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Stereoselective Organic Reactions in Water

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Contents

Ulf Lindström was born in 1971 in Malmö, Sweden. He studied Chemistry and Biology at Lund University to receive his B.Sc. degree in 1996. After earning a licentiate degree in Engineering at Lund Institute of Technology in 1998, he moved to Stockholm University to complete his doctoral thesis in 2000 under the supervision of Professor Peter Somfai. His Ph.D. work mainly concerned the development of new methods of preparing optically active nitrogen heterocycles. He then moved to California and Stanford University for postdoctoral research with Professor Eric T. Kool. There he was exposed to different aspects of nucleic acid chemistry, for example, the synthesis and molecular recognition of circular DNA. He joined the Department of Bioorganic Chemistry at Lund University as Assistant Professor in the spring of 2002. His research interest, in general, is molecular recognition and reactivity in water and, in particular, the development of chiral ligands for aqueous asymmetric synthesis.

I. Introduction

Many organic chemists, myself included, will remember being told in early undergraduate years “in organic synthesis water is a contaminant”. From the very beginning it was made clear to you that in order to become proficient in organic synthesis, the first step was knowing how to dry your glassware, reagents, and solvents. Extreme measures should always be taken to avoid even trace quantities of water in your reaction flask, unless of course water was used as a reactant. In undergraduate labs, water was always the usual suspect whenever a reaction gave an unexpected outcome; “My reaction did not work”! “Well, was your glassware properly dried?” With the paradigm being that water has an adverse effect on most organic reactions, it may require a significant mind leap to think of water as a versatile solvent for organic synthesis.

Nevertheless, in the most recent decades, chemists have begun investigating the possibility of using water as solvent for organic reactions, with sometimes surprising and unforeseen results. Without overlooking some earlier contributions, the discover-

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ies made in the laboratories of Breslow[1−3] and Grieco[4,5] in the early 1980s on the positive effect of water on rates and selectivities of Diels−Alder reactions are often recognized as the "Big Bang" in aqueous synthesis that triggered a more widespread interest in the field. Since then, significant progress has been made in the field of organic chemistry in water/aqueous media, and new additions are continuously being made to the list of organic transformations that can be performed efficiently in aqueous solvent. Besides the Diels−Alder reaction, other examples include Claisen-rearrangements,[6,7] aldol reactions,[8,9] allylation reactions,[10−12] and oxidations[13−15] and hydrogenations[16,17] of alkenes, to mention a few. These types of reactions have been among the most useful to the synthetic chemist for many decades and, indeed, still are. Their usefulness is reflected by the effort that has been devoted to the discovery of methods with which they can be executed catalytically and stereoselectively. With a few notable exceptions, however, the development of chiral ligands and catalysts for asymmetric synthesis has been carried out almost exclusively in organic media.

Is water, then, a viable alternative solvent? Over the last 5−10 years, the concept of efficient and stereoselective synthesis in water has been solidified as the rates, yields, and selectivities observed for many reactions in water have begun to match, or even surpass, those observed in organic solvents. In view of recent achievements, many of which will be highlighted in this article, the answer to the above question is "yes". From a less synthetic standpoint, increased appreciation of organic reactions in water may also contribute to our understanding of the basic mechanisms of life.

This review will focus on recent advances in performing diastereo- and enantioselective reactions in aqueous media. Examples of poorly selective transformations are only included if they add extra weight to a discussion or to illustrate an important concept. The reader will also be briefly introduced to fields of pertinence to any aspect of organic chemistry in water, such as means of solubilizing organic compounds and catalysis in water. Biocatalysis in aqueous media is beyond the scope of this article. Simple hydrolysis and phase-transfer reactions have also been arbitrarily excluded. Several review articles on organic synthesis in water have appeared during the past decade, and they are recommended to readers seeking a broader introduction to the topic.[18−21]

II. Water as Solvent

A. Why Water?

Until recently, the use of water as solvent for organic reactions was mainly restricted to simple hydrolysis reactions. Accordingly, most reagents and catalysts in organic synthesis have been imperiously developed for use in anhydrous, organic reaction media. Why should we now spend time "rediscovering" reactions for use in water that already work well in familiar organic solvents such as THF, toluene, or methylene chloride? Because there are many potential advantages of replacing these and other unnatural solvents with water. The most obvious are the following. (1) *Cost*. It does not get any cheaper than water! (2) *Safety*. Most of the organic solvents used in the lab today are associated with risks: Flammables, explosives, carcinogenics, etc. (3) *Environmental concerns*. The chemical industry is a major contributor to environmental pollution. With increasing regulatory pressure focusing on organic solvents, the development of nonhazardous alternatives is of great importance.

It is, however, important that the above listed benefits are not gained at the expense of synthetic efficiency. Even a small decrease in yield, catalyst turnover, or selectivity of a reaction can lead to a substantial increase in cost and amount of waste generated. Fortunately, many theoretical and practical advantages of the use of water as solvent for organic synthesis do exist. These will be elaborated upon below but are briefly introduced here. First, experimental procedures may be simplified since isolation of organic products and recycling of water-soluble catalysts and other reagents could be made by simple phase separation. Second, laborious protecting-group strategies for functionalities containing acidic hydrogens may be reduced. Third, water-soluble compounds could be used in their "native" form without the need for hydrophobic derivatization, again eliminating tedious protection−deprotection steps from the synthetic route. Fourth, as will be amply exemplified in this review, the unique solvating properties of water have been shown to have beneficial effects on many types of organic reactions in terms of both rate and selectivity.

B. Solubility of Organic Compounds in Water

Most chemical reactions are performed in solvents. The solvent provides a reaction medium in which reactants can be mixed over a very wide concentration range. In general, a good solvent should readily dissolve all or most of the participating reactants, should not interact adversely with the reaction, and should be easily separated during workup for facile isolation of products. On the basis of his/her knowledge of the chemical properties of the reactants, the chemist chooses a solvent which is suitable to meet these criteria. From this perspective, it is not surprising that water has found limited use as solvent for organic reactions. In truth, the poor solubility of reactants and the deleterious effect on many organic transformations are the main obstacles to the use of water as reaction solvent. Nonetheless, the fact that many of the most desirable target molecules, e.g., carbohydrates, peptides, nucleotides, and their synthetic analogues, as well as many alkaloids and important drugs are readily soluble in water is inconsistent with the disproportionate bias toward the use of organic solvents for their preparation. It can be argued that our shortcomings as synthetic chemists prompt the use of exhaustive protecting-group strategies, thus limiting the possibility of using water as solvent because of low solubility of the reactants. Moreover, with the limited arsenal of organic transformations in water that is presently available to the synthetic chemist, intermediates soluble in organic solvents are preferred to those soluble in water, even if it means adding extra synthetic steps for derivatization. This may have particular relevance in carbohydrate chemistry.

Notwithstanding the above, many organic targets and their intermediates have very low solubility in water, which may lead to thwarting of reactions due to phase separation and inefficient mixing of reactants, although heterogeneous mixtures may retain at least partly the positive influence of water, sometimes with the aid of sonication or microwave heating. A variety of strategies have been investigated in order to expand the scope of water-based organic synthesis to embrace also highly hydrophobic reactants, and these will be briefly discussed below. For a more comprehensive treatise, a thorough review of solubility and solubilization in aqueous media was recently published by Yalkowsky.[22]

1. Organic Cosolvents

One of the more efficient and versatile methods of increasing solubility and one that does not require modification of the solute is to use an organic cosolvent. The cosolvent reduces the hydrogen-bond density of aqueous systems, so that it is less effective in squeezing out nonpolar solutes from solution. Cosolvents can be structurally diverse, but they all carry hydrogen-bond donor and/or acceptor groups for aqueous solubility and a small hydrocarbon region that serves to disrupt the strong hydrogen-bond network of pure water, thereby increasing the solubility of nonpolar reactants.[22] Some of the most commonly used cosolvents are the lower alcohols, DMF, acetone, and acetonitrile. The increase in solubility, however, comes at the cost of many of the properties that make water a unique solvent for synthesis such as high polarity, high cohesive energy density, and the hydrophobic effect. The significance of this erosion of the bulk properties of water depends on the nature of the chemical reaction. Reactions that involve charged or highly polar species will suffer more by a decrease in solvent polarity than reactions involving only uncharged species. Likewise, reactions with a negative activation volume (Diels−Alder, Claisen rearrangement) are expected to be adversely affected by the addition of cosolvent because of the concurrent decrease in cohesive energy density. Nevertheless, because of the efficiency and flexibility of cosolvents in solubilizing organic solutes, the major part of the development of reactions in aqueous media has been made with water−cosolvent mixtures.

2. Ionic Derivatization (pH control)

Adding a positive or negative charge to an ionizable solute generally brings about a substantial increase in its solubility in water. Adjustment of solution pH is therefore an efficient method of solubilizing weak electrolytes in aqueous media.[23] This approach, of course, changes the chemical nature of the reactant and may limit its use as a method of solubilization for synthetic purposes. For some types of reactions, however, the presence of a charged, highly polar moiety can have a very positive effect. For example, the reactions of diene−carboxylates,[24] −sulfonates,[25] or −ammonium[26] salts with dienophiles in aqueous Diels−Alder reactions display significantly higher reaction rates over the corresponding neutral dienes. It is generally accepted that the rate enhancement of the Diels−Alder reaction in water is at least partly due to the influence of the hydrophobic effect in this media (see section V.A.1). In making the diene amphiphilic, increased solubility comes with the added bonus of an enhanced hydrophobic effect and faster reaction. This is principally the same effect one would achieve by adding “salting-out” agents known to increase the hydrophobic effect,[27] only in this case, the salt is the reactant itself. When a buffered reaction is feasible it is one of the more efficient ways to keep organic molecules solubilized. A potential practical advantage of using pH control in organic reactions is that the product may be recovered from solution by precipitation upon suitable adjustment of pH or by extraction after addition of appropriate phase-transfer counterions.

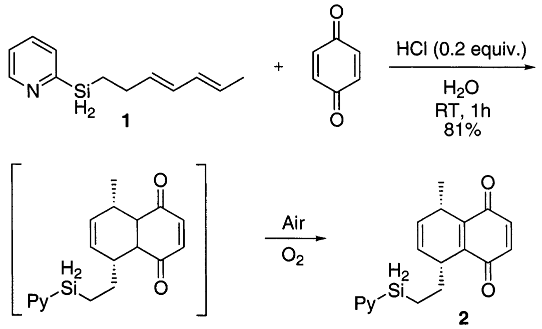
3. Surfactants

An intriguing means of achieving aqueous solubility is by using surfactants. These are amphiphilic molecules, that is, they contain one distinctly polar and one distinctly nonpolar region. In water, surfactants tend to orient themselves so that they minimize contacts between the nonpolar region and the polar water molecules and when the concentration of surfactant monomer exceeds a certain critical value (critical micelle concentration, CMC), micellization occurs. Micelles are spherical arrangements of surfactant monomers with a highly hydrophobic interior and a polar, water-exposed surface. Organic solutes interact with micelles according to their polarity; nonpolar solutes are buried in the interior of the micelle, moderately polar molecules locate themselves closer to the polar surface, while distinctly polar solutes will be found at the surface of the micelle. This compartmentalization of solutes is believed to be responsible for the observed catalytic or inhibitory influence on organic reactions in micellar media.[28] Micellar catalysis of organic reactions will be further discussed in section III.C.

4. Hydrophilic Auxiliaries

Another method to increase the solubility of aqueous organic reactions is by grafting hydrophilic groups onto insoluble reactants. This strategy has been only cautiously explored for synthetic purposes but has a pivotal role in medicinal chemistry and modern drug design because of the low water solubility of many drugs, which causes limited bioavailability and thus reduced therapeutic efficacy. One way of improving solubility of drugs is by converting them into water-soluble prodrugs through covalent attachment of a hydrophilic auxiliary. Ideally, the attachment should be of a transient and reversible nature, allowing for release of the parent drug from the auxiliary upon distribution, either by enzymatic or chemical means. The size and nature of the solubilizing function ranges from small to medium-sized, acidic and basic ionizable moieties (e.g., carboxylic

Scheme 1[a]



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acids, amines) to large, nonionizable side chains (e.g., poly(ethylene glycol) chains).[29]

Lubineau and co-workers demonstrated the usefulness of carbohydrates as solubilizing auxiliaries in the Diels–Alder reaction[30–33] and the Claisen rearrangement.[34,35] A more recent example of a removable hydrophilic auxiliary that may be of synthetic potential is the 2-pyridyldimethylsilyl group.[36] In its protonated form this group becomes miscible with water, and when attached to a hydrophobic side chain it induces molecular aggregation, much like a surfactant, creating a local hydrophobic microenvironment in which reactions can take place. The Diels–Alder reaction of **1** with *p*-benzoquinone in water containing 0.2 equiv of HCl was complete within 1 h to give the cycloadduct **2** as a single stereoisomer in 81% yield (Scheme 1). The auxiliary may be removed after reaction by oxidation with H_2O_2 to afford the corresponding alcohol.

