Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis "In-Water" and "On-Water"

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Contents

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1. Introduction

Water is the solvent used by nature for biological chemistry. Considering the enormous variety of biological organic synthetic pathways and the complicated molecular structures and materials, including precise arrangements of multitudes of asymmetric centers, which are found in biological systems, it is remarkable that up until recently in vitro organic synthesis has mainly shunned water and chemists and industries have been searching for acceptable organic solvents, for example, the replacement of the earlier widely used benzene with toluene, etc. Generations of organic chemists have been trained in such a manner that little serious consideration was given to water as a useful reaction solvent. This was probably partly the result of a combination of fear of the detrimental effects of hydrolysis and the influence of the ancient alchimia, which teaches that reactants must be in solution to produce a chemical reaction. The situation has been changing because of the early work of Breslow[1] 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] reviews[8−13] and articles[14−17] promoting organic synthesis in the water medium. Nevertheless our experience is that suggestions to industrial synthetic chemists that their reactions could be carried out in water are usually met with quite underwhelming enthusiasm.

Water is a green solvent; it is nontoxic and nonflammable, and it does not suffer from public fear or odium. In fact the public do not consider it to be a "chemical". It is on record that a member of HM Government informed the House of Commons that the cleaning of the exterior of said building would not involve the use of any chemicals because it was to be done with water and sand. However, chemical reactions carried out in or on water are not necessarily green reactions and rarely do they meet the requirements outlined for ideal green reactions (Figure 1).

In each case, the product C should have zero solubility in water and should be formed in quantitative yield, consuming all of A and B so that filtration of C should leave pure water. In reality, the filtrate will contain A, B, and C in levels of parts per million, parts per thousand, or higher, and the

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Anthony G. Coyne received his B.Sc from the National University of Ireland, Galway (1998) and his Ph.D (2002) from the same university under the direction of Richard Butler. His Ph.D work focused on the synthetic and mechanistic aspects of the Huisgen cycloaddition reaction with an emphasis on the role of water as a reaction solvent. He then moved to an industrial position with GlaxoSmithKline and returned to academia as a postdoctoral fellow (2004) to the group of Pat Guiry at University College Dublin. He then moved to a postdoctoral position (2006) at the University of Cambridge in the group of Martin Smith. In 2008, he moved to his current position to the group of Chris Abell at the University of Cambridge as a postdoctoral research associate. His current research is focused on fragment-based drug discovery approaches to targeting protein−protein interactions.

greenness and economic benefit of the process will depend on what extra processing is necessary to isolate the product and recover "organic-free" water for further use. Furthermore, successful reactions in water may require the presence of buffers or catalysts and potential ungreen characteristics of reactions in water have been highlighted by a number of researchers.[18,19] However, as described below, some reactions in/on water can come very close to the ideal green conditions (Figure 1), section 2.2.2.

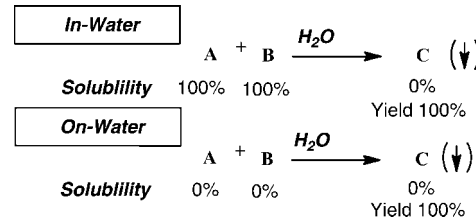


Figure 1. Ideal green reactions.

For clear solutions of soluble organic reactants in water, the effects operating are (i) the hydrophobic effect, which speeds reactions, (ii) hydrogen bonding effects on reactants and transition states, which may add to or oppose the hydrophobic effect, and (iii) water polarity effects, which may again increase or decrease reaction rates. For highly insoluble reactants involving two-phase systems the on-water effect involves trans-phase interactions of water with transition states and reactants. As the reactant solubilities decrease organic reactions in the water medium pass through wide boundary regions where in-water and on-water phenomena are occurring simultaneously and many reactions between small organic molecules take place in these realms. The extent of the insolubility of the reactants in water has rarely been quoted to date in accounts of reactions which are described as being on-water because of the visible appearance of two phases. Herein, we focus on the significance of declining reactant solubilities as a guide to the effects expected to operate for two-phase systems, one phase of which is a dilute solution. This allows an estimate of how the operating effects may influence a given reaction and whether reactions in the water medium may be successful or not. Extensive estimated water solubilities of organic compounds and classes are available from the CAS registry (Scifinder), and these are used importantly in the pharmaceutical and medicinal fields. These data are used herein to explore the boundaries between pure in-water reactions of soluble reactants and pure on-water reactions of highly insoluble reactants (the on-water limit; section 2.2.2). A table of water solubilities for the reactants quoted herein has been constructed from the CAS registry and is provided as Supporting Information. There is now an extensive and rapidly growing literature on organic chemistry in the water medium with literally thousands of references. This review is not a catalogue of this literature but rather a discussion of important features of the overall field and how it has impacted on many of the major reactions of modern organic chemistry.

2. Water Effects on Organic Reactions

2.1. In-Water

2.1.1. The Breslow Hydrophobic Effect

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.[3] 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.[20] With large hydrophobic surfaces some dangling hydrogen bonds (OH_{Free}) groups are orientated toward the barrier to maximize the packing density of the

molecules (see Figure 4).[21,22] Translational motion of the water molecules is severely limited near the barrier but molecular jump reorientations of some water molecules still occur.[23] 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 results in a rate acceleration. Both the hydrophobic interaction and the hydrophobic effect are complicated phenomena and different approaches have been adopted to seek understanding. Forced aggregates of organic reactants are raised in energy above their unaggregated ground states and are closer in energy to the activated complexes and transition states for reactions. This might not be of much significance if the same occurred in the activated complexes. However, Engberts has elegantly shown that the reactive sites of these activated complexes lose their hydrophobic character entirely, an extraordinary benefit that nature has conferred on water as a reaction facilitator.[20,24] Hence organic reactions arising from hydrophobic aggregates in water will have reduced activation energies and significant rate enhancements. The highly polarizable nature of the electronic changes occurring at the reactive sites, and nearby bonds, in the activated complex seems to make these states more easily accommodated in the liquid water structure. This should also have implications for reactants with strong H-bond acceptor sites, which are present in the activated complexes (section 2.1.2). Theoretical estimates of the lowering of the activation energy, ΔE^{act}, of Diels−Alder reactions by the hydrophobic effect are in general agreement with the observed rate increases.[25,26] For Diels−Alder reactions with cyclopentadiene, Jorgensen has calculated that the hydrophobic component contributes a factor of about 10 to the rates.[25]

Examples of Diels−Alder and Huisgen cycloadditions, where the hydrophobic effect appears to dominate the water rate enhancement, are in Table 1 (entries 1, 7−12, 16, 21).

For entries 7−9, there is little scope for H-bonding at the 2π reactant, and for the others, if it is present, its effects appear to be particularly weak. For entry no. 7, H-bonding is considered to be insignificant for the nitrosobenzene case, and there are no H-bonding sites for styrene and isoprene.[29,32] The free azine N-atom in compound **9** and **17** (Table 1) does not engage in H-bonding, and similar results were obtained with the isoquinoline analogue where it is absent.[30] Hydrogen bonding effects might be expected for entries 1, 10−12, and 16 (reactants **2**, **12**, **14**, Table 1), and the contrast between these and the conjugated vinyl and alknyl ketones in entries 3, 5, 13−15, 17, 18, and 20 is striking (section 2.1.2). The hydrophobic effect is increased by the presence of significant concentrations of salts, such as LiCl.[3,30,33] This is a parallel to the technique of "salting out" used in elementary organic laboratory classes for increasing the partition of an organic product into the organic layer from an aqueous−organic solvent extraction by adding NaCl to the water. Such salts are water structure makers and a reverse effect, a decrease in the hydrophobic effect, arises in the presence of large quantities (1−5 mol L^{-1}) of water structure breakers, such as guanidinium chloride.[3,30] Breslow has emphasized that the causes of these salt effects are more complicated than the relatively simple consequences of structure making and structure breaking.[3] Antihydrophobic additives act mainly by providing bridging between solutes and water rather than by disrupting the water structure.

A number of workers have compared the hydrophobic effect to the rate increases that result from increased external pressure on reactions with negative volumes of activation, ΔV^{act}.[11,34−40] The volume of activation is the difference between the molar volumes of the transition state and the sum of the molar volumes of the reactants and is negative for most bimolecular pericyclic reactions. The experimental values of ΔV^{act} are usually several tens of cm^3/mol and are readily measurable. The hydrophobic effect is looked upon as an internal cohesive pressure effect arising from the cohesive energy density (ced) of water ced $= (\Delta H_V - RT)/M\rho$, where ΔH_V is the vaporization enthalpy, and M and ρ are the molecular mass and density of the liquid. The square root of ced was used as a solubility parameter δ_s to explain the effect of solvents on the rates of nonpolar reactants.[41] The internal cohesive pressure, which is related to but not the same as ced, is the force that gives liquids their cohesion, and it influences the amount of energy required to create a cavity in a liquid by separating the molecules. D_2O has a higher ced (2365 J/cm^3) than H_2O (2297 J/cm^3), and since nonpolar compounds are slightly more soluble in D_2O, the enigmatic hydrophobic phenomenon is again not fully taken into account.[42]

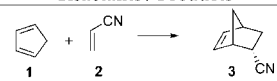
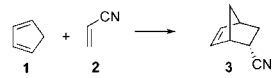
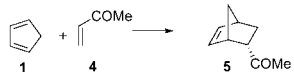
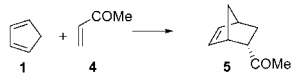
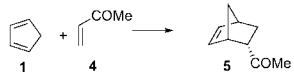
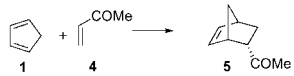
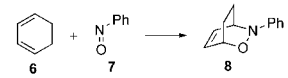
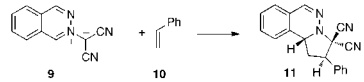
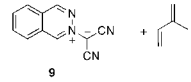
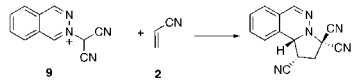
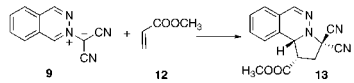
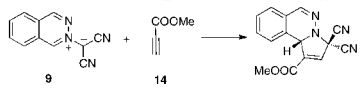
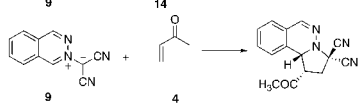
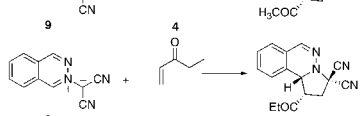
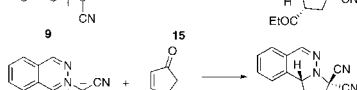
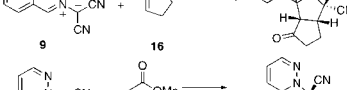
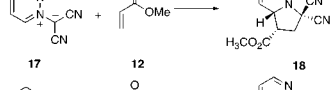
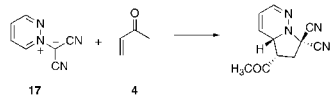
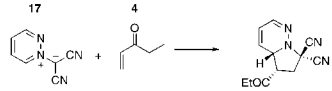
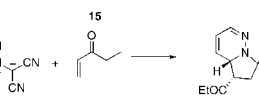
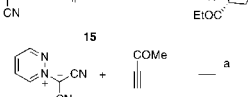
The hydrophobic effect has a major influence on the stereochemical outcome of reactions. It usually favors products from more compact transition states and the normal preference for *endo*-cycloadditions in Diels−Alder and Huisgen cycloadditions tend to be increased for reactions in water.[7,30,43,44] Mechanisms of reactions in water can be explored by addition of antihydrophobic agents, which reduce the hydrophobic rate acceleration. Reaction rates will be slowed or speeded depending on the extent to which the hydrophobic surfaces and substituents of the reactants are exposed to or shielded from water in the transition state relative to the initial state.[45−47] Such studies have been reported on comparative S_N2 displacements of substituted benzyl chlorides by substituted phenoxide and thiophenoxide ions,[48] Diels−Alder reactions of anthracenes with N-substituted maleimides, dimerization of cyclopentadiene,[49] selective reductions of ketones,[50] O versus C-alkylation of phenoxide ions,[51] and the benzoin condensation.[52]

2.1.2. Hydrogen-Bonding Effect

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, (Figure 2).

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 simplest case is where one of the reactants has no H-bond acceptor site. This is often the case with the 4π reactant, A, in Diels−Alder reactions and sometimes also with the Huisgen reactions. For reactions involving $4\pi_{HOMO}$ control in reactant A H-bonding to B will speed the reaction by lowering the HOMO−LUMO gap and the transition state, (Figure 2). The reverse occurs for

Table 1. Influence of Water on Diels−Alder and Huisgen Cycloaddition Reactions

Entry	Reactants / Products	Organic Solvent	$k_{Water}/k_{Solvent}$	Ref.
1		Isooctane	31 (30 °C)	1
2		Methanol	14.8 (30 °C)	1
3		Isooctane	740 (20 °C)	1
4		Methanol	58 (20 °C)	1
5		Acetonitrile	290 (25 °C)	27
6		Propanol	57 (25 °C)	28
7		Toluene	44 (25 °C)	29
8		Acetonitrile	15 (37 °C)	30
9		Acetonitrile	5 (37 °C)	30
10		Acetonitrile	6 (37 °C)	30
11		Acetonitrile	12 (37 °C)	30
12		Acetonitrile	7 (37 °C)	30
13		Acetonitrile	59 (37 °C)	30
14		Acetonitrile	45 (37 °C)	30
15		Acetonitrile	94 (37 °C)	30
16		Acetonitrile	15.3 (37 °C)	31
17		Acetonitrile	202 (37 °C)	30
18		Acetonitrile	164 (37 °C)	30,31
19		Methanol	14 (37 °C)	31
20		Acetonitrile	154 (37 °C)	30
21		Acetonitrile	12.7 (37 °C)	30

[a] Kinetic measurements only; product not isolated.

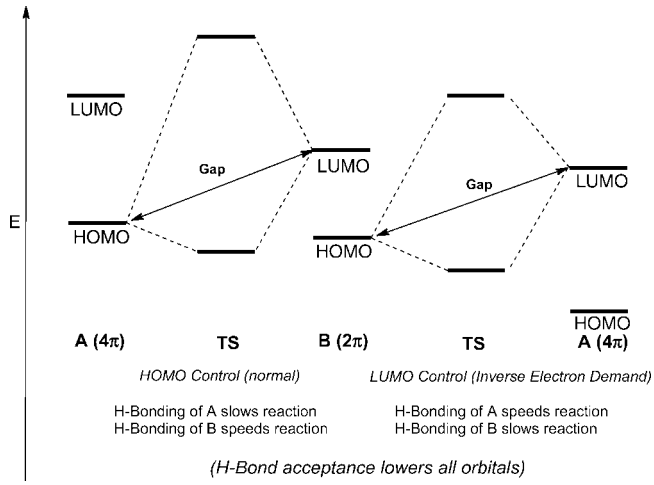


Figure 2. Frontier orbital energies, interactions, transition states for A + B → C: 4π and 2π refer to cycloaddition reactions.

reactions involving 4πLUMO control in A with H-bonding at B increasing the frontier gap (inverse electron demand). When both reactants A and B contain H-bond acceptor sites 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.[25,26,53−55] In the case of Diels−Alder reactions between cyclopentadiene with acrylonitrile and methyl vinyl ketone (MVK) they calculated that ΔG^{act} values were reduced by 1.5 and 2.8 kcal/mol on going from the gas phase to water.[26] Recent calculations of ΔG^{act} values for cycloadditions of cyclopentadiene with 1,4-naphthoquinone gave a fall in ΔG^{act} of 5.1 and 4.1 kcal/mol on going from hexane and acetonitrile to water, respectively.[55] Rate increases of 4500 and 790 times have been reported in water relative to hexane and acetonitrile for this reaction.[27] Enhanced H-bonding to polarized transition states, as well as the hydrophobic effect were invoked.[55] Furlani and Gao used the reaction of cyclopentadiene with isoprene, in a theoretical study, to eliminate H-bonding and calculated hydrophobic stabilization of the transition state by water at 4.5 kcal/mol. From a comparison with methyl vinyl ketone, they concluded that H-bonding and the hydrophobic effect each contribute half to the transition state stabilization ($\Delta\Delta E^{act}$) for cyclopentadiene with MVK.[56]

Recently, we measured the rates of the Huisgen cycloadditions of phthalazinium dicyanomethanide 1,3-dipole **9** (Table 1) with 25 alkene and alkyne dipolarophiles in water−acetonitrile mixtures up to 0.9 mol fraction of water.[30] The plots were extrapolated into neat water to give the rates shown in Table 1 (selected examples, entries 8−15). Rates were also measured in neat water with the water-soluble 1,3-dipole pyridazinium dicyanomethanide **17** for a number of the more significant dipolarophiles.[30,31] In Table 1, these results are compared with the earlier Diels−Alder reactions of cyclopentadiene with similar 2π-reactants. As stated H-bonding to compounds **9** and **17** is minimal and if it occurred it would inhibit the rates since the reactions of these compounds with these 2π-reactants are normal 4π_{HOMO} cases, (Figure 2). This includes styrene, which is on the crossover region of about equal frontier gaps.[57] Among the 25

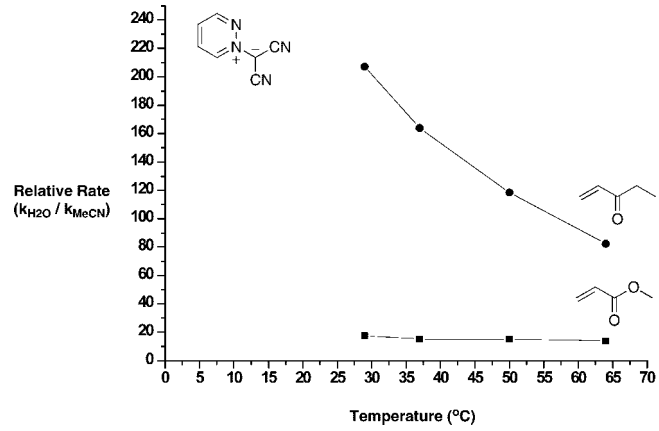


Figure 3. Comparative influence of temperature on the rate ratio k_{H_2O}/k_{MeCN} for ethyl vinyl ketone and methyl acrylate with pyridazinium dicyanomethanide.

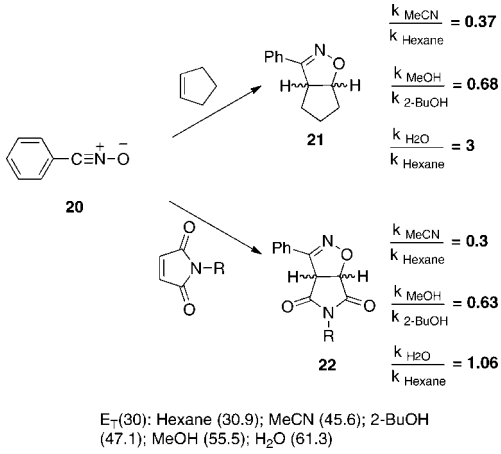
dipolarophiles measured six stood out because of the magnitude of the water rate enhancements and were termed water-super to distinguish them.[30] They were all conjugated vinyl and alkynyl ketones. In Table 1, the comparisons are illustrated by entries 1 vs 3 and 5, 11 vs 13, 16 vs 17, and 20 vs 21. For entry numbers 1, 11, 16, and 21, modest water enhancements are observed. They are comparable to entries 8 and 9 with the dipolarophiles styrene and isoprene where H-bonding contribution is not possible and the hydrophobic effect must dominate. For entries 3, 5, 13−15, 17, 18, 20 (Table 1) the rate enhancements are about 10 times greater. The difference between the reactants for entries 16 vs 17 and 20 vs 21 is one oxygen atom, a conjugated ester versus a conjugated ketone. Large changes in the hydrophobic effect could not be expected for such a small structural difference and H-bonding must be operating here. Because there is still a significant rate increase for these reactions on going from simple alcohols to water (Table 1, entries 4, 6, 19) we envisage that the rates imply not just single H-bonds but rather a growth of strong structured water clusters around the transition state which thereby fits into the water structure.[31] This was supported by (i) theoretical calculations showing much reduced E^{act} values for clusters of 6 water molecules growing from primary H-bonds to the oxygen of MVK in the transition states and the collapse of the clusters, with the loss of transition state stabilization, when one H_2O was replaced by one MeCN in the cluster, and (ii) a large fall in the water rate enhancement for the ethyl vinyl ketone, 15, (Table 1, entry 18) with rising temperature, (Figure 3) from 207 times to 82 for a temperature rise from 29 to 64 °C.[31]

The water rate increase for the reaction with methyl acrylate (Table 1, entry 16) was insensitive to rising temperature and it appears to arise from the hydrophobic effect alone with little or no H-bonding contribution.

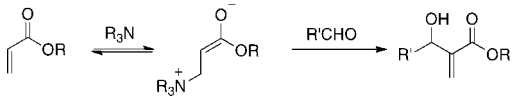
Huisgen cycloadditions of benzonitrile oxide **20** provide a striking example of the intertwined complexities of simultaneously operating hydrophobic, H-bonding, and solvent polarity effects (Scheme 1).

In a seminal study, Engberts et al. have unraveled these effects.[58,59] Benzonitrile oxide reacts almost 25 times faster with electron poor acrylic esters and about 80 times faster with electron rich enamines than it does with 1-alkenes.[60] It is a Sustmann type II 1,3-dipole which can react by the normal or inverse electron demand modes (Figure 2).[61,62] The transition state for its reactions are less polar than the initial

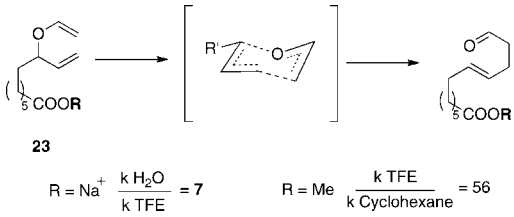
Scheme 1. Solvent Effects on Nitrile Oxide Cycloadditions[58,59]



Scheme 2. Baylis−Hillman Reaction[66]



Scheme 3. Claisen Rearrangement[67]



states for most reactions and rates are slowed by increasing solvent polarity, $E_T(30)$ values (Scheme 1).[63] The reaction with cyclopentene is nitrile oxide LUMO controlled (Figure 2), and rates are increased by H-bonding in alcohols and water, but within a series of alcohols they linearly decline against $E_T(30)$ values as increasing solvent polarity opposes the H-bonding effect (Scheme 1).[59] These same effects also operated with electron poor N-substituted maleimides but now H-bonding occurs at both reactants and the reaction changes to normal electron demand, nitrile oxide-HOMO control. H-bonding effects are strongest at the maleimide and are again opposed by polarity. Changing the maleimide N-substituent, R, from Et to n-Bu and CH_2Ph for reactions in water gave rate enhancements of 1.47 and 2.1, respectively, suggesting that hydrophobic enhancements are also present.[59] Relative to *n*-hexane the rates with maleimides were almost unchanged in water and with cyclopentene the rate was increased by a factor of 3.[58,59] Rate inhibiting solvent polarity effects have also been observed for Huisgen cycloadditions of C,N-diphenyl nitrone with dibutyl fumarate and monosubstituted alkenes.[64,65] Water increased the rate with fumarate by 12 times relative to *n*-hexane mainly because of hydrophobic effects as illustrated by its response to salting-out and salting-in agents.[64] The Baylis-Hillman reaction (Scheme 2) employing cyclohexenone and benzaldehyde is an example of a reaction enhanced by H-bonding alone.[66] Reactions in water were speeded by both salting-in as well as salting-out agents contrary to expectation and hydrophobic effects were ruled out.[66]

The Claisen rearrangement (Scheme 3) is an orbital symmetry allowed [3,3]-sigmatropic unimolecular reaction which is speeded by over 200 times in water relative to cyclohexane. H-Bonding plays a significant role in the acceleration.

