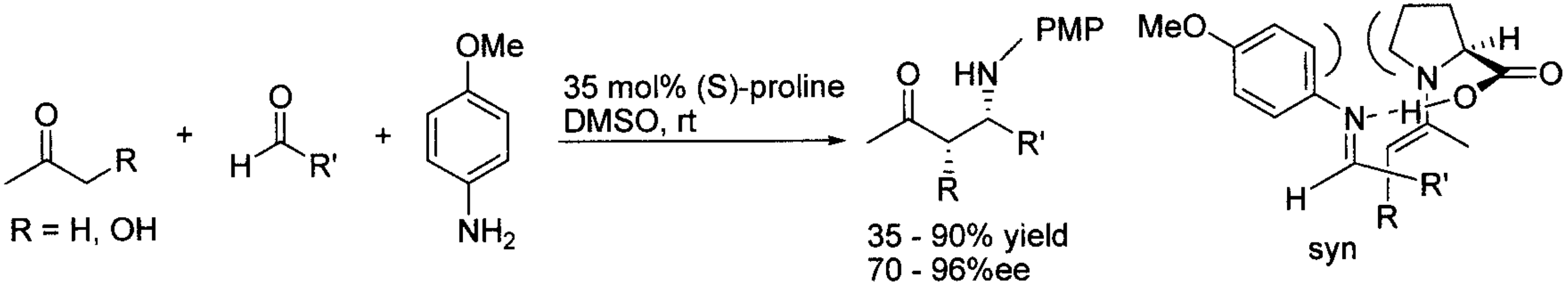
- Mono oxide gave the opposite enatiomer of product.

- Still 3 eq. chiral sulfoxide was used with *N*-acylhydrazone..

Aldol reactions and Mannich reactions.



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

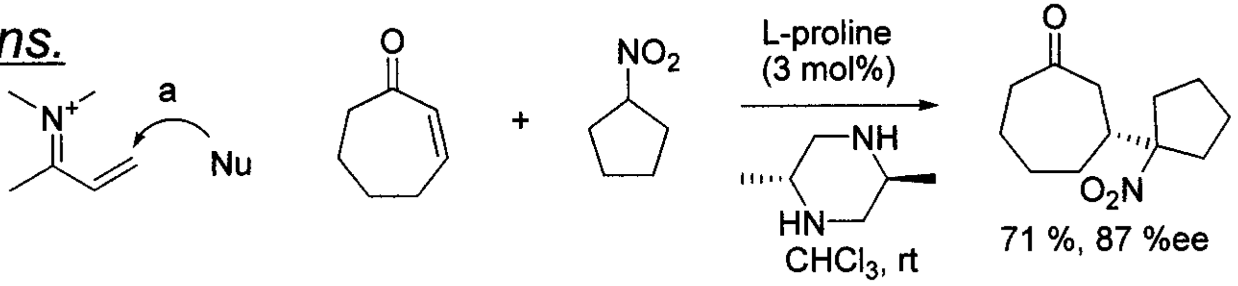


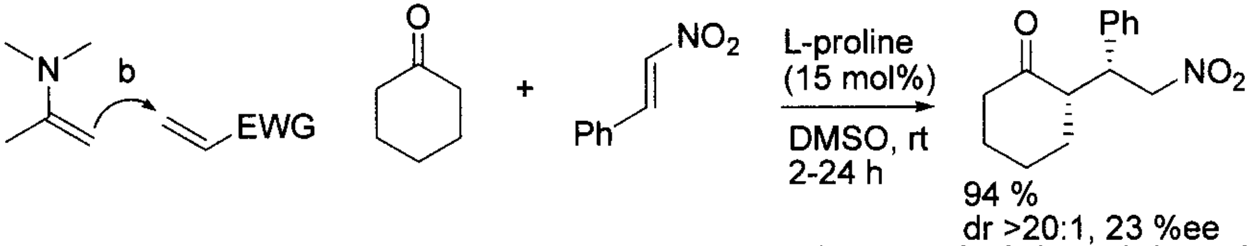
List, B. et al. *J. Am. Chem. Soc.* **2002**, *124*, 827.

- [Aldol] Aromatic aldehydes give moderate yield (60 – 70 %) and ee (~ 70 %ee).
- ☐ α-unbranched, enolizable aldehydes suffer lower yield due to selfaldolization.
- In R = OH, anti 1,2-diol like dihydroxylation.
- absence of non linear effect.

- [mannich] One pot Mannich reaction

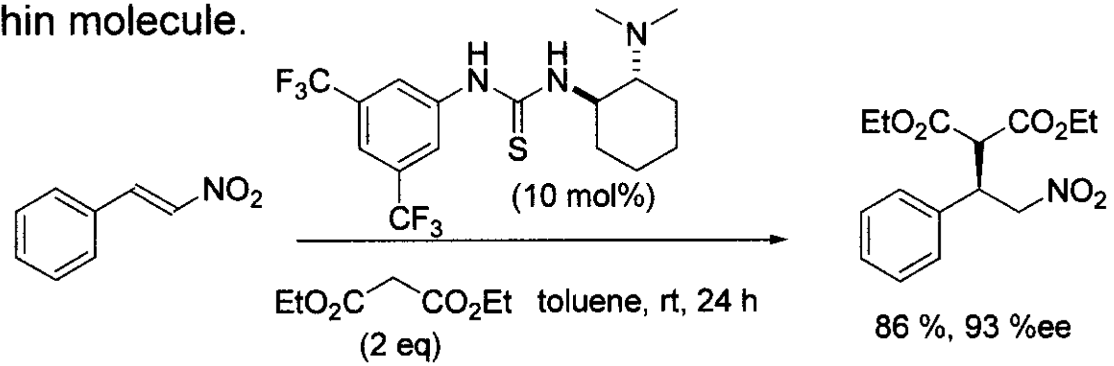
Michael additions.





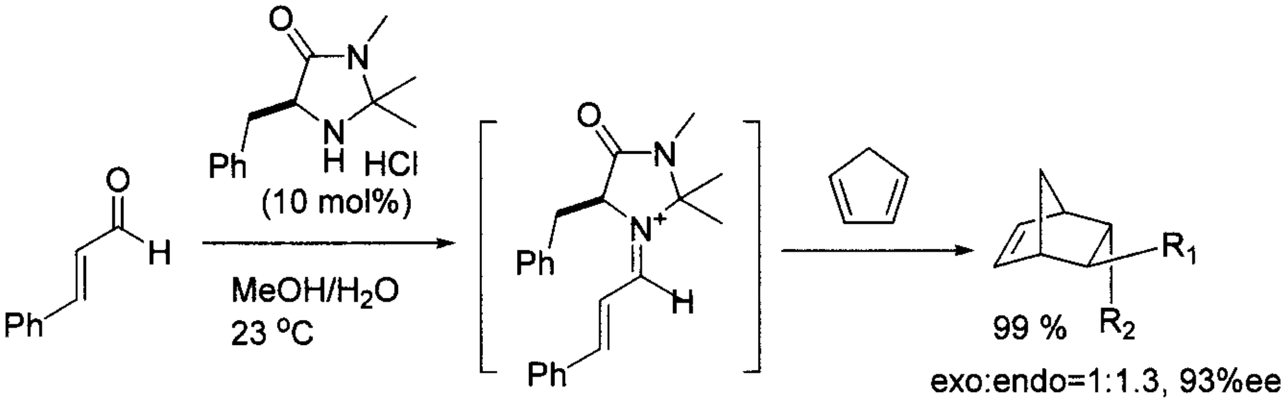
- Proline-catalysis proceed by both aminocatalysis pathways, iminium (a) and enamine catalysis (b).

