

## ***Solid-Supported Reagents for Organic Synthesis***

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MacMillan Group Meeting  
December 6, 2001

· A recent review on functionalized polymers with an emphasis on chiral catalysts: *Synthesis* **1997**, 1217-1239.

· Main text references:

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

*Polymer-Supported Reactions in Organic Synthesis*; Hodge, P. and Sherrington, D.C., Ed.; John Wiley & Sons: New York, 1980.

*Solid-Phase Organic Synthesis*; Burgess, K., Ed.; Wiley-Interscience: New York, 2000.

*Solid-Phase Synthesis: a Practical Guide*; Kates, S. A. and Albericio, F.; Marcel Dekker, Inc.: New York, 2000.

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### ***Advantages and Disadvantages of Solid-Support Reagents***

#### **\* Advantages**

- Solid-supported reagents are easily removed from reactions by filtration.
- Excess reagents can be used to drive reactions to completion without introducing difficulties in purification.
- Recycling of recovered reagents is economical, environmentally-sound, and efficient.
- Ease of handling is especially important when dealing with expensive or time-intensive catalysts which can be incorporated into flow reactors and automated processes.
- Finely tune chemical properties by altering choice of support and its preparation
- Toxic, explosive, and noxious reagents are often more safely handled when contained on solid support.
- *Reagents on solid-support react differently, mostly more selectively, than their unbound counterparts.*

#### **\* Disadvantages**

- Some reagents may not interact well with solid support.
- Ability to recycle reagents on solid support is not assured.
- Reactions may run more slowly due to diffusional constraints.
- Polymeric support materials can be very expensive to prepare.
- Stability of the support material can be poor under harsher reaction conditions.
- Side reactions with the polymer support itself may occur.

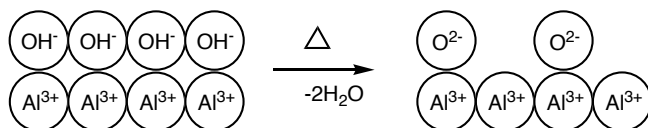
*Synthesis* **1997**, 1217-1239.

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

## Inorganic Supports: Alumina

### \* Alumina — $\text{Al}_2\text{O}_3 \cdot (\text{H}_2\text{O})_n, n=0-3$

- thermally-stable, high-surface-area forms lead to use as acid or base catalysis or as supports for other catalytic materials (e.g. metals, oxides, sulphides, etc.)
- composition depends on precursors, temperature, and mode of heating, thermolysis combines hydroxyls to generate water which is driven from the solids
- formed from  $\text{Al}(\text{OH})_3$  [ $\text{Al}_2\text{O}_3 \cdot (\text{H}_2\text{O})_3$ ] and  $\text{AlO}(\text{OH})$  [ $\text{Al}_2\text{O}_3 \cdot (\text{H}_2\text{O})$ ] to give 3 surface species:  $\text{OH}^-$ ,  $\text{O}^{2-}$ , and  $\text{Al}^{3+}$
- dehydrated and hydrated forms
- used as a drying agent, catalyst, catalyst support, and for column chromatography among other applications



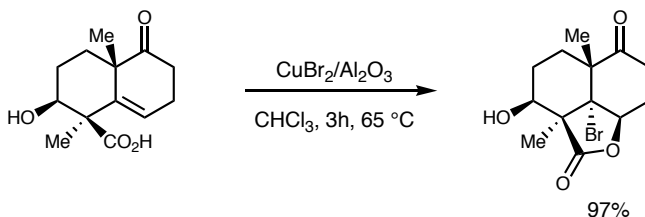
*Tetrahedron* **1997**, 53, 7999-8065.

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

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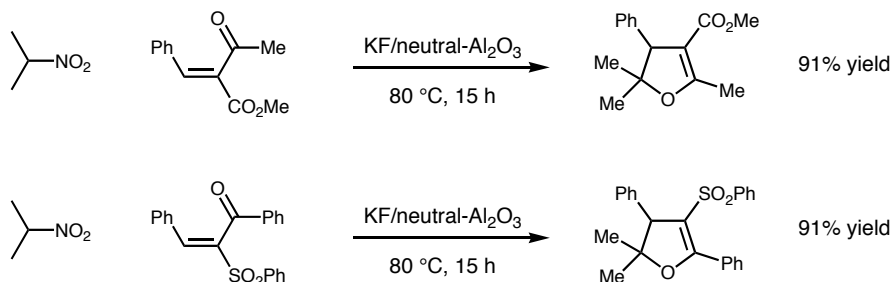
### Some Common Reagents on Alumina

- $\text{CuBr}_2/\text{Al}_2\text{O}_3$ : alternative to traditional halolactonization



*Tetrahedron* **1997**, 53, 799-8065.

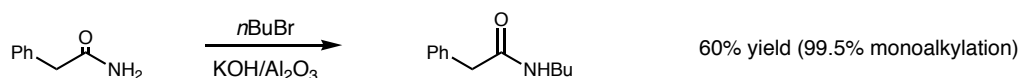
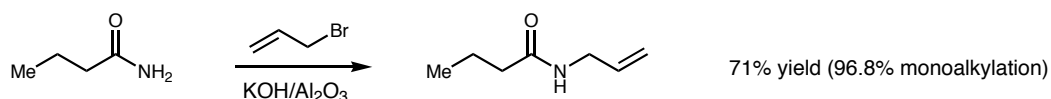
- $\text{KF}/\text{neutral-Al}_2\text{O}_3$  as a heterogeneous base for Pd-catalyzed allylic alkylations of carbon acids with  $5 < \text{pK}_a < 13$  and for Michael reactions of nitroalkanes (note: compares favorably with TEA and DBU but does not cause decarboxylation as DBU does)



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

## More Common Reagents on Alumina

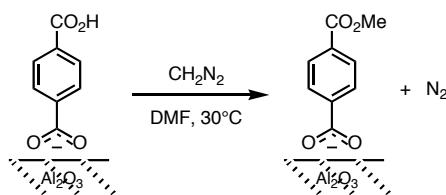
- $\text{NaBH}_4/\text{Al}_2\text{O}_3$  for selective reductions
- $\text{Al}_2\text{O}_3$ : Diels-Alder; sigmatropic rearrangements; epoxide ring-opening with amines, allyl alcohols etc.
- $\text{KF}/\text{Al}_2\text{O}_3$  for mild (compared to  $\text{NaNH}_2$ , for example) *N*-alkylation of carboxamides, lactams, and other *N*-heterocycles with alkyl halides or dialkyl sulfates; appears to be catalytic for *N*-alkylation of 2° amides, *N,N*-dialkylation of 1° amides
- $\text{KOH}/\text{Al}_2\text{O}_3$  for selective monoalkylation of 1° amides