III. Catalysis in Water

The development of novel catalysts is an important aspect of modern stereoselective synthesis. Considerable research has been focused on the development of chiral catalysts capable of selectively converting prochiral starting materials into homochiral products with great efficiency. A major driving force in this area has been the chemical industry and its continuous search for more cost- and performance-efficient processes. The chemical industry is, however, a major contributor to environmental pollution, largely due to the ubiquitous use of hazardous solvents. Out of the top 10 chemicals released or disposed of by the chemical industry in the mid-1990s, five were solvents, namely, methanol, toluene, xylene, methyl ethyl ketone, and methylene chloride.[37] With sharpened regulatory pressure focusing on organic solvents, the search for alternatives is of increasing importance. In this respect, the development of water-tolerant catalysts and water-soluble ligands has rapidly become an area of intense research.[38–42]

The field of chemical catalysis can be divided into two main categories: homogeneous catalysis, in which the catalyst is completely miscible with the solvent, and heterogeneous catalysis, in which the catalyst is a solid and catalysis occurs on a surface. There are clear advantages and disadvantages to both approaches. Homogeneous catalysis is characterized by superior activity and selectivity but usually involves a cumbersome process of separation of catalyst from reaction products and lowered activity of the recovered catalyst. On the other hand, heterogeneous catalysis allows for easy separation of the catalyst, but the reactions are often hampered by low activity and/or selectivity. Attempts aimed at heterogenizing homogeneous catalysts through attachment to organic or inorganic supports have so far not been very fruitful for a variety of reasons, such as metal leaching, poor catalyst efficacy, low reproducibility of activity and selectivity, and degradation of the polymer support.[40] A different method of combining high catalytic efficiency with easy recovery and reuse of the catalytic species is to use water as a second phase in which the organic products of the reaction are poorly soluble.[43] Employing water-soluble catalysts thus allows for isolation of organic products and quantitative recovery of the catalyst through simple phase separation. Recently, water has been shown to be a promising medium for heterogenized homogeneous catalysis, averting some of the problems mentioned above. This will be covered in section III.B.

A. Homogeneous Catalysis

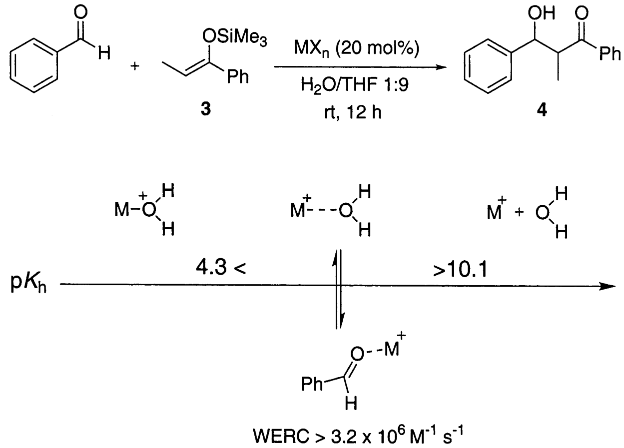
1. Brønsted Catalysis

When feasible, the use of a Brønsted acid is one of the more convenient and environmentally benign methods of catalyzing organic reactions in water. A potential synthetic advantage of water over organic solvents in Brønsted-catalyzed reactions is that the nucleophilicity of the corresponding base, which can lead to undesired side reactions, may be of less concern due to extensive solvation and diffusion of charge by hydrogen-bonding water molecules. In organic solvents such problems are usually averted by using a sterically hindered acid/base. Many reactions developed for use in water have been shown to benefit from the addition of catalytic amounts of Brønsted acids.[44–46]

2. Lewis-Acid Catalysis

Lewis-acid catalysis is one of the most useful methods in modern stereoselective synthesis. The coordination and activation properties of Lewis acids make them suitable not only for *intraligand* asymmetric induction, in which the absolute configuration of the newly formed stereocenter is determined by an element of chirality within the same ligand (the substrate) on the metal, but also for *interligand* asymmetric induction, in which chiral induction is governed by a ligand on the metal other than the substrate.[47] The former usually involves a chiral auxiliary, while the latter is accomplished through the attachment of chiral organic ligands to the central metal atom. Interligand asymmetric induction through the use of Lewis acids carrying chiral ligands is at the core of asymmetric catalysis. Consequently, to fully extend the concepts of interligand asymmetric induction and asymmetric catalysis to water-based organic reactions, it is imperative that metal species which retain Lewis-acid activity, even in pure water,

Scheme 2



are identified and that water-soluble ligands for these metals are developed.

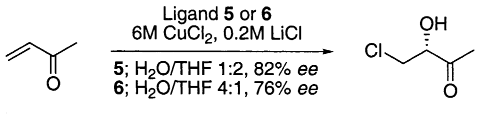
(a) Metal Salts as Water-Tolerant Lewis Acids. Many of the most commonly used Lewis acids are of a highly water-labile nature, and their use in organic synthesis is restricted to reactions performed under strictly anhydrous conditions. Lewis acids operate through coordination with one or more Lewis-basic sites of a reactant, usually a nitrogen atom or oxygen atom, thus inducing polarization of the reactant by shifting electron density from the reactant toward the catalyst. Herein lies the greatest obstacle to efficient Lewis-acid catalysis in aqueous media; water, too, has a Lewis-basic site and easily hydrates most Lewis acids to preclude binding to the organic reactant, especially when present in large excess as a solvent. Lewis-acid-promoted reaction in water is, nevertheless, far from inconceivable. For example, substrates with more than one Lewis-basic coordination site have been demonstrated to more effectively compete with water for Lewis-acid complexation.[48] Extensive studies by Kobayashi and co-workers revealed that a wide range of lanthanide triflates,[49] rare-earth metal triflates,[9] and some other metal salts can be useful as Lewis-acid promoters in aqueous media.[50] These water-tolerant Lewis-acid catalysts have been successfully applied to various types of water-based reactions (vide infra). On the basis of these groundbreaking observations, certain guidelines of what constitutes a good water-tolerant Lewis-acid catalyst have been formulated.[50,51] First, the metal salt should have an intermediate hydrolysis constant (K_h). When the pK_h value is too low, cations are easily hydrolyzed and oxonium ions are generated (Scheme 2). However, when the pK_h value is too high, the Lewis acidity is generally too weak for efficient catalysis. Second, the water exchange rate constant (WERC), which is a measure of the exchange rate for substitution of inner-sphere water molecules, should be large enough to allow for rapid exchange between water molecules and basic sites on the reactant. In the Mukaiyama aldol reaction between benzaldehyde and silyl enol ether **3**, the Lewis acids that were defined as active (>50% yield of adduct **4**) had pK_h values in the range 4.3–10.08 and WERC values greater than 3.2×10^6 M^{-1} s^{-1}. The correlation found between catalytic activity and pK_h and WERC allows for some general qualitative assessment to be made of which metal compounds may serve as effective Lewis acids in water. The lanthanide triflates, $Ln(OTf)_3$, gave consistently good yields and seemed to be particularly suitable to function as water-stable Lewis acids. This can be explained by their low hydrolysis constants, pK_h, and soft Lewis-acid character, which suggests a strong affinity for carbonyl oxygens.[50] In addition, lanthanide triflates are in fact more soluble in water than in organic solvents, which allows for simple and quantitative recovery of the catalyst. Other metals that were capable of catalyzing the aqueous Mukaiyama–aldol reaction and thus of potential as water-tolerant Lewis acids include Fe(II), Cu(II), Pb(II), Zn(II), Cd(II), as well as the rare-earth metals Sc(III) and Y(III).

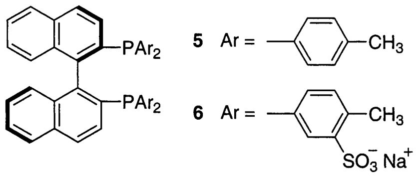
(b) Water-Soluble Chiral Ligands. The vast majority of chiral catalysts applied in modern synthesis possess low water solubility. Several strategies have been pursued to enhance solubility of metal–ligand complexes in water, three of which stand out: (i) perform the reaction in the presence of micelle-forming surfactants (see also sections II.B.2 and III.C), (ii) add solubilizing functionalities, commonly ionic groups, to poorly soluble ligands, and (iii) employ easily accessible, highly water-soluble sources of chirality from nature, such as carbohydrates or amino acids as ligands. The de novo design of chiral ligands specifically targeted for metal-assisted catalysis in water is an attractive but largely unexplored avenue of research.[52]

The need to develop water-soluble catalysts has been a concern addressed mainly by the chemical industry, likely because it is in large-scale processing that the most obvious advantages of two-phase catalysis exists. Hence, the range of reactions for which new catalysts for water-based synthesis have been prepared and applied has been narrow and largely confined to some of the most important catalytic reactions in industry, such as hydrogenation of C=C and C=O bonds and hydroformylation, where rhodium and ruthenium are the most commonly used metals.[42] Bisphosphine ligands are of versatile use in coordination chemistry and have been used with great success in many catalytic processes. Hence, building on the history of these ligands in metal catalysis, by far the most investigated type of ligands for water-based catalysis are bisphosphines carrying one or more polar substituent, such as sulfonate, carboxylate, ammonium, phosphonate, or hydroxyl groups. These were reviewed by Papadogianakis and Sheldon in 1997.[40] Driven by early success and lack of better performing alternatives, notwithstanding considerable research leading to a large number of new ligands, the most commonly employed water-soluble ligands are the sulfonated bisphosphines. Synthesis, separation, and characterization of these compounds, however, are often difficult.

Achiral and chiral water-soluble ligands that have been prepared and used in the literature up to 1996 have been summarized by Li and Chan.[19] Water-soluble metal complexes for enantioselective hydrogenation of dehydroamino acids were reviewed by Nagel and Albrecht in 1998.[17] For a selection of more

Scheme 3



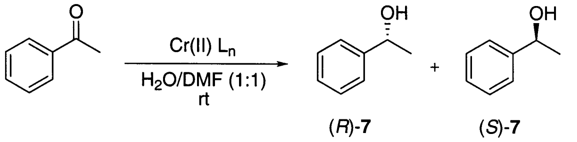


recent literature on enantioselective hydrogenations in water, see section IX of this review. Discussion herein will be exclusive to chiral ligands that have a documented effect of ligand-induced stereoselective catalysis in water; water solubility alone does not justify inclusion. Most recently, water-soluble bisphosphine−metal complexes have been used with some success in catalytic asymmetric reactions other than hydrogenations. Henry and co-workers developed a palladium(II)-catalyzed, modified Wacker oxidation of olefins leading to the excess formation of chlorohydrins rather than aldehydes normally obtained through this process.[53,54] When the Pd(II) catalyst was coordinated to a chiral bisphosphine ligand, (*R*)-Tol-BINAP, **5**, good asymmetric induction of up to 82% ee was achieved in a 1:2 mixture of water/THF (Scheme 3). The reactions could be performed in solvent of higher water content (water/THF 4:1) with similar catalytic efficiency and selectivity by using the corresponding sulfonated ligand **6**. Gratifyingly, in the preparation of the catalyst, sulfonation of (*R*)-Tol-BINAP did not lead to mixtures with mono-, di-, and trisulfonated products otherwise commonly encountered in aromatic sulfonation reactions, which further increases the utility of this new chiral ligand in aqueous asymmetric catalysis.

