Polymer Bound Catalysts

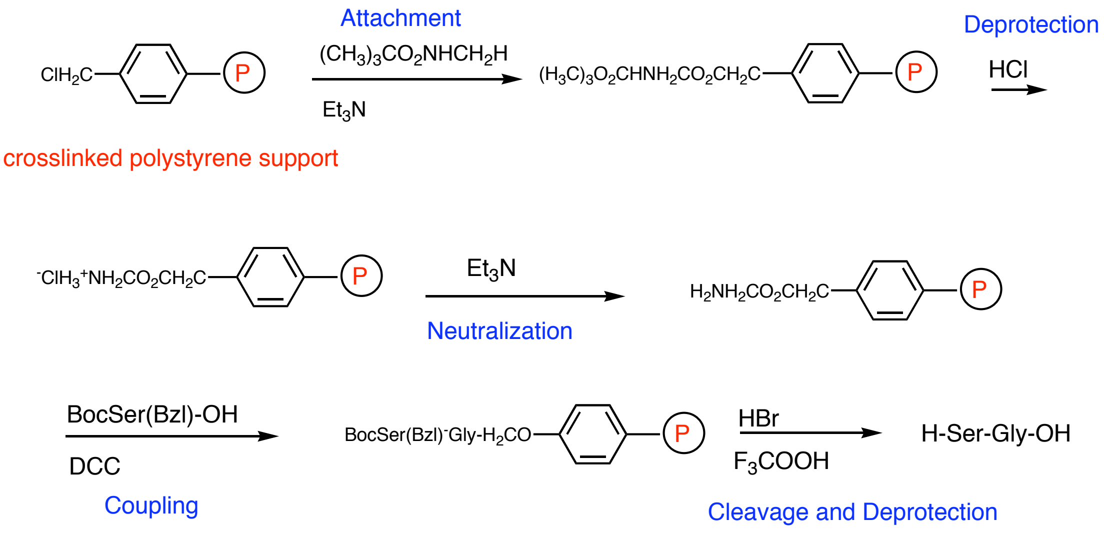
MacMillan Group Meeting
October 4, 2000
Vy Dong

- I. Introduction
- II. Chiral Catalyst
  - a) oxidations
  - b) reductions
  - c) C-C bond formation
- III. Novel Applications

Leading references:
Functionalized Polymers: Recent Developments and New Applications in Synthetic Chemistry. Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. Synthesis **1997**, 1217
Soluble polymers: New options in both traditional and combinatorial synthesis. Harwig, Curtis W.; Gravert, Dennis J.; Janda, Kim D. The Scripps Research Institute, USA. Chemtracts (1999), 12 (1), 1-26.
Ford, Warren T.; Polymeric Reagents and Catalysts American Chemical Society, **1985**

Chemistry on Solid Support

1963 R. Bruce Merrifield's Peptide Synthesis



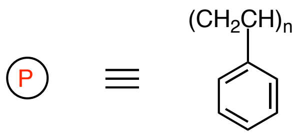
Since then thousands of reagent bound, substrate bound and catalyst bound supports and methods have been developed.

Basics of Polymer Chemistry

Definition of a polymer:

a polymer is a mixture of compounds composed of the same repeating structural unit (monomer)

e.g. polystyrene



n = degree of polymerization (average number of repeat units per molecule)

Mn = the number average molecular weight (usually 20,000 or more)

Definition of a copolymer:

comprised of more than one kind of repeating unit in an alternating, block or random fashion

ABABABABABABAB
AAAAAAABBBBBBB
ABAAAABABBBABA

Synthesis of Polymers

chain growth: formation from monomer via a highly reactive intermediate such as a radical, carbanion, a carbenium ion or a transition metal alkyl complex

step growth: polymerization

Advantages of Supported Reagents and Catalyst

Ease of separation

Reuse of catalyst

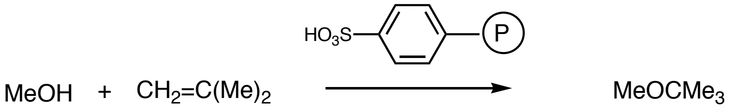
Adaptability to continuos flow processes

Reduced toxicity and odor

Chemical differences (potential altered selectivity or activity)