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

## Selective Esterification on Alumina

- Chromatographic alumina and EtOAc for the transesterification of 1° ROH of base-sensitive compounds
- Monoesters of dicarboxylic acids using neutral alumina and dimethyl sulfate or diazomethane



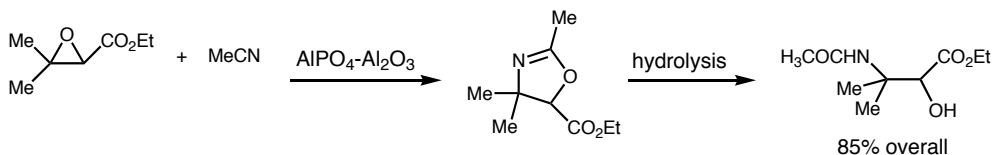
Selective Monomethyl Esterification of Dicarboxylic Acids using Alumina and Dimethyl Sulfate

Substrate	% yield of mono-Me	% yield of di-Me
$\text{C}_6\text{H}_4$ -1,4-( $\text{CO}_2\text{H}$ ) <sub>2</sub>	72	12
$\text{C}_6\text{H}_4$ -1,3-( $\text{CO}_2\text{H}$ ) <sub>2</sub>	63	19
$\text{C}_6\text{H}_4$ -1,2-( $\text{CO}_2\text{H}$ ) <sub>2</sub>	80	8
$\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$	93	7
$\text{HO}_2\text{C}(\text{CH}_2)_6\text{CO}_2\text{H}$	99	0
$\text{HO}_2\text{C}(\text{CH}_2)_{10}\text{CO}_2\text{H}$	97	3

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

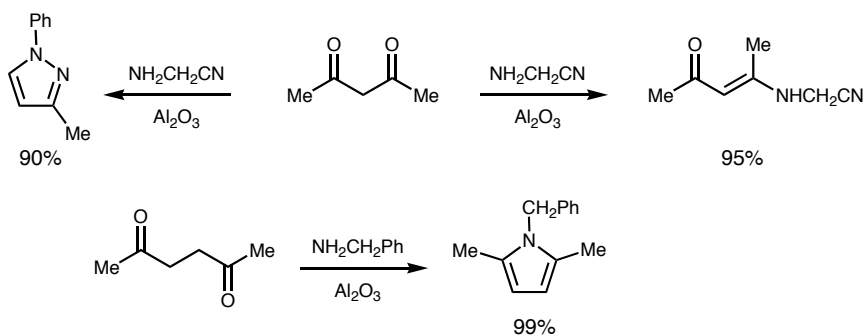
## Nitrogen Heterocycles from Alumina Reagents

- $\text{AlPO}_4\text{-Al}_2\text{O}_3$ : epoxide ring-opening with alcohols, carboxylic acids, and MeCN to give a  $\beta$ -acetamido moiety



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

- $\text{Al}_2\text{O}_3$ : formation of enamines, pyrroles, and pyrazoles

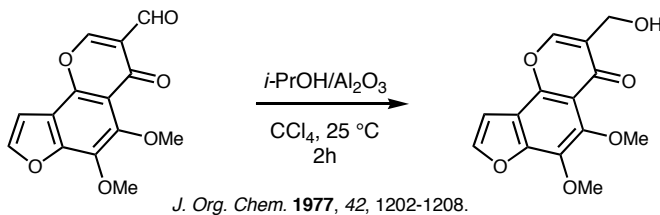


*Tetrahedron* **1997**, 53, 799-8065.

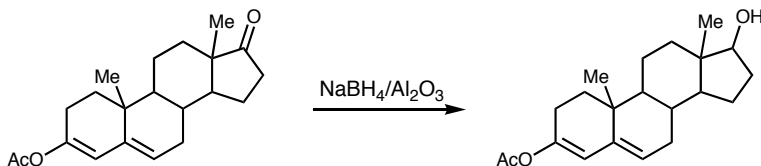
## Selective Reductions on Alumina

- \*  $\text{NaBH}_4/\text{Al}_2\text{O}_3$  is more selective and less acidic than its non-alumina counterparts.

- $\text{NaBH}_4$ ,  $\text{NaBH}_4\text{-AlCl}_3$ , DIBAL, and  $\text{NaBH}_3\text{CN}/\text{acid}$  all reduced aldehyde and the  $\alpha,\beta$ -double bond, but the chromone was inert to homogenous Meerwein-Ponndorf-Verley (MPV) conditions using  $\text{Al}(\text{O}i\text{-Pr})_3$ .

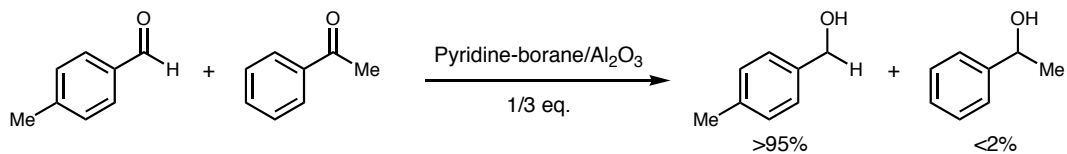


- Under normal  $\text{NaBH}_4$  conditions, the enol acetate undergoes rapid hydrolysis.



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

- \* Pyridine-borane/ $\text{Al}_2\text{O}_3$  selectively reduces aldehydes in the presence of ketones.



*J. Org. Chem.* **1977**, 42, 1202-1208.