- Urea and thiourea derivatives act as acid catalysts.
- activated by acidic hydrogen of thiourea.
- For a high yield and selectivity, catalyst should possess both thiourea and *t*-amino group within molecule.

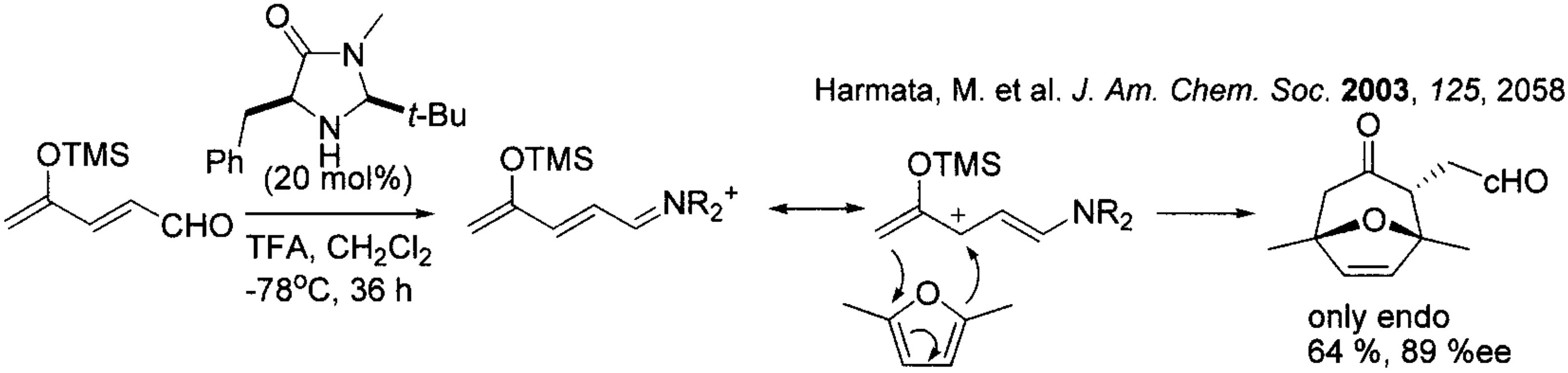


Okino, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

Cycloaddition reactions.



MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

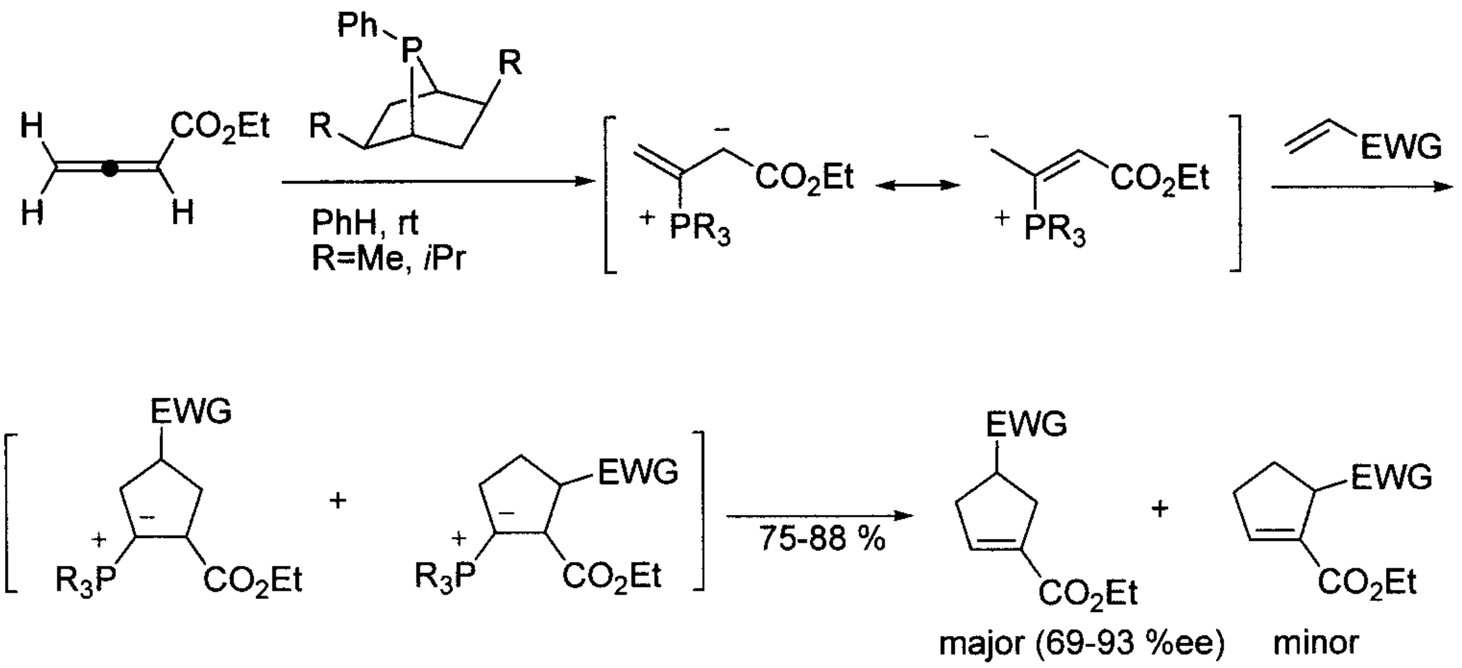


Harmata, M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

- By lowering LUMO of dienophile.
- the characteristics of Lewis acid catalysis.
- The presence of water results in increased rate and enantioselectivity, which indicates that the iminium ion is hydrolyzed in the catalytic cycle.

- [4+3] 2,5-disubstituted furans gave good yield and ee.

Cycloaddition reactions.

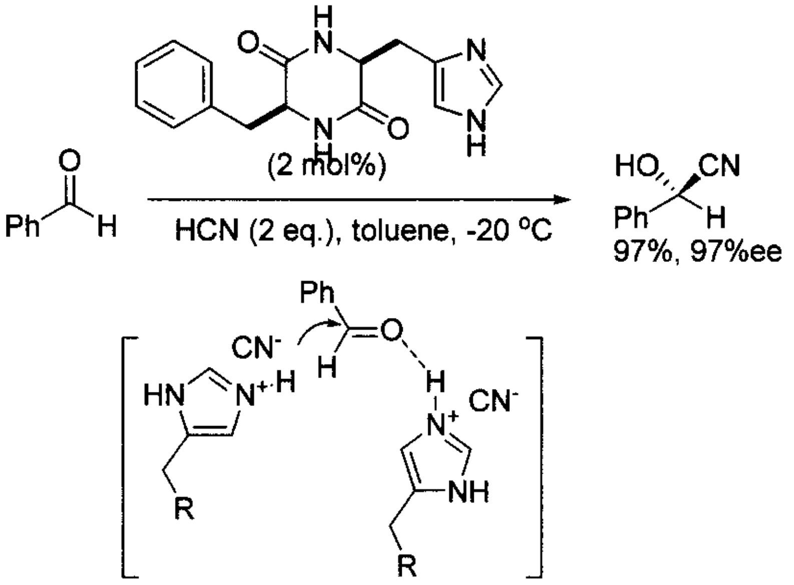


Zhu, G. et al. *J. Am. Chem. Soc.* 1997, *119*, 3836.

