

Organic chemistry in water

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Water has emerged as a versatile solvent for organic chemistry in recent years. Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivity. The types of organic reactions in water are broad including pericyclic reactions, reactions of carbanion equivalent, reactions of carbocation equivalent, reactions of radicals and carbenes, transition-metal catalysis, oxidations-reductions, which we discuss in this tutorial review. Aqueous organic reactions have broad applications such as synthesis of biological compounds from carbohydrates and chemical modification of biomolecules.

1. Introduction

Life, the most complex form of organic compounds on Earth, requires the construction of chemical bonds in an aqueous environment. Following nature's lead, we should think of water as a versatile solvent for organic chemistry. Since it was reported that Diels–Alder reactions could be greatly accelerated by using water as a solvent instead of organic solvents,¹ there has been considerable attention directed toward the development of organic reactions in water. Besides Diels–Alder reactions, other examples cover almost all of the most useful organic reactions, even reactions involving water-sensitive compounds.² It is obvious that water is the most inexpensive and environmentally benign solvent. In many cases, due to hydrophobic effects, using water as a solvent not only accelerates reaction rates but also enhances reaction selectivities, even when the reactants are sparingly soluble or insoluble in this medium. Furthermore, the low solubility of

oxygen gas in water, an important property in the early development of life in an anaerobic environment, can facilitate air-sensitive transition-metal catalysis in open air. The use of water as a solvent also implies the elimination of tedious protection–deprotection processes for certain acidic-hydrogen-containing functional groups, which contributes to the overall synthetic efficiency. Water soluble compounds such as carbohydrates, can be used directly without the need for laborious derivatization and water-soluble catalysts can be re-used after separation from water-insoluble organic products. Aqueous organic chemistry is also essential for the emerging field of chemical biology which uses chemical tools to study biological systems. Although aqueous organic chemistry has broad applications and a bright future, current organic chemistry textbooks do not touch on this subject. In order to compensate for this omission in organic chemistry textbooks, this introductory review will provide non-specialists with some insight into this field.

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2. Pericyclic reactions

Pericyclic reactions are important processes in organic synthesis for constructing cyclic structures and for controlling



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catalysis in air and water, Alkyne–Aldehyde–Amine coupling (A^3 -coupling), Asymmetric Alkyne–Aldehyde–Amine coupling (AA^3 -coupling), and Cross-Dehydrogenative–Coupling (CDC) reactions.



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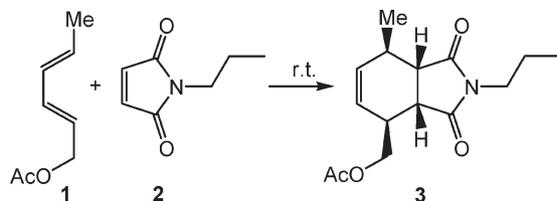
bonds. Currently, he is a postdoctoral fellow with Professor Yandulov at Stanford University, focusing on catalytic fluorinations.

stereochemistry. Since Breslow's discovery that Diels–Alder reactions proceed faster (as high as 700-fold) and have a higher *endo:exo* selectivity in water than in organic solvents, extensive experimental and theoretical studies have been carried out on this topic. The small size and high polarity of a water molecule, as well as a three-dimensional hydrogen bonded network system of bulk water, provide some unique properties which include a large cohesive energy density, a high surface tension, and a hydrophobic effect. These unique properties are believed to be responsible for the rate and selectivity enhancements of pericyclic reactions and the “on-water” effect. The hydrogen bonding between water and organic molecules is also believed to play an important role in the rate accelerations of some organic reactions in water.

It is worth mentioning that, in many cases, both water-soluble and water-insoluble reactants can be accelerated in water and, sometimes, larger rate increases are found with water-insoluble substrates (denoted by Sharpless and co-workers as the “on-water effect”).³ For instance, the Diels–Alder reaction (Scheme 1) of the water-insoluble *trans, trans*-2,4-hexadienyl acetate (**1**) and *N*-propylmaleimide (**2**) showed substantial rate acceleration in aqueous suspension over homogeneous solution. The reaction rate is faster in a protic solvent such as methanol than in nonprotic solvents such as acetonitrile and toluene.³ It suggests that hydrogen bonding and hydrophobic effects may both be important for the observed rate acceleration.