Aside from synthetic ligands, naturally occurring water-soluble compounds have also been investigated as catalytic ligands, albeit to a much lesser extent. For example, mono- and disaccharides have been used as precursors for the construction of chiral water-soluble ligands of bidentate coordination, usually bisphosphines,[55,56] but P,N-[57] and N,N-derivatives[58] have also been prepared. In general, ligands based on monosaccharides have only moderate solubility in water and often require incorporation of extra hydrophilic groups on the ligand or addition of a cosolvent or a surfactant for optimum efficiency. Disaccharide ligands have the advantage of higher aqueous solubility, and very high enantioselectivities have indeed been observed in reactions of these in pure water. For recent examples of the use of chiral ligands derived from sugars, see sections III.C, V.E, VII, and IX.

The use of unprotected amino acids as chiral elements in metal-catalyzed reactions is rare. This may be due to solubility problems in organic solvents traditionally used for such transformations. In water, however, this is not a concern and "naked" amino acids should be of great potential as asymmetric ligands in aqueous media. This concept was pursued by Micskei and co-workers, who used chromium(II)−amino acid complexes in the enantioselective reduction of acetophenone in water/DMF 1:1 to give methylphenylcarbinols (*R*)-**7** and (*S*)-**7** in up to 94% yield and 75% enantiomeric excess (Scheme 4).[59] The authors found that the enantioselectivities observed were highly dependent on the structure of the ligands and the stoichiometry of the metal−ligand complex **8** (Figure 1), where controlled conditions leading to CrL_2 complexes gave the best ee's. Engberts and co-workers employed amino acids as ligands in the first catalytic, enantioselective Diels−Alder reaction in water (section V.A.1).[60]

Scheme 4[a]



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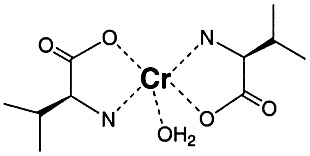

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B. Heterogeneous Catalysis

In terms of catalytic efficiency, heterogeneous catalysis is generally inferior to homogeneous catalysis.[40] The advantage of solid or immobilized catalysts is mainly due to practical and economic reasons as they are more easily recovered from reaction mixtures and can be reused many times without loss of catalytic activity. It has long been recognized that an ideal catalytic system would be to use highly active and selective homogeneous catalysts that have been 'heterogenized' for simple recovery and reuse. Even so, as mentioned above, progress toward a commercially viable process has been slow. In the past few years, however, catalysts heterogenized through covalent attachment to organic or inorganic supports such as polymers,[61] silica,[62,63] and layered clays[64] have been used with some success in aqueous media.[65] So far, the most promising approach seems to be through the use of organic polymers. Uozumi and co-workers achieved high enantioselectivities in Pd-catalyzed allylic alkylations (detailed in section VII) by attaching a chiral phosphine ligand to an amphiphilic polystyrene−poly(ethylene glycol) copolymer resin (Figure 2, **9**).[66] The described protocol approaches the realization of what may be considered

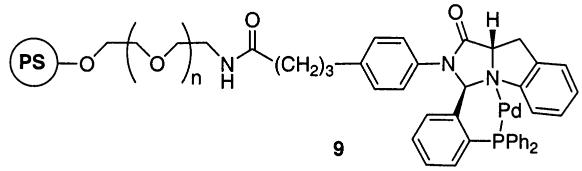

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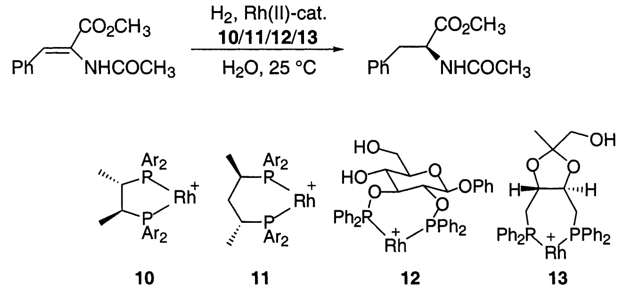
Figure 2.

an ideal catalytic asymmetric reaction: (i) chemical and optical yields ranged from high to excellent; (ii) reactions were performed in water without the use of any cosolvent; (iii) the catalyst was quantitatively recovered through simple filtration; and (iv) the catalyst could be reused many times without any observable loss of activity.

C. Micellar Catalysis

The concept of micellar catalysis goes back to the late 1960s.[67] However, the recent discovery in 1992[68] that rhodium-catalyzed asymmetric hydrogenations in water proceeded with higher enantioselectivity when micelle-forming surfactants were present in the reaction mixture has led to a newfound interest in the use of aqueous micelles to promote organic reactions. Since then, this strategy has been applied to enhance the performance of several other types of water-based reactions, such as Diels–Alder reactions,[69–72] aldol reactions,[73,74] and allylation reactions.[45] The addition of surfactant often leads to a significant increase in rate and/or selectivity and, sometimes, exceptional results are obtained. In one recent example, the enantiomeric excess obtained in an asymmetric hydrogenation reaction increased from 1.5% to 77%![75] Recent mechanistic investigations have provided some insight into the underlying processes of this phenomenon.[76] Although some general explanations can be invoked, such as solubilization and concentration of reactants, the detailed mode of action in any given system depends on the nature of the micelles and the substrates and the type of reaction. For example, it was observed that micelles were unable to catalyze Diels–Alder reactions,[77,78] actually often retarding them.[79] In the presence of Lewis acid, however, surfactant-aided rate acceleration becomes significant.[70,71] The origin of the increase in selectivity of many reactions, however, remains elusive despite extensive research efforts. In studies of rhodium(II)-catalyzed asymmetric hydrogenations of dehydroamino acid derivatives, enantioselectivities were shown to vary with the size of the cyclic chelate of the metal–bisphosphine catalyst (Scheme 5).[80] It was found that the observed ratios of the enantiomeric products (er) were almost unaffected by the addition of surfactant (10% sodium dodecyl sulfate, SDS) in reactions catalyzed by **10** and **11**, which forms rigid five- and six-membered cyclic chelates, respectively, while catalysts **12** and **13** that involve more flexible seven-membered chelates catalyzed the reactions to give a product distribution of much higher enantiomeric ratio in the presence of SDS than in pure water. It was argued that the nature of the surrounding solvent influences the conformational equilibria of the catalytic species, which may extend to effect also the catalyst-substrate complexes and, hence, the enantiomeric product distribution. Such an effect would logically be less operative on a small ring, in which conformational freedom is more limited.

Scheme 5[a]



	ee (%)	*ee* (%)	*ee* (%)	*ee* (%)
H_2O	17.6	31.1	83.4	1.5
H_2O+SDS	2.6	10.2	97.2	77
Δ *er*	0.7	0.7	6.4	7.5

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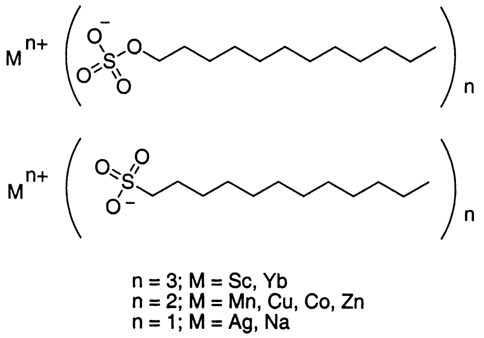


Figure 3.

Kobayashi and co-workers studied Lewis acids that work in aqueous media (vide supra). To avoid the use of cosolvents, which are often required for best efficiency, the effect of anionic surfactants such as SDS on Lewis-acid-catalyzed aldol reactions[81] and allylation reactions[82] in water was investigated. These reactions, too, benefited greatly from the addition of surfactants. Taking this concept one step further, Kobayashi and co-workers developed a new type of Lewis acids in which the active metal cation carries long anionic hydrocarbon sulfate or sulfonate ligands (Figure 3) that makes them form micellar aggregates in water. These so-called Lewis-acid–surfactant combined catalysts (LASCs) have been successfully employed in aqueous Diels–Alder reactions, aldol reactions, Mannich-type reactions, and allylation reactions.[83] Micellar catalysis of organic reactions in water has been reviewed extensively.[28,84,85]

IV. Stereoselectivity in Water

With a few notable exceptions, the majority of asymmetric reactions are performed in apolar and aprotic media, which precludes the use of water-soluble compounds. It is imperative that water, too, is fully explored as a reaction medium for asymmetric synthesis. Provided that substrates and reagents can be used that do not react with water, how will the selectivity of reactions in inert solvents be affected by the progression to a participating solvent such as water? Learning how to take advantage of the uniquely complex solvating properties of water may lead to new concepts and possibilities in asymmetric synthesis. Initial work in this area have indeed led to some interesting and sometimes surprising results, which will be discussed here.

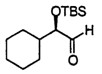
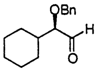
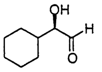
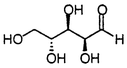
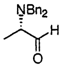
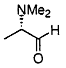
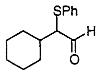
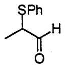
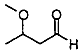
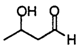
A. Stereocontrol in Water

In stereoselective synthesis, efficiency may be defined as to have knowledge and control of the factors that influence the spatial arrangement of the reactants as a reaction proceeds. These factors are seemingly easier to recognize and manipulate when solvent−reactant interactions are so insignificant that they can be excluded from the mechanistic picture. Such is often the case with aprotic solvents of low polarity. Water, however, is a participating solvent, exerted through hydrophobic and/or electrostatic interactions, and as such must be considered in any model attempting to explain or predict the outcome of a stereodifferentiating reaction. A most fundamental question may be to what extent we can use established rules, such as the Cram or Felkin−Anh models, which are based on observations in strictly anhydrous media, to account for selectivities observed in water?

1. Chelation Control

One of the main concerns of synthesis in water may be whether stereoselection through chelation control would still be operative. Recent experimental data suggests, perhaps contrary to what was expected, that chelation effects may indeed be relevant also in water. The most extensive studies in later years on chelation effects in organometallic addition reactions in water have been pursued by Paquette and coworkers.[86−90] Specifically, they investigated chelation control in indium-assisted allylations of α- and β-heteroatom-substituted aldehydes and ketones in organic, aqueous, and mixed solvent systems. Some representative examples are collected in Table 1. The main lesson of these studies was that water does not inhibit chelation control in indium-mediated reactions, and selectivities in aqueous media were significantly greater than those attained in anhydrous media using the corresponding reagents of other metals such as magnesium, cerium, and chromium.[91]

Table 1.

Entry	Aldehyde	Solvent	*Syn*	*Anti*	Yield (%)
1	 **14**	$H_2$0	1	3.9	90
2		$H_2$0:THF	1	4.2	87
3		THF	1	4.0	92
4	 **15**	$H_2$0	1	1.2	92
5		$H_2$0:THF	1	2.2	93
6		THF	1	3.9	87
7	 **16**	$H_2$0	9.8	1	85-90
8	 **17**	$H_2$0	10.2	1	90
9		$H_2$0:THF	8.2	1	87
10		THF	3.0	1	92
11	 **18**	$H_2$0	1	3.3	50
12	 **19**	$H_2$0	>99	1	50
13	 **20**	$H_2$0	1	1.4	89
14		$H_2$0:THF	1	1.2	91
15		THF	1	1.5	82
16	 **21**	$H_2$0	1	4	82
17		$H_2$0:THF	1	3	87
18		THF	1	3	70
19	 **22**	$H_2$0	1	4	77
20		$H_2$0:THF	1	4	74
21		THF	1	3.5	
22	 **23**	$H_2$0	1	8.5	78
23		$H_2$0:THF	1	8.2	78
24		THF	No reaction		