Clean Chemistry

example of an important industrial application



MTBE

anti-knock reagent
replacing tetraethyl lead in petrol

Sharpless Asymmetric Dihydroxylation

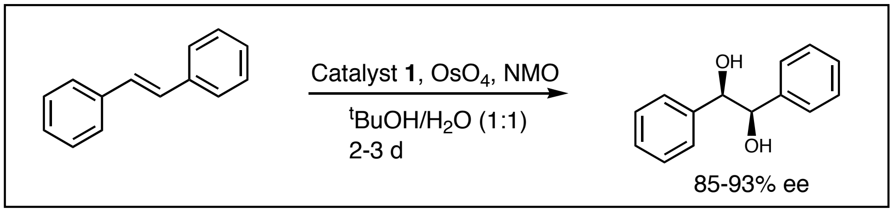
Why is there need for polymer-supported alkaloid ligands for AD?

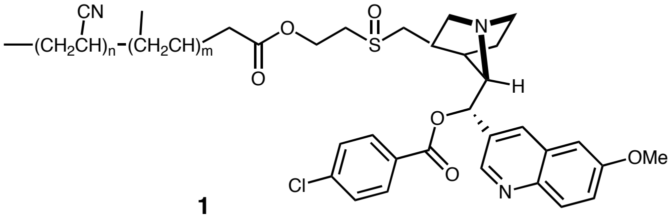
Important reaction for synthesis of optically pure vicinal diols

Inherent problems lie in the use of toxic osmium tetroxide

1,4-phthalazinediyl diether hydroquinidine [$(DHQD)_2PHAL$] ligands are expensive

1990 Initial investigations:





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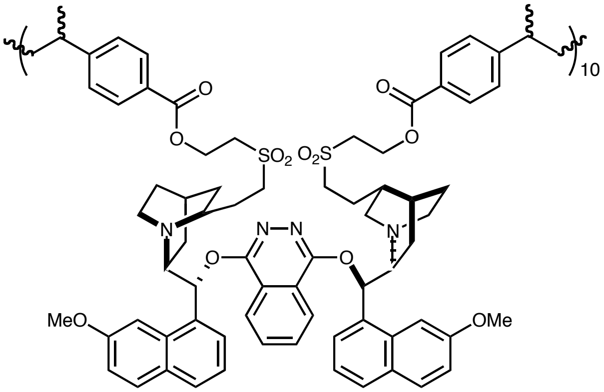
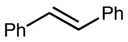
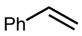
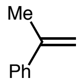
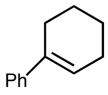
synthesized by radical copolymerization of 9-(*p*-chlorobenzoyl)quinidine acrylate with acrylonitrile)

Strategies for Ligand Recovery in Sharpless AD of Olefins

I. Attachment to a Solid Support

Organic Copolymer

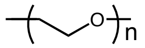


olefin	% ee
	> 99 (>99)
	91 (97)
	94 (94)
	97 (99)

First polmer-bound 1,4-bis-(9-*O*-dihydrochinidinyl)-phthalazine [$(DHQD)_2PHAL$]
Use of $K_3[Fe(CN)_6]$ as the secondary oxidant
Highest levels of enantiomeric excesses so far was achieved.
Insoluble polymeric ligand is quantitatively recovered.
Significant loss of OsO_4 occured (0.2 mol%)

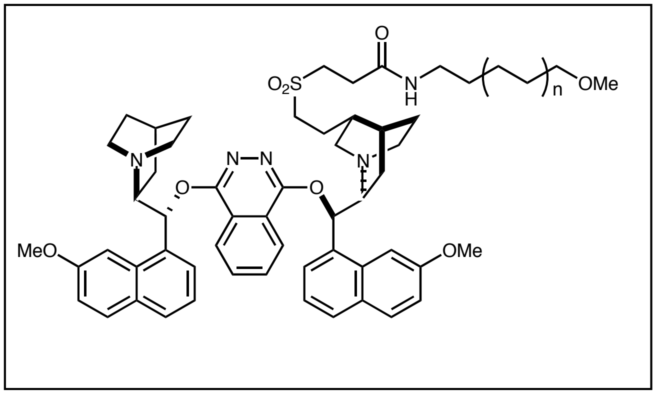
Salvodori, P.;Pini, D.; Petri, A.; Nardi, C.; Rosini P.; *Tetrahedron Lett.* **1991**, *32*, 5175-5178