Claisen rearrangements, which have negative volume changes of activation as compared to the Diels–Alder reactions, are also accelerated in water. The rearrangement of naphthyl ether (**4**) to **5** in aqueous suspension is completed within five days at room temperature, whereas it is much slower in organic solvents (Scheme 2). The neat reaction is also slower than the aqueous reaction.³

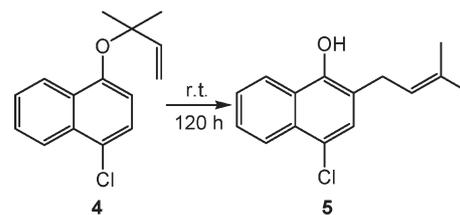
Beside Diels–Alder cycloadditions and Claisen rearrangements, other pericyclic reactions also show rate enhancements in water. For instance, $2\sigma + 2\sigma + 2\pi$ cycloaddition (Scheme 3)



Solvent	Concentration[M]	Time to completion	Yield (%)
toluene	1	144 h	79
CH ₃ CN	1	>144 h	43
MeOH	1	48 h	82
neat	3.7 ^a	10 h	82
H₂O	3.7 ^a	8 h	81

a. Calculated from the measured density of 1:1 mixture of **1** and **2**.

Scheme 1 Rate acceleration of Diels–Alder reactions by water solvent. (Reprinted with permission from ref. 3. Copyright 2005, Wiley-VCH.)



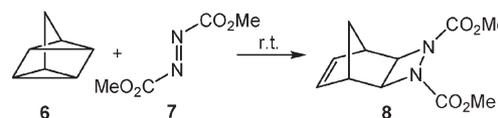
Solvent	Yield (%)
toluene	16
CH ₃ CN	27
MeOH	56
DMF	21
neat	73
H₂O	100

Scheme 2 Rate acceleration of Claisen rearrangements by water solvent. (Reprinted with permission from ref. 3. Copyright 2005, Wiley-VCH.)

of quadricyclane (**6**) with azodicarboxylates (**7**) at room temperature occurs much faster by using water as a solvent than organic solvents.³ The unusual reactivity described here is possibly due to the greater impact of the hydrophobic effect on the ground state than the transition state.

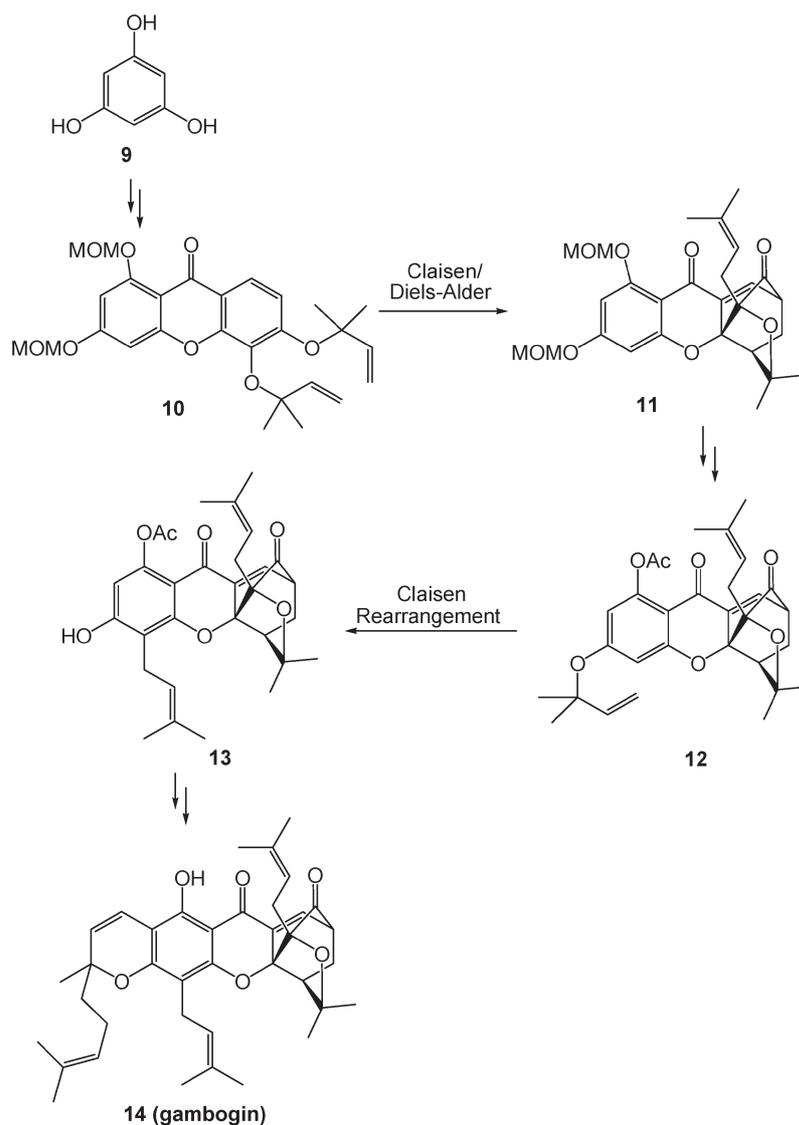
The rate accelerations of pericyclic reactions in aqueous solution have been applied to the total synthesis of a variety of biologically active compounds. Total synthesis of gambogin (**14**), a biologically active compound against the HeLa and HEL cell lines, includes two key steps of a Claisen rearrangement and a Claisen/Diels–Alder cascade reaction (Scheme 4). The Claisen/Diels–Alder cascade reaction from **10** to **11** showed dramatic rate accelerations in aqueous solutions (Table 1). The great rate enhancement of Claisen rearrangement from **12** to **13** is also observed in aqueous solutions (Table 2).⁴