## Oxidative Deprotection of TMS and THP Ethers Using Cr<sup>VI</sup>Oxide on Alumina

Table Oxidative Deprotection of Trimethylsilyl and Tetrahydropyranyl Ethers with Wet Alumina Supported Chromium(VI) Oxide

Entry	Substrate	Time (sec.)	Product	Yield	mp (°C) or bp (°C)/Torr	
					found	reported <sup>12</sup>
1	PhCH <sub>2</sub> OSiMe <sub>3</sub> (1a)	30	PhCHO (3a)	90	175–176	
2	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OSiMe <sub>3</sub> (1b)	30	4-MeC <sub>6</sub> H <sub>4</sub> CHO (3b)	90	217–218	
3	2-NO <sub>2</sub> -5-MeC <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> OSiMe <sub>3</sub> (1c)	50	2-NO <sub>2</sub> -5-MeC <sub>6</sub> H <sub>3</sub> CHO (3c)	88	64–65	
4	PhCH(Me)OSiMe <sub>3</sub> (1d)	60	PhCO(Me) (3d)	89	200–201	
5	PhCHOSiMe <sub>3</sub> (1e)	60	PhCO(Ph) (3e)	89	49–50	
6	c-C <sub>6</sub> H <sub>11</sub> OSiMe <sub>3</sub> (1f)	60	Cyclohexanone (3f)	90	154–155	
7	2-MeC <sub>6</sub> H <sub>10</sub> OSiMe <sub>3</sub> (1g)	60	2-Methylcyclohexanone (3g)	88	161–162	
8	(–) Menthol silyl ether (1h)	120	(–) Menthone (3h)	80	208–210	
9	PhCH=CH CH <sub>2</sub> OSiMe <sub>3</sub> (1i)	100	PhCH=CHCHO (3i)	72	246–247	
10	PhCH <sub>2</sub> OTHP (2a)	120	3a	82	175–176	
11	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OTHP (2b)	120	3b	80	216–217	
12	2-NO <sub>2</sub> -5-MeC <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> OTHP (2c)	140	3c	78	62–63	
13	PhCH(Me)OTHP (2d)	120	3d	88	199–200	
14	PhCHOTHP (2e)	120	3e	89	46–47	
15	c-C <sub>6</sub> H <sub>11</sub> OTHP (2f)	180	3f	88	154–155	
16	2-MeC <sub>6</sub> H <sub>10</sub> OTHP (2g)	180	3g	82	160–161	
17	(–) Menthol silyl ether (2h)	180	3h	78	208–210	
18	PhCH=CHCH <sub>2</sub> OTHP (2i)	120	3i	72	246–247	

CrO<sub>3</sub> is a mild, efficient, and inexpensive oxidant.

Simply mix finely ground wet alumina-chromium (VI) oxide with neat ethers (reaction does not work without wet alumina and is very slow without water).

Reactions are worked up by extraction with CH<sub>2</sub>Cl<sub>2</sub> and passage through a small bed of alumina.

Reactions are relatively clean with no tar formation typical for many CrO<sub>3</sub> oxidations.

No overoxidation to carboxylic acids is observed.

*Synthesis* 1998, 393-394.

## Inorganic Supports: Silica

### ✳ Amorphous Silica — polymorphic forms of SiO<sub>2</sub>

- May have short-range crystalline order depending on method of preparation
- Solubility markedly increases in solutions of pH > 9
- Primary particles of colloidal dimensions (1-100 nm) may be discrete (microparticulate), aggregated into larger secondary particles (1000x), or agglomerated to form a continuous 3-D network (e. g. silica gel).
- May be hydrated or anhydrous — SiO<sub>2</sub>·xH<sub>2</sub>O
- Acidic catalysis, consider silica as the polycondensation product of orthosilicic acid Si(OH)<sub>4</sub>
- Most often used as catalyst support due to high surface area and large pore volumes —> high dispersal
- Amenable as a stationary phase for continuous flow reactors

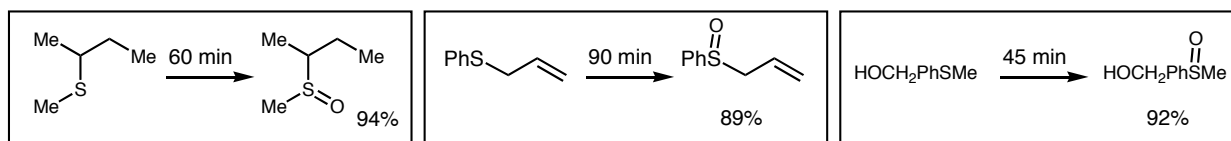
### ✳ Reagents

- Oxidants are the most common reagent; for example: KMnO<sub>4</sub>, FeCl<sub>3</sub>, Cu(NO<sub>3</sub>)<sub>2</sub>, Zn(NO<sub>3</sub>)<sub>2</sub>, sodium metaperiodate
- Reductants are also well-precedented: NaBH<sub>4</sub> (β-nitrostyrenes, aldehydes) and Bu<sub>3</sub>SnH (aldehydes >>ketones)
- Silica-bound Co(Salen) complexes have maintained catalyst activity under continuous flow conditions

## Oxidants on Silica

### \* Magnesium monoperoxyphthalate on wet SiO<sub>2</sub> oxidizes sulfides to sulfoxides without $\alpha$ -hydroxylating ketones.

· First examples of oxidation of sulfides with a carbonyl group with MMPP in aqueous media without Baeyer-Villiger reaction



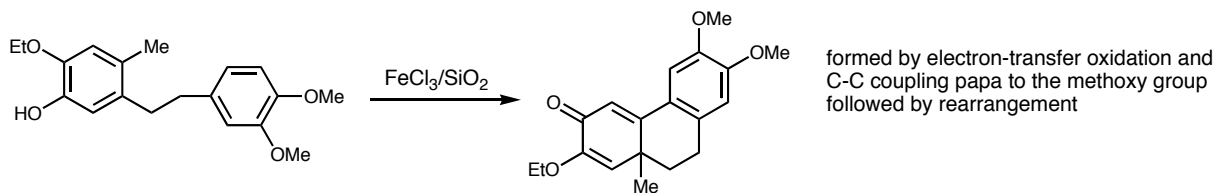
all yields in paper 89-100%

- MMPP normally extremely insoluble, limiting its utility
- Better than most sulfide oxidation reagents, which are expensive, toxic, or rare and difficult to prepare

*Synthesis* **1997**, 764-768.

