**Organic Reactions using Water-Based Solvent Systems**

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**Abstract**

Water is increasingly recognized as a versatile and environmentally friendly solvent in organic chemistry. Traditionally, organic reactions have relied heavily on organic solvents, which can pose significant environmental and health hazards. In contrast, water-based solvent systems offer numerous advantages, including lower toxicity, cost-effectiveness, and enhanced reaction conditions that can lead to higher yields and selectivity. Various types of organic reactions have been successfully performed in water-based solvent systems for example Aldol reaction, Biginelli Reaction, Claisen rearrangement, Diels Alder Reaction, Henry Reaction, Huisgen [3 + 2] Cycloaddition reaction, Knoevenagel condensation reactions, Mannich reaction, Michael Addition reaction, Strecker reaction, Suzuki reaction and Wittig reaction etc. In the context of these reactions, water-based solvent systems not only represent a promising avenue in organic chemistry but also aligning and achieving the goals of sustainability and efficiency.

**Keywords:** Water, Aqueous medium, Aldol, Biginelli, Claisen, Diels Alder, Henry, Huisgen, Knoevenagel, Mannich, Michael Addition, Strecker, Suzuki,Wittig.

**1. Introduction**

Water is the solvent in which biochemical reactions are performed in Nature, and it is environmentally benign. However, it is a good solvent only for organic chemicals that have polar groups, such as alcohols and carboxylic acids. The situation has been changing because of the early work of Breslow showing how water enhances the Diels-Alder reactions, one of the first cases of which was originally reported using water as a reaction medium.1,2

The subsequent exploration of the hydrophobic effect in organic reactions by the Breslow group greatly increased the interest in water by organic chemists.3,4 The use of water as a medium for organic synthesis has further mushroomed since the masterful use of concept and language by Sharpless et al. who described successful reactions as being “on-water” for cases where the reactants are insoluble in water.5 The literature now contains a range of important recent books,6,7 reviews8-13  and articles14-17 promoting organic synthesis in the water medium.

Water is not simply an environmentally benign solvent; it has special properties that are essentially unique, related to what is called the hydrophobic effect. This is the tendency for hydrocarbons or molecules with hydrocarbon components to avoid contact with water, and to associate instead with other hydrocarbon species in water. This is what makes aqueous soap solutions dissolve grease, and it is the driving force in biology for the associations that produce cell membranes, and that cause nucleic acids to form the famous double helix. It drives the folding of proteins into their shapes in enzymes and antibodies, and it also promotes the binding of biological substrates into enzymes and antibodies.18

The hydrophobic effect has now been used to mimic biological chemistry and to provide remarkable selectivity in the field called biomimetic chemistry. Small covalent organic molecules repel water molecules. When present in water they are forced to form aggregates in order to decrease the organic surface area exposed to water. These aggregates cause holes in the cluster structures of liquid water and the bulk water molecules surround or hydrate the aggregates. In the final layer of the hydration shell, as the bulk water molecules approach the surface of small aggregates their H-bond links run laterally along the hydrophobic surface.19 Translational motion of the water molecules is severely limited near the barrier but molecular jump reorientations of some water molecules still occur.20 The aggregates are held together by the hydrophobic interaction, and when these aggregates are composed of organic reactants, they give rise to the hydrophobic effect on organic reactions that result in a rate acceleration.

When organic reactions possess hydrogen bond acceptor sites water molecules will form H-bonds with them, both in their initial states and in the reaction transition state. The transition states of covalent reactions can be viewed in terms of frontier orbital interactions involving the HOMO and LUMO pairs of each molecule A and B for a reaction A + B = C. In the approximation the lower orbital interactions are excluded and attention is focused on the two frontier orbitals with closest HOMO-LUMO gap except when these gaps are equal. H-Bonding like electron-withdrawing substituents, lowers the energy of the frontier orbitals by reducing electron density and interorbital repulsion. The effect of water depends on the presence or absence of H-bonding interactions with the different reactants. The effect of water H-bonding on the rates will depend on relative lowering of the dominant frontier orbitals as to whether the gap is increased or decreased with consequent effect on the transition state energy. Jorgensen and co-workers have long proposed significant contributions from “enhanced hydrogen bonding” at the transition states of pericyclic reactions in water from high level theoretical calculations.21,22

In the recent years, there has been an explosion in the use of water as a solvent for organic reactions with almost all reaction types explored. The subject of this chapter is to thoroughly illustrate the versatility and scope of water as a medium for organic reactions.

**2. Aldol reaction**

The aldol reaction is one of the important carbon–carbon bond formation reactions in organic chemistry. A wide range of small organic molecules including L-proline are known to catalyze the asymmetric aldol reaction. Most of these reactions occur either in organic media or utilize water as a cosolvent or additive. The pioneering work by Janda *et al.* 23 utilized nornicotine to catalyze the aldol reaction of acetone and p-chlorobenzaldehyde in water (Scheme 1). Although they could achieve only a moderate enantioselectivity of 20%, it was the first experiment to show the role of water in an ‘organocatalytic aldol reaction’. They proposed that water plays a dual role in catalyzing this reaction and the explanation was supported by a computational study.24



**Scheme 1**. Nornicotine catalyzed aqueous Aldol reaction.

Armstrong and co-workers explored the asymmetric organocatalytic aldol reaction of cyclohexanoneand substituted benzaldehydesusing water as the reaction solvent.25 A range of proline type organocatalysts were examined in the reaction and the *tert*-butylphenyl proline catalyst was found to give the best enantioselectivity of all the catalysts screened (Scheme 2).



**Scheme 2**. Organocatalytic Aldol reaction in aqueous solvent.

Barbas *et al.*26 carried out a highly enantioselective direct aldol reaction catalyzed by a protonated diamine as a bifunctional organocatalyst. This enantioselective methodology was good only for cyclic ketones to get a maximum of 99% ee. Acyclic ketones gave only moderate enantioselectivities (Scheme 3). They hypothesized that a small organic catalyst with appropriate hydrophobic groups assembled with the hydrophobic reactants in water and sequestered the transition state from water.



