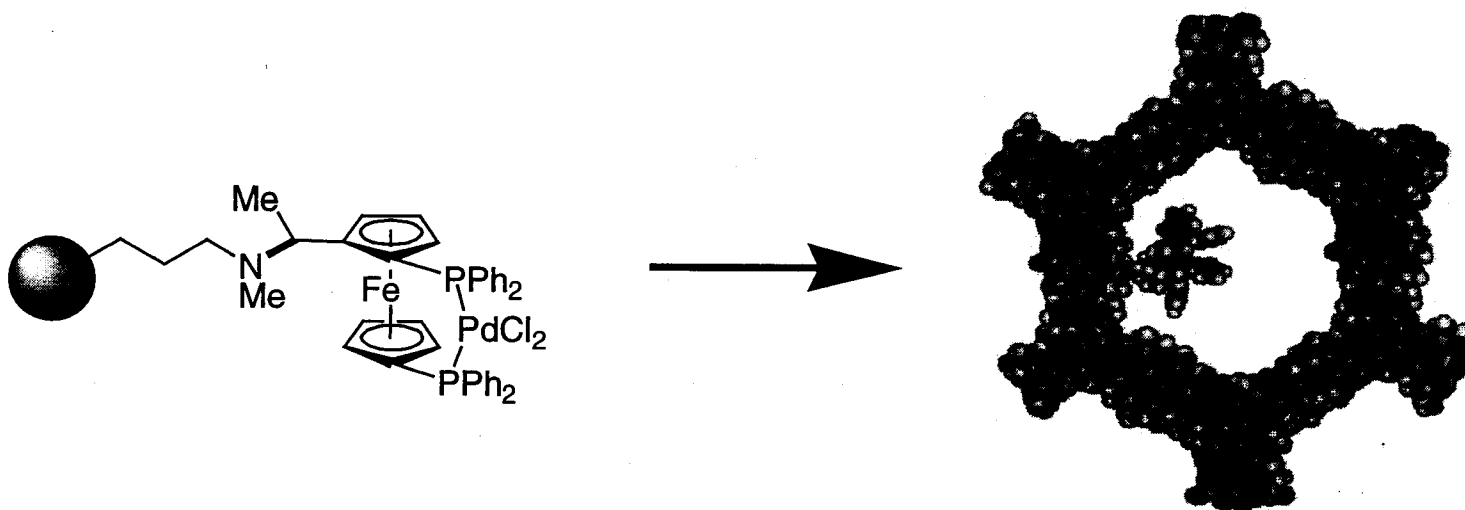


# ***“Solid Phase (Asymmetric) Organic Synthesis: Novelty or Fundamental Concept?”***



- Since the first report by Merrifield in 1963, the use of solid phase synthesis has steadily grown, mostly in the area of polypeptide synthesis.
- Great advances have been made in the types of polymers available, our understanding of their behavior and the essential differences between them.
- Can this be applied to asymmetric catalysis, facilitating catalyst recovery and making the process viable on large scale?

Greg Beutner 4/8/03

# Solid Phase Asymmetric Catalysts

Chem. Rev. 2002, 102, 3385–3466

3385

## Recoverable Catalysts for Asymmetric Organic Synthesis

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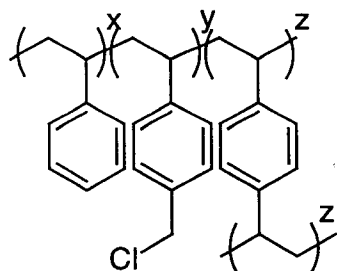
<sup>†</sup> Chinese Academy of Sciences.

<sup>‡</sup> The Hong Kong Polytechnic University.

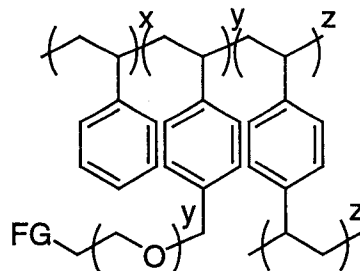
- A wide variety of structurally and mechanistically diverse catalysts have been bound to polymers.
- There have been varying degrees of success in terms of matching solution-state reactivity and selectivity.
- There have been three major issues encountered which are unique to solid phase catalysis:
  - Polymer Microenvironment Effects
  - Polymer Steric Effects
  - Site-Site Interactions
- Is there a rational understanding of these phenomena which allows for planning?

Hodge, P. *Chem. Soc. Rev.* **1997**, 26, 417.

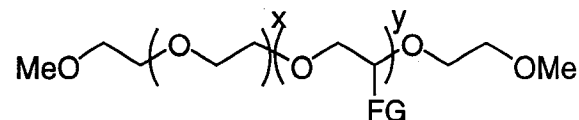
# The Polymer Support



*Merrifield Resins*  
suspension co-polymers  
vinyl benzene (x %)  
chlorovinyl benzene (y %)  
divinyl benzene (z %)



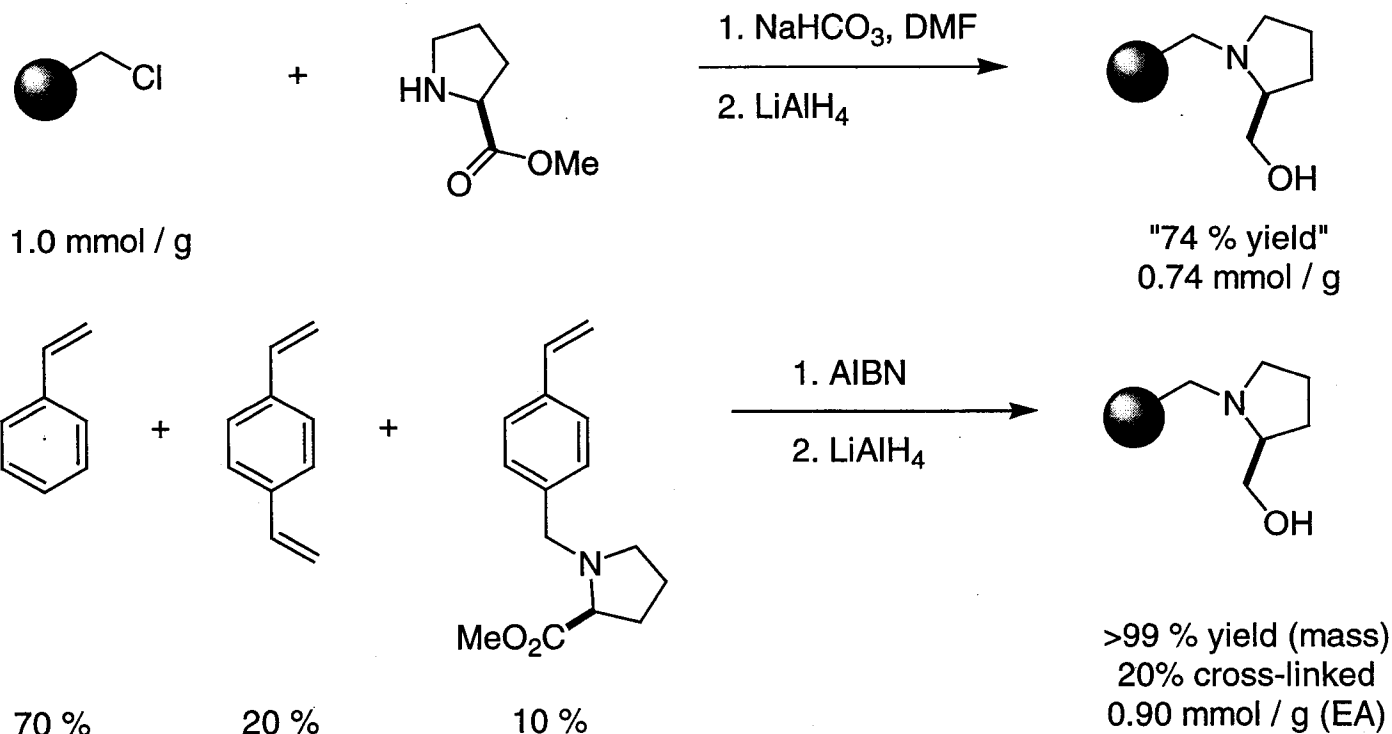
*"Solvent-like Resins": Tentagel, Jandagel, etc ...*  
grafted suspension co-polymers  
vinyl benzene (x %)  
chlorovinyl benzene (y %)  
polyethylene glycol (y %)  
divinyl benzene (z %)



*Soluble Polymers*  
suspension co-polymers  
ethylene glycol (x %)  
functional monomer (y %)

- Since only < 1% of the active sites sit on the outer surface of the bead, the reagents inevitably interact with the polymer, making polymer choice important.
- In insoluble polymers, the degree of cross-linking (% divinylbenzene) is predominant in determining the bead's properties.
- Mesoporous silica and soluble polymers are novel alternatives to traditional insoluble organic supports.

# From Polymer to Polymer Supported Reagent



Altava, B. *et al. Tetrahedron* **1999**, 55, 12897.