### \* Oxidative coupling of phenols and phenol ethers using FeCl<sub>3</sub>/SiO<sub>2</sub>.

· FeCl<sub>3</sub>/SiO<sub>2</sub> acts as an electron-transfer oxidant for intermolecular and intramolecular couplings.

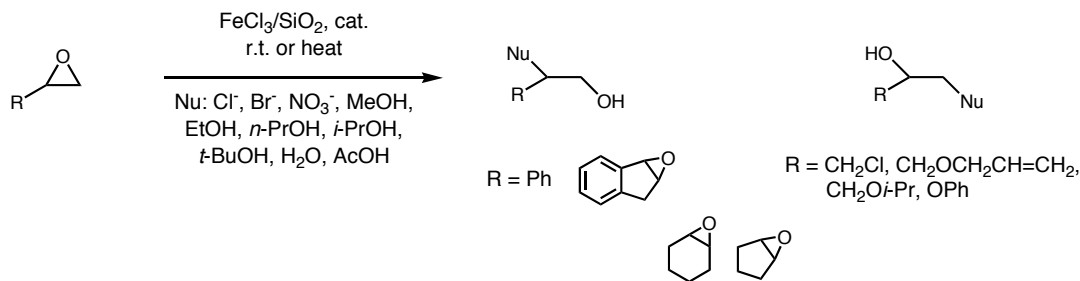


*J. Org. Chem.* **1980**, 749-751.

## Fe<sup>III</sup>-Catalyzed Epoxide Ring Opening on Silica

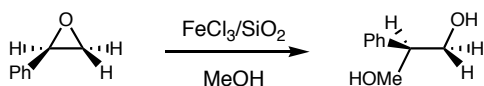
### \* FeCl<sub>3</sub>/SiO<sub>2</sub> for ring opening of epoxides:

· Iron is abundant, cheap, and non-toxic.



yields: 86-95% for ROH; 78-96% for Cl<sup>-</sup>, 78-92% for Br<sup>-</sup>, 51-54% for NO<sub>3</sub><sup>-</sup>, 79-89% for H<sub>2</sub>O, 78-91% for AcOH

· If the halide or nitrate epoxide opening is attempted with BF·OEt<sub>2</sub>, SnCl<sub>4</sub>, or anhydrous FeCl<sub>3</sub>, which have been reported for the alcoholysis of epoxides, there is no halide or nitrate addition.



Lewis Acid	Temp. (°C)	Yield (%)	ee (%)
FeCl <sub>3</sub> /SiO <sub>2</sub>	0	94	93
SnCl <sub>4</sub>	-30	88	95
TiCl <sub>4</sub>	-30	80	90
AlCl <sub>3</sub>	0	45	58
ZnCl <sub>2</sub>	-20	0	-
ZnCl <sub>2</sub>	-30	92	75
BF·OEt <sub>2</sub>			

*Synthesis* **1996**, 1473-1476.

## Inorganic Supports: Zeolites

※ **Zeolites** —  $C_x[(T_y, Si_{1-y})O_2]X_zwM$  where x, z, and w are # of non-framework cations (C), anions (X), and molecules (M, e.g. water); y is the # of tetrahedrally coordinated framework elements (T) other than silicon

Crystalline microporous aluminosilicates with molecular-sized intracrystalline channels and cages

· Natural zeolites contain a mixture of cations (e.g.  $Na^+$ ,  $K^+$ ,  $Mg^{2+}$ , and  $Ca^{2+}$ ) which can be ion-exchanged.

Most are aluminosilicates where T is Al, M is water, and  $[X] = 0$ .

· Offer shape-selective control, either by transition state selectivity or by exclusion of competing reactants, and provide controlled release of reactive reagents (e.g.  $Br_2$ ) by diffusion from host into liquid phase

· Highly selective adsorbants, can remove minute components of a reaction mixture

High-surface-area insoluble supports for stoichiometric reagents

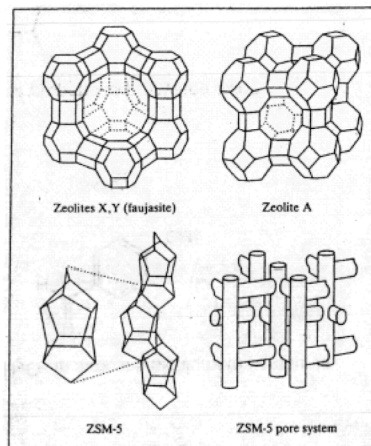
Minimum framework Si/Al ratio is 1

### Disadvantages:

Some zeolite reagents are air- and moisture-sensitive

Can require low loadings of reactants for acceptable rates in solution

Shape-selection excludes moderately large organic molecules

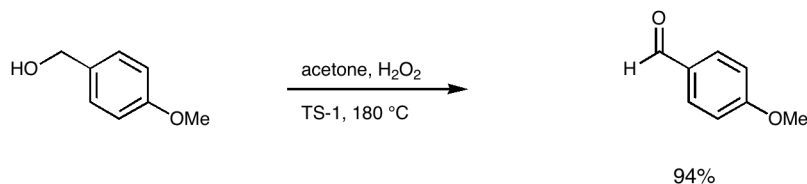


*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992

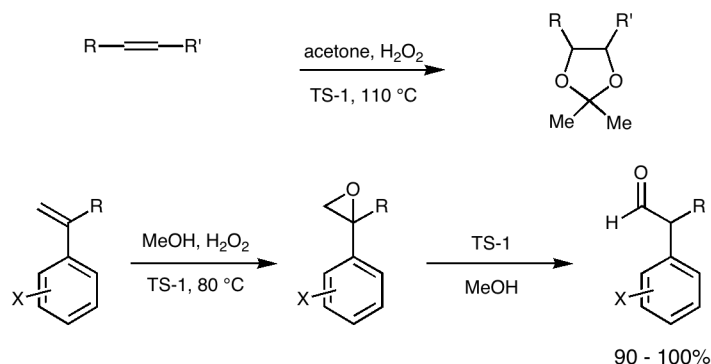
## Zeolite-Supported Oxidations

### ※ Titanosilicate Zeolite

· Titanium zeolite TS-1 catalyzes oxidations of alcohols with dilute aqueous  $H_2O_2$  in almost stoichiometric amounts



· Environmentally and commercially viable alternative to chlorohydrin route of propene to propylene oxide