Various experiments indicate that the hydrogen-bonding contributes, to a certain degree, to the rate enhancements of pericyclic reactions in water as well as the hydrophobic effect.⁵ For example, the rate of the cycloaddition reactions of



Solvent	Concentration[M]	Time to completion
toluene	2	>120 h
EtOAc	2	>120 h
CH ₃ CN	2	84 h
CH ₂ Cl ₂	2	72 h
dimethyl sulfoxide	2	36 h
MeOH	2	18 h
neat	4.5	48 h
D ₂ O	4.5	45 min
C ₆ F ₁₄	4.5	36 h
H₂O	4.5	10 min

Scheme 3 Rate acceleration of $2\sigma + 2\sigma + 2\pi$ cycloadditions by water solvent. (Reprinted with permission from ref. 3. Copyright 2005, Wiley-VCH.)



Scheme 4 Solvent effects for total synthesis of gambogin. (Reprinted with permission from ref. 4. Copyright 2005, Wiley-VCH.)

pyridazinium-dicyanomethanide 1,3-dipole (**15**) with the dipolarophile ethyl vinyl ketone (**16**) is enhanced by gradually increasing the mole fraction of water in the organic solvents (from 0 to 1) of acetonitrile, acetone, methanol, ethanol, and *tert*-butyl alcohol at 37 °C (Scheme 5). In each case, exponential rate enhancements are triggered as the mole fraction of water surpasses *ca.* 0.9. When methanol replaces water, no triggering effect is observed. These results suggest

that hydrogen-bonding and hydrophobic effects dominate the rate enhancements. The theoretical calculation of the transition state structure strongly supports this conclusion.⁵

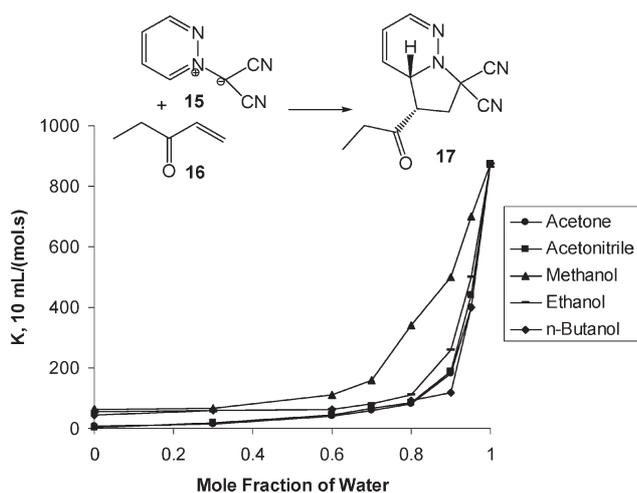
Beside the rate enhancement, the enhancement of *endo/exo* selectivity of aqueous reactions is observed not only in non-catalyzed Diels–Alder reactions but also in Lewis acid catalyzed-reactions. For instance, compared to organic solvents, the enantioselectivity of copper-catalyzed Diels–Alder reaction of

Table 1 Rate acceleration of the Claisen/Diels–Alder cascade reaction from **10** to **11** by aqueous solutions

