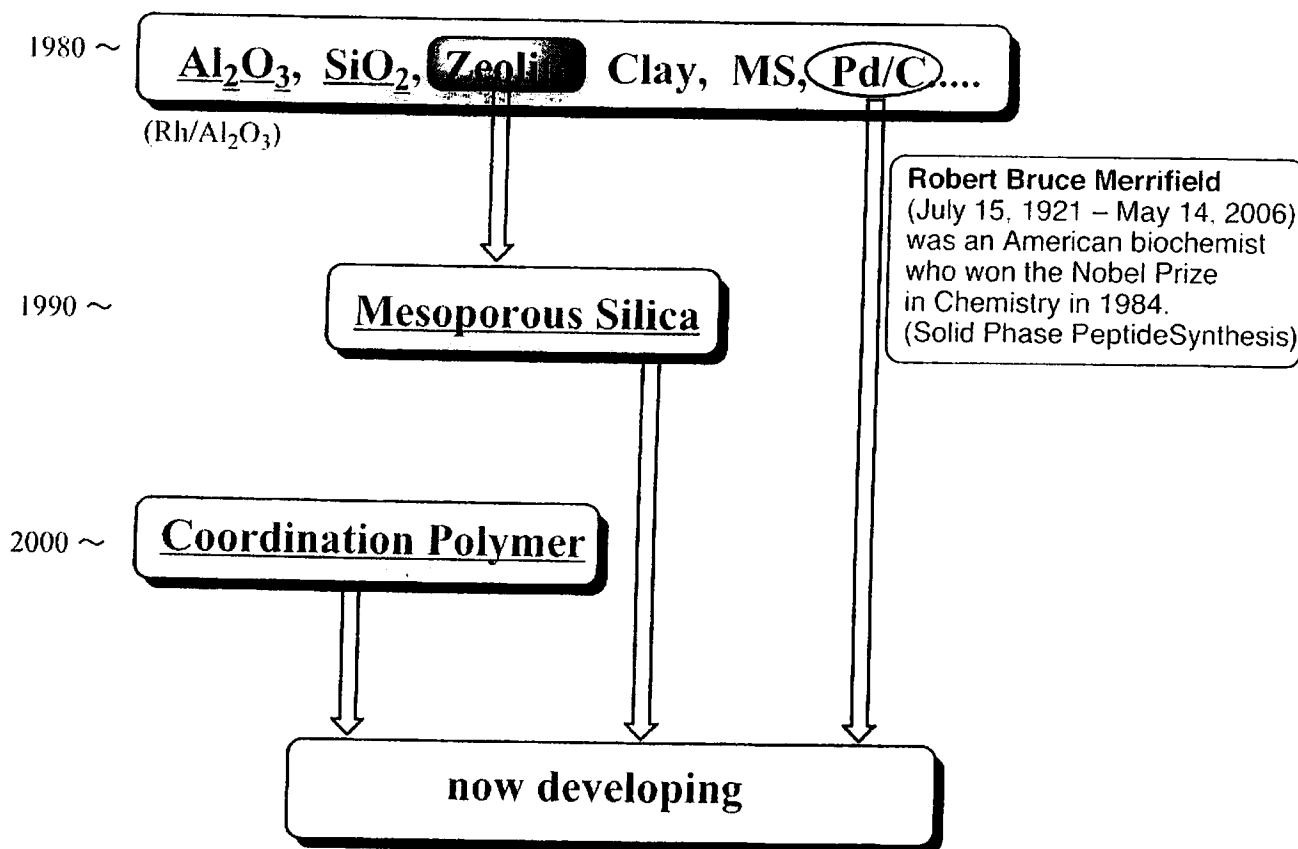


Solid-Supported Reagents for Organic Synthesis

30/05/07 Daisuke Tomita



Advantages and Disadvantages of Solid-Support Reagents

	solid-phase synthesis	liquid-phase synthesis
handling	easy	difficult
purification of each steps	unnecessary (impossible) just washing	necessary extraction, column..
automation	easy	difficult
mechanistic study	difficult	possible
reactivity	often lower	good

Today's Contents

I classical reaction using solid phase

- 1) Inorganic Supports: Alumina
- 2) Inorganic Supports: Silica
- 3) Inorganic Supports: Zeolite

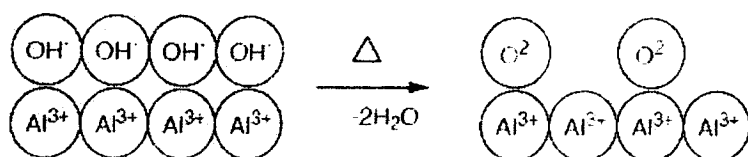
II Mesoporous silica

III Coordination Polymer for Organic Synthesis

I-i) Inorganic Support: Al₂O₃

* Alumina – Al₂O₃·(H₂O)_n, n=0-3

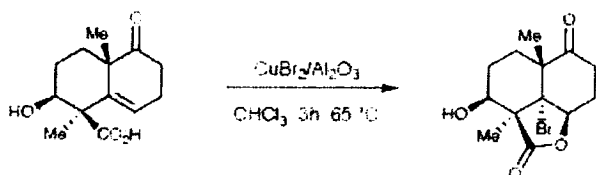
- thermally-stable, high-surface-area forms lead to use as acid or base catalysis or as supports for other catalytic materials (e.g. metals, oxides, sulphides, etc.)
- composition depends on precursors, temperature, and mode of heating, thermolysis combines hydroxyls to generate water which is driven from the solids
- formed from Al(OH)₃ [Al₂O₃·(H₂O)₃] and AlO(OH) [Al₂O₃·(H₂O)] to give 3 surface species: OH⁻, O²⁻, and Al³⁺
- dehydrated and hydrated forms
- used as a drying agent, catalyst, catalyst support, and for column chromatography among other applications