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

# Inorganic Supports: Clays

## \* Clay Minerals

- Occurrence of high surface area clay minerals is ubiquitous.
- Comprise a large family of fine-grained crystalline sheet silicates
- Sorptive and ion exchange properties due to composition and structure

## \* Functions in Solid Catalysis

- Catalytically active, generally as solid acids
- Bifunctional or 'inert' supports; e.g. for highly dispersed metals, metal complexes, enzymes, etc.
- Fillers to give solid catalysts required physical properties; e.g. attrition resistance, density, specific heat capacity

## \* Montmorillonite

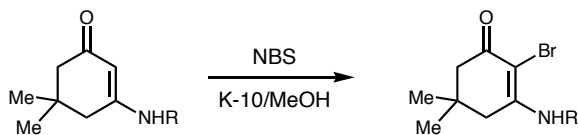
- Most versatile intermediate charge clay (high layer or low layer charge minerals do not swell much)
- High cation exchange capacity and good swelling properties allow a wide variety of catalytically active forms to be prepared: acidic cations, metal complexes, photocatalytically active cations, etc.
- Ideal formula:  $M^+_x[Si_8^{tet}(M^{3+}_{4-x}M^{2+}_x)^{oct}O_{20}(OH)_4]^{x-}$
- Interlayer species:  $Na^+$ ,  $K^+$ ,  $Ca^{2+}$ ,  $Mg^{2+}$  used to fine-tune catalyst selectivity; exchangeable cations:  $H^+$ ,  $Al^{3+}$ ,  $Cr^{3+}$ ,  $Fe^{3+}$

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

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## Selective Bromination Using Solid-Support Reagents

### \* NBS on K-10 Montmorillonite



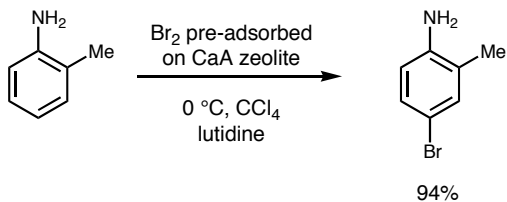
R = H, Me, *i*-Pr, Ph, Bn, allyl

yields = 60-74%

- Conventional methods (NBS/MeOH,  $Br_2/CCl_4$  or BrCN) give a mix of  $\alpha$ -bromination, allylic di-bromination, and salts
- Isolation is simplified because the succinimide formed during the reaction is adsorbed onto the support
- Decreased reaction time of 5 h

*Synthesis* **2001**, 1935-1937.

### \* $Br_2$ on Zeolite



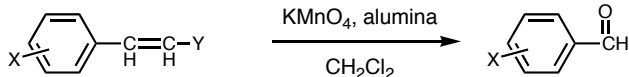
- Selectivity is attributed to aniline being too large to enter the pore cavities of CaA and the controlled release of bromine from the pore system
- Irreversible damage to wet zeolites by wet hydrogen halides limits zeolite lifetime

*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.



## Effect of Support Material Chosen for Permanganate

\* On acidic media such as alumina,  $\text{KMnO}_4$  affords cleavage of aryl-substituted olefins to aldehydes.



X = MeO, OH, Br, Cl,  $\text{CF}_3$ ,  $\text{CO}_2\text{Me}$ , H, Me

Y = H, COMe,  $\text{CO}_2\text{H}$ , Me

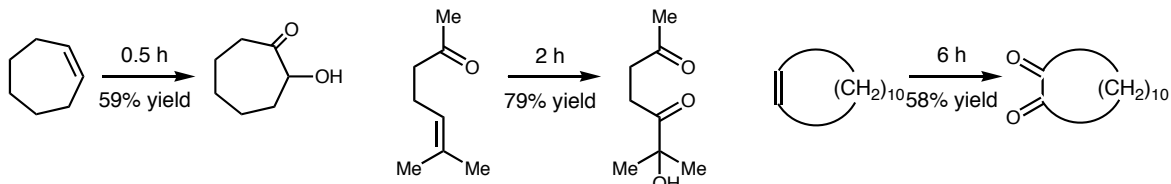
· Other good supports : Amberlite and Rexyn 101 (H)

· Among poor supports: molecular sieves,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,

· Substrate-dependent : Amberlite (sodium form), Florisil, and  $\text{SiO}_2$

*Synthesis* **2001**, 1645-1648.

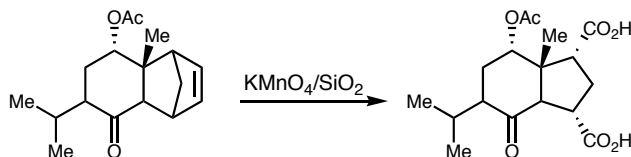
\* On neutral media such as  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,  $\text{KMnO}_4$  converts olefins to  $\alpha$ -hydroxy ketones and  $\alpha$ -diketones.



· Epoxidation (steroidal substrate) and cleavage (bis-aryl-substituted) not as common as with free  $\text{KMnO}_4$ , but still present

*J. Org. Chem.* **1989**, *54*, 5182-5184.

\* On  $\text{SiO}_2$ ,  $\text{KMnO}_4$  easily oxidatively cleaves olefins with 1-3 substituents, including electron-withdrawing groups.



*Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

· Conveniently performed by elution of a benzene solution through a short column of  $\text{MnO}_4/\text{SiO}_2$

· Traditional methods failed in this example:  $\text{KMnO}_4/\text{acid}$  or base;  $\text{KMnO}_4/\text{MgSO}_4$ ,  $\text{KMnO}_4/\text{NaIO}_4$ .

## Organic Supports: Polymeric Resins

\* Functionalized Polymers

· In addition to the construction of new compounds on polymer supports, functionalized polymers have long been used as stoichiometric reagents, catalysts, and reaction purifiers.<sup>1</sup>

· Reactions are easily monitored by TLC.

· Cross-linked polymeric species can be recycled many times without appreciable loss of reactivity.