- Activated alkenes undergo a formal asymmetric [3+2] cycloaddition in the presence of allenic esters and a catalytic chiral phosphine.
- Phosphine act as a nucleophile trigger.

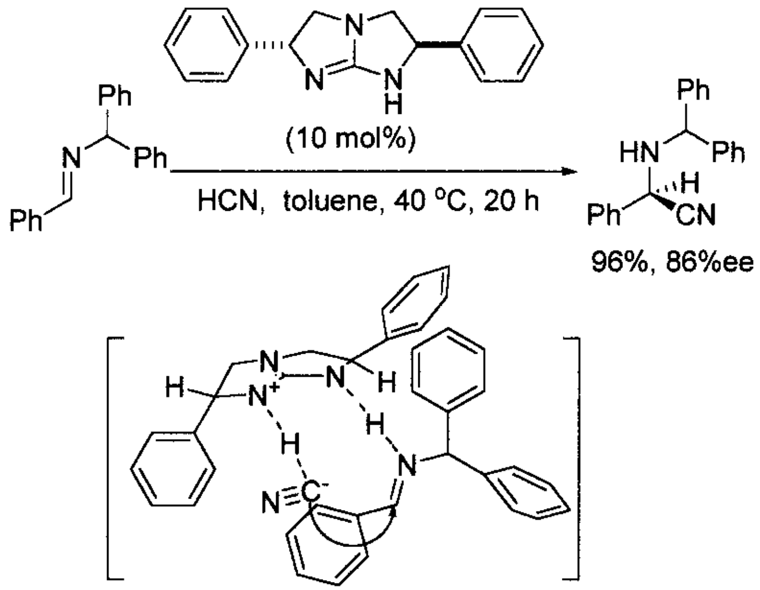
Hydrocyanation reactions.

- In 1981, Inoue reported the enantioselective hydrocyanation by diketopiperazine, cyclo(L-phenylalanine-L-histidine).
- broad substrate scope (electro rich aromatic aldehyde is best) and low loading.
- High-throughput screening of resin-supported oligopeptide-like catalyst.



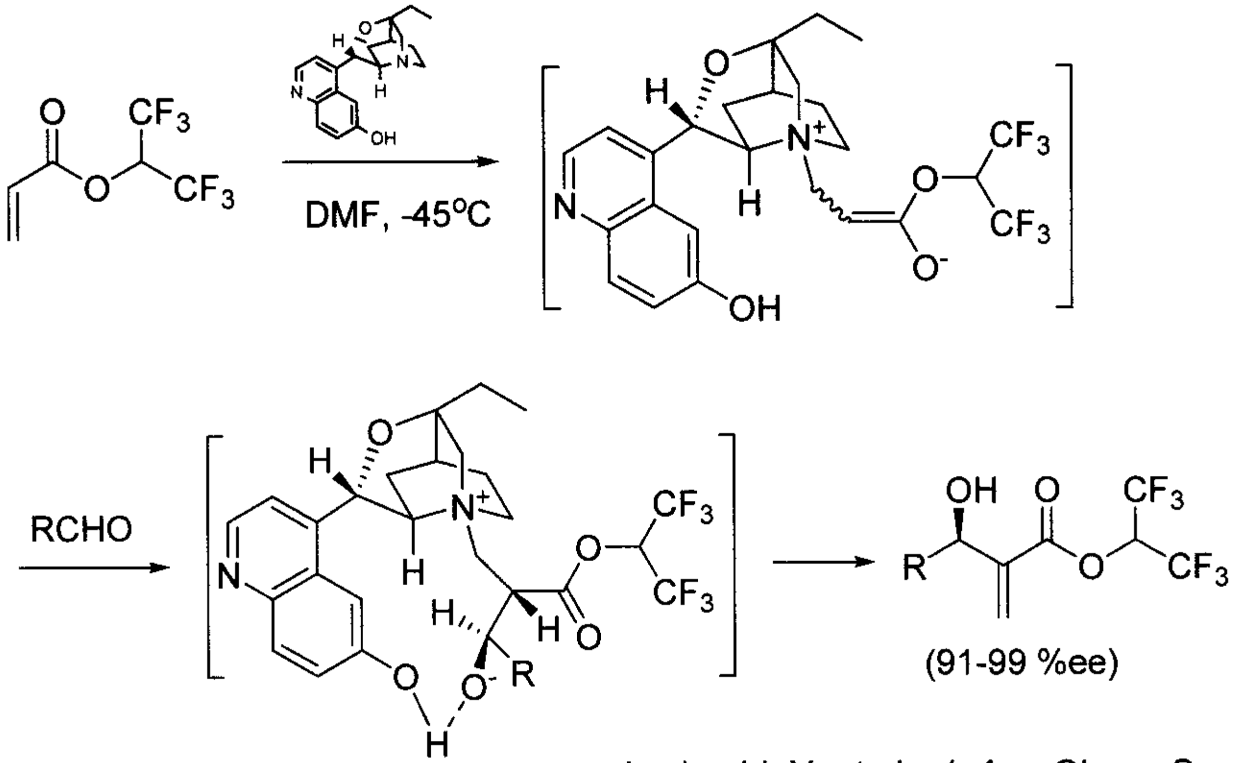
Inoue, S. et al. *Chem. Commun.* **1981**, 229.

- the replacement of imidazole with a more basic guanidine side chain provide better ee.
- the synthesis of unnatural α-amino acids.
- by formation of a guanidium cyanide complex, which activates the aldimine substrate by H-bonding.



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

Baylis-Hillman reaction.

