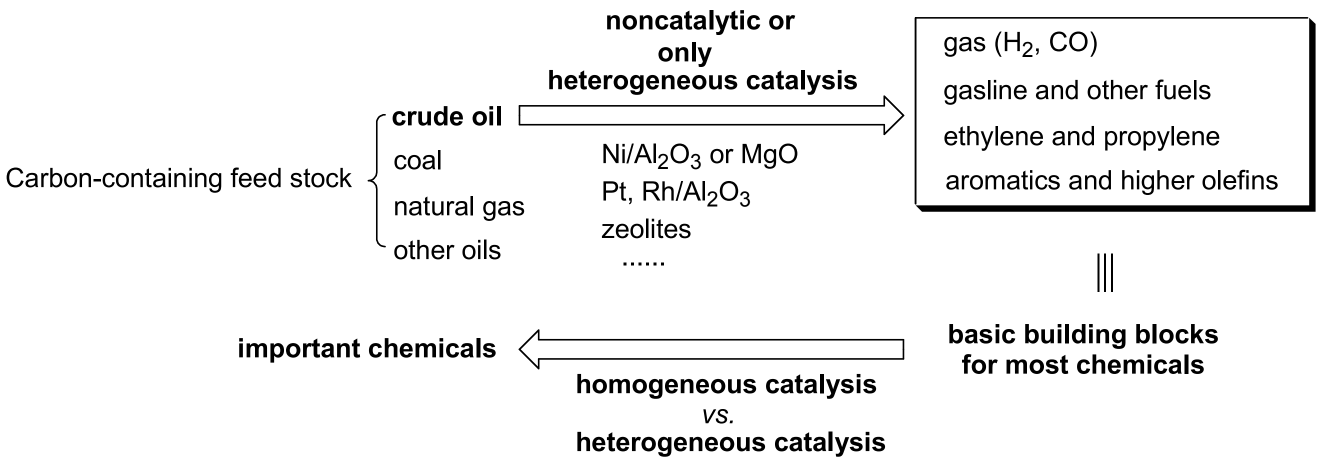
Gang LU

Asymmetric Heterogeneous Catalysis

***Figure 1*. Catalysis in chemical industry: heterogeneous *vs*. homogeneous**



"In terms of total tonnage and dollar value, the contribution of homogeneous catalytic processes in the chemical industry is significantly smaller than that of heterogeneous catalytic reactions. All the basic raw materials or building blocks for chemicals are manufactured by a small but very important set of heterogeneous catalytic reactions. Roughly 85% of all catalytic processes are based on heterogeneous catalysis."

(Bhaduri S. and Mukesh D., *Homogeneous Catalysis: Mechanisms and Industrial Applications* **2000**, pp1–8.)

Advantages of heterogeneous catalysis:

easy seperation, efficient recycling, mimization of metal leaching, improved handling and process control, low cost

even higher selectivity than homogeneous ones in some cases

$$\boxed{\mathbf{A} \xrightarrow{\textbf{chiral heterogeneous catalyst}} \mathbf{B^*}}$$

Pioneer reviews on asymmetric heterogeneous catalysis:

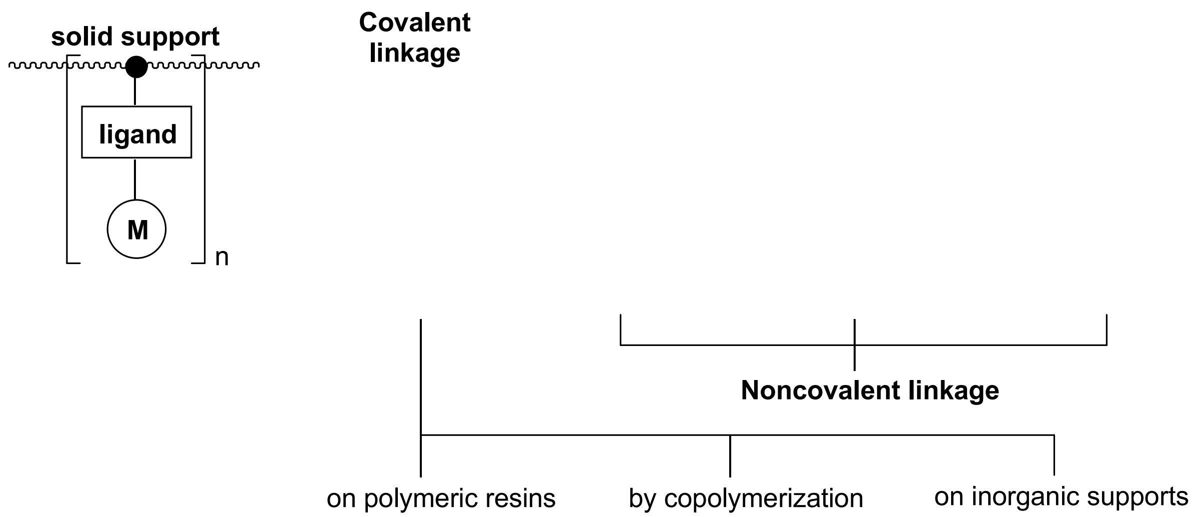
a) Blaser, H. U. *Tetrahedron Asymmetry* **1991**, *9*, 843;
b) *Chem Review* **2002** *102*, 3215–3892;
c) Hutchings, G. *Chem. Soc. Rev.* **2004**, *33*, 108;
d) Glorius, F. et al. *Angew. Chem*. **2006**, *45*, 4732.