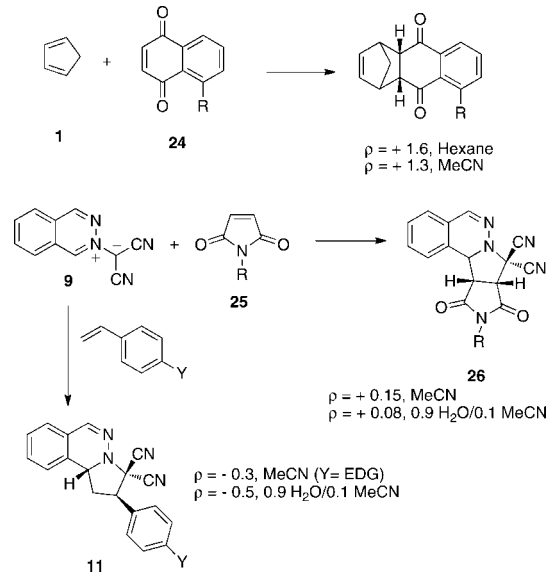
The reaction for substrate **23**, R = Me, is 8.6 times faster in MeOH and 56 times faster in strong H-bonding 2,2,2-trifluoroethanol (TFE) than in cyclohexane.[67] In water, an expected hydrophobic acceleration is added to the H-bonding effect and for substrate **23**, R = Na, the rate in water is 7 times higher than in TFE.[67]

2.1.3. Polarity Effect

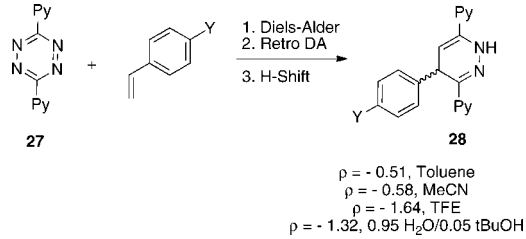
Water is a highly polar solvent with a Reichardt $E_T(30)$ of 61.3.[63,68] Hence reactions with transition states more polar than initial states will be speeded in water and slowed when the transition states are less polar than initial states.[68,69] A key question concerning water is whether it can induce polarity in otherwise nonpolar or weakly polar transition states, for example when there are no H-bonding sites. Many chemists would instinctively feel that this should be possible, particularly in biological chemistry where it might be necessary for a reaction to progress. However there seems to be little experimental support for it in the literature. The extent of charge separation in the transition state of the Diels−Alder reaction of cyclopentadiene with 5-substituted-1,4-naphthoquinones **24** (Scheme 4) was assessed using Hammett plots.[27] Relatively high ρ values indicated some polarity in the transition state even in organic solvents. Hammett plots in water were nonlinear but comparisons of 5-NO_2 and 5-OMe substituents indicated no increased charge separation in the transition state in water.[27]

Huisgen cycloaddition of the 1,3-dipole **9** with maleimides **25**, (Scheme 4), is a reaction that shows a linear negative rate response to Reichardt $E_T(30)$ solvent polarity values. In common with many 3 + 2 cycloadditions its transition state is less polar than the initial state.[30] The Hammett ρ was +0.15 in MeCN and +0.08 in 0.9 mol fraction water−MeCN indicating no increase in polarity in the water environment (Scheme 4).[30] Similar results were observed for substituted styrenes with electron donating (EDG) and electron withdrawing Y substituents, which gave different plots because styrene is on the frontier orbital crossover (Scheme 4).[70] Theoretical calculations of activation energies and transition states supported the experimental results with the styrenes.[70]

Scheme 4. Polarity Effects and Hammett ρ Values[27,30,70]



Scheme 5. Inverse-Electron Demand Diels−Alder Cycloaddition Reaction of 1,2,4,5-Tetrazine (Py = pyrid-2-yl; TFE = 2,2,2-trifluoroethanol)[71]



Inverse electron demand cycloaddition of 1,2,4,5-tetrazines **27** with styrenes is a reaction where strong H-bonding and hydrophobic effects play significant roles (Scheme 5).[71] Increased polarity of the transition state is evident in protic solvents with much higher Hammett ρ values in water and 2,2,2-trifluoroethanol (Scheme 5).[71]

There are six H-bond acceptor sites in **27** and H-bonding induces polarity and also lowers the $4\pi_{LUMO}-2\pi_{HOMO}$ gap (Figure 2) lowering the transition state. The rates in 0.95 mol fraction H_2O-tBuOH were 15−33 times faster than in the strong H-bonding alcohol TFE reflecting a hydrophobic contribution from water and possibly greater occupancy on the H-bond acceptor sites for **27** in water than in TFE for crowding reasons.[71] Directional strong H-bonding could increase the polarity more in TFE. This interesting reaction, (Scheme 5) is probably an exceptional case from the point of view of assessing water-induced extra polarity in organic transition states in general.

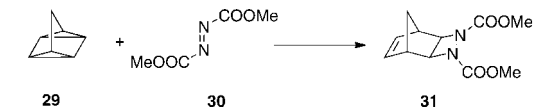
2.2. On Water

2.2.1. On-Water Reactions. Marcus trans-Phase H-Bonding

In 2005 Sharpless and co-workers reported a number of reactions where water insoluble reactants gave high yields of products when stirred vigorously in pure water for short periods of time.[5] These reactions included the cycloaddition of quadricyclane **29** with dimethyl azodicarboxylate **30** (Scheme 6) and the normal Diels−Alder reaction of *trans*,*trans*-2,4-hexadienylacetate **32** with N-propyl maleimide **33** (Scheme 7), as well as nucleophilic opening of an epoxide and an aromatic Claisen rearrangement. Since the reactants were insoluble in water, the reactions were described as being on-water.[5]

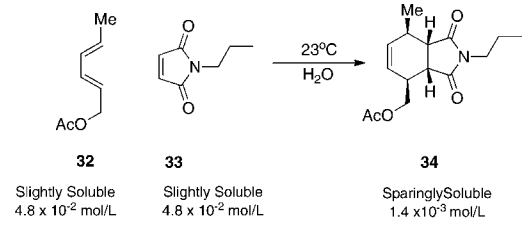
Organic liquids that remained separated from water in a clear organic phase were ideal reactants, but solids could also be used provided one reactant partner was a liquid and

Scheme 6. On-Water Reaction of Quadricyclane and Dimethyl Azodicarboxylate[5]



Solvent	T [°C]	Time	Yield (%)
Toluene	80	24 h	74
Neat	23	48 h	85
on H_2O	23	10 min	82

Scheme 7. On-Water Diels−Alder Reaction of *trans*,*trans*-2,4-Hexadienylacetate with *N*-Propyl Maleimide[5]



Solvent	Time (h)	Yield (%)
Toluene	144	79
MeCN	>144	43
Neat	10	82
On H_2O	8	81

adequate mixing was ensured. The dramatic effect of the on-water process is illustrated in (Scheme 6) where over 80% of product was obtained in 10 min, while a mixture of the neat liquid reactants required 48 h and the reaction in hot toluene solvent required 24 h. In some cases (Scheme 7), there was little difference between the on-water process and neat reactants. Pirrung and co-workers have explored the influence of mixing effects on a number of cases including Passerini reactions, Ugi reactions and Alder-Ene reactions by comparing the results of stirring, shaking and ultrasonication.[34] The efficiency of mixing proved important and enhanced phase-transfer arising with ultrasonication was particularly beneficial. The results were considered to be consistent with a hydrophobic based acceleration of the synthetic reactions.[34] In 2007 Marcus and Jung proposed that the key to understanding the on-water phenomenon was the unique chemistry that occurs at the water−oil phase boundary.[72] At large hydrophobic surfaces about 1 in 4 of the water molecules in the final layer has an OH_{free} group directed at the boundary in contrast to small hydrophobic aggregates which can be fully enclosed by hydration water clusters with lateral H-bonds along the boundary (Figure 4).[20−23,73,74]

Under vigorous agitation, penetration of the large oil boundary by these protons provides catalytic sites with almost bare protons inside the oil−water barrier. The impact of catalysis by such protons on transition states near the boundary should far exceed normal water solution H-bonding effects.[72] Marcus and Jung calculated expected rate increases on 1.5×10^5 times which agrees with the observed reduction in completion times of synthetic reactions.[72] The catalytic effect of Marcus trans-phase H-bonding provides a remarkable insight to the on-water phenomenon. For example a reaction-inhibiting trans-phase H-bonding at the 4π reactant

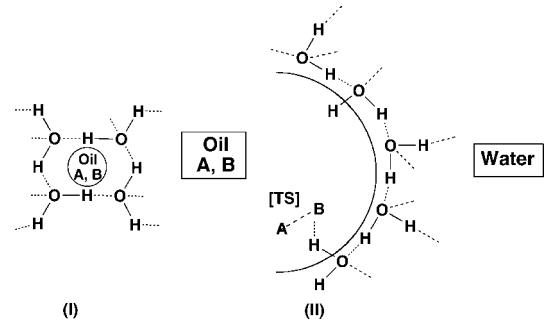
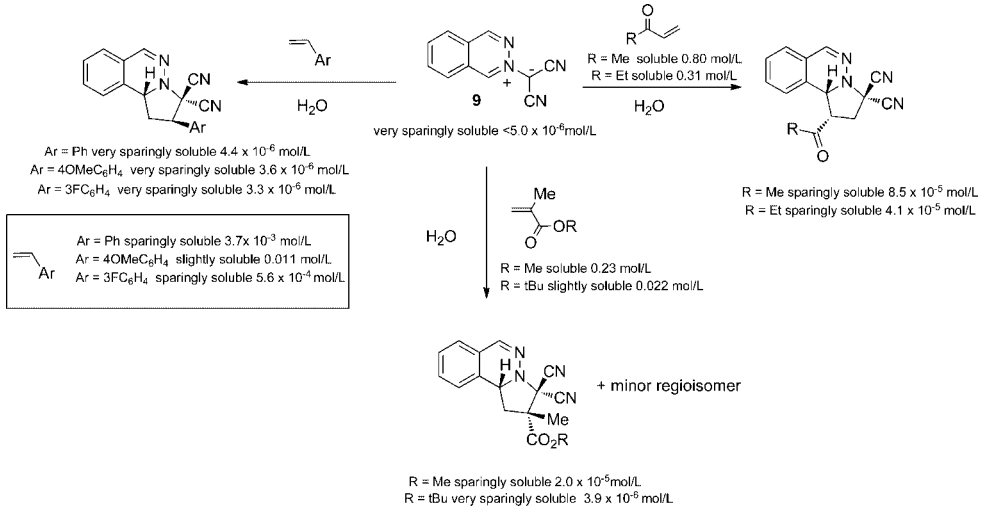


Figure 4. (I) Hydrated small hydrophobic aggregates. (II) Large hydrophobic water interface. Organic reactants **A** and **B**.

Table 2. In-Water/On-Water Boundaries for Water Insoluble Reactants

	slightly soluble: A	sparingly soluble: B	very sparingly soluble: C
solubility ranges (mol/l)	$\sim 10^{-2}$	$10^{-3}-10^{-5}$	$<10^{-5}$
active medium	solution small oily droplets solid particle surface	oily droplets small aggregates	oily regions large phase boundaries
reactant types	liquid−liquid solid−liquid solid−solid	liquid−liquid solid−liquid	liquid−liquid solid−liquid
operating effects	hydrophobic normal H-bonding trans-phase H-bonding	hydrophobic trans-phase H-bonding	trans-phase H-bonding
reaction occurs	mainly in-water some on-water	mainly on-water some in-water	on-water

Scheme 8. Products from Liquid Dipolarophiles on Water (Yields 63−96%)[30]

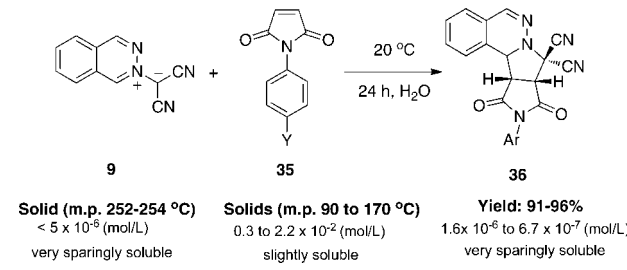


32, which opposes the catalytic effect at the 2π reactant **33**, could account for the quite modest on-water effect for the reaction in Scheme 7 relative to that of Scheme 6 where trans-phase H-bonding is confined to the 2π reactant only. A further feature of the poor on-water effect in Scheme 7 is that the reactant solubilities, place both reactants in category A along the transition boundary between in-water and on-water processes (Table 2) where opposing normal H-bonding effects on both reactants in water can also inhibit the overall on-water effect despite the physical appearance of a two-phase system.

The reactions in Schemes 6 and 7 involve organic liquid reactants and the requirement that at least one reactant should be a liquid seems to exclude solids from the on-water process.[5,14] In 2002, we reported synthetic Huisgen cycloadditions of compound **9** with 18 dipolarophiles in MeCN, water, and neat. Examples with liquid reactants are summarized in Scheme 8.[30]

The reactions in the water medium gave better yields and the endo/exo ratio of the products was 2.5−4 times higher in water than neat or in MeCN. Compound **9** is a high-melting yellow solid (mp 252−254 °C) with very low solubility in water and its reactions with the liquids in Scheme 8, are on-water reactions. However the cycloadditions of **9** with a range of insoluble solid N-aryl maleimides, **35**, worked equally well, (Scheme 9).[75] This brings up a point of unclarity in the on-water concept. What does "insoluble" mean, and where is the boundary between "in-water" and

Scheme 9. Huisgen Cycloaddition Reaction of 1,3-Dipole 9 with Substituted *N*-Phenylmaleimides[75]

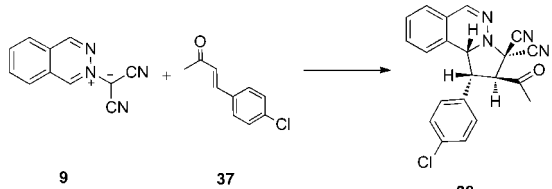


"on-water" reactions? We define this boundary as the on-water limit of reactant solubility below which all reactions are on-water and catalyzed by trans-phase H-bonding. Recently we repeated some of our earlier work with the water medium using ambient temperatures, and paying particular attention to the insolubilities of the various solid reactants in the context of the Sharpless on-water concept.[75]

2.2.2. "Insolubility". Solids vs Liquids. The on-Water Limit (See Supporting Information)

The synthetic reactions in Schemes 9−11 are cases involving suspensions of two insoluble solids on water. The reactant **9** has solubility less than 5×10^{-6} mol/L in water and the 2π-dipolarophiles **35**, **37**, **39** have decreasing solubilities from 10^{-2} to 10^{-5} mol/L.[75] For reactions carried out on suspensions containing 0.077−0.105 mol/L, the

Scheme 10. Huisgen Cycloaddition Reaction of 1,3-Dipole 9 with 4-Chlorobenzylideneacetone[75]



9 Solid (m.p. 252-254 °C) < 5 x 10^{-6} (mol/L) very sparingly soluble

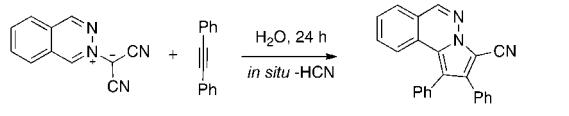
37 Solid (m.p. 58-62 °C) 1.2 x 10^{-4} (mol/L) sparingly soluble

38 3.3 x 10^{-7} (mol/L) very sparingly soluble

Solvent	Temp. [°C]	Time (h)	Yield (%)
On H_2O	20	48	0
On H_2O	75[a]	24	86

[a] Liquefaction of **37**.

Scheme 11. Huisgen Cycloaddition Reaction of 1,3-Dipole 9 with Diphenylacetylene[75]



9 Solid (m.p. 252-254 °C) < 5 x 10^{-6} (mol/L) very sparingly soluble

39 Solid (m.p. 59-61 °C) 1.8 x 10^{-5} (mol/L) sparingly soluble

40 Solid (m.p. 213-214 °C) 2.1 x 10^{-7} (mol/L) very sparingly soluble

Solvent	Temp. [°C]	Yield (%)
On H_2O	20	0
On H_2O	81[a]	71

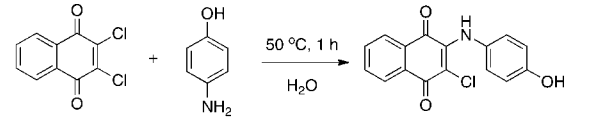
[a] Liquefaction of **39**.

insoluble portion of **9** was 99.994% (0.006% in solution), while for **35** (Y = Cl) 97.4% was insoluble with 2.6% in solution. These reactions between **9** and **35** (Scheme 9) gave product yields of 91−96% at ambient temperatures on water.[75] They are close to the requirements of ideal green chemistry described in Figure 1, and it is noteworthy that such reactions are possible.

While some effects could be operating at the surfaces of solid particles, on-water reactions between the two insoluble solids are a challenge. For the reactions in Scheme 9 it is likely that the small solublility of the maleimides **35** may be enough to bring compound **9** into an equilibrium shifted process passing through the solution, expelling the products and hence giving a mainly in-water reaction, facilitated by hydrophobic effects and normal H-bonding. In physical appearance, the reactions are like on-water processes with yellow suspension of reactants gradually changing to white product suspensions. The fact that for 2π reactants with solubilities lower by one or 2 orders of magnitude no reactions occurred in water at 20 °C, Schemes 10 and 11, suggests that the reaction in Scheme 9 may be mainly in-water.[75] While solid−solid reactions did not occur between **9** and **37** or **39**, once these 2π reactant partners were melted to liquids high yield reactions readily occurred again, Schemes 10 and 11. Since liquefaction of one of the reactant partners was necessary, providing oily phases to bring **9** into contact, these reactions are true trans-phase on-water processes.[75]

Trans-phase H-bonding can readily account for the reaction in Scheme 10, with strong H-bond acceptor sites of the 2π-reactant **37** once it is liquefied. The success of the on-water

Scheme 12. Nucleophilic Substitution of 1,4-Quinone Derivatives[76]



41 sparingly soluble 5.3 x 10^{-5} mol/L

42 soluble pH 7, 0.55 mol/L

43 Yield: 95% sparingly soluble pH 7, 2.2 x 10^{-5} mol/L

reactions with compounds, such as diphenylacetylene **39**, Scheme 11, and styrenes, Scheme 8, with no H-bond acceptor sites, raises the question as to whether the hydrophobic effects can still play a part in the on-water process. The results in Schemes 8−11 could be explained in terms of hydrophobic effects or trans-phase hydrogen bonding effects. As stated H-bonding of compound **9** does not influence its reactions with electron-poor 2π-reactants and for H-bonding to catalyze its reactions with styrenes and phenylacetylenes it must occur at the CN groups of **9**. It is of significance that styrenes and phenylacetylenes cluster at the bottom of the Sustmann U-shaped plots of log k_2 against ionization potentials and the frontier orbital gaps are about the same for normal and inverse-electron demand transition states.[57,61,62] Preferential strong trans-phase H-bonding catalysis of the inverse demand mode (via the LUMO of **9**) could account for the on-water effect here, and this may be a striking support of the Marcus explanation for the on-water phenomenon.[72] Reactions where the HOMO−LUMO frontier orbital gaps are about equal for the normal and inverse demand modes are readily identifiable experimentally from Sustmann plots and also by theoretical methods. Preferential catalysis of one or other of the frontier modes for such reactions should provide good tests for the Marcus trans-phase H-bonding effect for on-water reactions.

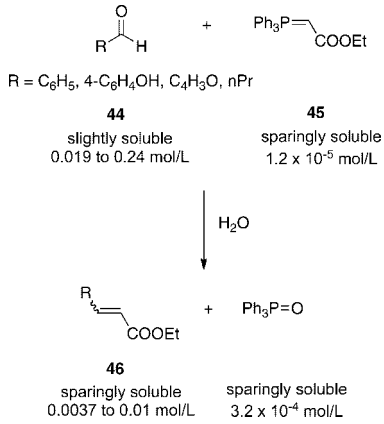
Another recent case where two solid reactants have given high yields of products is shown in Scheme 12, which is an example among a wide range of nucleophilic substitutions with 1,4-quinone derivatives carried out by vigorous stirring of on-water suspensions.[76]

In Table 2, we outline the spectrum of changes that we envision are involved as organic reactions in-water respond to growing reactant insolubility by changing from pure single phase in-water reactions to, in the limit, pure on-water reactions of totally insoluble reactants.

To date not enough attention has been paid to quantitative reactant solubilities to delineate the boundaries more satisfactorily. The solubilities shown in Scheme 12 place this reaction in category B along the in-water/on-water boundary (Table 2) where both the in-water and on-water effects are operating. More attention also needs to be paid to reactants with no-H-bond acceptor sites to establish how they fit in to the on-water phenomenon.