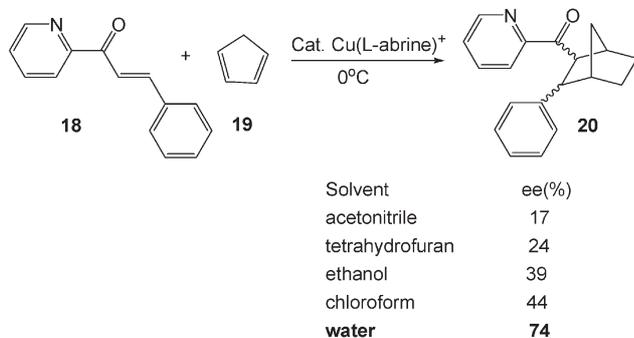
Solvent	<i>T</i> /°C	<i>t</i> /h	Conversion [%]
MeOH	65	4	0
Trifluoroethanol	65	4	0
EtOH	65	4	0
MeOH/H ₂ O (1 : 1)	65	4	100
TFE/H ₂ O (1 : 1)	65	4	100
EtOH/H ₂ O (1 : 1)	65	4	100

Table 2 Rate acceleration of the Claisen rearrangement from **12** to **13** by aqueous solutions

Solvent	<i>T</i> /°C	<i>t</i> /h	Conversion [%]
MeOH	50	4.5	50
Trifluoroethanol (TFE)	25	4	0
EtOH	25	4	0
MeOH/H ₂ O (1 : 1)	50	2.5	100
TFE/H ₂ O (1 : 1)	25	75	100
EtOH/H ₂ O (1 : 1)	25	72	100



Scheme 5 Triggering effect for the introduction of water to organic solvents in cycloaddition reactions.



Scheme 6 The enhancement of selectivity for Diels–Alder reaction by water.

3-phenyl-1-(2-pyridyl)-2-propen-1-one (**18**) with cyclopentadiene (**19**) is greatly enhanced by the use of water as the solvent (Scheme 6).⁶

In agreement with experiments, density functional theory studies show that the computed *endo* preference is enhanced to 2.4 kcal mol⁻¹ in an aqueous solution. The *endolexo* selectivity partly arises from hydrogen bonding, and partly from the bulk-phase effects, which includes enforced hydrophobic interactions and anti-hydrophobic co-solvent effects.⁷

3. Reactions of carbanion equivalent

The metal-mediated carbanion based reaction is one of the most important methods used to form carbon–carbon bonds. Traditionally, many metal-mediated carbanion based reactions involving organomagnesium and organolithium reagents are often very hard to handle because these reactions require strict exclusion of moisture and oxygen and often require low temperature (*e.g.* -78 °C) conditions. Recently, they have been modified to work successfully in water by using metals such as indium, tin and zinc as the metal mediators for reactions of carbonyl compounds and imines with allyl halides.⁴²

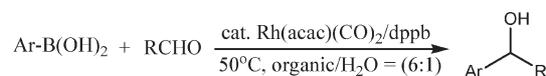
Miyaura reported a rhodium-catalyzed addition of aryl or alkenylboronic acids to α,β -unsaturated carbonyl compounds

(Scheme 7)⁸ and 1,2-addition to aldehydes in aqueous organic mixtures.⁹ Related asymmetric conjugate additions have been (most noticeably) reported by Hayashi and co-workers.¹⁰

The Rh(I) [Rh(COD)₂Cl or Rh(COD)₂BF₄]-catalyzed Grignard-type phenylation of carbonyl compounds from trimethylphenylstannane with aldehydes **21** occurs smoothly in water and under an atmosphere of air.¹¹ When methyl groups of organotin compounds are replaced by halogens, the reaction requires the addition of a base, which will generate PhSn(OH)_nX_{3-n} species *in situ* and enhance its reactivity (Scheme 8A).¹² Barbier–Grignard type carbonyl alkylation can be carried out in water as well. In the presence of Zn/CuI and a catalytic amount of InCl, the Barbier–Grignard type reaction of various aldehydes **24** with alkyl iodides **25** yields the desired alcohol products **26** in water (Scheme 8B).¹³ It is important to note that the aldehyde bearing hydroxyl group does not have to be protected prior to the reaction in water.

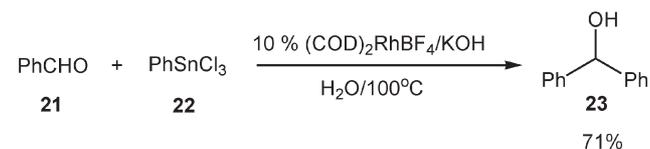
Although metal-mediated Barbier-type allylation reactions are highly regio- and stereoselective, α -adduct products are seldom to be obtained (Scheme 9A). With water as a solvent, regioselective allylation (α -adduct *versus* γ -adduct) becomes possible. In the presence of 2 mL of water solvent, reaction of 1 mmol of aldehyde **27** with 1.2 mmol allyl bromide (**28**) gives 100% of γ -adduct **29** in high yield; while in the presence of 6 equiv. of water solvent, 99% of α -adduct **30** is obtained (Scheme 9B).¹⁴ Here, water is not only a good solvent for the allylation reaction, but also is necessary for the formation of an oxonium ion intermediate which furnishes α -adduct products. Too much water solvent is believed to completely suppress the formation of the oxonium intermediate.