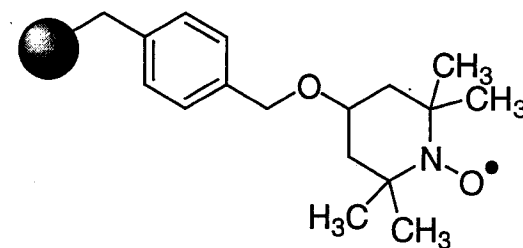
- Grafting, although operationally simpler, provides less control over loading, etc.
- Polymerization of a functionalized monomer is reliable and gives greater control.
- Use of SiO<sub>2</sub> supports gives equal control in terms of loading, but adds a degree of control in terms of support structure (e.g. pore size).

## “Solubilizing” the Polymer Support

	DMF (PI=6.4)	MeCN (PI=6.2)	THF (PI=4.2)	DCE (PI=3.7)	PhCH <sub>3</sub> (PI=2.3)
Polystyrene	5.2	2.0	6.0	4.4	4
Argopore	5.6	5.3	5.4	-	5.7
Jandagel	6.0	-	7.4	-	-
Tentagel	5	4	6	5	3.6
Novagel	7	5	7.5	-	-
PEGA	8	6	4	5	3

Walsh, D.P., et al. *J. Comb. Chem.* **2002**, 4, 204.

polymer (% DVB)	$\tau$ ( $10^{10}$ sec)	q (wet V/dry V)	$\eta$ (cP)
monomer in PhH	0.19	-	0.6
PS (1%) in PhH	0.22	5.4	0.7
PS (2%) in PhH	0.31	3.7	1.0
PS (4%) in PhH	0.49	2.8	1.5
PS (8%) in PhH	1.3	2.0	4.1
PS (12%) in PhH	1.9	1.9	6.0

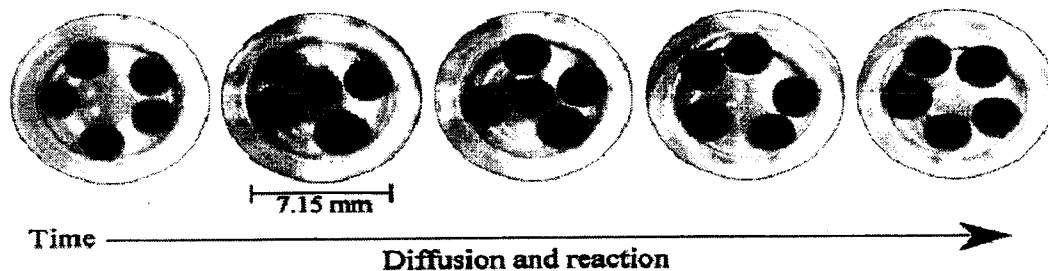


0.70 mmol / g  
persistent nitroxide radical

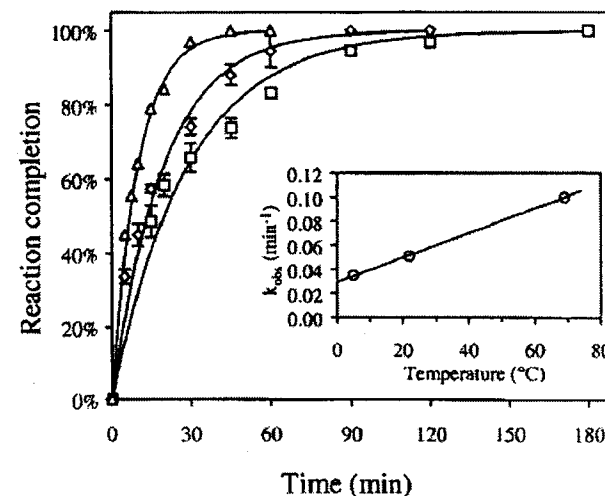
Regen, S.L. *Macromolecules* **1975**, 8, 689.

- As with other solids, the solvent molecules will attempt to solvate the polymer.
- The amount of swelling relates to polymer structure and rigidity (cross-linking).
- Swelling is *not* purely a function of solvent polarity.

# From Solution to Support: Diffusion Rates



	resin	swelling (mL/g)	solvent	reagent	conc. (M)	$k_{\text{obs}}$ ( $\text{min}^{-1}$ )	$t_{1/2}$ (min)
1	PS-2%	3.8	PhCH <sub>3</sub>	Ac <sub>2</sub> O	0.2	0.6	1.2
2	PS-2%	4.4	DMF	Ac <sub>2</sub> O	0.2	0.513	1.4
3	PS-2%	5.1	MeCN	Ac <sub>2</sub> O	0.2	0.55	1.3
4	PS-2%	7.1	CH <sub>2</sub> Cl <sub>2</sub>	Ac <sub>2</sub> O	0.2	1.05	0.66
5	PS-2%	4.4	DMF	Fmoc-Phe-OPfp	0.05	0.018	38.5
6	PS-2%	4.4	DMF	Fmoc-Phe-Opfp	0.2	0.051	13.6
7	PS-2%	4.4	DMF	Fmoc-Phe-Opfp	0.64	0.08	8.7
8	PS-1%	8.0	DMF	Fmoc-Phe-OPfp	0.2	0.14	5.0

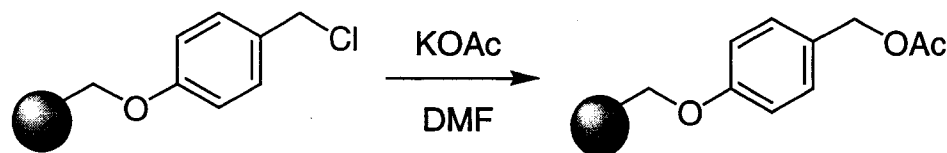


**Figure 5.** Reaction completion curves for Fmoc-Phe-OPfp acylations (0.2 M in DMF) of POEPOP-1 at various temperatures: 5 °C (squares), 20 °C (diamonds), and 68–70 °C (triangles). Inset: Diffusion rate constant  $k_{\text{obs}}$  as a function of temperature.

Groth, T., *et al. J. Comb. Chem.* **2001**, 3, 461.

- The rate of diffusion into the bead has been measured optically using a timed acylation followed by staining.
- The rate of diffusion is significantly effected by: concentration, swelling, solution-phase reagent structure and temperature.

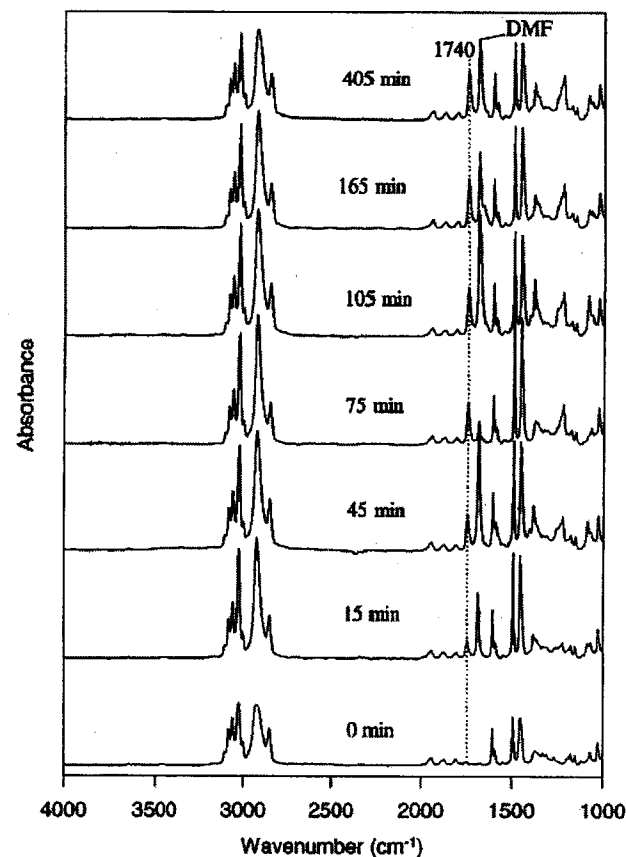
# On Bead Kinetic Analysis



- The  $S_N2$  displacement of a benzylic chloride with potassium acetate in DMF was compared to that of a similar reaction on a chloromethyl Merrifield resin.
  - solution:  $k=1.49 \times 10^{-3} \text{ s}^{-1} \text{ M}^{-1}$ ,  $t_{1/2}=170 \text{ min}$
  - on-bead:  $k=5.0 \times 10^{-4} \text{ s}^{-1}$ ,  $t_{1/2}=23 \text{ min}$
- A less polar environment should favor the  $S_N2$  reaction of charged nucleophiles due to decreased solvation of the reagent and dispersal of charge in the TS.