An example is the Diels−Alder reaction of anthracene and tetracene with the dienophile fullerene (C60). These unsubstituted hydrocarbon reactants give low yield reactions (13%) in hot toluene over three days. They are highly insoluble in water and highly hydrophobic. With no H-bond acceptor sites, they give no reaction in neat water, representing on-water conditions as expected for the Marcus explanation.[77] However yields of 45−55% were achieved in the water medium in the presence of supramolecular complexes constructed by self-assembly of linear amphiphilic copolymers of poly(ethylene glycol), poly(ethylene oxide), and

Scheme 13. Wittig Reaction of Aldehydes with Stabilized Phosphorus Ylide[78]



poly(benzyl ether), where the reactants were encapsulated in micellular nanoreactor entities.[77]

Recently, it has been reported that the pro-hydrophobic salts LiCl and NaCl (1−5 M) decreased the rates of the on-water Wittig reaction of insoluble aromatic and aliphatic aldehydes **44** with stabilized phosphorus ylides **45** (Scheme 13) when carried out at 25 °C.[78]

Such a result should suggest the absence of a hydrophobic effect. However the same salts caused measurable rate increases at 65 °C, and the antihydrophobic salt guanidinium chloride lowered the rates in neat water.[78] Under heterogeneous conditions at 25 °C, smaller particle sizes for the ylide **45** increased the rates suggesting an interfacial mechanism. The effects of high concentrations of LiCl and NaCl may be due to inhibition of the availability of OH_{free} groups at the phase boundary thereby reducing trans-phase H-bond catalysis more at 25 °C than for the more loosely structured water at 65 °C. The results of these salt effects for on-water reactions underline the need for further work in this area. It has also been suggested that unconventional rate increases for organic reactions in the water medium induced by small amounts of alcoholic cosolvents can serve as a signature test for the on-water process where trans-phase effects are operating.[79] Very recently the Jorgensen group has reported that Diels−Alder reactions of cyclopentadiene with 1,4-naphthquinone and methyl vinyl ketone were less accelerated at a water−vacuum interface ($\Delta\Delta G_{act}$ 3.6 kcal/mol, naphthoquinone) than in bulk water ($\Delta\Delta G_{act}$ 7.3 kcal/mol) using quantum mechanical/molecular modeling (QM/MM), thereby suggesting no special trans-phase H-bonding effect.[80] For pure on-water reactions of insoluble reactants (solubility $<10^{-5}$ mol/L) the liquid organic reactants are dissolved in each other in an oily phase and the available results suggest no reactions occur unless the reactants possess H-bond acceptor sites. The interesting results for the water-vacuum interface may suggest that the on-water effect could include, along with the key trans-phase H-bonding, a cooperative hydrophobic promoted pretransition state orientation-deformation of the reactant molecules on the oily side close to the oil−water phase boundary. Vigorous agitation should reduce the lateral dimensions of the oil phase boundary and enhance the hydrophobic contribution.

3. Synthetic Reactions

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 aim of this section is to thoroughly illustrate the versatility and scope of water as a medium for organic reactions, but it is not meant as a complete list of the papers in this area and further accounts can be found in previous reviews.[6,9−12] Only reactions carried out using water as a solvent or medium will be examined and reactions with an organic cosolvent will be mentioned as a guide for the reader but will not be examined in the context of this review.

3.1. Pericyclic Reactions

Pericyclic reactions are one of the most important classes in organic chemistry. The reactions include the Diels−Alder [4 + 2] and Huisgen [3 + 2] cycloaddition reactions.[81,82] Further named reactions in this area include the Claisen and Cope rearrangements along with other sigmatropic rearrangements. An interesting general mechanistic phenomenon of these reactions is that the reaction rate is not greatly influenced by solvent polarity but, as was discussed in sections 2.1 and 2.2, it has been shown that using water as the solvent can significantly enhance both the rate and stereoselectivity of these reactions.[83]

3.1.1. Diels−Alder [4 + 2] Cycloaddition Reaction

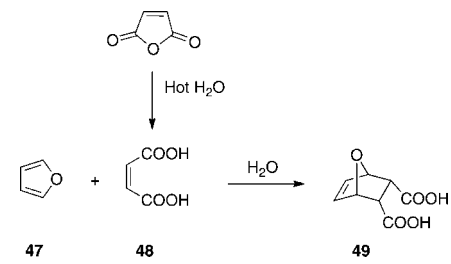
The Diels−Alder reaction is a one of the most synthetically useful reactions in organic chemistry for the synthesis of highly complex six-membered rings.[84−86] The versatility of this reaction has yet to be surpassed and it is not surprising that this reaction was one of the first to be explored using water as a solvent.[15] In the early 1930s Diels and Alder examined the reaction of furan **47** and maleic anhydride and this was subsequently re-examined by Woodward and Baer in 1948 (Scheme 14).[2,87]

The reaction was carried out by dissolution of the maleic anhydride in hot water, which readily hydrolyzed to maleic acid **48**. The oily diene furan **47** was added to the reaction and with shaking the diene went into solution and the crystalline adduct **49** was then isolated.

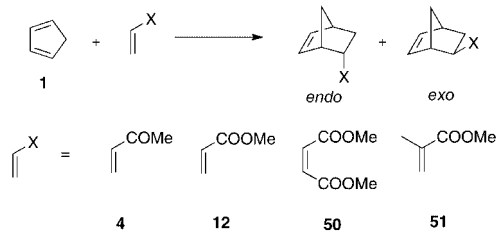
It would be another thirty years until Breslow published his seminal paper exploring the synthetic and kinetic aspects of using water as a solvent for the Diels−Alder reaction. Breslow showed that, as well as significant rate acceleration (section 2.1.1) there was also a significant increase in the endo selectivity of the reaction (Scheme 15).[1,43,44] The Diels−Alder reaction of cyclopentadiene and a range of dienophiles was examined using water as a solvent.

In neat cyclopentadiene **1**, the endo/exo ratio for buteneone **4** is 3.85:1; however, when the solvent is water, the endo/exo ratio climbs to 21.4:1. The dienophile buteneone **4** is completely soluble in water but cyclopentadiene **1** has poor solubility and a biphasic system is observed. In the case of dimethyl maleate **50**, this has much poorer solubility in water

Scheme 14. Diels−Alder Reaction of Furan and Maleic Anhydride Using Water as a Solvent[2,87]

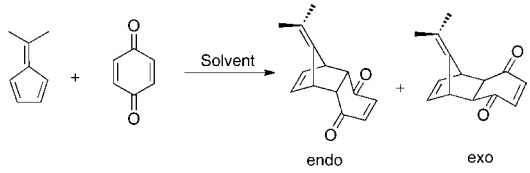


Scheme 15. Diels−Alder Reaction of Cyclopentadiene and Various Dienophiles Using Water as a Solvent and Showing the Influence on the Endo/Exo Ratio[43,44]



	Dienophiles (*endo:exo*)			
Solvent	**4**	**12**	**50**	**51**
Cyclopentadiene	3.85	2.9	2.8	0.43
EtOH	8.5	5.2	4.5	0.6
H_2O (0.15 M)	21.4	9.3	13.7	1.4
H_2O (0.30 M)	18.6	5.9	-	-
H_2O (0.45 M)	17.2	-	-	-

Scheme 16. Diels−Alder Cycloadddition Reaction of Dimethylfulvene and 1,4-Benzoquione[88]



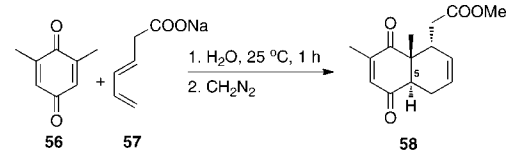
Solvent	**Conc (M)**	**Time**	**Conversion (%)**	***endo:exo***
CCl_4	0.15	14 d	40	55:45
Acetone	0.15	14 d	48	45:55
MeOH	0.150	10 d	95	44:56
H_2O	0.15	11 h	100	65:35
H_2O	0.001	24 h	-	14:86
H_2O	1.60	8 h	-	88:12

and the selectivity on changing to water as a solvent also gave high endo selectivity (13.7:1). At higher concentrations using water as a solvent a decrease in the endo selectivity was observed although in comparison to the reaction in cyclopentadiene this ratio is still quiet high. Breslow proposed that the hydrophobic effect was part of the reason for the increase in endo selectivity in comparison to organic solvents. This increase in the endo selectivity for pericyclic reactions has been observed by in other cycloaddition reaction types.[30]

Griesback reported the Diels−Alder reaction of dimethylfulvene **52** and 1,4-benzoquinone **53** using water as a solvent.[88] 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 16).

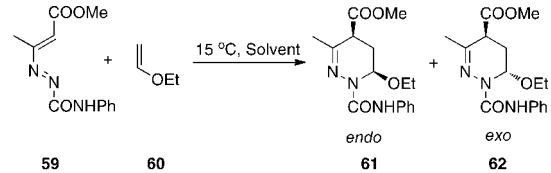
The 1,4-benzoquinone **53** is sparingly soluble and the dimethylfulvene **52** is insoluble. The reaction was found to go through a three-phase system where there is a liquid−liquid suspension with the fulvene **52** and a solid−liquid suspension with the benzoquinone **53**. Higher concentrations of the reactants were found to favor the endo isomer **54**, while lower concentrations were found to favor the exo isomer **55**. These effects were not observed when organic solvents were employed. Using maleic anhydride as the dienophile at high concentration favored the endo isomer; however, at lower concentrations, the hydrolysis of the maleic anhydride occurred and poorer yields were observed.

Scheme 17. Diels−Alder Reaction of Diene Carboxylate and Dimethylbenzoquinone in Aqueous Solution[90]



Solvent	**Time**	**Yield (%)**
H_2O	1 h	77
Toluene	1 wk	Trace

Scheme 18. Inverse Electron Demand Diels−Alder Reaction of Diazabutenes with Ethyl Vinyl Ether[91]



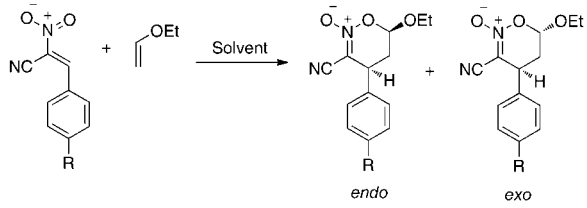
Solvent	**Time**	**Conversion**	**Yield (%)**	***endo:exo***
H_2O	13 h	100%	75	89:11
CH_2Cl_2	13 h	79%	55	91:9

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.[89,90] The reaction of the diene carboxylate **57** with the quinone dienophile **56** 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 17). The cis adduct was initially formed, and this equilibrated to the more stable trans form. This was confirmed when the reaction was carried out in D_2O, giving the adduct **58** with 90% deuteration at C-5.

Fringuelli and co-workers have explored the inverse-electron demand Diels−Alder reaction of diazenylbutene **59** with electron-rich dienophiles, such as ethyl vinyl ether **60**.[91] 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 18).

Fringuelli and co-workers also examined the inverse electron demand Diels−Alder reaction of nitroalkenes **63** and the electron-rich dienophile ethyl vinyl ether **60** to afford a mixture of endo and exo adducts **64** and **65**.[92] 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. This was reflected in the yield and stereoselectivity with the yield in water lower (75%) in comparison to that of dichloromethane (82%). There was

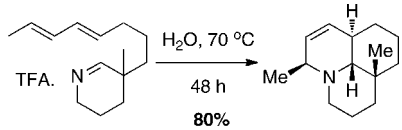
Scheme 19. Diels−Alder Reaction of Nitroalkene with Ethyl Vinyl Ether[92]



63 60 64 65

Nitroalkene (R)	Solvent	Temp (°C)	Time (min)	Yield (%)	*endo:exo*
H	H_2O	0	3	75	80:20
H	CH_2Cl_2	0	2	82	90:10
OMe	H_2O	20	10	85	98:2
OMe	CH_2Cl_2	20	5	85	97:3

Scheme 20. Intramolecular Diels−Alder Reaction[93]



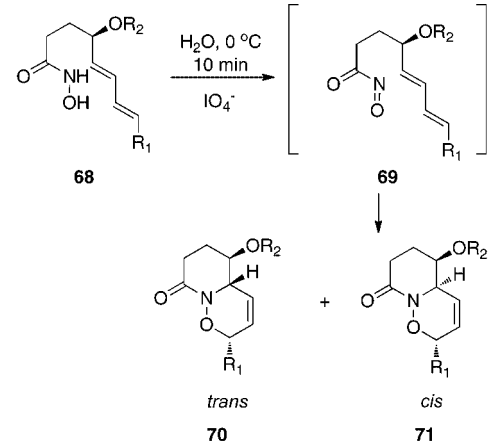
66 67

also a decrease in endo/exo selectivity using water as medium from 90:10 (CH_2Cl_2) to 80:20 (H_2O), (Scheme 19).

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 **66** with an iminium salt to afford a complex tricyclic ring system.[93] When the reaction was carried out using water as solvent the product was formed in 80% yield after 48 h as the sole isomer **67**. When the reaction was carried out in 5 M $LiClO_4$/Et_2O only 13% of the product **67** was formed after 66 h and approximately 80% of the imine was recovered with significant isomerization of the double bonds (Scheme 20).

Kibayashi examined the intramolecular Diels−Alder reaction of acylnitroso compounds which were generated in situ using water as a solvent.[94] The initial step of the reaction involved periodate oxidation of the hydroxamic acid **68** to the nitroso compound **69**, and this underwent subsequent intramolecular Diels−Alder cycloaddition to afford compounds **70** and **71**. The reactions were carried out with vigorous stirring at 0 °C using 10 mM solutions (or suspensions) of the substrates. In all cases the reactions were very rapid and were completed in 1 min although the reactions were allowed to stir for 5−10 min. For reactions using chloroform as a solvent the reaction time was similar, and the trans/cis (**70/71**) ratio was 1.3:1 with a 76% yield. On changing the solvent to water there was an increase in the trans/cis (**70/71**) ratio to 4.0:1 and an increase in yield to 89% (Scheme 21). There was no significant difference whether the reactions were carried out under homogeneous single phase or heterogeneous two-phase conditions.

Scheme 21. Intramolecular Diels−Alder Reaction of Acylnitroso Compounds[94]



68 69 70 71

R_1	R_2	Periodate	Solvent	Yield (%)	trans:cis
H	Bn	Pr_4NIO_4	$CHCl_3$	76	1.3:1
H[a]	Bn	$NaIO_4$	H_2O	89	4.0:1
H[a]	Bn	Pr_4NIO_4	H_2O	87	4.1:1
H	MOM[b]	$NaIO_4$	H_2O	97	4.4:1
Et	MOM	Bu_4NIO_4	H_2O	83	5.0:1

[a] Reaction carried out as two-phase suspension. All other reactions carried out under single-phase conditions. [b] MOM = methoxymethylether.

3.1.2. Huisgen [3 + 2] Cycloaddition Reaction

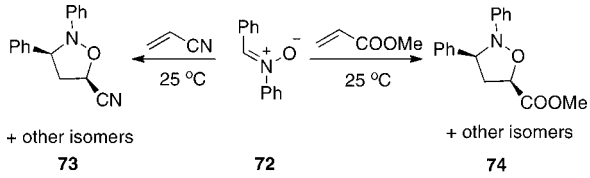
While the use of water as a solvent for the Diels−Alder reaction has been firmly established, the mechanistically similar Huisgen [3 + 2] cycloaddition reaction has received relatively little attention. Only in the last ten years has there been a focus on aqueous Huisgen [3 + 2] cycloaddition reactions. The Huisgen cycloaddition reaction is a highly versatile method for the synthesis of five membered heterocyclic rings.[95] For aqueous based synthesis a drawback of this reaction is that many 1,3-dipoles need to be generated in situ and are unstable, especially in aqueous environments. A review of this area has been presented by Molteni, and the aim here is to give important examples other than those already discussed in sections 1 and 2.[13]

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.[96,97] Pandey and Pandey examined the [3 + 2] cycloaddition reaction of C,N-diphenylnitrone **72** with various dipolarophiles using water as solvent.[65] The synthetic reactions in water were faster but there was no marked increase in either the regio- or stereoselectivity of the reaction, (Scheme 22). Subsequent kinetic experiments by Gholami quantified that cycloadditions of C,N-diphenylnitrone are significantly accelerated in water in comparison to organic solvents.[64,98]

Coutouli-Argyropoulou et. al recently examined the [3 + 2] cycloaddition reaction of different hydrophobic nitrones with acrylates in homogeneous organic solutions and heterogeneous aqueous suspensions. The reactions in aqueous suspensions were found to show enhanced acceleration over those in organic solutions.[99]

We have carried out a synthetic and mechanistic study on the dicyanomethanide class of azomethine ylide 1,3-dipoles using water as a solvent (see section 2). For example the reaction of phthalazinium-2-dicyanomethanide 1,3-dipole **9** was explored with a range of vinyl ketones (Scheme 23).[30]

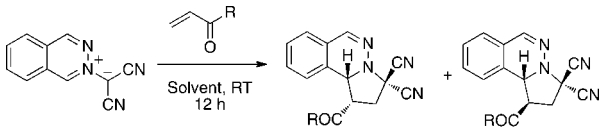
Scheme 22. Aqueous Nitrone [3 + 2] Cycloaddition Reaction with Various Dipolarophiles[65]



73 72 74

Dipolarophile	Solvent	Time (h)	Yield (%)
Acrylonitrile	Benzene	2.5	15
	Water	2.5	95
Methyl acrylate	Benzene	3	30
	Water	3	95

Scheme 23. Huisgen [3 + 2] Cycloaddition Reaction on Phthalazinium-2-dicyanomthanide with Vinyl Ketone Dipolarophiles (see Scheme 8)[30]



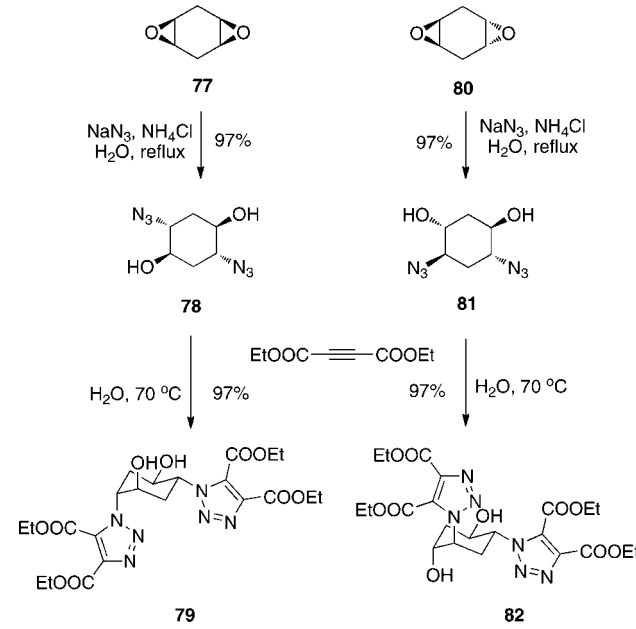
9 75 76

Dipolarophile	Solvent	Yield (%)	*endo:exo* (75:76)
Methyl vinyl ketone	MeCN	96	3:1
	H_2O	95	7:1
Ethyl vinyl ketone	MeCN	94	3:1
	H_2O	96	11:1
Cyclopent-2-ene-1-one	MeCN	80	3:1
	H_2O	95	16:1

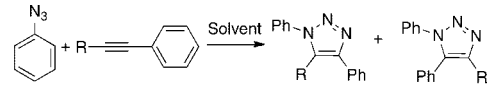
When an aqueous suspension of 1,3-dipole **9** is stirred with an equimolar amount of vinyl ketone there is a noticeable color change from yellow solid (1,3-dipole **9**) to white (product **75** and **76**). The yields in acetonitrile and water are comparable, but there was a significant difference is in the endo/exo ratio of **75** and **76** using water as a solvent. In acetonitrile, the ratio of **75/76** is 3:1. When the solvent is changed to water a significant increase in the endo selectivity was observed especially in the case of cyclopentenone (from 3:1 MeCN to 16:1 H_2O).