Tetrahedron 1997, 53, 7999-8065

Some Common Reagents on Alumina

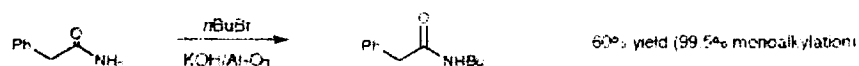
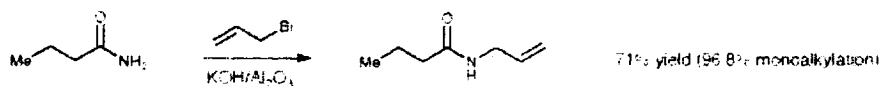
- CuBr₂/Al₂O₃**: alternative to traditional halolactonization
- I₂/KI, Br₂/CHCl₃, or NBS/THF/AcOH: failed to cyclize or did so poorly



ket intermediate for Podolide

Tetrahedron 1997, 53, 799-8065

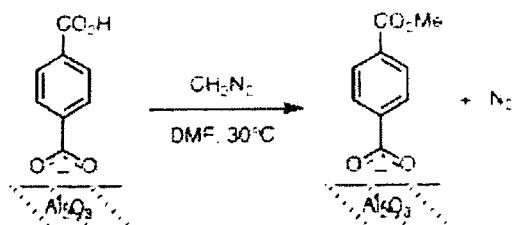
- KOH/Al₂O₃** for selective monoalkylation of 1^o amides



J. M. Melot.; T. Boulet.; A. Foucaud. *Tetrahedron*, 1988, 44, 2215

Selective Esterification on Alumina

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



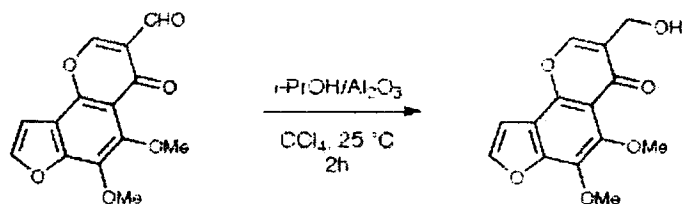
Selective Monomethyl Esterification of Dicarboxylic Acids using Alumina and Dimethyl Sulfate

Substrate	% yield of mono-Me	% yield of di-Me
$C_6H_4-1,4-(CO_2H)_2$	72	12
$C_6H_4-1,3-(CO_2H)_2$	63	19
$C_6H_4-1,2-(CO_2H)_2$	50	9
$HO_2C(CH_2)_2CO_2H$	93	7
$HO_2C(CH_2)_6CO_2H$	90	9
$HO_2C(CH_2)_{10}CO_2H$	97	3

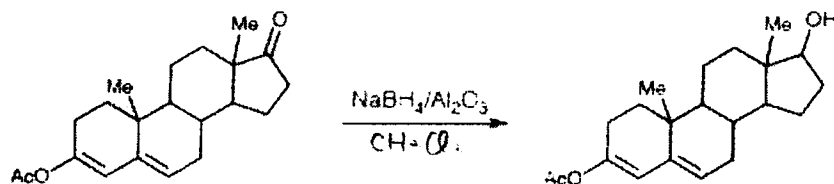
Ogawa, H.; Ighimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* 1986, **59**, 2481.

Selective Reduction on Alumina

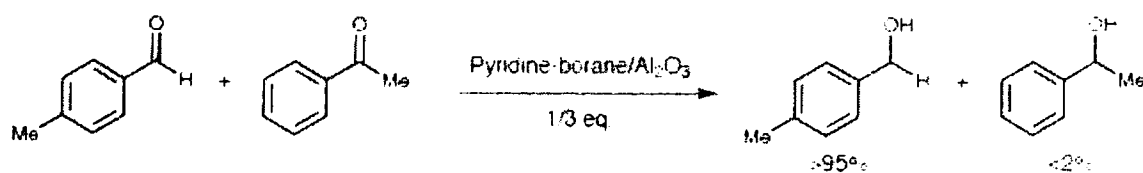
- * $NaBH_4/Al_2O_3$ is more selective and less acidic than its non-alumina counterparts.
- * $NaBH_4$, $NaBH_4 \cdot AlCl_3$, DIBAL, and $NaBH_3CN$ /acid all reduced aldehyde and the α,β -double bond, but the chromone was inert to homogeneous Meerwein-Ponndorf-Verley (MPV) conditions using $Al(O^iPr)_3$



- * Under normal $NaBH_4$ conditions, the enol acetate undergoes rapid hydrolysis.



- * Pyridine-borane/ Al_2O_3 selectively reduces aldehydes in the presence of ketones.



Gary H, P.; Alfonse, W.; Marc J. C. *J. Org. Chem.* 1977, **42**, 1202.

I-ii) Inorganic Supports: Silica

* Amorphous Silica - polymorphic forms of SiO_2

- May have short-range crystalline order depending on method of preparation
- Solubility markedly increases in solutions $\text{pH} > 9$
- 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 unhydrated - $\text{SiO}_2 \cdot x\text{H}_2\text{O}$
- Acidic catalysis, consider silica as the polycondensation product of orthosilicic acid $\text{Si}(\text{OH})_4$
- Most often used as catalyst support due to high surface area and large pore volumes \rightarrow high dispersal
- Amenable as a stationary phase for continuous flow reactors