**Scheme 3**. Organocatalyst diamine catalyzed Aldol Reaction in water.

Hayashi explored the self-aldol condensation of propanal using a wide range of amino acids and modified amino acids with water as the reaction medium.27 Of the nineteen amino acids screened the proline analogue Pro-NH2 was found to be the best giving a moderate yield and good enantioselectivity (syn 74% ee, anti 78% ee). The reaction mixture was initially a clear solution (suggesting an in-water reaction), and after thirty minutes, the reaction mixture went cloudy because of the formation of oily particles. When the reaction was explored with different concentrations of water, there was no significant change in yield or enantioselectivity. No reaction occurred when neat propanal was treated with catalyst. This suggests that water plays a significant role in the reaction mechanism (Scheme 4).



**Scheme 4**. Organocatalytic Aldol reaction of propanal using water as the reaction medium.

Gruttadauria and co-workers explored the organocatalysed asymmetric aldol reaction of cyclohexanone and substituted aldehydes using water with the substituted proline organocatalyst. High yields (up to 99%) and enantioselectivities (>99%) were achieved using a 2 mol % loading of the catalyst (Scheme 5).28 The initial screening was examined with a range of organic solvents, but it was found that the reaction using water as solvent gave the best conversion (99%) and enantioselectivity (98%).



**Scheme 5**. Organocatalytic Aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde under aqueous conditions.

Chimni and Mahajan29 in 2006, reported that a protonated chiral prolinamide catalyzed enantioselective direct aldol reaction in water. They found that there was no reaction in the absence of water. For the reaction of acetone with p-nitrobenzaldehyde, they could obtain a maximum of 50% ee (Scheme 6). The prolinamide catalysts have the limitation of giving moderate enantioselectivity with water miscible ketones such as acetone.



**Scheme 6**. Chiral prolinamide catalyzed enantioselective direct aldol reaction in water.

Chimni and co-workers have observed that the organocatalyzed reaction of cyclohexanone and *p*-nitrobenzaldehydehas an optimal reaction pH between 4-5 in aqueous solution.30 The pH range was explored between 0.94 and 6.4 and the optimum pH was found to be 4.5 with the highest enantioselectivity of 96% observed (Scheme 7). This study shows that the pH of the reaction in important for the optimum yield and enantioselectivity of organocatalytic reactions.



**Scheme 7**. Aqueous organocatalytic Aldol reaction at different pH.

On similar lines, other prolinamide based organocatalysts have been synthesized to carry out asymmetric aldol reactions in water. The L-proline based dipeptide31 was discovered by Li *et al.* and successfully applied to the asymmetric aldol reaction of unmodified ketones with various aldehydes such as aromatic, aliphatic, heteroaromatic and unsaturated aldehydes in water at 0 0C (Scheme 8). The products were obtained in high yields, diastereo- and enantioselectivities.



**Scheme 8.** Micelle promoted chiral prolinamide catalyzed aldol reaction in water.

Gryko and Saletra32 synthesized L-prolinethioamide catalyst for the direct asymmetric aldol reaction of cyclic ketones with aryl aldehydes in water (Scheme 9). Water is a suitable medium for this reaction as high yields and stereoselectivities were obtained. The reaction occurs in a hydrophobic organic phase i.e. in biphasic medium, which is evident from conducting the experiments with ‘salting in’ and ‘salting out’ salts.



**Scheme 9.** Pyrrolidine sulfonamide catalyzed aldol reaction in water.

T. He *et al.*33 synthesized proline-cholesterol and-diosgenin based amphiphilic organocatalysts for the first time, and performed the direct aldol reaction in between cyclic ketones and aromatic aldehydes. The presence of water with these organocatalysts leads to micelle formation and a significant enhancement in reactivity and stereoselectivity.



**Scheme 10.** Proline-cholesterol and-diosgenin based amphiphilic organocatalyzed reaction in water

W. Xiao *et al.*34 developed a controllable strategy for engineering polystyrene-supported acid base catalysts by using nanoprecipitation in water, because of the hydrophobic nature of the polystyrene chains, coil-globule collapse not only constructs hydrophobic environments but also brings catechol groups and benzylamine groups (attached to polystyrene chain) in close proximity to enable the synergistic effect.



**Scheme 11.** Pyrrolidine sulfonamide catalyzed aldol reaction in water.

**3. Biginelli reaction**

Suzuki and co-workers examined the Lewis acid catalyzed Biginelli reaction using water as the medium. Metal triflamides, such as Ni(NTf2)2, Cu(NTf2)2, and Yb(NTf2)2, catalyzed the multicomponent reaction to afford 3,4-dihydropyrimidine-2-(1H)-ones, (Scheme 10). A range of aldehydes were explored, and the yields were found to be moderate to excellent (>95%) using the Cu(NTf2)2. When the Lewis acid was changed to Ni(NTf2)2 or Yb(NTf2)2, the yields were much lower.35 Konwar *et al.* reported dodecyl sulfonic acid as an excellent surfactant-type Brønsted acid catalyzed synthesis of 3,4-dihydropyrimidin-2-ones in aqueous media at room temperature (Scheme 12).



**Scheme 12.** Aqueous lewis acid/brønsted acid catalyzed Biginelli reaction.

Lei and Hu observed that a Biginelli like three-component condensation reaction of aromatic aldehyde β-dicarbonyl compound and 2-aminobenzimidazole could be performed in water by using thiamine hydrochloride (VB1), which is a nonflammable, inexpensive, and non-toxic reagent, as catalyst (Scheme 13). This method offers a straightforward and eco-friendly method for synthesizing benzo[4,5]imidazo[1,2-a]-pyrimidine derivatives. Many other solvents, such as THF, DMF, toluene, acetonitrile, ethanol and dichloromethane, were also used in this reaction, but the yields obtained are inferior as compared with water.36



**Scheme 11/13.** Biginelli-type three-component reaction of 2-aminobenzimidazole, aromatic aldehydes and 1,2-diphenylethanone in water.

