# The Design and Synthesis of a True, Heterogeneous, Asymmetric Catalyst

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*To my mom and dad*

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**Abstract**

This work describes the design and synthesis of a true, heterogeneous, asymmetric catalyst. The catalyst consists of a thin film that resides on a high-surface-area hydrophilic solid and is composed of a chiral, hydrophilic organometallic complex dissolved in ethylene glycol. Reactions of prochiral organic reactants take place predominantly at the ethylene glycol-bulk organic interface.

The synthesis of this new heterogeneous catalyst is accomplished in a series of designed steps. A novel, water-soluble, tetrasulfonated 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP-4$SO_3Na$) is synthesized by direct sulfonation of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). The rhodium (I) complex of BINAP-4$SO_3Na$ is prepared and is shown to be the first homogeneous catalyst to perform asymmetric reductions of prochiral 2-acetamidoacrylic acids in neat water with enantioselectivities as high as those obtained in non-aqueous solvents. The ruthenium (II) complex, [Ru(BINAP-4$SO_3Na$)(benzene)Cl]Cl is also synthesized and exhibits a broader substrate specificity as well as higher enantioselectivities for the homogeneous asymmetric reduction of prochiral 2-acylamino acid precursors in water. Aquation of the ruthenium-chloro bond in water is found to be detrimental to the enantioselectivity with some substrates. Replacement of water by ethylene glycol results in the same high e.e's as those found in neat methanol. The ruthenium complex is impregnated onto a controlled pore-size glass CPG-240

by the incipient wetness technique. Anhydrous ethylene glycol is used as the immobilizing agent in this heterogeneous catalyst, and a non-polar 1:1 mixture of chloroform and cyclohexane is employed as the organic phase.

Asymmetric reduction of 2-(6'-methoxy-2'-naphthyl)acrylic acid to the non-steroidal anti-inflammatory agent, naproxen, is accomplished with this heterogeneous catalyst at a third of the rate observed in homogeneous solution with an e.e. of 96% at a reaction temperature of 3°C and 1,400 psig of hydrogen. No leaching of the ruthenium complex into the bulk organic phase is found at a detection limit of 32 ppb. Recycling of the catalyst is possible without any loss in enantioselectivity. Long-term stability of this new heterogeneous catalyst is proven by a self-assembly test. That is, under the reaction conditions, the individual components of the present catalytic system self-assemble into the supported-catalyst configuration.

The strategies outlined here for the design and synthesis of this new heterogeneous catalyst are general, and can hopefully be applied to the development of other heterogeneous, asymmetric catalysts.

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# CHAPTER ONE

## Introduction and Objectives

## INTRODUCTION

Organic synthesis involves the ability to direct a reaction strictly along a single desired chemical channel (chemoselectivity) and to dictate a specific point of attack by the reagent (regioselectivity) under conditions as mild as possible. In asymmetric synthesis, apart from the solution to these problems, the reaction must be directed toward the formation of one specific absolute configuration.

Living organisms are naturally chiral and so their biochemical metabolisms are subjected to the effects of chirality. Their chiral enzymes and receptors can interact in different ways with the two enantiomeric forms of a biologically active substrate - this applies to drugs and food additives, to pheromones, and to insecticides. The difference in the acceptance of the stereoisomeric forms of bioactive compounds into the body can be extremely substantial, and consequences of such differences are not always harmless (*1-3*).

The enantiomers of an bioactive compound introduced into the organism can show their effects at various stages and in various forms: during transport and absorption processes in cells; during the binding of inhibitors to enzymes and of agonists or antagonists to receptors; during distribution between various tissues. Stereoselectivity in the biochemistry of metabolism can show up both in the rates and the directions of biotransformation (*4,5*).

They are attributed to the stereospecific interactions of living organism with pharmaceutical products and food and flavor additives, and of plants and insects with various agents used for the protection of plants. Thus, for example, the difference in the binding of the two enantiomers or diastereomers with the respective receptors amounts to 1,000-fold in the case of beta blockers (*6*) and increases to 10,000-fold in the interaction between anticholinesteric products and muscarine receptors (*7,8*). During the *in vivo* metabolism, the (R)-enantiomer of ibuprofen (the well-known non-steroidal anti-inflammatory product of the "profen" group (*9*)) isomerizes to the (S)-form, whereas such transformations do not occur with the (S)-enantiomer (*10*). Only the (R)-enantiomer of nicotine undergoes metabolic N-methylation under the influence of the respective enzyme, and (S)-nicotine, while not participating in such a process itself, greatly inhibits the reaction for the (R)-form (*4*).

With pharmaceutical products, one enantiomer (eutomer) can have a substantially stronger therapeutic effect than the other less active enantiomer (distomer); in the extreme case of complete inactivity can be regarded as a contaminant in the drugs (*11*). Thus, for example, the activity of most "profens" lies in the (S)-enantiomers, and the ratio of the activity of the eutomer and distomer *in vitro* amounts to 878 in the case of flurbiprofen (*10,12-13*). Only the (+)-form of estrone gives a hormonal effect, whereas the (-)-form does not exhibit any hormonal activity (*1*). It is therefore obvious that the use of such products in the enantiomerically pure form can reduce the dose and, consequently, the stress on the organism. Sometimes, the two

stereoisomers of the same drug can have qualitatively different therapeutic effects. For instance, the (2R,3S)-isomer of propoxifen is used under the name "Darvon" as an analgesic product, whereas the (2S,3R)-enantiomer of the same compound is known as the anticough drug "Norvad" (*12*). The intake of a racemic drug with two different therapeutic effects is of course rarely desirable. In the extreme case that the distomer inhibits the action of the eutomer, the admission of the enantiomerically pure form greatly improves its therapeutic effect.

The strongest argument in favor of the use of enantiomerically pure drugs is the stereoselectivity found in the toxicological effects. There are a number of barbiturates where only one enantiomer exhibits a narcotic effect whereas the other enantiomer causes rise to convulsions (*1*). Of the two enantiomers of penicillamine only one has a useful antiarthritic effect, while the other one is highly toxic (*14*). The tragic story of the use of racemic thalidomide in therapeutic practice is well known. Here only the (-)-form is a powerful tranquillizer, whereas the (+)-form causes strong teratogenic effects (*15,16*). This last example has perhaps been the most menacing warning about the dangers of neglecting the stereochemistry in the therapeutic practice of pharmaceutical drugs.

Stereochemistry also plays an important in perfumery and food industry. It is known that one of the enantiomers of limonene has a lemon flavor while the other has an orange flavor; one of the stereoisomeric carvones smells of caraway while the other smells of menthol oil (*14*). There can also be

substantial differences in the taste perception and metabolism of the enantiomeric forms. For instance, (-)-asparagine has a bitter taste, while the (+)-isomer is sweet; the lysine used as an additive in certain animal foods is only assimilated in the (-)-isomer (*1*). Both the enantiomers of saccharose are perceived as identically sweet, but only the (+)-isomer is assimilated. Thus, the (-)-isomer can be used for dietary purposes (*14*).

Large quantities of bioactive chemical agents are used for the protection of plants (*17*). Herbicides and fungicides are used to suppress the growth of weeds and fungal diseases; plant hormones (*18*) regulate the growth and development of plants; insecticides and pheromones help control the population of insects (*19*). However, issues that involve the conservation of ecology requires their uses in maximum effectiveness with minimum strain on the environment (*20-22*). The interaction between the chemical agents used for the protection of plants and the living organism is the same as in the pharmaceutical products mentioned above. Cases where the active agent is concentrated predominantly in one of the stereoisomers are not uncommon. Thus, for example, the activity of herbicides of the phenoxypropionic acid type is due almost exclusively to the (+)-forms (*19,23*); as a rule herbicides that operate by the inhibition of photosynthesis is more active in the (S)-form (*24*). The biochemical and toxicological characteristics of organophosphorus pesticides, herbicides, and plant growth regulators vary by three to five orders of magnitude, depending on the absolute configuration of the phosphorus atom (*25-27*). The use of such products in the enantiomerically pure form

makes it possible to reduce the dose by half, and consequently, to reduce the strain on the environment.

Finally, there are situations where both stereoisomers of the same agrochemical agent have fundamentally different types of activity. The product paclobutrazole in the (2R,3R) configuration has high fungicidal activity, while its (2S, 3S)-enantiomer is a powerful herbicide (*12*); it is clear that if the protective function of the product is required, the herbicidal activity is extremely undesirable. Similar dualism is found in one of the acylalanine products CGA 29212; its (R)-form is proved to an excellent fungicide, whereas the (S)-form has strong herbicidal activity and has almost no fungicidal activity (*28*).

These examples show that change in the absolute configuration of the same functional groups in the molecule can have just as significant consequences as a change in the chemical nature of the groups. The two stereoisomers must therefore be treated as two different chemical substances when assessing their biological activity. Consequently, a pharmaceutical product marketed in the racemic form must be regarded as a mixture of two compounds or as a drug contaminated to the extent of 50% (*3,11*).

Before 1982, of all the synthetic pharmaceutical products, 40% were chiral compounds; and of these only 12% were produced in the optically pure form (*12,29*). By 1987 the proportion of enantiomerically pure synthetic drugs has increased to 26% (*30,31*); it is presumed that toward the end of the century

up to 80% of chiral synthetic drugs will be produced in the optically pure form (*30,32*). However, today more than 500 synthetic chiral drugs are marketed in the racemic form (*33*).

It is likely that in the near future most countries will adopt legal standards regulating the conditions for the production of drugs containing stereogenic centers. The Food & Drug Administration has already requested that new drug applications provide selected information on individual isomers in a mix.

The traditional multi-step synthesis of a racemic mixture followed by resolution has been widely used for obtaining single enantiomers from a racemate. Classical resolution uses a second optically pure resolving agent to form diastereoisomeric salts. These diastereoisomeric derivatives, which differ in energy and physical properties, are then separated by crystallization. This method is unavoidably laborious, may introduce toxic impurities into pharmaceuticals and does not work for all chiral compounds. The diastereomeric interactions that make classical resolution possible are also exploited in chiral chromatography columns where the stationary phase contains an optically pure molecule that interacts differently with each of the components of a racemate. Though this technique is well suited to analytical separations, it is very difficult and expensive to scale up for large batches of synthetic drugs. Because of the high cost associated with the resolution process (low yields per cycle (<50%), and requires recycling of large amounts of resolving agents as well as the racemization of the unwanted enantiomer)

simple and economical processes for the direct production of pure enantiomers are highly desirable.

Of all the possible methods for creating optically active molecules (chemical or enzymatic separation of racemates, transformation of natural chiral compounds, asymmetric synthesis from prochiral substrates, chemo- or biocatalytic synthesis), homogeneous, enantioselective catalysis by metal complexes is one of the most versatile and effective methodologies for asymmetric synthesis. Metal complexes with chiral organic ligands have been shown to act catalytically and multiply chirality (*34*). These organometallic catalysts are neither symmetrical or flat, but they are endowed with functionality and chirality which allow differentiation of diastereomeric transition states with accuracy of 10 kJ/mol. Such molecular catalysts not only accelerate reactions of associated substrates, but they also control the stereochemical outcome of reactions in an absolute sense. The advantages of this type of catalyst when compared to catalysis by optically active organic compounds and enzymatic catalysis is the great flexibility of the metal complex catalysts. Both the chiral ligand and the metal center can be varied for different organic transformations.

The first catalytic, asymmetric reaction of prochiral compounds mediated by soluble chiral metal complexes was reported in 1966 (*35*). A chiral Schiff base-Cu (II) complex was found to catalyze the enantioselective carbenoid reaction between styrene and ethyl diazoacetate to give *cis*- and *trans*-2-phenylcyclopropanecarboxylates in <10% enantiomeric excess (e.e.).

Since then, homogeneous, enantioselective metal complex catalysis has achieved truly remarkable results over the short history of its development. More recent advances have generated a number of impressive homogeneous catalysts that have greatly raised the potential of chemical synthesis for bioactive substances. Enantioselectivities of over 95% e.e.'s are not uncommon. Large amounts of chiral compounds can now be produced that have natural and unnatural configurations with the use of only a very small quantity of a selected chiral source.

It has been recognized for quite some time that one of the shortcomings of homogeneous catalysis is the obvious need for separating the catalyst from the product phase. The processes necessary to achieve the desired separation usually include thermal operations such as distillations, and these operations normally lead to thermal stresses on the catalyst. During the separation, the treatments can cause decomposition reactions and progressive deactivation during the lifetime of the catalyst. Furthermore, thermal separation processes seldom give quantitative recovery of the catalyst.

Some progress has been made in the synthesis of asymmetric, heterogeneous catalysts, but to the author's knowledge not a single commercial chiral synthesis is achieved by a heterogeneous catalyst. One approach to the preparation of heterogeneous catalysts involves attachment of a homogeneous catalyst onto a suitable support. Cation-exchange resins and polymers are among the most widely used supports (*36-41*). In general, the immobilized catalysts never approach the combined

activity/enantioselectivity performance levels of their homogeneous counterparts and tend not to retain the metal complexes for significant lengths of time (*42*). A second way of solving the problem of separating the product and the catalyst involves modifying the latter with suitable hydrophilic groups, e.g., sulfonate or quaternary ammonium, that make it possible to transfer the catalyst into the aqueous phase, leaving the product in the organic phase, i.e., two-phase system (*43-45*). Product separation is simpler for two-phase systems incorporating water-soluble catalysts. The hydrophilic catalyst, which is insoluble in the organic-phase is molecularly well defined like conventional homogeneous catalysts. These catalysts accomplish the asymmetric catalytic reaction in the aqueous-phase or at the phase boundary, and are removed from the desired product at the end of the reaction by a simple phase separation. Thermal separation processes, which can have detrimental effects on the active lifetime of the catalyst, are thereby avoided. Because of the high polarity of the water-soluble catalyst and its insolubility in the organic phase, leaching of the water-soluble catalyst into the organic-phase is often below the detection limit. Unfortunately, the reaction rates achievable with two-phase systems are strongly dependent on the polarity of the substrate and/or the limiting interfacial area between the two phases. In general, the reaction activities are orders of magnitude less active than the homogeneous catalysts (*48*). However, it is the poor enantioselectivity that really hinders the application of two-phase systems in asymmetric catalysis. Usually, poor enantioselectivities are found in aqueous media (*47,49-53*). Hence, new genuine heterogeneous, asymmetric catalysts have yet to be developed for practical asymmetric synthesis of optically pure compounds.

## OBJECTIVES

The objective of this research is to develop a heterogeneous, asymmetric, hydrogenation catalyst. The criteria for a successful heterogeneous asymmetric catalyst are that the catalyst has high activity and enantioselectivity without leaching of the active material into the product phase. Using these targets, we set out to design a true, heterogeneous, asymmetric catalyst. We began by using the concept of supported aqueous-phase catalysis (SAPC) (*54*). The reasons for choosing this starting point for the design are that SAPC has been proven to provide very active and selective heterogeneous analogues to known homogeneous catalysts (*55-57*). These catalysts are designed to facilitate chemical reactions at the interface of two immiscible liquids. They consist of a very water-soluble organometallic complex dissolved in a film of water which is supported on a high-surface-area hydrophilic solid. Reactions of liquid-phase organic reactants take place at the water-organic interface (Figure 1.1). Immobilization of the catalyst is accomplished through the use of a highly water-soluble ligand.

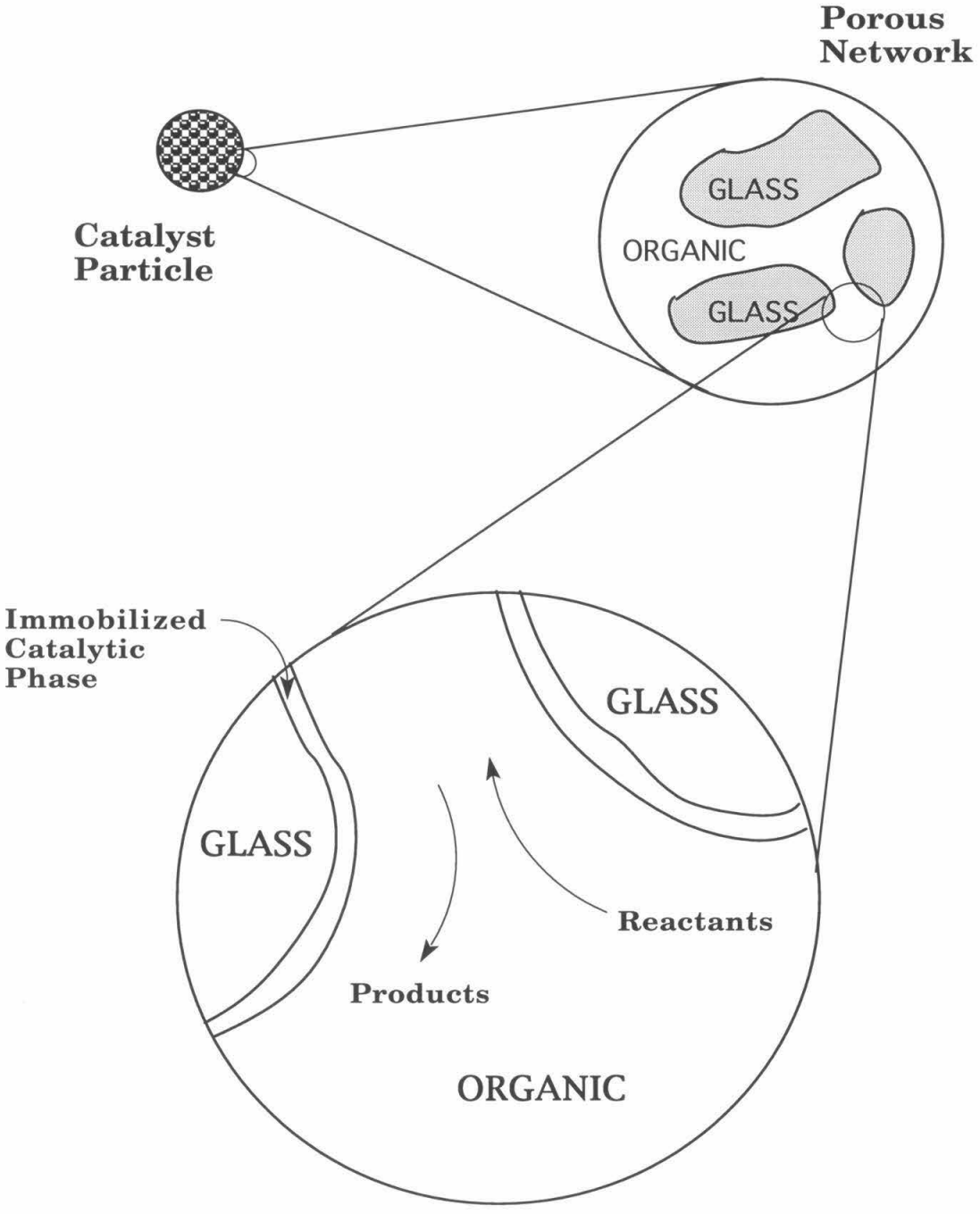
The first stage of this work involved the synthesis of a highly water-soluble, chiral diphosphine ligand. Because of the wide range of highly enantioselective reactions that have been achieved using organometallic catalysts with the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ligand (BINAP) (*58,59*), BINAP was chosen as the model chiral diphosphine for water-

solubilization. The development of the novel, heterogeneous, asymmetric, hydrogenation catalyst was divided into five stages,

I. Synthesis of a water-soluble sulfonated-BINAP ligand (*60*).
II. Homogeneous, asymmetric catalytic studies with a rhodium sulfonated-BINAP complex (*60*).
III. Homogeneous, asymmetric catalytic studies with ruthenium sulfonated-BINAP complexes (*61*).
IV. Development of a supported aqueous-phase asymmetric catalyst using the ruthenium catalyst for the asymmetric synthesis of naproxen (*62*).
V. Development of a new heterogeneous, asymmetric catalyst for the asymmetric synthesis of naproxen (*63*).