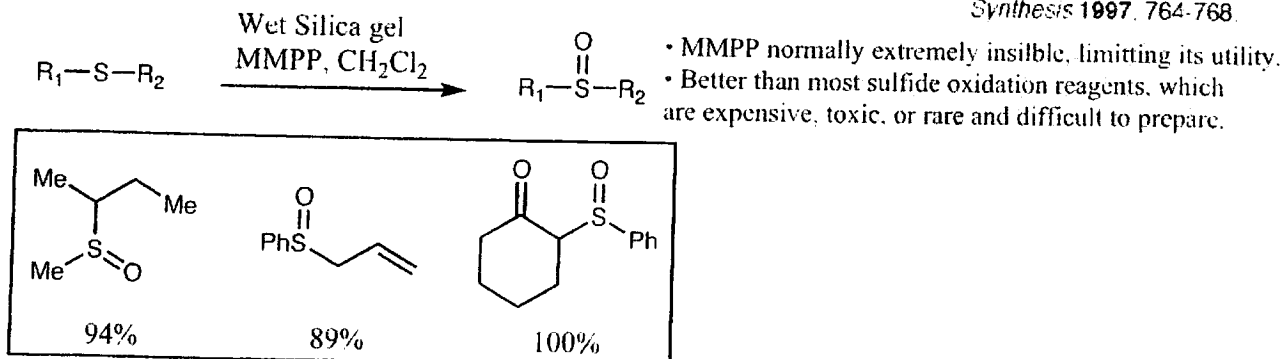
* Reagents

- Oxidants are the most common reagent; for example: FeCl_3 , KMnO_4 , $\text{Cu}(\text{NO}_3)_2$, $\text{Zn}(\text{NO}_3)_2$, sodium metaperiodate
- Reactant are also well-precedented: NaBH_4 and Bu_3SnH

* Magnesium monoperoxyphthalate on wet SiO_2 oxidizes sulfides to sulfoxides without α -hydroxylating ketones.

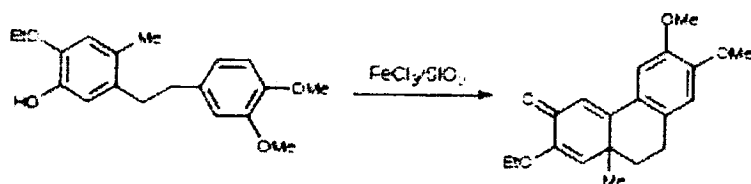
- First examples of oxidation of sulfides with a carbonyl group with MMPP in aqueous media without Baeyer-Villiger reaction

Synthesis 1997, 764-768



* Oxidative coupling of phenols and phenol ethers using $\text{FeCl}_3/\text{SiO}_2$

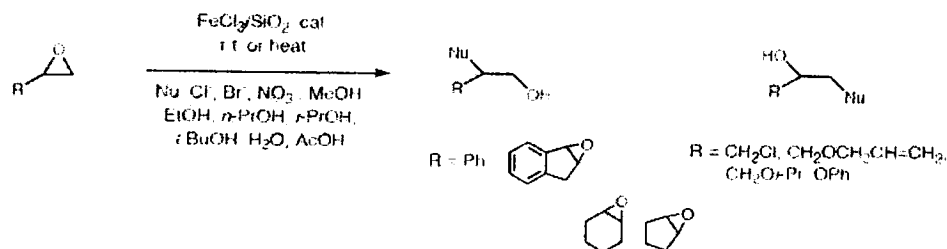
- $\text{FeCl}_3/\text{SiO}_2$ acts as an electron-transfer oxidant for intermolecular and intramolecular couplings.



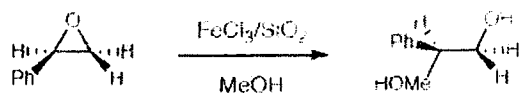
J. Org. Chem. 1980, 749-751

* $\text{FeCl}_3/\text{SiO}_2$ for ring opening of epoxides:

- Iron is abundant, cheap, and non-toxic



yields 86-95% for ROH, 78-96% for Cl, 78-92% for Br, 51-54% for NO_2 , 79-89% for H_2O , 78-91% for AcOH



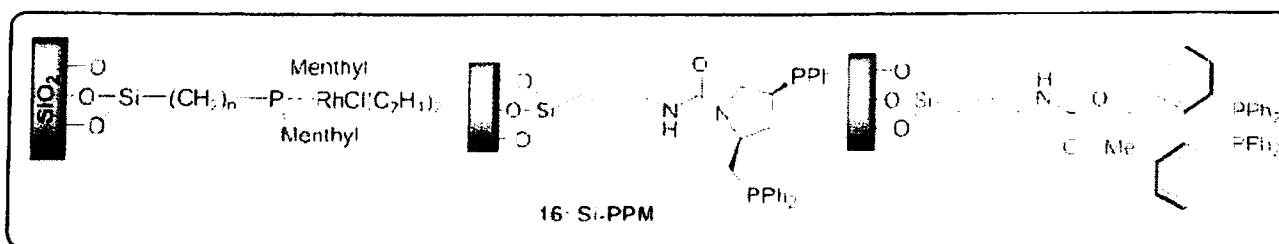
Lewis Acid	Temp. (°C)	Yield (%)	ee (%)
FeCl ₃ /SiO ₂	0	94	93
SnCl ₄	-30	88	95
TiCl ₄	-30	80	90
AlCl ₃	0	45	58
ZnCl ₂	-20	0	-
BF ₃ ·OEt ₂	-30	92	75

Synthesis 1996 1473-1476

Supported Chiral Catalysts on Inorganic Materials

Choong Eui Song* and Sang-gi Lee

Chem. Rev. 2002, 102, 3495-3524

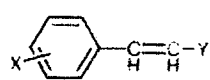


These functionalized Silica are useful for asymmetric hydrogenation.