Kumar and co-workers reported an easy, efficient and eco-friendly procedure for the one-pot synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one and amidoalkylnaphthols *via* Biginelli-type multicomponenet reaction of aldehydes, urea/thiourea/amides with 1/2-naphthol using SDS promoted cellulose sulfuric acid, a recyclable solid-supported acid catalyst in water (Scheme 14). They believed that the reaction may starts with the formation of *N*-acylimine intermediate with aldehyde and urea/thiourea/amides instead of ortho-quinonemethides (o-QMs).37



**Scheme 12/14.** Synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one and amidoalkylnaphthol catalyzed by micelle promoted cellulose sulphuric acid in water**.**

D. Bhattacharjee and B. Myrboh38 found that sodium dodecyl sulfate (SDS) has been demonstrated as an efficient surfactant mediated catalyst for the synthesis of dihydropyrimidinone derivatives by the Biginelli condensation of aldehydes, β-dicarbonyls, and urea/thiourea.



**Scheme 14.** SDS mediated Biginelli condensation for the one pot synthesis of dihydropyrimidine derivatives in water.

Puripat *et al.*39 proposed artificial force induced reaction (AFIR) method which was applied to search systematically all possible multicomponent pathways for the Biginelli reaction mechanism. The most favorable pathway starts with the condensation of the urea and benzaldehyde, followed by the addition of ethyl acetoacetate. In this case urea acts as a catalyst and water acts as a protic medium.



**Scheme 15.** Urea-Catalyzed Organocatalytic Multicomponent Reaction

**4. Claisen Rearrangement**

The Claisen rearrangement is a [3,3] sigmatropic rearrangement and is a prevailing method for the synthesis of new C-C bonds. The mechanism of this reaction is concerted and there is a minimal influence from solvent polarity. One of the first aqueous Claisen rearrangements was reported in 1973. The reaction studied was the conversion of chorismate to prephenate, a key step in the shikimate biosynthetic pathway for generating aromatic amino acids (Scheme 16).40

Grieco explored the kinetics of the Claisen rearrangement of carboxylate containing vinyl ethers and found that the rate in water was 20 times that of the corresponding reaction in organic solvents.41



**Scheme 16.** Claisen rearrangement of chorismate to prephenate in aqueous medium.

Auge´ and co-workers explored the Claisen rearrangement of 6-*β-*glycosylallyl vinyl etherin toluene and water. The rearrangement proceeds in 1 h at 80 °C in water, but in toluene, a reaction time of 13 days was necessary at 80 °C. Sodium borohydride was added to the reaction to reduce the aldehyde that was formed. In another example the same group of workers examined a reaction of an α-anomeric form of 6-glycosylallyl vinyl ether. In water, the Claisen rearrangement preceded over 1.5 h at 60 °C, but when the solvent was changed to toluene, no reaction was observed even heating at higher temperatures. Under these conditions, the main reaction led to decomposition of the 6-α-glycosylallyl vinyl ether (Scheme 17).42



**Scheme 17.** Claisen rearrangement of glycosylallyl vinyl ethers in water.

Sharpless and co-workers have reported the Claisen rearrangement of the 4-chloro-1-substituted naphthol. The reaction at room temperature in water for 5 days (0.28-0.46 M) gave the rearranged productin 100% yield (Scheme 18). The corresponding reaction in organic solvents such as toluene or methanol gave significantly reduced yields especially in the case of nonpolar toluene (yield = 16%).43



**Scheme 18.** Aqueous Claisen rearrangement of 4-Chloro-1-substituted naphthol.

Acevedo and Armacost used QM/MM Monte Carlo calculations on the Claisen rearrangement of allyl naphthyl ethers with water as a solvent. The simulations indicated that the water enhancements are derived from the ability of the interfacial waters to stabilize the polar transition state v*ia* enhanced trans-phase hydrogen bonding at the oil/water interface, which is an on-water reaction. The calculations were carried out in 16 different solvents and reflects the trends obtained from the synthetic study by Sharpless and co-workers.44

The Claisen rearrangement is a key reaction in a wide range of total syntheses.45 The application of aqueous conditions would increase its usefulness significantly because of the high temperature and long reaction times required for organic solvents which can cause decomposition. Nicolaou and co-workers reported a water-accelerated Claisen rearrangement and Diels-Alder cascade sequence in their synthesis of gambogin, a cytotoxic natural product isolated from the evergreen plants of the genus *Garcinia.*The authors noted the unprecedented facility of the Claisen rearrangement using the model substrate (Scheme 19), which proceeded at room temperature in ethanol/water mixture. The quantitative conversion of intermediate to the key gambogin precursorwas then accomplished by the Claisen rearrangement/Diels-Alder sequence in water at 65 °C.46



**Scheme 19.** Water-accelerated Claisen rearrangement/Diels-Alder cascade sequence in the synthesis of gambogin.

**5. Diels-Alder Reactions**

The Diels-Alder reaction is a one of the most synthetically useful reactions in organic chemistry for the synthesis of highly complex six-membered rings.47-49 The versatility of this reaction has yet to be surpassed and it is not surprising that this reaction was one of the first to be explored using water as a solvent.50 In the early 1930s Diels and Alder examined the reaction of furan and maleic anhydride and this was subsequently re-examined by Woodward and Baer in 1948 (Scheme 20).51



**Scheme 20.** Diels-Alder reaction of furan and maleic anhydride using water as a solvent.

In 1980, Rideout and Breslow reported that both rate enhancement and excellent selectivity could be achieved for certain Diels-Alder reactions when they were performed in dilute aqueous solutions.1 The authors studied the reaction of cyclopentadiene (0.4 mM) with butenone (12.1 and 25.5 mM) in water (Scheme 18) and followed its progress by UV-vis spectrometry. The reaction was accelerated more than 700-fold in water versus the aprotic nonpolar organic solvent, 2,2,4-trimethylpentane.



**Scheme 21.** Diels-Alder Reaction of cyclopentadiene and butenone in water.

The effects of different additives (lithium chloride, guanidinium chloride, and cyclodextrins) were also examined. Although 4.86 M guanidinium chloride did not significantly affect the rate, the reaction was accelerated in 4.86 M lithium chloride solution. The observed rate increase in water was explained by the hydrophobic effect, i.e., the propensity of hydrophobic molecules to associate in order to minimize their contact surface with water.52-54

Griesback reported the Diels-Alder reaction of dimethylfulvene and 1,4-benzoquinone using water as a solvent.55 As with the results reported by Breslow, it was found that using water as a solvent enhanced the rate. It was also found that the endo/exo ratio of products could be significantly altered by varying the formal concentration of the starting materials (Scheme 22). Higher concentrations of the reactants were found to favor the endo isomer while lower concentrations were found to favor the exo isomer.



