CATALYST IN A BOX: ZEOLITE-SUPPORTED ENANTIOSELECTIVE CATALYSIS

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INTRODUCTION

Enantioselective Catalysis

Beginning with the first homogeneous asymmetric metal-catalyzed reaction performed by Noyori—a cyclopropanation—the area of enantioselective catalysis in organic chemistry has become a major topic of discussion and research.[1] Homogeneous, asymmetry-inducing catalysts have been developed for a wide range of reactions, especially notable are those developed by Knowles, Noyori and Sharpless, for which they jointly received the 2001 Nobel Prize in Chemistry.[2] Although these reactions can be highly stereoselective, there are disadvantages associated with homogeneous catalysis: namely (1) expense of the catalyst, which is often lost upon work-up of the reaction, (2) the difficult separation of the organic ligands and metal catalyst from the resulting products, and (3) the inability of homogeneous catalysis to provide high stereoselectivity for all substrates and reaction types.[3]

The first two of these difficulties can be avoided by immobilizing the chiral catalyst on a solid support. This support allows for easy separation of the solid catalyst and product by simple filtration, and in optimal conditions the supported catalyst can be reused multiple times without significant loss in activity or enantioselectivity, thereby decreasing cost. A number of different solid supports have been applied for the formation of heterogeneous chiral catalysts. Of these, the synthetic and bio-polymers, solid metal, amorphous silica or alumina, and zeolite-based catalysts have received the most attention.[4] Zeolites are especially promising in their application as heterogeneous, chiral catalysts or catalyst carriers due to their ordered structure and high porosity. This structure allows for ready incorporation and immobilization of the chiral catalyst onto the surface of the zeolitic pores, and not only enhances the surface area available for catalyst integration but also creates a highly structured and confined cavity which can positively affect stereoselectivity.[3-4]

Zeolites

Zeolites are traditionally defined as microporous, crystalline, aluminosilicate compounds of the general formula $M_{2/n}O•Al_2O_3•ySiO_2•wH_2O$, where M is an alkali or alkali earth metal, n is the charge of the cation, y correlates the ratio of Al_2O_3 to SiO_2, and w is the number of water molecules trapped in the porous space of the zeolite.[5] The ordered structure of the zeolite is composed of staggered AlO_4^- and SiO_4 tetrahedra, which are linked by shared oxygens, with each aluminum tetrahedron contributing a single negative charge to the lattice. These negative charges can be offset by a number of organic or inorganic cations, including protons, oxidized metals, and ammonium ions. In the last three decades,

research has expanded the definition of zeolites to include the neutral pure silica (SiO_2) and aluminophosphate ($AlPO_4$) zeolites, and the mesoporous silicates, which have large pores templated by micellular tubes.[5-6]

The interesting properties of these porous minerals were first discovered in 1756 by the Swedish mineralogist Cronsted, who christened them 'zeolites' from the Greek *zeo* "to boil" and *lithos* "stone" because of their nature to steam and foam when heated with a blowpipe.[5] Since the first laboratory synthesis of a natural zeolite (mordenite) in 1948 by Barrer and the subsequent formation by Milton and Breck of non-natural zeolites, Linde types A, X, and Y, in the late 1940's and 1950's, there has been a massive amount of research focused on their synthesis and structural determination, producing over 133 different identified zeolite framework types.[6] Because of their unique adsorption properties, zeolites were first applied as a means of purification and separation. Their use has since expanded to include catalytic and ion-exchange properties, which have proven especially important in the petroleum and detergent industries.[5]

The formation of zeolites follows a relatively straightforward hydrothermal synthesis, consisting of heating and aging a mixture of a SiO_2 source, an Al_2O_3 source, a mineralizer (often OH^-), a positively charged counter ion, an optional organic template, and water.[7] The resulting solid is then filtered and can be heated at a high temperature (calcined) to removed any organic material and water. The ratio of Al_2O_3 to SiO_2 sources used in the formation of the zeolite as well as the metal or organic cations employed to balance the negatively charged cavity determine the 3-dimensional macromolecular structure of the zeolite. Neutral organic templating agents can also play a significant role in zeolite structure.[5-7]