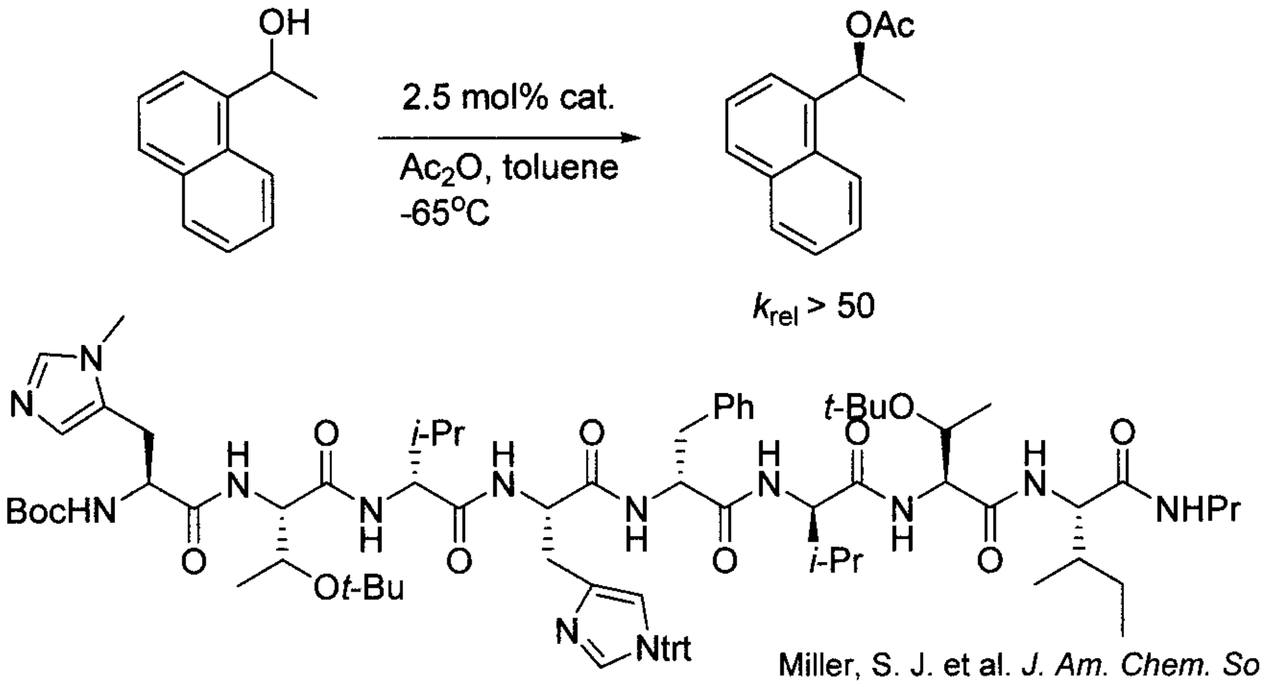


Iwabuchi, Y. et al. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

- hydroxylated chiral amine.
- by formation of betaine intermediate, which is stabilized by intramolecular H-bonding between oxy anion and phenolic hydroxy group.
- without phenolic OH, very low ee (10 %ee).

- Phosphorous-based chiral molecule work efficiently.

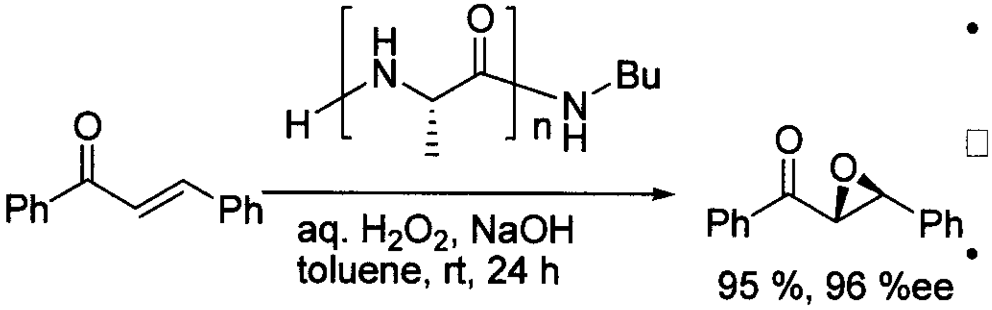
Acyl transfer reaction-Kinetic resolution.



Miller, S. J. et al. *J. Am. Chem. Soc.* **2001**

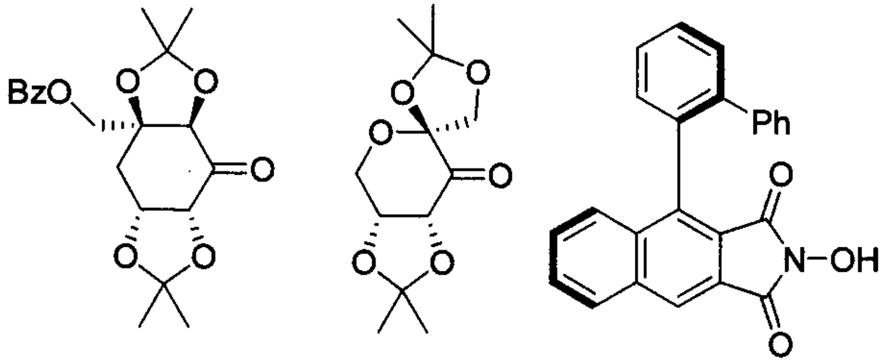
- Linear peptides were considered unsuitable for catalysis due to flexibility and variable conformation.
- But by the well defined secondary structure of linear peptides (β-turn conforamation, decreasing catalyst flexibility), they show proper property as catalysts.
- substrate ; participate in H-bonds with catalyst.
- This oligopeptide was discovered by screening a split-pool library of polypeptides for acylation of *sec*-phenyethanol.
- In this group, tripeptide containing histidine showed asymmetry addition of azides to α,β-unsaturated corbonyl compound. (high yield, up to 92 %ee)

Oxidation.



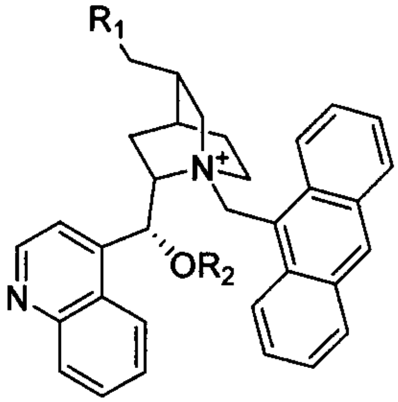
Julia, S. et al. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929.

- triphasic mixture.
- In MeOH, selectivity and yield drop, due to interruption of H-bonding.
- ☐ α-helical peptide more succesful (poly-L-leucine).
- about 30 amino acids show the most enentioselectivity.
- using urea-H_2O_2 and DBU, now two-phase and no more excess oxidant.
- as low as 2.5 mol% cat.

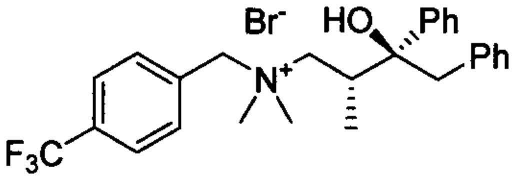


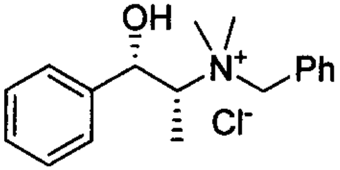
- chiral ketones form dioxiranes in situ with oxidents to give epoxide; up to 87 %ee.
- molecular oxygen as co-oxidant; *N*-oxyl radical by one-electron oxidation; oxidation at benzylic positions (8%ee)

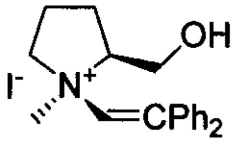
PTC

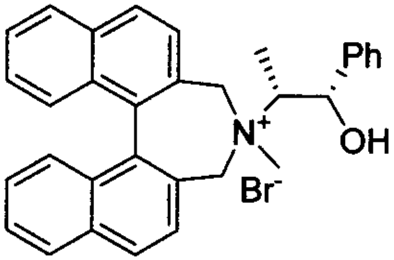


Corey's modified cinchonium catalysts.