Stages I and II are described in chapter two, while stages III, IV and V are described in chapters three, four and five, respectively.

Figure 1.1. Schematic diagram of supported aqueous-phase catalysis.



**REFERENCES**


1. Brunner, H., *J. Organometal. Chem.* **300**, No. 1/2, 39 (1986).
2. Kagan, H.B., *Bull. Soc. Chim.* No. 5, 846 (1988).
3. Deutsch, D.H., *Chemtech* **21**, No. 3, 157 (1991).
4. Testa, B., *Biochem. Pharm.* **37**, No. 1, 85 (1988).
5. Eichelbaum, M., *Biochem. Pharm.* **37**, No. 1, 93 (1988).
6. Walle, T., Webb, J.G., Bagwell, E.E., *Biochem. Pharm.* **37**, No. 1, 115 (1988).
7. Laduron, E.M., *Biochem. Pharm.* **37**, No. 1, 37 (1988).
8. Lambrecht, G., Feifel, R., and Mutschler, E., *Chirality* **1**, No. 2, 170 (1989).
9. Lombardino, J.G., *Nonsteroidal Antiinflammatory Drugs* in "Chemistry and Pharmacology of Drugs" (Lombardino, J.G. Ed.), Wiley-Interscience, New York, Singapore, Vol. 5, 253 (1985).
10. Caldwell, J., Hutt, A.J., and Fournel-Gigleux, S., *Biochem. Pharm.* **37**, No. 1, 105 (1988).
11. Laird, T., *Chem. Ind.* No. 13, 418 (1990).
12. Ariens, E.J., Wuis, E.W., and Veringa, E.J., *Biochem. Pharm.* **37**, No. 1, 9 (1988).
13. De Camp, W.H., *Chirality* **1**, No. 1, 2 (1989).
14. Brown, J.M., Fleet, G.W.J., Davies, S.G., and Pratt, A.J., *Chem. Brit.* **25**, No. 3, 259 (1989).
15. Brown, J.M., and Davies, S.G., *Nature* **342**, No. 6250, 631 (1989).

16. Coutts, R.T., and Baker, G.B., *Chirality* **1**, No. 2, 99 (1989).

17. Kelly, D.R., *Chem. Brit.* **26**, No. 2, 124 (1990).

18. Henrick, C.A., and Staal, G.B., *Stereoselectivity of Pesticides* **1**, 303 (1988).

19. Naber, J.D., and Van Rensen, J.J.S., *Stereoselectivity of Pesticides* **1**, 263 (1988).

20. Mel'nikov, N.N., *Usp. Khim.* **60**, No. 3, 545 (1991).

21. Kamernitskii, A.V., and Reshetova, I.G., *Usp. Khim.* **60**, No. 3, 552 (1991).

22. Kartsev, V.G., *Usp. Khim.* **60**, No. 3, 553 (1991).

23. Muller, M.D., Wacker, R., and Bosshardt, H.P., *Chimia* **45**, No. 5, 160 (1991).

24. Phillips, J.N., *Stereoselectivity of Pesticides* **1**, 183 (1988).

25. Van der Goot, H. and Timmerman, H., *Stereoselectivity of Pesticides* **1**, 11 (1988).

26. De Jong, L.P.A., and Benschop, H.P., *Stereoselectivity of Pesticides* **1**, 109 (1988).

27. Feringa, B.L., *Stereoselectivity of Pesticides* **1**, 453 (1988).

28. Fuchs, A., *Stereoselectivity of Pesticides* **1**, 203 (1988).

29. Ariens, E.J., *Stereoselectivity of Pesticides* **1**, 39 (1988).

30. Botteghi, C., Paganelli, S., Schionato, A., and Marchetti, *Chirality* **3**, No. 4, 355 (1991).

31. Shindo, H. and Caldwell, J., *Chirality* **3**, No. 2, 91 (1991).

32. Laird, T., *Chem. Ind.* No. 12, 366 (1989).

33. Cayen, M.M., *Chirality* **3**, No. 2, 94 (1991).

34. Noyori, R., and Kitamura, M., *in* "Modern Synthetic Methods" (Scheffold, R. Ed.) Springer-Verlag, Berlin, pp. 115-198 (1989).

35. Nozaki, H., Moriuti, S., Takaya, H., and Noyori, R., *Tetrahedron Lett.* 5239 (1966).

36. Hartley, F.R., *in* "Supported Metal Complexes" (Ugo, R. and James, B.R., Eds.) Reidel, New York, 1985.

37. Pittman, C.U., and Evans, G.O., *Chemtech* 560 (1973).

38. Manassen, J., *in* "Catalysis Progress In Research" (Basolo, F., and Burwell, R.L., Jr., Eds.) Plenum Press, New York, N.Y., pp. 117 (1973).

39. Bailar, J.C., *Catal. Rev.* **10**, 17 (1974).

40. Leznoff, C., *Chem. Soc. Rev.* **3**, 65 (1974).

41. Manassen, J., *in* "Catalysis, Heterogeneous and Homogeneous" (Delmon, B., and Jannes, G., Eds.) American Elsevier, New York, N.Y., pp. 293 (1975).

42. Dumont, W., Poulin, J.C., Dang, T.P., and Kagan, H.B., *J. Am. Chem. Soc.* **95**, 8295 (1973).

43. Joo, F., and Toth, Z., *J. Mol. Catal.* **8**, 369 (1980).

44. Sinou, D., *Bull. Soc. Chim. Fr.* 480 (1987).

45. Kalck, P., and Monteil, F., *Adv. Organomet. Chem.* **34**, 219 (1992).

46. Toth, I., Hanson, B.E., and Davis, M.E., *Catal. Lett.* 183 (1990).

47. Toth, I., Hanson, B.E., and Davis, M.E., *Tetrahedron: Asymmetry* **1**, 913 (1990).

48. Herrmann, W.A., Kohlpaintner, C.W., Bahrmann, H., and Konkol, W., *J. Mol. Catal.* **73**, 191 (1992).

49. Amrani, Y., and Sinou, D., *J. Mol. Catal.* **24**, 231 (1984).

50. Sinou, D., and Amrani, Y., *J. Mol. Catal.* **36**, 319 (1986).

51. Benhanza, R., Amrani, Y., and Sinou, D., *J. Organomet. Chem.* **288**, C37 (1985).

52. Lecomte, L., and Sinou, D., *J. Organomet. Chem.* **370**, 277 (1988).

53. Oehme, G., Paetzold, E., and Selke, R., *J. Mol. Catal.* **71**, L1 (1992).

54. Arhancet, J.P., Davis, M.E., Merola, J.S., and Hanson, B.E., *Nature* **339**, 454 (1989).

55. Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **121**, 327 (1990).

56. Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **129**, 94 (1991).

57. Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **129**, 100 (1991).

58. Miyashita, A., Yasduda, A., Takaya, H., Toriumi, K., Itok, T., Souchi, T., and Noyori, R., *J. Am. Chem. Soc.* **102**, 7932 (1980).

59. Miyashita, A., Takaya, H., Souchi, T., and Noyori, R., *Tetrahedron* **40**, 1245 (1984).

60. Wan, K.T., and Davis, M.E., *J.C.S., Chem. Commun.* 1262 (1993).

61. Wan, K.T., and Davis, M.E., *Tetrahedron: Asymmetry* **4**, 2461 (1993).

62. Wan, K.T., and Davis, M.E., *J. Catal.* 1994, in press.

63. Wan, K.T., and Davis, M.E., submitted to *Nature*, 1994.

# CHAPTER TWO

## Asymmetric Hydrogenation in Water by a Rhodium Complex of Sulfonated-BINAP

[Wan, K.T., and Davis, M.E., J. Chem. Soc., Chem. Commun. 1262, 1993]

**Abstract:**

The synthesis of sulfonated 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) is reported; a rhodium complex of this ligand is the first to perform asymmetric hydrogenation in neat water with optical yields as high as those obtained in non-aqueous solvent.

There is an increasing interest in the synthesis and application of water-soluble organometallic catalysts (*1*). The water solubilization of known organometallic catalysts is typically performed by incorporating highly polar functional groups such as amino, carboxylic acid, hydroxide or sulfonate into phosphine ligands (*1*). In addition to the advantages of being able to use an environmentally benign solvent, water-soluble complexes can be employed in various configurations, e.g., organic-aqueous two-phase (*1c,2*), supported aqueous-phase (*3*), in order to achieve effective catalyst immobilization. Here, we report the synthesis of a new water-soluble ligand, sulfonated 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (*4*) and its use in the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins.

The sulfonation of (R)-BINAP requires specific reaction conditions to eliminate the formation of phosphine oxides and to achieve a high yield of a single phosphine species. The sulfonation of (R)-BINAP was accomplished by dissolving (R)-BINAP (1g) in concentrated sulfuric acid (3.5 ml) with subsequent dropwise addition of 15 ml (during 2-3 hours) of fuming sulfuric acid (40 wt% sulfur trioxide in concentrated sulfuric acid) and stirring for 3 days at 10°C under argon. The reaction was quenched by pouring the solution into 100 ml of ice-cooled water and the product neutralized by dropwise addition of aqueous sodium hydroxide (50 wt% NaOH) until a pH 7 was reached. The volume of the solution was reduced to 30 ml *in vacuo* and methanol (100 ml) added to precipitate any sodium sulfate present. Sulfonated-BINAP was recovered as solid by vacuum drying the filtered methanolic solution. The product was then purified by re-dissolving in neat

methanol, filtered and vacuum dried. Elemental analysis (Galbraith Lab., Knoxville, TN) of the recovered solid is consistent with the sample containing about 85% tetrasulfonated BINAP [calculated for BINAP-4$SO_3Na$ : S/P: Na/P:C/Na = 2:2:11; found, S/P: Na/P:C/Na = 2.34/2.02/11.31]. This result is in agreement with the $^{31}P$ NMR spectrum that shows a single major resonance at $\delta \approx -11.1$ with a second small peak around $\delta = -12.7$ (relative intensities are 86:14). The $^{33}S$ NMR spectrum of the oxidized form of this sample (in $D_2O$) indicates that no sodium sulfate is present, to at least the detection limits of NMR (150,000 scans employed) and that no further information on the sample composition is possible because the sulfonate groups on the BINAP give a broad peak around $\delta = -13$ (relative to ammonium sulfate). Because of the difference in $\pi$-stabilization energy, the phenyl rings in BINAP are relatively more reactive towards electrophilic aromatic substitution by sulfur trioxide as compared to the naphthyl rings. Thus, we speculate that in the major species obtained, only the four phenyl rings in the BINAP are sulfonated under the conditions described above. Otherwise, at least two distinct signals with equal intensities should appear in the $^{31}P$ NMR spectrum. Although definitive assignments are not yet possible owing to the complexity of the $^{1}H$ and $^{13}C$ NMR spectra, our NMR data are consistent with the premise that only the four phenyl rings are sulfonated in the major species obtained in 85% abundance. The remaining species is likely to be penta- or hexa-sulfonated BINAP with one or two extra sulfonated group(s) on the naphthyl ring(s). As the origin of chiral recognition is attributed to the interaction of the four phenyl rings and the substrate, the presence of any extra sulfonated groups on the naphthyl rings is unlikely to

affect the enantioselectivity. In fact, similar activity and selectivity are found with catalysts prepared from several batches of ligand with different ratios of major to minor species (*vide infra*).

The rhodium sulfonated-BINAP catalyst was prepared as follows. $[Rh(cod)Cl]_2$ (cod = cycloocta-1,5-diene) was treated with 2 equiv. of BINAP-$4SO_3Na$ in water at room temperature with an excess of sodium perchlorate. The cationic species, $[Rh(BINAP\text{-}4SO_3Na)(cod)](ClO_4)$, is formed and contacted with one atmosphere of dihydrogen to give the active catalyst $[Rh(BINAP\text{-}4SO_3Na)(H_2O)_2]^+$. Further addition of 2 equiv. of BINAP-$4SO_3Na$ or initial mixing of 4 equiv. with $[Rh(cod)Cl]_2$ gives the inactive complex $[Rh(BINAP\text{-}4SO_3Na)_2]^+$. Assignments of these species are based on the data in Table 2.1.

Asymmetric hydrogenations of 2-acetamidoacrylic acid (substrate **1**) and its methyl ester (substrate **2**) were conducted at room temperature and one atmosphere of dihydrogen in batch autoclaves. The conversion was measured by $^1H$ NMR spectroscopy and the enantiomeric excess (e.e.) determined by gas chromatography using a J. & W. Scientific CDX-B chiral capillary column after derivatization of the reaction products (*6*).

Table 2.2 shows the results of hydrogenating 2-acetamidoacrylic acid and its methyl ester using the water-soluble rhodium complex with BINAP-$4SO_3Na$. Like the non-sulfonated version of the rhodium BINAP catalyst, the enantioselection favors the (S)-enantiomers (*4b*). However, we do not observe

a dependence of e.e.'s on the concentration of substrate as is reported for the non-sulfonated rhodium-BINAP catalyst (*4b*). The e.e. is found to be 58±1% for substrate **1** in MeOH solvent over a substrate concentration range of 0.003-0.078 M, 49±2% for substrate **2** in MeOH solvent over a substrate concentration range of 0.007-0.134 M and 68±1% for substrate **2** in $H_2O$ solvent over a substrate concentration range of 0.007-0.039 M. Note that the results in Table 2.2 illustrate that the e.e. in pure water is approximately the same as observed with the non-sulfonated rhodium-BINAP catalyst in ethanol (70.4-68.0% *vs.* 67.0% (*4b*)). This is the first example of asymmetric hydrogenation in neat water where the optical yield obtained is as high as that observed in non-aqueous solvents. Normally, large losses in enantioselectivity are observed when water is used as solvent (*2b,8*). Additionally, loss in enantioselectivity is also reported with sulfonation of phosphine ligands (*8a,d*). Here, not only are high enantioselectivities retained upon sulfonation and uses in neat water, the e.e.'s obtained with the rhodium sulfonated-BINAP catalyst increases with the proportion of water in the solvent; the e.e. is 70.4% in pure water compared to 58.0% in neat methanol. The trend observed with 2-acetamidoacrylic acid (substrate **1**) is also found with methyl-2-acetamidoacrylate (substrate **2**).

We attempted a comparison between the hydrogenation behavior of non-sulfonated and sulfonated-BINAP rhodium complexes in ethanol. A direct comparison between these two complexes is not possible in water because non-sulfonated BINAP is not soluble in water. Also, the non-sulfonated complexes prepared here or purchased from Aldrich gave very

low e.e.'s under one atmosphere of dihydrogen pressure as compared with that reported under four atmospheres (*4b*). Because of this, we are only able to compare initial turnover frequencies in water and ethanol for the sulfonated-BINAP catalyst (Table 2.2). The activity of the rhodium sulfonated-BINAP catalyst in neat water (45 $hr^{-1}$) is only 6 to 7 times less active than that in neat ethanol (302 $hr^{-1}$). The solubility of dihydrogen in ethanol and water at 25°C at 1 atm is $38.2x10^{-4}$ and $8.53x10^{-4}$ mol/l, respectively (*9*).Thus, the loss in initial turnover frequency when water is used as solvent is most likely due to the lowering of the dihydrogen solubility. The cause of the low e.e. in the non-sulfonated system is unclear but catalyst decomposition is likely since a black precipitate appeared during the course of one of the reactions.