ENANTIOSELECTIVE ZEOLITE-SUPPORTED CATALYSIS

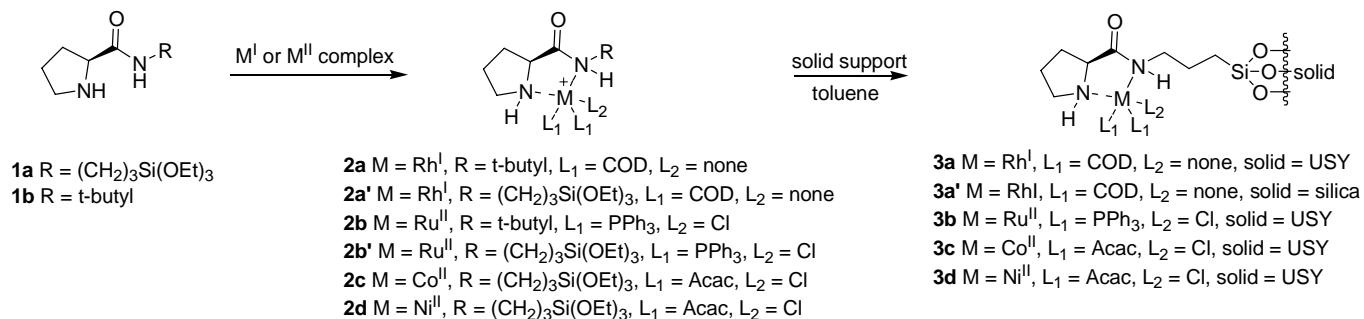### Formation of the Heterogeneous Catalyst

Many methods have been developed for the formation of heterogeneous, asymmetric catalysts using zeolites as a solid support. These methods take advantage of the silanol- and siloxane-lined surface and negatively-charged nature of the confined zeolite pores. Some of the most promising results have arisen from covalent modification of the silanol surface with a linker that irreversibly binds to either the organic ligand or metal of the catalyst.[8-13] Ion exchange of Na^+ or other ion present during zeolite formation with the catalytic metal ion, followed by subsequent complexation of the chiral organic ligand can also produce stable, asymmetric catalysts.[14-17] Although crude in its approach, simple mixing of the chiral catalyst with a given zeolite, either prior to, or during the catalytic reaction, also produces heterogeneous catalysts that provide good enanteoselectivites.[18-21] In the case of bulky catalysts, such as Jacobsen's *tert*-butyl-modified salen complex, the chiral ligands have even been

assembled directly onto the catalytically-active metal inside the pores of the zeolite.[22] Finally, the chiral catalyst can be incorporated into the solution-gel of zeolite formation, producing an only slightly structurally-modified chiral catalyst-encapsulating zeolite.[23]

Hydrogenation

The first reaction performed using zeolite-supported, chiral catalysts was the transition metal-catalyzed hydrogenation of *N*-acylphenylalanine derivatives by Corma and coworkers in 1991.[8] The heterogeneous catalyst is formed from the proline-derived amide **1a**, by chelation of the metal [Rh(I), Ru(II), Co(II), or Ni(II)] to the bidentate ligand and then tethered to a modified Y zeolite (USY) by a silane linker to form the heterogeneous catalysts **3a-d** (Scheme 1). The metal-chelated *N-t*-butyl amides **2a** and **2b** were also synthesized as homogeneous catalysis analogues of **3a** and **3b**. Finally, metal-bound **2a′** was also tethered to non-porous silica, producing surface-bound heterogeneous catalyst **3a′**. Hydrogenation of ethyl (*Z*)-α-benzoylaminocinnamate **5** (see Table 1) was accomplished in a batch reactor at 65 $^\circ$C under 5 atm of H_2 in a mixture of toluene/ethanol or isobutyl methyl ketone.

Scheme 1. Formation of Proline-Based Asymmetric Hydrogenation Catalysts.