Effect of Support Material Chosen for Permanganate

* On acidic media such as alumina, KMnO₄ affords cleavage of aryl-substituted olefins to

ald:



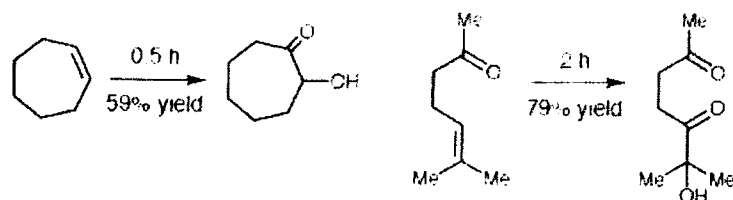
X = MeO, OH, Br, Cl, CF₃, CO₂Me, H, Me

Y = H, COMe, CO₂H, Me

Synthesis 2001, 1645-1648

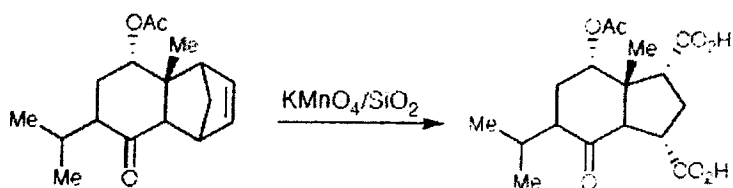
- Other good supports: Amberlite and Rexyn 101 (H)
- Among poor supports: molecular sieves, CuSO₄·5H₂O

* On neutral media such as CuSO₄·5H₂O, KMnO₄ converts olefins to α-hydroxy ketones.



J. Org. Chem. 1989 54 5182-5184

* On SiO₂, KMnO₄ easily oxidatively cleaves olefins with 1-3 substituents, including electron-withdrawing groups.



- Conveniently performed by elution of benzene solution through a short column of KMnO₄/SiO₂.
- Traditional methods failed in this example: KMnO₄/acid or base; KMnO₄/MgSO₄; KMnO₄/NaIO₄.

I-iii) Inorganic Supports: Zeolite

* Zeolites – $C_x[(T_ySi_{1-y})O_2]X_zwM$ 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.

- Offer shape-selective control, either by transition state selectivity or by exclusion of competing reactions, 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.
- Shape-selection excludes moderately large organic molecules.

Zeolite Surface

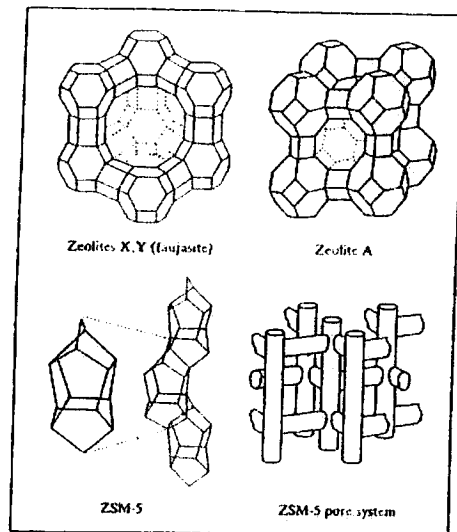
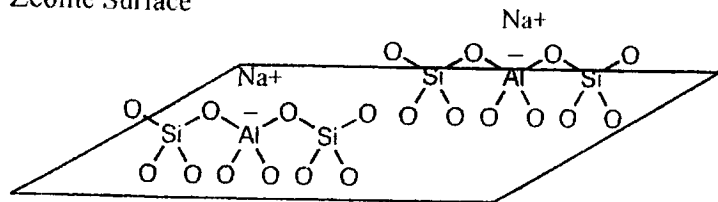
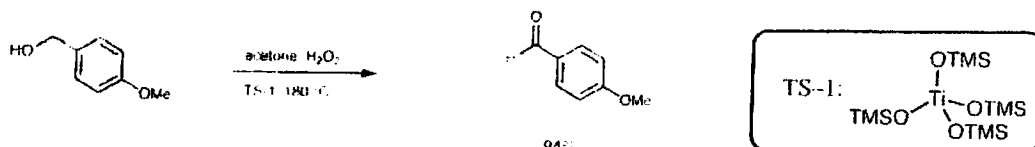


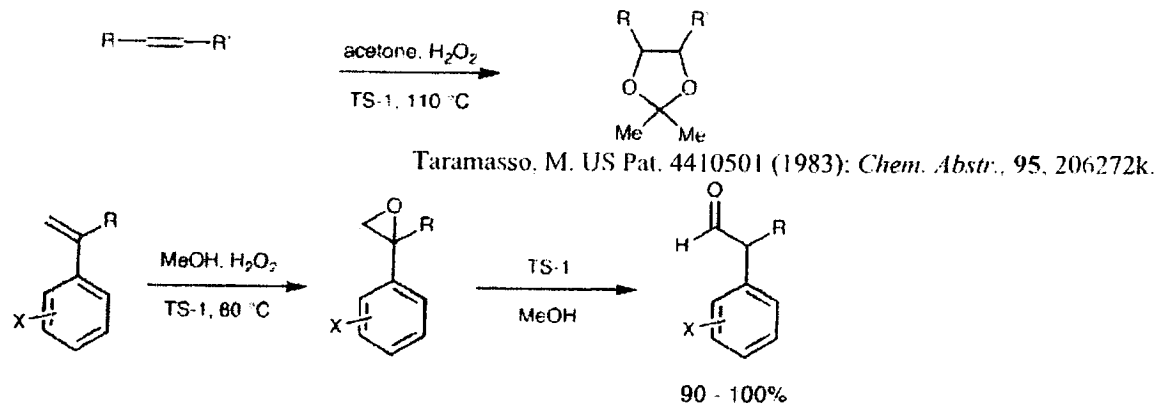
Fig. 1.11 — Zeolites X, Y; zeolite A and ZSM-5 structures and ZSM-5 pore system.

* Titanosilicate Zeolite

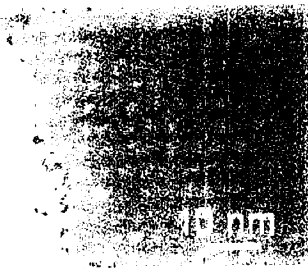
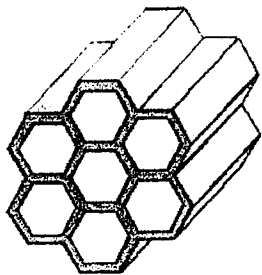
- Titanium zeolite TS-1 catalyzes oxidations of alcohol with dilute aqueous H_2O_2 in almost stoichiometric amount.