Today's topics:

- **Immobilized (Supported) Catalysis**
  - **1. Classical immobilization of chiral homogeneous catalysts**
  - **2. Self-assembly chiral metal-organic catalysts**
- **3. Catalysis at Chiral Surfaces**
  - **3.1 Chiral modifiers**
  - **3.2 Macromolecular catalysis**
- Chiral substrate-induced catalysis, others

1. Classical immobilization of chiral homogeneous catalysts

***Figure 2*. Strategies for immobilization of chiral homogeneous catalysts**



The choice of a suitable support plays an important, although not fully understanding, role.
Possible problems can diminish the performance of catalyst:

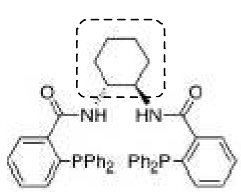
- ♦ undesired interactions between of the support and the homogeneous complex → low enantioinduction;
- ♦ unstability of the linkage between the catalyst and support or the catalyst itself → metal leaching;
- ♦ limited accessibility of the active site from substrate → low reactivity.

To achieve minimal levels of interaction, which has been the predominant strategy, the *anchoring point* in the ligand structure should be as far away from the active site of the catalyst as possible. Furthermore, a long and flexible linker between the catalyst and support or a highly swellable polymer should be chosen. However, the catalyst can also be attached to the support in proximity to the active site, which has led to improved catalytic performances in a few cases

1.1 Covalently immobilized catalysts on polymeric resins

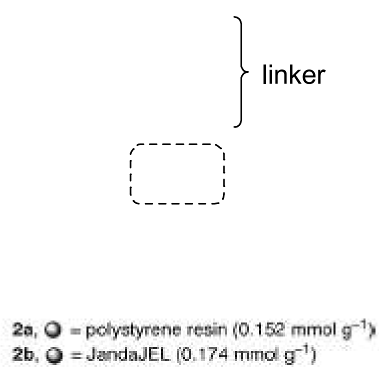
- ♦ Merrifield resins: poly(styrenedivinylbenzene) polymers
- ♦ JandaJEL: polystyrene polymers containing a tetrahydrofuran-derived crosslinker
- ♦ TentaGel: polystyrene-polyethyleneglycol-OC_2H_4-$NHCOC_2H_5$
- ♦ PS-PEG: polystyrene polyethyleneglycol resins

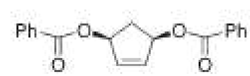
Scheme 1.



1

Trost ligand





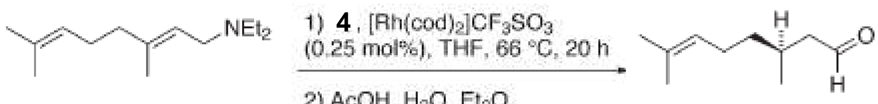
Han, A. H. *ACIE* **2002**, *41*, 3852.

Scheme 2. **Polystrene(PS)-bound binap ligand**

3
4

using **3** (80 ppm loading)

Noyori et al. *Adv. Synth. Catal.* **2001**, *343*, 369.



5

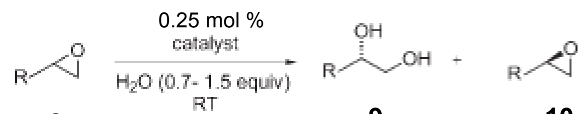
100% conversion
98% *ee*

6

key intermediate for fragrance and flavour industry

Lemaire et al. *Helv. Chim. Acta.* **2001**, *84*, 230.