For the acyclic α-heterosubstituted substrates, it was presumed that the predominantly observed *syn*-selectivity was the result of chelation controlled addition according to Cram's chelate model (Figure 4, **A**). When the *anti*-products were observed, a nonchelate, sterically controlled Felkin−Anh transition state was more likely to have been involved (Figure 4, **B**). Additional evidence for the involvement of chelation control was provided by comparison of reaction rates with a similar substrate known not to be involved in chelation. Previous studies have shown that when chelated intermediates are involved in a reaction, there will be an increase in the reaction rate due to preformation of the transition-state complex.[92,93] Hence, for the Felkin−Anh (nonchelation) products, no rate acceleration was observed relative to a nonchelating standard. In the allylation reaction of dimethylamino aldehyde **19**, excellent *syn*-selectivity of >99% is observed (Table 1, entry 12). However, substituting methyl for benzyl, as in **18**, leads to a reversal of diastereofacial preference to favor the *anti*-isomer in a ratio of 3.3:1 (entry 11) in accordance with the Felkin−Anh model. Allylation of α-hydroxy aldehyde **16** leads to the 1,2-diol of significant *syn*-predominance (entry 7). Again, heteroatom substitution leads to erosion of *syn*-selectivity (**14** and **15**, entries 1 and 4), which suggests that protecting-group strategies may not only be unnecessary in many aqueous reactions, but even have a pronounced negative effect. It was also found that β-hydroxyaldehyde **23** underwent addition by allylindium reagents, in this case to give the 1,3-diol with a syn/anti ratio of 8.5:1 (entry 22). According to the proposed transition-state model (Figure 4, **C**), bidentate coordination of the indium metal to the β-hydroxyl group and the carbonyl oxygen directs addition to occur syn to the β-substituent, leading to the *anti*-product. In comparing α-oxy, α-amino, and α-thio aldehydes in the indium-mediated allylation reaction in water, it appears that amino derivatives are the best at forming chelates with the metal. The allylations of the α-thia substrates **20** and **21** gave products of reversed selectivity (entries 13 and 16), i.e., favoring the *anti*-products, suggesting that the reaction is under nonchelation control, proceeding through the Felkin−Anh transition state. An important observation in these reactions is that when chelation control

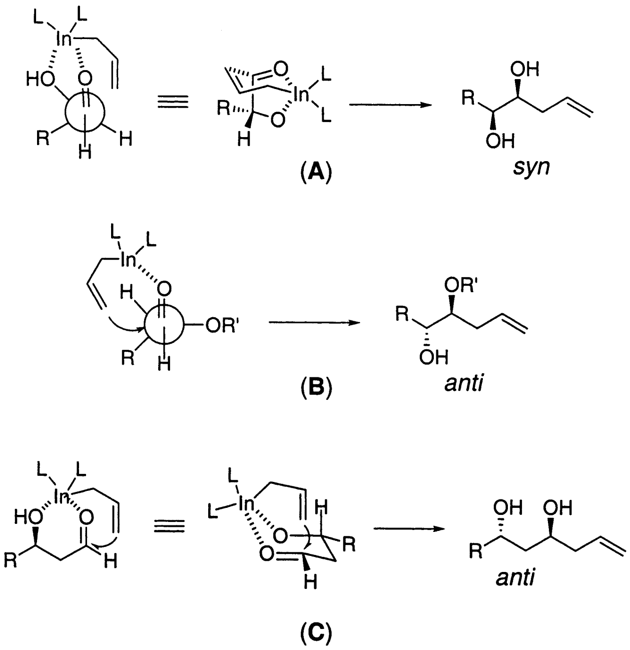


Figure 4.

appears to be involved, water as solvent is preferred in terms of selectivity over THF or a THF/water mixture.

2. Hydrophobic Control

Beyond chelation control, experimental data suggests that the unique solvating properties of water can sometimes be used to enhance selectivity. For example, hydrophobic interactions have been used to explain improved selectivities of chiral recognition events on transition from organic to aqueous solvent.[94−98] In the cycloaddition of **24** with acrolein, hydrophobic effects were invoked to account for the observed enhancement of diastereoselectivity in water compared to toluene.[96] One of the diastereotopic faces of the reactive conformation appears to be more hydrophilic and thus more heavily hydrated (Figure 5, **A**). Reaction therefore occurs preferentially from the opposite, more hydrophobic side. Also, as expected from Diels−Alder reactions, the reaction in water was 50 times faster than in toluene. In a similar experiment, methacrolein reacted with the chiral diene carboxylate **25** in pure water to give adducts of a 4.7:1 diastereomeric ratio.[97] Assuming that the transition state adopts the conformation of the most stable allylic rotamer as shown (Figure 5, **B**), the dienophile approaches the diene mainly from the side opposite the hydrophilic carboxylate group. Highly stereoselective indium-promoted allylation reactions in aqueous media under apparent hydrophobic, nonchelation control have also been reported. In synthetic studies toward dysiherbaine, Loh and co-workers found that the allylindation of ketoester **26** in THF/water 1:1 with various allylic bromides proceeded to give 1,3-amino alcohols **27** in good yields (60−80%) and with excellent 1,3-induction (72−99% de, Scheme 6).[94] It was argued that the high selectivities observed were based on a remote substituent effect due to a conformational preference as shown in Scheme 6. That the selectivity was not due to any favorable $\pi-\pi$ interactions between the aromatic ring and the carbonyl group was confirmed by substituting the phenyl group for a cyclohexyl ring, a change that did not lead to any significant difference in diastereoselectivities.

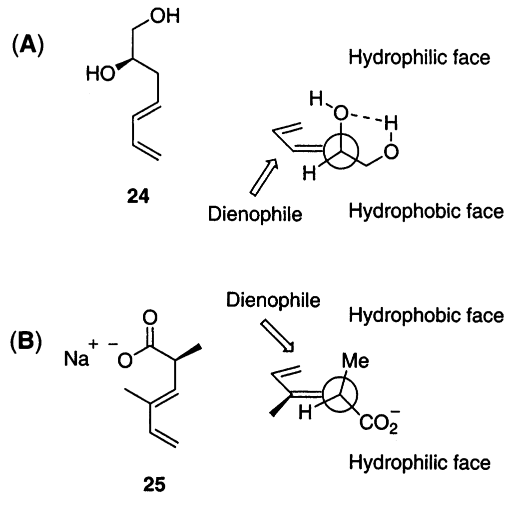
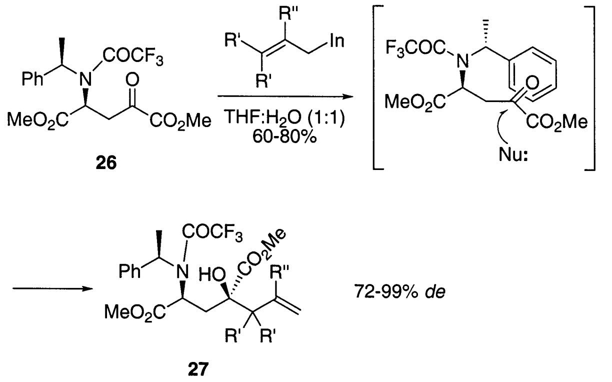


Figure 5.

Scheme 6[a]

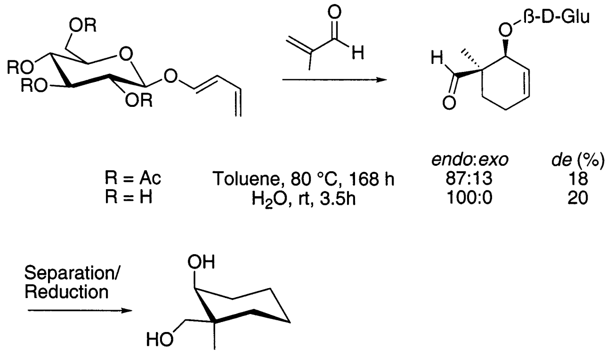


[a] Reprinted with permission from ref 94. Copyright 2000 Elsevier Science.

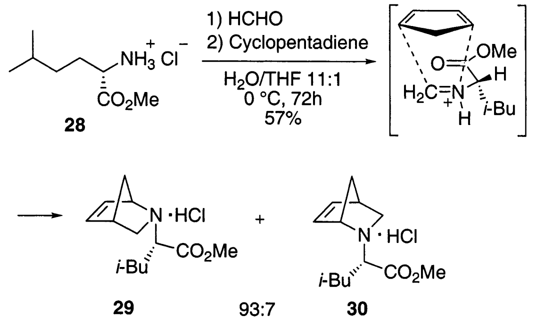
B. Water-Soluble Chiral Auxiliaries

As discussed above, attachment of a water-soluble auxiliary is one way of solubilizing hydrophobic compounds. If the auxiliary is of a chiral nature, asymmetric induction may be achieved. Lubineau and co-workers demonstrated this concept by using sugars to simultaneously introduce water solubility and an element of chirality.[30−33] Diels−Alder reactions of dienes that were attached at the anomeric position of a carbohydrate proceeded much faster and with higher *endo*/*exo* selectivity in water than the corresponding reactions of dienes attached to a peracetylated carbohydrate in toluene. A representative example is shown in Scheme 7. Although the asymmetric induction was low (20% de), separation of the crystalline diastereomers and hydrolytic cleavage of the sugar moiety gave enantiomerically pure adducts. It is noteworthy that in these reactions diastereofacial preference was determined by the anomeric configuration of the sugar. The use of carbohydrates as chiral, solubilizing auxiliaries has also been demonstrated to give modest asymmetric induction (20% de) in Claisen rearrangements in water.[34,35]

Scheme 7



Scheme 8



Amino acids and their derivatives are of interest as potential chiral auxiliaries in aqueous synthesis. Waldman and co-workers have shown that amino acid esters can be used to induce chirality in aza-Diels–Alder reactions.[99–101] For example, in water/THF 1:1, the condensation reaction between (*S*)-isoleucine methyl ester hydrochloride, **28**, and formaldehyde, followed by addition of cyclopentadiene, results in the azanorbornene products **29** and **30** in a diastereomeric ratio of 93:7 (Scheme 8). The observed stereoselectivity was explained by invoking a transition state as illustrated in Scheme 8, where the addition of diene is controlled by the steric influence of the amino acid side chain and secondary orbital interactions with the diene.

V. Additions to C–C Multiple Bonds

A. Cycloadditions

Cycloaddition reactions are among the most important and useful processes in organic chemistry inasmuch as they enable the construction of complex polycyclic compounds, often with a high degree of regio- and stereocontrol. A seminal discovery in water-based organic synthesis was that the Diels–Alder reaction and other cycloaddition reactions often proceed faster and with higher *endo*/*exo* selectivity in water than in organic media. Consequently, cycloaddition reactions in water have been subjected to more scrutiny than any other type of reaction in water.[70] In view of the fact that several reviews on Diels–Alder reactions in water have appeared in later years,[20,48,102–104] the discussion on this topic below will be more stringently limited to the most significant and recent achievements.

1. Diels–Alder Reaction

Prior to 1980, this powerful transformation was mainly performed in organic solvents while only incidental reports were made of the use of water as solvent. In pioneering studies by Breslow and Grieco on water-based Diels–Alder reactions, surprising and remarkable discoveries were made about the unique solvent effect of water on this reaction.[1–5] Compared to reactions carried out in organic solvent, the corresponding reactions in water displayed significant rate acceleration. Substantial experimental[77,78,105–108] and theoretical[109–113] evidence indicates that the origin of the water effect on the rate of Diels–Alder reactions is due to differential solvation of reactants and transition states. This explanation is in contrast with the generally accepted concept that concerted reactions, such as the Diels–Alder reaction, display very modest solvent effects, reflecting a small difference in polarity between the initial state and the transition state.[114,115] Hence, the surprising discoveries made with water as solvent have subsequently been attributed not so much to the increase in polarity[116] but to hydrophobic interactions and hydrogen bonding, although a complete qualitative and quantitative understanding of how these forces contribute individually and collectively is still not at hand. Terms such as *enhanced hydrogen bonding* and *enforced hydrophobic interactions* have been introduced to emphasize that these interactions occur because they are an integral part of the activation process. Hydrogen bonding between water and the activating group of the dienophile is likely to be responsible for part of the rate enhancement, probably similar to the way a Lewis acid would operate.[77,78,107,112] The suggested positive influence of the hydrophobic effect is presumed to originate in the negative activation volume of the Diels–Alder reaction, which leads to a compacting of the reactants in the transition state compared to the initial state, thus removing water molecules from the hydrophobic hydration shells of the reactants as the reaction proceeds.[105,108,117,118]