Table 2.1 $^{31}P$ NMR data for various ligands and rhodium complexes

| Compound | Solvent | δ (ppm)[a] | $^{1}J_{Rh-P}$/Hz |
|---|---|---|---|
| BINAP-4$SO_3Na$ ($L^1$) | $D_2O$ | -11.0 (s) | -- |
| [Rh($L^1$)(cod)]$ClO_4$ | $D_2O$ | 31.0 (d) | 144 |
| [Rh($L^1$)($D_2O$)$_2$]$ClO_4$ | $D_2O$ | 51.0 (d) | 196 |
| (S)-BINAP ($L^2$) | $C_6D_6$-$CD_3OD$ (4:1) | -12.8 (s) | -- # |
| [Rh($L^2$)(nbd)]$ClO_4$[b] | $CD_3OD$ | 25.1 (d) | 156# |
| [Rh($L^2$)(MeOH)$_2$]$ClO_4$ | $CD_3OD$ | 53.1 (d) | 206# |
| (S,S)-Cyclobutanediop-4$SO_3Na$ ($L^3$)[c] | $D_2O$ | -20.2 (s) | -- ‡ |
| [Rh(cod)Cl]$_2$ + ($L^3$) | $D_2O$ | 20.2 (d) | 144‡ |
| [Rh($L^3$)($H_2O$)$_2$]$^+$ | $D_2O$ | 43.5 (d) | 182‡ |
| (S,S)-BDPP-4$SO_3Na$ ($L^4$)[d] | $D_2O$ | 0.7 (s) | -- ‡ |
| [Rh(cod)Cl]$_2$ + $L^4$ | $D_2O$ | 29.3 (d) | 144‡ |
| [Rh($L^4$)($H_2O$)$_2$]$^+$ | $D_2O$ | 53.2 (d) | 185‡ |

a: $^{31}P$ NMR chemical shifts relative to $H_3PO_4$; downfield shifts are positive.

b: nbd = norbornadiene.

c: (S,S)-Cyclobutanediop = (S,S)-1,2-bis(diphenylphosphinomethyl)-cyclobutane.

d: BDPP = bis(2-diphenylphosphinoethyl)(phenyl)phosphine.

#: ref. 4(b)

‡: ref. 5

Table 2.2 Hydrogenation of 2-acetamidoacrylic acids at room temperature under 1 atm $H_2$

| Substrate[a] | Solvent | [Substrate]/ mol $l^{-1}$ | Substrate/ catalyst | e.e. (%)[b] |
|---|---|---|---|---|
| **1** | $H_2O$ | 0.007 | 25 | 70.4, 68.0 |
| **1** | 7:1 $H_2O$/MeOH | 0.017 | 40 | 67.0 |
| **1** | 1:1 $H_2O$/MeOH | 0.017 | 41 | 56.0 |
| **1** | 1:2 $H_2O$/MeOH | 0.042 | 75 | 55.0 |
| **1** | MeOH | 0.017 | 40 | 58.0 |
| **1** | EtOH | 0.017 | 41 | 58.6 |
| **1** | EtOH | 0.031 | 76 | 35.0[e,f](264)[d] |
| **1** | 1:1 EtOH/THF | -- | 100 | 67.0[g] |
| **2** | $H_2O$ | 0.017 | 75 | 68.5, 68.3[c] |
| **2** | $H_2O$ | 0.039 | 76 | 69.0(41)[d] |
| **2** | $H_2O$ | 0.039 | 76 | 68.0[c](45)[d] |
| **2** | 4:1 $H_2O$/MeOH | 0.017 | 76 | 61.2 |
| **2** | MeOH | 0.017 | 75 | 47.8 |
| **2** | EtOH | 0.031 | 75 | 56.0(302)[d] |
| **2** | EtOH | 0.031 | 76 | 20.0[e,h](389)[d] |
| **2** | EtOH | 0.031 | 76 | 22.0[e,f](467)[d] |

a: substrates: **1**, $CH_2$=C(NHAc)COOH; **2**, $CH_2$=C(NHAc)COOMe

b: 100% conversion and mainly (S) product configuration

c: repeated experiments with different ligand syntheses and/or reaction runs

d: initial turnover frequency ($hr^{-1}$)

e: [Rh{(R)-BINAP}(solvent)$_2$]$ClO_4$ as catalyst

f: synthesized here

g: [Rh{(R)-BINAP}(solvent)$_2$]$^+$ as catalyst and at 4 atm $H_2$ (ref. 4b)

h: obtained from Aldrich.

## REFERENCES


1. (a) Joo, F., and Toth, Z., *J. Mol. Catal.* **8**, 369 (1980).
   (b) Sinou, D., *Bull. Soc. Chim. Fr.* 480 (1987).
   (c) Kalck, P., and Monteil, F., *Adv. Organomet. Chem.* **34**, 219 (1992).
2. (a) Toth, I., Hanson, B.E., and Davis, M.E., *Catal. Lett.* 183 (1990).
   (b) Toth, I., Hanson, B.E., and Davis, M.E., *Tetrahedron Asymmetry* **1**, 913 (1990).
3. (a) Arhancet, J.P., Davis, M.E., Merola, J.S., and Hanson, B.E., *Nature* **339**, 454 (1989).
   (b) Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **121**, 327 (1990).
   (c) Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **129**, 94 (1991).
   (d) Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **129**, 100 (1991).
   (e) Davis, M.E., *Chemtech* 498 (1992).
4. (a) Miyashita, A., Yasduda, A., Takaya, H., Toriumi, K., Itok, T., Souchi, T., and Noyori, R., *J. Am. Chem. Soc.* **102**, 7932 (1980).
   (b) Miyashita, A., Takaya, H., Souchi, T., and Noyori, R., *Tetrahedron* **40**, 1245 (1984).
5. Amrani, Y., Lecomte, L., Sinou, D., Bakos, J., Toth, I., and Heil, B., *Organometallics* **8**, 542 (1989).
6. El Baba, S., Poulin, J.C., and Kagan, H.B., *Tetrahedron* **40**, 4275 (1984).

7. Ikariya, T., Ishii, Y., Kawano, H., Arai, T., Saburi, M., Yoshikawa, S. and Akutagawa, S., *J.C.S., Chem. Commun.* 922 (1985).

8. (a) Amrani, Y., and Sinou, D., *J. Mol. Catal.* **24**, 231 (1984).

(b) Sinou, D., and Amrani, Y., *J. Mol. Catal.* **36**, 319 (1986).

(c) Benhanza, D., Amrani, Y. and Sinou, D., *J. Organomet. Chem.* **288**, C37 (1985).

(d) Lecomte, L., and Sinou, D., *J. Organomet. Chem.* **370**, 277 (1988).

(e) Oehme, G., Paetzold, E., and Selke, R., *J. Mol. Catal.* **71**, L1 (1992).

9. Fogg, P.G.T., and Gerrard, W., *in* "Solubility of Gases in Liquids," Wiley, New York, 1991.

# CHAPTER THREE

## Ruthenium (II)-Sulfonated BINAP : A Novel Water-Soluble Asymmetric Hydrogenation Catalyst

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## ABSTRACT

Ruthenium (II)-sulfonated-BINAP has been synthesized and this novel water-soluble complex is shown to be an excellent asymmetric hydrogenation catalyst for 2-acylamino acid precursors and methylenesuccinic acid in both methanolic as well as in neat water solvent systems. Enantiomeric excesses approaching 90% have been obtained in aqueous and methanolic solvents. Effects of solvent, pressure and the addition of organic base on enantioselectivity are described.

## INTRODUCTION

One of the most recent advances in asymmetric synthesis is the use of water-soluble organometallic catalysts (*1,2*). Numerous water-soluble, chiral phosphines have been used as ligands for transition-metal-catalyzed asymmetric syntheses in aqueous-organic two-phase solvent systems (*3-6*). For asymmetric hydrogenation, chiral sulfonated di-tert-phosphines have been the most widely used in preparing water-soluble catalysts (*7,8*). Thus far, highly stereoselective two-phase hydrogenations have been achieved almost exclusively with Rh (I)-based complexes (*3-5, 9-11*). Although, most of these water-soluble rhodium (I) complexes are very active catalysts, they are in general less robust than ruthenium catalysts. Also the variety of Rh (I)-catalyzed reaction is not wide. Several studies have led to the conclusion that the double-bond geometry and, with some exceptions, the presence of the 2-acyl amino group is obligatorily important for chiral efficiency (*2*). In view of the general synthetic significance of asymmetric hydrogenation, development of water-soluble chiral catalytic systems that are able to reduce a wider range of substrates has long been desired.

Catalytic, asymmetric hydrogenation by means of a large variety of rhodium complexes with chiral ligands such as DIOP (*12*), BPPM (*13*), CHIRAPHOS (*14*), etc., has been extensively used to achieve high enantioselectivity. In contrast, there are relatively few reports on corresponding ruthenium complexes (*15*). With the advent of the outstanding

performance of various ruthenium-BINAP complexes (*16*), several preparation methods for mononuclear ruthenium catalysts in non-aqueous media have been devised (*17-24*). However, to our knowledge, no such methods have been developed for water-soluble ruthenium complexes. In fact, no water-soluble ruthenium chiral diphosphine catalysts have ever been reported in the literature. We have described earlier preliminary results concerning the use of a Rh (I)-sulfonated BINAP complex as an asymmetric hydrogenation catalyst in water (*25*). We now report the synthesis of a novel Ru (II)-sulfonated BINAP complex and its use in asymmetric hydrogenation with aqueous solvent. This ruthenium catalyst reveals superior enantioselectivity and stability when compared to the corresponding rhodium analogue.

## RESULTS AND DISCUSSION

### *Catalyst Preparation*

From a practical standpoint, it is of interest to devise a one-step synthesis with water. When $[Ru(benzene)Cl_2]_2$ (0.0037g) is reacted with BINAP-$4SO_3Na$ (0.0182g) [details concerning the preparation and characterization of this ligand can be found elsewhere (*25*)] in 5 ml water at 55-60°C for 2 hours, a complex revealing a $^{31}P$ NMR spectrum with two peaks in strictly 1:1 ratio [$^{31}P$ NMR ($D_2O$): $\delta$ = 57.5 and 63.7 ppm] is formed. From the difference in line shape, the two resonances appear to be originated from

two non-equivalent phosphorus atoms. A $^{2}J_{PP}$ coupling could not be observed in water. This complex is not very active for hydrogenation. Because P-C bond cleavage on Rh-phosphine complexes is well known (*26*), we speculate that a similar oxidative addition of the phosphorus-naphthyl bond to the Ru center is occurring. P-C bond cleavage has been observed during the synthesis of Ru-BINAP complexes in organic solvents (*27*). Since the oxidative addition of a P-C bond from a phosphine to a transition metal center is promoted by the presence of a vacant coordination site, an aromatic co-solvent (a weakly coordinating agent) can be used to suppress the formation of the above mentioned "unsaturated species" that is proposed to be the responsible "intermediate" for the P-C bond cleavage (*27*). P-C bond cleavage has also occurred when combining BINAP-4$SO_3$Na with $[Ru(cod)Cl_2]_n$ in water. A species with 19% abundance [$^{31}$P NMR ($D_2O$): $\delta$ = 76.0 and 85.0 ppm in 1:1 ratio] is detected and is likely to be a complex with a coordinated 1,5-cyclooctadiene.

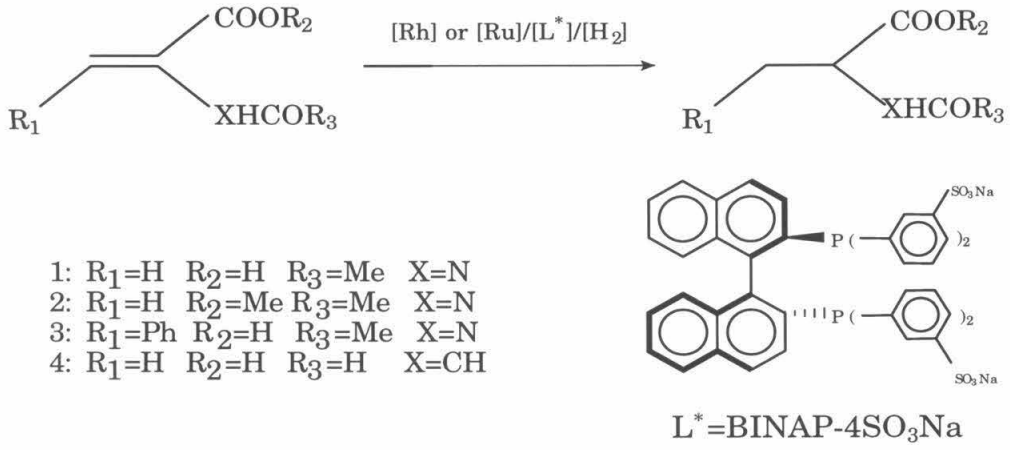
Treatment of $[Ru(benzene)Cl_2]_2$ (0.0037g) with two equivalents of water-soluble BINAP-4$SO_3$Na (0.0187g) in 4.5 ml of a 1:8 benzene/methanol solvent mixture at 55-60°C for one hour produces a clear, brownish-yellow colored solution. The $^{31}$P NMR spectrum of this solution in $CD_3OD$ reveals two doublets at $\delta$ = 63.0 and 68.8 ppm ($J \approx 45$Hz). Identical results are obtained with $[Ru(cod)Cl_2]_n$ as precursor. These data indicate that the same species is formed in these syntheses. Thus, the complex contains no 1,5-cyclooctadiene. The splitting is attributed to a loss in symmetry in the molecule; most likely due to a coordinated benzene molecule in [Ru(BINAP-4$SO_3$Na)(benzene)X]$^{n+}$

(X = Cl or solvent; n=1 or 2). When this species is dissolved in $D_2O$, only a singlet is found in the $^{31}P$ NMR spectrum regardless of the ruthenium precursor used [$^{31}P$ NMR ($D_2O$): $\delta$ = 57.5 ppm]. Such degeneracy indicates that the two P-C bonds are still intact. Vacuum drying of this $D_2O$ solution yields a dark brown solid that when dissolved in $CD_3OD$ regenerates the same $^{31}P$ NMR spectrum as before [$^{31}P$ NMR ($CD_3OD$): $\delta$ = 63.0 and 68.8 ppm]. This reversible process indicates the species in $D_2O$ retains a coordinated benzene molecule. We therefore speculate that the complex is $[Ru(BINAP\text{-}4SO_3Na)(benzene)]^{2+}$, obtained through the aquation of the Ru-Cl bond. These two ruthenium complexes are found to be active asymmetric hydrogenation catalysts (*vide infra*). In addition, polymeric ruthenium complexes can also be the active catalytic components.

*Catalytic Studies*

The brownish yellow solid isolated from the 1:8 benzene/methanol solvent was used as a catalyst for olefin hydrogenation without further purification. Asymmetric hydrogenations of prochiral 2-acylamino acid precursors and methylenesuccinic acid (Figure 3.1) were conducted with a solution of 0.014-0.017M of substrate at either room temperature or 50°C and atmospheric to 100 atmospheres of hydrogen pressure in batch autoclaves.

Figure 3.1 Reaction scheme for the reduction of prochiral substrates




1: $R_1$=H $R_2$=H $R_3$=Me X=N
2: $R_1$=H $R_2$=Me $R_3$=Me X=N
3: $R_1$=Ph $R_2$=H $R_3$=Me X=N
4: $R_1$=H $R_2$=H $R_3$=H X=CH

$L^*$=BINAP-4$SO_3Na$

In a typical run, a conversion of 80-100% was found in 48 hours. The conversion was measured by $^1H$ NMR spectroscopy and the enantiomeric excess (e.e.) determined by gas chromatographic analysis using either a J. & W. Scientific CDX-B chiral capillary column or a Heliflex Chirasil-Val capillary column after derivatization of the reaction products (*28*).

In all the reductions catalyzed by the water-soluble, ruthenium sulfonated-BINAP complex, the directions of enantioselection are found to be the same as those obtained from Ru-BINAP in organic solvent (from now on denoted as the parent system) (*20b*). Representative examples of the asymmetric hydrogenation of prochiral olefins are shown in Table 3.1. Enantiomeric excesses as high as 85-88% have been achieved in both the hydrogenations of methyl-2-acetamidoacrylate and 2-acetamidocinnamic acid.

To our knowledge, this is the first example of a water-soluble, ruthenium-based, chiral sulfonated diphosphine catalyst for asymmetric hydrogenation of prochiral alkenes. Similar to its parent system, the chirality induced in the products by this water-soluble ruthenium catalyst is opposite to that obtained from its water-soluble Rh-BINAP-4$SO_3Na$ catalyst in a similar solvent system (*20b, 25*). In contrast to our previous findings with the water-soluble rhodium analogue, the enantioselectivity from the ruthenium-catalyzed hydrogenation of 2-acetamidoacrylic acids and methylenesuccinic acid shows an opposite trend in solvent dependence, the highest e.e. (up to 85%) is found in neat methanol (Tables 3.1 & 3.2). The drop in e.e. in neat water is recoverable by an increase in reaction temperature and an 82% e.e. in neat water is obtained at a reaction temperature of 50°C (vs. 85% e.e. in neat MeOH at 50°C). An increase in reaction temperature is not possible with the rhodium-based catalysts because of their lack of thermal stability in either organic or aqueous solvents. For the reduction of 2-acetamidocinnamic acid, the water-soluble ruthenium catalyst appears to give a slightly higher e.e. in neat water (87.7%) than when using methanolic solvents (81.3% Tables 3.1 & 3.2).