The area of azide [3 + 2] cycloaddition reactions has undergone a renaissance in the past decade since Sharpless and Meldal independently first described the "click" azide−alkyne cycloaddition reaction, a modification of a reaction reported by Huisgen in the 1960s.[100−102] The organic azide 1,3-dipole is stable and ideal for study as an aqueous Huisgen [3 + 2] cycloaddition reaction. Engberts and co-workers examined the kinetics of phenyl azide and norbornene and found that significant acceleration in the rate was observed in aqueous media. However due to limited solubility the rate was not determined in pure water.[103] While the click cycloaddition reactions are copper catalyzed (these will be examined in section 4) because of the unreactivity of the terminal alkynes, some dipolarophiles may have sufficient reactivity to undergo aqueous azide−alkyne [3 + 2] cycloaddition reaction. Sharpless and co-workers developed an elegant series of reactions where the initial step is the

Scheme 24. Aqueous Ring-Opening of Bisepoxide with Sodium Azide and Subsequent Aqueous Huisgen Cycloaddition Reaction[102]



Scheme 25. Huisgen [3 + 2] Cycloaddition Reaction of Phenylazide and Substituted Acetylenes[104]



83 84 85 86

R	Solvent	Temp	Yield	Ratio (85:86)
H	Toluene	110 °C	-	1:1[a]
H	H_2O	85 °C	81%	-[b]
Ph	H_2O	120 °C[c]	72%	-[b]

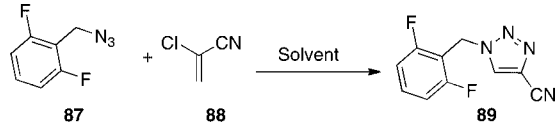
[a] Reference 105.
[b] 1,4-substituted triazole **85** is only isomer observed.
[c] Bath temperature.

nucleophilic opening of isomeric epoxides **77** and **80** with sodium azide and subsequent aqueous Huisgen [3 + 2] cycloaddition reaction with diethyl acetylenedicarboxylate affords the highly functionalized products **79** and **82** in 97% yield (Scheme 24).[102] 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.[104] 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 triazole **85** was the predominant isomer (Scheme 25).[104,105]

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 **87** with 2-chloroacrylonitrile **88** to afford cyanotriazole **89** 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

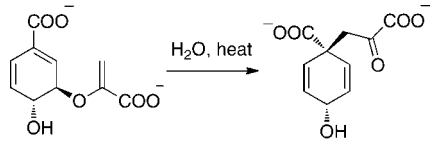
Scheme 26. Huisgen [3 + 2] Cycloaddition Reaction of Azides with Chloroacrylonitrile in Various Solvents[106]



87 88 89

Solvent	Temperature	Yield (%)
Neat	80 °C	72
n-Heptane	80 °C	46
EtOH	77 °C	40
H_2O	80 °C	98

Scheme 27. Claisen Rearrangement of Chorismate to Prephenate in Aqueous Medium



90 91

occurred and caused polymerization of the unreacted chloroacrylonitrile **88** 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 26).[106]

Molteni and co-workers have carried out an extensive study on the Huisgen [3 + 2] cycloaddition reaction of nitrilimine 1,3-dipoles with a range of dipolarophiles. These reactive 1,3-dipoles were generated in situ and in the presence of tetrahexylammonium chloride. This prevented the unwanted formation of the dimer of the 1,3-dipole. Molteni suggested from a computational study that water does not have a significant effect on the rate of cycloaddition, and it is more likely that the acceleration observed is from the tetrahexylammonium chloride and not as an artifact of using water as a solvent.[107−109]

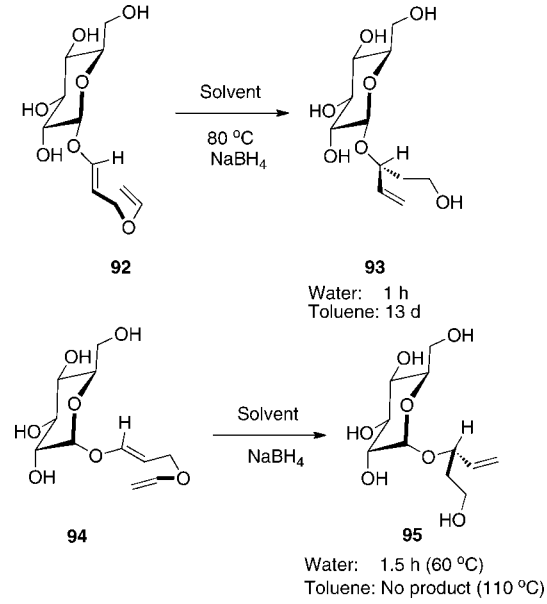
3.1.3. Claisen Rearrangement

The Claisen rearrangement is a [3,3] sigmatropic rearrangement and is a powerful method for the synthesis of new C−C bonds. The mechanism of this reaction is concerted and similar to the Diels−Alder and Huisgen cycloaddition reaction, and there is a minimal influence from solvent polarity.[110] One of the first aqueous Claisen rearrangements was reported in 1973. The reaction studied was the conversion of chorismate **90** to prephenate **91**, a key step in the shikimate biosynthetic pathway for generating aromatic amino acids (Scheme 27).[111,112]

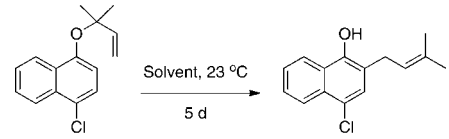
There have been a number of reported studies of aqueous Claisen rearrangements but not to the same extent as other pericyclic reactions such as cycloadditions. Jorgensen has explored the theoretical aspects of this reaction and found that the solvent dynamics calculations revealed an increase in hydrogen bonding from reactant to transition state in an aqueous environment.[54,113] 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.[114]

Augé and co-workers explored the Claisen rearrangement of 6-β-glycosylallyl vinyl ether **92** in toluene and water. The

Scheme 28. Claisen Rearrangement of Glycosylallyl Vinyl Ethers in Water and Toluene[115,116]



Scheme 29. Aqueous Claisen Rearrangement of 4-Chloro-1-substituted Naphthol[5]



96 97

Solvent	Yield (%)
Toluene	16
MeOH	56
Neat	73
H_2O	100

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 **94**. In water, the Claisen rearrangement proceeded 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 **94** (Scheme 28).[115,116]

Sharpless and co-workers have reported the Claisen rearrangement of the 4-chloro-1-substituted naphthol **96**.[5] The reaction at room temperature in water for 5 days (0.28−0.46 M) gave the rearranged product **97** in 100% yield. The corresponding reaction in organic solvents such as toluene or methanol gave significantly reduced yields especially in the case of nonpolar toluene (yield = 16%) (Scheme 29).

Recently, 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 *via* 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.[117]

The Claisen rearrangement is a key reaction in a wide range of total syntheses.[110] 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. While there has been a number of aqueous-mediated Claisen rearrangements in total synthesis there needs to be significantly more mechanistic and synthetic investigation using water as a medium for this reaction to realize its full potential.[118]

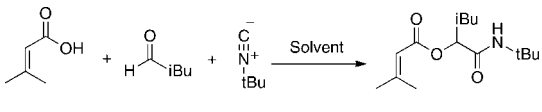
3.2. Multicomponent Reactions

Reactions that contain more than two starting materials are generally classed as multicomponent reactions.[119,120] Among the most commonly used of these are the Ugi and Passerini reactions.[121,122] These reactions are synthetically important as highly functionalized compounds can be synthesized in one-pot. Pirrung and co-workers have examined both of these reactions using in water medium. The Passerini reaction displayed significant rate acceleration using water as a solvent (Scheme 30).[123−125]

On changing the solvent from dichloromethane to water, the yield increased from 50% to 95% and the reaction was complete in 3.5 h. As the reaction progressed the product **101** precipitates from solution and can be isolated by filtration. Pirrung associated the large rate acceleration in water to the hydrophobic effect and cohesive energy density although it is difficult to distinguish between these two phenomena. Interestingly, there is an inverse temperature dependence, and the reaction at 4 °C is complete after 2 h, while the reaction at 25 °C is complete after 3.5 h. Pirrung further applied this methodology to the Ugi reaction where β-amino acids were used to synthesize a library of β-lactams. The β-lactams were synthesized in 71−89% yield over three hours.

Shapiro and Vigalok have explored an interesting Passerini multicomponent reaction examining both the on-water and in-water reactions by changing the solubilities of the reactants.[126] The two reactants **102** and **103** were added to the reaction mixture, and the aldehyde underwent in situ oxidation to form an acid, which then reacted in the Passerini reaction. The reaction was explored with a range of aldehydes and water insoluble isocyanides. In all cases, the water insoluble aldehydes gave the three-component Passerini product **104** in high yields, while partially soluble aldehydes gave a mixture of both products **104** and **105**. This shows that the reactivity in-water and on-water are mechanistically different. An interesting observation is that the reaction in-water was slower than the reaction on-water (Scheme 31).[126]

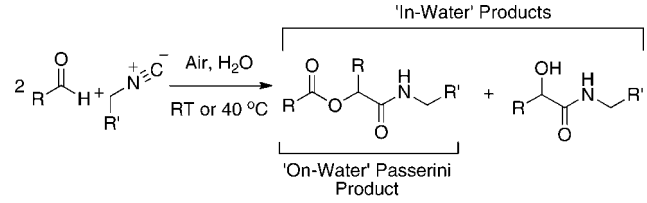
Scheme 30. Passerini Reaction Using Water as a Solvent[125]



98 99 100 101

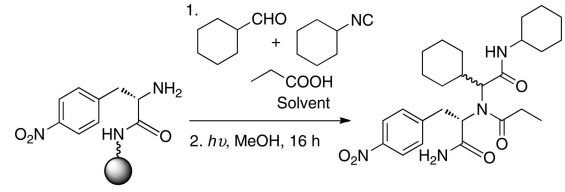
Solvent	Time (h)	Temperature (°C)	Yield (%)
CH_2Cl_2	18	25	50
Formamide	24	25	15
H_2O	3.5	25	95
H_2O	2	4	93
H_2O	5	50	91

Scheme 31. Tandem Oxidation/Passerini Reaction Using Water as a Solvent[126]



102 103 104 105

Scheme 32. Ugi Four-Component Reaction on Cellulose Solid Support[127]



106 107

Solvent	Temperature (°C)	Purity (%)
None	25	13
DMF	25	51
H_2O	25	91

[a] Ratio aldehyde:isocyanide:acid 1:1:2.

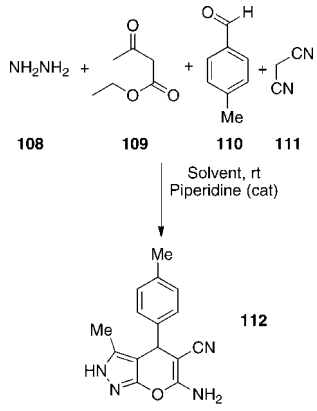
Blackwell and co-workers explored the Ugi four-component reaction using an array synthesis on a cellulose support. The use of water as medium was found to accelerate the heterogeneous solid-phase multicomponent reaction rates. Using water as a solvent, it was found the compounds were isolated in purities over 85% in comparison to organic solvents, such as DMF where purities of 51%, were observed (Scheme 32).[127]

Vasuki and Kumaravel explored an interesting four-component reaction for the synthesis of pyrano[2,3-*c*]pyrazoles using water as a solvent. The reaction of hydrazine hydrate **108**, ethyl acetoacetate **109**, 4-tolylaldehyde **110**, and malononitrile **111** was carried out in the presence of catalytic piperidine (5−10 mol %). This was explored in a range of solvents and resulted in varying yields. However, when the reaction was examined in water, the product **112** was obtained in a yield of 94% was after 5 min, and the reaction work up was simple filtration of the precipitated product (Scheme 33).[128]

3.3. Nucleophilic Ring-Opening Reactions

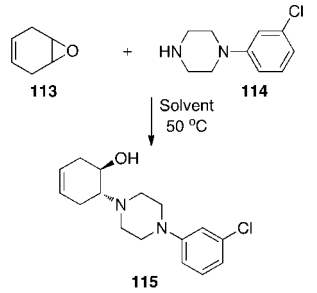
The nucleophilic ring-opening of three-membered rings, such as epoxides and aziridines, is a versatile method for the synthesis of highly functionalized molecules. Sharpless and co-workers investigated the nucleophilic ring-opening of cyclohexadiene monoepoxide **113** with *N*-(3-chlorophenyl)piperazine **114**. When the reaction was carried out using toluene as a solvent, only a 10% yield was observed by NMR after 120 h at 50 °C. However, when the reaction was carried out using water at 50 °C as the solvent, the reaction was complete after 12 h and in 88% yield. When the reaction was carried out in ethanol the yield was 89% for a reaction time of 60 h but taking into account the concentration of the reactants in comparison to water the rates are similar (Scheme 34).[5]

Scheme 33. Four-Component Reaction Using Water As a Solvent for the Synthesis of Pyranopyrazoles[128]



Solvent	Time (min)	Yield (%)
Toluene	15	71
CH_2Cl_2	60	31
THF	120	Trace
DMSO	120	0
DMF	120	0
H_2O	5	94

Scheme 34. Nucleophilic Opening of Monoepoxide with Substituted Phenylpiperazine[5]



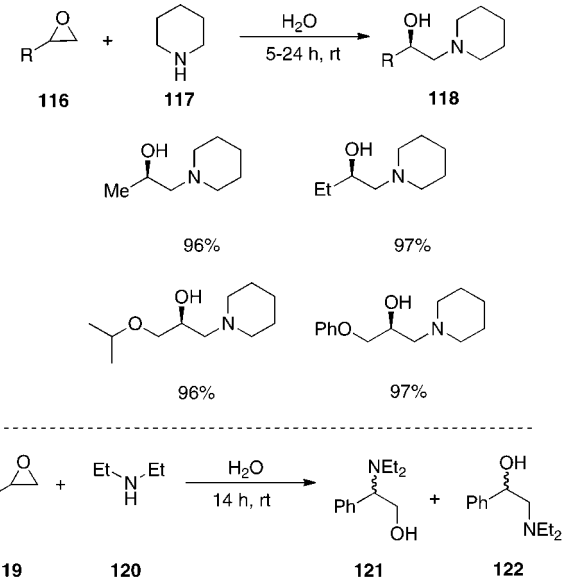
Solvent	Conc (M)	Time (h)	Yield (%)
Toluene	1	120	<10[a]
EtOH	1	60	89
H_2O	3.88	12	88

[a] Yield determined by ^1H NMR.

Saidi and Azizi examined the aminolysis of a variety of epoxides by aliphatic and aromatic amines using water as a solvent and synthetically useful β-amino alcohols were formed in high yields.[129] These reactions were carried out at room temperature with a wide range of substrates **116**, and in some cases, the β-amino alcohols were isolated by filtration. This methodology was further extended to the aminolysis of styrene oxide **119** and with diethylamine **120**, two isomers **121** and **122** were formed. When the identical reactions were carried out in organic solvents (toluene and diethyl ether), no reaction was observed after two days. However, with more protic solvents such as ethanol a yield of 50% was observed after 1 day with an isomeric ratio (**121**/**122**) of 45:55 (Scheme 35). When the reaction solvent was water a yield of 92% was observed after 14 h with a isomeric ratio of **121** and **122** (24:76), which is significantly enhanced in comparison to the organic solvents.

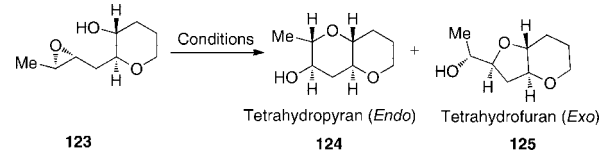
Carlier and Monceaux examined the nuclophilic ring-opening of bisepoxides with substituted anilines using water as a solvent. Interestingly, both the 1,3- and 1,4-diol were

Scheme 35. Aminolysis of Epoxides Using Aliphatic and Aromatic Amines[129]



Solvent	Time (h)	Yield (%)	Ratio 121:122
Toluene	48	-	-
Et_2O	48	-	-
EtOH	24	50	45:55
H_2O	14	92	24:76

Scheme 36. Cyclization of Templated Epoxides under Various Conditions[131]



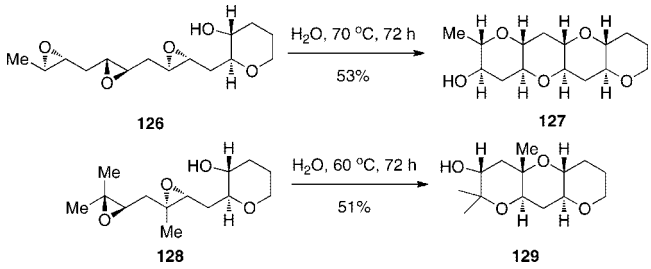
Conditions	Ratio 124:125
Cs_2CO_3, MeOH	1:2.7
AcOH, Toluene	1.6:1
Ethylene glycol	9:1
Methanol	8:1
H_2O	>10:1

observed, and the reaction was found to be sensitive to the electronic effects in the aniline and the reaction conditions.[130]

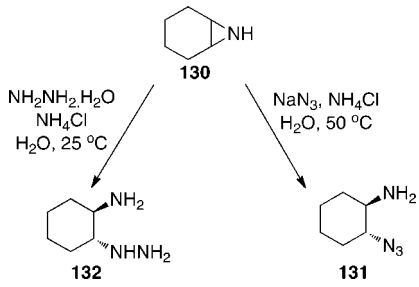
One of the most elegant approaches to nucleophilic ring-opening of epoxides using water as a solvent has been demonstrated by Jamison and co-workers. A domino cascade of water promoted epoxide-opening and ring-closure affords complex subunits of the ladder polyethers found in natural products such as Maitotoxin and Brevetoxin A and B.[131] Jamison explored the cyclization studies of templated epoxides and found that water enhanced the selectivity of tetrahydropyran over the tetrahydrofuran structure and this was observed when a templating tetrahydropyran is present (Scheme 36).

The above reaction clearly shows that water can be used to promote the cyclization closure of ring opened epoxides. In less-polar solvents, the selectivity was poor (<3:1).

Scheme 37. Cascade Approach to Polyether Ladder Systems Using Water as a Solvent[133,134]



Scheme 38. Nucleophilic Ring-Opening of Aziridines Using Water as a Solvent



However, in the more polar solvents, such as ethylene glycol and methanol, the selectivity was increased (>8:1), but the conversions are poorer in comparison to using water as a solvent.[132] Jamison further expanded this methodology to a more complex cascade approach to polycyclic tetrahydropyran ring systems (Scheme 37).[133,134] The development of this methodology could be applied to the Maitotoxin and Brevetoxin natural products, and this could be envisaged as a possible biomimetic pathway to these complex molecules.

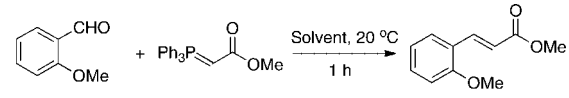
As well as nucleophilic epoxide-opening reactions, nucleophilic opening reactions of aziridines are also possible using water as a solvent. Sharpless and co-workers have explored the nucleophilic ring-opening of 1-azabicyclo[4,1,0]-heptane **130** with buffered sodium azide using water as a solvent to afford the product **131** in 90% yield. A similar type of reaction was observed when hydrazine hydrate was used instead of sodium azide. The ring opened product **132** was observed in 95% yield (Scheme 38).[135]

3.4. Wittig Reaction

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.[136] For a reaction that has widespread use there are very few reported examples of the Wittig reaction under aqueous conditions. 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. These results were discussed in section 2.[78,79]

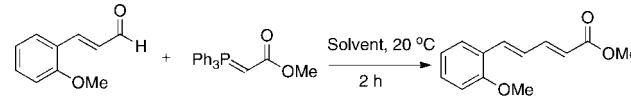
Bergdahl and co-workers have explored the Wittig reaction employing a wide range of stabilized ylides and aldehydes.[137,138] It was found that the solubility of the reactants was poor in some cases but the yields were high and the reactions were highly *E*-selective. The reactions were found

Scheme 39. Wittig Reaction in Different Solvents[137,138]



132 133 134

Solvent	Yield (%)	*E/Z*
Water	81	76:24
MeOH	92	65:35
CH_2Cl_2	47	81:19
Toluene	36	82:18
THF	25	84:16



135 133 136

Solvent	Yield (%)	*E/Z*
Water	88	84:16
MeOH	94	67:33
CH_2Cl_2	78	84:16
Toluene	59	91:9
THF	33	92:8

to work best when large hydrophobic groups, such as heterocyclic rings were present. A comparison study was explored with two different aldehydes (anisaldehyde **132** and 2-methoxycinnamaldehyde **135**) with the stabilized ylide methoxycarbonyl methylene triphenylphosphorane **133** in a range of different solvents (Scheme 39).

The general trend is that the reaction is faster when carried out in water in comparison to organic solvents, even though there is the low solubility of the reactants. However, one drawback is that the faster the reaction the lower the *E*/*Z* ratio and in some cases the *E*/*Z* ratio is more favorable in organic solvents.

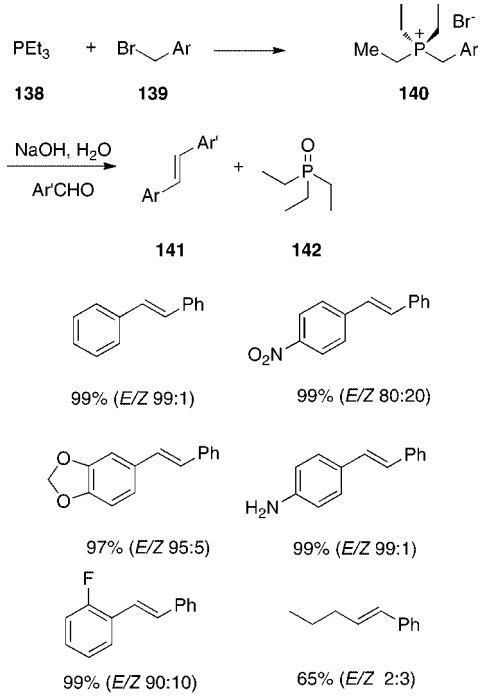
McNulty and co-workers explored the synthesis of *E*-stilbenes and alkenes using the chemoselective formation of trialkyl(benzyl)phosphonium salt **140** in water and their subsequent aqueous Wittig reaction with aldehydes (Scheme 40).[139,140]

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.[140] The yield for the reactions were generally in the 70−90% range with modest *E*-selectivity. The water-soluble phosphine oxide **142**, a byproduct of the reaction, is removed by aqueous partition of the organic products.

3.5. Bioorthogonal Reactions

The area of bioorthogonal chemistry has emerged as one of the most interesting applications of organic reactions using water a solvent. Bioorthogonal reactions are essentially reactions that can be carried out in cells and animals.

Scheme 40. Aqueous Wittig Reaction of Alkyl Ylide with Various Aldehydes[139,140]



However these are limited to reactions that have high rate constants and show reactivity in using water as a solvent. Many of the synthetic reactions developed using water as a solvent could be applied in this area but by far the most widespread reaction type applied has been cycloaddition reactions, especially using the click methodology.[101,102] Bertozzi and co-workers have been at the forefront in developing this area.[141−143] The initial work was focused on the Cu-catalyzed azide−alkyne cycloaddtion (CuAAC) reaction however, one of the major drawbacks was the toxicity of the Cu(I) in biological environments. This problem was overcome by using strain-promoted azide−alkyne cycloaddition (SPAAC) reactions, where the reactivity was determined by the strain in the alkyne dipolarophile triple bond. These alkyne dipolarophiles **143**−**147** have undergone several iterations and with these iterations has come increased reactivity in aqueous environments (Scheme 41). In all cases, these reactions would be in-water to occur within the biological environments. The alkyne dipolarophile **145** was designed as to increase the solubility of these type of dipolarophiles in water.[144−147] The ultimate applicability of these reactions was reported by Bertozzi and co-workers where these strain-promoted organic azide−alkyne cycloadditions were explored in the labeling of azido sugars in a live mouse.[148]

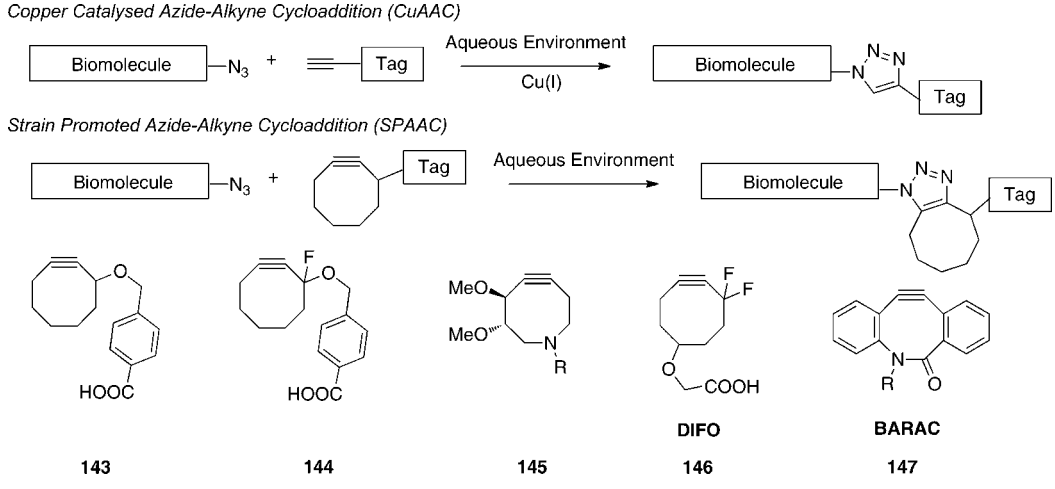
Another bioorthogonal reaction that has been reported is the Diels−Alder cycloaddition reaction of 1,2,4,5-tetrazine with strained dienophiles. This was independently reported by Fox and Hilderbrand and the methodology developed was as a result from work carried out previously by Engberts and co-workers where the cycloaddition reactions were examined using water as a solvent (see Scheme 5, section 2.1.3).[71,149,150] Sauer demonstrated that these Diels−Alder cycloaddition reactions occur exceptionally fast with certain dienophiles; however, one major problem is that these 1,2,4,5-tetrazines are unstable in water.[151] Engberts found a 3,6-dipyridyl-1,2,4,5-tetrazine has sufficient stability for reactions to be explored in-water, and this has been used by both Fox and Hilderbrand in their bioorthogonal tagging reactions.