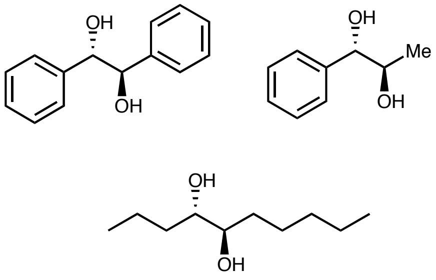
Advantages of the Polyethylene Glycol Support (PEG)



soluble in wide range of organic solvents and water, but is insoluble in hexane, diethyl ether and *tert*-butyl methyl ether

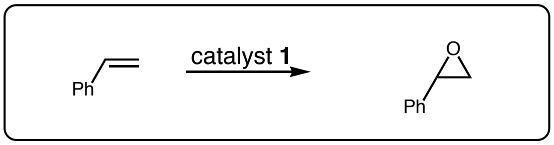
permits homogenous reaction conditions while allowing for easy reuse





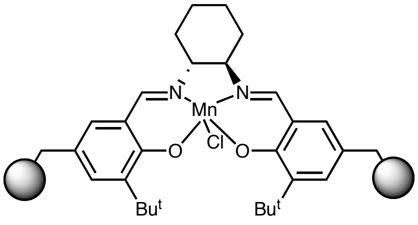
> 96 % ee

Asymmetric Epoxidation



High yields (78-99%) but poor to moderate ee's were obtained (14-40 %)

Catalyst preserved its unmodified activity in terms of yield and ee's after 5 recycles.



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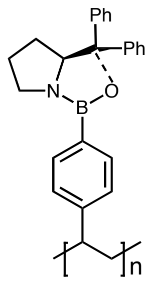
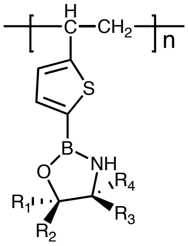
Salvadori, P.; Minutolo, F. Pini, D.; Tetrahedron Letters, Vol. 37, No. 19, 3375

Asymmetric Catalyst for Reductions

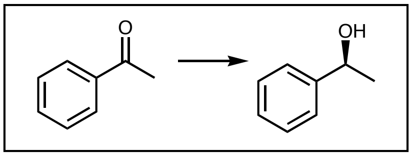
Boron catalyst



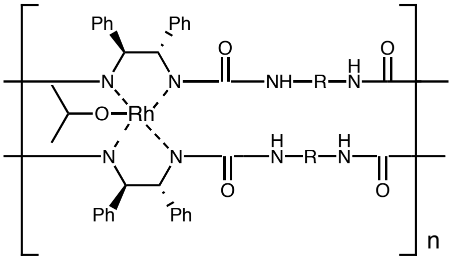
93% yield, 98 % ee



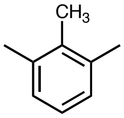
95% yield, 61 %ee



Rhodium catalyst



R =



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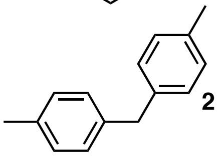

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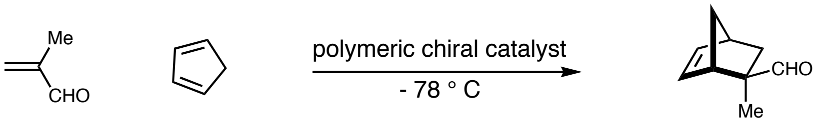
98 % yield, 55% ee

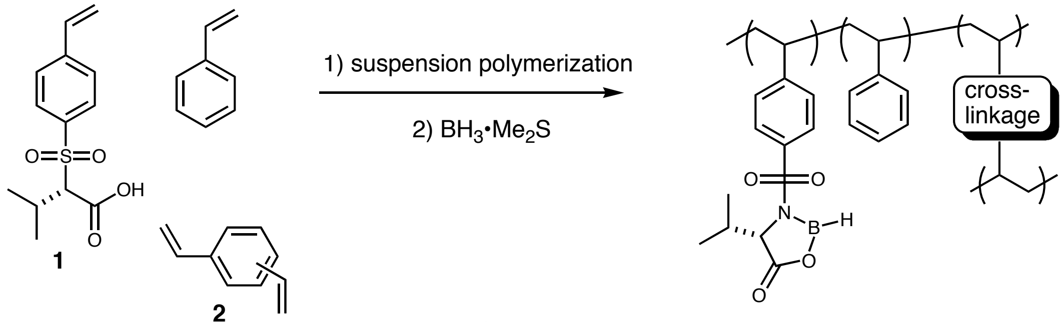
Carbon-Carbon Bond Forming Catalyst

I. Diels-Alder Reaction
II. Diethyl Zinc Additions
III. Aldol
IV. Carbene Insertion

Diels-Alder Reaction



Cross-linking structure greatly affects the performance of the polymeric catalyst