Scheme 3. **Immobilized Co-Salen complex**



8 **9** **10**

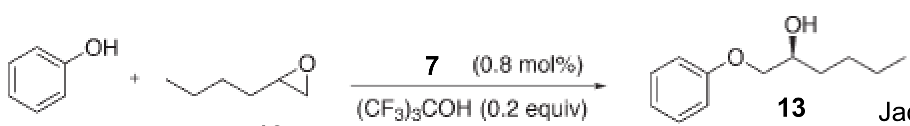
over 5 cycles; yield: 51–52%, ee: 92–95%; ee: > 99%

7

Jacobsen et al.*JACS* **1999**, *121*, 4147.

reaction mixture → [residue —(toluene-HOAc washing, under air)→ active catalyst **7**

filtrate → [water layer → diol **9**; organic layer → product **10**]

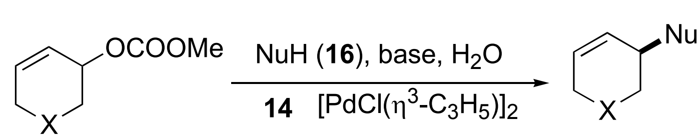


11 **12** **13**

98% yield
>99% *ee*

Jacobsen et al.*OL* **1999**, *1*, 1245.

Scheme 4. **Immobilized Pd-phosphine complex**



NuH (**16**), base, H_2O

14 $[PdCl(\eta^3\text{-}C_3H_5)]_2$

(2–10 mol % complex)

15 **17**

14

$X = CH_2, C_2H_4$, NBoc

NuH: malonate, Bn_2NH, phenol

yield: up to 99%
ee: up to 99%

Uozumi et al.*PAC* **2007**, *79*, 1481.

1.2 Covalently immobilized by copolymerization

- Radical polymerization of vinyl-modified ligands with styrene and divinylbenzene
- Polymerization of amines with isocyanates

Scheme 5. **Copolymerization of pybox ligands**

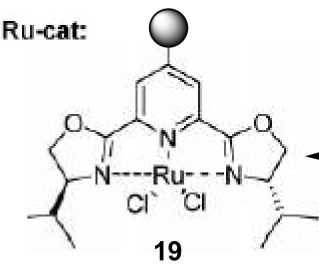
styrene

18

divinylbenzene
(cross linker)

x% = degree of cross-linkage $\Longrightarrow$ accessibility of aactive site $\Longrightarrow$ activity and selectivity

Ru-cat:



19

immobilized ligand
$[RuCl_2(p\text{-cymene})]_2$

x = 2: *trans*/*cis*: up to 90/10, ee (*trans*): up to 91 recycling use 6 times

Mayoral, J. A. *JOC* **2005**, *70*, 5536.

3.6 mol% **20**
2 mol% $Cu(OTf)_2$

yield: 60%, *trans*/*cis*: 67/33, ee: 93% (*trans*), 90%(*cis*)

20 = (x = 54, y = 4.2, z = 42)
R = *t*Bu

21 = (x = 52, y = 2.8, z = 45)
R = Ph

20 was found swelling in a solution of $Cu(OTf)_2$ in THF. The rapid uptake of 0.18-0.20 mmol/g of the metal salt took place, demonstrating that about 60% of the supported box units could be readily engaged in the metal complexation.

Salvadori et al. *CC* **2003**, 2466.

21

(glyoxylate-ene reaction)

Salvadori et al. *TA* **2004**, 3233.

***Scheme 6.* Immobilization of binap with diisocyanate**

23

22

24

25

Lemaire et al. *BMCL* **2002**, *12*, 1841.

Lemaire et al. *TA* **2002**, *13*, 1141.

rigidity increasing

23
24
25

***Scheme 7.* Salen copolymers**

26 **28**

27 **29**

Kim et al. *Catalyst Today* **2003**, *87*, 145.

used for the Co-catalyzed hydrolytic kinetic resolution of epoxide, > 96% ee.
These copolymers could also be recycled and reused up to 7 times without any loss of activity and selectivity, and do not need to be regenerated.

1.3 Covalent immobilization on inorganic support

♦ zeolites, amorphous silica gel

♦ mesoporous silicas (2~50 nm pore size):

MCM-41 ("mobile crystalline material", ordered hexagonal, 3~4 nm pore diameter)

SBA-15 (ordered hexagonal, 1.2~3 nm pore diameter)

♦ crystalline nanoparticles

advantage: rigid structure avoids the aggregation of active catalyst; insoluble in organic solvents

Scheme 8.

silanol moiety

linker

30

31

31
32
33

Tu,Y. Q. *OL* **2004**, *6*, 169.