Conjugate addition of unsaturated carbonyl compounds with arylmetallic reagents also proceeds well in water. In the presence of a Rh(I) catalyst, the reaction of phenyl tin chloride **32** with conjugated enone **31** successfully gives the desired

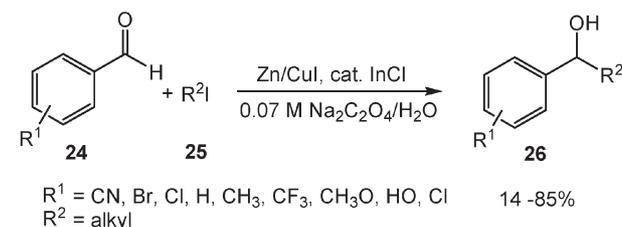


Scheme 7 Addition of boronic acid derivative to aldehydes in aqueous conditions.

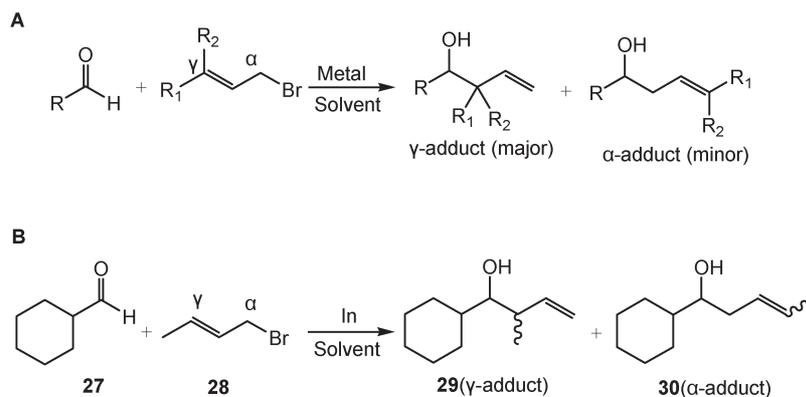
A. Phenylation in Water



B. Alkylation in Water



Scheme 8 Barbier–Grignard type reaction in water.



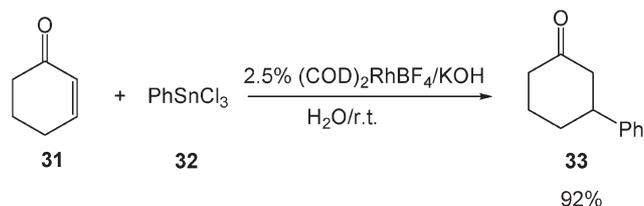
entry	solvent	amount (equiv)	time (h)	yield % (α : γ)
1	DMF	6	72	65 (0:100)
2	THF	6	72	20 (0:100)
3	CH ₂ Cl ₂	6	24	none
4	CH ₃ CH ₂ OH	6	72	97 (0:100)
5	neat		24	none
6	H ₂ O	2 mL	72	90 (0:100)
7	H ₂ O	6	24	85 (99:1)
8	H ₂ O	6	72	87 (86:14)

Scheme 9 Water-induced selective allylation. (Reprinted with permission from ref. 14. Copyright 2003, American Chemical Society.)

addition product **33** in high yield in water under basic conditions (Scheme 10).¹²

4. Reactions of carbocation equivalent

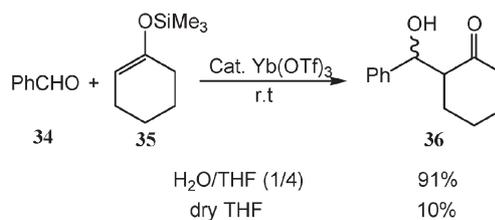
In organic reactions, carbocations are often initiated by the coordination/reaction of protonic and Lewis acids. A variety of Lewis and protonic acids-catalyzed reactions of carbocation equivalent have been developed and many have been applied in industry. However, these reactions generally are moisture sensitive and even a small amount of water stops the reactions because most acids react with water instead of the substrates. Recently, various kinds of protonic and various Lewis acids have been found to retain catalytic activities in aqueous media. Particularly, many of them are not only compatible with water, but also activated by water. Rare earth metal salts such as Sc(OTf)₃ and Yb(OTf)₃ can be used for aqueous organic reactions. For example, Yb(OTf)₃ is found to be highly effective for catalyzing the Mukaiyama aldol reaction of benzaldehyde (**34**) with silyl enol ether **35** in aqueous solution which is much less effective in dry organic solvents