\* Reagents

· Highly-enantioselective insoluble polymer bound (IPB) catalysts: Sharpless dihydroxylation, oxazaborolidine reduction, oxazaborolidine Diels-Alder, N-butylnorephedrine for diethylzinc additions to aldehydes,<sup>2</sup> polybinaphthols for diethylzinc additions to aldehydes,<sup>3</sup> dihydroxylation using Cinchona alkaloid ligands,<sup>4</sup>

· Not nearly as many soluble polymer bound (SPB) catalysts: Janda's  $(\text{PHQD})_2\text{PHAL}$  for catalytic asymmetric dihydroxylations<sup>2</sup>

· Polymer-supported chiral auxiliaries: Leznoff's primary amine for asymmetric synthesis of 2-alkylcyclohexanones, Evans' oxazolidinone on Merrifield resin<sup>5</sup>

· Oxidants: poly(vinylpyridinium chlorochromate), poly(vinylpyridinium dichromate),  $\text{Cr}^{\text{III}}$  and  $\text{Ce}^{\text{IV}}$  on resin

1. *Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood and PTR Prentice Hall: New York, 1992.

2. *Synthesis* **1997**, 1217-1239.

3. *J. Am. Chem. Soc.* **1997**, *119*, 4313-4314.

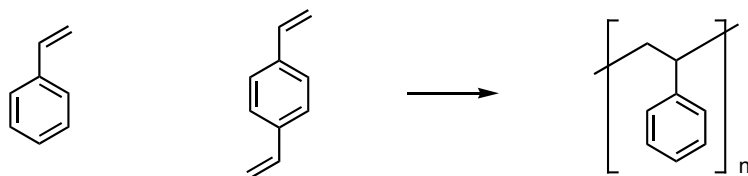
4. *J. Am. Chem. Soc.* **1997**, *119*, 6929-6930.

5. *Tetrahedron Let.* **1996**, *36*, 8023.

## Synthesis of Polymeric Supports

\* In 1963, Merrifield unveiled the original cross-linked polystyrene-divinylbenzene polymer.

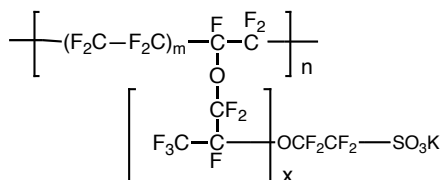
· Merrifield resin is an addition polymer prepared by free radical initiated suspension copolymerization of styrene and 1% divinylbenzene as cross-linkage. It is sold commercially in Aldrich for \$4 / g .



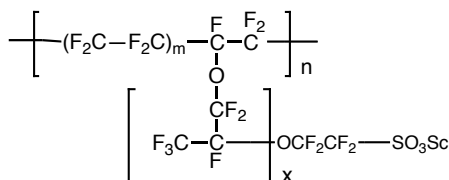
**Procedure:** The comonomer mixture is suspended in an excess of an immiscible solvent which acts as an efficient heat transfer agent. Hydrophobic monomers like styrene are suspended in water with vigorous stirring and with suspension stabilizers such as polyvinylalcohol and calcium phosphate. During polymerization, spherical liquid monomer/comonomer droplets are converted into spherical solid droplets, often referred to as 'beads' or 'pearls'. The beads are collected by filtration, washed free of stabilizer and other contaminants, and dried for use.

*Polymer-Supported Reactions in Organic Synthesis*; Hodge, P. and Sherrington, D.C., Ed.; John Wiley & Sons: New York, 1980.

\* Nafion 511



\* Nafion NR-50-Sc



*Synthesis* **1997**, 1217-1239

## Polymer-Supported Scandium

- Few examples of polymer-supported Lewis acids are known
- Sc(OTf)<sub>3</sub> can catalyze reactions in both organic solvents and water
- Compounds that would not undergo nucleophilic attack under general Lewis acid conditions do react with the nucleophile when Sc-Nafion is used

### Sc-Nafion-Catalyzed Allylation Reactions

R <sup>1</sup> Ph    CH <sub>2</sub> CH <sub>2</sub> Ph    CH=CHPh
yield(%)    91        83        98        78
solvent    A, B        A,B        B        A

R <sup>2</sup> Ph    CH <sub>2</sub> CH <sub>2</sub> Ph    CH=CHPh    CO <sub>2</sub> Me
yield(%)    57        87        95        84
solvent    A, B        A,B        B        A

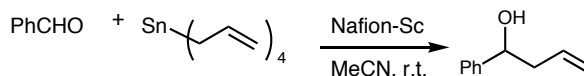
### Sc-Nafion reagent preparation:

3 eq. Nafion beads (NR-50, \$8 / g) were treated with ScCl<sub>3</sub>·6H<sub>2</sub>O in MeCN under reflux. After 40 h, 96% of ScCl<sub>3</sub>·6H<sub>2</sub>O was consumed, and the polymer contained 1.3% Sc.

### Sc-Nafion recovery:

Filtered and washed with suitable solvent. Activity is comparable to that of fresh catalyst.

### Nafion-Sc-Catalyzed Allylation Using a Flow System



run	yield
1	75
2	93
3	84
4	84

### Procedure:

Nafion-Sc (2 g) and sea sand (2 g, 15-20 mesh) were combined, and the mixture was packed in a 6 mm glass tube. A carbonyl compound (0.5 mmol) and tetraallyltin (0.5 mmol) were dissolved in MeCN (4 mL) and passed through the column using a peristaltic pump.

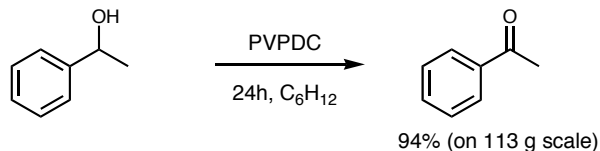
A: H<sub>2</sub>O/THF (1:9)    B: MeCN

*J. Org. Chem.* **1996**, 61, 2256-2257.

## Oxidants on Polymeric Resins

### \* Poly(vinylpyridinium dichromate) (PVPDC) for the non-acidic oxidation of alcohols

- PVPDC used in 1.1 eq. to oxidize 1° and 2° aliphatic, benzylic, and allylic alcohols to the corresponding aldehyde or ketone without overoxidation even at longer reaction times (1.7 was used for faster reaction times).

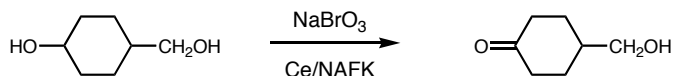


- Poly(vinylpyridine) resin is treated with a slight excess of  $\text{CrO}_3$  in water at r.t. and washed with water before use. PVPDC may also be dried to a yellow-brown powder for prolonged storage.