1a R = $(CH_2)_3Si(OEt)_3$
1b R = t-butyl

2a M = Rh^I, R = t-butyl, L$_1$ = COD, L$_2$ = none
2a' M = Rh^I, R = $(CH_2)_3Si(OEt)_3$, L$_1$ = COD, L$_2$ = none
2b M = Ru^{II}, R = t-butyl, L$_1$ = PPh$_3$, L$_2$ = Cl
2b' M = Ru^{II}, R = $(CH_2)_3Si(OEt)_3$, L$_1$ = PPh$_3$, L$_2$ = Cl
2c M = Co^{II}, R = $(CH_2)_3Si(OEt)_3$, L$_1$ = Acac, L$_2$ = Cl
2d M = Ni^{II}, R = $(CH_2)_3Si(OEt)_3$, L$_1$ = Acac, L$_2$ = Cl

3a M = Rh^I, L$_1$ = COD, L$_2$ = none, solid = USY
3a' M = RhI, L$_1$ = COD, L$_2$ = none, solid = silica
3b M = Ru^{II}, L$_1$ = PPh$_3$, L$_2$ = Cl, solid = USY
3c M = Co^{II}, L$_1$ = Acac, L$_2$ = Cl, solid = USY
3d M = Ni^{II}, L$_1$ = Acac, L$_2$ = Cl, solid = USY

The results of the heterogeneous and homogeneous hydrogenations are shown in Table 1. Though fair to good enantiomeric selectivities are obtained with the homogeneous catalysts (er = 80:20 to 93:7), in all cases the zeolite-bound catalyst outperformed the soluble amides (er = 87:13 to >99:1). Of special interest is the comparison of the reactions catalyzed by **3a** and **3a′**. Whereas the silica bound catalyst **3a′** affords the product in higher enantioselectivity than the homogeneous catalyst **2a**, it is still lower than that given by the zeolite catalyzed (**3a**) reactions (99:1 vs. 96:4 er). These results emphasize the role the defined micropores of the zeolite have in stereoselective induction of the catalyzed reaction.

Table 1. Comparison of the Asymmetric Hydrogenation of 5 with Homogeneous and Heterogeneous Catalysts.
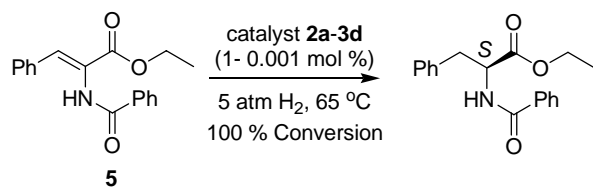
catalyst	support	Time, h	er (S:R)
2a	None	10	93:7
3a	USY	12	>99:1
3a′	Silica	16	96:4
2b	None	30	88:12
3b	USY	20	96:4
2c	None	52	80:20
3c	USY	48	87:13
2d	None	48	85:15
3d	USY	32	93:7

Other successful attempts have also been made using zeolite-supported enantioselective catalytic hydrogenation of alkenes. Rouzaud and coworkers reports the use of chiral bidentate ligands **6-9** incorporated into the mesoporous zeolite MCM-41 for the Rh(I)-catalyzed asymmetric hydrogenation of α-phenylcinnamic acid.[9,19] Both the covalent attachment of the ligands to the zeolite using a propylsilane linker as well as simple trapping of catalyst molecules in the cages of the zeolite give the reduced product in moderate yields and good stereoselectivities (er > 98:2; Table 2). Holderich also reported good stereoselectivity in the hydrogenation of alkenes using a Rh(I)-zeolite-anchored catalyst, obtaining a maximum of 94:6 er for the adsorbed *S,S*-Me-Duphos-catalyzed reduction of dimethyl itaconate (data not shown).[19] In all of the above hydrogenation systems the zeolite catalyst can be recovered and reused without significant loss of activity or stereoselectivity.