**Scheme 22.** Diels-Alder Cycloadddition Reaction of Dimethylfulvene and 1,4-Benzoquione in water.

Grieco was one of the first to examine the use of water as a solvent for the Diels-Alder cycloaddition reaction as a key step in the synthesis of complex polycyclic ring systems.56,57 The reaction of the diene carboxylate with the quinone dienophile was carried out using water as a solvent. The diene was in 5-fold excess, and the concentration of the diene in the water was 2.0 M. The reaction was found to proceed in 77% yield over one hour, while in the organic solvent toluene, only a trace of the product was formed after one week (Scheme 23).



**Scheme 23.** Diels-Alder reaction of diene carboxylate and dimethylbenzoquinone in aqueous solution.

Fringuelli and co-workers have explored the inverse-electron demand Diels-Alder reaction of diazenylbutene with electron-rich dienophiles, such as ethyl vinyl ether.58 The reactions were faster in the heterogeneous aqueous medium in comparison to the homogeneous organic solvents. The reaction proceeded with high endo selectivity in both organic and aqueous solvents and the difference in selectivity was negligible (Scheme 24).



**Scheme 24.** Inverse electron demand Diels-Alder reaction of diazabutenes with ethyl vinyl ether.

M Fringuelli and co-workers also examined the inverse electron demand Diels-Alder reaction of nitroalkenes and the electron-rich dienophile ethyl vinyl etherto afford a mixture of endo and exo adducts.59 The reaction was carried out using water and for comparison dichloromethane as solvents. The reactions in aqueous solutions were heterogeneous and using dichloromethane the reaction medium was a homogeneous solution. The heterogeneous aqueous reaction was slower than the reaction in dichloromethane solution (Scheme 25).



**Scheme 25.** Diels-Alder reaction of nitroalkene with ethyl vinyl ether.

Intramolecular variants of the Diels-Alder reaction have been explored using water as a solvent but not to the same extent as the intermolecular variant. Grieco investigated the intramolecular Diels-Alder reaction of a diene with an iminium salt to afford a complex tricyclic ring system.60 When the reaction was carried out using water as solvent the product was formed in 80% yield after 48 h as the sole isomer (Scheme 26).



**Scheme 26.** Intramolecular Diels-Alder reaction.

Kibayashi examined the intramolecular Diels-Alder reaction of acylnitroso compounds which were generated in situ using water as a solvent.61 The initial step of the reaction involved periodate oxidation of the hydroxamic acidto the nitroso compound and this underwent subsequent intramolecular Diels-Alder cycloaddition to afford corresponding cis and trans compounds (Scheme 27).



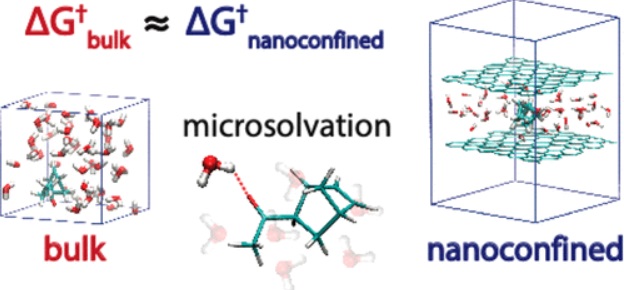
**Scheme 27.** Intramolecular Diels-Alder reaction of acylnitroso compounds.

In 2005, Sharpless and co-workers demonstrated the on water effect on the Diels-Alder reaction of *trans*,*trans*-2,4-hexadienyl acetate and *N*-propylmaleimide.5 For example, the reaction in toluene took 144 h, in methanol it took 48 h, and it still required 10 h when no solvent was used to obtain similar product yields (81-82%), whereas pure product was isolated in 81% yield after 8 h of stirring on water (Scheme 28).



**Scheme 28.** On-Water Diels-Alder Reaction of *trans*,*trans*-2,4-Hexadienylacetate with *N*-Propyl Maleimide.

L. R. Pestana *et al.*62 used ab initio molecular dynamics simulations to characterize the free energy of a retro-Diels−Alder reaction in bulk water at very different densities and in water nanoconfined by parallel graphene sheets (Scheme 29).



**Scheme 29.** Diels−Alder Reactions in Water Are Determined by Microsolvation

**6. Henry reaction**

Nitro-aldol (or Henry) reaction is an important carbon–carbon bond formation reaction widely used in organic synthesis. It involved the reaction between aldehyde and nitromethane which is usually performed in organic solvents. Li *et al.* used double-stranded DNA as a catalyst to facilitate the Henry reaction in aqueous solution under mild reaction conditions (Scheme 30).63



**Scheme 30.** DNA as catalyst for Henry reaction in water.

Ballini and Bosica reported the use of cetyltrimethylammonium chloride as a phase transfer agent for the synthesis of 2-nitro alcohols in water containing sodium hydroxide.64 Reddy et al reported an efficient synthesis of 2-nitro alcohols under ambient conditions catalyzed by a zinc–proline complex using the environmentally benign solvent, water, as the reaction medium (Scheme 31).65



**Scheme 31.** Nitroaldol reaction between p-nitrobenzaldehyde and nitromethane with NaOH and zinc-pro catalysts in water.

An efficient catalytic asymmetric aza-Henry reaction has been developed by *Bengoa et al.* under phase transfer conditions. The direct aza-Henry reaction holds as interesting features the validity for both nonenolizable and enolizable aldehyde-derived azomethines and the tolerance of nitroalkanes, other than nitromethane, for the production of *β-*nitroamines (Scheme 32).66



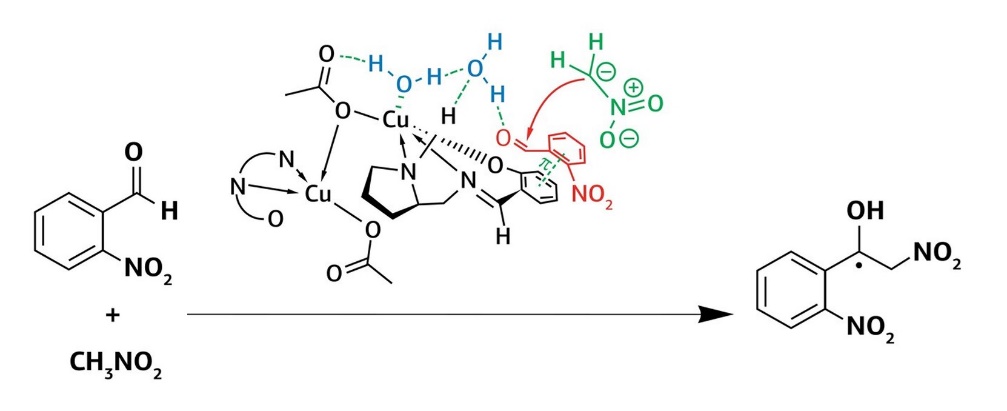
**Scheme 32.** Aza-Henry reaction of nitromethane with Azomethines generated from α-amido Sulfones under PTC in water.