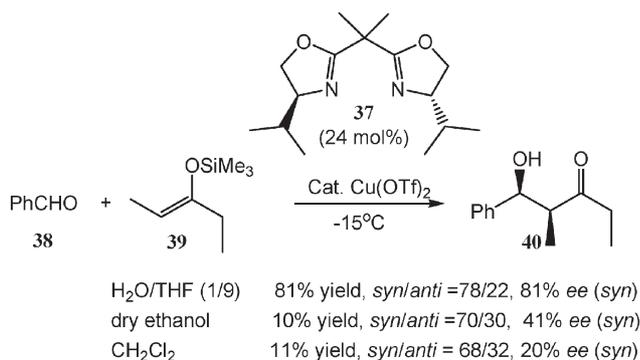
Scheme 10 Conjugate addition of unsaturated carbonyl compounds with arylmetallic reagents in water.

(Scheme 11).¹⁵ The enhancement of the reaction rate by water is very likely due to the change of the acid catalyst's structure and activity caused by water, or to the regeneration of the active catalyst from the corresponding intermediate which is faster in water than in dry organic solvents.

Most catalytic asymmetric reactions of carbocation are conducted at low reaction temperatures (*e.g.*, -78 °C) in aprotic anhydrous solvents such as dry toluene, dichloromethane, and propionitrile. Recently, Cu(II) together with a chiral ligand has been found to be effective for asymmetric aldol reactions in an aqueous solution. In the presence of a catalytic amount of Cu(OTf)₂ and bis(oxazoline) ligand **37**, the reaction of benzaldehyde (**38**) with silyl enol ether **39** furnishes the desired aldol product **40** in a high yield with good enantioselectivity (Scheme 12). In contrast, dry organic solvents such as dry ethanol and dry dichloromethane, give much lower yields and selectivities.¹⁵ The possible reason for the higher enantioselectivity in water is that water rapidly hydrolyzes the silyl cation equivalent, which is generated during the aldol reactions and is responsible for the decrease of



Scheme 11 The enhancement of the reaction rate for Mukaiyama aldol reaction by water.

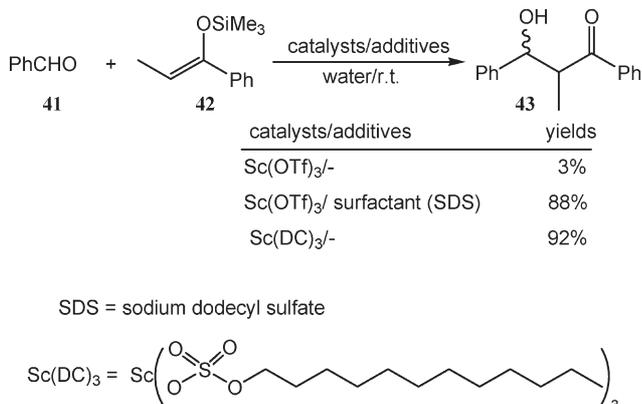


Scheme 12 Lewis acid-catalyzed asymmetric reaction in aqueous solution.

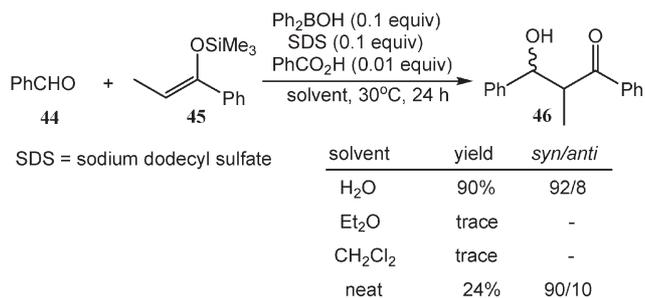
enantioselectivity by catalyzing aldol reactions to give racemic products.