4. Catalyzed Reactions

4.1. Metal-Catalyzed Reactions

In the previous sections (sections 3.1−3.4), the reactions discussed involve two or more reactants undergoing reaction using water as a reaction medium to form products. When reactions are explored under metal-catalyzed conditions this further complicates the aqueous reaction mixture. The nature and stability of the metal and where applicable the ligands, needs to be taken into consideration. The area of metal-catalyzed reactions in aqueous media has been extensively reviewed by a number of researchers.[152−155] One of the major concerns when aqueous phase metal catalyzed reactions were first explored was the stability of both the metal salt and ligands. In the case of metals, the ability of water to form aqua complexes needs to be taken into account. With ligands, such as phosphines, the stability in aqueous solution needs also to be taken into account as the metal−ligand combination may not be the active species that catalyzes the reaction. In recent years, a large number of metal-catalyzed reactions have been explored using water as a reaction medium with some reactions being more successful than others.

Scheme 41. Bioorthogonal Reactions Using the Strain Promoted Organic Azide−Alkyne Cycloaddition Reaction in Aqueous Environments



4.1.1. Pericyclic Reactions

The Diels−Alder reaction has been examined by numerous groups in metal mediated aqueous environments. Kobayashi and co-workers have been at the forefront of exploring lanthanide metals in aqueous media as catalysts for organic reactions.[156−158] Kobayashi found that metallic triflates, $Sc(OTf)_3$ and $La(OTf)_3$, are stable under aqueous reaction conditions.[159] Kobayashi examined the AgOTf catalyzed aza-Diels−Alder reaction of Danishefsky's diene **148** with a range of imines using water as a reaction medium (Scheme 42).[160]

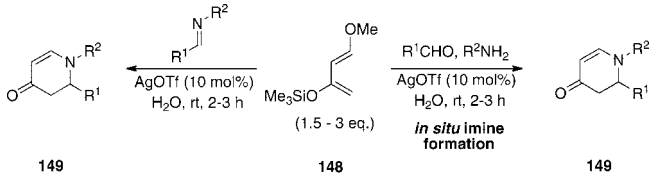
Two strategies were explored where the imine was synthesized before the aza Diels−Alder reaction and in the other case the imine was formed in situ. In both cases, the same product **149** was synthesized. The reaction in water was found to be more efficient than the corresponding reaction in THF/water because the rate of hydrolysis of Danishefsky's diene **148** under heterogeneous conditions was slower. In both cases, where the imine was either preformed or generated in situ, the yields for the reaction were excellent. In some cases, where the imine was formed in situ, the addition of the surfactant Triton-X was found to increase the yield, although this trend was not observed in the case of cyclohexyl C-substituted imine where the yield decreased from 70% to 51% on addition of the surfactant Triton-X.

Engberts and Otto reported the first enantioselective Diels−Alder reaction with $Cu(NO_3)_2$ and *N*-methylated tryptophan **151** using water as the reaction medium.[161,162] The dienophile **150** coordinates the copper through the carbonyl group and the pyridine nitrogen and the coordination of the tryptophan ligand **151** forms the chiral complex in situ that undergoes chiral Diels−Alder reaction with cyclopentadiene **1** to form the enantiopure bicyclo[2,2,1]-heptane **152**, in excellent yield (94%) and in moderate enantioselectivity (74% ee) (Scheme 43).

Engberts and co-workers further expanded the scope of this reaction and explored the reaction in conjunction with micelles where the rate was found to have increased 1×10^6 times in comparison to the uncatalyzed reaction in acetonitrile.[163,164] In many cases, the metal-catalyzed Diels−Alder reaction in aqueous solutions had an organic cosolvent present.

The metal-catalyzed Huisgen [3 + 2] cycloaddition reaction has been dominated in recent years by the copper-catalyzed organic azide−alkyne cycloaddition reaction (CuAAC) that was reported independently by Sharpless and Meldal.[101,102] Even

Scheme 42. Aqueous Aza-Diels−Alder Reaction of Danishefskys Diene under AgOTf-Catalyzed Conditions[160]



149

R^1	R^2	Yield (%)
Ph	Ph	83
4-$OMeC_6H_4$	Ph	77
Ph	4-BrC_6H_4	83
4-$NO_2C_6H_4$	Ph	69

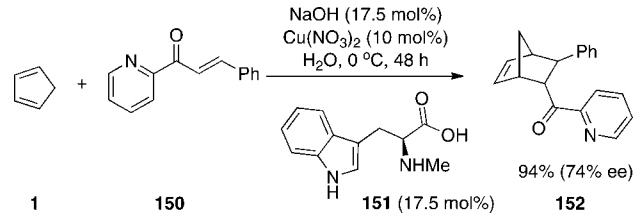
148

149

R^1	R^2	Yield (%)
Ph	Ph	80
Ph	4-$OMeC_6H_4$	56
Ph	4-BrC_6H_4	90[a,b]
$(CH_3)_2CHCH_2$	Ph	72
C_6H_{11}	Ph	70 (51)[b]

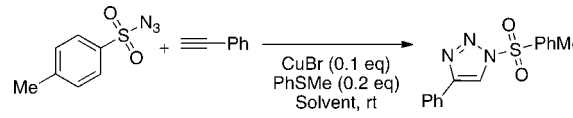
[a] With 10 mol% Triton X. [b] 3 eq. Diene.

Scheme 43. Asymmetric Diels−Alder Reaction Using Water As an Aqueous Medium[161,162]



1 150 151 (17.5 mol%) 152

Scheme 44. CuBr/PhSMe-Catalyzed Reaction of Sulfonyl Azides 153 and Terminal Alkynes in Aqueous Media[168]



153 154 155

Solvent	Time (h)	Yield (%)
H_2O	12	88
H_2O	16	92
tBuOH	12	22
$CHCl_3$	12	6
tBuOH/H_2O (2:1)	12	61

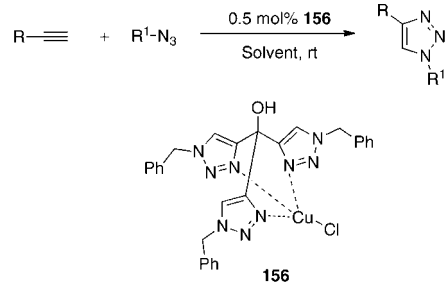
since these reactions were reported in 2001, there has been over a thousand papers published on this area. The versatility of this reaction has now spread to diverse areas such as polymer chemistry and biotechnology.[165−167]

While the initial copper catalyzed organic azide−alkyne cycloaddition reactions were reported using an organic cosolvent, many reactions have emerged where they are carried out using only water as a solvent. Fu and co-workers explored the CuBr/PhSMe catalyzed reaction of sulfonyl azides **153** and terminal alkynes **154** using water as the reaction medium. These reactions did not need to be carried out under air sensitive conditions and could be run in air and at room temperature (Scheme 44).[168]

The reaction was explored under a variety of conditions using CuBr and thioanisole as the ligand. The optimum solvent was found to be water where a yield of 88% was observed after 12 h, which could be increased to 92% after 16 h. In the corresponding reaction, using organic solvents, such as chloroform or *t*-butanol, a significant decrease in yield was observed (22%). The reaction scope was expanded using a range of sulfonyl azides and terminal alkynes and the yields were found to be moderate to excellent (45−94%). In the cases where the terminal alkyne was a solid, the yield was found to be poor (<45%); however, dissolving the alkyne in ethyl acetate and adding it to the reaction increased the yield significantly (up to 88%). Fu and co-workers further applied this methodology to the reaction of aliphatic and aryl azides with a range of terminal alkynes in an aqueous medium. The reactions were found to be fast, but the downside is a 50 mol % of the thioanisole ligand was required.[169]

Vauzeilles and co-workers explored the phenylenediamine-catalyzed click reaction for the preparation of neoglycoconjugates from unprotected glucosyl azides in water. The reactions were carried out in under two hours in excellent yield (75−98%).[170] Pericas and co-workers explored the copper-catalyzed organic azide−alkyne cycloaddition reaction using a novel tris(triazolyl)methanol ligand.[171] The ligand

Scheme 45. Tris(triazolyl)methanol-copper 156 Catalyzed Organic Azide−Alkyne Cycloaddition Reaction[171]



R	R^1	Solvent	Time (h)	Yield (%)
Ph	Ph	H_2O	4	99
Ph	nOct	H_2O	4	99
Ph	$PhCH_2$	H_2O	4	94
Ph	$PhCH_2$	Neat	15	99
CH_2NH_2	$PhCH_2$	nBuOH:H_2O (2:1)	5	47

was synthesized in three steps from commercially available starting material. The ligand.CuCl complex **156** was found to be stable to both air and moisture. The reaction was explored with a range of organic azides and terminal alkynes. The reactions were found to be fast at room temperature under neat conditions or in water. The catalyst loading was typically 0.5 mol %, and this could be lowered to 0.23 mol % but at the expense of a longer reaction time (Scheme 45).

The initial reaction screening showed that water as a reaction medium gave excellent yields. In *n*BuOH/H_2O (2:1) the yields observed were much lower at 47%. A modification of the reaction involving in situ formation of the organic azide from the corresponding bromides also gave excellent yields (up to 99%).

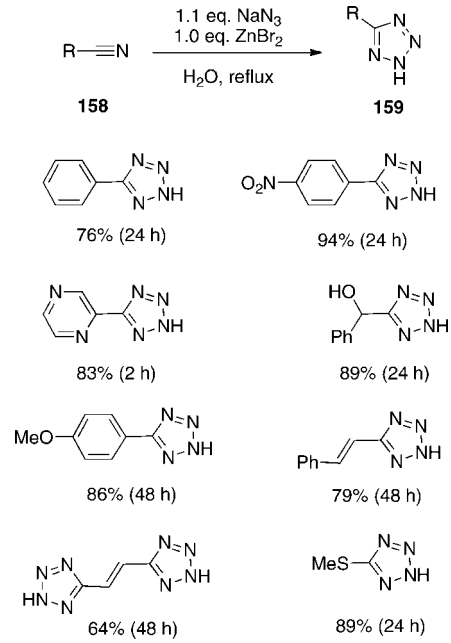
Sharpless and co-workers Finn, Kolb and Fokin have been at the forefront of expanding the application of the copper catalyzed organic azide−alkyne cycloaddition reaction. One of the most interesting applications of this methodology has been applied to in situ click chemistry where a protein is used as a template. This allows the application of the click methodology to a combinatorial method for drug discovery. The advantage of using the CuAAC reaction is that it gives almost quantitative yield and can be carried out using water as a solvent. A range of protein structures has been explored using this methodology, and these include carbonic anhydrase, HIV protease, and acetylcholine esterase.[172−175]

One of the first reports of the click methodology devised by Sharpless was the zinc catalyzed formation of tetrazoles from the corresponding nitriles using water as the reaction medium.[176] The scope of the reaction incorporated a broad range of substituted tetrazoles and interestingly the use of zinc in the reaction was found to accelerate the reaction in comparison to the noncatalyzed variant. However, the mechanistic rationale for the role of zinc is still not clear (Scheme 46).

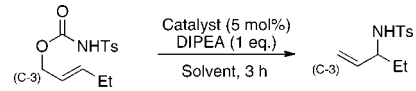
Sharpless showed that the zinc-catalyzed reaction of organic azides and nitriles is an excellent method for the synthesis of tetrazoles in high yields. When the reaction was carried out on a large scale (100 g) the tetrazole could be isolated by simple filtration from the aqueous medium.

The use of water as a solvent for other metal-catalyzed pericyclic reactions is not as widespread in comparison to

Scheme 46. Zinc-Catalyzed Reaction of Azides and Nitriles in Aqueous Medium[176]



Scheme 47. Au-Catalyzed Decarboxylative Amination of Allylic-*N*-tosylcarbamates 160 via a Base-Induced Claisen Rearrangement



Catalyst	Solvent	Conversion (%)[a]
AuCl	Toluene	10
$AuCl_3$	Toluene	12
AuCl/AuOTf	Toluene	62
AuCl/AuOTf	DCE	92
AuCl/AuOTf	H_2O	90

[a] Conversion determined by ^1H NMR.

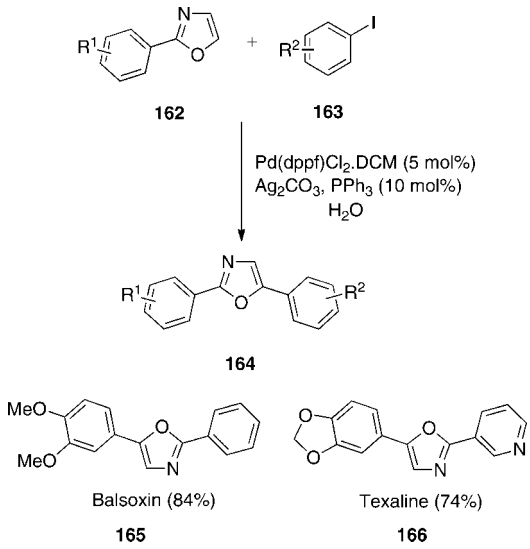
cycloaddition reactions. Recently Xing and Yang explored the Au-catalyzed decarboxylative amination of allylic-*N*-tosylcarbamates **160** via a base induced Claisen rearrangement using water as the reaction medium (Scheme 47).[177]

When the reaction was carried out in toluene, the conversion was poor (<62%), but in DCE (dichloroethane), there was a significant increase in conversion (92%), and in water, a comparable yield to DCE was observed (90%). When these optimized conditions were used to explore the substrate scope, the yields were found to be as high as 95% using water as a solvent. When the C-3 position was substituted with either alkyl or aryl groups high stereoselectivities were observed with *E*/*Z* ratios of 88:12 to 97:3 observed, with the *E* isomer always predominant.

4.1.2. Arylation Reactions

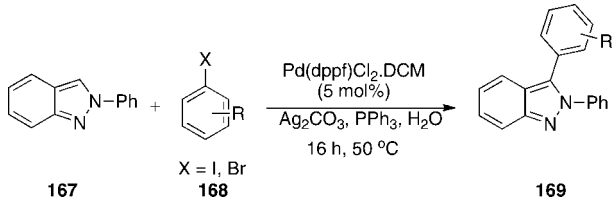
Transition metal-catalyzed carbon-heteroatom bond formation allows the construction of C−N, C−O, and C−S linkages using arylation reactions. This is a highly versatile method that can be used for the synthesis and functionalization of heterocycles. Recently, this group of reactions has been complemented by C-arylation reactions where the arylation of a C−H bond adjacent to a heteroatom can be

Scheme 48. Palladium-Catalyzed Arylation of Oxazoles Using Water as a Solvent[179]



162 163 164 165 166

Scheme 49. Palladium-Catalyzed Arylation of Indazoles Using Water as a Solvent[181]



167 168 169

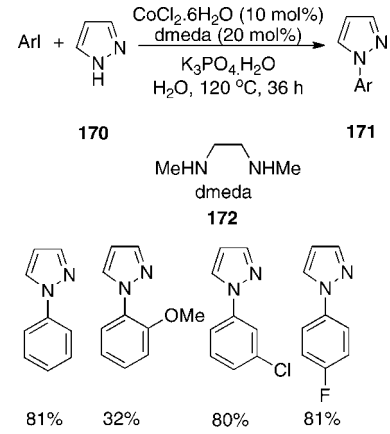
achieved. Interestingly, when water has been used for these reactions, there has been an increase in chemoselectivity and rate acceleration, and using water for these reactions is highly advantageous from a green chemistry prespective.[178]

Greaney and co-workers have been at the forefront of exploring transition metal catalyzed C-arylation reactions using water as the reaction medium. A major advantage of this methodology has been that the reactions can be carried out using readily available starting materials and unlike other metal-catalyzed coupling reactions the starting materials do not have to be highly functionalized. Greaney and co-workers explored the palladium catalyzed direct arylation of oxazoles using water as a solvent, (Scheme 48).[179]

When the reactions were examined using water as the reaction medium, the yields were in excess of 85% illustrating the versatility of this arylation strategy. This methodology was applied to the synthesis of the natural products balsoxin **165** and texaline **166** in 84% and 74%, respectively. Previous synthesis of these natural products required multistep routes and in moderate to poor yields, balsoxin (40%, seven steps) and texaline (4%, six steps). Greaney and co-workers further applied this methodology to the C-arylation of thiazoles using water as the solvent.[180] The reaction in acetonitrile at 60 °C required three days, while the reaction in water was complete after 24 h. The reaction methodology is comparable to existing arylation methods, but there is a much greater substrate scope and a cheaper catalyst system. This methodology was recently applied to the palladium catalyzed arylation of 2-H-indazoles **167** (Scheme 49).[181] The indazole ring system is an important heterocycle especially in medicinal chemistry.

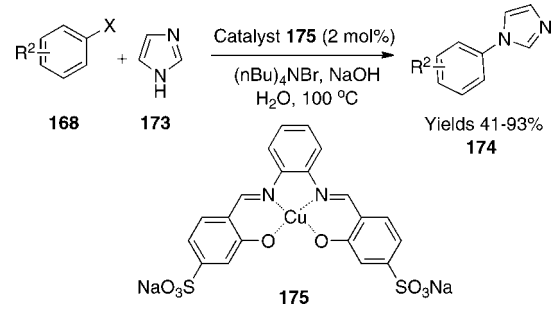
The reaction was found to be effective for both aryl iodides and aryl bromides. The reaction also showed good functional

Scheme 50. Cobalt-Catalyzed Arylation of Pyrazole Using Water as the Reaction Medium[182]



170 171 172

Scheme 51. Cu(salen)-Catalyzed Arylation Reaction of Imidazoles Using Water as a Solvent[183]



168 173 174 175

group tolerance on the aryl ring **168** and in general the yields were found to be high (up to 96%). A key practical consideration for the reaction was that efficient stirring was required for a successful reaction.

Another key metal-catalyzed arylation reaction is the arylation of the nitrogen on heterocyclic rings. Teo and Chua explored the cobalt-catalyzed arylation of pyrazoles with aryl iodides using water as the reaction medium.[182] A range of ligands was examined and the optimum catalyst system was found to be a *N*,*N*-dimethylenediamine (dmeda) ligand and $CoCl_2 \cdot 6H_2O$ as the metal source (Scheme 50).

The reaction gave good yields (>80%) using aryl iodides, but with aryl bromides, the yields in general were low (<24%). The scope of the reaction was explored using other heterocycles, such as indole and azaindole, and the arylation was achieved in moderate to excellent yields (up to 86%).

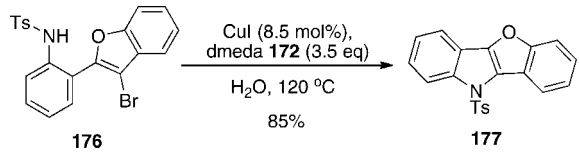
Zhou and co-workers used a Cu(salen) complex to explore the arylation of imidazole **173** using water as the reaction medium.[183] The catalyst was modified with sulfonate groups to improve the solubility in aqueous medium (Scheme 51).

The yields for this reaction were moderate to excellent (up to 93%), and there was no need to carry out the reaction under nitrogen or argon. The Cu(salen) catalyst **175** could also be recovered and reused. The catalyst showed good applicability to the N-arylation reaction of other heterocycles in good to excellent yields (up to 97%).

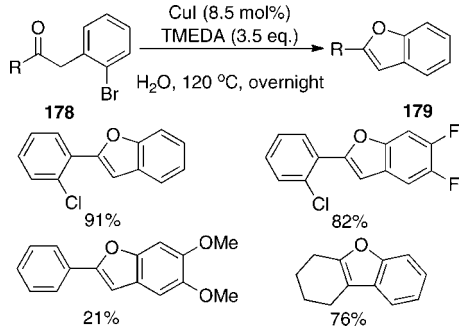
SanMartin and co-workers examined the copper-catalyzed intramolecular N- and O-arylation reaction for the synthesis of benzofuroindole framework using water as the solvent (Scheme 52).[184]

When the reaction was carried out using the catalyst system (CuI/dmeda), the benzofuroindole was obtained in 85% yield; however, the ligand loading of 3.5 equiv was not ideal. When the solvent was changed to toluene, the yield

Scheme 52. Copper-Catalyzed N-Arylation Reaction for the Synthesis of Benzofuroindole Framework Using Water as the Reaction Medium[184]



Scheme 53. Copper-Catalyzed O-Arylation Reaction in Aqueous Medium[186]



fell to 73% showing that water is beneficial for the reaction. The intramolecular metal-catalyzed O-arylation reaction was used for the synthesis of a number of interesting oxygen heterocycles by employing the Cu/TMEDA catalyst system using water as solvent, one such case being the benzo[*b*]furan system (Scheme 53).[184−186]

The benzo[*b*]furans were obtained in moderate to excellent yields (up to 99%), but a drawback of these reactions was the amount of TMEDA (3.5 equiv) required. It was possible to recycle the aqueous reaction medium for further reactions, but additional TMEDA needed to be added to obtain moderate yields.

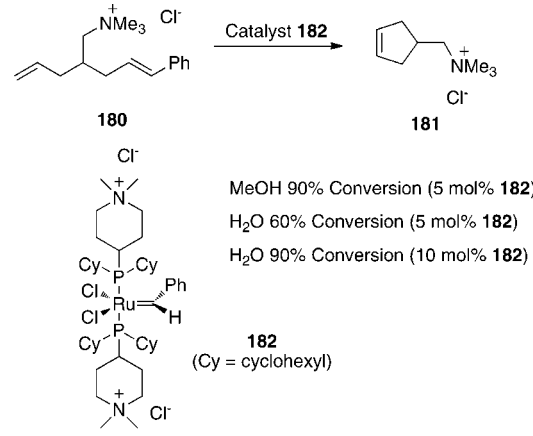
In comparison to N- and O-arylation reactions, there has been only been a small number of metal-catalyzed S-arylation reactions in aqueous media reported. SanMartin and co-workers reported the copper-catalyzed reaction of thiophenol derivatives and aryl halides to afford diarylsulfides using water as medium.[187,188] The yields were excellent (up to 99.9%) using the copper/*trans*-1,2,-diaminocyclohexane catalyst system. An interesting observation was that there was an optimal volume of water (13 mL $mmol^{-1}$), and any increase or decrease caused a drop in yield. The authors proposed that this optimal volume could be the result of a portion of the reactants being dissolved at the aqueous organic interface and in a partially homogeneous process.