The Henry products act as Michael acceptors and have attracted significant interest in recent years, because of the activating effect of the nitro group. Various derivatives of nitroamines and nitrothiols have been synthesized in high yields by the Michael addition of amines and thiols to nitroolefins without using any catalyst in water (Scheme 33).67



**Scheme 33.** Synthesis of aza-Henry products by addition of thiols and amines to nitroolefins in water.

Larionov V. A. *et al.*68 demonstrated that chiral NNO-type copper(II) complexes effectively catalyzed a benchmark reaction of o-nitrobenzaldehyde condensation with nitro methane only in the presence of water. Additionally, the copper(II) ion was not involved in the direct Lewis acid type activation of the aldehyde carbonyl group contrary to the generally held view on the copper complex Henry reaction catalysis (Scheme 34).



**Scheme 34.** Henry reaction catalyzed by new copper complexes in water.

The first examples of highly effective Henry reactions between nitroalkanes and aldehydes or trifluoromethyl ketones that proceed under catalyst-free and additive-free conditions, in a recyclable tap water medium, and at room temperature are reported by Z. H. Du et al.69. This process tolerates a broad range of aldehydes and trifluoromethyl ketones to give a series of β-nitro alcohol products in excellent yields (Scheme 35).



**Scheme 35.** Catalyst-Free Henry Reaction between Nitroalkanes and Aldehydes or Trifluoromethyl Ketones Promoted by Tap Water

B. Saikia70 used a very simple and highly abundant waste material to prepare natural base such as ‘Water Extract of Leaf Ash of Neem’ (WELAN). It is remarkable that the catalytic system does not require activation or any toxic ligand, additive/promoter, base, organic solvent and so on (Scheme 36).



**Scheme 36.** Henry reaction in WELAN

**7. Huisgen [3 + 2] Cycloaddition reactions**

While the use of water as a solvent for the Diels-Alder reaction has been firmly established, the mechanistically similar Huisgen [3 + 2] cycloaddition reaction has receivedrelatively little attention. Only in the last ten years has there been a focus on aqueous Huisgen [3 + 2] cycloaddition reactions. The Huisgen cycloaddition reaction is a highly versatile method for the synthesis of five membered heterocyclic rings.71 One of the first class of Huisgen [3 + 2] cycloaddition reactions carried out in an aqueous solvent was with nitrile oxides. These reactive 1,3-dipoles are generated in biphasic aqueous/organic mixtures and undergo [3 + 2] cycloaddition with a range of dipolarophiles to afford substituted isoxazoles.72,73 Pandey and Pandey examined the [3 + 2] cycloaddition reaction of C,N-diphenylnitrone with various dipolarophiles using water as solvent.74 The synthetic reactions in water were faster but there was no marked increase in either the regio- or stereoselectivity of the reaction, (Scheme 37).



**Scheme 37**. Aqueous nitrone [3 + 2] cycloaddition reaction with various dipolarophiles.

The Huisgen cycloaddition reactions of phthalazinium ylides on water, reported by Butler and co-workers, are noteworthy because they involve at least one solid reactant. For example, phthalazinium-2-dicyanomethanide which is a solid compound insoluble in water, reacted with methyl methacrylate,75 substituted styrenes76 or 2-buteneone76 providing dihydropyrrolophthalazines respectively, in high yield when the reaction was performed in water (Scheme 38).



**Scheme 38**. Huisgen [3 + 2] cycloaddition reaction on phthalazinium-2-dicyanomthanide with dipolarophiles.

Sharpless and co-workers developed an elegant series of reactions where the initial step is the nucleophilic opening of isomeric epoxides and with sodium azide and subsequent aqueous Huisgen [3 + 2] cycloaddition reaction with diethyl acetylenedicarboxylate affords the highly functionalized products in 97% yield (Scheme 39).77 The triazoles are crystalline solids and can be collected by filtration.

Wang and Qin explored the reaction of substituted aryl azides and alkynes using water as a solvent.78 The reactions gave high yields, up to 96% of cycloadducts. Interestingly when the reactions were compared in organic solvents there was a significant difference in the regioselectivity. Previously, Rees and co-workers reported the reaction of phenyl azide and phenylacetylene in refluxing toluene and obtained the two regioisomeric products in approximately 1:1 ratio. When solvent was changed to water and the reaction heated at 120 °C (bath temperature) the 1,4-substitiuted triazolewas the predominant isomer (Scheme 40).79



**Scheme 39.** Aqueous Ring-Opening of Bisepoxide with Sodium Azide and Subsequent Aqueous Huisgen Cycloaddition Reaction.



**Scheme 40**. Huisgen [3 + 2] cycloaddition reaction of phenylazide and substituted acetylenes.

An interesting industrial application of the aqueous organic azide Huisgen cycloaddition reaction was reported by chemists at Novartis. The reaction of a substituted benzyl azide with 2-chloroacrylonitrileto afford cyanotriazole was examined in a range of solvents. In organic solvents the reaction gave a yield of 46% while in water a yield of 98% was achieved. The reason for this significant change was that in the organic solvent an in situ elimination of HCl occurred and caused polymerization of the unreacted chloroacrylonitrile and thereby decreasing yield. When the reaction was carried out in water, a biphasic system allowed the HCl to be extracted into the water phase removing it from the organic layer and preventing polymerization of the chloroacrylonitrile (Scheme 41)80.