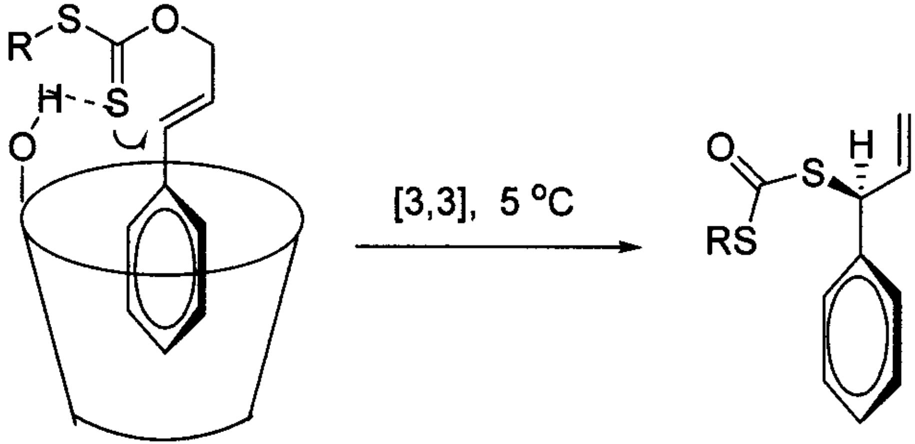




- In 1990's. Corey demonstrated the utility of modified catalyst in alkyation, Michael addition, aldol, nitroaldol and epoxidation; in cinchona-catalysts, the substitution pattern (like bulker group on quaternary ammonium) plays a crucial role (high ee).
- mechanism: a unique ion-pair-mediated reaction by chiral quaternary ammonium salts, based on X-ray structure. and van der Waals interaction between aromatic rings.
- Non polar solvents gave higher ee.

- Oligopeptides are also used.

Chiral-cavity-accelerated asymmetric transformation



Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013.

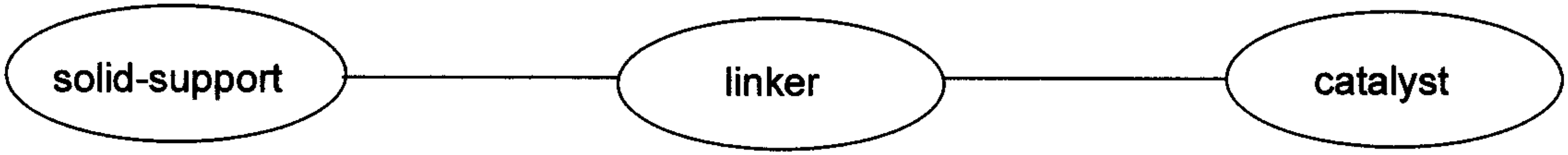
- [3,3]-Sigmatropic rearrangement of allylic xanthane in β-CD complex.
- 80 % yield, up to 46 %ee.

- The selective recognition of substrates followed by chemical transformation with the help of a molecular cavity based on chiral host-guest chemistry.
- Cyclodextrins form complex with hydrophobic guest based on size, structure and polarity.
- The formed host-guest complex is often too stable to allow catalytic turnover.

- Imprinted Polymers with memory for small molecules, proteins or crystals.
  Sellergren, B. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1031.

Polymer-supported Organic catalysts

Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.



soluble
insoluble
cross-linking
swelling
additinal steric and electric factor
particle size
recovery

space

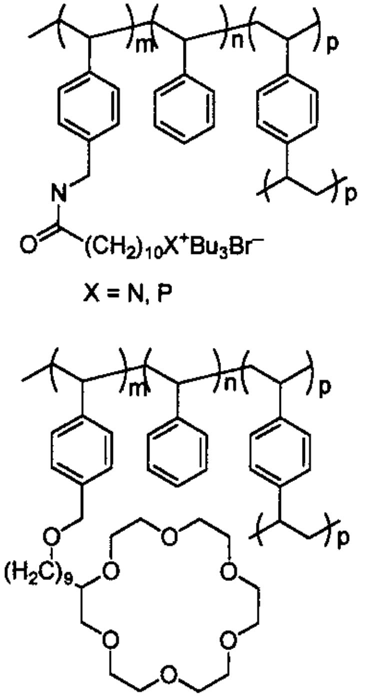
loading
stability
turn over
how modified
recycle

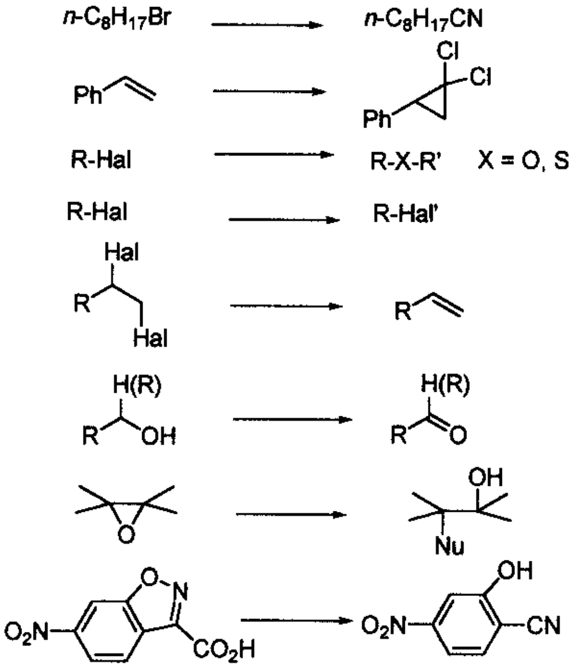
stirring rate - microwave
solvent effect
Temperature

Recovery and Recycling without the loss of reactivity of catalysts.

*1. Phase-Transfer Catalysts anchored to **insoluble** supports.*

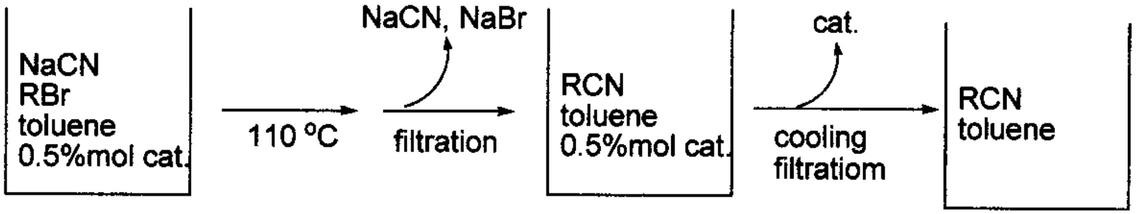
- Triphase catalysis
- Polystyrene or polyacryamide-supported catalysts; easy recovery.
- Diffusion of reagent and substrate in and out of polymer matrix.
- Generally, reaction rates were faster with the higher stirring, relatively low cross-linking and good swelling.
- The catalytic activity of polymer-supported catalyst was usually lower than nonsuppored catalyst; the insertion of spacer can enhance the activity.