Table 3.1 Asymmetric hydrogenation of 2-acylamino acid precursors and methylene-succinic acid by water-soluble ruthenium (II) sulfonated BINAP complex under one atm. of hydrogen.†

| Catalyst | Substrate | Solvent | S/C‡ | Temp.(°C) | e.e. (%) |
|---|---|---|---|---|---|
| [Ru(BINAP-4$SO_3Na$)$Cl_2$] | **1** | MeOH | 71 | RT | 84.2(R) |
| " | **1** | $H_2O$ | 18 | RT | 68.5(R) |
| " | **2** | $H_2O$ | 80 | RT | 75.9(R) |
| " | **2** | $H_2O$ | 76 | 50 | 82.0(R) |
| " | **2** | MeOH | 75 | 50 | 85.0(R) |
| *$Ru_2Cl_4(BINAP)_2(Et_3N)$* | ***1*** | *1:1 EtOH/THF* | - | *35* | *76.0*[a] |
| [Ru(BINAP-4$SO_3Na$)$Cl_2$] | **3** | MeOH | 75 | RT | 81.3(R) |
| " | **3** | EtOH | 75 | RT | 80.1(R) |
| " | **3** | $H_2O$ | 75 | RT | 87.7(R) |
| *$Ru_2Cl_4(BINAP)_2(Et_3N)$* | ***3*** | *1:1 EtOH/THF* | - | *35* | *86.0*[a,b] |
| [Ru(BINAP-4$SO_3Na$)$Cl_2$] | **4** | MeOH | 75 | RT | 81.1 |
| " | **4** | MeOH | 75 | RT | 90.0[b] |
| " | **4** | $H_2O$ | 18 | RT | 50.0 |
| $Ru_2Cl_4(BINAP)_2(Et_3N)$ | ***4*** | *1:1 EtOH/THF* | - | *35* | *88.0*[a,b] |

**1**: 2-acetamidoacrylic acid
**2**: ethyl-2-acetamidoacrylate
**3**: 2-acetamidocinnamic acid
**4**: methylenesuccinic acid
†: substrate conc. = 0.014-0.017M
‡: S/C = substrate to catalyst ratio
a: from ref. 20b and two atm. of hydrogen
b: with the addition of triethylamine, $Et_3N$/Substrate = 1

Table 3.2 Asymmetric hydrogenation of 2-acetamidoacrylic acid and 2-acetamidocinnamic acid by water-soluble ruthenium sulfonated BINAP catalyst in various water/methanol mixtures at room temperature and 1 atm. of $H_2$.

| Substrate | Solvent | S/C‡ | Concentration† (M) | e.e. (%) |
|---|---|---|---|---|
| **1** | $H_2O$ | 18 | 0.017 | 68.5 (R) |
| **1** | 7:3 $H_2O$/MeOH | 23 | 0.017 | 71.7 (R) |
| **1** | 3:7 $H_2O$/MeOH | 55 | 0.017 | 76.9 (R) |
| **1** | MeOH | 71 | 0.017 | 84.2 (R) |
| **3** | MeOH | 75 | 0.015 | 81.3 (R) |
| **3** | 1:1 MeOH/$H_2O$ | 75 | 0.015 | 84.0 (R) |
| **3** | $H_2O$ | 75 | 0.017 | 87.7 (R) |
| **3** | EtOH[a] | 75 | 0.016 | 80.1 (R) |

**1**: 2-acetamidoacrylic acid **3**: 2-acetamidocinnamic acid
‡: S/C = substrate to catalyst ratio †: substrate concentration
a: catalyst prepared from $[Ru(p\text{-cymene})Cl_2]_2$ in neat ethanol

The enantiomeric excess obtained in neat ethanol is almost the same as that from neat methanol. At this stage, it is impossible to explain the origin of the solvent dependent enantioselectivity. It is quite clear that the solvent effect is not only ligand-sensitive but also substrate dependent. For example, methylenesuccinic acid is hydrogenated with 81% e.e. in neat methanol as compared to only 50% e.e. in neat water. In spite of this, the 50% e.e. for this

substrate is already among the most enantioselective water-soluble systems ever reported in the literature (*9*).

Reductions at higher pressure have also been examined and the results are summarized in Table 3.3. The data show that the enantioselectivity declines with increasing hydrogen pressure regardless of substrate. In particular, the hydrogenation of methylenesuccinic acid is the most pressure-sensitive. These results are in agreement to those observed from the parent system where high hydrogen pressure and low reaction temperature lowered the enantiomeric excesses in the asymmetric hydrogenation of these types of substrates (*27*).

For the reduction of methylenesuccinic acid, the addition of triethylamine to the reaction system gave interesting results (Table 3.4). A 9% increase in e.e. is found in neat methanol with the addition of triethylamine (in 1:1 molar ratio between the base and the substrate). A maximum of 90% e.e. is obtained in neat methanol. However, an almost 16% drop in e.e. is observed in neat water when triethylamine is added.

Table 3.3 Pressure effect on the enantioselection for the asymmetric hydrogenation of 2-acylamino acid precursors and methylenesuccinic acid by water-soluble ruthenium (II) sulfonated BINAP catalyst at RT.

| Substrate | Solvent | Conc.† (M) | S/C‡ | Pressure (atm) | e.e. (%) |
|---|---|---|---|---|---|
| **3** | MeOH | 0.015 | 75 | 1 | 81.3(R) |
| **3** | MeOH | 0.012 | 75 | 50 | 64.0(R) |
| **3** | 1:1 MeOH/$H_2O$ | 0.045 | 75 | 1 | 84.0(R) |
| **3** | 1:1 MeOH/$H_2O$ | 0.045 | 75 | 50 | 61.0(R) |
| **3** | 1:1 MeOH/$H_2O$ | 0.012 | 75 | 55 | 64.0(R) |
| **3** | $H_2O$ | 0.017 | 75 | 1 | 87.7(R) |
| **3** | $H_2O$ | 0.017 | 76 | 5 | 82.5(R) |
| **3** | $H_2O$ | 0.017 | 75 | 50 | 68.3(R) |
| **2** | MeOH | 0.015 | 75 | 1 | 84.7(R) |
| **2** | MeOH | 0.015 | 76 | 10 | 72.0(R) |
| **2** | $H_2O$ | 0.017 | 75 | 1 | 75.9(R) |
| **2** | $H_2O$ | 0.017 | 77 | 10 | 50.6(R) |
| **4** | MeOH | 0.015 | 75 | 1 | 81.1 |
| **4** | MeOH | 0.017 | 75 | 50 | 18.2 |
| **4** | MeOH | 0.017 | 75 | 100 | 10.1 |

**2**: methyl-2-acetamidoacrylate
**3**: 2-acetamidocinnamic acid
**4**: methylenesuccinic acid
†: substrate concentration
‡: S/C = substrate to catalyst ratio

Table 3.4 Effect of added triethylamine on the enantioselectivities for the asymmetric hydrogenation of methylenesuccinic acid and methyl-2-acetamidoacrylate by water-soluble ruthenium (II) sulfonated-BINAP catalyst at RT and one atmospheric pressure of hydrogen.

| Substrate | Solvent | Conc.† (M) | S/C‡ | $Et_3N$/Substrate (M/M) | e.e. (%) |
|---|---|---|---|---|---|
| **4** | MeOH | 0.015 | 75 | 0 | 81.1 |
| **4** | MeOH | 0.015 | 75 | 1 | 90.0 |
| **4** | $H_2O$ | 0.014 | 18 | 0 | 49.6 |
| **4** | $H_2O$ | 0.015 | 75 | 1 | 34.0 |
| *4* | *EtOH/THF* | *0.050* | *50* | *0* | *86.0*[a] |
| *4* | *EtOH/THF* | *0.050* | *50* | *1.2* | *88.0*[b] |
| **2** | MeOH | 0.017 | 85 | 0 | 84.7(R) |
| **2** | MeOH | 0.015 | 76 | 1 | 62.7(R) |

**2**: methyl-2-acetamidoacrylate **4**: methylenesuccinic acid

†: substrate concentration ‡: S/C = substrate to catalyst ratio

a: $RuHCl(BINAP)_2$ [$Et_3N$ being added during the catalyst synthesis] as catalyst at 35°C and 2 atm. of hydrogen (ref. 20b)

b: $Ru_2Cl_4(BINAP)_2(Et_3N)$ as catalyst at 35°C and 2 atm. of hydrogen (ref. 20b)

In the literature, there are no other studies on the effect of the addition of organic base on enantioselectivity for other water-soluble systems and it is therefore impossible for us to make any comparison.

Further experiments are currently being conducted on: (i) improved catalyst preparation, (ii) catalyst characterization, (iii) hydrogenations of other substrates with pharmaceutical applications, (iv) activity studies, (v) the effects of additions of inorganic bases and weakly coordinating co-solvents on enantioselectivity and (vi) catalysis in supported aqueous-phase configuration (*29*). Promising results from the SAPC system have been obtained and these data will be published later.

## CONCLUSION

A one-step synthesis of a water-soluble, chiral ruthenium (II) sulfonated BINAP complex in methanolic solvent is accomplished. This is the first literature reported water-soluble ruthenium (II)-sulfonated chiral diphosphine complex. Similar to the synthesis of the non-sulfonated complex, a weakly coordinating co-solvent is required to inhibit the oxidative cleavage of P-C bonds when synthesizing the ruthenium complex with the water-soluble diphosphine ligand. The performance of the water-soluble ruthenium complex as an asymmetric hydrogenation catalyst is found to be as enantioselective as its non-water-soluble analogue in alcoholic solvents. In some circumstances, the present system is superior to the non-sulfonated complexes, e.g., an 85.0% e.e. is obtained for the hydrogenation of 2-acetamidoacrylic acid by the sulfonated ruthenium complex in methanol at RT, where only an 76% e.e. is obtained by $Ru_2Cl_4(BINAP)_2(Et_3N)$ even at

35°C and 2 atm of hydrogen pressure (*20b*). Similarly, a 90.0% vs. 88.0% e.e. is found in the reduction of methylenesuccinic acid (*20b*). However, when the hydrogenation is carried out in neat water, there is a drop in enantioselectivity for some of the substrates. Nevertheless, a 75.9% e.e. is found when this water-soluble ruthenium catalyst is used to hydrogenate methyl-2-acetamidoacrylate in neat water and this value is comparable to the parent system that gives a 76.0% e.e. even after the addition of triethylamine (*20b*). Additionally, the hydrogenation of 2-acetamidocinnamic acid yields a slightly higher e.e. (87.7% vs. 86.0%) in neat water than that obtained from the parent system in organic solvent.

## REFERENCES


1. Kagan, H.B. *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F.G.A.; Abel, E.W., Eds.; Pergamon Press: Oxford, Vol. 8, p 463 (1982).
2. *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, Vol. 5 (1985).
3. Amrani, Y.; Sinou, D. *J. Mol. Catal.* **24**, 231 (1984).
4. Amrani, Y.; Sinou, D. *J. Mol. Catal.* **36**, 319 (1986).
5. Benhamza, R.; Amrani, Y.; Sinou, D. *J. Organomet. Chem.*.288, C37 (1985).
6. Nagel, U.; Kingel, E. *Chem. Ber.* **119**, 1731 (1986).
7. Kuntz, E. US Patent 4,248,802, Rhone-Poulenc 1981.
8. Kuntz, E. *CHEMTECH* **17**, 570 (1987).
9. Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I. and Heil, B. *Organometallics* **8**, 542 (1989).
10. Alario, F.; Amrani, Y.; Collenille, Y.; Dang, T.P.; Jenck, J.; Morel, D. and Sinou, D. *J. C.S., Chem. Commun.* 202 (1986).
11. Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P. and Sinou, D. *J. C. S., Chem. Commun.* 1684 (1991).
12. Kagan, H.B. and Dang, T.P. *J. Am. Chem. Soc.* **94**, 6429 (1972).
13. Achiwa, K. *J. Am. Chem. Soc.* **98**, 8265 (1976).
14. Fryzuk, M.D. and Bosnich, B. *J. Am. Chem. Soc.* **99**, 6262 (1977).

15. (a) Matteoli, U.; Frediani, P.; Bianchi, M.; Botteghi, C. and Gladiali, S. *J. Mol. Catal.* **12**, 265 (1981).

(b) James, B.R.; Wang, D.K.W. and Voight, R.F. *J. C. S., Chem. Commun.* 574 (1975).

(c) James, B.R.; McMillan, R.S.; Morris, R.H. and Wang, D.K.W. *Adv. Chem. Ser.* **167**, 122 (1978).

(d) James, B.R.; Pacheco, A.; Rettig, S.J.; Thorburn, I.S.; Ball, R.G. and Ibers, J.A. *J. Mol. Catal.* **41**, 147 (1987).

16. Noyori, R. and Takaya, H. *Acc. Chem. Res.* **23**, 345 (1990).

17. Ohta, T.; Takaya, H. and Noyori, R. *Inorg. Chem.* **27**, 566 (1988).

18. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H. and Akutagawa, S. *J. Am. Chem. Soc.* **109**, 5856 (1987).

19. Kitamura, M.; Tokunaga, M.; Ohkuma, T. and Noyori, R. *Tetrahedron Lett* Vol. 32, 4163 (1991).

20. (a) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S. and Akutagawa, S. *J. C. S., Chem. Commun.* 922 (1985).

(b) Kawano, H.; Ikariya, T.; Ishii, Y. Saburi, M.; Yoshikawa, S.; Uchida, Y. and Kumobayashi, H. *J. C. S., Perkin Trans. I* 1571 (1989).

21. Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R. and Takaya, H. *J. C. S., Chem. Commun.* 1208 (1989).

22. Alcock, N.W.; Brown, J.M.; Rose, M. and Wienand, A. *Tetrahedron: Asymmetriy* Vol. 2, 47 (1991).

23. Heiser, B.; Broger, E. and Crameri, Y. *Tetrahedron: Asymmetry* Vol. 2, 51 (1991).

24. Genet, J.P.; Mallart, S.; Pinel, C.; Juge, S. and Laffitte, J.A. *Tetrahedron: Asymmetry* Vol. 2, 43 (1991).

25. Wan, K.T. and Davis, M.E. *J. C. S., Chem. Commun.* 1262 (1993).

26. Abatjoglou, A.G.; Billig, E. and Brian, D.R. *Organometallics* **3**, 923 (1984).

27. Chan, A.S.C.; Laneman, S.A. and Miller, R.E. *Selectivity In Catalysis*, Davis, M.E. and Suib, S.L., Eds., ACS Symposium Series 517, Chap. 3, 27 (1993).

28. El Baba, S.; Poulin, J.C. and Kagan, H.B. *Tetrahedron* **40**, 4275 (1984).

29. Arhancet, J.P.; Davis, M.E.; Merola, J.S. and Hanson, B.E. *Nature* **339**, 454 (1989).

# CHAPTER FOUR

## Asymmetric Synthesis of Naproxen by Supported Aqueous-Phase Catalysis

[Wan, K.T., and Davis, M.E., J. Catal. 1994 in press]

## ABSTRACT

A supported aqueous-phase, asymmetric, hydrogenation catalyst, SAP-Ru-BINAP-4$SO_3Na$, is synthesized. Impregnation of water from an organic phase, ethyl acetate, is used to hydrate the SAP catalyst. Both the activity and enantioselectivity for the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid to naproxen are found to be dependent on the water content. Maximum activity and e.e. are observed when water saturated ethyl acetate is used to hydrate the SAP catalyst, an initial turnover frequency of 18.2 $hr^{-1}$ and an 70.0% e.e. at room temperature under ~1350 psig of hydrogen pressure. At similar conditions, initial turnover frequencies of 131 $hr^{-1}$ and 0.34 $hr^{-1}$ are observed from Ru-BINAP-4$SO_3Na$ in homogeneous (methanol as solvent) and two-phase (water-ethyl acetate) reaction systems, respectively. Though an excellent 96.1% e.e. (at 4°C and 1230 psig of $H_2$) is found in neat methanol (homogeneous), the enantioselectivity of the SAP catalyst (up to 70% e.e.) is bounded by the intrinsic enantioselectivity limit of the ruthenium complex in water. Recycling of the SAP catalyst is easily achieved without any leaching of ruthenium into the organic phase.

## INTRODUCTION

Homogeneous catalysts are known to exhibit high activities and selectivities at relatively mild reactions conditions giving few by-products (*1*). These characteristics are especially true in the synthesis of chiral compounds (*2-4*). Among the numerous types of chiral transformations, asymmetric, catalytic hydrogenation of prochiral alkenes is one of the most impressive achievements in catalytic selectivity (*5*). However, it has long been recognized that a shortcoming of homogeneous catalysis is the obvious need for separating the catalytic species from the reaction mixture. Depending upon the system: (i) the catalytic species can be very expensive (*6,7*), e.g., rhodium phosphine complexes, (ii) the catalytic species may not be robust enough for a particular separation and/or the separation may not be as complete or cost effective as desired, and (iii) catalyst contamination in pharmaceutical products must be minimized. Therefore, there continues to be a need for the immobilization of the catalytically active organometallic species in order to enhance the economic viability of the reaction system by eliminating separation and/or catalyst recovery steps and to minimize the possible toxicity hazards by contamination of trace transition metal complexes. Techniques used to immobilize homogeneous catalysts have centered on the retention of the structure and properties of the homogeneous counterpart. Comprehensive reviews on immobilization techniques are available (*8-11*). Also, there are several informative reviews concerning numerous aspects of heterogeneous, enantioselective catalysis (*12-22*).

Hydrogenation is arguably the most important synthetic application of asymmetric catalysis because of its potential to produce a wide variety of chiral functional groups. It is therefore not surprising that the largest number of catalytic systems has been described for this reaction type. However, a closer inspection of the literature reveals that there are really only two families of synthetically useful heterogeneous, asymmetric catalytic systems: (i) a Ni catalyst modified with tartrate/NaBr (*12*) and (ii) Pt(Pd) catalysts modified with cinchona alkaloids (*23,24*). Though many functionalized olefins can now be hydrogenated with optical yields > 95% using homogeneous catalysts (*25*), the performances of many heterogeneous systems are not that impressive. In fact, at this time there is no heterogeneous system for the enantioselective reduction of C=C bond that is preparatively useful. One way to create a heterogeneous catalyst is through the immobilization of a homogeneous catalyst onto a support. In this way, the catalyst can in principle acquire the property of insolubility and at the same time, retain the same reactivity and selectivity exhibited by its homogeneous analogue. In attempts to do these, homogeneous catalysts have been attached to a variety of supports including cross-linked polymers (*9,26-30*). Cross-linked polystyrenes are one of the most widely used polymer supports for the attachment of phosphine ligands through chemical modifications. In some cases, in highly polar solvents, enhanced rates (*31,32*) and greater selectivity for non polar olefins (vs. polar ones) (*32,33*) have been reported in hydrogenations mediated by polymer-attached achiral phosphine systems. However, results with polystyrenes containing optically active phosphine ligands aimed at effecting asymmetric

syntheses have been disappointing (*34*). In polar solutions of the substrates, the polystyrene beads collapse preventing entry of the substrate to the catalytic site. Problems of polymer shrinking in polar solvents (*34*) and leaching of catalytic species from the support have always been the main obstacles.