**Scheme 41.** Huisgen [3 + 2] cycloaddition reaction of azides with chloroacrylonitrile in water.

**8. Knoevenagel condensation reactions**

Base-catalyzed condensation of aldehydes with active methylene compounds (Knoevenagel reaction) is widely used to synthesize various polyfunctionalized organic compounds. A convenient and rapid method for Knoevenagel condensation has been developed by using DABCO-base ionic liquid catalysts in water at room temperature and affords the corresponding substituted electrophilic alkenes in excellent yields (up to 100%) within short times (Scheme 42).81



**Scheme 27.** Knoevenagel condensations catalyzed by [C4dabco][BF4]

Gu and Jérôme have reported the synthesis of 2,5,6-trisubstituted dihydropyrans, a water-mediated three-component reaction of 1,3-dicarbonyl compounds, formaldehyde and α-methylstyrene. The reaction was performed through Knoevenagel reaction of 1,3-dicarbonyl compound and formaldehyde, which can then be trapped by α-methylstyrene by oxo Diels–Alder reaction.82 Indole can also be used as a nucleophile instead of α-methylstyrene. In this case, the Knoevenagel intermediate was trapped by a Michael reaction of indole (Scheme 43).83



**Scheme 43.** MCRs based Knoevenagel/oxo Diels–Alder, and Knoevenagel/Michael domino reaction in water.

In 2008, Kumar *et al.* described a boric acid-catalyzed three component reaction of *N,N*-dialkylaniline, 1,3-dicarbonyl compound and formaldehyde in aqueous micelles constructed by SDS and water (Scheme 44). The mechanism of the reaction seems to be a tandem Knoevenagel– Michael domino reaction pathway for the formation of corresponding compound. It should be noted that the use of boric acid as a catalyst is the key to render the reaction possible because a side reaction between *N,N*-dialkylaniline and formaldehyde was predominant under catalyst-free conditions.84



**Scheme 44.** Boric acid-catalyzed Knoevenagel/Michael domino reaction in water.

Zhou *et al.* have developed an efficient three-component reaction of indole, aldehyde, and malononitrile that provides 3-indole derivative *via* Knoevenagel/Michael domino reaction in excellent yield.85 Use of copper(II) sulfonato salen complex and a weak acid, KH2PO4, was used in order to improve the reaction selectivity, in which KH2PO4 most likely played a role of controlling the pH value of the aqueous solution (Scheme 45).



**Scheme 45.** Three-component reaction of indole, aldehyde, and malononitrile in water.

A convenient approach to the synthesis of dihydropyrano[2,3-c]-pyrazoles via four-component reaction of aromatic aldehydes, hydrazine, ethyl acetoacetate and malononitrile was also developed in water with the aid of ultrasound irradiation (Scheme 46).86 This reaction can also be performed by using piperidine as a catalyst in water.87



**Scheme 46.** Four-component reactions of hydrazine, ethyl acetoacetate and malononitrile in water

**9. Mannich reactions**

The asymmetric Mannich reaction is an excellent method for the synthesis of optically active *β-*amino carbonyl compounds. A number of groups have explored the Mannich reaction using water as solvent. Xu and co-workers explored the bismuth-catalyzed Mannich reaction using water as the reaction medium.88 The Mannich reaction is a useful reaction for the synthesis of substituted cyclohexanones. Bismuth is not a widely used metal for catalysis, and there are only a few reports where it has been used in Lewis acid catalysis. When the cationic organobismuth complexwas examined in the Mannich reaction, it was found to proceed smoothly and both the *syn* and *anti-*isomers were formed. The reaction was found to be highly anti selective in all solvents, but using water as solvent gave superior yields (98%) (Scheme 47).



**Scheme 47.** Bismuth-Catalyzed Mannich Reaction.

Lu and co-workers explored the reaction using an L-threonine derived organocatalyst(Scheme 48).89 The reaction of benzylhydroxyacetone with p-anisidineand a range of aromatic aldehydes gave yields of up to 95%. The anti/syn selectivity was moderate (typically 3:1), although selectivities up to 20:1 were observed.



**Scheme 48.** Aqueous Mannich reaction using threonine-derived organocatalyst.

Several Brønsted acids were tested as catalysts in a model Mannich-type reaction in water, and it was found that DBSA afforded the desired product in high yield (Scheme 49). It should be noted that *p-*toluenesulfonic acid, which has a shorter alkyl chain than DBSA, gave only a trace amount of the product. Based on this result, it was suggested that the long alkyl chain of the acid was indispensable for efficient catalysis. probably due to the formation of hydrophobic reaction environments, and that the strong acidity of DBSA was essential for the catalysis because a carboxylic acid having a long alkyl chain, lauric acid, was much less effective than DBSA.90



**Scheme 49.** DBSA catalyzed Mannich Reaction in water.

Hayashi and co-workers explored a siloxyproline tetrazole organocatalyzed Mannich reaction using water as the reaction solvent.91 The three-component Mannich reaction of dimethoxyacetaldehyde, *p*-anisidine, and cyclohexanonewas carried out in water with catalyst. The reaction was carried out, where the anisidineand aqueous aldehyde were premixed and stirred for 0.5 h in the presence of the tetrazole catalyst and an oily material separated from the water. The yields were up to 95% with ee values up to 97% (Scheme 50).



**Scheme 35/50.** Aqueous organocatalytic Mannich reaction.

When Hayashi explored the Mannich reaction with the imine already preformed before introduction of the catalyst, it gave yields of only <5%. The presence of a preformed imine was not detrimental to the reaction when the sodium salt of catalyst was used in the reaction (Scheme 51).92 Thus, the use of the sodium salt of the proline organocatalystin the reaction of imineand ketonegave excellent yields (up to 88%) and enantioselectivity (up to 97%).