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



II Mesoporous Silica



According to IUPAC
 microporous: $< 2 \text{ \AA}$
 mesoporous: $2 \text{ \AA} - 50 \text{ \AA}$
 macroporous: $> 50 \text{ \AA}$

Typical mesoporous materials include some kinds of silica and alumina that have similarly-sized fine mesopores. A material that contains mesopores in part but is not regular, like silica gel, is not considered a mesoporous material. Notable examples of prospective applications are catalysis, sorption, gas sensing, optics, and photovoltaics.

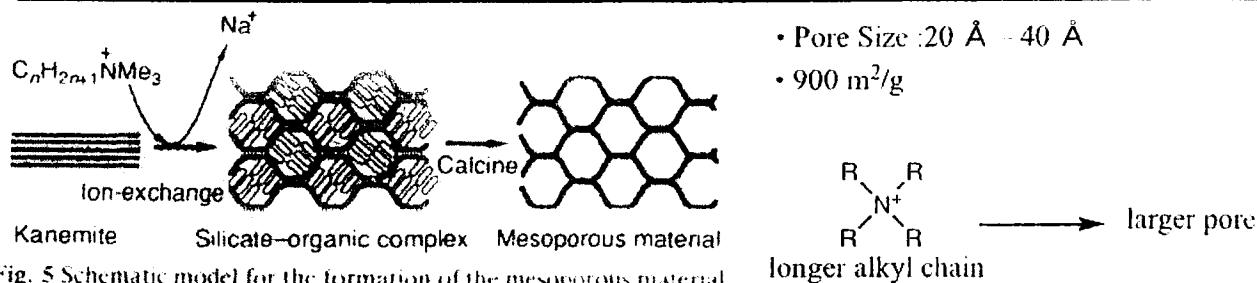
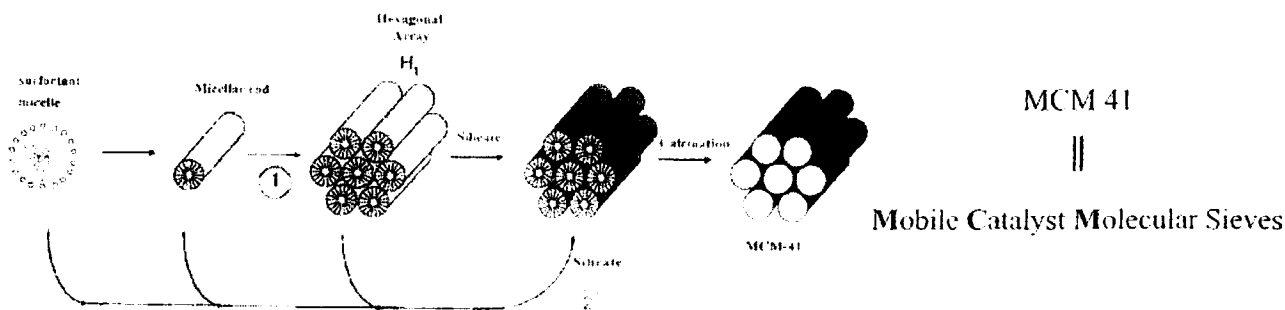


Fig. 5 Schematic model for the formation of the mesoporous material from kanemite

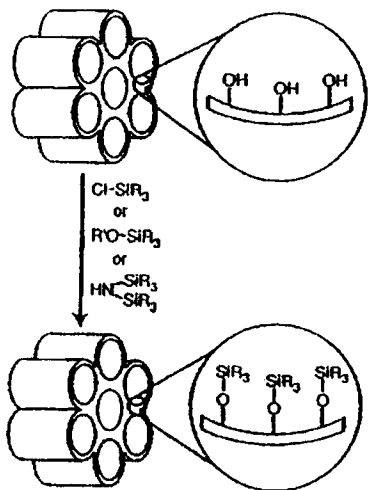
Yanagisawa, T.; Shimizu, T.; Kuroda, K.; Kato, C. *Bull. Chem. Soc. Jpn.*, 1990, 63, 988.



C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck. *Nature*, 1992, 359, 710.

- Pore Size : $16 \text{ \AA} - > 100 \text{ \AA}$
- $> 1000 \text{ m}^2/\text{g}$

Synthetic Modification



- simple grafting
- simple coating with Ti, V, Mn, Co, ...
 \rightarrow electrochemistry
- simple modification with SO_3H , $-\text{NR}_3\text{OH}$

expected : Aldol, Michael, Knoevenagel!
 oxidation, reduction, ...

developing mesoporous chemistry \longrightarrow

developing new analytical method
 (SEM: 走査型電子顕微鏡 TEM: 透過型電子顕微鏡)

Functionalization on Silica Gel with Allylsilanes. A New Method of Covalent Attachment of Organic Functional Groups on Silica Gel

Toyohi Shimada, Kazuko Aoki, Tetsuo Shimizu, Tomonori Nakamura, Noriaki Takemura,
Shinji Inagaki, and Tamio Hayashi*

J. AM. CHEM. SOC. 2003, 125, 4688-4693

Scheme 1

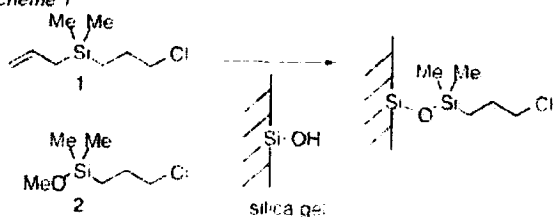


Table 1. Loadings of (3-Chloropropyl)silanes 1 and 2 on Silicas^a

entry	organosilane (mmol)	silica gel	time (h)	loading ^b (mmol/g)
1	1 (3)	FSM-16	15	1.1
2	1 (5)	FSM-16	15	1.3
3	1 (10)	FSM-16	15	1.6
4	1 (15)	FSM-16	15	1.7
5	1 (10)	FSM-16	0.5	1.1
6	1 (10)	FSM-16	48	1.6
7	2 (3)	FSM-16	15	0.8
8	2 (5)	FSM-16	15	0.8
9	2 (10)	FSM-16	15	1.3
10	2 (15)	FSM-16	15	1.3
11	2 (10)	FSM-16	0.5	0.6
12	2 (10)	FSM-16	48	1.6
13	1 (10)	amorphous silica	15	0.3
14	2 (10)	amorphous silica	15	0.5

^a All reactions were carried out for 10 g of silica gel support in 30 mL of refluxing toluene. ^b Obtained by elemental analysis of Cl.