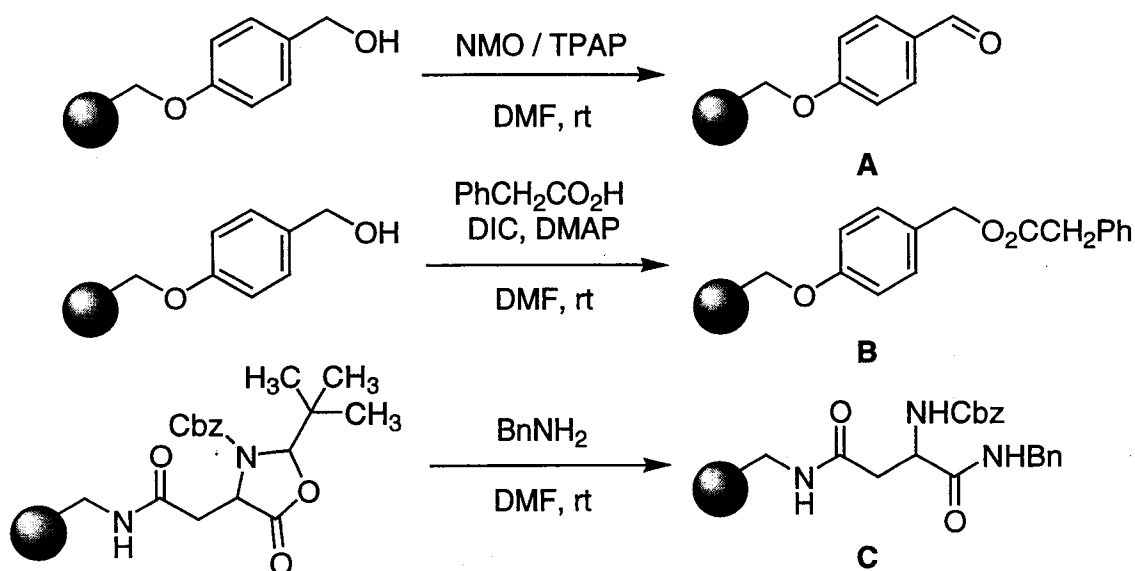
Yan, B., et al. *J. Org. Chem.* **1996**, 61, 7467.

Shinoda, K., et al. *J. Org. Chem.* **1991**, 56, 4081.

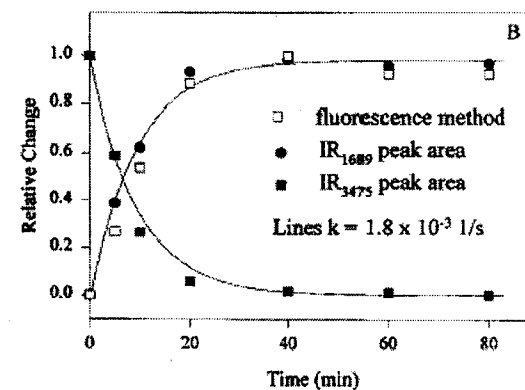
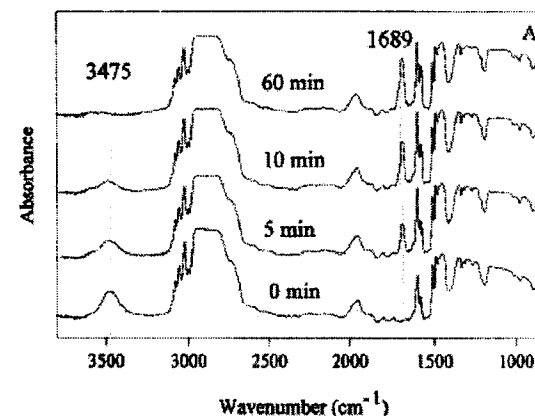


**Figure 1.** IR spectra from a single bead taken at specified times during the course of reaction I. The absorbance spectra were taken as described in the Experimental Section. The carbonyl peak at  $1740 \text{ cm}^{-1}$  is highlighted with the dotted line. The peak at  $1658 \text{ cm}^{-1}$  is from residual solvent DMF. The irregular intensity of this peak may be due to the insufficient drying and the different solvent-adsorbing property of the individual bead. See Figure 2 for the kinetic analysis and the rate constant.

# On Bead Kinetic Analysis



reaction	bead?	$k_{ps}$ ( $s^{-1}$ )	$q_{ps}$ (mL/g)	$k_{tg}$ ( $s^{-1}$ )	$q_{tg}$ (mL/g)	$k_{tg}/k_{ps}$
A	whole	$4.6 \times 10^{-4}$	6.1	$1.8 \times 10^{-3}$	3.3	3.9
B	whole	$4.8 \times 10^{-4}$	6.1	$4.2 \times 10^{-4}$	3.3	0.9
B	whole*	$5.0 \times 10^{-3}$	-	-	-	-
B	surface*	$4.6 \times 10^{-3}$	-	-	-	-
C	whole	$1.13 \times 10^{-4}$	-	$6.26 \times 10^{-6}$	-	0.055

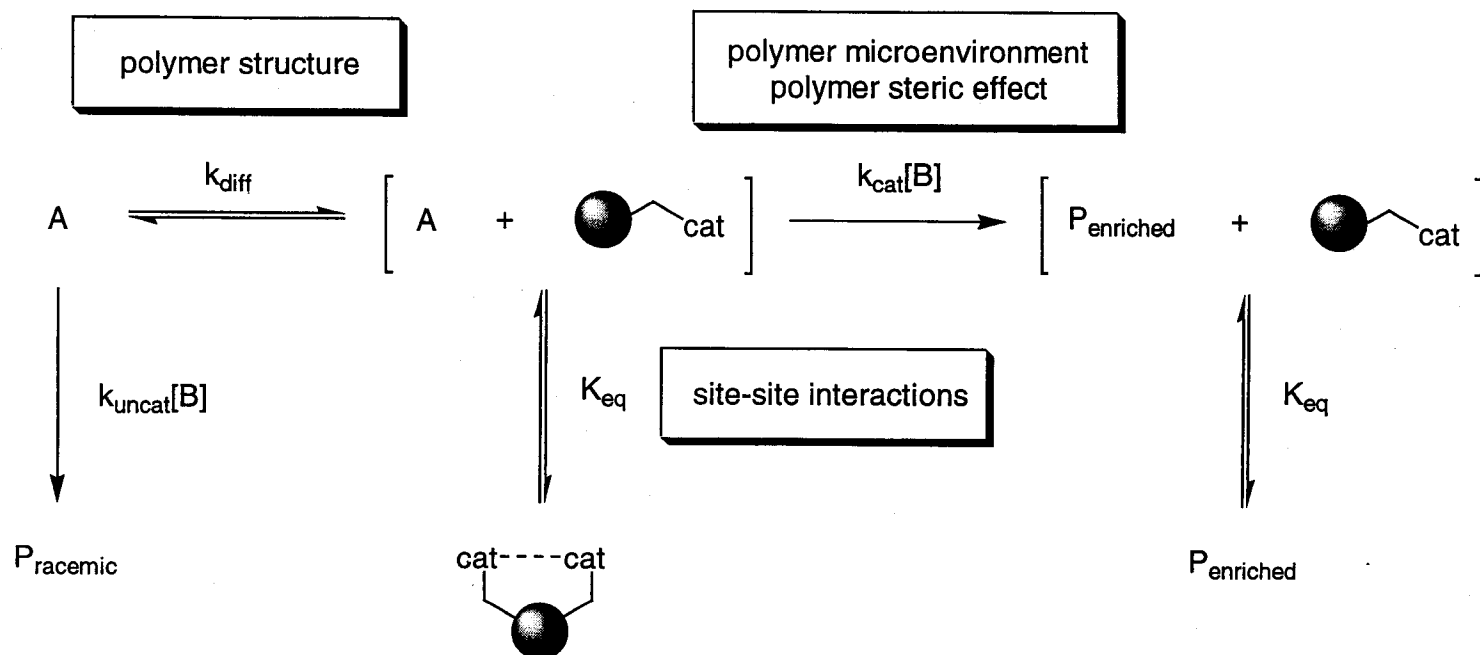


Yan, B., et al. *J. Org. Chem.* **1996**, *61*, 7467.

- The effect of bead structure on rate is not the same for all reactions.
- Reaction on the *surface* of and *inside* the bead do not differ considerably in rate.

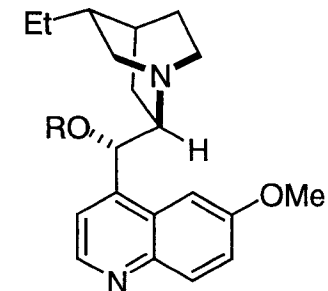
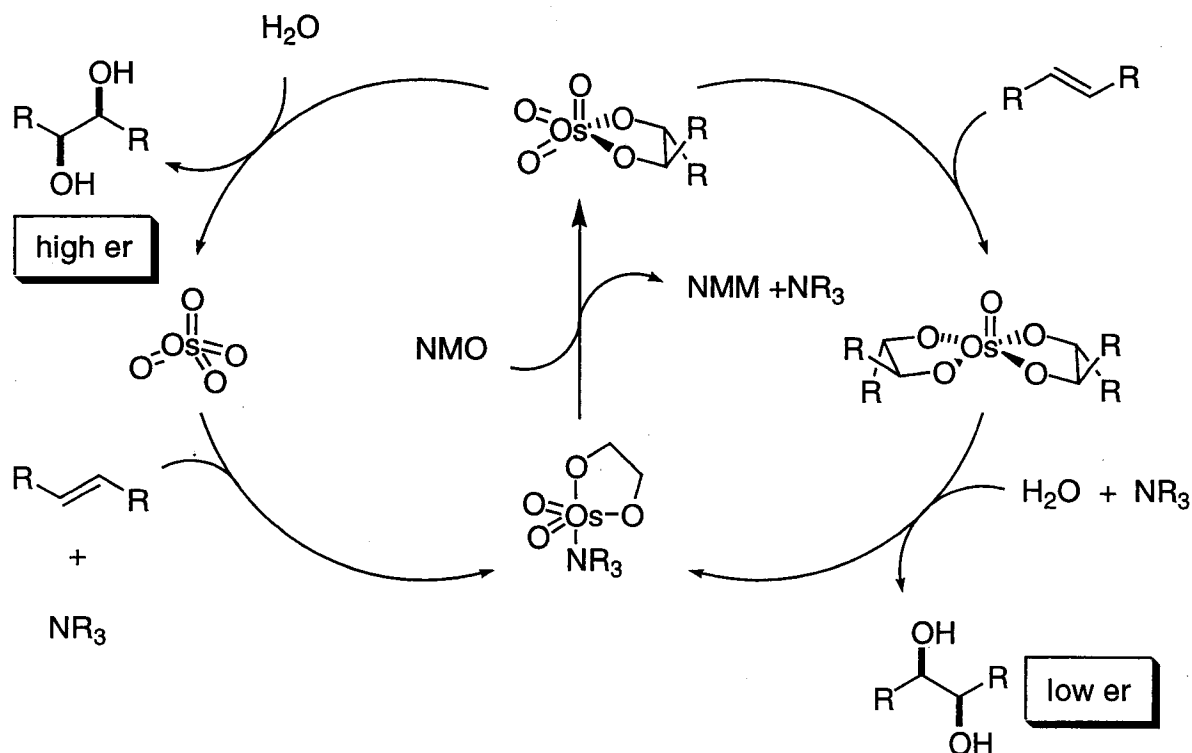