Ru:ligand:ketone = 1 : 1.7 : 100

Figure 3.

dpen in MCM-41

restricted approach of the reactant
to the active catalyst in concave pore

dpen on carbosil

homo

hetero

Thomas, B. F. G. *ACIE* **2003**, *42*, 4326.

Figure 4.

34

super-paramagnetic
magnetite crystalline nanopart

0.1 mol % catalyst loading

recycled by magnetic decantation

Lin et al. *JACS* **2005**, *127*, 12486.

Figure 5.

5 mol %
Silica-supported BINOL
(1.5 eq)

up to 94% ee

Abdi,SHR *J. Mol. Cat. A* **2008**, *280*, 106.

Silica-supported BINOL

***Scheme 9.* Ru complex immobilized in a pore of SBA-15**

Lin et al. *CC* **2004**, *2284*.

Scheme 10.

35

3535

Corma et al. *CC* **2002**, *1058*.

For other similar examples of recent, see:
a) *J. Cat.* **2008**, *254(1),* 91.
b) *J. Mol. Cat. A.* **2008**, *280(1-2),* 106.
c) *JOC* **2007**, *72,* 9353.

1.4 Noncovalent immobilization by adsorption

♦ physisorption via van der Waals interaction (synthetic modification of ligand is no necessary)
♦ immobilized by H-bonding on a polar support (eg. SiO_2, stability is improved)
♦ SAPC (*s*upported *a*qeous-*p*hase *c*atalyst, immobilized on a hydrophilic support such as SiO_2)

Figure 6.

H-bonding of support with ligand

H-bonding of support with counterion

Figure 7. **SAPC model**

Scheme 11.

CPG-240: controlled pore glass-240, pore diameter 242 Å

36

37

naproxen

100% conversion
96% *ee*

36

without CPG-240 support: < 2% conversion

dissolved in ethylene glycol and adsorbed on CPG-240

Davis et al. *Nature* **1994**, *370*, 449.

ethylene glycol was the hydrophilic liquid phase containing the chiral catalyst, which effectively prevents the leaching of the complex into the organic phase

1.5 Noncovalent immobilization by ion exchange

Ion exchange between a chiral, cationic metal¨Cligand complex and an acidic resin represents an elegant method for immobilization through electrostatic interactions. Moreover, ion exchange is the only method that allows the direct immobilization of the metal itself. Therefore, it is a method of choice for the recycling of expensive or very toxic metal derivatives such as osmium tetroxide.

***Figure 8.* Immobilization of OsO_4^{2-} by ion exchange**

(O = OH)

LDH: layered double hydroxides, it contains cationic $M(II)_{1-x}M(III)_x(OH)_2^{x+}$ and anionic A^{n-}• zH2O layers, the exchange of Cl^- for OsO_4^{2-} in $Mg_{1-x}Al_x(OH)_2(Cl)_x$• zH2O (x = 0.25) gives LDH-OsO4

Choudary et al. *JACS* **2001**, *123*, 9220.

(NMO: *N*-methylmorpholine-*N*-oxide)

1.6 Noncovalent immobilization by encapsulation or others

The encapsulation of chiral catalysts in a support, often referred to as ¡°ship in a bottle¡± (*Figure 2*), is the only type of immobilization that does not require any favorable interaction between the metal¨Cligand complex and the support. In general, chiral complexes can either be successively assembled in the pores of a mesoporous material or the presynthesized complex is entrapped by polymerization or in a polydimethylsiloxane (PDMS) film. In both cases, reaction conditions are required that are well tolerated by the support and the chiral complex.

Scheme 12.

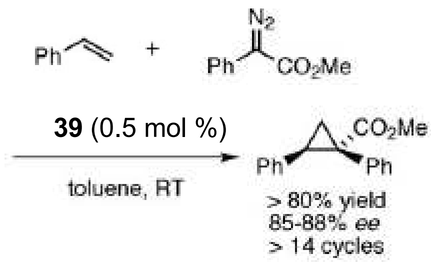
38

[(*R*,*R*-Meduphos)Rh-PDMS 97% *ee*

[(*R*,*R*-MeduphosRh(cod)]BF_4 (homog.) 96-99% *ee*

Geresh et al. *CC* **2002**, *388*.

Scheme 13.



Davis et al. *JACS* **2004**, *126*, 4271.