2. Catalysts anchored to **soluble** supports.

- More homogeneous condition.
- no more diffusion.
- now the issue is recovery and recycling and loading.
- Polyethylene-supported catalysts.
- i) temperature-dependent solubility. Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345.
- ii) the intrinsic thermal instability like phosphonium salts.



NaCN
RBr
toluene
0.5%mol cat.

110 °C

NaCN, NaBr

filtration

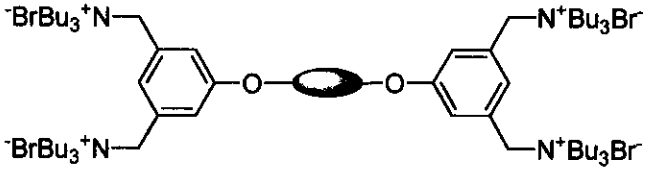
RCN
toluene
0.5%mol cat.

cat.

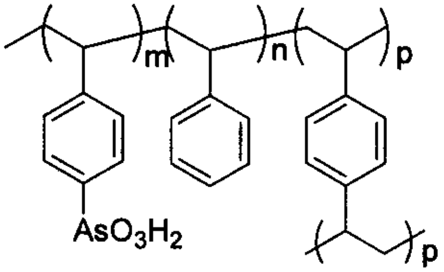
cooling
filtratiom

RCN
toluene

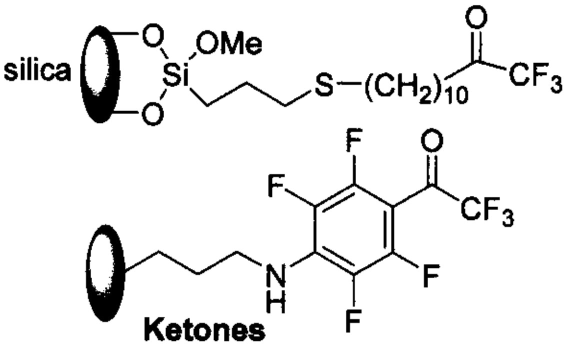
- Poly(ethylene glycol)-supported catalysts.
- i) inexpensive, easily functionalized
- ii) solubility as phase separation device; simply by decreasing the solvent polarity, to precipitate, recover and recycle.
- iii) high Mw of PEG is essential for efficient recovery and recycling. But 55 g catalyst is required for 1 mol of substrate. (1 mol% cat. with Mw of 5500 Da)
- iv) for high loading; dendrimeric catalyst.



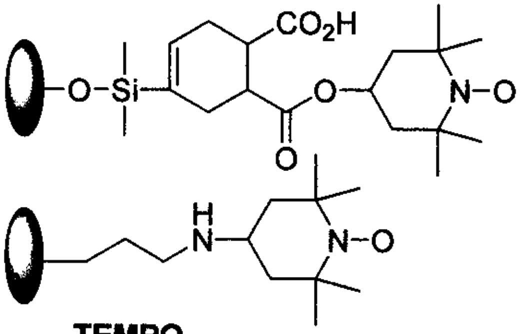
3. Polymer-supported Oxidation catalysts



Arsonic Acids



Ketones



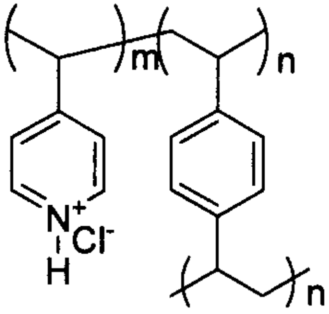
TEMPO

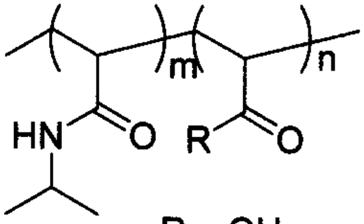
- 1) In 1979, PS-arsonic acid was used in Bayer-Villiger oxidation of ketones and epoxidation of alkenes. (3 mol% cat.)
- three times slower than unsupported arsonic acid.
- readily recoverable and recyclable.

- 2) Silica-supported polymer gave a good property.
  high yield, readily recovered, 9 times recycled
  non-supported fluoro ketone is rapidly degraded under reaction condition.

- 3) Silica supported TEMPO was recycled 45 times.
- 0.6 mol% cat. yields 99% yield for 1h in oxidation of primary and secodary alcohol.

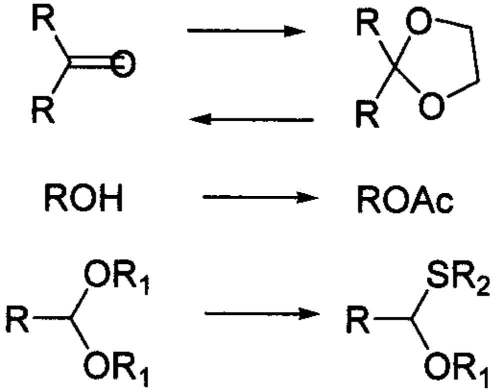
4. Acidic catalysts.





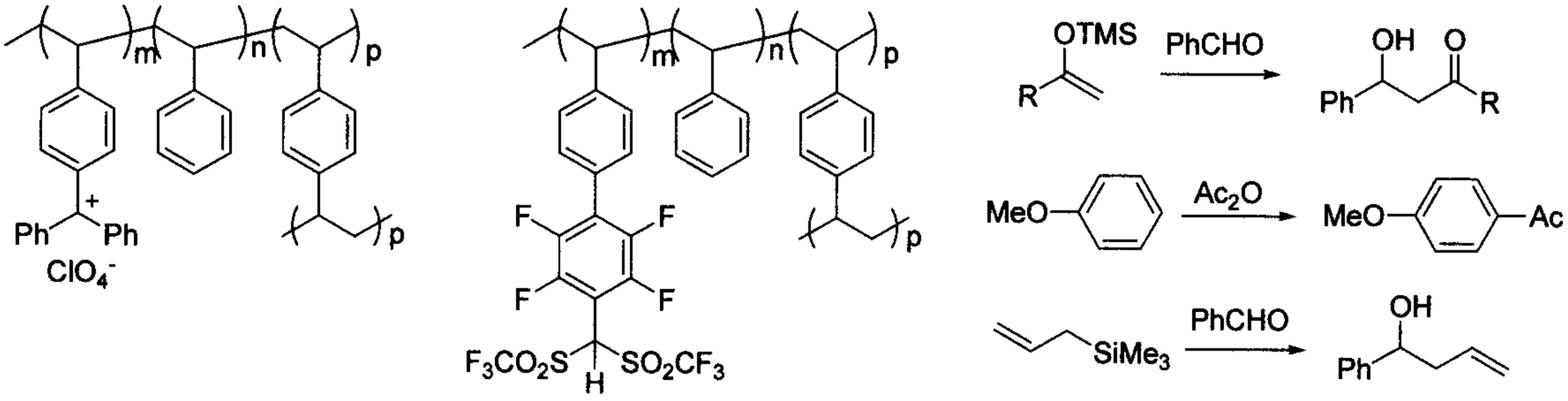
PNIPAM R = OH

R = $NHCMe_2CH_2SO_3H$



- In protection and deprotection reactions, pyridinium salts, poly(*N*-isopropylacrylamide)(PNIPAM), dicyanoketene acetals, phosphonium salts polymer are reported.
- PNIPAM as a 'smart polymer', which is soluble in cold water and insoluble in the same solvent when heated above its lower critical solution temperature.