# From Solution to Support: Reaction Mechanism

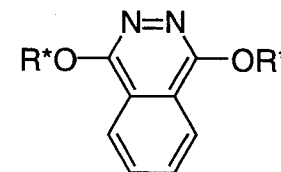


- There are numerous steps where the can polymer effect the *rate* of the reaction.
- If there is a background reaction, this can cause serious selectivity problems.
- In order to better understand these effects, we will look at some examples:
  - Polymer structure effect: diffusion of reagents in the Sharpless AD
  - Polymer microenvironment effect: rate of the Mitsunobu reaction
  - Polymer steric effect: diethylzinc addition to aldehydes
  - Site-site interactions (positive or negative): hydrolytic DKR of epoxides

# Sharpless Asymmetric Dihydroxylation



Dihydroquinidine (DHQD)

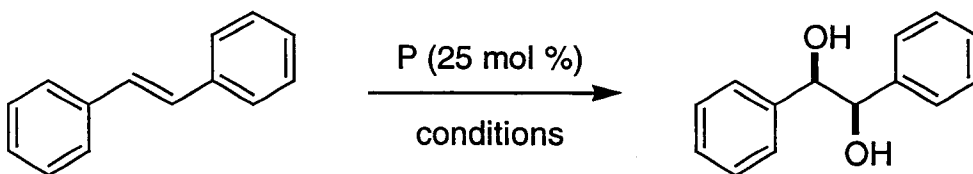


Phthalazine dimers (PHAL)

Sharpless, K.B., *et al. Chem. Rev.* **1994**, *94*, 2483.

- The asymmetric dihydroxylation of olefins with  $\text{OsO}_4$  catalyzed by cinchona alkaloids yields 1,2-diols with high selectivity as long as a secondary, unselective cycle can be suppressed.
- This is accomplished either through slow addition of the olefin or use of biphasic conditions and  $\text{K}_3\text{Fe}(\text{CN})_6$  as a co-oxidant rather than  $\text{NMO}$ .

# AD on Polymers: Insoluble Polymers



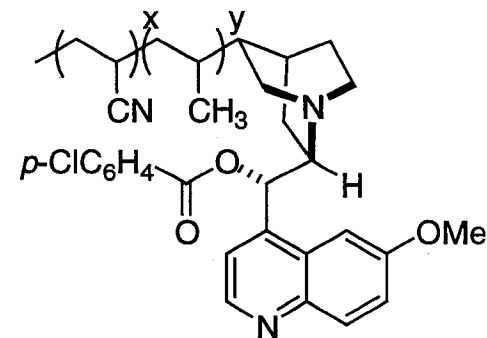
conditions **A**: 1 mol % OsO<sub>4</sub> / 1 equiv NMO / RT / acetone-H<sub>2</sub>O

conditions **B**: 1.25 mol% OsO<sub>4</sub> / 1 equiv K<sub>3</sub>Fe(CN)<sub>6</sub> / tBuOH-H<sub>2</sub>O

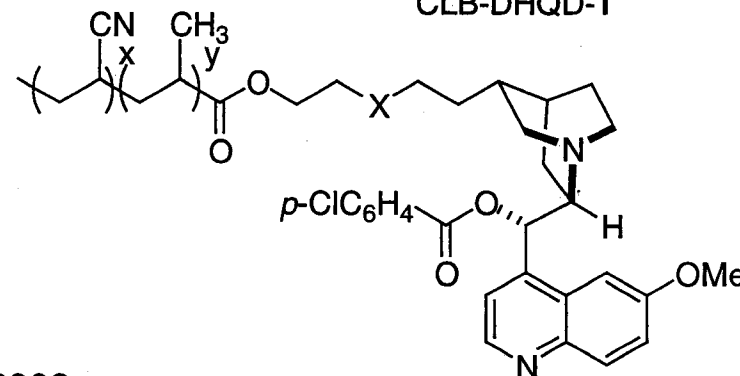
entry	catalyst	cond.	time (h)	yield (%)	er
1	CLB-DHQD	B	18	98	>99:1
2	1	A	148	68	ND
3	2	A	72	81	93:7
4	3	A	48	85	90:10
5	3	B	18	96	94:6

Sharpless, K.B., *et al. Tetrahedron Lett.* **1990**, 31, 3003.

Sharpless, K.B., *et al. J. Org. Chem.* **1991**, 56, 4586.



CLB-DHQD-1

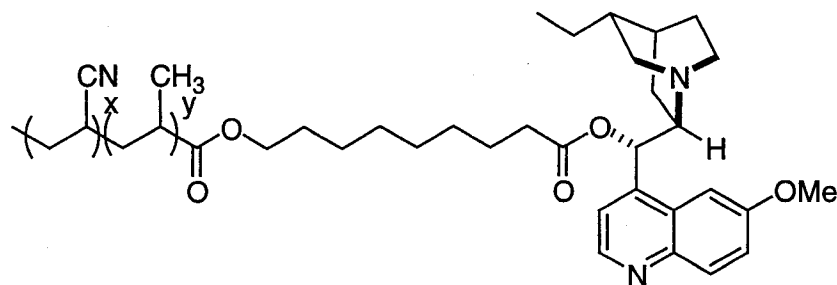


CLB-DHQD-2: X = SO

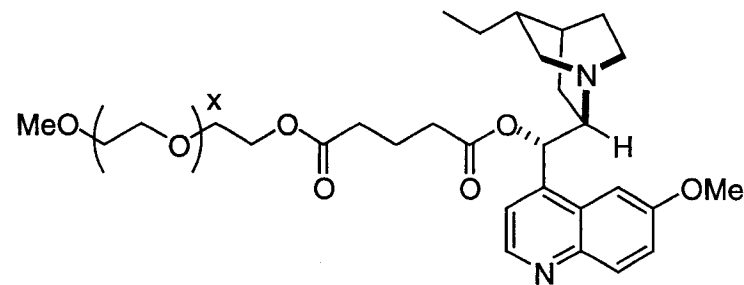
CLB-DHQD-3: X = SO<sub>2</sub>

- In all cases, the polymeric ligand is outperformed by the monomer.
- Increasing polymer polarity greatly increases yield, but slow hydrolysis may still be a problem contributing to lowered selectivity.

# AD on Polymers: Soluble vs. Insoluble Polymers



DHQD-1

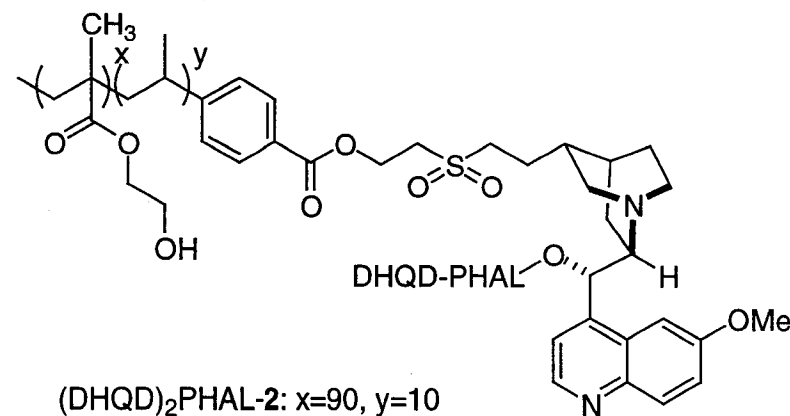


DHQD-2

try	catalyst	cond.	time (h)	yield (%)	er
1	CLB-DHQD	A	18	98	>99:1
2	DHQD-1	A	48	87	91:9
3	DHQD-2	A	5	89	96:4
4	DHQD <sub>2</sub> PHAL	B	20	95	>99:1
5	DHQD-3	B	20	90	>99:1

Janda, K.D., *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 7623.