Recently, new generations of asymmetric hydrogenation catalysts have been synthesized and consist of Rh (I), Ru (II), Ni (II) or Co (II) complexes anchored in modified USY zeolites (*35-37*). These catalysts reveal a remarkable support effect on the enantioselectivity for the catalytic hydrogenation of prochiral alkenes. However, this system suffers from a constraint that limits its potential applications, i.e., the small pore size (~8Å) only allows small substrate molecules to be reacted. Hence, a new type of support as well as the active catalytic species has to be found to achieve a practical heterogeneous, asymmetric hydrogenation catalyst for general use.

The supported aqueous-phase catalysis (SAPC), developed by Arhancet *et al.* in 1989 (*38*), in combination with recent developments in the synthesis of water-soluble, chiral ruthenium sulfonated-BINAP complexes (*39*) allows the extension of the SAPC concept to chiral chemistry. We now describe an asymmetric version of supported aqueous-phase catalysis. The catalytic phase that is immiscible with the organic phase containing the reactants/products consists of an aqueous solution of a water-soluble ruthenium (II) sulfonated-BINAP catalyst (see Figure 4.1). Here, we report the preparation of this supported aqueous-phase, ruthenium, asymmetric hydrogenation catalyst and

its use in the asymmetric synthesis of naproxen. This immobilized ruthenium catalyst is shown to be an enantioselective hydrogenation catalyst. Furthermore, the SAPC is compared to its homogeneous and aqueous-organic two-phase counterparts.

## EXPERIMENTAL

### *Materials*

Controlled pore glass CPG-240 (CPG Inc.), benzeneruthenium (II) chloride dimer, ethyl acetate, pyridine, triethylamine, sodium hydroxide, 3-pyridinesulfonic acid and tetrahydrofuran were purchased in their highest purity available and used as received. 2-(6'-Methoxy-2'-naphthyl)acrylic acid was obtained as a gift from the Monsanto Company. The sodium salt of tetra-sulfonated BINAP was prepared as reported previously (*40*). Sodium 3-pyridinesulfonate was synthesized by neutralizing an aqueous solution of 3-pyridinesulfonic acid with sodium hydroxide, followed by recrystallization in methanol. Unless stated otherwise, all manipulations were performed under argon or nitrogen. Deionized water, distilled over potassium permanganate was used in all operations requiring water. All solvents, including water, were degassed by four to five freeze-pump-thaw cycles.

*Catalyst Preparation*

0.0050 g of [Ru(benzene)$Cl_2$]$_2$ were reacted with two equivalents of water-soluble BINAP-4$SO_3$Na in 4.5 ml of a 1:8 benzene/methanol solvent mixture at 55-60°C for one hour. The resulting clear, brownish-yellow colored solution of [Ru(BINAP-4$SO_3$Na)(benzene)Cl]Cl was then vacuum dried at room temperature. The crude solid was re-dissolved in 2.5 ml water and the solution blended with 0.8-1.0 g of degassed CPG-240 [a narrow pore-size distribution glass: mean pore diameter = 242 Å, pore volume = 0.89 ml/g, surface area = 79 $m^2/g$, mesh size = 120/200] for two hours, followed by vacuum drying at 40-50°C. The final product was a dry, free-flowing yellow powder that was stored under argon at room temperature. The water content of this "dried" catalyst was estimated by thermogravimetric analysis to be 1.9 wt%, while the ruthenium contents were 1.2-2.5x$10^{-5}$ mol/g. Since the ruthenium catalyst is not as hydrophilic as the Rh-TPPTS catalyst used in previous SAPC studies on hydroformylation (*38,41-42*), re-hydration of the solid catalyst by vapor-phase impregnation is not feasible in the present system. The dried catalyst was re-hydrated from an organic phase that had been previously premixed with a controlled amount of water. It was found that most of the water remains in the organic phase upon contact with the CPG. The maximum water loading was obtained by using a water-saturated organic phase. Catalysts used in the homogeneous and the two-phase systems were prepared as described in our previous paper (*39*).

*Reaction Conditions and Analytical Methods*

Asymmetric hydrogenations of 2-(6'-methoxy-2'-naphthyl)acrylic acid were conducted at various temperatures and hydrogen pressures in a 25 ml stainless steel Parr batch reactor. Special care was taken in order to avoid the presence of oxygen at all times. The conversion was measured by $^{1}H$ NMR spectroscopy on a G.E. QE-300 spectrometer at 300MHz and the enantiomeric excess (e.e.) determined by HPLC using a 25cmx4.6mm i.d. Regis (S,S)-Whelk-O 1 column without derivatization. Thermogravimetric analyses (TGA) were obtained in air on a Du-Pont 951 thermogravimetric analyzer. Ruthenium analyses were performed by Galbraith Laboratories Inc. (Knoxville, TN).

## RESULTS AND DISCUSSION

Since naproxen and many other chiral 2-arylpropionic acids are high-valued pharmaceutical products, there is great economic incentive for the development of a practical process for the efficient asymmetric hydrogenation of 2-arylacrylic acids. Previous studies have shown that high hydrogen pressure and low reaction temperature elevated the optical yields in the asymmetric hydrogenation of 2-arylacrylic acids (*43*). Hence, the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid (substrate **1**; a precursor to naproxen) was chosen to be our model reaction in this study.

Both the homogeneous and the two-phase reaction systems were examined in order to establish a basis for comparison with the SAPC results.

*Homogeneous Catalytic Studies*

In contrast to most other sulfonated phosphine systems (*44,45*), the ruthenium sulfonated-BINAP catalyst is quite soluble in neat methanol and methanol is known to give highest e.e. in many of the asymmetric reactions catalyzed by non-sulfonated complexes. In fact, the asymmetric hydrogenation of substrate **1** by the parent Ru-BINAP system ( the term parent system will be used here to denote the non-sulfonated analogue) was also carried out in neat methanol (*43*). Homogeneous, asymmetric hydrogenations of substrate **1** were conducted in methanolic solvents to allow a direct comparison between the sulfonated and parent system. Table 4.1 summarizes the results obtained from the homogeneous reductions of substrate **1** in methanolic solvents. Reductions were carried out under a hydrogen pressure of 500-1400 psig. It was observed that the enantioselectivity was not very pressure-sensitive in this pressure range (less than a 2% variation in e.e. over this range; entries 1 & 2). It is clear that the presence of water tends to lower the e.e.'s (entry 3). This may be attributed to the compositional change of the ruthenium catalyst in the presence of water. The chloro ligand dissociates in the presence of water through the aquation of the Ru-Cl bond. Our present results suggest that a coordinated chloro ligand in [Ru(BINAP-4$SO_3Na$)(benzene)Cl]Cl found only in neat methanol, assists in enhancing the e.e. The retention of the chloro ligand in neat methanol may

provide the necessary molecular configuration to facilitate a more enantioselective binding with the substrate. Our speculation is reinforced by a recent report that the cationic complex [(Cp)Ru(BINAP)](PF$_6$) is completely non-selective in the asymmetric hydrogenation of methyl acetoacetate, while its neutral chloro complex [(Cp)Ru(BINAP)Cl] gives a 76% e.e. (*46*).

The addition of triethylamine in neat methanol not only improves the e.e. to 91.5% at a reaction temperature of 23°C (entry 8) and 96.1% at 4°C (entry 15) but also enhances the activity by a factor of seven. Initial turnover frequencies of 927hr$^{-1}$ and 131hr$^{-1}$ are observed in the presence and absence of triethylamine, respectively (entries 7 & 8). As the substrate chelation to the metal center is unlikely to be the rate-determining step, the base-induced deprotonation of the substrate carboxylic group for facile metal chelation cannot be responsible for this rate enhancement. In addition, no such rate enhancement effect is found in the [Ru(BINAP)(O$_2$CR)$_2$] catalyzed hydrogenation of α,β-unsaturated carboxylic acids with the addition of tetrabutylammonium hydroxide (*47*). However, a slow initial turnover frequency of 0.77hr$^{-1}$ (entry 11) under acidic conditions is found with the addition of excessive amount of concentrated sulfuric acid. Consistent with this, addition of trifluoromethanesulfonic acid to the [Ru(BINAP)(O$_2$CR)$_2$] system results in complete loss in activity (*47*).

An opposite effect on enantioselectivity of added triethylamine is found in aqueous methanolic solvent. An almost 4% drop in e.e. (entry 4) is found in 1:1 methanol/water solvent system although the same rate enhancement is

again observed with the addition of triethylamine. These results are in agreement with our previous findings of the solvent-dependent effects of added triethylamine on enantioselectivity with other substrates (*39*). Other bases were also tested in these initial screening experiments. Water-soluble sodium 3-pyridinesulfonate is found to have little effects on enantioselectivity either in neat methanol or in aqueous methanolic solvents (entries 9 & 10). These findings lead us to further investigate the origin of the enantioselectivity enhancement through the addition of triethylamine. It is apparent that the chiral modification is a direct consequence of the ligand effect and probably involves the coordination of triethylamine to the ruthenium center (thus, allowing a fine tuning of the enantioselectivity through steric and electronic effects). Because of the presence of an electron withdrawing sulfonate group, sodium 3-pyridinesulfonate is not expected to coordinate with the metal, and no change in enantioselectivity is found. In contrast, un-substituted pyridine is known to be a good ligand for $d^6$ ruthenium (II) complexes and it generally gives species that are even more stable than those formed from aliphatic amines, e.g., triethylamine. No conversion is observed with the addition of pyridine in 1:1 methanol/water solvent under 1350 psig of hydrogen pressure. In addition, the effects of added tetrahydrofuran were also examined. Tetrahydrofuran, being a moderately σ-donating ligand, gives an almost unchanged 77.6% e.e. in 1:1 methanol/water solvent system at 1350 psig of hydrogen pressure (entry 12). Further experiments are currently being conducted in search for an aqueous-counterpart of triethylamine for applications in two-phase and SAP systems. Nevertheless, in neat methanol, the present system (96.1% at 4°C and 1230 psig of $H_2$ in entry 15) is as

enantioselective as its parent system (96.0% at 0°C and 500 psig of $H_2$ in entry 16) (*43*).

*Two-Phase Catalytic Studies*

We examined a simple two-phase reaction system (results listed in Table 4.2) for comparison with the homogeneous catalytic results (Table 4.1) as well as the SAP catalysis discussed below. Anhydrous ethyl acetate was chosen as the organic solvent. When substrate **1** was charged into the hydrogenation reactor along with an aqueous solution of the ruthenium catalyst (10 ml of 1:1 ethyl acetate/water and S/C=50), a 53.6% conversion was observed in 3.5 days with an initial turnover frequency of 0.34 $hr^{-1}$ (entry 1). The two-phase reaction is therefore at least 350 times slower than the homogeneous reaction system. Because of the limited solubility of this substrate in water, most of the reaction is taking place at the interface of aqueous-organic phase and the rate is therefore limited by the interfacial surface area between the catalyst containing aqueous phase and the substrate containing organic phase. As will be mentioned in the next section, the present two-phase system is at least 50 times less active than the SAP system where a much larger interfacial surface area is provided from the high surface area CPG support. Because of a limited solubility of the substrate in water, we cannot rule out the possibility that a small portion of the conversion is by reaction in the bulk aqueous phase. An 78.4% e.e. is obtained from the two-phase reaction. Recycling of the catalyst containing aqueous phase after phase separation is possible without any loss in enantioselectivity (entries 2, 3 & 4),

the e.e.'s range from 78.0-82.7% over several recycles of the catalytic solution. Similar e.e.'s but lower activities (0.20 $hr^{-1}$) were found at a reaction temperature of 5-6°C (entry 5). Addition of triethylamine increased the reaction rate at a slight expense of enantioselectivity (entry 6). Similar results on the effects of added triethylamine have been reported in our previous work on other substrates (*39*).

*Supported Aqueous-Phase Catalytic Studies*

In the supported aqueous-phase configuration, anhydrous ethyl acetate is used as the organic phase and the catalytic data obtained from this system are listed in Tables 4.3 and 4.4. The activities of the SAP catalysts are improved over the two-phase system due to the much higher interfacial area of SAP catalyst. When substrate **1** (S/C=25) is hydrogenated with a "dried" sample of the SAP catalyst (1.9 wt% water), no detectable conversion is observed even after 70 hours at room temperature under 1300psig of hydrogen pressure (T.O.F. < 0.008 $hr^{-1}$, entry 1 in Table 4.4). Significantly, when water-saturated ethyl acetate is used as solvent, a 100% conversion (S/C=31.5) is achieved in ~3 hours under the same reaction conditions with an initial turnover frequency of 18.2 $hr^{-1}$ and an 70% e.e. (entry 5 in Table 4.3 and entry 8 in Table 4.4). This enantioselectivity is only slightly lower than that found in the water-organic two-phase system. Similar results are also observed from other batches of SAP catalysts (entries 2, 6 & 9 in Table 4.3). Additionally, when using a SAP catalyst with 40µl water in 10ml of ethyl acetate as the organic solvent, the e.e. of the hydrogenated product is found to be only 28.7% (R)

(entry 1 in Table 4.3). It is therefore evident that the water content in the SAP catalyst has dramatic effects both on the activity and the enantioselectivity. Since the present ruthenium-sulfonated-BINAP catalyst is not as hydrophilic as the rhodium-TPPTS catalyst, developed by Arhancet *et al.*, vapor-phase impregnation of water onto the CPG support is not feasible for the present system (*38,41*). The revised method of in-situ rehydration by water-loaded blank CPG also requires higher reaction temperatures (80-100°C) for the redistribution of water over the SAP catalyst (*42*). Again, this approach for loading water in the present SAP catalyst is not possible. However, another rehydration procedure that is more feasible, especially in terms of scale-up, was devised for this particular system; namely, the organic-phase impregnation. The "dried" SAP catalyst is rehydrated from an organic-phase that has been previously premixed with a controlled amount of water. In order to achieve a reasonable activity, the amount of water added to the organic phase is found to be greater than the void volume of the CPG support (60-70 μl) suggesting a large portion of water is still retained in the organic phase. A maximum water loading of 2.8-3.1 wt% (g $H_2O$/g AcOEt x 100, i.e., ~275 μl water in 10 ml of ethyl acetate) was accomplished by using a water-saturated organic phase. The initial turnover frequencies as a function of water content are listed in Table 4.4 (reaction conditions: substrate/ruthenium~30, [substrate]=4.6-4.8x$10^{-3}$M, pressure=1350-1400psig, T=25°C, stirring speed=350rpm). Water is introduced to the "dried" SAP catalyst from the ethyl acetate (10 ml) and the content controlled by adding variable amounts of water, e.g., 0, 40, 125, 145, 160, 195, 215 and 270 μl. The maximum activity, as determined by the initial turnover frequency, is

observed at the highest water content (~3 wt% water in ethyl acetate) with an initial turnover frequency of 18.2 $hr^{-1}$ (entry 8 in Table 4.4). The enantioselectivity of the SAP catalyst is also dependent on the water content and shows a similar trend to that observed in the activity; the observed range is 28.7% to 70.0%(R) (entries 1 & 5 in Table 4.3). Thus, as previously mentioned, the water content affects the activity and enantioselectivity of the SAP catalyst. The present findings are quite different from what have been observed in the hydroformylation of 1-octene by a SAP-rhodium-TPPTS catalyst (*41*). In the hydroformylation of 1-octene, the activity is much more sensitive to the water content of the SAP catalyst with a bell-shaped curve that describes the activity dependence on water content. Maximum activity is observed at ~8 wt% (g $H_2O$/g SAPC x 100) water content of the SAP catalyst and complete loss of activity is observed at ~50 wt% (*41*). Two factors appear to be responsible for the difference in behaviour towards the water content of these two SAP catalysts. First, the $[Ru(benzene)(BINAP\text{-}4SO_3Na)]^{2+}$ complex is stable even in neat water while $HRh(CO)(TPPTS)_3$ is not at high synthesis gas pressure. At high water loading, the $HRh(CO)(TPPTS)_3$ complex decomposes, resulting in a drop in activity. Second, the decrease in the interfacial area of the SAP catalyst with increasing water loading also contributes to the rapid decline in the activity of the more hydrophilic SAP-Rh-TPPTS catalyst. Because of the small partition coefficient of water between the CPG support and the ethyl acetate, conditions have not yet been reached in the present SAP-Ru-BINAP-$4SO_3Na$ that approximates the high water loading obtained with the SAP-TPPTS catalyst. Thus, the actual amount of water being loaded onto the SAP-Ru-BINAP-$4SO_3Na$ catalyst is far below the

amount loaded by the vapor-phase impregnation into the much more hydrophilic SAP-Rh-TPPTS catalyst.