Alternatively, the cohesive energy density (CED) is a measure of the energy required to create a cavity in a solvent and as such relates to all the intermolecular forces acting within a solvent. The rate constants of several Diels–Alder reactions have indeed been correlated with the CED of the solvent.[114,119] It was also found that the established preference for the formation of *endo*-cycloadducts was enhanced in water.[2,3] Again, the hydrophobic effect is presumed to be intrinsically involved by favoring the compact *endo* transition state more than the extended *exo* transition state. Hydrogen bonding is also believed to play an important part, once more drawing on the analogy with Lewis-acid catalysis, which is known to have a dramatic effect on *endo*/*exo* selectivity.[120,121] In addition, positive effects on regio- and diastereoselectivity when switching from organic to aqueous solvent have been reported.[96,116,122,123]

In an attempt to combine the beneficial effects of water and Lewis-acid catalysis on the Diels–Alder reaction, Engberts and co-workers investigated Di-

Scheme 9

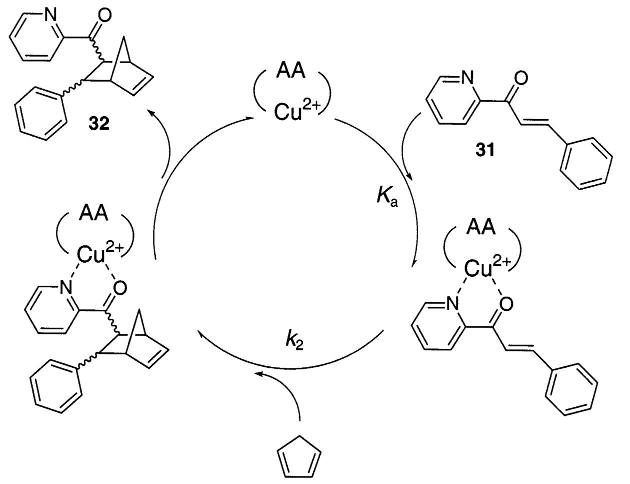


Table 2.

ligand	K_a (M^{-1})	k_2 (M^{-1} s^{-1})	ee (%)
water	1.2×10^{-3}	2.56	0
glycine	7.4×10^{-4}	1.89	0
L-valine	5.7×10^{-4}	1.90	3
L-leucine	5.1×10^{-4}	2.01	3
L-phenylalanine	8.7×10^{-4}	2.01	14
L-tyrosine	1.4×10^{-3}	1.68	26
L-tryptophan	3.0×10^{-3}	1.44	25
L-abrine	5.0×10^{-3}	1.47	74

els–Alder reactions catalyzed by Lewis acids in water.[60,124,125] Four divalent metal cations (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}) were screened for their effect on the rate and *endo*/*exo* selectivity of the reaction between the bidentate dienophile **31** and cyclopentadiene (Scheme 9). All four metals studied successfully catalyzed the cycloaddition, and the catalytic efficiency of the Lewis acids was found to be of the order $Co^{2+} < Ni^{2+} < Cu^{2+} \gg Zn^{2+}$. However, the rate-enhancing effect of water on the catalyzed reaction was much less pronounced than the corresponding effect on the uncatalyzed reaction. Also, the increase of the *endo*/*exo* selectivity observed for the uncatalyzed reaction in water is completely thwarted for the catalyzed reaction.

These observations imply that the positive influence of hydrogen-bonding and hydrophobic interactions on Diels–Alder reactions in water is attenuated in the presence of Lewis acids. Hence, the conclusion was that the beneficial effects of water and Lewis-acid catalysis in these reactions are not additive. Nevertheless, the Cu^{2+}-catalyzed reaction between **31** and cyclopentadiene was 79 300 times faster than the same uncatalyzed reaction in acetonitrile. Having established that Lewis-acid-catalyzed Diels–Alder reactions in water proceed efficiently, focus was turned to examining possible ligand effects in these reactions. For this purpose, a series of chiral α-amino acid ligands was screened for rate and enantioselectivity in the Diels–Alder reaction between **31** and cyclopentadiene (Scheme 9).[60,124] It was found that α-amino acids carrying an aromatic substituent caused a significant increase in the K_a of the ligand–Cu^{2+}–dienophile complex (Table 2). The authors speculate that the increase in K_a is due to attractive arene–arene interactions between dienophile and ligand. Additionally, in the projected transition-state complex (Figure 6), one face of the dienophile is effectively shielded from attack and, upon reaction with cyclopentadiene, addition product **32** was indeed obtained in enantiomeric excess (Table 2). This study also demonstrated that enantioselectivity is enhanced in water as compared to organic solvents. It may be argued that any favorable interaction operating between two arenes is strengthened in water due to the hydrophobic effect. Support for the crucial participation of a stabilizing arene–arene interaction came from the fact that only insignificant enantioselectivities were obtained with nonaromatic amino acids. A strongly nonlinear dependence of ee on the ligand/catalyst ratio suggested that ligand-accelerated catalysis was taking place. Even when 50% of the Cu(II) catalyst was present in its achiral hydrated form, most of the reaction was still mediated by the chiral Cu(II)–ligand complex to give high ee. These results were the first examples of enantioselective Lewis-acid-catalyzed Diels–Alder reactions in water. Chiral induction in uncatalyzed Diels–Alder reactions in water has, however, been achieved through the use of chiral auxiliaries attached either to the dienophile[126] or to the diene.[31] The latter approach was exemplified in section IV.2.B.

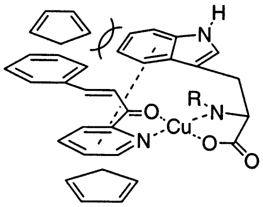
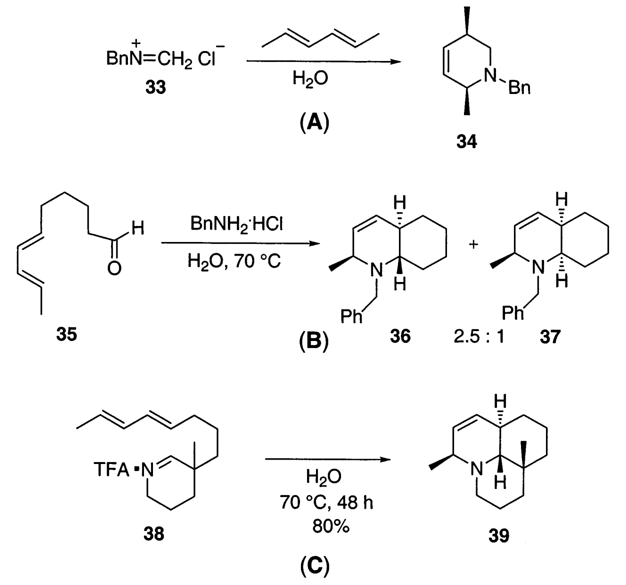


Figure 6.

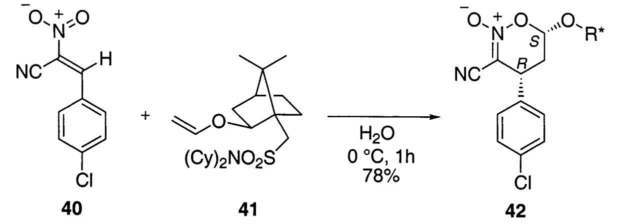
2. Hetero Diels–Alder Reaction

The hetero Diels–Alder cycloaddition is a potentially very useful reaction for the construction of heterocycles of defined relative and absolute configuration. However, the use of hetero Diels–Alder reactions in organic synthesis has been of limited scope because the normally unreactive dienophile generally requires some external activation. This can be accomplished through the use of electron-withdrawing substituents on the dienophile, through Lewis-acid catalysis, or by using very reactive dienes. Alternatively, in aqueous media, these reactions can proceed under milder conditions, with simple protonation of the dienophile being the most convenient approach.[127] The potential of using reactions between protonated imines and dienes in water as an efficient entry to various heterocycles and alkaloids was established in the mid-1980s through work by Grieco and Larsen.[128] For example, the condensation of iminium ion **33** with (*E*,*E*)-2,4-hexadiene in water afforded the tetrahydropyridine derivative **34** as a single diastereomer (Scheme 10, **A**). In an intramolecular variant, the dienyl aldehyde **35** reacted with benzylamine hydrochloride in ethanol/water 1:1 at 70 °C to give the reduced quinoline derivatives **36** and **37** in 63% combined yield and a 2.5:1 diastereomeric ratio (**B**). Also, in a more recent study, Grieco and Kaufman reacted diene **38** in hot water to give the tricyclic amine **39** as the exclusive diastereomer

Scheme 10



Scheme 11



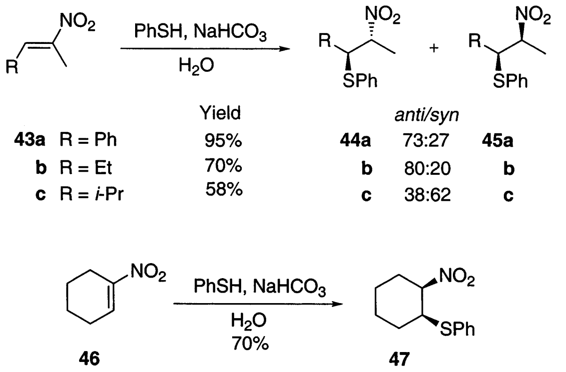
in 80% yield (**C**).[129] According to Grieco, water appears to be the polar solvent of choice for intramolecular imino-Diels–Alder reactions as described. Lanthanide Lewis acids can also be used as catalysts in the aqueous imino-Diels–Alder reaction, as demonstrated by Wang and co-workers in their syntheses of azasugars and their analogues, compounds which are of interest as potential glycosidase inhibitors.[130]

High asymmetric induction has recently been achieved in hetero Diels–Alder reactions of inverse electron demand. Fringuelli and co-workers performed [4+2] cycloadditions of nitroalkenes with vinyl ethers to provide synthetically useful cyclic six-membered nitronates (Scheme 11).[131] The reaction of nitroalkene **40** with enantiopure vinyl ether **41** in pure water proceeded with total regio- and diastereoselectivity to afford *cis*-substituted nitronate **42** in good yield. The strong preference for *cis*-products was rationalized by secondary orbital interactions between the electron-rich oxygen on the vinyl ether and the positively charged nitrogen on the nitroalkene. In related work, conjugated 3-diazenylbut-2-enes were found to be good substrates in the inverse electron demand hetero Diels–Alder reaction in water, leading to tetrahydropyridazines with high *endo*/*exo* selectivity.[132]

B. Michael-Type Addition

Many variations of this important reaction for the formation of new carbon–carbon and carbon–hetero bonds have been reported to work well in water/aqueous media.[133–140] Both basic catalysis and Lewis-acid catalysis have been applied, and nucleophiles range from neutral amines, alcohols, and thiols to anionic species including carbanions. It is therefore somewhat surprising that little effort has been made to perform stereoselective conjugate additions in aqueous media. One study, however, found that moderate diastereoselectivities were achieved in the Michael addition of thiophenol to nitro olefins in basic media (Scheme 12).[133] The reaction of (*E*)-1-methyl-1-nitrostyrene **43a** with thiophenol in 0.5 M aqueous $NaHCO_3$ gave the *syn*- and *anti*-addition products **44a** and **45a** with 73:27 selectivity in a combined yield of 95%. The analogous reaction with (*E*)-2-nitro-2-pentene, **43b**, gave even higher *anti*-selectivity (**44b**/**45b** 80:20), but when the slightly bulkier isopropyl substituent was present, as in **43c**, the selectivity was lower and of reversed nature (**44c**/**45c** 38:62). The best result was obtained with the cyclic substrate **46**, which gave exclusively the *cis*-adduct **47** in 70% yield upon reaction with thiophenol. The selectivities observed in these additions were explained by a conformational preference of the intermediate nitronate anion to orient the larger substituent perpendicular to the double bond. Protonation will thus preferentially occur from the opposite, less hindered side.

Scheme 12[a]



		Yield		anti/syn	
43a	R = Ph	95%	**44a**	73:27	**45a**
b	R = Et	70%	**b**	80:20	**b**
c	R = *i*-Pr	58%	**c**	38:62	**c**

[a] Reprinted with permission from ref 132. Copyright 2001 Brazilian Chemical Society.