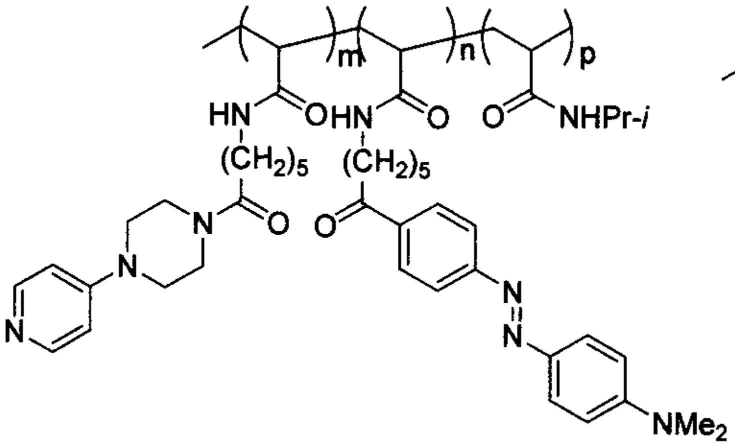
4. Acidic catalysts.

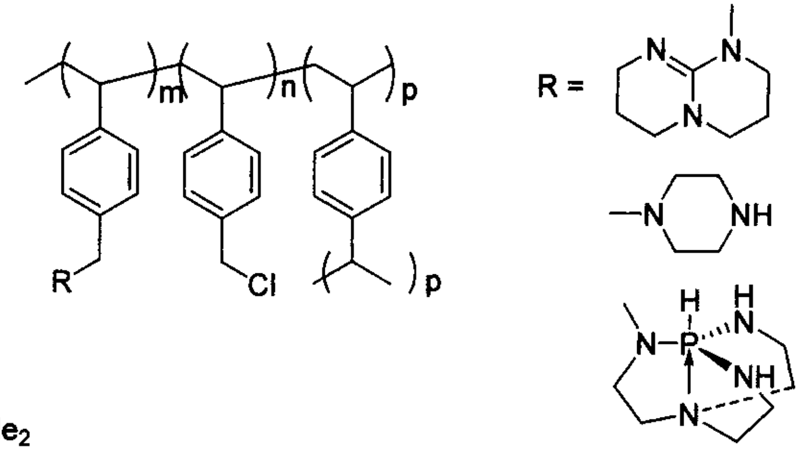


- In C-C bond-forming reactions, trityl perchlorate, dicyanoketene acetals and tetrafluoropnenylbis(trifluoromethanesulfonyl)metnane polymers were reported.

- 0.1 mol% - 1 mol% catalyst promoted acetylation of menthol with acetic anhydride (1h, rt, 100 %).
- 10 cycles without loss of activity.

5. Basic catalysts.



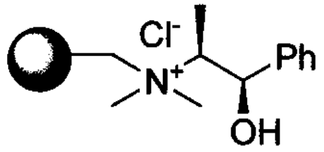


- Since 1979, DMAP-like molecules supported on polymer have been reported.
- with 5 mol% cat., acetylation was catalyzed efficiently and with 0.25 mol%, the reaction between phenols and di-*t*-butoxycarbonate was catalyzed.

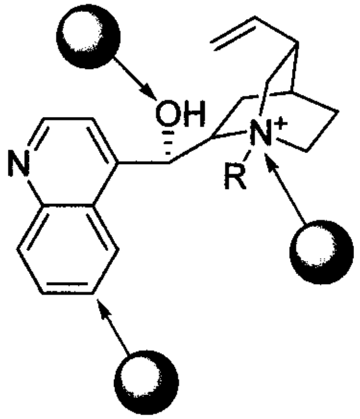
- Catalyst, soluble in polar solvent and water, was recovered by precipitation with hexanes and the residue of cat. was determined by UV-vis spectroscopy, which showed less than 0.1 % of cat. was remained. Berbreiter, D. E.; Osburn, P. L. *Org. Lett.* **2002**, *4*, 737.

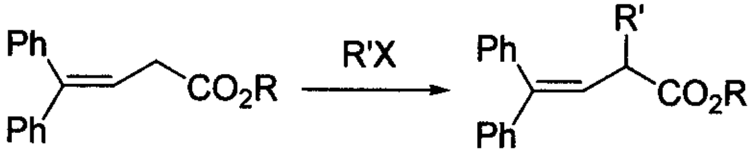
6. Chiral polymer-supported catalysts.

- chiral Phase-Transfer catalysts.
- different sites for polymer attachment.
- The use of spacer improved ee of (R)-product slightly.
- Catalyst recovery and recycling were reported.
- Soluble catalyst gave lower ee.
- Just the presence of Me-PEG depressed to 66 %ee with nonsupported catalyst.



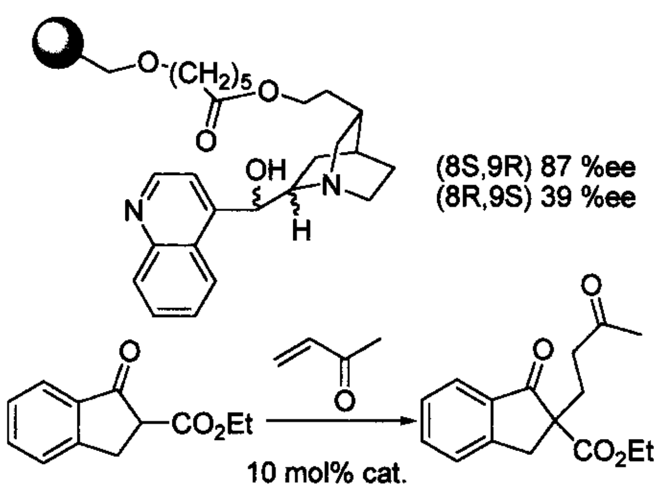
Ephedrine (1977)
low but definite stereoselectivity





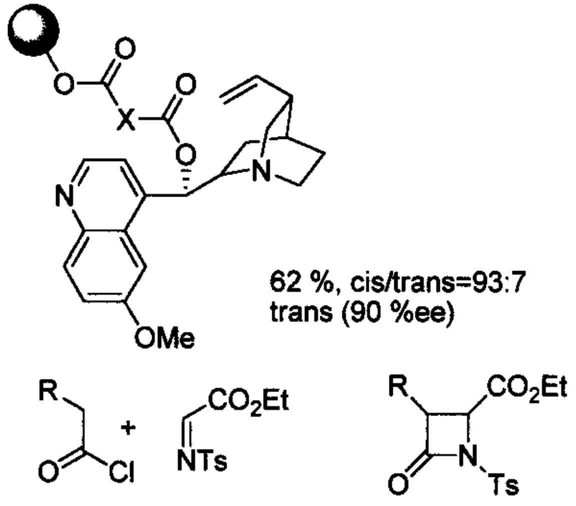
10 mol% Cat. 67 % yield
94 %ee (S), 23 %ee (R)

6. Chiral polymer-supported catalysts.



(8S,9R) 87 %ee
(8R,9S) 39 %ee

Thierry, B. et al. *Tetrahedron: Asymmetry*, **2001**, *12*, 983.