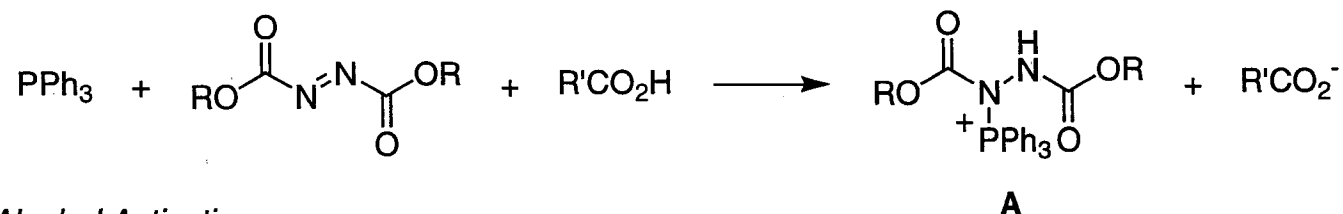
Salvadori, P., *et al.* *J. Am. Chem. Soc.* **1997**, *119* 6929.



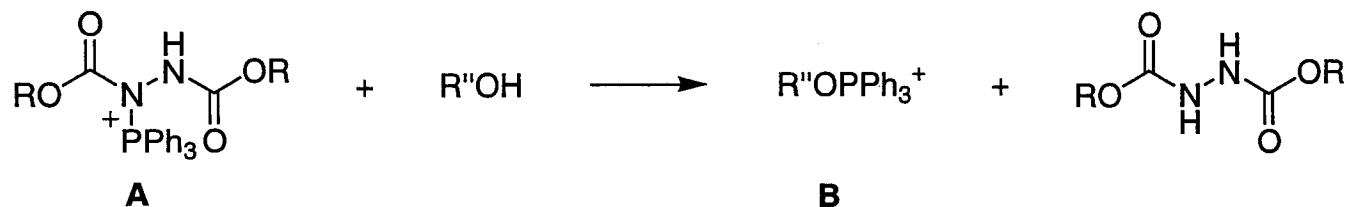
- A highly polar, highly soluble polymer backbone aides in generating a polymer supported catalyst which closely mimicks the solution-phase catalyst.

# The Mitsunobu Reaction

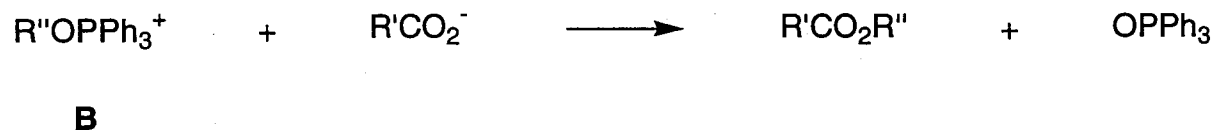
## Adduct Formation



## Alcohol Activation

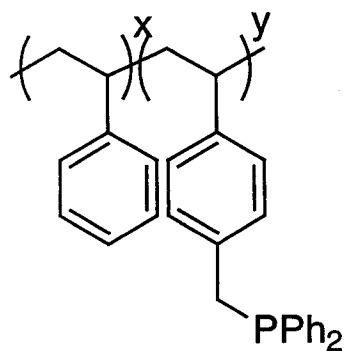


## S<sub>N</sub>2 Reaction



- The mechanism of the Mitsunobu reaction between alcohols and acids has been well studied (*J. Am. Chem. Soc.* **1988**, 110, 6487).
- It is known that:
  - Excess acid stabilizes the initially formed adduct **A**
  - Excess acid also slows the S<sub>N</sub>2 displacement on the phosphonium **B**
  - Use of electron rich triarylphosphines slows attack of alcohols on **B** (ρ=1.5)

# The Mitsunobu Reaction on Polymer

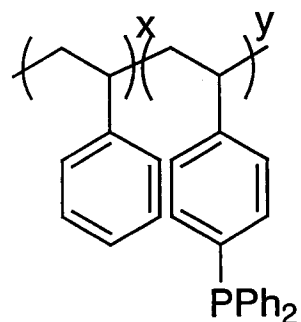


A: x=0%, y=100%

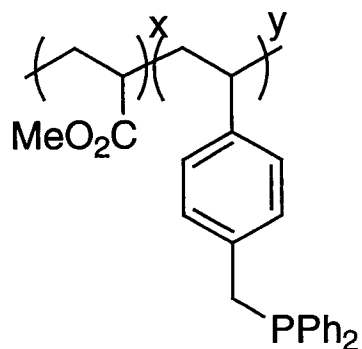
B: x=33%, y=67%

C: x=60%, y=40%

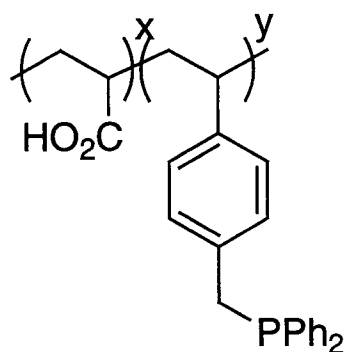
D: x=82%, y=18%



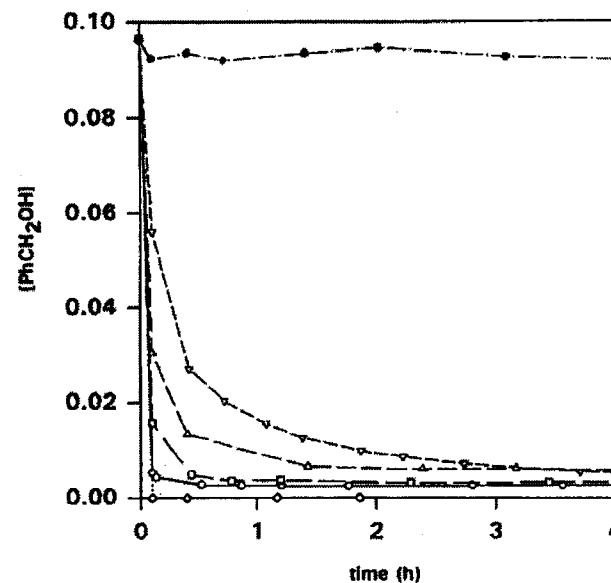
F: x=82%, y=18%



E: x=82%, y=18%



G: x=82%, y=18%



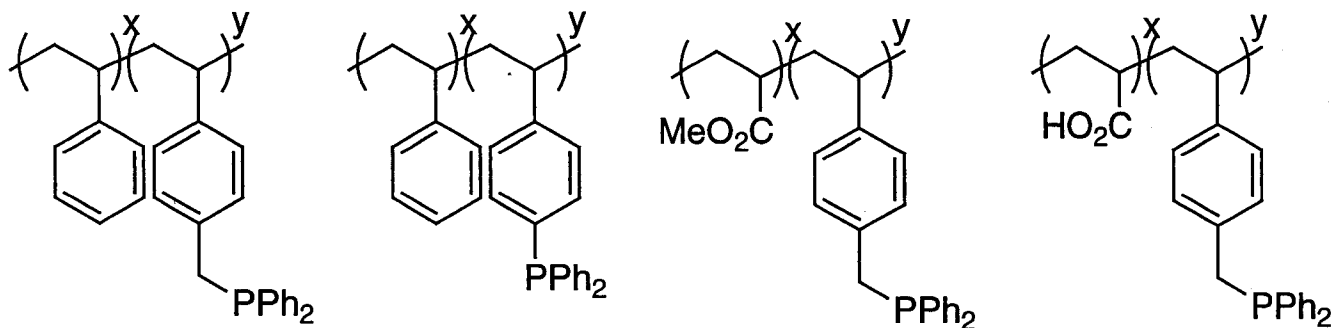
**Figure 1.** Concentration of benzyl alcohol as a function of time for the Mitsunobu reaction in the presence of triphenylphosphine ( $\diamond$ ) and polymer-supported phosphines (polymer A,  $\nabla$ ; polymer B,  $\Delta$ ; polymer C,  $\square$ ; polymer D,  $\circ$ ; polymer E,  $\bullet$ ; polymer F,  $\diamond$ ).

**Table 1.** Percent Conversion of Benzyl Alcohol and Percent Yield of Ester in the Mitsunobu Reaction of Benzyl Alcohol and Benzoic Acid at 25 °C

time (h)	percent conversion of benzyl alcohol						
	PPh <sub>3</sub>	A <sup>a</sup>	B <sup>b</sup>	C <sup>c</sup>	D <sup>d</sup>	E <sup>e</sup>	
0	0	0	0	0	0	0	0
0.10	100	41.7	68.4	83.7	94.5	1.3	100
0.40		71.9	86.1	95.0	97.2	2.7	
equil <sup>g</sup>	100	96.6	94.2	97.0	97.6	56.3	100
% yield <sup>h</sup>	85.3	79.8	77.8	96.0	95.1	29.8	84.6

Alexandratos, S.D., *et al. Macromolecules*. 1996, 29, 8025.