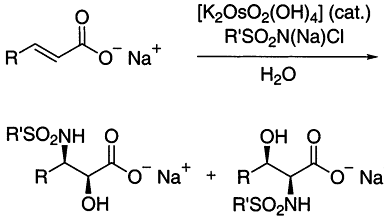
C. Dihydroxylation

The single most common and powerful method of stereoselectively oxidizing unactivated olefins is the asymmetric dihydroxylation (AD) reaction developed by Sharpless and co-workers.[14,141] In contrast with the Sharpless asymmetric epoxidation of allylic alcohols, water-free conditions are not required. In fact, the best medium for the catalytic AD is usually a water/*tert*-butyl alcohol mixture as it suppresses the undesired second catalytic cycle, thus preventing the formation of racemic products by keeping osmium tetroxide as the only oxidant in the organic phase. The most interesting modification of this reaction in recent years may be the immobilization of osmium tetroxide to allow for recovery of the highly toxic and expensive catalyst, which cannot be achieved so easily in solution. Using a special microencapsulation technique, Kobayashi and co-workers attached osmium tetroxide to phenoxyethoxymethyl–polystyrene (PEM) polymers, which could then be used to execute AD of olefins in water/acetone (1:1) with complete recovery of catalyst and retention of catalytic activity.[142] In most cases, the diols were obtained in good yields with high enantiomeric excesses. The stereoselective dihydroxylation of olefins leading to racemic *anti*-1,2-diols can be achieved in aqueous solution using hydrogen peroxide in the presence of tungstic oxide.[143]

D. Aminohydroxylation

The direct conversion of achiral alkenes into the synthetically useful 1,2-amino alcohols of high enantiomeric purity can effectively be achieved via asymmetric aminohydroxylation (AA).[144−146] Similar to the AD reaction, AA can be performed with catalytic amounts of osmium tetroxide in aqueous media (e.g., water/*tert*-butyl alcohol or water/acetonitrile). Recently, Sharpless and Fokin found that α,*β*-unsaturated acids were excellent substrates for the catalytic aminohydroxylation, leading to the exclusive formation of *syn*-1,2-amino alcohols in near quantitative yields (Scheme 13).[13] Using the sodium salts of the acids, the reactions could be performed in high concentrations in water without any organic cosolvent. When unsymmetrically substituted alkenes were employed, the reactions afforded exclusively the regioisomer with nitrogen on the less substituted carbon. However, the lack of ligand acceleration, even in the presence of a large excess of ligand, led to racemic products only.

Scheme 13[a]



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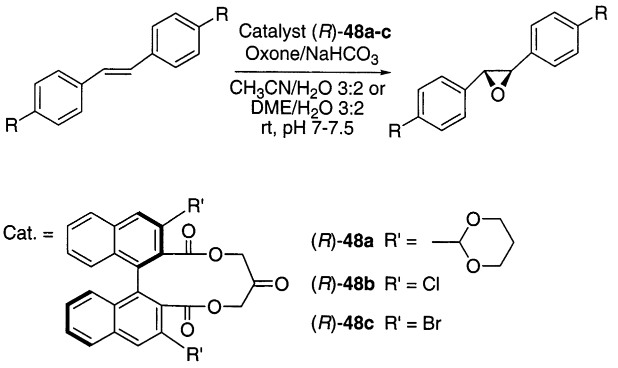
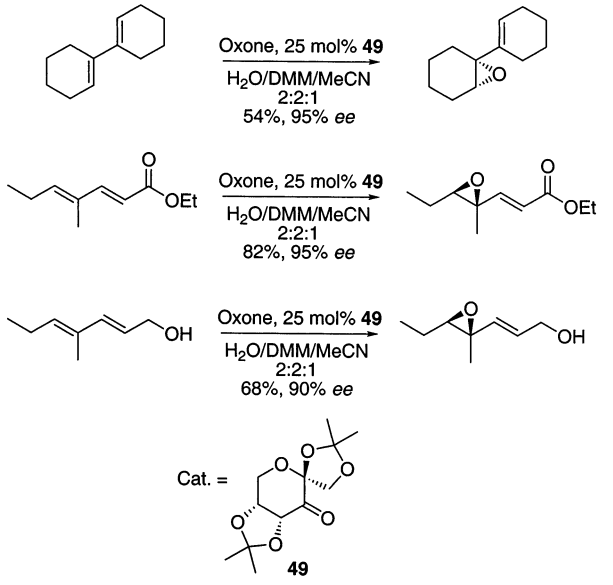
E. Epoxidation

Enantiomerically pure epoxides are very useful synthetic intermediates. The most powerful means by which these are obtained are the Sharpless epoxidation and the Jacobsen epoxidation. Both of these reactions, however, demand strictly anhydrous conditions for optimum performance. Recently, a catalytic asymmetric version of the highly stereospecific, dioxirane-mediated epoxidation of alkenes in aqueous media was developed. Yang and co-workers obtained good to high enantioselectivity (71−95% ee) in the epoxidation of disubstituted and trisubstituted olefins using BINAP-derived ketones (*R*)-**48a**−**c** as catalysts and Oxone as the stoichiometric oxidant (Scheme 14).[147] Almost simultaneously, Shi and co-workers found that the fructose-derived chiral ketone **49** was an efficient catalyst in the epoxidation of conjugated dienes leading to synthetically useful vinyl epoxides of high enantiomeric excess (89−97%).[148] A few representative examples are shown in Scheme 15. The reactions were generally carried out in water/dimethoxymethane/acetonitrile 2:2:1, and in this system even highly hydrophobic dienes were good substrates. As the authors pointed out, the observed regioselective epoxidation of the alkene distal to the electron-withdrawing group nicely complements the Sharpless epoxidation of conjugated dienes, which preferably oxidizes the olefin proximal to the hydroxyl functionality. It also complements the chiral (salen)Mn-catalyzed epoxidation of conjugated dienes, in which *cis*-olefins are preferentially epoxidized. Additionally, the catalyst **49** was found to be efficient in the asymmetric epoxidation of a wider range of substrates, including enynes, allylic alcohols, homoallylic alcohols, and bishomoallylic alcohols.[15,149]

Scheme 14



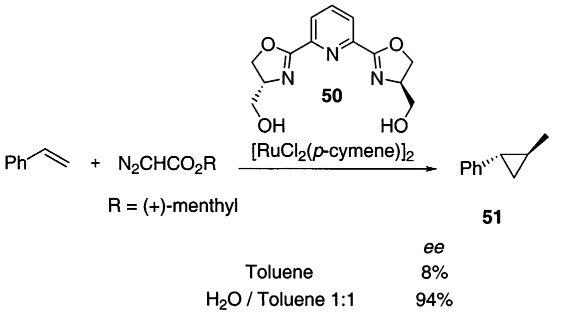
Scheme 15



F. Cyclopropanation

The ruthenium-catalyzed asymmetric cyclopropanation of styrene with menthyl diazoacetates in aqueous media was recently disclosed by Nishiyama and co-workers.[150] The water-soluble, chiral ligand bis(hydroxymethyl-dihydroxyoxazolyl)pyridine **50** (Scheme 16) was used in these transformations. While the reaction proceeded with low enantioselectivity (8% ee) in pure THF or toluene, the addition of water dramatically increased the selectivity, producing cyclopropane **51** in 78% ee in THF/water 2:1 and 94% ee in toluene/water 1:1.

Scheme 16[a]



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VI. Additions to C–X Multiple Bonds

The use of organometallic reagents to effect addition reactions to carbon–heteroatom multiple bonds is among the most important C–C bond-forming reaction available to the organic chemist. Organometallic additions have been particularly instrumental in the development of asymmetric synthesis. The presence of a coordinating metal often leads to a transition state of higher structural order due to chelation of the metal to Lewis-basic atoms in the substrate. Attack of the nucleophile from the sterically less challenging side of the preorganized complex is then usually preferred. Hence, when chelated intermediates are involved, mechanistic analysis is often simplified. As discussed above and exemplified extensively below, when water-tolerant reagents are used, metal coordination chemistry and chelation effects can be expected to operate in aqueous media.

A. Aldol-Type Reactions

Stereoselective aldol and aldol-type reactions have been carried out successfully in aqueous media.[8,9] While the classical aldol addition commonly employs a basic catalyst in protic solvents, undesired byproducts are frequently formed that reduce the synthetic value of the reaction. In this respect, Lewis-acid-catalyzed aldol-type reactions of silyl enol ethers with aldehydes and ketones have been found useful due to the higher regio- and stereoselectivities that can generally be obtained.[151] The rapid deactivation of many promoters and the decomposition of silyl enol ethers in protic solvents, however, seemed to exclude the use of water as solvent. Pioneering experiments by Lubineau and co-workers demonstrated that the uncatalyzed aldol reaction of silyl enol ethers in water could proceed, though yields were poor.[152] The development of Lewis acids tolerant of aqueous solvent in the past decade (see also section III.A.2) has allowed for successful catalytic, stereoselective aldol-type reactions in water.[52,73,153–156]

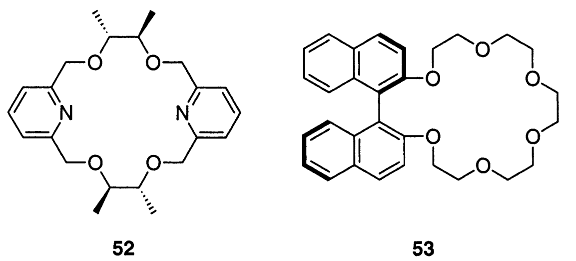
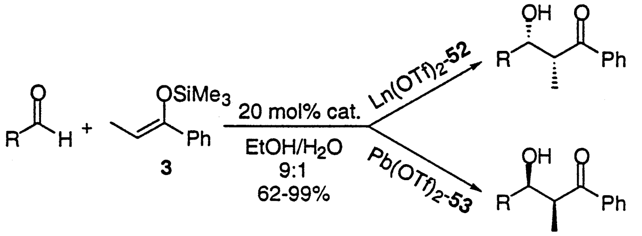


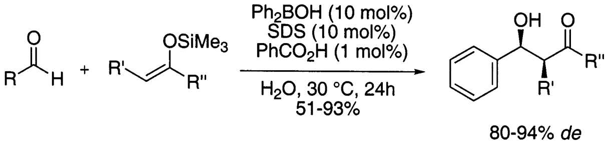
Figure 7.

Table 3.



catalyst	R	de (%)	ee (%)
Ce(OTf)$_2$-**52**	Ph	86	82
Pr(OTf)$_2$-**52**	Ph	80	79
La(OTf)$_2$-**52**	Ph	78	79
Nd(OTf)$_2$-**52**	Ph	86	75
Pb(OTf)$_2$-**53**	Ph	80	55
Pb(OTf)$_2$-**53**	*n*-hexyl	84	80
Pb(OTf)$_2$-**53**	*n*-nonyl	80	82
Pb(OTf)$_2$-**53**	isovaleryl	88	87

Scheme 17[a]



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Early work on aldol reactions in aqueous media focused primarily on lanthanides as catalysts. In a recent example, various lanthanide triflates were complexed with the chiral crown ether **52** (Figure 7) and screened for their ability to induce diastereo- and enantioselectivity in the reaction between benzaldehyde and silyl enol ether **3** in EtOH/water 9:1.[52] It was shown that for larger lanthanide cations, such as Ce(II), La(II), Pr(II), and Nd(II), which may have a better size fit for the cyclic ligand than smaller ions, both diastereomeric (78–86% de) and enantiomeric (75–82% ee) selectivity were good (Table 3). A range of other metals have also been shown to execute aqueous aldol-type reactions with good stereoselectivity. Kobayashi and co-workers found that, in EtOH/water 9:1, lead(II)–triflate efficiently catalyzed the aldol reaction of benzaldehyde and **3** upon complexation to the chiral 18-crown-6 ligand **53** (Figure 7).[153] Again, good *syn*/*anti*-selectivities (80–88% de) and enantioselectivities (75–87% ee) were obtained (Table 3).