In view of the high water content of the ethyl acetate in the present system, the leaching of the catalytic species into the organic phase may be more likely than with anhydrous solvents. Filtration of the reaction mixture to remove the solid catalyst after the hydrogenation reaction yields a colorless solution of product in ethyl acetate. All filtrates were found not to contain any ruthenium at a detection limit of 1 ppm (entries 2, 4-5 & 15 in Table 4.3 and entries 3-8 in Table 4.4). In addition, for some of the experiments, filtrates were tested indirectly for the presence of ruthenium by attempting the catalytic hydrogenation of methylenesuccinic acid using the filtrate alone as catalyst. In no case was catalytic activity observed from the filtered solutions. For example, filtered solutions gave no conversion of methylenesuccinic acid at room temperature with one day of contact under a pressure of 30 psig of hydrogen. The inactivity of these filtered solutions together with the elemental analyses suggests that no soluble ruthenium species have leached out into the organic phase.

It is reasonable to suggest that the ruthenium complex becomes increasingly mobile (does not necessarily imply translational mobility but rather rotational mobility) as the water loading increases, as evidenced from the data in Table 4.4 that the hydrated SAP catalyst is at least 2000 times more active than the "dried" SAP catalyst. With a higher degree of mobility, the SAP catalyst can approach the same enantioselectivity as its counterpart in the two-

phase system. (Increased mobility with higher water contents was shown previously to occur with the SAP-Rh-TPPTS catalyst (*41*)). Because of the much larger interfacial surface area between the catalyst containing aqueous-phase and the substrate containing organic-phase, the SAP system is found to be at least 50 times more active than the two-phase system. In the best cases, T.O.F.'s obtained using hydrated SAP catalysts are only a factor of 7 times slower than homogeneous catalyst in neat methanol under the same conditions. We have observed a similar drop (6.7 times) in initial turnover frequency in the homogeneous hydrogenation of methyl-2-acetamidoacrylate by $[Rh(BINAP\text{-}4SO_3Na)(H_2O)]^+$ in neat water (*40*), where both the substrate and the catalyst are mixed together in one single phase and attributed this to the fact that hydrogen solubility is four to five times higher in alcoholic solvents (oxidative addition of hydrogen to the rhodium catalyst is rate determining).

The effect of added base on the SAP system was examined and the results are listed in Table 4.3. The addition of either aqueous sodium hydroxide or triethylamine is found to have little effect on the enantioselectivity (entries 13, 15-16 in Table 4.3). In the presence of sodium hydroxide, the enantioselectivity is found to be rather pressure-insensitive in the pressure range of 500-1,400 psig (entries 17-19 in Table 4.3). The e.e.'s are almost constant from the hydrated SAP catalyst in the pressure range of 500-1,400 psig (entries 2 & 3 in Table 4.3). Similar to the case of the homogeneous analogue, higher e.e.'s (77%) are achieved with a lower reaction temperature of 8°C, but at the expense of activity (T.O.F.=$0.43hr^{-1}$). The possibility of

catalyst decomposition during the synthesis of SAP material is ruled out by the fact that a hydrogenation of substrate **1** with an 86% e.e. is accomplished by using a redissolved catalyst solution from a used SAP catalyst in methanol. Thus, the ruthenium complex is still stable in the SAP configuration. It is therefore apparent that the performance of the hydrated SAP catalyst is bounded by the intrinsic enantioselectivity limit of the ruthenium sulfonated BINAP catalyst in water. Additionally, it is clear that the CPG support plays no important role in the enantioselection.

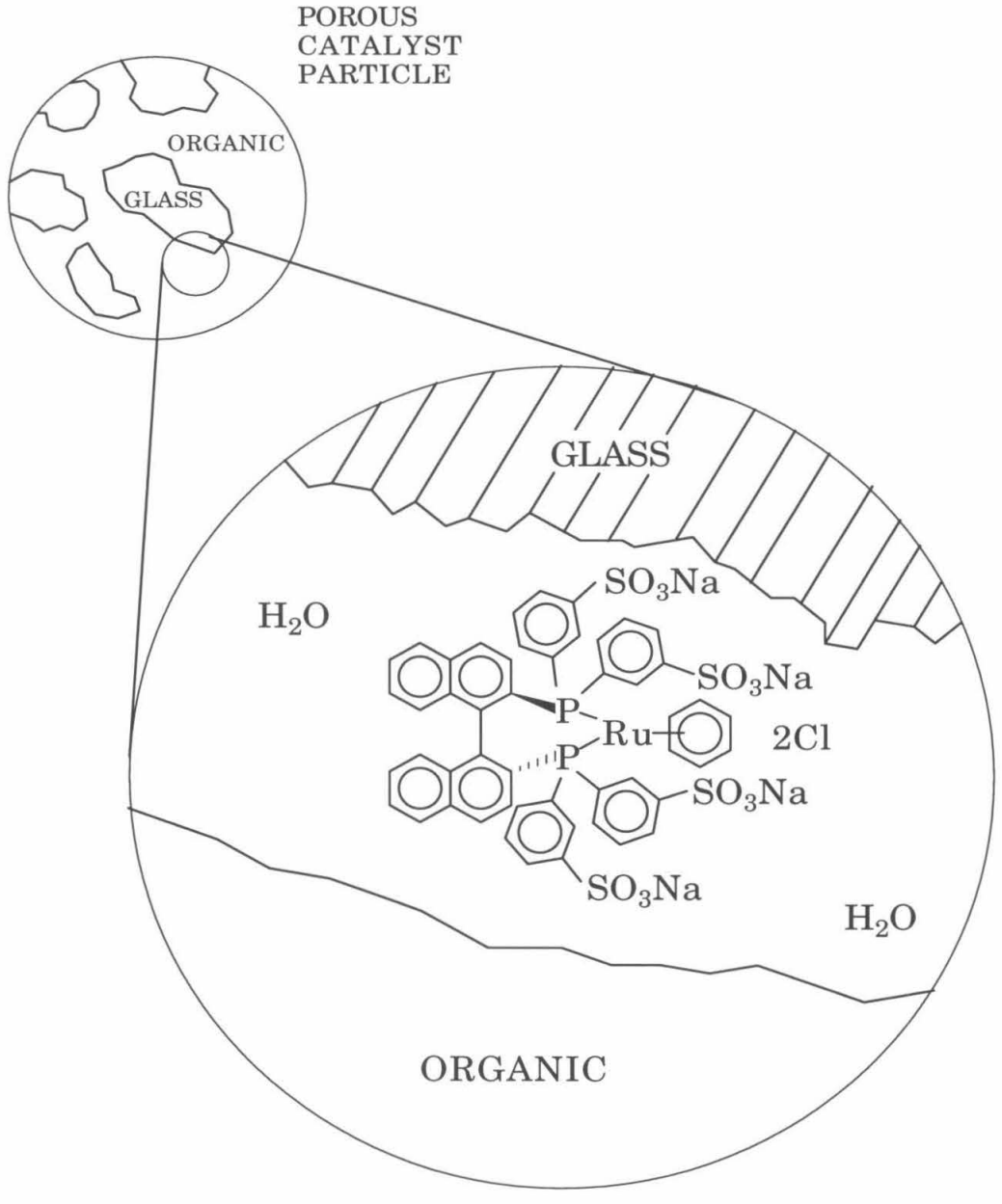
Series of reactions were carried out to test the possibility of recycling the SAP catalyst. The used SAP catalyst was removed from the hydrogenation mixture by simple filtration. It was then washed several times with fresh ethyl acetate, followed by the addition of fresh substrate and solvent. Similar values of e.e. (65-70%) were found throughout the recycling of the SAP catalyst (entries 2, 4-5, 6-8 & 9-11 in Table 4.3).

## CONCLUSION

A supported aqueous-phase, asymmetric, hydrogenation catalyst, SAP-Ru-BINAP-4$SO_3Na$, is prepared. Because of the much larger interfacial area due to the CPG support, the SAP catalyst is found to be at least 50 times more active than its two-phase counterpart and only 7 times less active than its homogeneous analogue. Both the catalytic activity and enantioselectivity are

dependent on the water content of the SAP catalyst, with the hydrated SAP catalyst being at least 2,000 times more active than the dried catalyst. It is suggested that the mobility of the ruthenium sulfonated-BINAP complex on the surface of the CPG support is very critical to the overall performance of this SAP catalyst. Although the active ruthenium sulfonated BINAP catalyst (96.1% e.e.) is as enantioselective as its non-sulfonated analogue (96.0% e.e.) under homogeneous conditions, the performance of its SAP version is only moderate and bounded by the intrinsic enantioselectivity limit of the ruthenium catalyst in water. The loss of the chloro ligand through aquation of the Ru-Cl bond in water is proposed to be responsible for the decline in enantioselectivity. From this work, the concept of supported aqueous-phase catalysis has been demonstrated to be applicable to asymmetric catalysis. The advantage of easy catalyst separation and recycling makes this system attractive in the transition-metal-catalyzed asymmetric synthesis of high-valued specialty chemicals, though further refinements on detailed configurations have to be developed before a genuine practical heterogeneous chiral catalyst can be achieved for general use.

Figure 4.1 Schematic diagram of supported aqueous phase asymmetric catalysis



# TABLE 4.1

Homogeneous, asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid by $[Ru(BINAP\text{-}4SO_3Na)(benzene)]^{2+}$ complex in methanolic solvents at room temperature.

| Entry | Solvent | S/C[a] | Hydrogen Pressure (psig) | T.O.F. ($hr^{-1}$)[b] | e.e. (%)[c] |
|---|---|---|---|---|---|
| 1 | MeOH | 50 | 1370 | -- | 86.0 (R) |
| 2 | MeOH | 53 | 500 | -- | 84.7 (R) |
| 3 | 1:1 MeOH/$H_2O$ | 25 | 1320 | -- | 78.9 (R) |
| 4 | 1:1 MeOH/$H_2O$ | 25 | 1340 | -- | 75.1 (R)[d] |
| 5 | MeOH | 25 | 1370 | -- | 89.5 (R)[d] |
| 6 | MeOH | 25 | 1360 | -- | 91.0 (R)[d] |
| 7 | MeOH | 101 | 1350 | 131 | 88.2 (R) |
| 8 | MeOH | 101 | 1350 | 927 | 91.5 (R)[d] |
| 9 | MeOH | 51 | 1370 | -- | 86.2 (R)[e] |
| 10 | 1:1 MeOH/$H_2O$ | 51 | 1320 | -- | 75.7 (R)[e] |
| 11 | 1:1 MeOH/$H_2O$ | 50 | 1350 | 0.77[f] | -- |
| 12 | 1:1 MeOH/$H_2O$ | 52 | 1350 | -- | 77.6 (R)[g] |
| 13 | MeOH | 52 | 500 | -- | 87.5 (R)[d] |
| 14 | MeOH | -- | 500 | -- | 93.3 (S)[d,h] |
| 15 | MeOH | 100 | 1230 | -- | 96.1 (R)[d,i] |
| 16 | MeOH | -- | 500 | -- | 96.0 (S)[d,h,j] |

*a* substrate to ruthenium ratio

*b* initial turnover frequency

*c* e.e. determined at 100% conversion

*d* with added triethylamine, $Et_3N$/substrate = 1

*e* with added sodium 3-pyridinesulfonate, m-$SO_3Na$-pyridine/substrate = 1

*f* with added concentrated sulfuric acid in 10 times excess of substrate

*g* with added tetrahydrofuran in 1.9 times excess of substrate

*h* ref. 43

*i* reaction temperature = 4°C

*j* reaction temperature = 0°C

TABLE 4.2

Two-phase, asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid by [Ru (BINAP-4$SO_3Na$)(benzene)]$^{2+}$ complex in 1:1 ethyl acetate/water solvent mixture at room temperature.

| Entry | S/C[a] | Hydrogen Pressure (psig) | Stirring Speed (rpm) | Reaction Time (D) | Conv. (%) | T.O.F. ($hr^{-1}$)[b] | e.e. (%) |
|---|---|---|---|---|---|---|---|
| 1 | 50 | 1380 | 250 | 3.5 | 53.6 | 0.34 | 78.4 |
| 2 | 25 | 1360 | 250 | 1.5 | 56.7 | -- | 81.1 |
| 3 | 25 | 1360 | 250 | 1.5 | 56.4 | -- | 78.0[c] |
| 4 | 25 | 1370 | 250 | 1.5 | 57.0 | -- | 82.7[d] |
| 5 | 15 | 1365 | 450 | 2.8 | 90.0 | 0.20 | 77.2[e] |
| 6 | 14 | 1320 | 400 | 2.5 | 100.0 | -- | 73.0[f] |

*a* substrate to ruthenium ratio

*b* initial turnover frequency

*c* aqueous solution recycled once

*d* aqueous solution recycled twice

*e* reaction temperature = 5°C

*f* with added triethylamine, $Et_3N$/substrate = 1

# TABLE 4.3

Heterogeneous, asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid by SAP-Ru-BINAP-4$SO_3Na$ catalyst in ethyl acetate.

| Entry | Cycle[a] | Solvent | S/C[b] | Hydrogen Pressure (psig) | Stirring Speed (rpm) | e.e. (%) |
|---|---|---|---|---|---|---|
| 1 | 0 | AcOEt (40µl $H_2O$) | 25 | 1300 | 350 | 28.7 (R) |
| 2 | 0 | AcOEt ($H_2O$ sat.) | 33 | 1300 | 350 | 69.0 (R)[c] |
| 3 | 1 | AcOEt ($H_2O$ sat.) | 30 | 500 | 350 | 68.3 (R) |
| 4 | 1 | AcOEt ($H_2O$ sat.) | 25 | 1330 | 350 | 68.6 (R)[c] |
| 5 | 2 | AcOEt ($H_2O$ sat.) | 25 | 1330 | 350 | 70.0 (R)[c] |
| 6 | 0 | AcOEt ($H_2O$ sat.) | 30 | 1360 | 300 | 67.0 (R) |
| 7 | 1 | AcOEt ($H_2O$ sat.) | 30 | 1360 | 300 | 67.0 (R) |
| 8 | 2 | AcOEt ($H_2O$ sat.) | 31 | 1360 | 300 | 66.0 (R) |
| 9 | 0 | AcOEt ($H_2O$ sat.) | 30 | 1330 | 500 | 69.0 (R) |
| 10 | 1 | AcOEt ($H_2O$ sat.) | 30 | 1250 | 500 | 65.0 (R) |
| 11 | 2 | AcOEt ($H_2O$ sat.) | 30 | 1050 | 550 | 66.0 (R) |
| 12 | 3 | AcOEt ($H_2O$ sat.) | 30 | 1260 | 350 | 77.0 (R)[d] |
| 13 | 5 | AcOEt ($H_2O$ sat.) | 31 | 1360 | 350 | 62.8 (R)[e] |
| 14 | 6 | AcOEt ($H_2O$ sat.) | 30 | 1350 | 350 | 63.6 (R) |
| 15 | 7 | AcOEt ($H_2O$ sat.) | 30 | 1370 | 350 | 64.6 (R)[c,e] |
| 16 | 0 | AcOEt (200µlNaOH) | 30 | 1380 | 350 | 62.8 (R)[f] |
| 17 | 1 | AcOEt (NaOH sat.) | 30 | 1380 | 350 | 59.9 (R)[f] |
| 18 | 2 | AcOEt (NaOH sat.) | 30 | 1000 | 350 | 59.8 (R)[f] |
| 19 | 3 | AcOEt (NaOH sat.) | 30 | 500 | 350 | 58.6 (R)[f] |
| 20 | 4 | AcOEt ($H_2O$ sat.) | 30 | 1350 | 350 | 62.7 (R) |

*a* number of catalyst recycles

*b* substrate to ruthenium ratio

*c* no ruthenium found in the filtrate with a detection limit of 1 ppm

*d* reaction temperature = 8°C

*e* with added triethylamine, $Et_3N$/substrate = 1

*f* with 0.22 M sodium hydroxide solution

## TABLE 4.4

Catalytic activity as a function of water content in the heterogeneous, asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid by SAP-Ru-BINAP-4$SO_3Na$ catalyst in ethyl acetate.

| Entry | S/C[a] | Hydrogen Pressure (psig) | Water Content (μl)[b] | T.O.F. ($hr^{-1}$)[c] |
|---|---|---|---|---|
| 1 | 33 | 1330 | 0 | <0.008 |
| 2 | 25 | 1330 | 40 | 0.22 |
| 3 | 30 | 1350 | 125 | 0.25[d] |
| 4 | 30 | 1360 | 145 | 1.06[d] |
| 5 | 31 | 1370 | 160 | 2.35[d] |
| 6 | 30 | 1400 | 195 | 2.84[d] |
| 7 | 30 | 1370 | 215 | 5.12[d] |
| 8 | 32 | 1370 | 270 (saturated) | 18.21[d] |

[a] substrate to ruthenium ratio

[b] hydrogenations were carried out in 10 ml of ethyl acetate at room temperature and with 350 rpm stirring speed, [substrate]=4.6-4.8x$10^{-3}$M

[c] initial turnover frequency

[d] no ruthenium found in the filtrate with a detection limit of 1 ppm.

## REFERENCES


1. Parshall, G.W., "Homogeneous Catalysis," Wiley: New York, 1980.
2. Parshall, G.W., and Nugent, W.A., *Chemtech* March, 184 (1988).
3. Parshall, G.W., and Nugent, W.A., *Chemtech* May, 314 (1988).
4. Parshall, G.W., and Nugent, W.A., *Chemtech* June, 376 (1988).
5. Noyori, R., *Chem. Soc. Rev.*, 187 (1989), and references cited therein.
6. Kagan, H.B., *in* " Asymmetric Synthesis," (Morrison, J.D., Ed.) Vol. 5, p.1, Academic Press: Orlando, 1985, and references cited therein.
7. Karim, A., Mortreaux, A., and Petit, F., *J. Organomet. Chem.* **312**, 375 (1986).
8. Bailey, D.C., and Langer, J.H., *Chem. Rev.* **81**, 109 (1981).
9. Hartley, F.R., *in*" Supported Metal Complexes," (Ugo R., and James, B.R., Eds.) Reidel, New York, 1985.
10. Pittman, C.U., *in*" Comprehensive Organometallic Chemistry," (Wilkinson, G., Stone, F.G.A., and Abel, E.W., Eds.) Chap. 55. Pergamon Press: Oxford, 1982.
11. Lamb, H.H., Gates, B.C., Knozinger, H., *Angew. Chem. Int. Ed. Engl.* **27**, 1127 (1988).
12. Tai, A., and Harada, T., *in* " Taylored Metal Catalysts," (Iwasawa, Y., Ed.) p. 265. Reidel, D., Dordrecht, 1986.
13. Morrison, J.D.," Asymmetric Synthesis," Vol. 5. Academic Press: Orlando, 1985.