*J. Org. Chem.*, **1981**, 1728-1730.

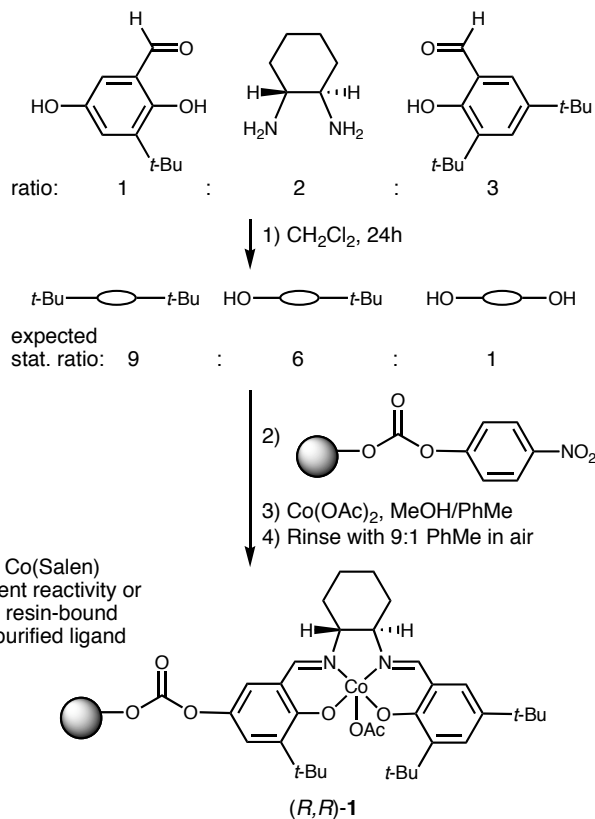
### \* $\text{Cr}^{\text{III}}$ or $\text{Ce}^{\text{IV}}$ impregnated perfluorinated resin-sulfonic acid catalyst for alcohol oxidation

- *t*-BuOOH oxidizes alcohols to the corresponding carbonyl compounds effectively with  $\text{Cr}^{\text{III}}$  or  $\text{Ce}^{\text{IV}}$  impregnated Nafion 511 (Nafion SAC-13, 10-20% fluorosulfonic acid with Nafion polymer on amorphous silica, \$8/g).
- Cr/NAFK and Ce/NAFK catalysts are reusable after simple washing with EtOAc.
- Cr/NAFK gives 81-98% yields; Ce/NAFK gives 71-98% yields
- Oxidations are selective for 2° alcohols; 1° alcohols give complex mixtures of products
- $\text{NaBrO}_3$  in AcOH can also be used as a co-oxidant.



*Tetrahedron Let.*, **1984**, 3317-3320.

## Synthesis of Polystyrene-Bound Chiral Co(Salen) Complex

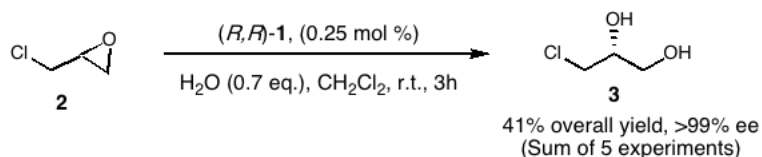


- Resin capture synthesis of Co(Salen) complex showed no apparent reactivity or selectivity differences from resin-bound catalyst synthesized from purified ligand

*J. Am. Chem. Soc.* **1999**, 121, 4147-4154.

## HKR with Polystyrene-Bound Chiral Co(Salen) Complexes

※ Resin-Bound Co(Salen) Complex Exhibits No Loss of Catalyst Reactivity or Enantioselectivity in the Hydrolytic Kinetic Resolution of Terminal Epoxides



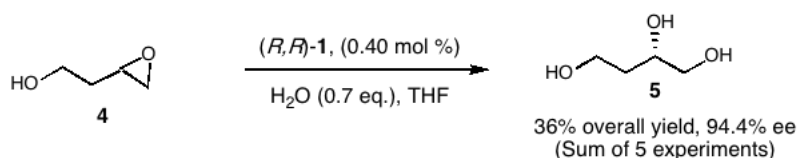
HKR of Epichlorohydrin with Resin-Bound Co(Salen) Catalyst

cycle	conversion	ee <b>2</b> (%)	ee <b>7</b> (%)	$k_{\text{rel}}$
1	52	>99	92.4	133
2	51	>99	95.0	206
3	51	>99	93.6	159
4	51	>99	93.4	154
5	52	>99	93.0	145

$$\text{conversion} = \frac{ee_{\text{sm}}/ee_{\text{prod}}}{1 + (ee_{\text{sm}}/ee_{\text{prod}})}$$

$$k_{\text{rel}} = \ln[(1-\text{conversion}) \times (1 + ee_{\text{prod}})]$$

$$\ln[(1-\text{conversion}) \times (1 - ee_{\text{prod}})]$$

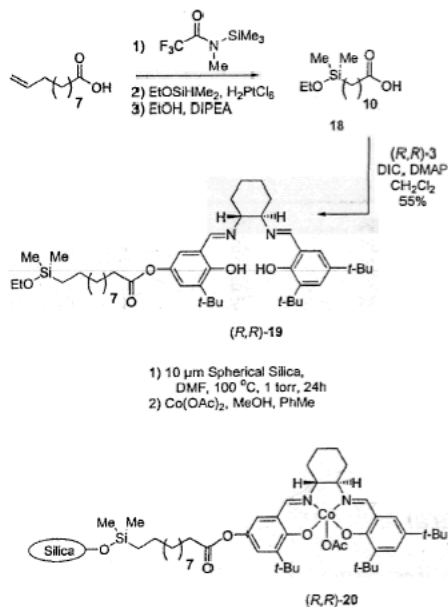


· Addition of  $(\text{CF}_3)_3\text{COH}$ , a volatile, non-nucleophilic protic acid additive, was found to accelerate the reaction of phenol with epibromohydrin with no reduction in enantioselectivity of yield (90% yield over 5 cycles, 96% ee), presumably by helping to maintain the catalyst in the  $\text{Co}^{\text{III}}$  oxidation state