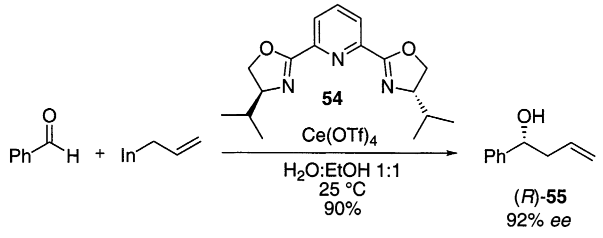
Boron has been shown to be an efficient mediator of stereoselective aldol reactions.[73] In water/SDS mixtures, 10 mol % of diphenylborinic acid, Ph_2BOH, catalyzed the reaction between aldehydes and silyl enol ethers to give *syn*-substituted β-hydroxy ketones in high diastereomeric excesses (80–94% de, Scheme 17). While the reaction proceeded sluggishly with only Ph_2BOH, the addition of 0.01 equiv of benzoic acid dramatically improved the yields. In organic solvents (Et_2O, CH_2Cl_2) the reaction was almost completely thwarted. A mechanism was proposed in which a boron enolate generated by silicon–metal exchange was the reactive intermediate. The positive effect of benzoic acid on the reaction rate was presumably due to acceleration of the Si–B exchange, which was thought to be the rate-determining step. The high *syn*-selectivities observed when (*Z*)-enolates were used were rationalized by invoking a chairlike six-membered cyclic transition state for the reaction between the aldehyde and the boron enolate.

Copper(II)-catalyzed aldol reactions have also been reported recently. Indeed, the first catalytic asymmetric aldol reactions in aqueous media were performed with $Cu(OTf)_2$ as catalyst and bisoxazolines as chiral ligands.[154,157] Other metals used with some success as catalysts in aqueous aldol reactions are bismuth[158] and indium.[159] Interestingly, the predominance of *syn*-aldol products in the water-based aldol reactions discussed above is in contrast with the analogous reactions run under anhydrous conditions where the *anti*-isomer is usually the major product.

B. Allylation Reaction

The fairly recent, unexpected discovery that metal-mediated allylations can be performed in water led to a surge of interest in these reactions, and recent literature is abundant with potentially useful examples. Particular attention has been focused on the allylation of carbonyls and imines to give the corresponding homoallylic alcohols or amines. While a number of metals, such as Zn,[160–163] Sn,[164–169] Sb,[170] Co,[171] Mn,[172,173] Mg,[174,175] or Hg,[176] have been reported to be useful for this purpose, indium (In) has showed the most promise due to its unique properties that make it particularly suitable for use in water: (i) it is stable even in boiling water; (ii) it is resistant to oxidation by air; and (iii) it has an unusually low first ionization potential. The literature on indium-mediated reactions in aqueous media up to 1998 has been recently reviewed[12] and will not be discussed here. More recent work on indium-mediated allylations show significant progress toward achieving high levels of stereocontrol for the preparation of natural products and synthetic intermediates. For example, Loh and Zhou described the first enantioselective indium-mediated allylation of aldehydes.[11] Using (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine, **54**, as a chiral ligand and $Ce(OTf)_4$ hydrate as Lewis-acid promoter, the reaction of allylindium with benzaldehyde in water/ethanol (1:1) afforded the homoallylic alcohol (*R*)-**55** in 90% yield and 92% ee (Scheme 18). The same authors later reported a catalytic enantioselective version of the same transformation using allyltributyltin in place of allylindium and a modified version of Yamamoto–Yanagisawa's catalyst (*S*)-BINAP·$AgNO_3$, **56**.[164] Initial attempts using 5 mol % of catalyst **56** in various solvent systems resulted only in moderate yields and enantioselectivities, but the use of 5 mol % (*S*)-Tol-BINAP·$AgNO_3$, **57**, in 1:9 water/ethanol transformed aromatic aldehydes into (*S*)-allylic alcohols in near quantitative yields and good selectivities (71–81% ee, Scheme 19). Much lower selectivities were observed with aliphatic, olefinic, and acetylenic aldehydes.

Scheme 18[a]



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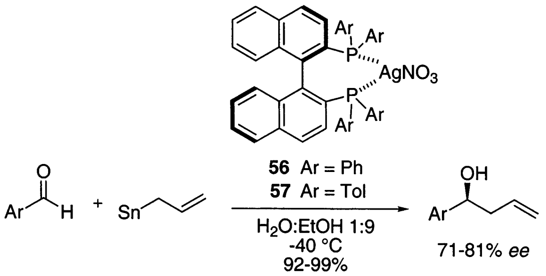
Scheme 19[a]



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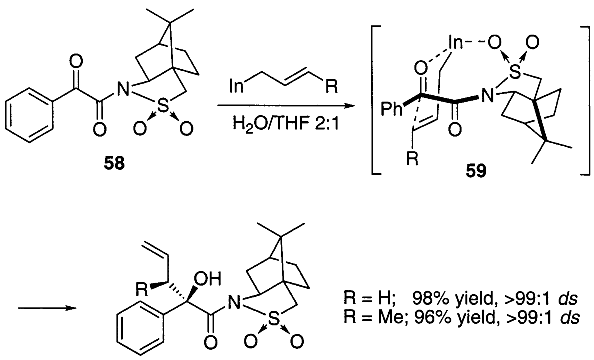
Scheme 20[a]



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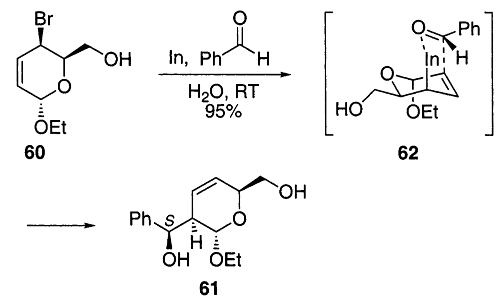
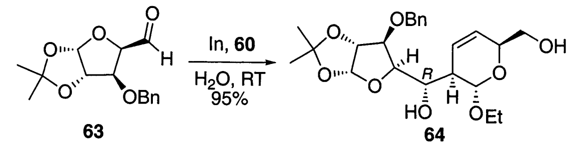
Excellent asymmetric induction has been achieved by grafting a chiral auxiliary onto the substrate. For example, Cho and co-workers studied the indium-mediated allylation reactions of α-ketoimide **58** derived from Oppolzer's sultam with various allyl bromides and found that in water/THF 3:1, diastereoselectivities of >99% were obtained (Scheme 20).[177] The high diastereoselectivity was explained by transition state **59** in which the carbonyl oxygen is involved in a six-membered ring chelation with indium, which may be further coordinated with one of the oxygens of the sulfoxide. Allylation then occurs from the least hindered side. The chelating properties of indium in water leading to enhanced stereoselectivity considerably increases the synthetic value of the indium-mediated allylation reaction. Canac and co-workers investigated this new methodology in an effort to find an efficient entry to the synthetically useful *C*-branched sugars.[178] The reaction of 4-bromo-2-enopyranoside **60** with benzaldehyde in pure water containing powdered indium metal afforded the addition product **61** as a unique stereoisomer in 95% yield (Scheme 21). Again, a six-membered cyclic transition state, **62**, involving indium chelation was invoked to explain the observed selectivity. With butyraldehyde, however, lower yield (71%) and no selectivity was observed, suggesting that less reactive

Scheme 21



Scheme 22



and/or sterically less demanding aldehydes are poorer substrates in this reaction. In the reaction between **60** and the furanose aldehyde **63** to give the *C*-disaccharide **64**, a complete reversal of the diastereoselectivity was observed compared to the reaction with benzaldehyde (Scheme 22). Using the cyclic transition-state model, this outcome was explained by additional chelation of the indium atom either with the exocyclic C-3′ oxygen (Figure 8, **65**) or with the endocyclic oxygen (**66**), both favoring the same product. Most noteworthy, in these conformations the chelating factor overrides the steric effect since the sugar substituent is in an unfavorable axial position, thus again indicating that significant chelation control can be expected in indium-mediated allylations in water. The effect of neighboring groups and solvent in allylindation reactions has recently been studied in detail (see section IV.A.1).[10,87−89,91,94,179−181]

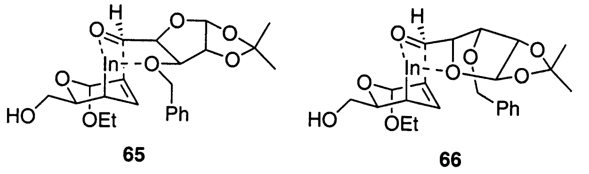
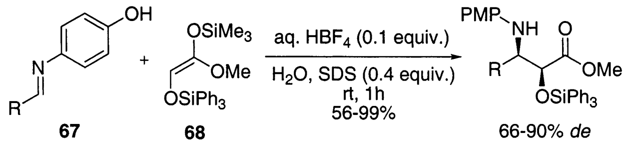


Figure 8.

C. Mannich Reaction

The development of Mannich-type reactions in aqueous media has been made with the incentive of finding a milder and more convenient approach toward the construction of β-amino ketones or esters. Classical protocols for Mannich reactions are sometimes of limited synthetic potential as they often involve harsh reaction conditions and are plagued with severe side reactions as well as poor regio- and stereocontrol.[182] Toward this end, several research groups have recently reported on the one-pot Mannich-type reaction in water to give β-amino carbonyl compounds using either Lewis-acid[83,183−185] or Brønsted catalysis,[186−190] with or without the addition of surfactants. Both types of reactions generally proceed smoothly in good yields, albeit with diastereoselectivities that are usually moderate at best. Good *syn*-selectivities of up to 95:5 were obtained, however, in HBF_4-catalyzed Mannich reactions between aldimines such as **67** and ketene silyl acetal **68** in a water/SDS mix (Scheme 23).[186]

Scheme 23[a]



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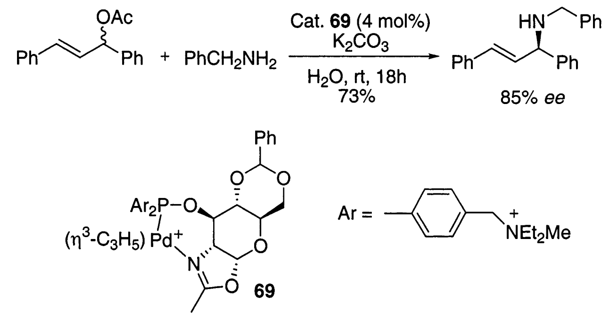
D. Hydride Addition

The stereoselective reduction of prochiral ketones with $NaBH_4$ as the hydride source to give secondary alcohols has been accomplished in aqueous media containing carbohydrate-based amphiphiles. The presence of the glycosidic amphiphiles serves two purposes: they are solubilizing agents, probably through formation of aggregates similar to micelles, and they also provide a stereodiscriminating environment for selective recognition of enantio- or diastereotopic faces of the ketone. A range of ketones was selectively reduced through this approach by Plusquellec and co-workers.[95] In their work, high regio- and stereoselectivities were achieved in the reduction of cyclic α,β-unsaturated ketones using various types of sugar-based additives. In a more recent example, Rico-Lattes and co-workers took this concept one step further by incorporating D-gluconolactone into polyamidoamine (PAMAM) dendrimers.[191] Supported by a solid core, these amphiphilic dendrimers acted as unimolecular micelles with a chiral surface. In an impressive demonstration of this strategy, acetophenone was reduced by $NaBH_4$ in water in 92% yield and 98% ee.[192]

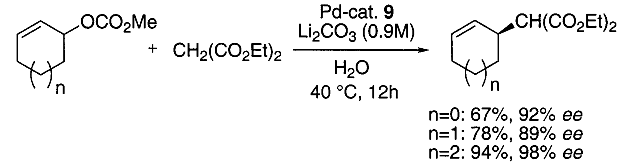
VII. Substitution Reactions

Little attention has been devoted to the development of substitution reactions in water. A likely explanation for this is that in many types of nucleophilic reactions in water, hydrolysis of the electrophile may compete with the desired reaction pathway. General hydrolysis reactions, in which the reaction between water and an electrophile is the preferred outcome, will not be discussed here. Nevertheless, a few reports of palladium-catalyzed allylic substitutions in water have surfaced in recent years.[63,193−195] Uemura and co-workers used a carbohydrate-based phosphinite−oxazoline ligand **69** in the palladium-catalyzed substitution of 1,3-diphenyl-3-acetoxyprop-1-ene with both carbon and nitrogen nucleophiles.[57] A representative example is shown in Scheme 24. The substitution products were obtained in moderate to high yields (66−95%) and in good enantiomeric excess when performed in water alone (85% ee) or in water/acetonitrile mixes (77−84% ee), but the best result was obtained in acetonitrile alone (92% ee). A year later, Uozumi and Shibatomi reported of an immobilized palladium complex of a *P*,*N*-chelate chiral ligand (**9**, Figure 2), which cata-

Scheme 24



Scheme 25



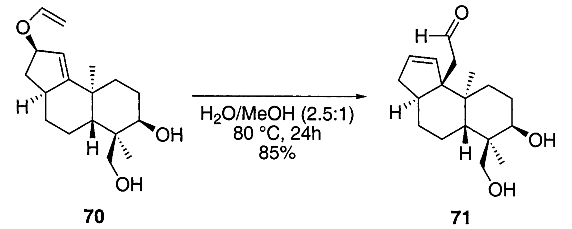
lyzed the asymmetric alkylation of allylic esters in 0.9 M aqueous Li_2CO_3 with up to 99% enantioselectivity (Scheme 25).[66] The catalyst was found to be effective for both cyclic and acyclic substrates. Conveniently, the catalyst could be recovered by simple filtration and reused without any loss of activity or stereoselectivity.