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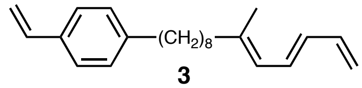

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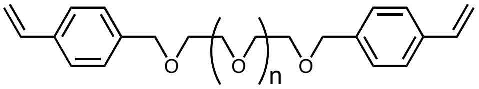


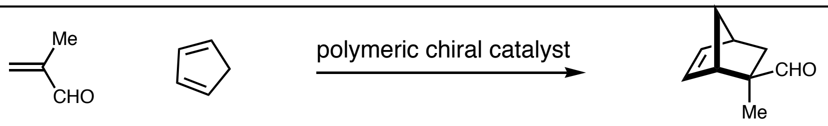
4a: n = 0
4b: n = 3
4c: n = 7.7

catalyst	%yield	endo:exo	% ee (R)
5: crosslinked with **2**	87	1:99	65
6: crosslinked with **3**	86	8:92	84
7a: crosslinked with **4a**	85	5:95	77
7b: crosslinked with **4b**	93	1:99	92
7c: crosslinked with **4c**	88	4:96	95

Itsuno, S.; Ito, K.; Kamahori, K.; *J. Org. Chem.* **1996,** *61*, 8321.

Realization of a Continuous Flow System

Diels-Alder Reaction



A solution of the starting materials in DCM is added to a column containing insoluble polymer **7b** and a solution of the chiral product was continuously eluted from the column.

picture of a column

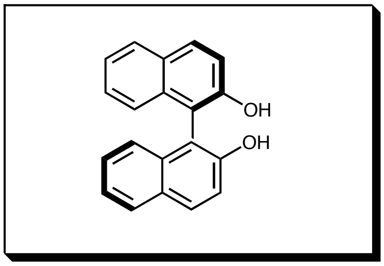
5.7 mmol of catalyst

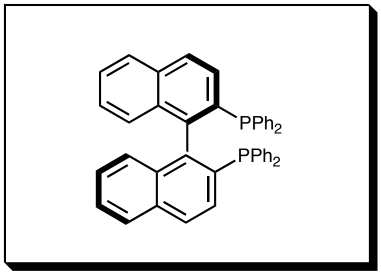
↓

138 mmol of (R)-adduct with 71% ee

A Novel BINOL-BINAP Copolymer

two important classes of chiral biaryl ligands that have found extensive applications in asymmetric catalysis





hard oxygen atoms that coordinate hard metal centers (e.g. Al(III), Ti(IV), Zn(II), Ln(III)