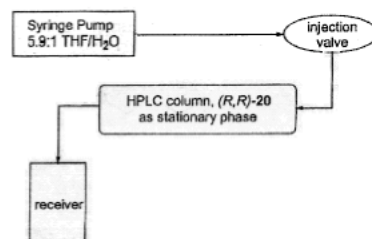
*J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

## Silica-Bound Chiral Co(Salen) Complex

Synthesis of Silica-Bound Complex:



Continuous-flow apparatus for HKR of **8** over catalyst **20**:



· HKR of 4-hydroxy-1-butene oxide with silica-bound Co(Salen) complex  $(R,R)$ -**20**:

$\text{HO-CH}_2\text{-CH}_2\text{-CH(O)-CH}_2 \xrightarrow[\text{elute with 5.9:1 THF/H}_2\text{O}]{(R,R)\text{-20 (0.5 mol \%)}}$ 
  
 $\text{HO-CH}_2\text{-CH}_2\text{-CH(OH)-CH}_2$ 
  
**(±)-8**
  
**(S)-9**

Cycle	Conversion (%)	ee <b>8</b> (%)	ee <b>9</b> (%)	$k_{\text{rel}}$	yield <b>9</b> (%)
1	36	54.0	94.7	63	34
2	39	61.1	94.2	63	39

Catalyst regeneration by elution of a small volume of AcOH/toluene.

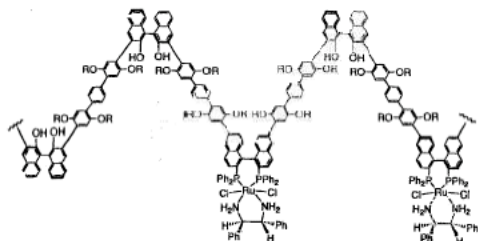
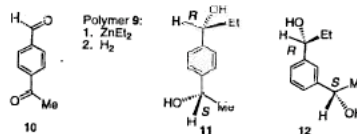
*J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

## BINOL-BINAP Copolymer Catalyst

· BINOL ligands with hard metal centers such as Al<sup>III</sup>, Ti<sup>IV</sup>, Zn<sup>II</sup>, and Ln<sup>III</sup> generate highly enantioselective Lewis acid catalysts: diethyl zinc addition to aryl, alkyl, and  $\alpha,\beta$ -unsaturated aldehydes

· BINAP ligands with soft phosphorus atoms coordinate with soft late transition metals such as Rh and Ru: hydrogenation of ketones

**Scheme 2. Tandem Asymmetric Reaction Involving Diethylzinc Addition and Hydrogenation**



**Table 1. Tandem Asymmetric Reactions of Acetyl Benzaldehydes in the Presence of the Multifunctional Chiral Polymer Catalyst**

entry	substrate	solvent		conv. (%) <sup>a</sup>	ee (%) <sup>b,c</sup>	de (%) <sup>b,d</sup>
		Et <sub>2</sub> Zn addition	H <sub>2</sub> addition			
		toluene	<sup>t</sup> PrOH		92	86
2		toluene	toluene + <sup>t</sup> PrOH <sup>e</sup>	>99%	94	87
3 <sup>f</sup>		toluene	<sup>t</sup> PrOH	>99%	93	78
4		toluene	<sup>t</sup> PrOH	>99%	94	75

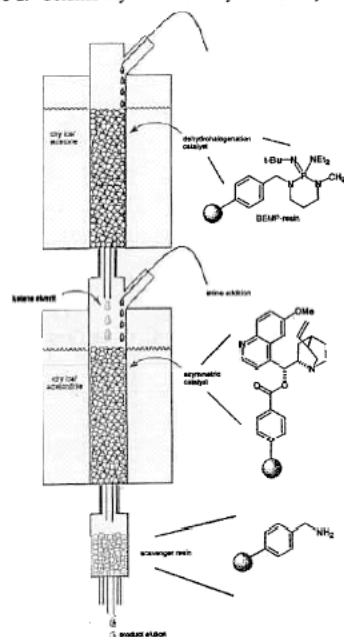
<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Determined by GC-chiral  $\beta$ -Dex 120 column after converted to the diacetate. <sup>c</sup> For the diethylzinc addition. <sup>d</sup> For the hydrogenation. <sup>e</sup> Toluene:PrOH = 1:1. Toluene in the ZnEt<sub>2</sub> addition step is not removed. <sup>f</sup> The recovered catalyst was used.

Catalyst regenerated by simple precipitation and filtration.

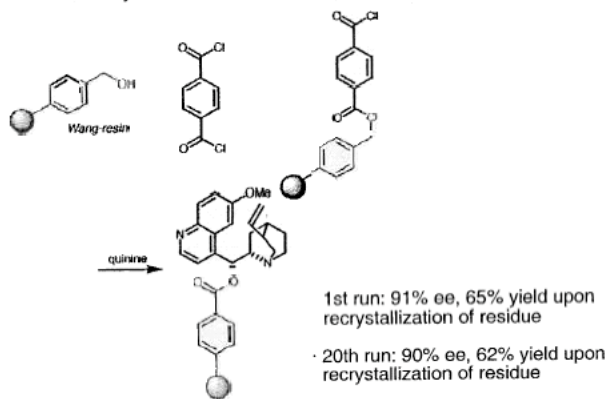
*J. Am. Chem. Soc.* 2000, 122, 6500-6501.

## Column Asymmetric Catalysis for $\beta$ -Lactam Synthesis

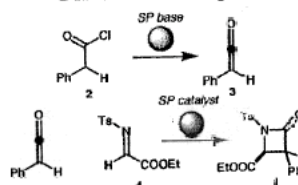
**Figure 1. Column asymmetric catalysis assembly.**



**Scheme 1. Synthesis of Solid-Phase Catalyst**



**Scheme 2. Synthesis of Optically Enriched  $\beta$ -Lactams through Dual Solid-Phase Reagents**



· Catalyst column was regenerated by washing with MeOH and drying under vacuum. BEMP resin was regenerated by rinsing with a phosphazene base in THF/MeCN (1:1) until eluent was free from Cl<sup>-</sup> and drying by heating to 120 °C under vacuum. Scavenger resin was washed with ammonia and dried under high vacuum.

*Org. Let.* 2000, 2, 3963-3965.