**Scheme 51.** Aqueous Mannich reaction using proline organocatalyst.

Kobayashi and co-workers reported a three-component Mannic-type reaction with aromatic aldehydes, primary amines, and indoles (Scheme 52) for the synthesis of 3-amino alkylated indoles. Many catalysts were screened, and Sc(DS)3 and DBSA promoted the reaction effectively. It was revealed that decanoic acid (C9H19COOH) efficiently promoted the reaction to afford the desired compound predominantly without the formation of bis-indole.93



**Scheme 52.** Decanoic acid catalyzed three-component Mannich-type Reaction in water.

Recently Kumar *et al*. reported micelle-promoted three-component Mannich-type Reaction in water from aldehydes, secondary amines and 2-naphthol/4-hydroxy coumarins/indoles. They reported an easy, efficient and green protocol for the synthesis of novel benzylamino coumarin derivatives in water. Non-ionic surfactant (Triton X-100) is a useful surfactant to form a stable colloidal medium which stabilizes imine intermediate to accelerate the reaction in water. The advantages of this method are the improvement in the synthesis of benzylamino coumarin derivative without formation of any side product as seen with the use of organic solvent.94 Similarly they demonstrated highly efficient, rapid and green method for synthesis of 3-amino alkylated indoles *via* Mannich-type reaction of aromatic/heteroaromatic aldehyde, secondary amine/N-alkylanilines and indoles in water. The synthesis of desired product was explained on the basis of stabilizes imines by the micelle. The formation of hydrogen bond between indolic NH and SO3O- group of SDS increases the electron density at C3 position of indole favoring nucleophilic addition to stabilized imines. In the subsequent step aromatization gives the desired 3-amino alkylated indole derivatives (Scheme 53). The beneficial aspects of reported procedure are high yield, operational simplicity, eco-friendliness and very mild reaction condition for the synthesis of 3-amino alkylated indole derivatives without the formation of bis-indole.95

Three-component Mannich-type reactions of aldehydes, amines, and silicon enolates also proceeded smoothly using PS-SO3H in water (Scheme 54).96 In general, ketene silyl acetals are known to be easily hydrolyzed in the presence of water however, such water-labile compounds could be successfully used in this reaction.



**Scheme 53.** Micelle-promoted three-component mannich-type reaction for the synthesis of amino alkylated naphthols/coumarins/indoles in water.



**Scheme 54.** Polystyrene supported sulfonic acids catalyzed three-component Mannich-type reaction in water.

On the other hand, significant progress has been made in the catalytic mannich-type reaction of C-H bonds adjacent to heteroatoms such as nitrogen and oxygen, which are applicable in organic synthesis. Li and coworkers recently found that copper could catalyze the direct alkynylation of an sp3-hybridized C-H bond adjacent to nitrogen, and the reaction can tolerate water (Scheme 55).97



**Scheme 55.** Copper catalyzed Mannich-type reaction *via* C-H bond activation in water.

Subsequently, Li and co-workers also found that the reaction is highly efficient and widely applicable with gold as the catalyst (Scheme 41). No cocatalyst or activator is needed for the gold-catalyzed reaction. Less than 1 mol % of catalyst is enough to generate an excellent yield of the corresponding propargylamine products.98



**Scheme 56.** Gold catalyzed three-component Mannich-type reaction for the synthesis of propargylamine in water.

**10. Michael addition reactions**

A novel, highly efficient, fast and green procedure for nitro-Michael addition of indoles and pyrroles using a combination of water and microwave irradiation without any catalyst have been developed. The ability of water to carry out the reaction is due to a change of its chemical and physical properties under microwave mediated ‘superheated conditions’. The reaction is applicable to different kinds of pyrroles and indoles, and their addition on the β-nitrostyrene which makes it a useful and attractive strategy for the synthesis of natural products with indole and pyrrole moiety (Scheme 57).99



**Scheme 57.** Catalyst-free aqueous nitro-Michael addition of indole, and pyrrole to various β-nitrostyrenes under MW irradiation.

A number of organocatalytic Michael reactions using water was a solvent have been reported by a number of groups. Jorgensen and coworkers have explored the aqueous organocatalytic Michael reaction using a TMS-prolinol organocatalyst with the reaction of *β-*ketoesters to α,β unsaturated aldehydes.100 The methodology developed was applied to a one-pot, five-step asymmetric synthesis of optically active cyclohexene-2-one derivatives, which are important building blocks in synthetic and medicinal chemistry (Scheme 58). The reaction was explored with a range of different functionalities of the aldehyde, and in general, the yields were found to be excellent (up to 97%) as was the enantioselectivity (up to 96%).



**Scheme 58.** Aqueous organocatalytic asymmetric Michael reaction.

Xiao and co-workers explored a pyrrolidine-thiourea organocatalystin the Michael addition reaction of ketones, such as cyclohexanone to nitroolefins using water as the reaction medium. The organocatalystcould be easily tuned to obtain optimum selectivity (Scheme 59).101 The reaction was found to give high yields and enantioselectivities (>99% ee), and there was significant functional group tolerance on the nitroolefin. Whereas, Zhong and co-workers examined an identical reaction and explored the use of a novel pyrrolidine-phosphine oxide as organocatalyst in the aqueous Michael reaction of ketones with nitroolefins (Scheme 60).102



**Scheme 60.** Aqueous organocatalytic Michael addition using pyrrolidine-thiourea, and pyrrolidine-phosphine oxide organocatalyst.

**11. Strecker reactions**

The three-component reaction of an aldehyde or ketone, a primary amine and a cyanide ion constitutes one of the most efficient manifolds for the synthesis of α-aminonitriles, versatile precursors of α-amino acids. García-Tellado *et al.* developed a Strecker reaction of ketones and aniline using acetyl cyanide as a cyanide source and utilizing *N,N*-dimethylcyclohexylamine as a Lewis base catalyst in brine (Scheme 61).103 Remarkably, the reaction did not produce *N*-acylated α-aminonitriles, which indeed constituted the main products in organic media using this cyanide source.



**Scheme 61.** Strecker reaction of ketones and aniline using acetyl cyanide in water.

A simple and practical method for the synthesis of α-amino nitriles through a one-pot, three-component Strecker reaction of a carbonyl compound, amine, and acetone cyanohydrin in water has been recently developed (Scheme 62). The protocol is particularly efficient for both aliphatic and aromatic aldehydes, and cyclic ketones, in combination with primary and secondary amines.104



**Scheme 62.** Strecker reaction of benzaldehyde, benzylamine, and acetone cyanohydrin in water.

A mild, efficient and environmentally friendly method also has been developed for the synthesis of α-aminonitriles *via* a three-component condensation of aldehyde, amine and TMSCN in the presence of a catalytic amount of indium(III) iodide in water. The reactions proceeded smoothly at room temperature in water to generate the corresponding products in moderate to excellent yields (Scheme 63).105



**Scheme 63.** indium(III) iodide catalyzed Strecker reaction in water.

**12. Suzuki reactions**

The Suzuki reaction involves the palladium-catalyzed reaction of aryl or alkenyl halides and a borane to form new carbon-carbon single bonds. The Suzuki reaction is often carried out in organic-aqueous mixed solvents however the reaction proceeds more rapidly in a homogeneous medium. Najera and Botella have examined the Suzuki reaction of aryl chloridesand phenyl boronic acidsin aqueous medium with a range of palladcycles (Scheme 64).106 This reaction was found to proceed in good to excellent yields (up to 100%) without the need for degassing of the solvent and an inert atmosphere as is often required with the Suzuki reaction.