# The Mitsunobu Reaction on Polymer



**A:** x=0%, y=100%

**B:** x=33%, y=67%

**C:** x=60%, y=40%

**D:** x=82%, y=18%

**E:** x=82%, y=18%

**F:** x=82%, y=18%

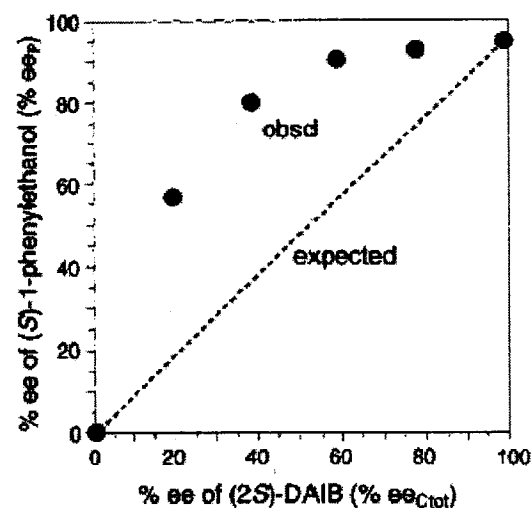
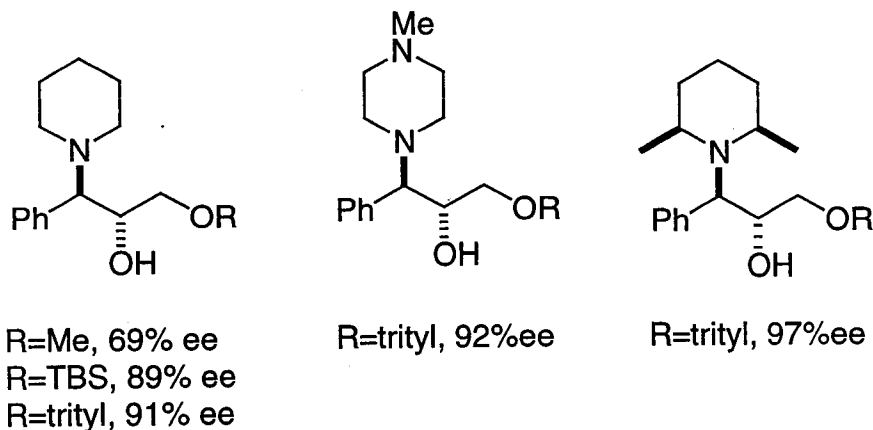
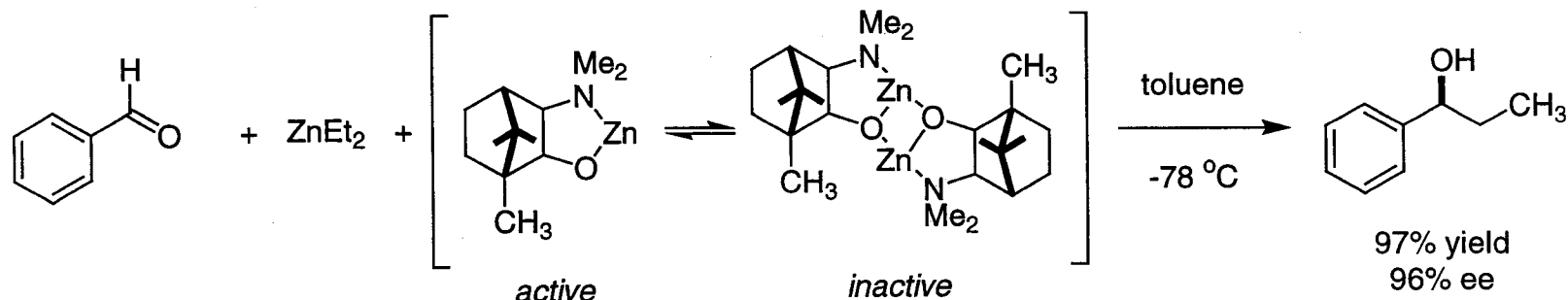
**G:** x=82%, y=18%

**Table 1. Percent Conversion of Benzyl Alcohol and Percent Yield of Ester in the Mitsunobu Reaction of Benzyl Alcohol and Benzoic Acid at 25 °C**

time (h)	percent conversion of benzyl alcohol						
	PPh <sub>3</sub>	A <sup>a</sup>	B <sup>b</sup>	C <sup>c</sup>	D <sup>d</sup>	E <sup>e</sup>	
0	0	0	0	0	0	0	0
0.10	100	41.7	68.4	83.7	94.5	1.3	100
0.40		71.9	86.1	95.0	97.2	2.7	
equil <sup>g</sup>	100	96.6	94.2	97.0	97.6	56.3	100
% yield <sup>h</sup>	85.3	79.8	77.8	96.0	95.1	29.8	84.6

- As the polarity of the polymer decreases, the rate increases (**F** << **A** < **B** < **C** < **D**).
- This agrees with an S<sub>N</sub>2-RDS with a charged SM and a neutral product.
- The inactivity of polymer **G** agrees with the observation that excess acid inhibits the reaction by stabilizing the phosphonium intermediates.
- The increased reactivity of **E** over **D** agrees with a positive rho value.

# Diethylzinc Additions to Aldehydes

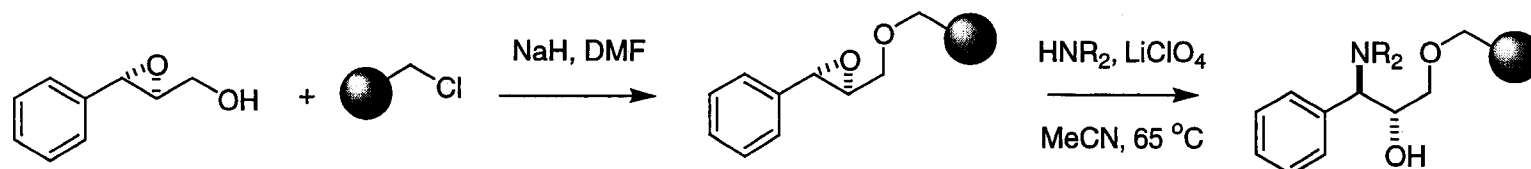


Pu, L., *et al.* *Chem. Rev.* **2001**, *101*, 757.

- The addition of diethylzinc to aldehydes catalyzed by amino alcohols is a highly selective method for formation of enantioenriched alcohols.
- There is a strong non-linear effect in these reactions owing to aggregation of the catalytic species, the zinc alkoxide.



# Diethylzinc Addition on Polymer: Site Interaction

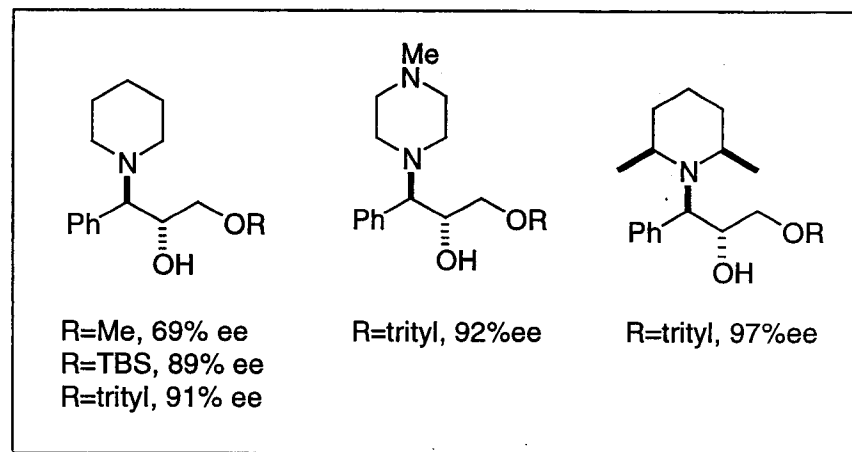


**Table 2. Catalytic Behavior of the Resin-Anchored Ligands 5a–c in the Addition of Et<sub>2</sub>Zn to Benzaldehyde<sup>a</sup>**

ligand (%DVB; <i>f</i> )	amount (%) <sup>b</sup>	ee of resulting alcohol (%)
5a (1; 0.8)	5	36
5a (2; 1.6)	4	22
5a (2; 1.8)	3	20
5b (1; 0.9)	5	39
5b (2; 1.6)	4	20
5b (2; 1.7)	3	19
5c (1; 1.0)	3	69 <sup>c</sup>
5c (2; 1.6)	4	57
5c (2; 1.7)	3	57

<sup>a</sup> All reactions were performed in toluene at room temperature for 24 h using a Et<sub>2</sub>Zn/PhCHO molar ratio of 2/1. Conversions were higher than 95% in all cases (determined by GC). <sup>b</sup> Amount of catalyst (% molar with respect to benzaldehyde). <sup>c</sup> Mean of two experiments.