4.1.3. Olefin Metathesis

Olefin metathesis has emerged as one of the most widely used reactions in organic synthesis for the formation of carbon−carbon double bonds. The pioneering work of Grubbs, Schrock and Hoveyda has enabled the development of catalysts that can be applied to a diverse array of metathesis reactions such as ring closing metathesis (RCM), cross metathesis (CM), and ring-opening metathesis polymerization (ROMP).[189,190] Like many other organometallic reactions, olefin metathesis is usually carried out under anhydrous conditions. However, a number of groups have explored using water as a solvent, especially for the Grubbs-type catalysts.[191]

Grubbs and co-workers developed a number of highly successful catalysts for olefin metathesis, and they have also explored a number of modified catalysts to allow reactions using water as the reaction medium.[192,193] The ring closing metathesis reaction was explored for acyclic dienes in both methanol and water using the water-soluble ruthenium alkylidenes **182** (Scheme 54).[194]

Scheme 54. Cross-Metathesis Reaction of Acyclic Dienes Using Water-Soluble Ruthenium Alkylidenes



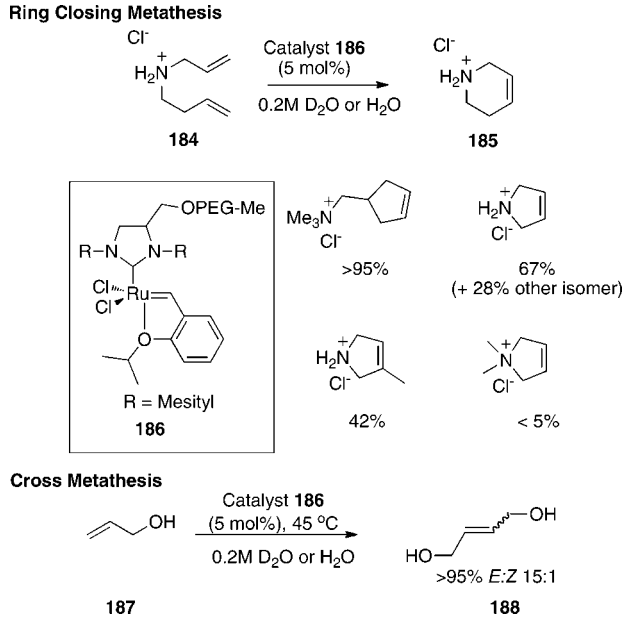
The reaction of the diene **180** was found to proceed as a homogeneous solution in both methanol and water with good to excellent conversion using 5 mol % of catalyst **182**. When the catalyst loading of **182** was increased to 10 mol % using water, a comparable conversion to that in methanol was observed. A major problem that was observed was the decomposition of the catalyst **182**. It was also found that there was a limited substrate scope, and the catalyst **182** was inactive in cross-metathesis. Grubbs and co-workers looked at improving the ruthenium-catalyzed olefin metathesis reaction in water.[195,196] Using the more stable N-heterocyclic carbene (NHC) type ligands, a modified catalyst was developed where the NHC portion was functionalized with a water-soluble polyethylene glycol chain. The activity of the catalyst **186** was much improved in the ROMP of the *endo*-norbornene monomer. The catalyst was further applied to the RCM of α,ω-dienes using water as the reaction medium to yield five- and six-membered rings (Scheme 55).

The corresponding ring closing metathesis (RCM) products were obtained in high conversion; however, the diallyldimethylamine was only formed in <5% conversion. The catalyst **186** was applied to the homogeneous cross metathesis reaction of allyl alcohol **187**. The corresponding reaction was examined in a heterogeneous system by Blechert and Connon where a conversion of 80% was observed.[197] The catalyst **186** showed excellent activity in the homodimerization of allyl alcohol **187** with a conversion of >95% and in excellent *E*/*Z* selectivity (approx 15:1).

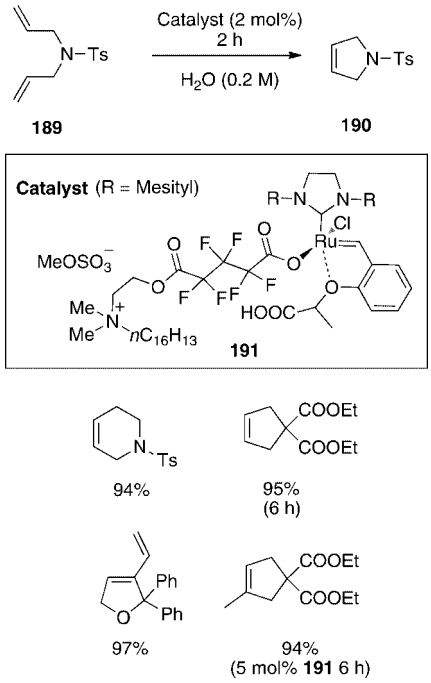
Grela and co-workers explored a number of aqueous olefin metathesis reactions. In one case, an unmodified Grubbs type II catalyst was examined in a ring-closing (RCM) and cross metathesis (CM) using ultrasonication to obtain a water emulsion.[198] The reactions were found to proceed in high yields and selectivity. Grela and co-workers further explored a surfactant type metathesis catalyst in both ring closing (RCM) and cross metathesis (CM) reactions, (Scheme 56).[199]

The reactions were found to proceed in high yields (up to 97%) for the ring-closing metathesis reaction with catalyst **191**. When the catalyst **191** was applied to the cross metathesis (CM) reaction the yields were found to be good (up to 78%). A major advantage of catalyst **191** was that the reactions could be carried out at room temperature.

Scheme 55. Ring-Closing Metathesis and Cross Metathesis Reactions of Water-Soluble Catalyst 186[195,196]

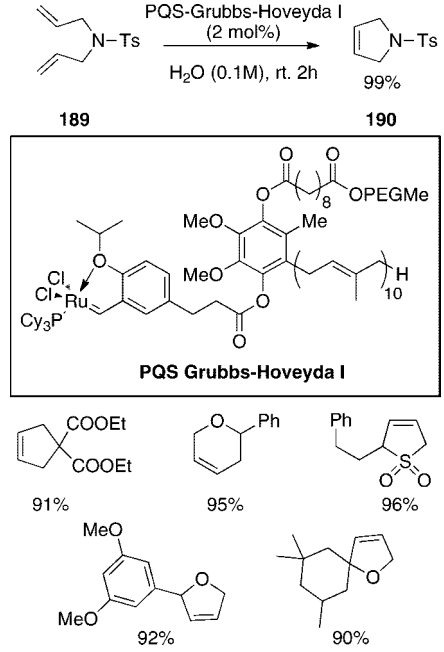


Scheme 56. Ring-Closing Metathesis Reaction Using Water as a Solvent[199]



Lipshutz and co-workers have also explored using the aqueous olefin metathesis reaction incorporating surfactants (PQS = PEG−ubiquiniol−sebacate) into the Grubbs Type II catalyst structure, whereby the insoluble reactants undergo reaction in nanometer micelles which are formed to accommodate water insoluble substrates.[200−202] Using this modified Grubbs catalyst the ring closing metathesis reactions were found to give excellent yields at room temperature with moderate catalyst loading (2 mol %). Lipshutz and co-workers further explored the PQS surfactant in the ring-closing metathesis (RCM) reaction.[203] The PQS was found to dissolve freely in water forming nanomicelles in which the RCM reactions of water insoluble diene substrates can occur in pure water at room temperature (Scheme 57).

Scheme 57. PQS Grubbs−Hoveyda I Mediated Ring-Closing Metathesis[203]



The ring-closing metathesis reactions were rapid with all reactions going to completion within two hours and in excellent yield (89−99%) Unlike the free Grubbs−Hoveyda I catalyst, the PQS derived catalyst could be recycled and reused up to 10 times with only a minimal loss in reactivity. Interestingly the reaction could be carried out in seawater instead of HPLC grade water where there was no significant change in the yield. The area of aqueous metathesis reactions is in the early stages of development and novel catalysts need to be developed for use in aqueous media.

4.1.4. Mizoroki−Heck Reaction

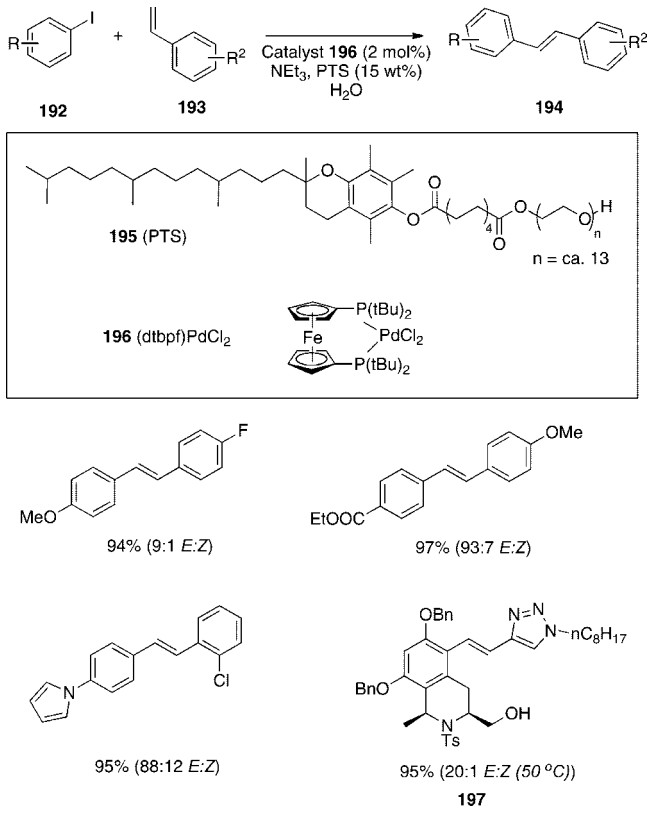
The palladium-catalyzed Mizoroki−Heck reaction is an excellent method for the synthesis of C−C bonds and is an important reaction in organic synthesis.[204] Both inter- and intramolecular variants of this reaction have been developed and more recently the focus has been to develop asymmetric variants, some of which have shown considerable success.[205] For such a well-known reaction, there have only been limited examples of the Mizoroki−Heck reaction using water as the reaction medium.

Lipshutz and co-workers have explored the aqueous Mizoroki−Heck reaction of aryl iodides and styrenes using a $Pd(dtbpf)Cl_2$ catalyst in the presence of PTS nonionic amphiphiles.[206] This system was found to form nanomicelles in water that promotes the reaction of non-water-soluble partners at room temperature (Scheme 58).

The reaction was found to occur in high yields (>90%) and in many cases in high *E*-selectivity (>9:1). The highly functionalized tetrahydroisoquinoline product **197** was obtained from an easy coupling to the water insoluble vinyl triazole component in excellent yield (95%) and excellent *E*-selectivity (20:1).

Thore and co-workers examined the palladium(II) acetate/pyridylethylaminosulfonate catalyzed Mizoroki-Heck reaction of alkyl halides and alkenes using water as a solvent. The yields for the reaction were excellent (up to 94%) and the reactions were found to be favorable in aqueous medium in comparison to organic solvents (DME) where the yields

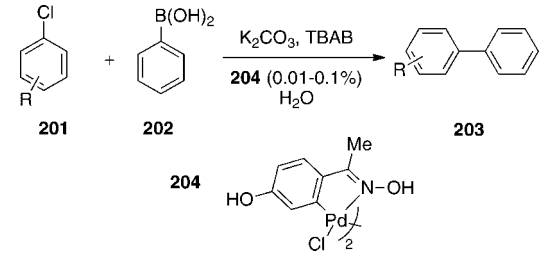
Scheme 58. Heck Coupling Using Aqueous Micelles[206]



were only moderate (51%).[207] Firouzabadi and co-workers examined the palladium catalyzed Mizoroki−Heck reaction of aryl halides and styrenes using a phosphonite ligand **200** in aqueous medium.[208] The reactions were carried out under conditions where there was no exclusion of air or containing any organic cosolvents. The catalyst could be filtered from the reaction and could be recycled without the loss of any catalytic activity, (Scheme 59).

In all cases where aryl iodides/bromides **168** were used the reactions proceeded smoothly and the yields were excellent (>80%). For the reaction with *n*-butylacrylate, a weaker base cesium carbonate was used as sodium hydroxide was not tolerated under the reaction conditions.

Scheme 60. Suzuki Reaction in Aqueous Medium Using Palladacycle 204[210]



4.1.5. Suzuki Reaction

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. This reaction is synthetically important and has widespread use in natural product and drug synthesis.[209]

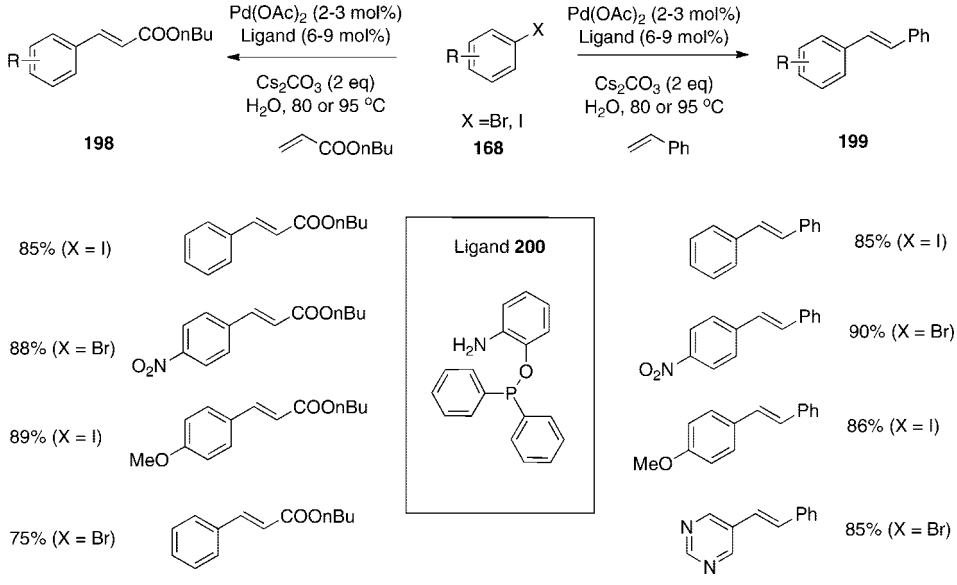
Najera and Botella have examined the Suzuki reaction of aryl chlorides **201** and phenyl boronic acids **202** in aqueous medium with a range of palladcycles **204** (Scheme 60).[210] This reaction was found to proceed in good to excellent yields (up to 100%) without the need for degassing of the solvent and an inert atmosphere as is often required with the Suzuki reaction.

Buchwald and Anderson explored the aqueous Suzuki reaction of a range of highly functionalized aryl chlorides and boronic acids.[211] A modified ligand with a water solubilizing sulfonate group was incorporated into the structure. The reaction gave an excellent yield (up to 99%) using 1 mol % of the catalyst.

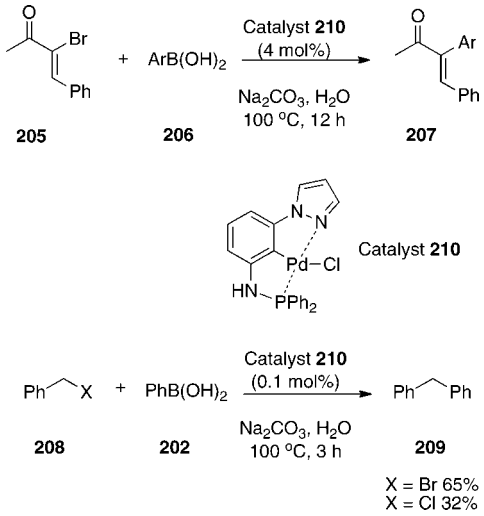
SanMartin and co-workers have examined a number of PCN-type palladium pincer complexes in the Suzuki reaction employing unusual substrates such as benzyl halides, α-haloeneones, and alkyl boronic acids in aqueous solvent (Scheme 61).[212−214]

The reaction of the α-bromoeneones **205** with a range of aryl boronic acids **206** using catalyst **210** and water as the solvent, gave good to moderate yields with arylation at the α-position. The catalyst **210** was further examined in

Scheme 59. Palladium-Catalyzed Heck Reaction of Aryl Iodides and Styrenes Using a Phosphonite Ligand in Aqueous Medium[208]



Scheme 61. PCN-Type Ligands in the Aqueous Suzuki Coupling Reaction[214]



the Suzuki coupling of benzyl halides **208** and phenylboronic acid **202** in water. The reaction gave a moderate yield (65%) with benzylbromide and a poorer yield (32%) with the corresponding benzyl chloride. In addition the catalyst loading could be lowered to 0.1 mol % without any significant effect on the yield. These optimized conditions when applied to the reaction of a range of commercially available benzyl halides and aryl boronic acids, using catalyst **210**, gave moderate to excellent yields (up to 99%). A drawback was observed in reusing catalyst **210** as it gave diminished yields in the subsequent reactions suggesting some decomposition/deactivation under aqueous conditions. SanMartin and co-workers further examined the Suzuki coupling reaction using CNC-type palladium pincer complexes with water as the solvent. The yields for coupling of aryl bromides and aryl boronic acids were excellent (>99%) even when the catalyst loading was reduced to 0.01 mol %.[212]

SanMartin and co-workers further examined the Suzuki coupling reaction of a range of arylboronic acids and aryl bromides using a novel CNC pincer palladium complex in aqueous medium. In most cases the yields were excellent (>99%) with extremely high turnover numbers and turnover frequencies (up to 10^9, catalyst loading down to 10^{-7} mol %). The catalyst could be reused without any loss in catalytic activity.[215]

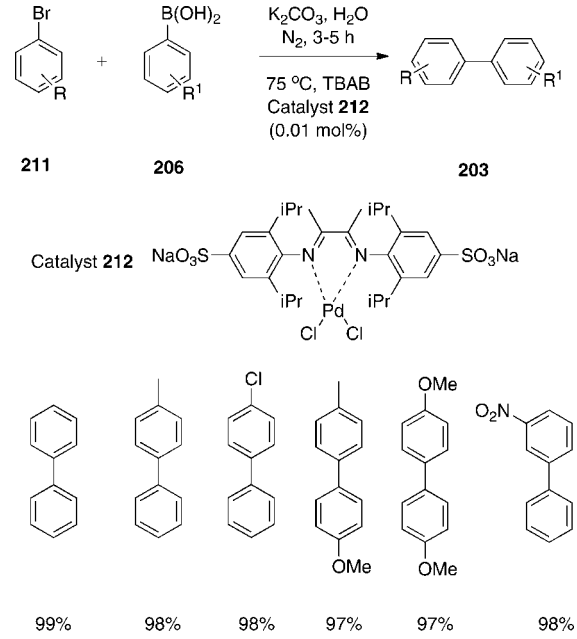
Sun and co-workers explored a series of water-soluble diimine ligands in the Suzuki coupling of aryl boronic acids and aryl bromides in water.[216] The yields were moderate (up to 70%); however, upon addition of tetrabutylammonium bromide (TBAB) the yields were significantly increased (up to 85%). The addition of ethanol as an organic cosolvent shortened the reaction time (Scheme 62).

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%).

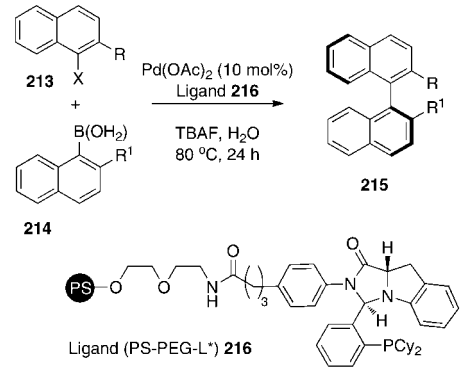
Uozumi and co-workers explored aqueous asymmetric Suzuki coupling using a chiral palladium catalyst supported on an amphiphilic resin. The asymmetric Suzuki coupling has not been extensively studied in the area of asymmetric catalysis and in this case the enantioselectivities were found to be excellent (up to 99% ee) (Scheme 63).[217]

The reaction was found to have good functional group tolerance, and in most cases, the yields were excellent. The

Scheme 62. Suzuki Coupling Reaction of Aryl Bromides and Aryl Boronic Acids with Water-Soluble Diimine Ligands[216]



Scheme 63. Asymmetric Suzuki Coupling Reaction in Aqueous Medium with an Palladium Catalyst Supported on a Amphiphilic Resin[217]



X	R	R^1	Yield (%)	ee (%)
I	Me	Me	95	94 (S)
Br	Me	Me	90	88 (S)
Cl	Me	Me	53	89 (S)
I	OEt	Me	90	92 (R)
I	OMe	OEt	90	92 (S)
Br	P(O)(OEt)$_2$	OMe	70	99 (S)[a]

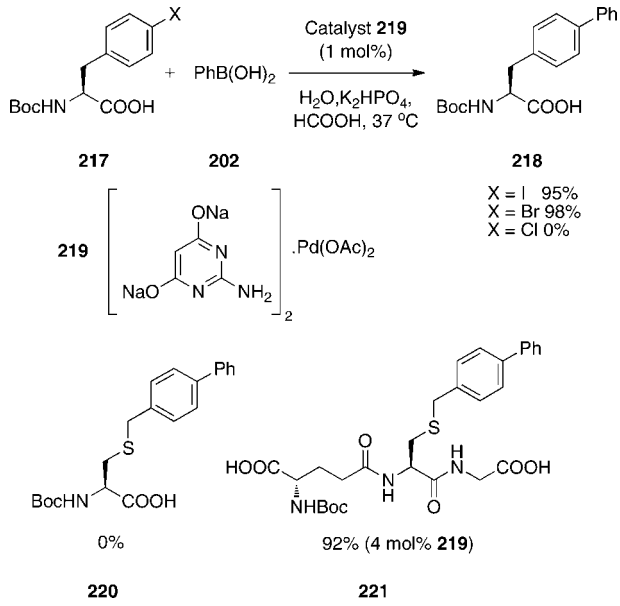
[a] After recrystallization.

catalyst **216** could be recovered and reused up to four times and, on average, gave a yield of 86% with an average stereoselectivity of 88% without any loss in catalytic activity.