VIII. Rearrangements

A. Claisen Rearrangement

Water has a fundamental influence on the Claisen rearrangement.[6,7] Experimental data have indicated that the Claisen rearrangement of allyl vinyl ether is 1000 times faster in water than in the gas phase.[196,197] Because of the relative simplicity of the reaction, extensive theoretical studies have also been performed on the influence of various solvents, water in particular.[198] Both experimental and theoretical data have suggested that upon hydration, the Gibbs energy of activation is reduced by between 3.5 and 4.7 kcal/mol. Similar to the Diels–Alder reaction, differential solvation of the initial state and transition state seems to be intrinsically involved in effecting the observed rate enhancement. However, in contrast to the Diels–Alder reaction, the exploration of aqueous Claisen rearrangements for synthetic purposes has been minimal. The reason behind this discrepancy is not clear, especially considering the importance of the Claisen rearrangement in synthetic organic chemistry. In the late 1980s, Grieco and coworkers investigated the accelerating effect of water on Claisen rearrangements and also demonstrated its potential in organic synthesis on a number of substrates.[199] For example, rearrangement of the allyl vinyl ether **70** in basic water/methanol 2.5:1 afforded the aldehyde **71** in 85% isolated yield, without the need for protection of the hydroxyl groups (Scheme 26). Rearrangement of the protected substrate in organic media was more difficult and led to elimination of acetaldehyde.

Scheme 26



IX. Hydrogenations

Catalytic asymmetric hydrogenation have been among the most important reactions in the manufacturing of chiral compounds from achiral starting materials ever since its inception in the early 1970s. Over the years, many hundreds of chiral catalysts have been prepared and screened against alkenes of diverse structural composition. Water-soluble chiral catalysts have also been developed. The aqueous-phase asymmetric hydrogenations of olefins, ketones, imines, and α,*β*-unsaturated acids have been well documented in the literature.[16] Only recently, however, have reports appeared describing enantioselectivities that can match those achieved in the corresponding transformations in organic solvents. A seminal observation was that higher ee's are generally obtained in aqueous micellar media than in water alone. For example, Grassert and co-workers investigated the asymmetric hydrogenation of dialkyl 1-benzamido-2-phenyl-ethenephosphonates with chiral rhodium complexes as catalysts and found that water was a poor solvent leading to low activities and enantioselectivities.[200] With the addition of surfactants, however, ee's of up to 99% were obtained. Studies into the mechanism behind the effect of amphiphiles on the enantioselectivity of rhodium-catalyzed hydrogenations have been made. These are discussed in further detail in section III.C.

The enantioselective reduction of dehydroamino acid derivatives to yield optically pure amino acids has been by far the most investigated asymmetric hydrogenation reaction.[17] Several groups have recently reported on the use of water as solvent for this reaction.[55,56,201,202] For example, Uemura and coworkers described water-soluble chiral Rh(I) complexes derived from α,α- and *β*,*β*-trehalose (Figure 9), which proved to be highly efficient catalysts of the asymmetric hydrogenation of enamides.[56,201] Again, higher enantioselectivities were observed with water/surfactant mixtures than with water alone. In water/SDS mixtures, enantioselectivities of more than 99% could be achieved. Interestingly, these catalysts displayed amphiphilic nature in solubility, which made them equally good hydrogenation catalysts in 1,2-dichloroethane as in water/SDS.

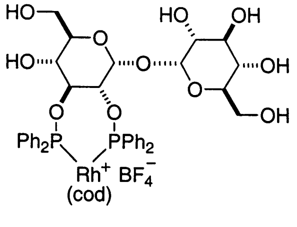
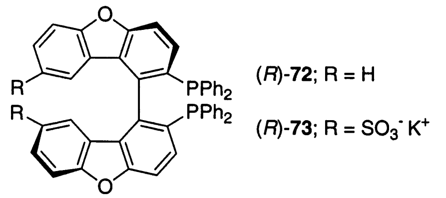


Figure 9.



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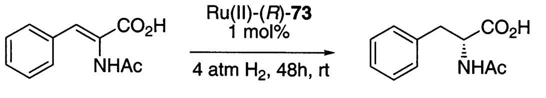
Scheme 27[a]



74 (*R*)-**75**

	conversion	*ee*
MeOH	100%	72%
H$_2$O/EtOAc	18%	72%

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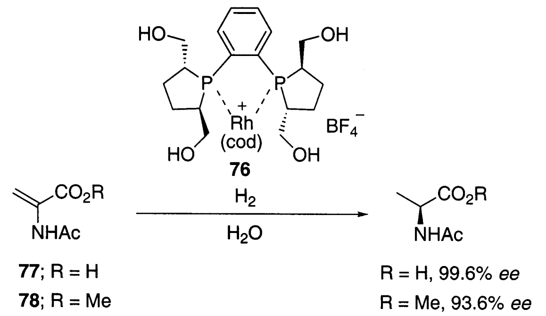
Scheme 28[a]



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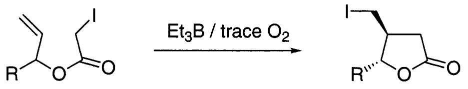
Phosphine ligands have been used successfully in ruthenium- and rhodium-catalyzed aqueous hydrogenations. Hiemstra and co-workers developed the diphosphines BIFAP, **72**, and the sulfonated, water-soluble BIFAPS, **73** (Figure 10), and investigated them as ligands for the ruthenium-catalyzed hydrogenations of (*Z*)-acetamidocinnamic acid, **74**, and methyl acetoacetate.[44] For the reaction of (*Z*)-acetamidocinnamic acid, the use of (*R*)-BIFAPS in methanol or a 1:1 water/ethyl acetate mixture resulted in hydrogenated product (*R*)-**75** of 72% ee (Scheme 27). The reaction rate in water/ethyl acetate was, however, much lower than that in methanol. The hydrogenation of methyl acetoacetate with (*R*)-BIFAPS in water proceeded to give 86% ee after the addition of 1% sulfuric acid. For both substrates, however, the nonsulfonated BIFAP, **72**, in methanol was superior to BIFAPS, **73**, in water. Without sulfuric acid in the latter reaction the ee dropped dramatically, but the nature of the acid effect was not clear to the authors. The tetrahydroxylated, water-soluble analogue of the widely used DuPHOS ligand named BASPHOS, **76**, was remarkably efficient in the Rh(I)-catalyzed asymmetric hydrogenation of 2-acetamido acrylic acid, **77** (99.6% ee, Scheme 28), and its methyl ester, **78** (93.6% ee).[203]

A slightly different strategy of solubilizing hydrogenation catalysts has been pursued by Malmström and Andersson.[204,205] They prepared acrylic acid polymers coupled to chiral rhodium–bisphosphine complexes and applied them to the asymmetric hydrogenation of dehydro amino acids and their esters. While good yields and moderate enantioselectivities could be obtained in water (pH 8) in the presence of 1% of Rh catalyst, quantitative yields and ee's of up to 89% were observed when the same reaction was run in a 1:1 mixture of water/ethyl acetate.

X. Radical Reactions

The use of water as solvent for radical reactions in organic synthesis is rare. This may be because early attempts did not reveal any special effect of water compared to organic solvents. In general, radical reactions are not believed to be influenced by the reaction medium to any greater extent. This is in contrast with many other reaction types developed for use in aqueous media where the solvent effect is usually significant. Nevertheless, water should be a good medium for radical reactions considering that it has no functionalities that are reactive toward free radicals and a strong OH bond that makes undesired hydrogen abstraction unlikely. The recent surge of general interest in water-based synthesis may lead to a reexamination of water as solvent for radical reactions.[206–211] Toward this end, significant solvent effects have in fact recently been reported in radical cyclizations, especially in water. For example, the triethylborane-mediated intramolecular radical cyclization reaction of allyl iodoacetates **79a**–**c** to give γ-butyrolactones **80a**–**c** was shown to be much more efficient in water than in traditional solvents such as benzene or hexane (Scheme 29).[212] Indeed, no formation of lactone was observed in hexane or benzene, but a yield of 78% of **80a** was obtained at low concentration (0.01 M) in water. Significant diastereoselectivity was observed in the analogous cyclization reaction with the substituted allyl iodoacetates **79b** and **79c**, yielding lactones **80b** (trans/cis 86:14) and **80c** (trans/cis 88:12), respectively. Unfortunately, the yields dropped dramatically with increasing chain length of the 5-substituent (**80b** 67%, **80c** 32%), and the reaction was completely thwarted when R = *n*-butyl. In general, increasing the hydrophobicity of the substrates tended to sharply decrease reactivity. This concern was addressed in a recent paper by Kita and co-workers where they used water-soluble radical initiators in water/surfactant systems to effect the radical cyclization of a variety of hydrophobic substrates.[213] However, while yields were dramatically improved by addition of surfactant, the diastereoselectivities observed were only moderate at best. The Et$_3$B-induced radical cyclization has

Scheme 29



79a; R = H	hexane or benzene	**80a**; 0%
79a; R = H	water	**80a**; 78%
79b; R = Me	water	**80b**; 67%, 86% *ds*
79c; R = Et	water	**80c**; 32%, 88% *ds*

found further application in the cyclization of *N*-allyl-2-iodo amides in water to provide synthetically attractive γ-lactams. Again, good *trans*-selectivities were obtained, especially with an electron-withdrawing sulfonate substituent on the nitrogen (90% ds).[214]

XI. Conclusions

The past decade has seen extraordinary strides in water-based organic synthesis, and research in this field still seems to be in an exponential mode of development. This article has attempted to summarize key discoveries in this area as well as some of the most promising new methods of achieving stereocontrol in organic reactions developed in the last 5 years. In this period, many catalytic stereoselective reactions in water have been realized, mainly through the rational development of water-stable catalysts and water-soluble chiral ligands. Many of the most fundamentally useful reactions in asymmetric synthesis such as aldol reactions, allylations, aminohydroxylations, cycloadditions, cyclopropanations, dihydroxylations, epoxidations, hydrogenations, and others can now be performed with similar, or even improved, rates, yields, and selectivities in aqueous media compared to the corresponding reactions in organic solvents. The unique hydrophobic properties of water have led to the formulation of the concept of hydrophobic control, an intriguing new mode of achieving stereoselectivity that has yet to be extensively explored.

Concerns of the solubility of organic compounds in water were also addressed. Many attractive target molecules are actually highly soluble in water, and with improved synthetic methods in water, these may be accessible directly without the need for derivatization. For compounds insoluble in water, the use of cosolvents, buffers, surfactants, or hydrophilic auxiliaries may be useful. Here it is necessary to emphasize that the ultimate goal of developing synthetic methods that are amenable with the use of water as solvent should not be to substitute organic solvents for water in every transformation known but rather to expand the options available to the synthetic chemist. We will arguably never get close to realizing the full potential and scope of synthetic organic chemistry through the exclusive use of organic solvents.

Aqueous chemistry predominates in biological processes, and the development of synthetic aqueous chemistry may also aid our understanding of the detailed mechanisms of the chemistry of life, e.g. biocatalytic processes. This may have implications for biotechnological applications, such as artificial biomimetic systems.

On a final note, the greatest restriction to the wider implementation of aqueous synthesis may be one of a mental nature. It is hoped that this article will serve to rectify some of the misconceptions that might persist with many chemists regarding the inadequacy of water as solvent for organic reactions.

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XIII. References

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