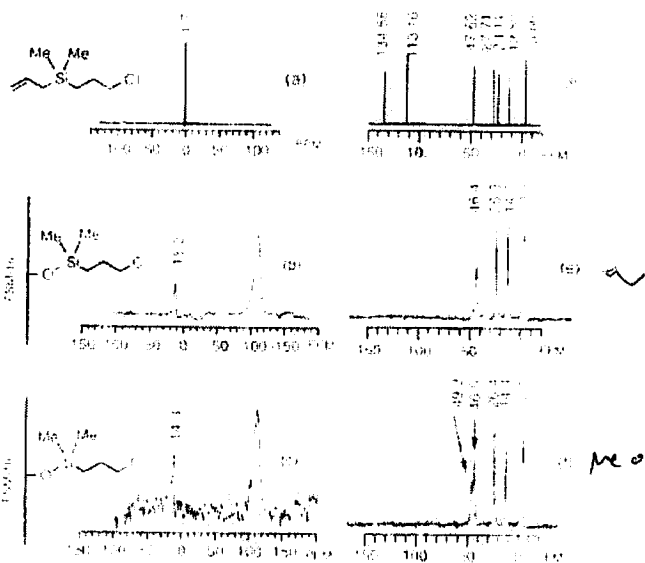


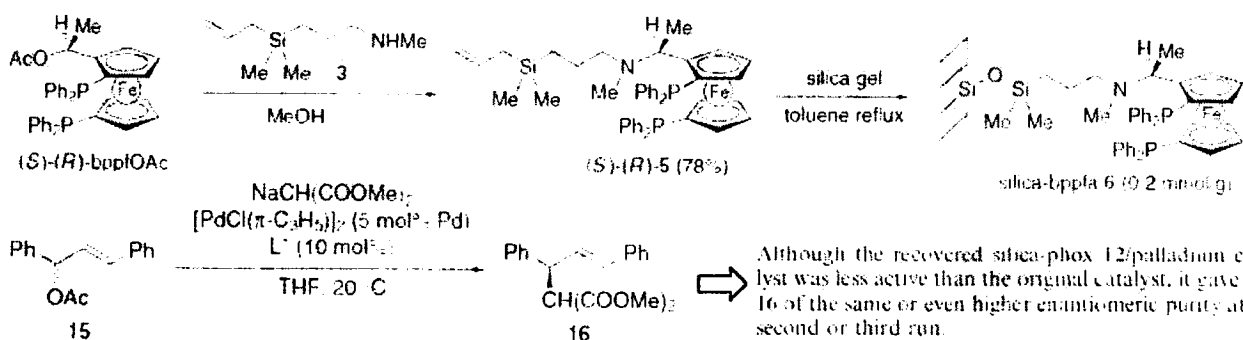
Figure 1. ²⁹Si and ¹³C NMR spectra of 2-propenyl(3-chloropropyl)dimethylsilane 1 in CDCl₃ (a and c). ²⁹Si and ¹³C CP-MAS NMR spectra of the reaction products of 1 with FSM-16 (b and d), and those of 2 with FSM-16 (e and f).

They found a new method for the modification of the silica gel surface by use of allylorganosilanes. The present method will have broad applications in the surface-modifying technology on the silica gel as a reliable functionalization method.

Immobilization of chiral phosphine ligands on silica gel by means of the allylsilane method and their use for catalytic asymmetric reactions

Kazuko Aoki, Toyohi Shimada and Tamio Hayashi*

Tetrahedron Asymmetry 15 (2004) 1771-1777



Although the recovered silica-phox 12/palladium catalyst was less active than the original catalyst, it gave (S)-16 of the same or even higher enantiomeric purity at the second or third run.

Table 2. Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate 15 with dimethyl malonate in the presence of silica-phox 12^a

Entry	Ligand	Run	Time (h)	Conversion ^b (%)	ee (%) (config)
1	Silica-phox 12	First	6	100	81 (S)
		Second	34	100	82 (S)
		Third	34	100	90 (S)
2	(S)-(-)-Pr-phox	First ^c	6	100	98 (S)

^a The allylic alkylation was carried out with 15 (0.20 mmol), dimethyl sodiummalonate (0.60 mmol), [PdCl(π-C₃H₅)₂] (10 mmol Pd), and silica-phox 12 or (S)-(-)-Pr-phox (20 mmol) in 2.0 mL of THF at 20°C. The catalyst recovered by centrifuging was used for the next run.

^b Determined by ¹H NMR spectra of the reaction mixture.

^c Determined by HPLC with a chiral stationary phase column.

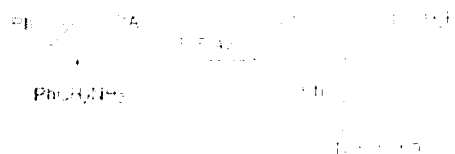
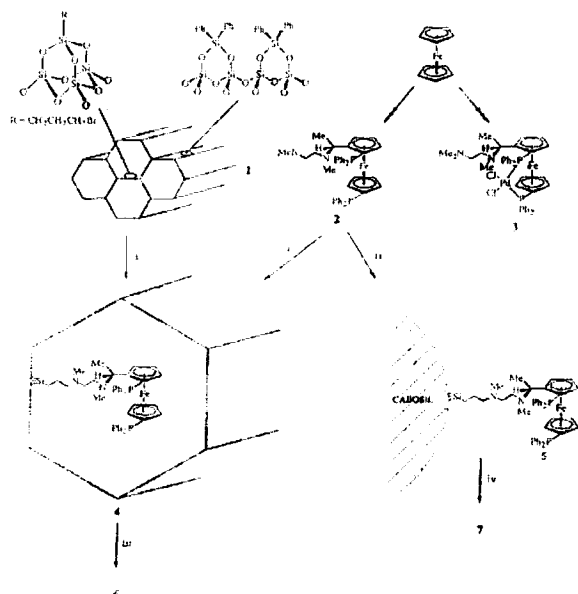
^d Homogeneous reaction.