Davis and co-workers explored the aqueous Suzuki-Miyaura coupling reaction using a novel palladium dihydroxypyrimidine catalyst.[218] 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 64).

The reaction gave excellent yields in the case of 4-bromo and 4-iodophenylalanine, but no reaction was observed in

Scheme 64. Aqueous Suzuki Coupling Reaction of Modified Amino Acids[218]



the case of 4-chlorophenylalanine. In the case of C-terminal cysteine **220**, no reaction was observed, but when it was incorporated into a peptide chain, a yield of 92% of the coupled product **221** was observed. Davis and co-workers further extended the application of this methodology to the Suzuki coupling of a 4-iodophenylcysteine residue of Substilisin *Bacillus lectus* (SBL) mutant S156C, a serine protease. Using phenyl boronic acid the coupling was complete in 30 min at 37 °C as determined by LCMS, although excess palladium (50 equiv) and boronic acid (500 equiv) was required. A range of boronic acids were explored and in all cases conversions in excess of 95% were observed. No organic solvents were required for these reactions as the borate allows aqueous solubility to an otherwise insoluble substrates.

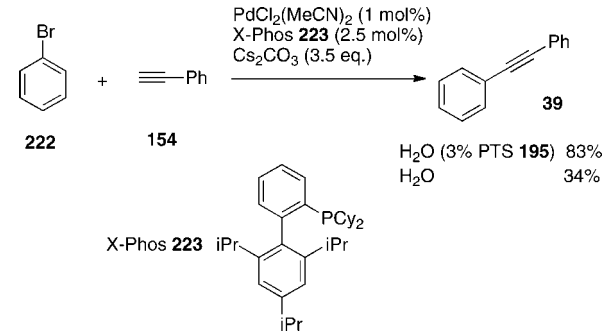
4.1.6. Sonogashira Reaction

The Sonogashira reaction involves the coupling of terminal alkynes with aryl or vinyl halides, and it has found widespread use in organic synthesis.[219] While the Sonogashira reactions under mixed organic/aqueous solvents have been reported, reactions in pure water are quiet rare. Lipshutz and co-workers explored the Sonogashira reaction between lipophilic terminal alkynes and aryl bromides.[220] A small amount of the amphiphile PTS (see section 4.1.4) was added to water, and it was thought that the reaction occurs through nanometer-sized micelles formed in the aqueous medium (Scheme 65).

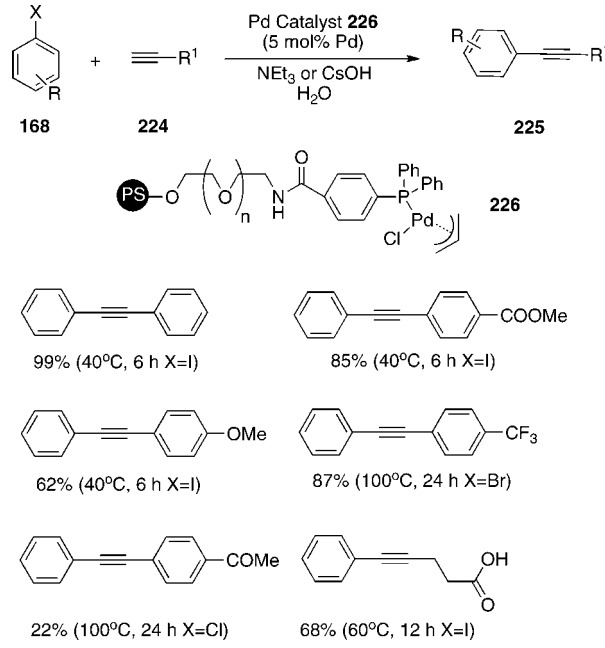
The reaction was explored with a range of functionalized aryl bromides and terminal alkynes, and the yield was found to be good to excellent. However the amphiphile PTS **195** was needed in order to obtain good yields. Without the PTS **195**, the yields were poor (<35%). This methodology was also applied to other substrates such as heterocycles with excellent yields. An advantage is that no copper was needed in the reaction as is found in other Sonogashira reactions in aqueous media.[221]

Costa and co-workers explored the Sonogashira reaction of free and Boc-protected propargylic amines using water as the reaction medium.[222] A combination of $Pd(PPh_3)_4$ and CuI were used in the reaction in an argon atmosphere, and Costa

Scheme 65. Sonogashira Reaction Using the Amphiphile PTS in Water[220]



Scheme 66. Sonogashira Reaction Using Amphiphilic Resin Supported Palladium Complex[223]



proposed that the reaction was an on-water process. In the alkynalation of a range of aryl iodides, the products were formed in moderate to good yield. In cases where more than one iodine was present on the aryl group the Sonogashira reaction occurred at each of the halogen sites in good yields (up to 75%). The substrate scope of this reaction was limited and further exploration is needed for wider applicability.

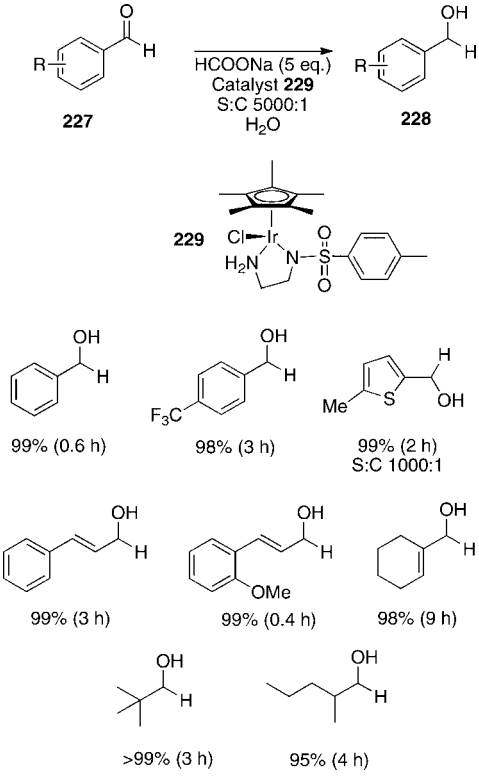
Uozumi and co-workers explored the copper-free Sonogashira reaction in water with an amphiphilic resin-supported palladium complex (Scheme 66).[223] The reactions were explored with a range of aryl halides and terminal alkynes. The yields were found to be good to excellent (up to 99%) for aryl iodides but the aryl chlorides and bromides needed harsher conditions and in general the yields were found to be lower than the corresponding aryl iodides. The catalyst **226** could be recycled up to four times without any significant loss in activity.

There are only a handful of reports on the aqueous Sonogashira reaction, and there is further scope for this reaction to be developed using water as the medium.

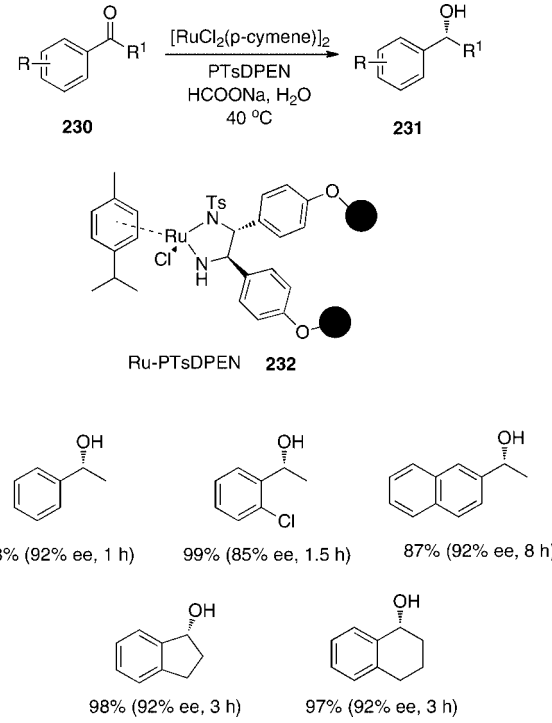
4.1.7. Transfer Hydrogenation

Transfer hydrogenation has emerged as an alternative to hydrogenation using hydrogen gas and provides an excellent method for the reduction of ketones and carbon−carbon

Scheme 67. Aqueous Transfer Hydrogenation Reaction Using Iridium(III) Catalyst[226]



Scheme 68. Aqueous Transfer Hydrogenation Reaction Using PEG-Supported Ruthenium Catalyst[227]



double bonds.[224] The transfer hydrogenation reaction was generally carried out using isopropyl alcohol (IPA), which acts as the hydrogen source and solvent, and it is only in the past decade that water has been considered as a useful solvent for the transfer hydrogenation reaction using formate as the hydrogen source. The emergence of aqueous mediated transfer hydrogenation has been pioneered by a number of groups but most notably by the group of Xiao.[225]

Xiao and co-workers examined the transfer hydrogenation reaction of aryl aldehydes using an iridium(III) catalyst using water as the reaction solvent. The methodology was found to work for aromatic and α,β-unsaturated and aliphatic aldehydes. The reaction could be carried out in air without the need for an inert atmosphere. Interestingly no reaction was found to occur with water-soluble substrates (containing COOH groups) but the corresponding esters were easily reduced. The authors suggest that the reaction was occurring on-water, although other possibilities exist, such as inhibition because of a high concentration effects in-water (Scheme 67).[226]

The Ir-Ts(en) catalyst **229** was found to be highly active for the aqueous mediated transfer hydrogenation reaction of aliphatic and aromatic aldehydes. The catalyst was found to tolerate a wide range of functionality, including nitro groups and halogens, and there was no need for an inert atmosphere.

Xiao and co-workers explored the asymmetric transfer hydrogenation of ketones using a PEG-supported Noyori−Ikariya catalyst **232** using water as the reaction solvent, (Scheme 68).[227]

The substrate scope consisted of aromatic ketones and cyclic ketones indanone and tetralone, and the reaction gave excellent yields (up to 99%) and enantioselectivities (up to 94% ee). A notable feature of the reactions using water is that there was significant rate acceleration in comparison to the HCOOH-NEt_3 azeotrope as solvent, and the reactions can, therefore, be run at a lower temperature. As the catalyst was supported on a PEG support the recovery of the catalyst was possible, and it could be reused up to a further 14 times with a small drop in yield and no difference in enantioselectivity. Xiao further explored the reaction with the catalyst **232** and found pH selectivity and that water is involved in the catalytic cycle where it stabilizes the 16-electron complex as an aqua complex. The water was further found to be involved in the transition state of hydrogen transfer by hydrogen bonding to the ketone oxygen. This has mechanistic implications whereby the transition barrier is lowered, and the hydrogen transfer goes from a concerted to a stepwise mechanism.[226,228]

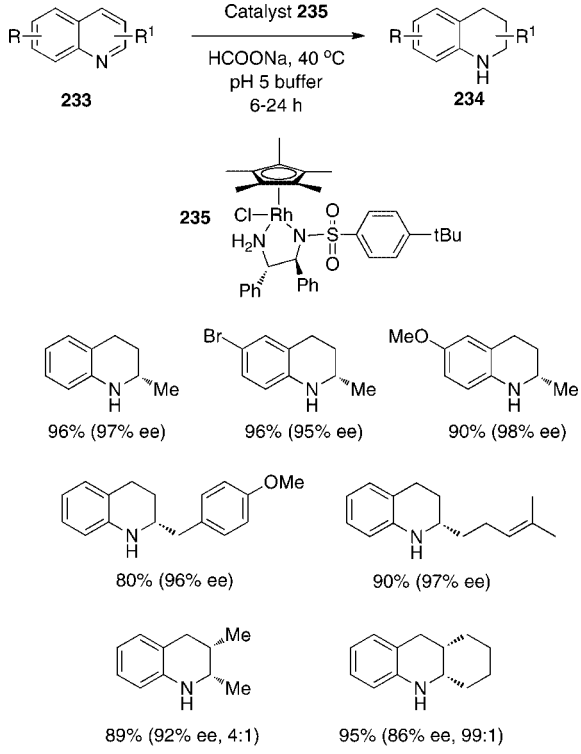
Xiao further applied the aqueous asymmetric transfer hydrogenation to the reduction of quinolines **233** to tetrahydroquinolines **234**.[229] The pH of the reaction proved critical with optimal results at pH 5. This low pH was considered to facilitate an equilibrium protonation of the quinoline **233** and dissociation of the formic acid giving concentration of both species that leads to higher reaction rates. A range of catalysts were screened and the rhodium catalyst **235** was chosen for the asymmetric transfer hydrogenation in aqueous formate buffered at pH 5 (Scheme 69).

A series of quinolines was explored using the rhodium catalyst **235** at pH 5 giving excellent yields and enantioselectivities (up to 97% in both cases). There was no difference to the reaction rate or enantioselectivity under an inert atmosphere. When more sterically demanding groups were introduced in the 2-position of quinoline **233** excellent enantioselectivities were observed. This methodology could be applied to a range of other heterocycles.

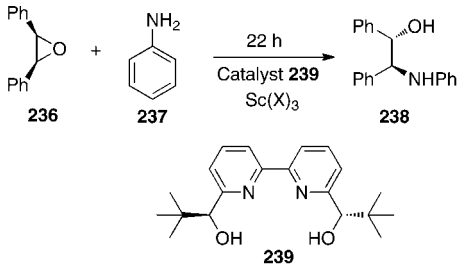
4.1.8. Lewis Acid Catalysis

Lewis acid catalysis has been a major area of research in organic synthesis, and it has found application in a wide array of reaction types. Not surprisingly, this has also become a

Scheme 69. Aqueous Transfer Hydrogenation of Quinolines Using Rhodium Catalysis[229]



Scheme 70. Aqueous-Mediated Ring-Opening of Mesoepoxides Using Amines[232]



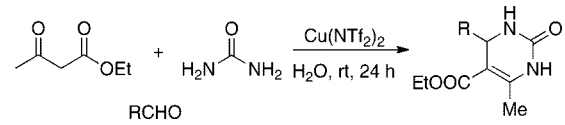
Catalyst	Solvent	$Sc(X)_3$ (mol%)	239 (mol%)	Yield (%)	ee (%)
$Sc(DS)_3$	H_2O	10	20	91	94
$Sc(DS)_3$	H_2O	1	1.2	89	91
$Sc(OTf)_3$	H_2O	1	1.2	15	85
$Sc(OTf)_3$	$CHCl_3$	1	1.2	85	74

major area of research in the application of aqueous mediated Lewis acid catalysis. This area has been pioneered by Kobayashi, who has applied a wide range of water stable Lewis acids to a variety of reaction types.[156−158,230,231]

Kobayashi and co-workers examined the catalytic asymmetric ring-opening of mesoepoxides with aromatic amines using water as solvent.[232] The reaction was explored using a scandium tris(dodecylsulfate) ($Sc(DS)_3$) and a chiral bipyridine ligand **239**. This afforded β-amino alcohols **238** in both high yields and enantioselectivities (Scheme 70).

The ring-opening reaction proceeded cleanly in water and without any diol formation. When the reaction was carried out with 10 mol % of $Sc(DS)_3$ and 20 mol % of the ligand **239**, the yield was excellent (91%) as were the enantioslectivities (94%). When the catalyst loading was lowered, a longer reaction time of 30 h was required. On changing the

Scheme 71. Aqueous Lewis Acid-Catalyzed Biginelli Reaction[234]



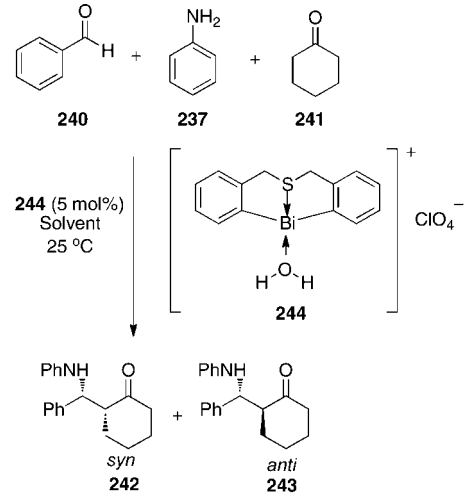
Lewis acid to $Sc(OTf)_3$, both the yields and enantioselectivities were lower in both water and chloroform. However, the $Sc(DS)_3$ was found to be the optimal Lewis acid for the reaction. Application of this system to a broader substrate scope gave excellent enantioselectivities of up to 96% ee. Kobayashi further extended this reaction by applying both zinc(II) and copper(II) surfactant type catalysts to the ring-opening of mesoepoxides in aqueous solvents.[233] The products of the reaction were obtained in moderate to excellent yield (up to 100%) and excellent enantioselectivities (up to 95%). In dichloromethane, the reaction was much slower than in water.

Suzuki and co-workers examined the Lewis acid catalyzed Biginelli reaction using water as the medium.[234] Metal triflamides, such as $Ni(NTf_2)_2$, $Cu(NTf_2)_2$, and $Yb(NTf_2)_2$, catalyzed the multicomponent reaction to afford 3,4-dihydropyrimidine-2-(1H)-ones, (Scheme 71).

A range of aldehydes were explored, and the yields were found to be moderate to excellent (>95%) using the $Cu(NTf_2)_2$. When the Lewis acid was changed to $Ni(NTf_2)_2$ or $Yb(NTf_2)_2$, the yields were much lower.

Xu and co-workers explored the bismuth-catalyzed Mannich reaction using water as the reaction medium.[235] 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 complex **244** was examined in the Mannich reaction, it was found to proceed smoothly and both the *syn*

Scheme 72. Bismuth-Catalyzed Mannich Reaction[235]



Solvent	Time(h)	Yield (%)	*syn* 242: *anti* 243
Hexane	24	33	5:95
CH_2Cl_2	24	52	5:95
MeCN	6	87	5:95
H_2O	2	98	5:95

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 72).

A range of substituted aldehydes **240** and anilines **237** were examined and the yields were found to be as high as 98% with up to 95% anti stereoselectivity. The catalyst showed excellent stability in air and in the aqueous solution.

4.2. Organocatalyzed Reactions

Organocatalysis has emerged as a alternative catalytic method to metal-catalyzed reactions in organic synthesis. Organocatalysed reactions have been around since the late 1960s; however, it has only come into the mainstream since the late 1990s, where researchers, such as Barbas, Hayashi, Jacobsen, Jorgensen, List, and Macmillan, have established this as major area of research.[236−241] Organocatalysis involves a reaction carried out with a substoichiometric amount of an organic compound, which can activate through covalent interactions (e.g., enamine or imine formation) or through hydrogen bonding. Many of the organocatalysts developed are highly stable to air and moisture and some of the earlier developed organocatalytic reactions contained water, as well as an organic cosolvent. Recently, there has been some debate as to whether organocatalytic reactions using water as a solvent are in-water or on-water; however, further study is needed in order to fully deduce the role water plays in these reactions.[17,18] The area of aqueous-mediated organocatalytic reactions has been extensively reviewed.[242,243] The aim of this section will be to examine a range of organocatalytic reactions using water as a medium and suggest where there is further scope for the application of water for other organocatalytic reactions.

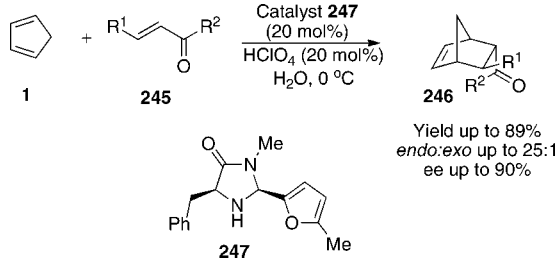
4.2.1. Pericyclic Reactions

Macmillan and Northrup reported one of the first organocatalytic Diels−Alder reactions using water as the solvent following earlier work using water containing organic cosolvents. The reaction of simple dienes, such as cyclopentadiene **1** and α,β-unsaturated ketones **245** using the organocatalyst **247** were carried out in water. Perchloric acid was added to the reaction in catalytic amounts (20 mol %) to further increase the yield and enantioselectivity (Scheme 73).[244,245]

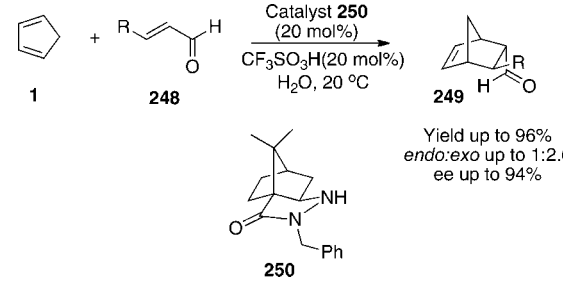
The reaction proceeded with excellent yields (up to 89%) and stereo- and enantioselectivities. Interestingly, the LUMO-lowering catalyst was found to be stable in the aqueous environment, and there was no need for an inert atmosphere.

Ogilive and Lemay examined novel hydrazide organocatalysts in the aqueous Diels−Alder reaction of cyclopentadiene **1** and α,β-unsaturated aldehydes **248**.[246,247] The chiral organocatalyst **250**, derived from camphor, was found to

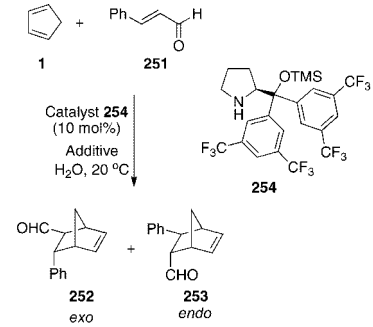
Scheme 73. Organocatalytic Diels−Alder Reaction Using Water as the Solvent[244]



Scheme 74. Aqueous Diels−Alder Reaction Using Camphor-Derived Organocatalyst[246]



Scheme 75. Asymmetric Organocatalytic Diels−Alder Reaction[248]



Solvent	Additive (mol%)	Time (h)	Yield (%)	*exo:endo*	ee (*exo:endo*)
Toluene	CF_3COOH (20)	20	86	84:16	95: 83
H_2O	CF_3COOH (20)	20	54	76:24	58:41
H_2O	$HClO_4$ (10)	4	100	80:20	95:90

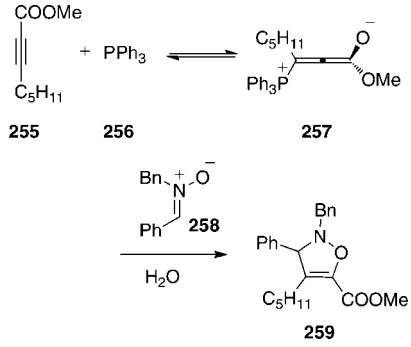
accelerate the reaction by lowering the LUMO of the dipolarophile, a similar effect to the Macmillan organocatalyst (see Scheme 73). However, unlike the Macmillan organocatalyst **247**, the rate of iminium formation was very rapid and the determination of the rate-determining step is still unclear. Relative to organic solvents, the optimal performance was with water as solvent for both the yield and enantioselectivities which were high (>80%). The reaction was found to be biphasic and enantioselectivities were maintained when the optimal reaction concentration was 2 M (Scheme 74).