39

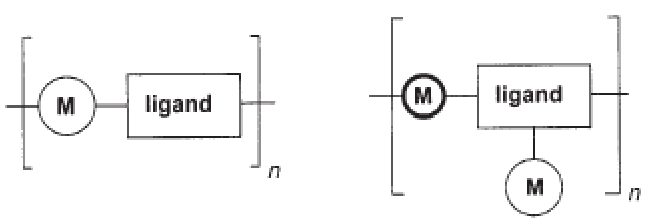
♣ **Summary**

By choosing a suitable support, especially mesoporous materials, a heterogeneous catalyst can be prepared that gives similar or even enhanced selectivities and activities. In other words, the role of the support has changed from an inevitable appendage to a well-defined material that can be used to beneficially influence the outcome of a catalyzed reaction. Is a covalent or a noncovalent immobilization of the catalyst preferential? For a long time, covalent immobilization of chiral complexes was unrivaled because of the stability and recyclability of the resulting catalysts. In contrast, catalysts prepared by the often synthetically more facile noncovalent immobilization strategy most often suffered from severe stability problems. However, recent results with cationic complexes immobilized by surface-supported counteranions or ion exchange have demonstrated that these noncovalently immobilized catalysts can show good stabilities, can be recycled several times, and in addition result in good selectivities and activities.

2. Self-assembly chiral metal-organic catalysts

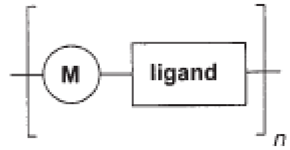
This new immobilization technique is based on the skillful application of multitopic ligands and metals and allows for a simple and efficient assembly of solid metal¨Corganic structures by complexation without the need additional support (*Figure 9*). This self-assembly can give highly porous, in some cases very regular, coordination polymers that mainly consist of the metal and the chiral ligand.

Figure 9. **Three types of chiral metal-organic catalysts**



a) b) c)

2.1 *One metal-one ligand* self-assembly catalyst (type a)

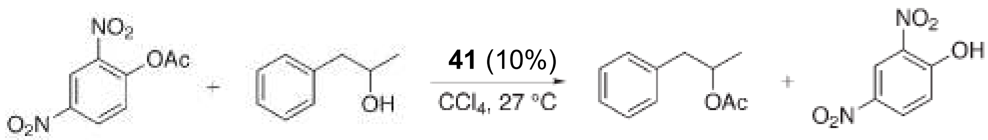


Scheme 14. **First example by Kim et al. on *Nature* 2000, *404*, 982**

40

41

stable to air



42 **43** (racemic) **(*S*)-44**

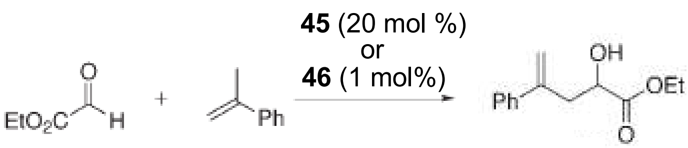
18% yield, 8% ee

Scheme 15.

45

46

a: X = H, Y = 1,4-phenylene
b: X = H, Y = 1,3-phenylene
c: X = H, Y = single bond
d: X = Br, Y = 1,4-phenylene



a) Sasai et al. *ACEI* **2003**, *42*, 5711. (for cat. **45**)
b) Ding et al. *TL* **2004**, *45*, 2009. (for cat. **46**)

47 **48**

up to 98% *ee*

49a

a: Y = single bond
b: Y = 1,4-phenylene
c: Y = 1,3-phenylene
d: Y = 1,2-phenylene

49

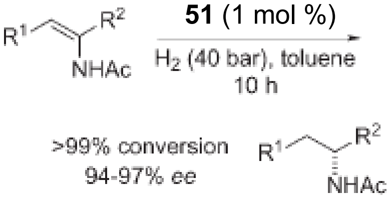
50

R^1 = H, 4-Me, 4-Br, 4-F, 3-Br, 4-NO_2
R^2 = Me, Et

30-45%
76->99.9% *ee*

Ding et al. *CEJ* **2005**, *11*, 4078.

Scheme 16.

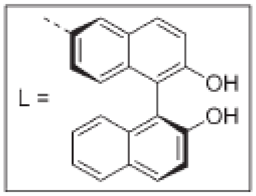


a: Y = single bond
b: Y = 1,4-phenylene
c: Y = 1,3 phenylene
[Rh] = [Rh(cod)]BF_4

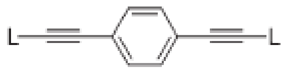
51

Ding et al. *JACS* **2004**, *126*, 10524.