**Scheme 64**. Suzuki reaction in aqueous medium using palladacycle.

San Martin and co-workers have examined a number of PCN-type palladium pincer complexes in the Suzuki reaction employing unusual substrates such as benzyl halides, α-haloeneones, and alkyl boronic acids in aqueous solvent (Scheme 65).107-109



**Scheme 65.** PCN-type ligands in the aqueous Suzuki coupling reaction.

The reaction of the α-bromoeneones with a range of aryl boronic acids using catalystand water as the solvent, gave good to moderate yields with arylation at the α-position. The catalyst was further examined in the Suzuki coupling of benzyl halides and phenylboronic acidin water. A drawback was observed in reusing catalystas it gave diminished yields in the subsequent reactions suggesting some decomposition/deactivation under aqueous conditions.

Sun and co-workers explored a series of water-soluble diimine ligands in the Suzuki coupling of aryl boronic acids and aryl bromides in water.110 The yields were moderate (up to 70%); however, upon addition of tetrabutylammonium bromide (TBAB) the yields were significantly increased (up to 85%). The addition of ethanol as an organic cosolvent shortened the reaction time (Scheme 66). The coupling reactions were found to occur in high yields (>95%), but the reactions needed to be carried out under nitrogen as the reaction in air gave lower yields. The Suzuki coupling reactions with the corresponding aryl chlorides gave poor yields (<20%).



**Scheme 66.** Suzuki coupling reaction of aryl bromides and aryl boronic acids with water-soluble diimine ligands.

Uozumi and co-workers explored aqueous asymmetric Suzuki coupling using a chiral palladium catalyst supported on an amphiphilic resin. The asymmetric Suzuki coupling has not been extensively studied in the area of asymmetric catalysis and in this case the enantioselectivities were found to be excellent (up to 99% ee) (Scheme 67).111 The reaction was found to have good functional group tolerance, and in most cases, the yields were excellent.



**Scheme 67.** Asymmetric Suzuki coupling reaction in aqueous medium with a palladium catalyst supported on amphiphilic resin.

Davis and co-workers explored the aqueous Suzuki-Miyaura coupling reaction using a novel palladium dihydroxypyrimidine catalyst.112 The initial focus of this study was on the coupling of modified amino acids and peptides. The reactions were carried out in buffered water at 37 °C without any attempt to exclude oxygen, (Scheme 68). The reaction gave excellent yields in the case of 4-bromo and 4-iodophenylalanine, but no reaction was observed in the case of 4-chlorophenylalanine.



**Scheme 68.** Aqueous Suzuki coupling reaction of modified amino acids.

**13. Wittig reactions**

Ever since the landmark papers by Wittig and co-workers in the 1950s, the reaction that now bears his name has become a standard method for organic chemists for the synthesis of C=C bonds. It is only in the last number of years with the emergence of the Heck and Metathesis reactions has the Wittig reaction been challenged as a mainstay for the synthesis of C=C bonds.113 Kumar and co-workers have recently reported the kinetics of the Wittig reaction under aqueous conditions where they examined the interfacial reactivity and selectivity of the on-water reactions in the presence of alcoholic cosolvents.114,115

Bergdahl and co-workers have explored the Wittig reaction employing a wide range of stabilized ylides and aldehydes.116,117 It was found that the solubility of the reactants was poor in some cases but the yields were high and the reactions were highly *E*-selective. The reactions were found to work best when large hydrophobic groups, such as heterocyclic rings were present. A comparison study was explored with two different aldehydes (anisaldehyde and 2-methoxycinnamaldehyde) with the stabilized ylide methoxycarbonyl methylene triphenylphosphorane in a range of different solvents (Scheme 69).



**Scheme 69.** Wittig reaction in water.

McNulty and co-workers explored the synthesis of *E*stilbenes and alkenes using the chemoselective formation of trialkyl(benzyl)phosphonium salt in water and their subsequent aqueous Wittig reaction with aldehydes (Scheme 70).118,119



**Scheme 70.** Aqueous Wittig reaction of alkyl ylide with aldehydes.

One-pot Wittig reactions of α-bromoacetate (or bromoacetonitrile) with aldehydes (Scheme 71) were carried out in refluxing aqueous 1.2 M LiCl in the presence of LiOH and PPh3. Good-to-excellent yields were obtained with varying *E*/*Z* ratios. Wittig reactions of ylides formed in situ from PPh3 and α-bromoesters with aldehydes 146 were also successfully carried out in saturated aqueous NaHCO3 solutions (Scheme 71).120





**Scheme 71.** Wittig reaction with *in-situ* generated alkyl ylide with aldehydes.

The reaction was found to proceed in high yields and high *E*-selectivity for aryl aldehydes but when alkyl aldehydes were examined there is a drop in both the yield and *E*/*Z* selectivity. McNulty further explored this reaction and applied this methodology in the synthesis of 1,3-dienes and 1,3,5-trienes using semistabilized ylides. The yield for the reactions was generally in the 70-90% range with modest *E*-selectivity. The water-soluble phosphine oxide, a byproduct of the reaction, is removed by aqueous partition of the organic products.

**14. Conclusion**

As this chapter describes, there are many reasons to use water as a solvent for chemical reactions. In manufacturing, it is both, green solvent and an inexpensive one. The finding that some of the effects seen in water solution can be seen also in water suspensions suggests that even insoluble compounds might be better used in water. However, the major real reason to pursue water as a solvent is that the hydrophobic effect leads to such remarkable new chemistry not otherwise achievable.

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 chapter 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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