The reactions were found to proceed in excellent yield (up to 96%) and in excellent enantioselectivity (up to 94%); however, the diastereoselectivity was found to be only moderate at 1:2.6 where the exo isomer was in excess.

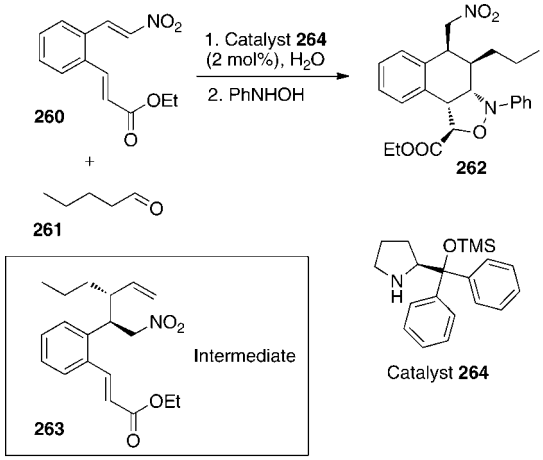
Hayashi and co-workers explored the use of a diarylprolinolsilyl ether organocatalyst **254** in the asymmetric Diels−Alder reaction of cyclopentadiene **1** and α,β-unsaturated aldehydes **251** containing catalytic amounts of acids as additives, using water as the reaction medium (Scheme 75).[248]

The reaction in toluene was found to be complete after 20 h. When the corresponding reaction was examined using water as a solvent, a biphasic system was observed, and the reaction proceeded more slowly and with poorer selectivity. When the additive acid was changed to perchloric acid, the rate of the reaction significantly increased and the reaction was complete within 4 h with excellent yields and enantioselectivity of both exo and endo isomers. The authors propose that the reaction does not go through an on-water process but that further exploration of the reaction would be needed to deduce the exact role water plays.

Scheme 76. Aqueous Huisgen Cycloaddition Reaction of Nitrones and Allenolates[249]



Scheme 77. Aqueous Organocatalytic Tandem Michael/Nitrone Formation/Intramolecular [3 + 2] Cycloaddition Reaction for the Synthesis of Substituted Tetrahydronaphthalenes[251]



Solvent	Additive	Yield (%)	d.r	ee (%)
CH_2Cl_2	AcOH	71	68:32	>99
Hexane	None	35	72:28	>99
H_2O	PhCOOH	67	92:8	>99
H_2O	PhCOOH	73	98:2	>99

Garcia-Tellado and co-workers explored the organocatalytic reaction of nitrones and allenolates using water as medium.[249,250] The reaction was catalyzed with either triphenylphosphine **256** or quinuclidiene organocatalyst. The reaction was found to involve the in situ formation of a β-phosphonium (or ammonium) allenolate **257**, and the subsequent Huisgen [3 + 2] cycloaddition reaction afforded 2,3,4,5-tetrasubstituted-2,3-dihydroisoxazoles **259** (Scheme 76).

The reaction showed excellent substrate scope and the yields were found to be good to excellent (up to 94%). When the corresponding reactions were examined in organic solvents, such as toluene or dichloromethane, no reaction was observed, and hence water was critical for the reaction. The reagents did not need to be water-soluble, and it was proposed that the reaction occurred through an on-water process.

Zhong and co-workers explored a novel one-pot synthesis of tetrahydronaphthalenes **262** using water as the reaction medium.[251] The reaction involved an organocatalytic tandem Michael/nitrone formation/intramolecular [3 + 2] cycloaddition reaction (Scheme 77).

The reaction was found to work in organic solvents, such as dichloromethane and hexane, where the yields and diastereoselectivity were only moderate. When the solvent was changed to water, a significant increase in diastereoselectivity was observed. In all cases (both organic solvents and water), the enantioselectivity was found to be excellent with ee values of >99%. A significant variation of the hydroxyphenyl amine was explored, and moderate to good yields were observed. The authors suggested that the reaction is occurring through a concentrated organic phase. The addition of benzoic acid to the reaction was proposed to induce accelerated formation for the enamine species and promote hydrolysis of the iminium ion in the presence of water.

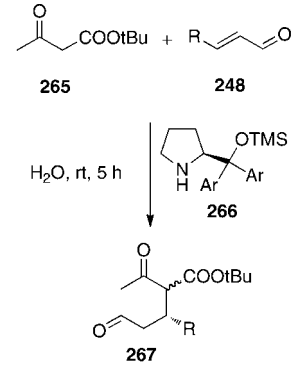
4.2.2. Michael Reaction

The Michael reaction is an important carbon−carbon bond-forming reaction in organic synthesis. A number of organocatalytic Michael reactions using water was a solvent have been reported by a number of groups. Jorgensen and co-workers have explored the aqueous organocatalytic Michael reaction using a TMS-prolinol organocatalyst **266** with the reaction of β-ketoesters **265** to α,β-unsaturated aldehydes **248**.[252] 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 78).

The reaction was explored with a range of different functionalities of the aldehyde **248**, and in general, the yields were found to be excellent (up to 97%) as was the enantioselectivity (up to 96%).

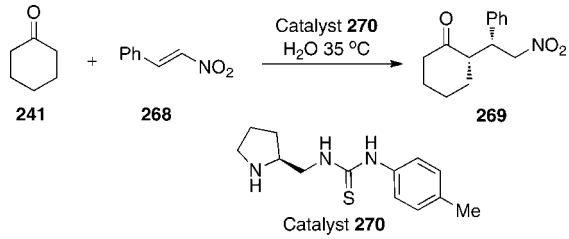
Xiao and co-workers explored a pyrrolidine-thiourea organocatalyst **270** in the Michael addition reaction of ketones, such as cyclohexanone **241**, to nitroolefins **268** using water as the reaction medium. The organocatalyst **270** could be easily tuned to obtain optimum selectivity (Scheme 79).[253] The reaction was found to give high yields and enantioselectivities (>99% ee), and there was significant functional group tolerance on the nitroolefin.

Scheme 78. Aqueous Organocatalytic Asymmetric Michael Reaction[252]

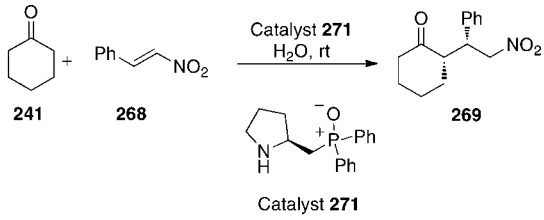


R	Solvent	Yield (%)	ee (%)
Ph	H_2O	97	94
Ph	Neat	90	94
Me	H_2O	82	84

Scheme 79. Aqueous Organocatalytic Michael Addition Using a Pyrrolidine-Thiourea Organocatalyst[253]



Scheme 80. Aqueous-Mediated Organocatalytic Michael Reaction Using a Novel Pyrrolidine-Phosphine Oxide Organocatalyst[254]



Solvent	Time (h)	Yield (%)	dr	ee (%)
CH_2Cl_2	24	67	99:1	99
THF	24	61	98:2	98
Neat	16	99	99:1	>99
H_2O	24	27	>99:1	98
Brine	24	95	>99:1	99

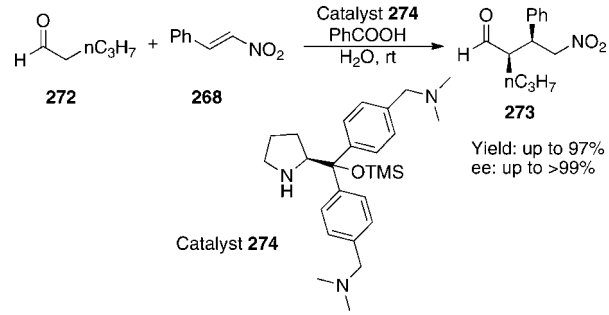
Zhong and co-workers examined an identical reaction to Xiao and explored the use of a novel pyrrolidine-phosphine oxide **271** as organocatalyst in the aqueous Michael reaction of ketones with nitroolefins (Scheme 80).[254]

The reaction was found to give moderate yields in organic solvents, such as dichloromethane and tetrahydrofuran, and the enantioselectivites were excellent (>98%). When the solvent was changed to water, the yield decreased to 27% although the diastereoselectivity and enantioselectivity was comparable to that of the organic solvents. When brine was used instead of water the yield increased to 95%. It is possible that with the reaction in brine the organocatalyst is complexed by metal cations that could contribute to an increase in the reaction yield.

Ni and co-workers examined a diarylprolinolsilyl ether salt **274** as organocatalyst in the aqueous Michael reaction of nitroolefins and alkyl aldehydes. The reaction between *n*-pentanal **272** and *trans*-β-nitrosytrene **268** was explored using organocatalyst **274** that was found to be soluble in water (Scheme 81).[255]

The reaction worked best when 30 mol % of benzoic acid was added, and it afforded the Michael adduct in excellent selectivity (syn:anti 97:3) and enantioselectivity (99%). The catalyst loading could be lowered to 2 mol % without any decrease in enantioselectivity. Interestingly, the aqueous phase of the reaction could be recovered and reused up to six times without any significant decrease in yield or enantioselectivity but any further recycling of the catalyst after this resulted in a decrease in both yield and enantioselectivity.

Scheme 81. Asymmetric Aqueous Michael Reaction of *trans*-β-Nitrosytrene and *n*-Pentanal with Water-Soluble Organocatalyst[255]



4.2.3. Mannich Reaction

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 organocatalytic Mannich reaction using water as solvent. For example Lu and co-workers explored the reaction using a L-threonine derived organocatalyst **277** (Scheme 82).[256]

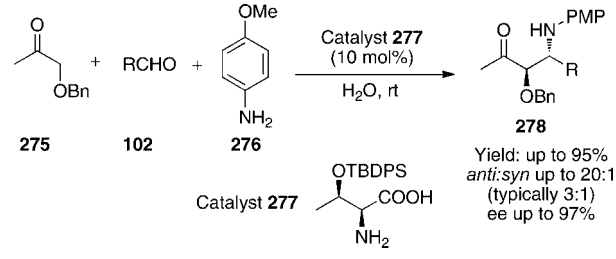
The reaction of benzylhydroxyacetone **275** with p-anisidine **276** and a range of aromatic aldehydes **102** gave yields of up to 95%. The anti/syn selectivity was moderate (typically 3:1), although selectivities up to 20:1 were observed.

Hayashi and co-workers explored a siloxyproline tetrazole **281** organocatalyzed Mannich reaction using water as the reaction solvent.[257] The three-component Mannich reaction of dimethoxyacetaldehyde **279**, *p*-anisidine **276**, and cyclohexanone **241** was carried out in water with catalyst **281**. The reaction was carried out, where the anisidine **276** and aqueous aldehyde **279** were premixed and stirred for 0.5 h in the presence of the catalyst **281** and an oily material separated from the water. When 2 equiv of the ketone **241** was added, the reaction was found to proceed through a biphasic system and afforded the product **280** (Scheme 83).

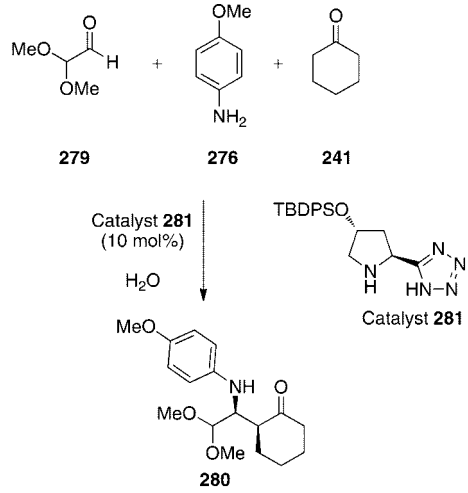
The yields were up to 95% with ee values up to 97%. When excess water was used, the high yields and enantioselectivites were still apparent although the reaction was slowed. When Hayashi explored the Mannich reaction with the imine already preformed before introduction of the catalyst **281**, it gave yields of only <5%. The presence of a preformed imine was not detrimental to the reaction when the sodium salt of catalyst **281** (i.e., **285**) was used in the reaction (Scheme 84).

Thus, the use of the sodium salt of the proline organocatalyst **285** in the reaction of imine **282** and ketone **283** gave excellent yields (up to 88%) and enantioselectivity (up to 97%). The reaction work up was simple. The crude reaction mixture could be placed onto a column of silica gel and the products eluted.

Scheme 82. Aqueous Mannich Reaction Using Threonine-Derived Organocatalyst[256]



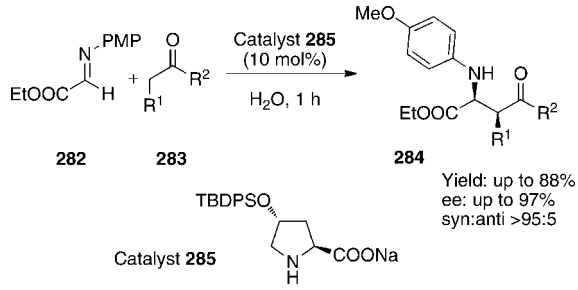
Scheme 83. Aqueous Organocatalytic Mannich Reaction[257]



Solvent	Temp (^{0}C)	Time (h)	Yield (%)	*syn:anti*	ee (%)
H_2O	20	16	95	4.4:1	93
H_2O	0	48	61	6.1:1	96
H_2O[a]	0	70	95	4.2:1	93

[a] reaction performed with 100 eq. water (typical reaction 18 eq.).

Scheme 84. Aqueous Mannich Reaction using Proline Organocatalyst[257]

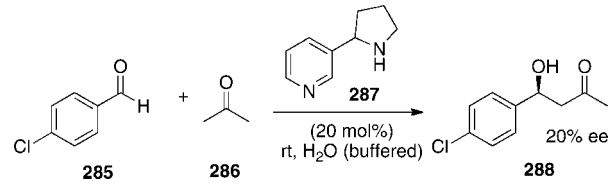


4.2.4. Aldol Reaction

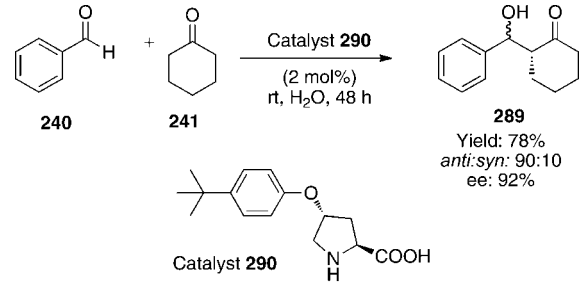
The aldol reaction is a classical reaction in organic chemistry and is a highly useful method for carbon−carbon bond formation. A wide range of small molecule organocatalysts have been explored in the aqueous aldol reaction, but much of the focus has been on catalyst development and not so much on the role water plays in the reaction.[38,258−263] Some of the earliest work in this area was pioneered independently by both Barbas and Hayashi, who explored the organocatalyzed Aldol reaction in aqueous media. A wide range of proline-type organocatalysts were examined, and in both cases, high yields and enantioselectivities were observed.[259,264]

Janda and co-workers were one of the first to explore the role water plays in the aqueous organocatalytic aldol reaction. The nornicotine **287** organocatalyzed reaction of *p*-chlorobenzaldehyde **285** and acetone **286** was explored, and Janda proposed that water plays a dual role where initially hydrogen bonded water activates the aldehyde **285** for nucleophilic attack by transferring a proton. Another molecule of water then initiates the hydrolysis of the intermediate imine resulting in the product **288** along with catalyst regeneration. This in effect increases the rate of the reaction although the enantioselectivity of the reaction was only

Scheme 85. Nornicotine-Catalyzed Aqueous Aldol Reaction[265,266]



Scheme 86. Organocatalytic Aldol Reaction in Aqueous Solvent[268]



H_2O (mol%)	Yield (%)	*anti:syn*	ee (%)
0	85	69:31	61
100	84	90:10	91
200	84	90:10	94
300	83	89:11	93

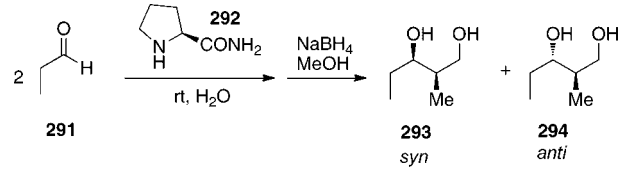
20%.[265,266] When the corresponding reaction was examined in organic solvents, no reaction was observed. The proposed mechanism was further supported by a computational study (Scheme 85).[267]

Armstrong and co-workers explored the asymmetric organocatalytic aldol reaction of cyclohexanone **241** and substituted benzaldehydes **240** using water as the reaction solvent.[268] A range of proline type organocatalysts were examined in the reaction and the *tert*-butylphenyl proline catalyst **290** was found to give the best enantioselectivity of all the catalysts screened (Scheme 86).

The authors suggested that association of the catalyst **290** with the hydrophobic reactants formed tiny "oil droplets", which were required to carry out the reaction on-water, so the bulk water was excluded from the reaction transition state. In an exploration of the addition of water to a stoichiometric aldol reaction of aldehyde **240** and cyclohexanone **241** a significant enhancement was observed with only 100 mol % addition of water. The addition of a sulfonated-β-cyclodextrin was examined, and this showed increased enantioselectivity (up to 99% ee) because of the complexation of the organocatalyst **290** and the cyclodextrin.

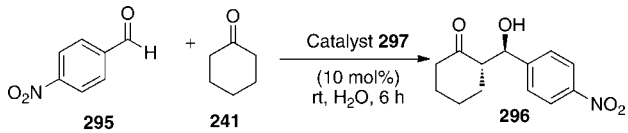
Hayashi explored the self-aldol condensation of propanal **291** using a wide range of amino acids and modified amino acids with water as the reaction medium.[269] Of the nineteen amino acids screened the proline analogue Pro-NH_2 **292** was found to be the best giving a moderate yield and good enantioselectivity (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. The reaction was examined by C-13 NMR and it was found that in the first 2.5 h of the reaction the propanal is completely dissolved in D_2O and exists as a hydrated and nonhydrated mixture in the ratio of 1:1. When the reaction was explored with different concentrations of water, there was no signifi-

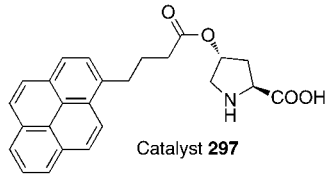
Scheme 87. Organocatalytic Aldol Reaction of Propanal Using Water as the Reaction Medium[269]



Solvent	Conc. H_2O	Yield (%)	*syn:anti*	ee (*syn*)	ee (*anti*)
None	-	0	-	-	-
H_2O	1 eq.	29	1.1:1	66	69
H_2O	20 eq.	23	1.3:1	74	78
H_2O	50 eq.	48	1:1	67	67

Scheme 88. Organocatalytic Aldol Reaction of Cyclohexanone and *p*-Nitrobenzaldehyde under Aqueous Conditions[270]





Solvent	Conversion (%)	*anti:syn*	ee (%)
Toluene	47	69:31	96
$CHCl_3$	66	69:31	94
H_2O	99	95:5	98
H_2O (μL)[a]	Conversion (%)	*anti:syn*	ee (%)
9	30	90:10	96
90	>99	97:3	99
175	>99	99:1	>99

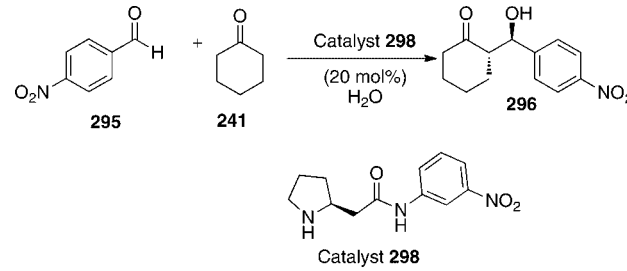
[a] Cyclohexanone (260 μL, 2.5 mmol), aldehyde (75.5 mg, 0.5 mmol), catalyst **297** (2 mol%), 24 h at room temperature.

cant change in yield or enantioselectivity. No reaction occurred when neat propanal was treated with catalyst **292**. This suggests that water plays a significant role in the reaction mechanism (Scheme 87).

Gruttadauria and co-workers explored the organocatalysed asymmetric aldol reaction of cyclohexanone **241** and substituted aldehydes **295** using water with the substituted proline organocatalyst **297**. High yields (up to 99%) and enantioselectivities (>99%) were achieved using a 2 mol % loading of the catalyst **297** (Scheme 88).[270]

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%). Interestingly, as was observed with other organocatalytic reactions using water as the solvent, the amount of water present was important for the reaction for both conversion and enantioselectivity. The optimum result was found where a volume of 90 μL or greater gave much superior results in comparison to smaller amounts of water.

Scheme 89. Aqueous Organocatalytic Aldol Reaction at Different pH[271]



pH	Yield (%)	*anti:syn*	*ee* (anti)
6.4	92	68:32	71
5.7	92	84:16	89
4.5	92	92:8	96
3.5	91	95:5	93
1.4	88	96:4	92
1.5	76	94:6	93

Chimni and co-workers have observed that the organocatalyzed reaction of cyclohexanone **241** and *p*-nitrobenzaldehyde **295** has an optimal reaction pH between 4−5 in aqueous solution.[271] 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 89). This study shows that the pH of the reaction in important for the optimum yield and enantioselectivity of organocatalytic reactions.

In the last ten years, the area of organocatalysis has emerged as a major area of research, and there has been a significant range of different reaction types explored using water as the reaction medium. While there have been some mechanistic investigations as to the role water plays in these reactions, further in-depth investigations need to be carried out to fully understand the exact role of the water in these reactions.

5. Conclusion

In conclusion what we can draw from this review is as follows: (i) When organic and industrial chemists seek to chose a solvent for synthesis, water should be high or at the top of the list. (ii) If the reactants are insoluble in water, it does not matter as long as one is a liquid. (iii) If all of the reactants are sparingly soluble solids (as defined), one must be liquefied. (iv) Trans-phase H-bonding is the key factor in the "on-water" effect; it should become obvious when more reactions involving competing H-bonding rate accelerations and inhibitions have been explored. (v) Understanding of the interplay between cooperating and conflicting effects for all of the factors governing in vitro organic chemistry in the water medium is still very much in the early stages and further research is needed to fully understand the role water plays.

6. Supporting Information Available

The solubility of all compounds (mol/L) in section 2 are included in the Supporting Information. This information is available free of charge via the Internet at http://pubs.acs.org/.

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