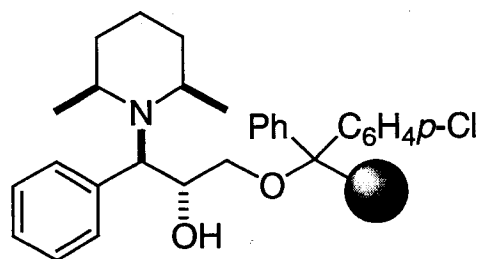
5a R=piperdiny  
5b R=4-Me-piperazin-1-yl  
5c R=*cis*-2,6,-DiMepiperadino



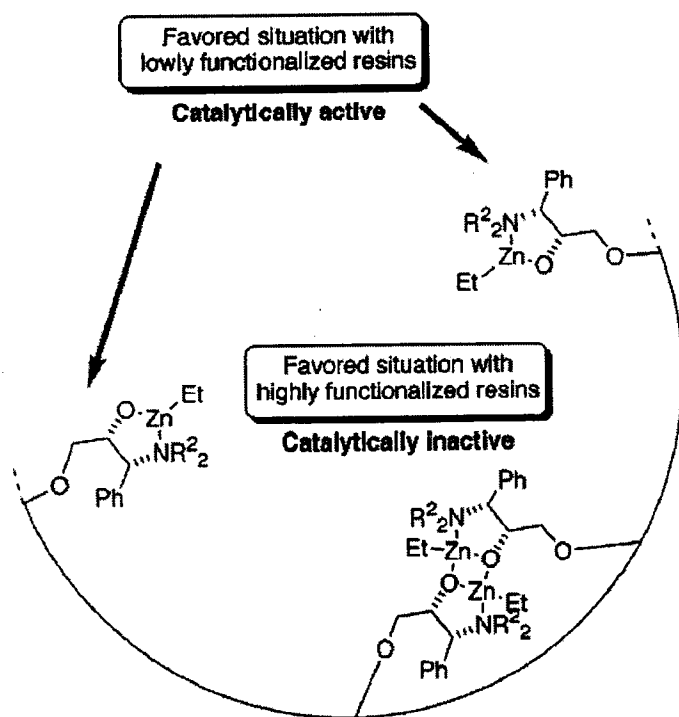
Pericas, M.A., *et al. J. Org. Chem.* **1998**, 63, 6309.

- The polymer bound ligands **5a–c** show greatly diminished selectivity relative to their solution phase counterparts, likely due to the bulk of the ether group.
- The selectivity decreases with increased bead loadings.

# Diethylzinc Addition on Polymer: Linker Bulk



Barlos Resin Ligated **5c**



**Table 4. Catalytic Properties of Functionalized Tritylated Resins in the Amino Alcohol Promoted Addition of Diethylzinc to Benzaldehyde<sup>a</sup>**

entry	<i>f</i> (mmol ligand/ g of resin)	% molar ligand	temp, °C	ee (%) <sup>b</sup>	config <sup>c</sup>
I	0.9	4	rt	79	<i>S</i>
II	1.1	5	rt	92	<i>S</i>
III	1.1	5	0	93	<i>S</i>
IV	1.2	5	0	94	<i>S</i>

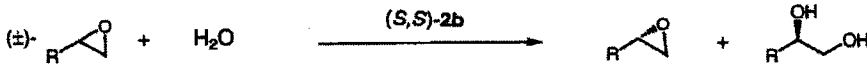
<sup>a</sup> Resins prepared as described in Table 3. The polymer needs to be stirred smoothly in the appropriate solvent to swell properly prior to use. The resin was left to stir for 24 h in toluene before adding the aldehyde and Et<sub>2</sub>Zn in molar ratio of 1:2. Stirring was further continued for 24 h in order to achieve conversions higher than 90% (determined by GC). <sup>b</sup> Enantiomeric excess in the resin promoted addition of diethylzinc to benzaldehyde (determined by GC: β-DEX 120 column). <sup>c</sup> Configuration of the addition product (1-phenylpropanol).

- Due to the importance of the bulk of the ether, a larger linker is used to enhance selectivity.
- It is interesting to note that with these ligands, there is an inverse loading effect as compared to the Merrifield resin.

Pericas, M.A., *et al. J. Org. Chem.* **1998**, *63*, 6309.

# Hydrolytic Kinetic Resolution of Epoxides

**Table 1.** Hydrolytic kinetic resolution of terminal epoxides with water catalyzed by **2b**. The values for  $k_{rel}$  were calculated using the equation  $k_{rel} = \ln[(1 - c)(1 - ee)] / \ln[(1 - c)(1 + ee)]$ , where  $ee$  is the enantiomeric excess of the epoxide and  $c$  is the fraction of epoxide remaining in the final reaction mixture (4).



Entry	R	Concentration		Time (hours)	Epoxide		Diol		$k_{rel}$
		<b>2b</b> (mol %)	Water (equiv)		$ee$ (%)	Isolated yield (%)	$ee$ (%)	Isolated yield (%)	
1	CH <sub>3</sub>	0.2	0.55	12	>98	44	98	50	>400
2	CH <sub>2</sub> Cl	0.3	0.55	8	98	44	86	38	50
3	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	0.42	0.55	5	98	46	98	48	290
4	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	0.42	0.55	6	99	45	97	47	260
5	Ph	0.8	0.70	44	98	38	98*	39*	20
6	CH=CH <sub>2</sub>	0.64	0.50	20	84	44	94	49	30
7	CH=CH <sub>2</sub>	0.85	0.70	68	99	29	88	64	30

\*After recrystallization.



Jacobsen, E.N., *et al. Science* **1997**, *277*, 936.

**Figure 15.** Proposed cooperative mechanism for the hydrolytic kinetic resolution of terminal epoxides.

- The opening of epoxides with protic nucleophiles (water, alcohols) is effectively catalyzed by cobalt-salen complexes.
- High selectivities and high  $s$  factors are obtained for unfunctionalized epoxides as well as more highly functionalized epoxides containing sensitive functionalities which may not be stable under other conditions used to open epoxides.

# Hydrolytic KR of Epoxides on Polymer

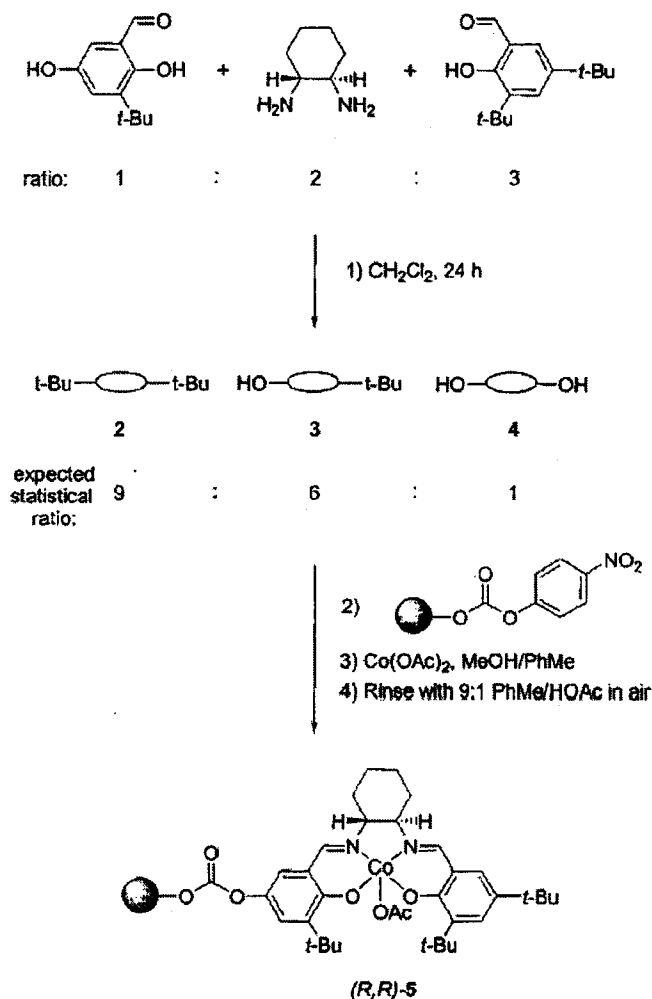
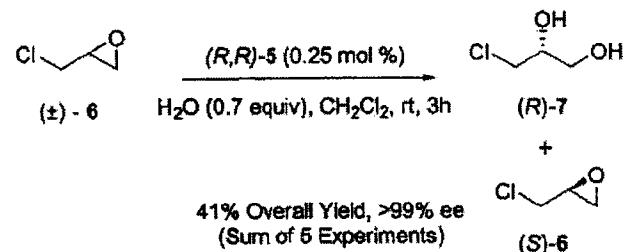


Figure 2. Resin-capture synthesis of polystyrene-bound chiral Co-(salen) complexes.



cycle	conversion <sup>a</sup> (%)	ee 6 (%)	ee 7 (%)	k <sub>rel</sub>
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

<sup>a</sup> Estimated based on the ee of recovered epoxide and diol product (see experimental section).

- Using a polystyrene bead supported with 0.87 mmol / g Co<sup>III</sup>, excellent results which were comparable to solution were obtained.
- Loadings of 0.16 – 0.87 mmol / g were investigated.

Jacobsen, E.N., *et al.* *J. Am. Chem. Soc.* **1999**, *121*, 4147.

# Hydrolytic KR of Epoxides on Polymer

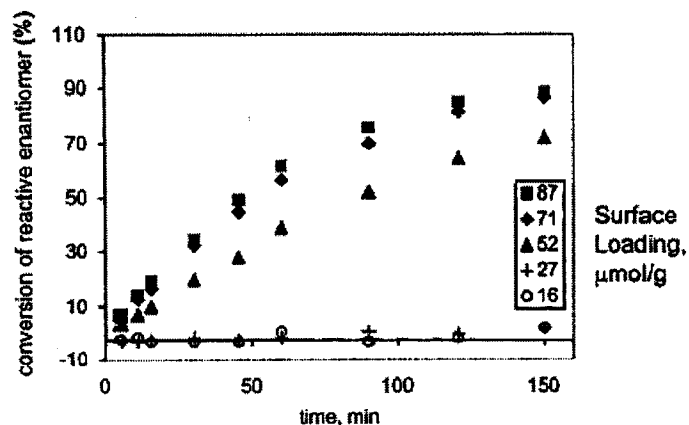


Figure 16. Plot of epichlorohydrin conversion vs time in the HKR using various loadings of catalyst on the silica surface.