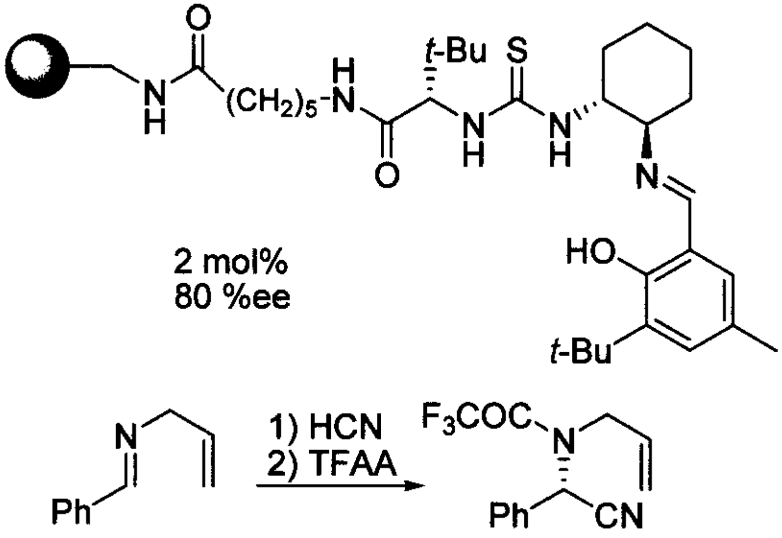
62 %, cis/trans=93:7
trans (90 %ee)

Hafez, A. M. et al. *J. Am. Chem. Soc.* **2001**,*123*, 10853.

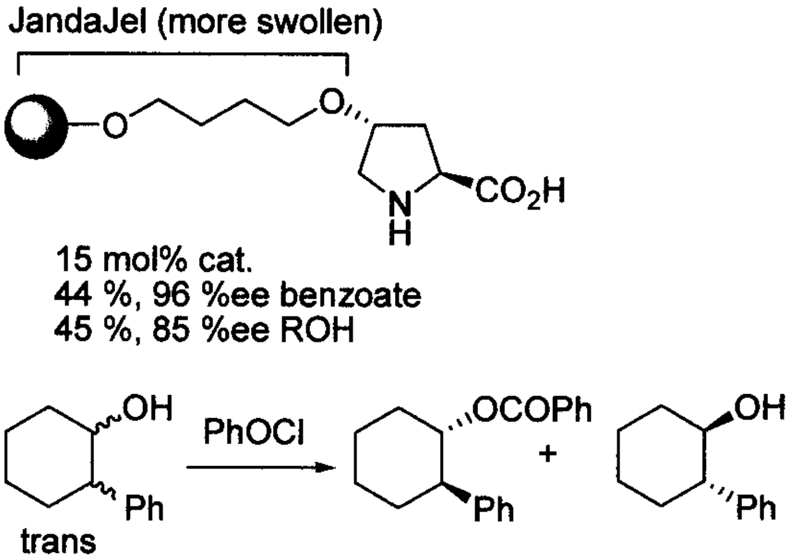
- Non-ionic catalysts derived from Cinchona alkaloids. (since 1978)
- From 42 %ee (1978) to 87 %ee (2001) in Michael addition.
- Relatively small changes in polymer/catalyst ensemble may produce dramatic and unexplicable effects in stereochemical outcome of the reaction.

- Quinine derivatives act as catalyst for [2+2] Staudinger reaction between ketene and imines.
- A properly aged resin was necessary to afford consistent results, by quinine “bleeding”.

6. Chiral polymer-supported catalysts – from amino acids.



2 mol%
80 %ee

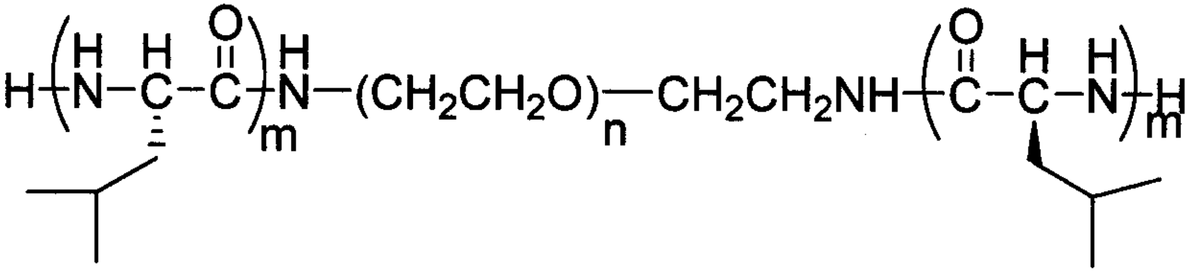


15 mol% cat.
44 %, 96 %ee benzoate
45 %, 85 %ee ROH

- Optimized catalyst by combinatorial approach (12, 48 and 132 elements). 19 %ee to 80 %ee.
- nonsupported counterpart gave 91 %ee.
- Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

- JandaJel-supported Proline to catalyze kinetic resolution of cyclic secondary alcohol.
- Clapham, B.; Cho, C.-W.; janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.

6. Chiral polymer-supported catalysts – from poly(amino acids).



a. m = 1.8, n = 71
b. m = 3.9, n = 71
c. m = 7.5, n = 71
d. m = 12.2, n = 71
e. m = 8.0, n = 454

- In 1980's, by Julia and colonna, immobilized polyalanin promoted epoxidation of chalcone. (1st cycle; 82 %, 84 %ee, 2nd and 3rd cycle; 75 and 52 %ee)
- By Roberts and co-workers, good recovery and recycling of catalyst was achieved in the adsorption of poly(aminoacid) on silica gel. (5 times without loss of activity)

- Polymer b and c were more efficient than a and d for epoxidation of chalcone.
- Polymer b, c and d showed similar ee (up to 98 %ee) and better than a.
- Polymer e promoted the epoxidation of chalcone (99 %, 94 %ee) in a continuously (25 cycles) operated membrane reactor, where catalyst retention was achieved by means of a nanofiltration membrane. Tsogoeva, S. B. et al. *Synlett*, **2002**, 707.

Conclusion

- Although the breadth of possible reaction in the field is not as large as that of its organometallic counterpart, with critical mechanistic insight and novel catalyst development, it's a growing field that offers an interesting complement to other catalytic approaches.
- Combinatorial approaches to peptide-based catalysts show the scope for future development.

- But, more mechanistic study is necessary.
- Loading of catalysts should be lower.
- The new catalysts, which can show high ee with wide range of substrate, need to be developed.