One of the major drawbacks of using water as a solvent is the low solubility of most organic substrates in water. It could be overcome by the use of surfactants, which solubilize organic substances in water. While the reaction of benzaldehyde (**41**) with silyl enol ether **42** gives almost no desired aldol product **43** in the presence of a catalytic amount of Sc(OTf)₃ in water, a high yield of the corresponding aldol adduct is obtained when the reaction is carried out in the presence of a catalytic amount of Sc(OTf)₃ and sodium dodecyl sulfate (SDS, a surfactant) in water (Scheme 13).¹⁵ Recently, a new type of catalyst, “Lewis acid-surfactant combined catalyst (LASC)” has been developed. It acts both as a Lewis acid to catalyze the reaction and as a surfactant to solubilize organic substrates in water. Scandium tris(dodecyl sulfate) (Sc(DS)₃) is a good example because it is very effective for catalyzing the reaction of benzaldehyde (**41**) with silyl enol ether **42** in water (Scheme 13).¹⁵

Boron compounds have also been developed as catalysts for the reaction of carbocation equivalents in water. In the presence of a catalytic amount of a boron source, SDS and benzoic acid, the reaction of benzaldehyde (**44**) with silyl enol ether (**45**) gives a highly diastereoselective aldol adduct (**46**) in water at ambient temperature (Scheme 14).¹⁶ In contrast, traditional boron aldol reactions are performed at a lower temperature and need strictly anhydrous conditions. It is



Scheme 13 LASC-catalyzed organic reaction in water.



Scheme 14 Boron compound-catalyzed organic reactions in water. (Reprinted with permission from ref. 16. Copyright 2001, Wiley-VCH.)

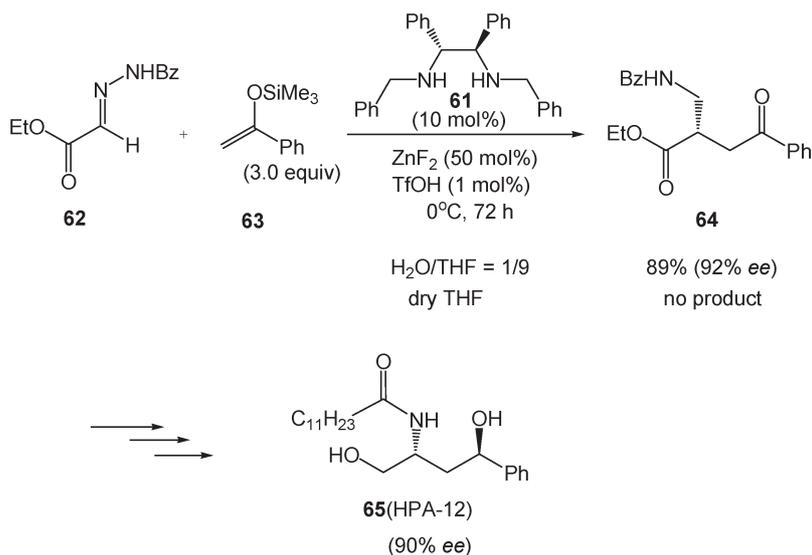
important to note that the use of water as a solvent is essential in this reaction. Almost no corresponding products are obtained in organic solvents, such as ethyl ether and dichloromethane, and a very low yield of product is obtained under the neat condition (Scheme 14).

Dehydration is a very common reaction in organic chemistry. It is difficult to carry out in water because water molecules generated during the reaction must be removed to shift equilibrium toward the side of the dehydrated product. With a surfactant-type acid catalyst, dehydration has been successfully developed in water. Emulsion droplets are formed in water in the presence of a surfactant-type catalyst and organic substrates. The emulsion droplets have a hydrophobic interior which would concentrate acid catalysts onto the surface of droplets and enhance the reaction rate toward the side of the dehydrated product. On the other hand, water molecules generated during the reaction are removed from droplets due to the hydrophobic nature of their interior, which shift the equilibrium toward the desired side (Scheme 15).