Table 2. Hydrogenation of (E)-2,3-Diphenylpropenoic Acid on MCM-41-Supported Chiral Bidentate Rh[I] Catalysts.
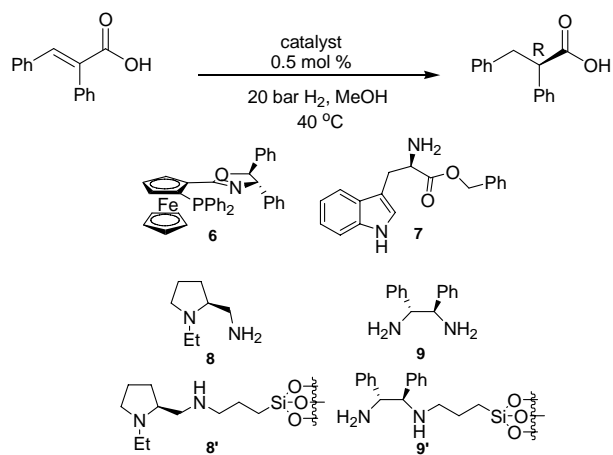
form of Rh[I] catalyst	ligand	conversion @ 24 h, %	selectivity, %	er (R:S)
homogeneous	**6**	65	70	87:13
	7	88	59	84:16
	8	86	84	92:8
	9	64	84	83:17
heterogeneous	**6**	79	64	97:3
	7	81	47	85:15
	8	90	84	99:1
	9	70	91	95:5
	8′	80	74	98:2
	9′	98	80	97:3

The transition metal-catalyzed hydrogenation of α-keto esters and acids as well as simple ketones has also been performed using heterogeneous zeolite-supported catalysts. Bohmer, et al.[14] used ion-exchange and reduction methods to modify NaY zeolites, producing zeolite-impregnated Pt(0)

catalysts. When the chiral modifier (–)-cinchonidine was added to the zeolite catalyst and the reduction of ethyl pyruvate was performed under hydrogen in acetic acid, (R)-(+)-ethyl lactate was formed with ers as high as 92:8. It is important to note that while the Pd-modified zeolite remains competent for subsequent reactions, the chiral modifier must be added prior to each cycle to retain high enantioselectivities.

A significant improvement on the Pt/cinchonidine method was reported by Ghosh and Kumar with the successful use of Ru(II)-zeolite catalysts bound to two different chiral ligands.[10] In this procedure, (S,S)-1,2-diphenylethylenediamine covalently bound to an MCM-41 or MCM-48 zeolite through a silicon tether is complexed with a Ru(II) chloride, which is subsequently chelated by a chiral (S)-BINAP ligand (Scheme 2). The resulting heterogeneous catalyst promotes the enantioselective hydrogenation of a variety of aliphatic and aromatic ketones to produce chiral secondary alcohols in good yields (75-99 %) and excellent stereoselectivities (er = 95:5 to >99:1; Table 3). The decrease in selectivity of catalyst **10b**, which lacks a chiral diamine ligand, suggests that both chiral elements are necessary for optimal enantioselectivity.

Scheme 2. Formation of Heterogeneous Ru(II) Catalysts with Two Chiral Ligands.
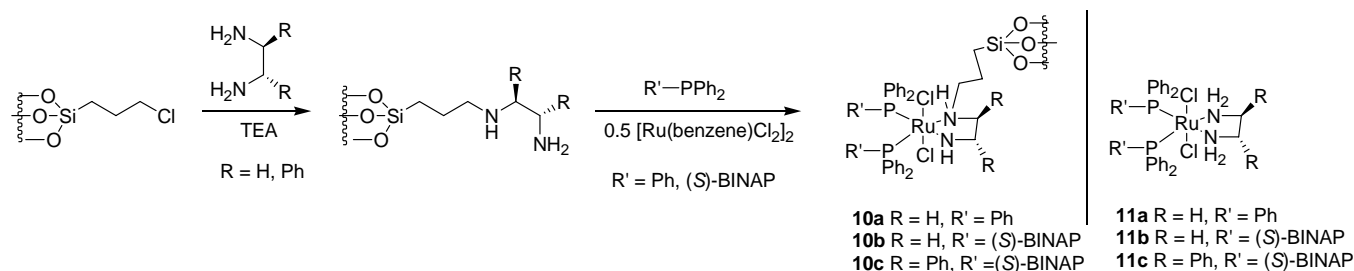

10a R = H, R' = Ph
10b R = H, R' = (S)-BINAP
10c R = Ph, R' =(S)-BINAP

11a R = H, R' = Ph
11b R = H, R' = (S)-BINAP
11c R = Ph, R' = (S)-BINAP

Table 3. Hydrogenation of Ketones Using Ru-MCM-48 Catalysts.