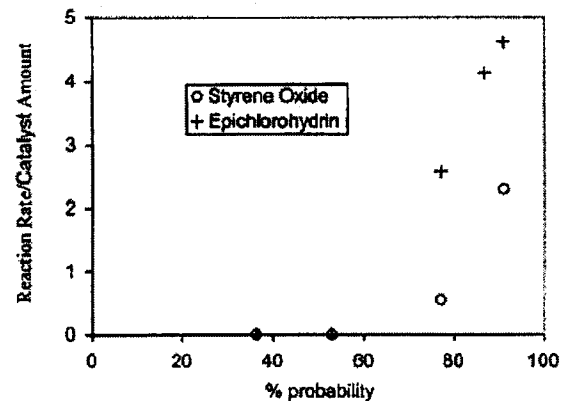
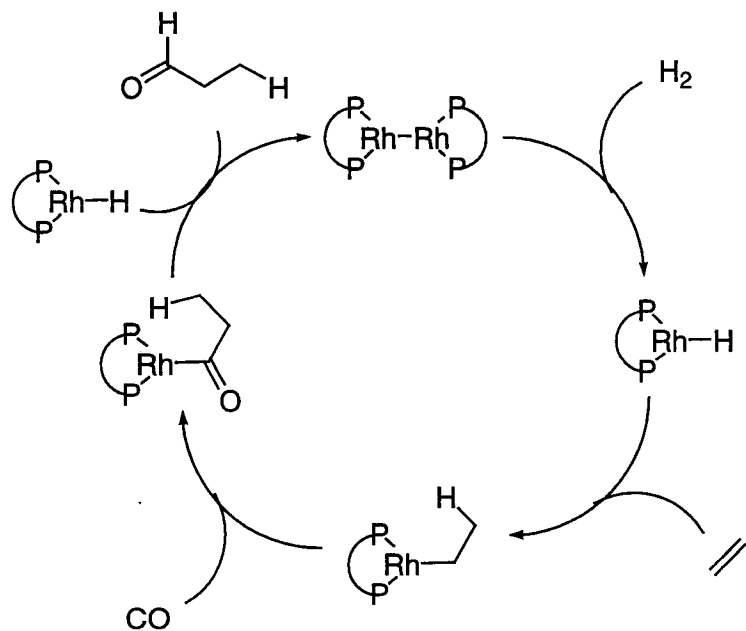


Figure 17. Plot of the rate of the HKR of styrene oxide and epichlorohydrin vs the probability of catalyst interaction on the silica surface.

Jacobsen, E.N., *et al. J. Am. Chem. Soc.* **1999**, *121*, 4147.

- Kinetic analysis of reaction with beads of different loadings shows a strong loading dependence, suggesting a mechanism involving two equivalents of catalyst.
- This conclusion is further supported by use of a mathematical model which predicts the *probability* of catalyst interaction.

# Modelling the Site-Site Interaction



$$P = 1 - [1 - (\pi((r_2/2)^2 - (r_1/2)^2))]^N$$

N = number of molecules on bead (moles)

$r_1, r_2$  = physical dimensions of the molecule (Angstrom)

- Interaction between two metal centers in hydrogenolysis of metal acyls is an essential step in olefin hydroformylation.

Table VII. Hydroformylation Catalyzed by 17/Et<sub>3</sub>N Using 1:1 H<sub>2</sub>/CO<sup>a</sup>

catalyst	turnovers per Rh per h	calcd % isolation
17f	0.60, 0.65, 0.71, 0.73, 0.70	27
17g	0.71, 0.72	34
17h	0.47, 0.56, 0.44, 0.49	61
17i	0.51, 0.47, 0.48	80
17j	0.32	95

<sup>a</sup> Conditions: styrene, 0.74 M; Et<sub>3</sub>N, 105 mM; 17 as needed to contain 0.001 to 0.004 mmol Rh. Experiments run in anisole solution (1-1.5 mL) at ambient temperature with 1:1 H<sub>2</sub>/CO at 50 psi.

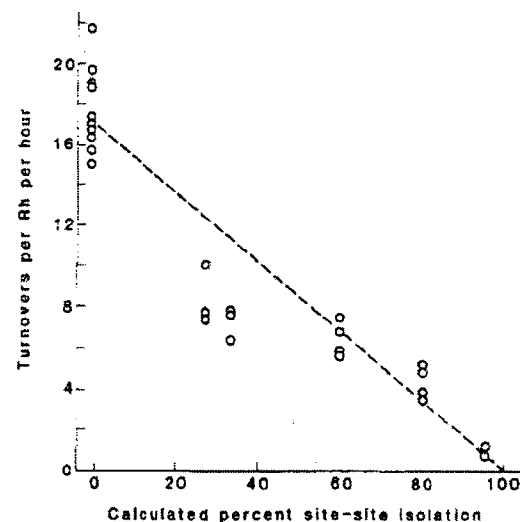
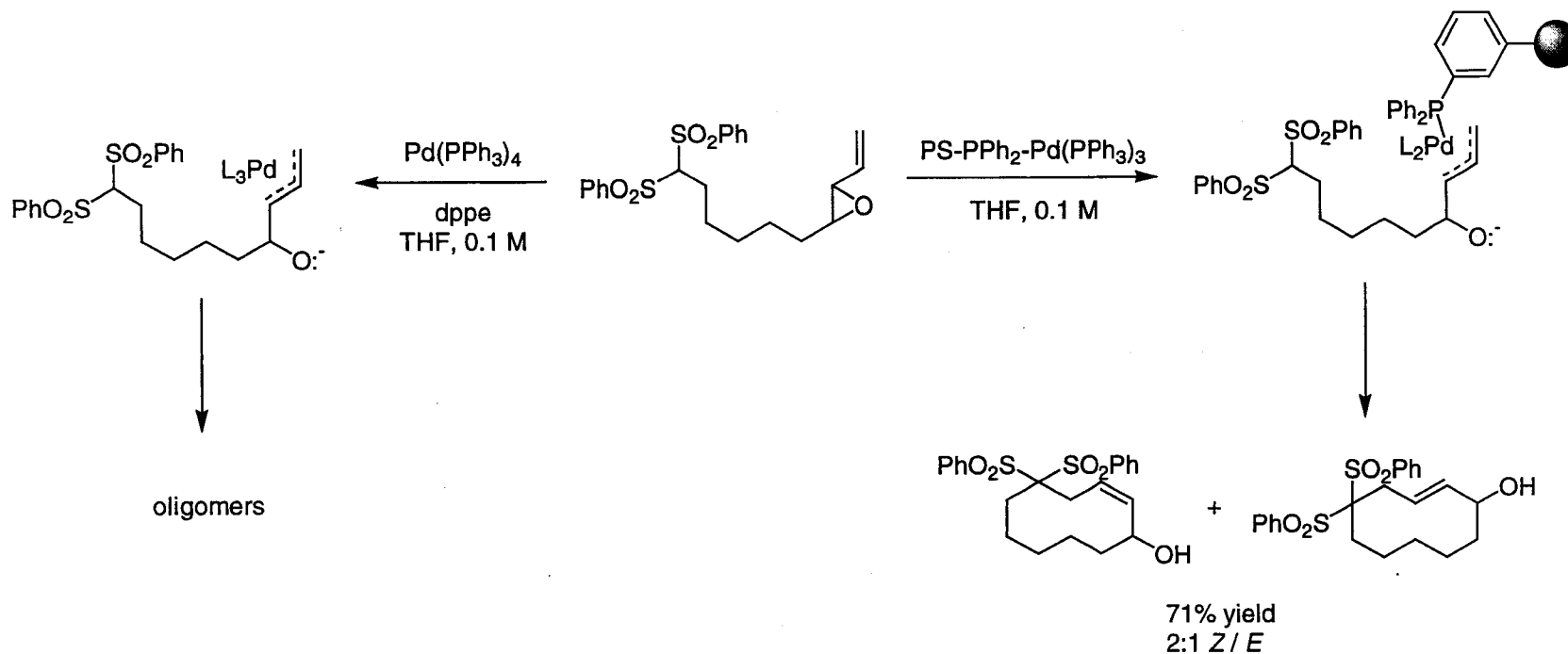


Figure 8. Hydroformylation catalyzed by 17/Et<sub>3</sub>N using 19:1 H<sub>2</sub>/CO. Conditions shown in Table VI. Data at zero isolation obtained with soluble catalyst.

Collman, J.P., *et al.* *J. Am. Chem. Soc.* **1983**, *105*, 7288.

# Hyperentropic Effects on Polymers



Trost B.M., *et al. J. Am. Chem. Soc.* **1982**, 104, 6612.

- Formation of large ring systems is often problematic due to entropic effects.
- High dilution conditions are used to overcome this problem ( $< 0.003 \text{ M}$ ).
- If reactive sites are isolated, a similar effect can be achieved using a polymer supported reagent.

# ***Solid Phase Asymmetric Organic Synthesis: Novelty or Fundamental Concept?***

- Attachment of catalysts to the solid phase can provide benefits in terms of catalyst recovery and immobilization of toxic compounds / side-products.
- A set of rules are emerging to rationalize the behavior of solid supported reagents.
- Comparable reactivity and selectivity can be achieved after some optimization with an understanding of mechanism, leading to industrially viable catalysis.