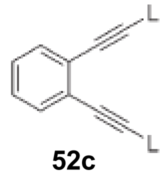
Scheme 17.



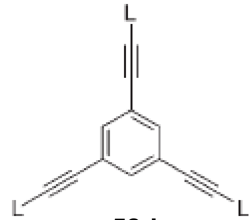
52a
(83% ee)



52b
(96% ee)



52c
(84% ee)



52d
(planar tridentate) (92% ee)

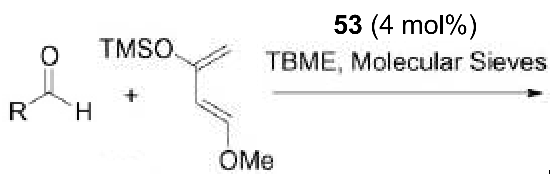
91 to >99 % yield
85 - 97.6% *ee*

R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, Ph, *i*Pr
R^2 = Ph, 4-$MeOC_6H_4$

52e
(3D tetratendate) (95% ee)

(ee in each bracket is for substrate of R^1 and R^2 = Ph)
Ding et al. *ACIE* **2005**, *44*, 6362.

Scheme 18.



up to 82% ee

Schulz, E. et al. *J. Mol. Cat. A* **2007**, *272*, 20.

X = Cl or BF_4
53

2.2 *Two metals-one ligand* self-assembly catalyst (type b)

Scheme 19.

$\xleftarrow{\text{reflux}}$ Ru-L + Zr(O*t*Bu)$_4$

54 (1 mol%)

quant. yield and up to 95% ee

54

Lin et al. *ACIE* **2003**, *42*, 6000.

amorphous, highly porous, large pore distribution

2.3 *One metal-two ligands* self-assembly catalyst (type c)

Scheme 20.

Ding et al. *JACS* **2005**, *127*, 7694.

dpen

binap

dpen

55

binap

55b

94.5-98.1% *ee*

for R = Ph: **a**: 78.2% *ee*
b: 97.4% *ee*

♣ **Summary**

The attractive properties of these metal¨Corganic catalysts are their ready separation from the product and their reusability. Moreover, in contrast to homogeneous catalysts immobilized on an external support, they have the advantage of possessing an especially high density of catalytically active units. In some cases, the structure of these systems is highly ordered on the microscopic level. Therefore, in contrast to most other heterogeneous catalysts, their structure can be solved and the information used for a better mechanistic understanding.

3. Catalysis at Chiral Surfaces

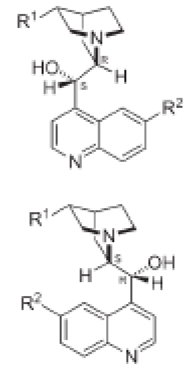
3.1 Chiral modifiers

An achiral heterogeneous catalyst and small enantiomerically pure, organic molecules (*chiral modifiers*) work together as catalysts. This kind of ¡°tandem catalysis¡± is at the boundary between homogeneous and heterogeneous catalysis.

often used chiral modifiers: cinchona alkaloids, tartaric acid, glucose

Scheme 21.

modifier: 0.3%~0.1%; Pt /modifier: 5~12



natural cinchina alkaloids and deriv.

review: *Adv. Syn. Cat.* **2003**, *345*, 45.

An expanded aromatic ring, a basic N atom, a properly located asymmetric center are benificial

3.2 Macromolecular catalysis (polypeptide catalysis)

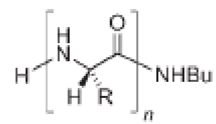
Scheme 22. **Julia-Colonna epoxidation**

56a (n = 30)

three phase
(water,
organic solvent,
insoluble catalyst)

two phase

56b



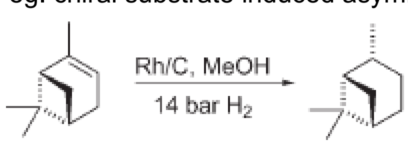
56a R = CH_3
b R = $CH_2CH(CH_3)_2$

Julia et al. *T* **1984**, *40,* 5207.
Roberts et al. *CC* **1998**, 1159.

For application in the syntheses of diltiazem, Taxol side chain and SK&F 104353, see:
a) *JOC* **1993**, *58*, 6247; b) *JCSPT1* **1997** 3501.

4. Other asymmetric heterogeneous catalysis

eg. chiral substrate induced asymmetric heterogeneous catalysis:



pinene

99% *de*