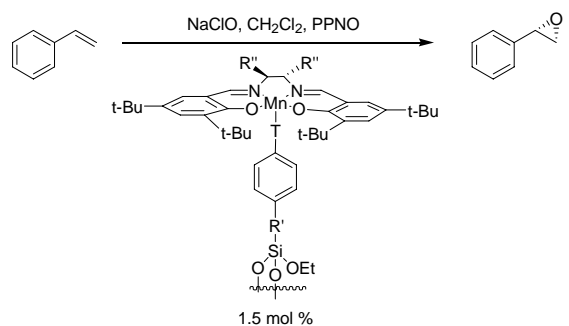| catalyst	ketone	conversion at 4 h, %	er (R:S)
10a	R^1 = Et, R^2 = Me	90	57:43
10b	R^1 = Et, R^2 = Me	94	65:35
10c	R^1 = Et, R^2 = Me	97	>99:1
11c	R^1 = Et, R^2 = Me	>99	>99:1
10c	R^1 = Cy, R^2 = Me	79	97:3
10c	R^1 = Ph, R^2 = Me	96	98:2
10c	R^1 = Ph, R^2 = Et	96	96:4
10c	R^1 = 4′-MeOPh, R^2 = Me	91	98:2
10c	R^1 = Ph, R^2 = Cy	79	96:4

Epoxidation and Aziridination

A number of Jacobsen's salen catalysts have been immobilized on zeolites and used for heterogeneous, catalytic, enantioselective epoxidation of alkenes. The most stereoselective catalyst for *trans*-alkenes is created by the sol-gel incorporation of the Jacobsen manganese salen complex, forming

a modified MCM-22 zeolite with the salen catalyst trapped in the zeolite pores.[23] This 'ship-in-a-bottle' catalyst selectively performs the epoxidation of α-methylstyrene with NaOCl as the oxidant in 85% yield and enantiomeric ratio of 96:4. This selectivity is impressive, especially when compared to the analogous homogeneous catalysis which produced the epoxide with an er of only 76:24.

Jacobsen's salen catalyst has also been used for asymmetric epoxidation as a covalently bound species incorporated into the zeolite through a phenoxide or phenyl sulfonate tether chelated to the Mn(II) center of the catalyst.[11-12] This approach allows for the study of various tether lengths as well as pore sizes of the microporous and mesoporous materials on the effect of enantioselectivity. In the case of the phenoxide-tethered catalysts, the heterogeneously catalyzed reactions produce ers that are similar or better than the homogeneous reactions for the majority of alkenes tested.[11] The phenyl sulfonate-tethered catalysts give similar results, while generally increasing the stereoselectivity of the reaction (Table 4).[12] The epoxidation studies with the sulfonate-tethered salen complexes also showed a slight increase of stereoselectivity when tether length is increased from one to five atoms and as the pore diameter decreased by permethylation of the free surface silanols. In the case of epoxidation of *cis*-β-methylstyrene, a significant reversal is observed from the preferential formation of the *trans* epoxide in homogeneous catalysis (*cis/trans* = 0.38-0.46) to the *cis* epoxide for the heterogeneous case (*cis/trans* = 4.2-21, er >95:5), with the effect becoming more pronounced as pore size of the support decreases.