They have successfully applied their allylsilane modification method to the preparation of some silica-supported chiral phosphine ligands and used them as chiral ligands for palladium-catalyzed asymmetric allylic alkylation.

Superior performance of a chiral catalyst confined within mesoporous silica

Brian L. G. Jolsson,^a Stuart A. Raynor,^a Douglas S. Shephard,^a Thomas Mechnieveyer,^a John Meurig Thomas,^a Gopinath Sankar,^b Stefan Bromberg,^b Richard Oldroyd,^b Lynn Gladden^c and Mike D. Mantle^a

Chem. Commun., 1999, 1153–1158



Scheme 2 The catalytic reaction between enantiomeric acetate and benzylamine

Table 1 Catalytic results

Catalyst	Conversion ^a (%)	straight chain (%)	branched (%)	ee (%) ^b
1 (S)	76	79+	0	0
2 (S)	98	48	0	41
6 (S)	99+	19	0	79+
6 (R)	99+	0	0	81

^a Symbols in parentheses denote chirality of the directing group. ^b Conversion is stated relative to the use of benzylamine. Regio- and enantio-selectivity determined by gas chromatography on a Chiralcel OD-DA column (Alltech) with cyclodextrin as the active phase (25 nm). Conditions: He pressure 12.5 psi, temperature ramped 50–150 °C at 10 °C min⁻¹ and then held for the duration of the run. Major stereoisomer possesses the same chirality as the catalyst. Retention time = 1.35 min.

These results indicate that the control exercised by the MCM-41 on the activity of the ferrocenyl catalyst is considerable. The profound changes in the regio- and enantio-selectivity are clearly apparent from the data listed in Table 1.

Extrusion Polymerization: Catalyzed Synthesis of Crystalline Linear Polyethylene Nanofibers Within a Mesoporous Silica

Keisuke Kageyama, Jun-ichi Tamazawa, Takuzo Aida^{*}

SCIENCE VOL 285 24 SEPTEMBER 1999

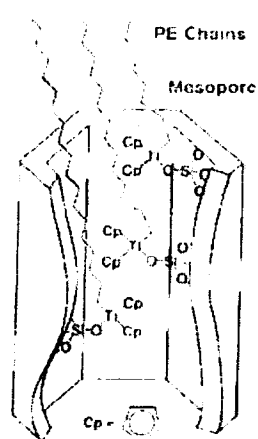
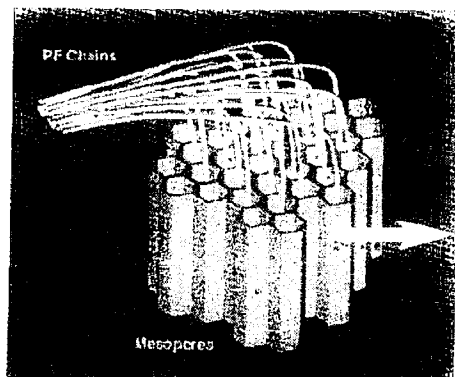
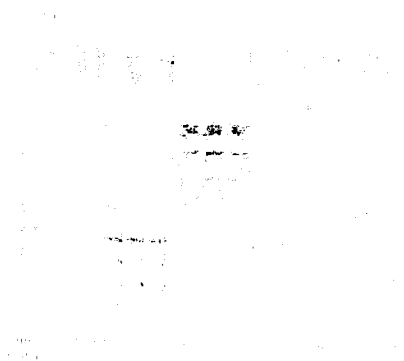


Fig. 1. Conceptual scheme for the growth of crystalline fibers of polyethylene by mesoporous silica-assisted extrusion polymerization.

• This observation indicates a potential utility of the honeycomb-like porous framework as an extruder for nanofabrication of polymeric materials.

III) Coordination Polymer



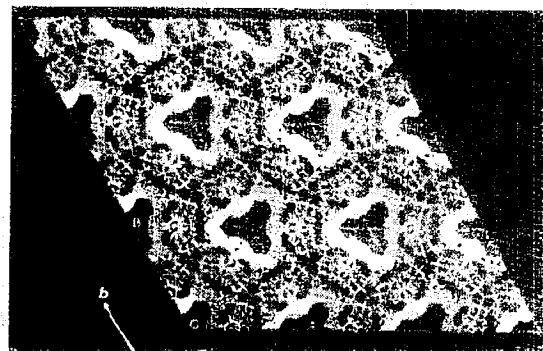
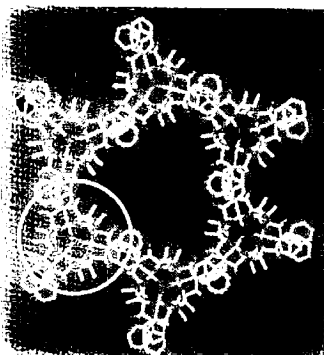
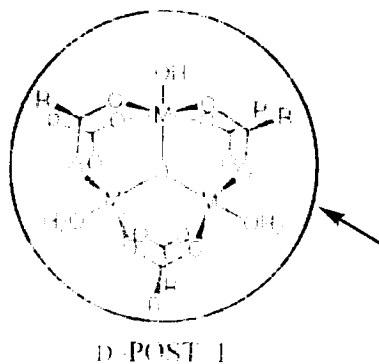
Porous coordination polymers exhibit significant characteristic features, such as

- 1) highly regular channel structures
- 2) controllable pore size approximating molecular dimensions
- 3) flexible pores that respond to guest molecules
- 4) unique surface potentials and functionality which are beyond the scope of conventional microporous materials.