BINOL polymer ⇨ asymmetric alkylation

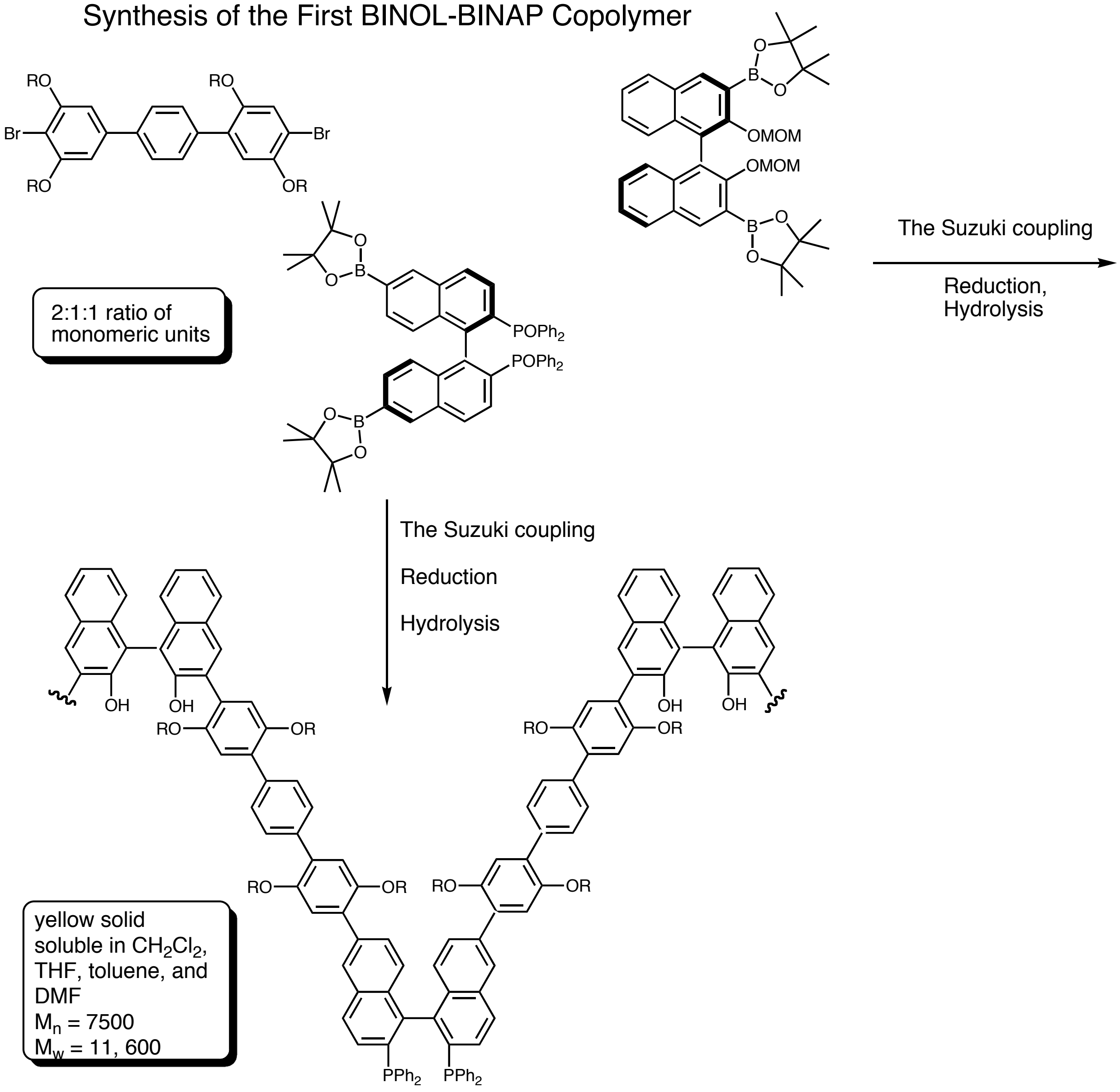
soft phosphorous atoms that coordinate with soft late transition metals such as Rh and Ru

BINAP polymer ⇨ asymmetric reduction

Distinct coordinative ability provides opportunity for desing of a novel mutifunctional catalyst

Pu, L.; Yu, H.B.; Hu, Q.S.; *J. Am. Chem Soc.* **2000**, *122,* 6500

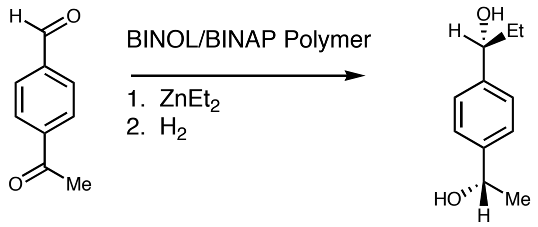
Synthesis of the First BINOL-BINAP Copolymer



2:1:1 ratio of
monomeric units

yellow solid
soluble in CH_2Cl_2,
THF, toluene, and
DMF
M_n = 7500
M_w = 11, 600

A Tandem Asymmetric Reaction Involving Diethylzinc Additon and Hydrogenation



>99% conv.,
94 % ee for diethyl zinc addition
87 % ee for the hydrogenation
2 d

Significance:

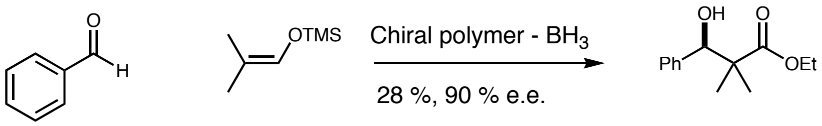
First optically active BINOL-BINAP copolymer catalyst had been designed and synthesized

Use of a copolymer rather than a mixture of monomers simplifies recovery and purification