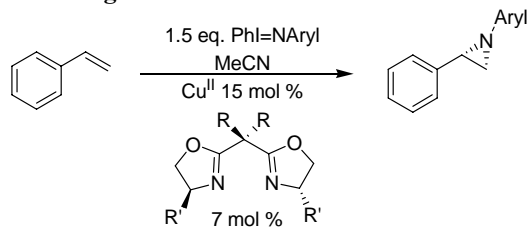**Table 4. Asymmetric Epoxidation Using Zeolite-Tethered Mn-Salen Catalysts.**

catalyst	pore size, nm	er (*S:R*)
T = O⁻, R' = none, R'' = –(CH$_2$)$_4$–	9.7 (SiO$_2$)	70:30
T = SO$_3$⁻, R' = none, R'' = Ph	9.7 (SiO$_2$)	74:26
T = SO$_3$⁻, R' = (CH$_2$)$_4$, R'' = Ph	9.7 (SiO$_2$)	79:21
T = SO$_3$⁻, R' = (CH$_2$)$_4$, R'' = Ph	1.6 (MCM-41)	70:30

Zeolite-based heterogeneous catalysts for the aziridination of alkenes have been extensively studied by Hutchings.[16-17] The heterogeneous catalyst is formed by ion exchange of NaY zeolite with Cu(OAc)$_2$. The CuY zeolite is then pre-mixed with a chiral bis(oxazoline) ligand in acetonitrile, followed by addition of a nitrene donor PhI=NNs or PhI=NTs and the alkene. The resulting aziridines are produced in moderate yields and enantiomeric ratios as summarized in Table 5.

Table 5. Asymmetric Aziridination Using Zeolite Y-Immobilized Cu^{II}-Bis(oxazoline) Catalysts. The Associated Homogeneous Results are in Parenthesis.

Bis(oxazoline)	Aryl = Ts		Aryl = Ns	
	yield, %	er (*R:S*)	yield, %	er (*R:S*)
R = H, R′ = Ph	78(91)	88:12(86:14)	78(96)	92:8(90:10)
R = H, R′ = t-Bu	58(78)	62:38(56:44)	68(79)	92:9(72:28)
R = H, R′ = Ph	70(14)	88:12(64:36)	80(85)	91:9(77:23)
R = H, R′ = t-Bu	28(8)	64:36(54:46)	72(42)	88:12(66:34)

Kinetic Resolution

The use of zeolite-catalyzed, enantioselective reactions has been expanded to kinetic resolution. The first reported case involves the use of chiral dithiane oxides adsorbed onto zeolite Y for the selective dehydration of racemic 2-butanol.[20-21] Although this reaction shows significant stereoselectivity (*R/S* = 1/39.3) at low conversion (9.9 %), as the reaction progresses, this selectivity is washed out. Much more promising results are obtained by Kim and Park using zeolite-catalyzed hydrolytic kinetic resolution of epoxides.[13] In this study, salen-Co(III) complexes based on a modified Jacobsen catalyst are immobilized on the surface of MCM-41 zeolite by the use of a siloxane tether linked to the meta position of one of the aromatic rings on the ligand. These heterogeneous catalysts show good enantioselective differentiation in the opening of both terminal and meso epoxides, as evidenced by both the yield and enantioselectivity of the associated chiral diols (for reactions of neat epoxides: yield = 29-42 % and er = 80:20 to 99:1).

Miscellaneous Reactions

A wide variety of other reactions has been performed using asymmetrically-modified zeolite catalysis with variable success. Some of the most interesting examples include the photoreductions described by Shailaha, et al.[24] and the highly selective carbonyl and imino-ene reactions reported by Caplan, et al.[27] Cyclopropanations,[26] Michael reactions,[27] dihydroxylations,[28] and Diels-Alder reactions have also been reported.[29]

CONCLUSIONS

Zeolites can be used as solid supports for a wide range of enantioselective organic transformations. Because of their crystalline, porous nature, zeolite-immobilized catalysts can enhance stereoselectivities of the corresponding homogeneous catalyst by the confinement effect associated with the inner cavities of the zeolite. They can also facilitate catalyst recovery and product purification. Nonetheless, in some cases a decrease in selectivity is observed for the zeolite-immobilized catalyst, most likely arising from size exclusion from the zeolite pores of the bulky chiral catalysts. Although this area of heterogeneous catalysis is promising, it has been explored only minimally, leaving significant room for further study. Especially promising is the development of catalysts that are

designed specifically for zeolite systems and not simply based on immobilization of current homogeneous catalysts.

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