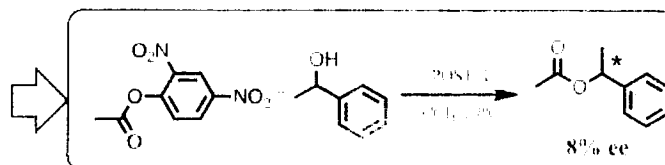
A homochiral metal-organic porous material for enantioselective separation and catalysis

Jang Soo Seo, Dongmok Whang, Hyeonju Lee, Sang In Jun, Jinho Oh, Young Il Jeon & Kimoon Kim

Nature, 2006, 404, 982



• catalytic activity of POST-1 for transesterification



Although ee was modest, asymmetric induction had never been observed in reactions mediated by modular porous materials.

Such size selectivity suggests that the catalytic mainly occurs in the channels.

A Homochiral Porous Metal-Organic Framework for Highly Enantioselective Heterogeneous Asymmetric Catalysis

J. AM. CHEM. SOC. 2005, 127, 1041-1048

Chen-de Wu, Aiqing Liu, Lin Zhang, and Wenting Lin*

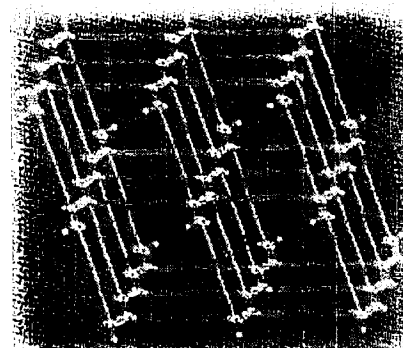
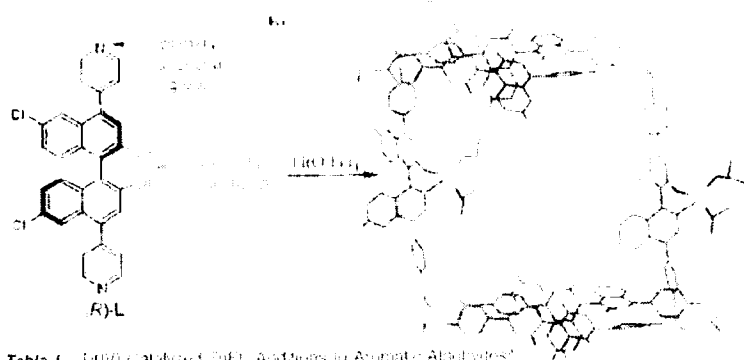


Table 1. Ti(OEt)₄ catalyzed ZnEt₂ Additions to Aromatic Aldehydes^a

Ar	Yield (%)		[α] _D ^b (deg)	[α] _D ^c (deg)
	1•Ti	1b•Ti		
1-Naph	99	94	-99	95
Ph	99	88	-99	10
4-Cl-Ph	99	86	-99	20
3-Br-Ph	99	84	-99	60
4-G ₁ -OPh	99	80	-99	95
4-G ₂ -OPh	99	75	-99	13
4-G ₃ -OPh	99	73	-99	54
4-G ₄ -OPh	99	67	-99	0

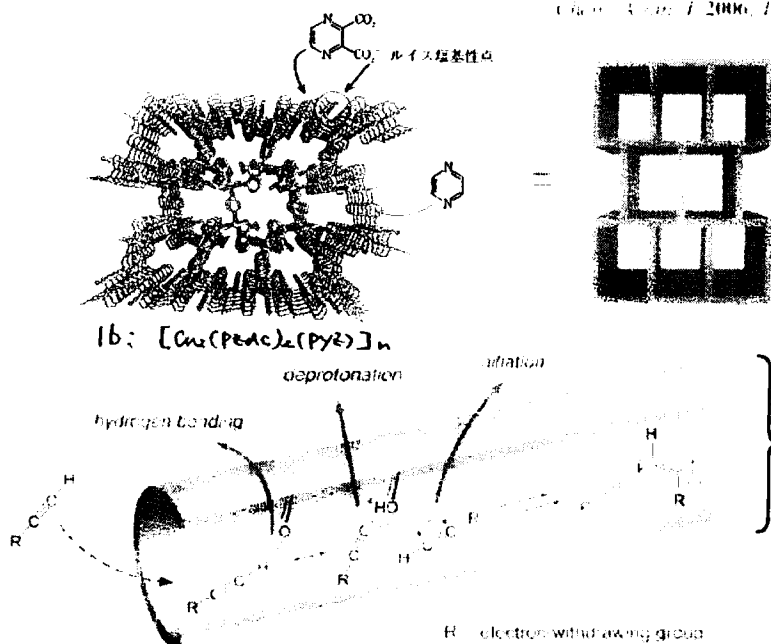
As expected, the efficiency for homogeneously catalyzed ZnEt₂ additions is not affected by the dendron size.

In contrast, the yields of ZnEt₂ addition products catalyzed by 1•Ti greatly depend on the dendron size.

Polymerization in Coordination Nanospaces

Eakashi Uemura, Satoshi Horike, and Susumu Kitagawa¹³

Chem. Commun. 2006, 1-2, 36-41



In the case of acidic monosubstituted acetylenes, the basic oxygen atoms from the carboxylate ligands in **1b** produce reactive acetylide species that subsequently initiate anionic polymerization in the nanochannel (Figure 5).

channel size: 8.2 x 6.0 Å

Figure 5. Catalytic, spontaneous, polymerization of substituted acetylenes in **1b**.

They have demonstrated that truly designable PCPs with specific basic interaction sited in the nanochannels allow the highly accelerated, stereocontrolled, and monomer selective polymerization of substituted acetylenes.