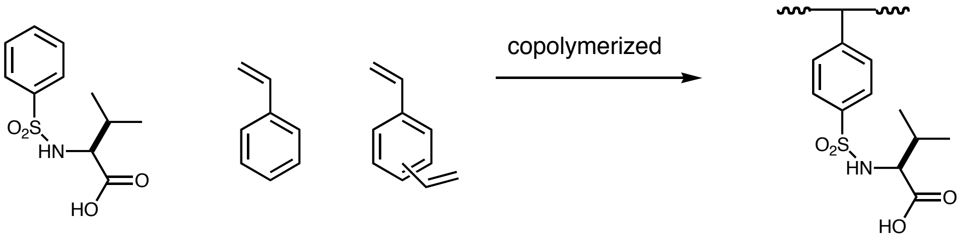
Conceptually new alternative to using polymer mixtures

Besides the tandem asymmetric catalysis, the copolymer can be used for individual reactions that require either BINOL or BINAP.

Chiral Borane Promoters for an Asymmetric Aldol Reaction

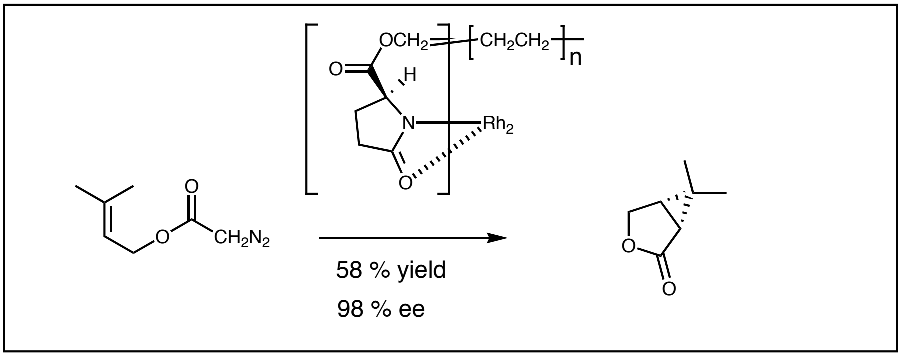


Valine Sulfonamide-derived catalyst



Kiyooka, S.; Kido, Y,; Kaneko, Y.; Tet. Lett, **1994,** Vol. 35, No. 29., 5243

Enantioselective Metal Carbene Transformation



58 % yield

98 % ee

Attachment of dirhodium (II) to the chiral , polyethylene-bound 2-pyrrolidone-5(*S*)-carboxylate ligand

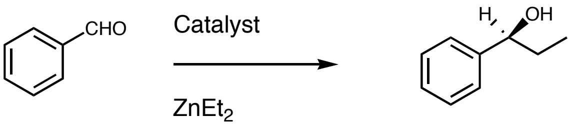
Promising Results for Reuseability of the catalyst for metal carbene transformations

Run	% ee
2	98
3	83
7	61

Doyle, M. P.; Eismont, M. Y.; *J. Org. Chem.* **1992,** ***57,*** 6103

Asymmetric Alkylation of Aldehydes

Diethyl Zinc Additions



catalyst	% ee	% yield
1	86	93
2	99	88

Itsuno's Catalyst

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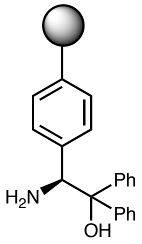
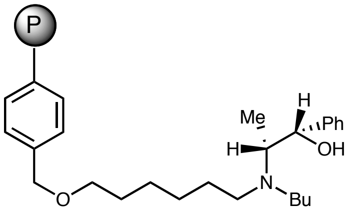




Soai's Catalyst

2

immobilization of *N*-butylnorephedrine onto polystyrene

Itsuno, S and *et tal.*; *J. Org. Chem.* **1990,** *55*, 304 and Soai, K and *et tal.; J. Org. Chem.* **1988,** 53, 927**.**

Smart Ligands

Smart materials: materials that undergo some physical property change (e.g.) phase change in response to a stimuli.

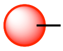
Commercially available poly(alkene oxides) block copolymers have inverse temperature dependent solubility in water.

e.g. oligomer of M_n =2500 and 20 mol% ethylene oxide is soluble at 0 °C in water, but insoluble at room temperature.