14. Morrison, J.D., and Mosher, H.S.," Asymmetric Organic Reactions." ACS Washington D.C., 1976.

15. Izumi, Y., *Adv. Cat.* **32**, 215 (1983).

16. Brunner, H., *Topics in Stereochemistry* **18**, 129 (1988).

17. Bartok, M., *in*" Stereochemistry of Heterogeneous Metal Catalysts" Chap. XI, p. 511. J. Wiley, New York, 1985.

18. Pracejus, H., *Fortschr. Chem. Forsch.* **8**, 493 (1967).

19. Inoue, S., *Adv. Polym. Sci.* **21**, 78 (1976).

20. Aglietto, M., Chiellini, E., D'Antone, S., Ruggeri, G., and Solaro, R., *Pure & Appl. Chem..***60**, 415 (1988).

21. Fish, M.J., and Ollis, D.F., *Cat. Rev.-Sci. Eng.* **18**, 259 (1978).

22. Mathieu, J., and Weill-Raynal, J., *Bull. Soc. Chim. Fr.* 1211 (1968).

23. Blaser, H.U., Jalett, H.P., and Wiehl, J., *J. Mol. Catal.* **68**, 215 (1991).

24. Blaser, H.U., Boyer, S.K., and Pittelkow, U., *Tetrahedron: Asymmetry* **2**, 721 (1991).

25. Noyori, R., and Kitamura, M., *in*" Modern Synthetic Methods," (Scheffold, R., Ed.) p. 115. Springer Verlag, Berlin, 1989.

26. Pittman, C.U., and Evans, G.O., *Chemtech* 560 (1973).

27. Manassen, J., " Catalysis Progress in Research," (Basolo, F., and Burwell, R.L., Jr., Ed.) p. 117. Plenum Press, New York, N.Y., 1973.

28. Bailar, J.C., *Catal. Rev.* **10**, 17 (1974).

29. Leznoff, C., *Chem. Soc. Rev.* **3**, 65 (1974).

30. Manassen, J., *in*" Catalysis, Heterogeneous and Homogeneous," (Delmon, B., and Jannes, G., Ed.) p. 293. American Elsevier, New York, N.Y., 1975.

31. Grubbs, R.H., Gibbons, C., Kroll, L.C., Bonds, W.D. Jr., and Brubaker, C.H. Jr., *J. Am. Chem. Soc.* **95**, 2373 (1973).

32. Bruner, H., and Bailer, J.C. Jr., *Inorg. Chem.* **12**, 1465 (1973).

33. Grubbs, R.H., Kroll, L.C., and Sweet, E.M., *J. Macromol. Sci., Chem.* **7**, 1047 (1973).

34. Dumont, W., Poulin, J.C., Dang, T.P., and Kagan, H.B., *J. Am. Chem. Soc.* **95**, 8295 (1973).

35. Corma, A., Iglesias, M., Pino C.del, and Sanchez, F., *J. C. S., Chem. Commun.* 1253 (1991).

36. Sanchez, F., Iglesias, M., Pino C.del, and Corma, A., *J. Mol. Catal.* **70**, 369 (1991).

37. Corma, A., Iglesias, M., Pino C. del., and Sanchez, F., *J. Organomet. Chem.* **431**, 233 (1992).

38. Arhancet, J.P., Davis, M.E., Merola, J.S., and Hanson, B.E., *Nature* **339**, 454 (1989).

39. Wan, K.T., and Davis, M.E., *Tetrahedron: Asymmetry* **4**, No. 12, 2461-2468, 1993.

40. Wan, K.T., and Davis, M.E., *J. C. S., Chem. Commun.* 1262 (1993).

41. Arhancet, J.P., Davis, M.E., Merola, J.S., and Hanson, B.E., *J. Catal.* **121**, 327 (1990).

42. Arhancet, J.P., Davis, M.E., and Hanson, B.E., *J. Catal.* **129**, 94 (1991).

43. Chan, A.S.C., Laneman, S.A., and Miller, R.E., *in*" Selectivity In Catalysis," (Davis, M.E., and Suib, S.L., Eds.) Chap. 3, p. 27.ACS Symposium Series 517, 1993.

44. Amrani, Y., Lecomte, L., Sinou, D., Bakos, J., Toth, I., and Heil,. B., *Organometallics* **8**, 542 (1989).

45. Bartik, T., Bartik, B., Hanson, B.E., Guo, I., and Toth, I., *Organometallics* **12**, 164 (1993).

46. Hoke, J.B., Hollis, L.S., and Stern, E.W., *J. Organomet. Chem.* **455**, 193 (1993).

47. Halpern, J., and Ashby, M.T., *J. Am. Chem. Soc.* **113**, 589 (1991).

# CHAPTER FIVE

## Asymmetric Synthesis of Naproxen
## by
## A New Heterogeneous Catalysis

## ABSTRACT

A new heterogeneous, asymmetric catalyst is described. The catalyst is a modified version of the supported aqueous-phase catalyst reported previously (*1*), ethylene glycol is used in place of water as the hydrophilic phase. Both the enantioselectivity and the activity of this new heterogeneous catalyst are comparable to the homogeneous analogue in neat methanol (or ethylene glycol); e.e.'s: 95.7% vs. 96.1% and t.o.f.'s: 40.7 $hr^{-1}$ vs. 131.0 $hr^{-1}$, respectively. Recycling of the catalyst is possible without leaching of ruthenium at a detection limit of 32 ppb.

## INTRODUCTION

Recently, we reported on the development of an asymmetric version of supported aqueous phase catalysis (SAPC) (*1*). SAP catalysis enables the efficient use of a water-soluble organometallic complex to promote the reaction of substrates soluble in organic solvents (*2*). In our previously reported SAP system (*1*), the water-soluble ruthenium complex, [Ru(BINAP-4SO3Na)(benzene)Cl]Cl (BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ), was impregnated onto a CPG support by the incipient wetness technique and the bulk water vacuum evaporated away. Both the activity and the enantioselectivity of the SAP catalyst were found to be sensitive to the amount of water on the catalyst. An *in-situ* organic-phase impregnation of water onto the "dried" SAP catalyst was developed to activate the catalyst. We speculated that the increase in mobility of the ruthenium complex on the support with increasing water loading led to increases in both the activity and the enantioselectivity of the hydrated SAP catalyst. It was shown also that the enantioselectivity limit of the hydrated SAP catalyst could approach that of its two-phase ( ethyl acetate - water ) analogue. This indicates that the ruthenium complex on the CPG support is more or less as mobile as in homogeneous medium. This is an important point in the immobilization of homogeneous catalysts onto solid supports. Usually, the homogeneous catalysts are covalently bonded to the support and reveal limited mobility (*3*). This normally leads to an undesirable loss in activity and/or selectivity. In the SAP system, it is the

aqueous catalyst solution that is immobilized on the support, not the individual organometallic complexes. This unique feature of the SAP catalyst may allow for the development of the first genuine hybrid of an active/selective homogeneous catalyst with all the features of a heterogeneous catalyst.

The organometallic ruthenium catalyst used in the asymmetric SAP catalyst was found to exhibit a solvent dependent enantioselectivity when operated homogeneously (*1,4*). Although the homogeneous organometallic ruthenium catalyst was effective in promoting the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid with 96% e.e. in neat methanol, its enantioselectivity dropped to about 80% e.e. in water (*1*). As a result, the enantioselectivity of the hydrated SAP catalyst (up to 77% e.e.) was bounded by the intrinsic enantioselectivity limit of the organometallic ruthenium complex in neat water. Hence, further refinements on the SAP catalyst have to be made before a practical, heterogeneous, chiral catalyst can be developed for general use.

We now report a new heterogeneous catalyst and its use in the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid to naproxen. Here, we describe the new catalyst composition, a new method for the activation of the "dried" catalyst and reaction conditions that prevent leaching.

## EXPERIMENTAL

### *Materials*

Controlled pore glass CPG-240 (a narrow pore-size distribution glass: mean pore diameter = 242Å, pore volume = 0.89ml/g, surface area = 79$m^2$/g, mesh size = 120/200), benzeneruthenium (II) chloride dimer, ethyl acetate, cyclohexane, chloroform, ethylene glycol and triethylamine were purchased in their highest purity available and used as received. 2-(6'-Methoxy-2'-naphthyl)acrylic acid was received as a gift from Monsanto Company. The sodium salt of tetra-sulfonated BINAP was prepared as reported previously (*5*). Unless stated otherwise, all manipulations were performed under argon or nitrogen. Deionized water, distilled over potassium permanganate was used in all operations requiring water. All solvents, including water, were degassed by four to five freeze-pump-thaw cycles.

### *Catalyst preparation and activation procedure*

The active organometallic ruthenium catalyst, [Ru(BINAP-4$SO_3$Na)(benzene)Cl]Cl, was prepared and impregnated onto the CPG support by the previously described procedures (*1*). The water content of this "dried" catalyst was estimated by thermogravimetric analysis to be 1.9 wt%, while the ruthenium contents were 1.2-2.5x$10^{-5}$ mol/g. Anhydrous

ethylene glycol was used to activate the "dried" catalyst. The impregnation was performed by two different techniques: (A) by the *in-situ* activation with ethylene glycol in ethyl acetate (ethylene glycol partitions between the organic solvent and the surface of the CPG), and (B) as follows. The "dried" catalyst was stirred in ethyl acetate that had been previously premixed with a controlled amount of ethylene glycol. The highly polar ethylene glycol was allowed to partition between the ethyl acetate phase and the CPG surface for about an hour. Because of a small partition coefficient for ethylene glycol between the CPG support and the ethyl acetate, it was found that most of the ethylene glycol remained in the organic phase upon contact with the "dried" catalyst. This procedure was then repeated. The bulk organic phase was then removed by filtration and the resulting catalyst was washed several times with a 1:1 chloroform and cyclohexane mixture that had been pre-mixed with ethylene glycol.

*Reaction conditions and analytical methods*

Asymmetric hydrogenations of 2-(6'-methoxy-2'-naphthyl)acrylic acid were conducted at various temperatures in a 25 ml stainless steel Parr batch reactor. Special care was taken in order to avoid the presence of oxygen at all times. Catalysts with various amount of ethylene glycol loading were used. Both the neat ethyl acetate and the 1:1 mixture of chloroform/cyclohexane were used as the bulk organic phase (5ml). The conversion was measured by $^{1}H$ NMR spectroscopy on a G.E. QE-300 spectrometer at 300 MHz and the enantiomeric excess (e.e.) determined by

HPLC using a 25cm x 4.6cm i.d. Regis (S,S)-Whelk-O 1 column without derivatization. Thermogravimetric analyses (TGA) were obtained in air on a Du-Pont 951 thermogravimetric analyzer. Ruthenium analyses of the reaction filtrates were performed by Galbraith Laboratories Inc. (Knoxville, TN).

## RESULTS AND DISCUSSION

With a multi-million-dollar-a-year market, naproxen is currently the object of intense study by generic drug manufacturers (*6*). Hence, the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid (substrate **1**; a precursor to naproxen) was again chosen to be our model reaction in this study (Figure 5.1). The results from this new heterogeneous catalyst are compared to those from the original hydrated SAP catalyst as well as the homogeneous and two-phase analogues (*1*).

In our early study, we have shown that the presence of water tends to lower the enantioselectivity in the homogeneous hydrogenation of substrate **1** in methanolic solvents (*1*). Aquation of the ruthenium-chloro bond in water was found to be responsible for this solvent dependent enantioselectivity. To prevent the cleavage of the ruthenium-chloro bond, anhydrous ethylene glycol is used here in place of water. The $^{31}P$ NMR spectrum of the ruthenium complex in 1:1 $CD_3OD$/ethylene glycol reveals

the same two doublets ( $\delta$ = 63.0 and 68.8 ppm; J $\approx$ 45 Hz ) as is found in neat methanol indicating that the ruthenium-chloro bond in [Ru(BINAP-4$SO_3$Na)(benzene)Cl]Cl is still intact. Upon addition of water, only a singlet ( $\delta$ = 57.5 ppm ) is observed in the $^{31}P$ NMR spectrum. These data suggest that a rapid hydrolysis of the ruthenium-chloro bond has occurred in the presence of water. As a result, hydrogenations of substrate **1** are carried out in the presence of ethylene glycol. Similar enantioselectivities (88-89% e.e.'s as shown in Table 5.1) are observed for reactions carried out in neat methanol, 1:1 methanol/ethylene glycol and also in neat ethylene glycol. These findings further support the premise that the cleavage of the ruthenium-chloro bond has a detrimental effect on enantioselectivity. Only a 79% e.e. was observed in a 1:1 MeOH/$H_2O$ solvent mixture (Table 5.1) (*1*). Since the highly polar ethylene glycol is not miscible with most organic solvents, it can be used as a substitute for the aqueous phase in the original SAP system; it replaces the role of water in the immobilization of the ruthenium catalyst onto the CPG support.

This new heterogeneous catalyst now consists of a ruthenium organometallic complex dissolved in a film of ethylene glycol which is supported on a high-surface-area hydrophilic CPG support (Figure 5.2). Similar to our previous findings with the hydrated SAP catalyst, both the activity and the enantioselectivity of the new catalyst are sensitive to the amount of ethylene glycol in the system. By using the *in-situ* organic-phase impregnation of ethylene glycol, controlled amounts of ethylene glycol are introduced into the ethyl acetate and used as the bulk organic

phase. Replacement of neat water with ethylene glycol results in at least a 3 times enhancement in the activity. An initial turnover frequency of 54.2 $hr^{-1}$ is observed at an ethylene glycol loading of 400 µl in 5 ml of ethyl acetate (Table 5.2), whereas only an 18.2 $hr^{-1}$ of initial turnover frequency was observed from the original hydrated SAP catalyst (*1*). More importantly, this activity is only 2-2.5 times slower than the homogeneous analogue in either neat methanol or neat ethylene glycol (Table 5.2). We speculate the higher intrinsic activity of the ruthenium organometallic catalyst in neat ethylene glycol be responsible for the high activity of the new catalyst. This is further evidenced by the finding of a reasonably high rate in the two-phase system (15.3 $hr^{-1}$). An almost 50-fold increase in activity is observed when ethylene glycol is used in place of water in the two-phase system ( 15.3 $hr^{-1}$ vs. 0.34 $hr^{-1}$ ).

With the *in-situ* activation (method A) using ethylene glycol, enantioselectivities are found to increase with increasing amount of ethylene glycol in the system. The enantioselectivities as a function of ethylene glycol content are listed in Table 5.3 (reaction conditions: substrate/ruthenium = 30, [substrate] = 3.6 x $10^3$ M, solvent volume = 5 ml, pressure = 1400 psig, T = 24°C, stirring speed = 350 rpm). At a maximum ethylene glycol loading of 400 µl ( in 5 ml of ethyl acetate ), an 87.7% e.e. is observed while only 45.0% e.e. is found for the system with 75 µl of ethylene glycol. This is in agreement with our previous findings for the hydrated SAP systems where the higher the water content the higher the enantioselectivity (*1*). More importantly, the new heterogeneous

catalyst with ethylene glycol as substitute for the aqueous phase has already achieved the same high enantioselectivity as its homogeneous analogue in neat methanol ( 87.7% vs. 88.2% ). By lowering the reaction temperature to 3°C, the e.e. is increased to 94.8%. However, unlike the homogeneous analogue in neat methanol (*1*), addition of triethylamine to the heterogeneous catalyst is found to have a detrimental effect on enantioselectivity. An almost 15% drop in e.e. is observed at room temperature upon addition of triethylamine. This is rather unexpected since we believe that the active ruthenium catalyst is nearly the same as the one in neat methanol. Solvation of the ruthenium complex with ethylene glycol may be responsible for the decline in enantioselectivity upon addition of base, but the detailed mechanism is still unclear. Similar drop in e.e. is also reported in our original hydrated SAP system (*1*).

For long-term stability, the heterogeneous catalyst must remain assembled. To test for this type of stability, a self-assembly test is performed in the following way: $1.1 \times 10^{-6}$ moles of [Ru(BINAP-4$SO_3$Na)(benzene)Cl]Cl is dissolved in 400 µl of ethylene glycol and loaded into a 25 ml Parr reactor. $5.7 \times 10^{-5}$ moles of substrate **1** in 5 ml of ethyl acetate is then added. Finally 0.1 g CPG-240 is added. The reactor is pressurized to 1,400 psig with hydrogen and stirred at 350 rpm and at room temperature. The reaction is stopped after one hour and analyzed. A control experiment is carried out in using exactly the same procedure with the exception that no CPG is added. Complete conversion of **1** is observed when CPG is added, while no detectable conversion is found in the control experiment. After the

reaction, the CPG support turns pale yellow and the bulk organic phase is colorless. These results indicate that, under the reaction conditions, the individual components of the heterogeneous catalyst self-assemble into a more thermodynamically stable supported-catalyst configuration. Therefore, the reverse, i.e., the separation of the solution and complex from the support, is unlikely to happen under reaction conditions because it is thermodynamically unfavorable. These results also support the inference that the reaction chemistry is taking place at the liquid-liquid interface. In the control experiment, most of the added ethylene glycol dissolved into the bulk organic phase and left behind small droplets of catalyst solution. The limited interfacial area of the catalyst solution that remains immiscible with the bulk organic phase results in the lack of activity in the control experiment.