$HO\text{-}(CH_2CH_2O)_n((CH_3)CHCH_2O)_m(CH_2CH_2O)_n\text{-}H$

= HO-PEO-PPO-PEO-OH

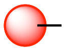
Synthesis of a "smart" hydrogenation catalyst



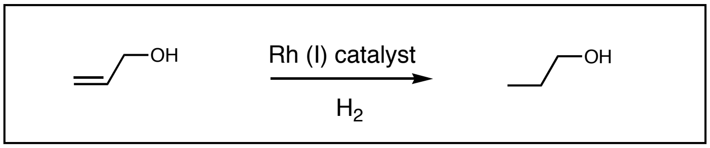
$—CH_2CH_2PPh_2)]Rh^+CF_3SO_3^-$

Bergbreiter, D.E. *et tal. J. Am. Chem. Soc.* **1993,** *115*, 9295.

Smart Ligands



$—CH_2CH_2PPh_2)]Rh^+CF_3SO_3^-$



Effect of Hydgrogenation rate versus Reaction Temperature

Anti-Arrhenius behavior is observed !

Heating reaction to 40-50 °C stops reaction

Cooling to 0 °C rehydrates ligand and catalyst redissolves

Explanation: polymer becomes more hydrophobic with increase in temperature

Implications:

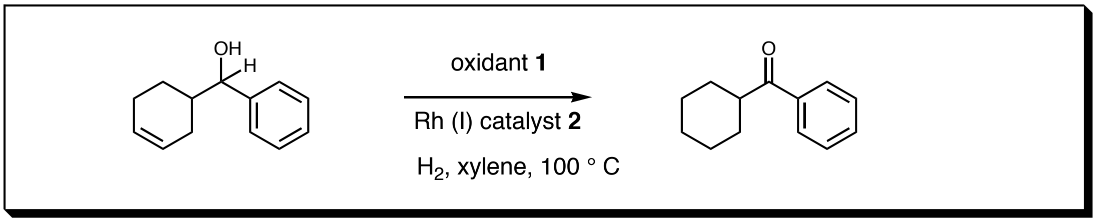
Control of exothermic reactions

Control of temperature-dependent selectivity changes in asymmetric catalysis

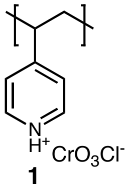
Control of temperature throughout a reactor

Application of Macromolecular Catalysts to Multistep Chemistry

One pot oxidation/hydrogenation reaction



Frechet's polyvinylpyridinium chlorochromate oxidant



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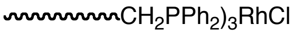


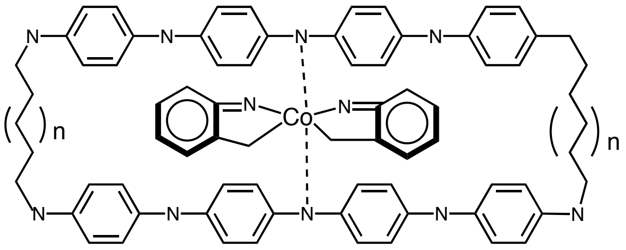
$CH_2PPh_2)_3RhCl$

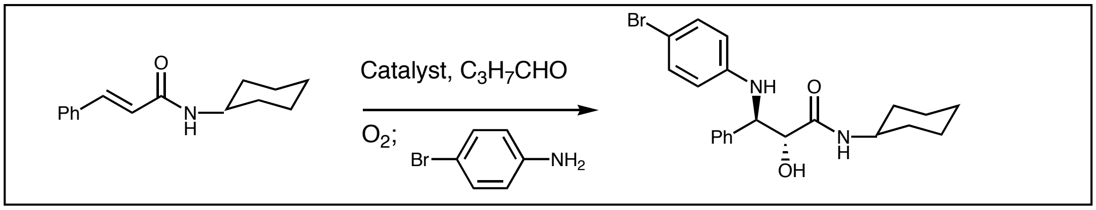
2

Bergbreiter's diphenylphosphinated ethylene oligomer

Diffusional restrictions of polyethylene ligands prevents rhodium complex from diffusing into and reacting with the chromium oxidizing agent.

A Novel Polyaniline Supported Co(II)-catalyst





one-pot conversion of cinnamoyl amides to the corresponding b-phenylisoserine derivatives by epoxidation and aniline opening sequence.

Iqbal, J.; Bhaskar, D.; Tetrahedron Letters, Vol. 38, No. 16, 2903.