Unlike the original hydrated SAP catalyst, traces of ruthenium are found in the reaction filtrates. The extent of ruthenium leaching was found to be correlated with the ethylene glycol content in the organic phase as evidenced by the data shown in Table 5.4. Since ethylene glycol is less polar than water, it is at least 3 times more soluble than water in ethyl acetate. The higher solubility of ethylene glycol in ethyl acetate may be responsible for the observed leaching of ruthenium into the bulk organic phase. In order to minimize the leaching of ruthenium into the bulk organic phase, a new method of activation of the "dried" catalyst with ethylene glycol was devised, and is described below.

The "dried" catalyst was activated by stirring it in an ethylene glycol/ethyl acetate solvent mixture. After equilibration for an hour at room temperature, the solid catalyst was filtered and dried at low vacuum ( 0.2 atm. ). The procedure was then repeated. Only a thin film of non-volatile ethylene glycol was deposited onto the solid catalyst. The amount of ethylene glycol in the film is more or less the same as that found with the original *in-situ* activation procedure, and a similar degree of mobility of the ruthenium complex on the support is to be expected. However, now an ethylene glycol-saturated organic phase is used so as to maintain the integrity of this film during the reaction. To minimize the amount of ethylene glycol used in the bulk organic phase, a rather non-polar 1:1 solvent mixture of cyclohexane and chloroform ( for solubilization of substrate ) is used. As shown in Table 5.5, the same high enantioselectivity (88.4% e.e. at room temperature) is still obtained with this kind of activation procedure and more importantly, no ruthenium is found in the reaction filtrate at a detection limit of 32 ppb! By lowering the reaction temperature to 3°C, an 95.7% e.e. is obtained with this new heterogeneous catalyst. As shown in Table 5.5, the present system is already as enantioselective as its homogeneous analogue ( 95.7% vs. 96.1% ). Recycling of the used catalyst is possible without any loss in enantioselectivity.

Using the new formulation, a self-assembly test was again carried out to test the long-term stability of the catalyst. $1x10^{-7}$ mole of the ruthenium complex in 50 μl of ethylene glycol was mixed with $4x10^{-6}$

moles of substrate **1** in 5 ml of 1:1 chloroform/cyclohexane. 0.2g of CPG-240 were added, then the reactor pressurized to 1,400 psig with hydrogen and then stirred at room temperature for 2 hours. Complete conversion was observed. However, less than 2% conversion was found from the control experiment where no CPG was added. These results again indicate that, under these new reaction conditions, the individual components of the present catalytic system self-assemble into the more stable supported-catalyst configuration.

As shown by the data in Table 5.2, the new heterogeneous catalyst activated by method B is slightly less reactive than the *in-situ* activated analogue ( 40.7 $hr^{-1}$ vs. 54.2 $hr^{-1}$ ). However, it is still only 2.5 times less active than its homogeneous counterpart in neat ethylene glycol. In principle, the catalyst activated by procedure B should be able to attain the same high activity as the *in-situ* activated analogue by using an impregnating solvent with higher content of ethylene glycol. As ethylene glycol will form two phases with ethyl acetate, there exists a certain upper limit for the ethylene glycol content in ethyl acetate. Therefore, it will be more desirable to have an impregnating solvent miscible with ethylene glycol. In this way, higher ethylene glycol content can be reached in a single impregnation. Since the ruthenium complex cannot be dissolved in acetone, acetone can be used as the impregnating solvent (in place of ethyl acetate). After the impregnation, the acetone can easily be removed by exposure to vacuum while leaving behind a thin film of ethylene glycol.

This type of impregnation method will allow for a fairly quantitative deposition of ethylene glycol onto the CPG support.

With comparable activity and enantioselectivity to the homogeneous catalyst, the present heterogeneous catalyst can be considered as a genuine hybrid of homogeneous and heterogeneous catalysts. As compared to the asymmetric hydrogenation catalysts anchored in modified USY zeolites (*7,8*), our system has several distinguishing features. The CPG support possesses large and uniform pore diameters that allow large bio-substrates access to the catalytic sites. Also, CPG supports are commercially available in a wide range of pore diameters ( 75 - 3000Å ); for the zeolite-supported catalyst (*7*), the small pore size (~8Å) limits the size of substrates. Furthermore, the active rhodium complex is covalently bonded to the zeolite framework and reasonable activity can only be reached at elevated temperature (60°C). In contrast, the active ruthenium complex in the present system is dissolved in ethylene glycol, which is immobilized as a thin film on the CPG support. At molecular level, this method of immobilization yields a heterogeneous catalyst that is basically the same as its homogeneous analogue, thus allowing for the high enantioselectivity and activity.

Figure 5.1 Reaction scheme for the reduction of substrate **1** to naproxen

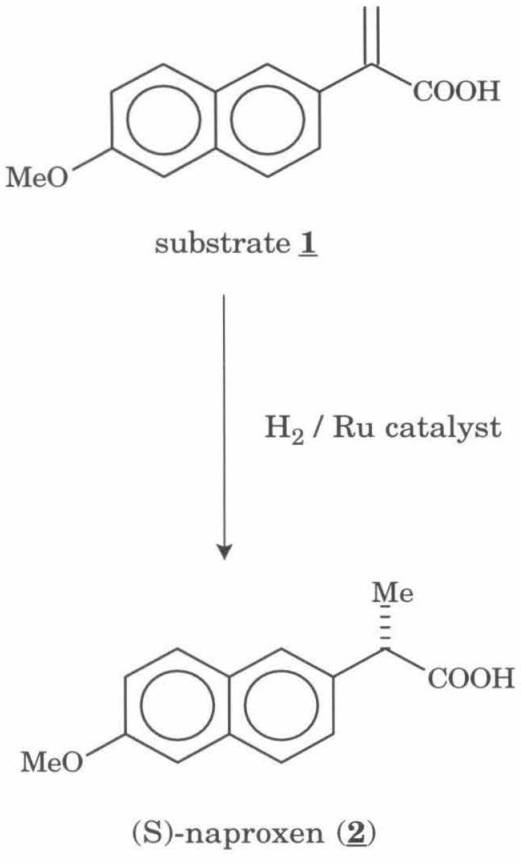


Figure 5.2 Schematic diagram of the new heterogeneous catalyst

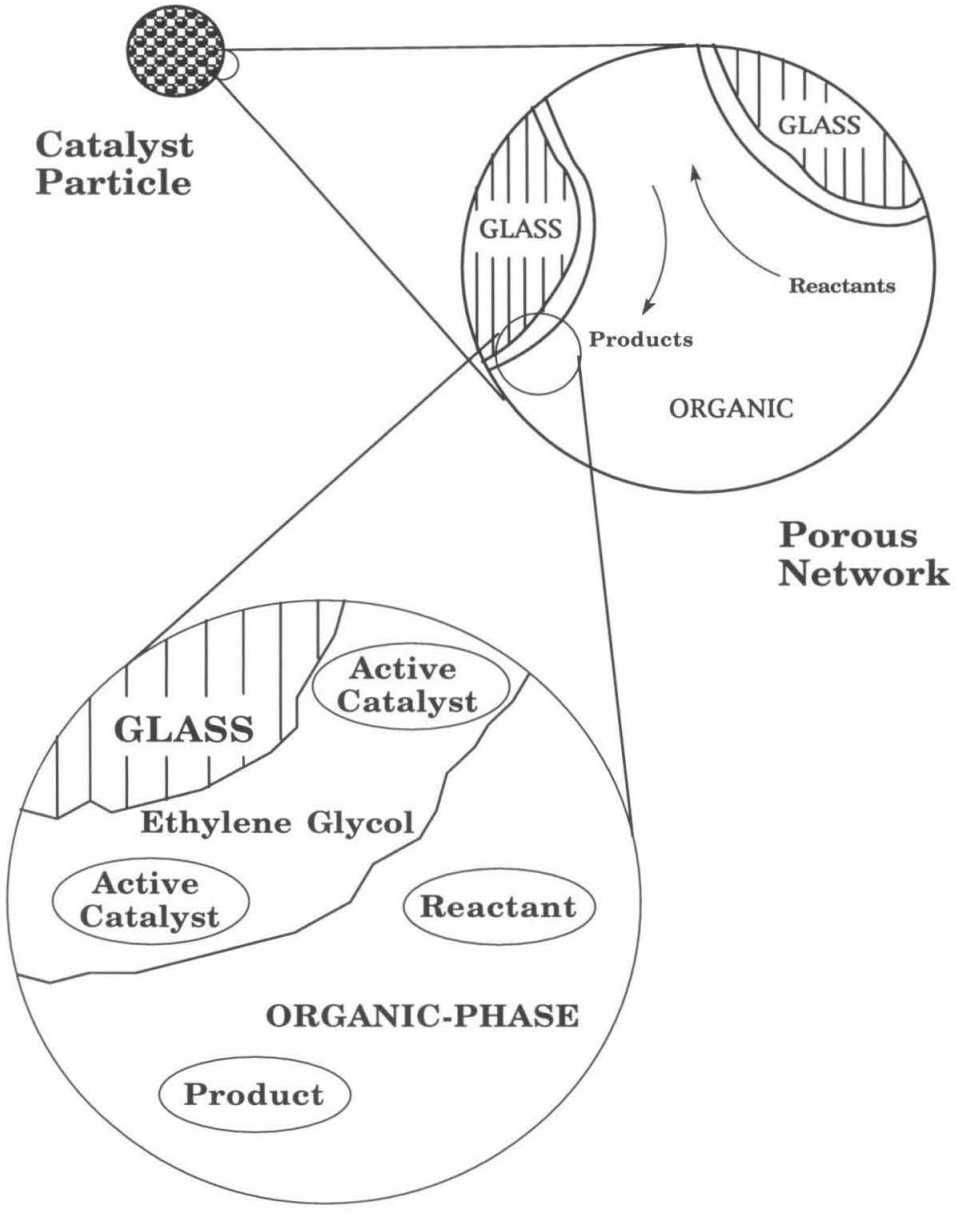


Table 5.1 Homogeneous reduction of substrate **1**†

| Solvent | e.e. (%) |
|---|---|
| MeOH | 88.2 |
| 1:1 MeOH/$HOCH_2CH_2OH$ | 89.1 |
| $HOCH_2CH_2OH$ | 88.7 |
| 1:1 MeOH/$H_2O$ | 78.9# |

†: substrate/ruthenium = 100; 1350-1450 psig of hydrogen and at room temperature

#: ref. 1

Table 5.2 Activities of various catalytic systems in the reduction of substrate **1***

| Catalyst | Solvent | t.o.f. ($hr^{-1}$) |
|---|---|---|
| Homogeneous# | MeOH | 131.0 |
| Homogeneous | $HOCH_2CH_2OH$ | 103.4 |
| Two-phase | $HOCH_2CH_2OH$/AcOEt | 15.3 |
| Two-phase# | $H_2O$/AcOEt | 0.34 |
| Heterogeneous† | AcOEt | 54.2 |
| Heterogeneous‡ | 1:1 $CHCl_3$/Cyclohexane | 40.7 |
| SAP (hydrated)# | AcOEt | 18.2 |

*: substrate/ruthenium = 30-100; $H_2$ pressure = 1350-1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm

#: ref. 1

†: *in-situ* catalyst activation with method (A)

‡: catalyst activation with method (B) and reaction carried out in 1:1 chloroform/cyclohexane

Table 5.3 Enantioselectivities in the reduction of substrate **1** as a function of ethylene glycol content in the organic phase†

| Ethylene glycol content (µl) | e.e. (%) |
|---|---|
| 75 | 45.0 |
| 150 | 72.1 |
| 270 | 82.1 |
| 350 | 84.2 |
| 350 | 71.3[a] |
| 350 | 91.1[b] |
| 400 | 87.7 |
| 400 | 94.8[b] |

†: catalysts were activated by *in-situ* organic-phase impregnation with 5 ml of ethyl acetate; substrate/ruthenium = 30; pressure = 1400 psig and at room temperature

a: with addition of triethylamine

b: reaction temperature = 3°C

Table 5.4 Ruthenium leaching as a function of ethylene glycol content in the reduction of substrate **1**[*]

| Ethylene glycol content[†] (μl) | Ruthenium[‡] (ppm) |
|---|---|
| 150 | 0.17 |
| 270 | 0.27 |
| 350 | 0.23[a] |
| 400 | 0.37 |

*: substrate/ruthenium = 30; $H_2$ pressure = 1350-1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm

†: *in-situ* catalyst activation with method (A)

‡: ruthenium content in the reaction filtrates

a: reaction temperature = 3°C

Table 5.5 Enantioselectivities in the reduction of substrate **1** with ruthenium catalysts in different configurations*

| Catalyst | Solvent | e.e. (%) |
|---|---|---|
| Heterogeneous‡ | 1:1 $CHCl_3$/Cyclohexane | 88.4 |
| Heterogeneous‡ | 1:1 $CHCl_3$/Cyclohexane | 95.7[a] |
| Heterogeneous† | AcOEt | 87.7 |
| Heterogeneous† | AcOEt | 94.8[a] |
| Homogeneous# | MeOH | 88.2 |
| Homogeneous# | MeOH | 96.1[b] |

*: substrate/ruthenium = 30-100; $H_2$ pressure = 1350-1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm

‡: catalysts activation with method (B)

†: *in-situ* catalyst activation with method (A)

#: ref. 1

a: reaction temperature = 3°C

b: reaction temperature = 4°C in ref. 1

## REFERENCES


1. Wan, K.T. and Davis, M.E., *J. Catal.* 1994, in press.
2. Arhancet, J.P., Davis, M.E., Merola, J.S. and Hanson, B.E., *Nature* **339**, 454 (1989).
3. Hartley, F.R. , *in* "Supported Metal Complexes," (Ugo, R., and James, B.R. Eds.) Reidel, New York, 1985.
4. Wan, K.T. and Davis, M.E., *Tetrahedron: Asymmetry* **4**, 2461 (1993).
5. Wan, K.T. and Davis, M.E., *J.C.S., Chem. Commun.* 1262 (1993).
6. Stinson, S.C., *Chem. Eng. News*, Oct. 16, 37 (1989).
7. Corma, A., Iglesias, M., Pino, C. del, and Sanchez, F., *J.C.S., Chem. Commun.* 1253 (1991).
8. Sanchez, F., Iglesias, M., Pino, C. del, and Corma, A., *J. Mol. Catal.* **70**, 369 (1991).

# CHAPTER SIX

## Conclusions

In this work, a water-soluble analogue of BINAP was synthesized. A rhodium complex of this ligand was found to be the first water-soluble catalyst to exhibit higher enantioselectivities in the reduction of 2-acylamino acid precursors in neat water than in other alcoholic solvents. More importantly, the e.e. obtained in neat water is as high as that of the non-sulfonated Rh-BINAP system in organic media. Additionally, the presence of four bulky sulfonate groups results in an enantioselectivity that is independent of the substrate concentration.

The versatility of this new water-soluble ligand was further enhanced by the preparation of the first reported ruthenium (II) sulfonated chiral diphosphine complex. Because of a wider range of substrates that can be converted at high e.e.'s, the ruthenium sulfonated-BINAP system greatly expands the use of asymmetric catalysis by water-soluble organometallic complexes. Being more stable than the rhodium analogue, the ruthenium complex was used in the fabrication of the asymmetric version of the supported aqueous-phase catalyst. Both the activity and the enantioselectivity of the hydrated SAP catalyst are dependent on the water content. These results suggest that the mobility of the active organometallic complex on the surface of the CPG support is critical to the overall performance of the SAP catalyst.

During the progress of this work, it was found that the aquation of ruthenium-chloro bond in water was detrimental to the enantioselectivity with some substrates, and so the performance of the hydrated SAP catalyst

was bounded by the intrinsic enantioselectivity limit of the ruthenium complex in water. Nevertheless, the concept of supported aqueous-phase catalysis was proven to be applicable to asymmetric catalysis.

Replacement of water with anhydrous ethylene glycol was found to allow for the retention of the ruthenium-chloro bond and thus the same high level of enantioselectivity was obtained in the reduction of 2-(6'-methoxy-2'-naphthyl)acrylic acid (**1**) either in neat methanol, neat ethylene glycol or 1:1 mixture of methanol and ethylene glycol. Through a modification in the composition of the original hydrated SAP catalyst, a new generation of heterogeneous catalyst was prepared. Anhydrous ethylene glycol was used in place of water as the hydrophilic film that was supported on the CPG, and a hydrophobic solvent immiscible with the components of the supported film was used as the bulk organic phase (1:1 v/v mixture of chloroform and cyclohexane). The asymmetric reduction of 2-(6'-methoxy-2'-naphthyl)acrylic acid (**1**) to the commercially important, non-steroidal, anti-inflammatory agent, naproxen was used to illustrate the efficacy of this new catalyst. The reaction proceeds over the catalyst at one-third of the rate observed in homogeneous solution and gives an 96% e.e. with no leaching of the organometallic complex into the bulk organic phase at a detection limit of 32 ppb. The long-term stability of this new catalyst composition was proven by a self-assembly test.

One of the unique features of this new heterogeneous, asymmetric catalyst, which is also one of the reasons for its success, is the method of

immobilization. Rather than immobilizing the active organometallic complex through a covalent bond to a supporting surface; which usually leads to a significant loss in activity, here the hydrophilic phase containing the organometallic complex and ethylene glycol is immobilized onto the support. At molecular level, this method of immobilization yields a heterogeneous catalyst that is basically the same as its homogeneous analogue, thus allowing for high enantioselectivity and activity.

By successful implementation of prescribed steps, a true, heterogeneous, asymmetric catalyst with high enantioselectivity and activity was developed. The strategies outlined here are general, and can hopefully be applied to the development of other heterogeneous, asymmetric catalysts.