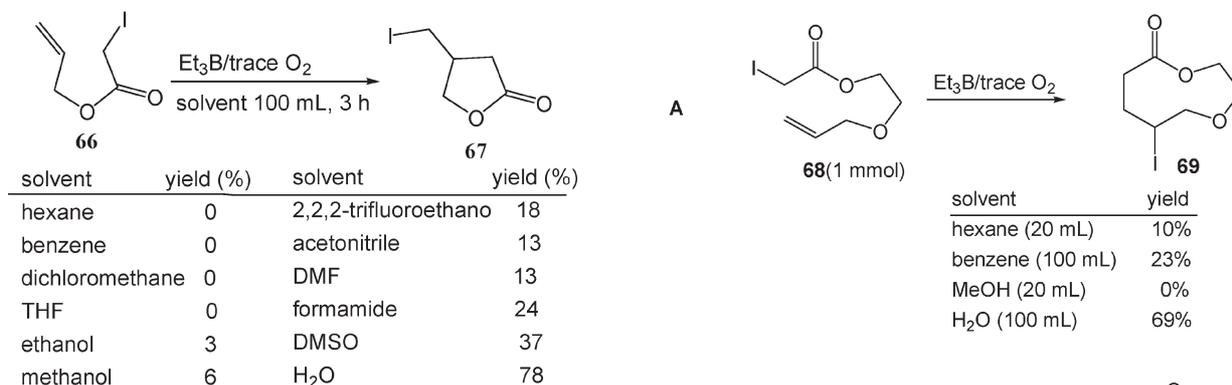
A representative example of dehydration in water is protonic acid-catalyzed dehydrative esterification. Dodecylbenzenesulfonic acid (DBSA), which acts as a protonic acid-surfactant-combined catalyst (BASC), is very effective for catalyzing esterification of acids with alcohols in water (Scheme 16A).¹⁷ Beside the esterification, etherification (Scheme 16B) and thioetherification (Scheme 16C) also proceed smoothly in water by the catalyst DBSA.

Dithioacetals are very useful in organic synthesis as powerful protective groups for carbonyl compounds. The DBSA-catalyzed system is also applicable to dithioacetalization in water which yields dithioacetal products (Scheme 17). The reaction proceeds very well not only for ketones but also for aldehydes.¹⁷

The use of water as a solvent is the key to obtaining high yield and selectivity for the asymmetric Mannich-type reaction. With the combination of catalyst ZnF₂ and a chiral diamine **61**, the reaction of hydrazono ester **62** and silyl enol ether **63** gives the corresponding product (*R*)-**64** in a high yield with a high enantioselectivity in an aqueous solution. However, in dry organic solvents, such as tetrahydrofuran, no product is obtained in this reaction. This asymmetric reaction can be used for a four-step enantioselective synthesis of HPA-12 (**65**), the first compound of a specific inhibitor for sphingomyelin synthesis in mammalian cells (Scheme 18).¹⁸



Scheme 18 Asymmetric Mannich-type reaction in water and its application for total synthesis of HPA-12.



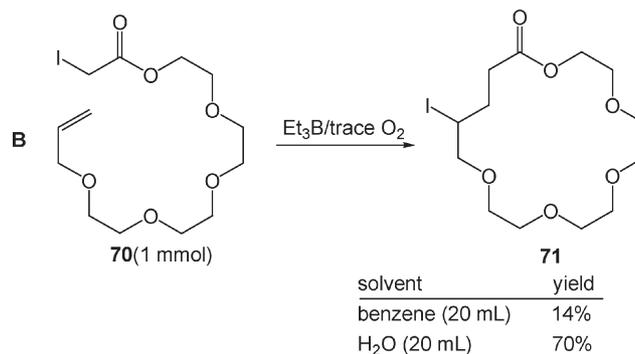
Scheme 19 Atom-transfer radical cyclization in water. (Reprinted with permission from ref. 19. Copyright 2000, American Chemical Society.)

transfer of the heat from polymerization. Compared to organic solvents, the high polarity of water distinguishes remarkably the miscibility of many monomers from polymers. Today, aqueous free-radical polymerization is applied in industries.²¹

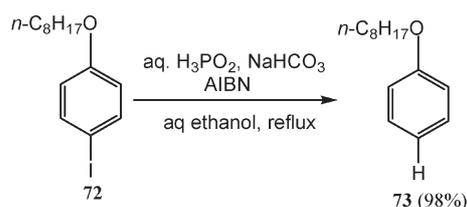
Reactions of carbenes take place in water too. An example is that water-soluble ruthenium alkylidenes **76** bearing cationically functionalized phosphine ligands are stable and initiate olefin metathesis reactions in water. In the presence of **76**, monomer **77** is quantitatively polymerized in aqueous environments (Scheme 23).²²

6. Transition-metal catalysis

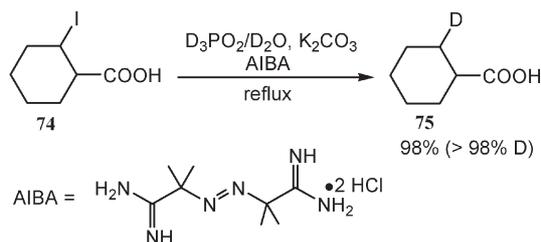
The use of late transition metals for catalyzing reactions is of growing importance in modern organic chemistry.²³ Conventionally, organometallic chemistry and transition-metal catalysis are carried out under an inert gas atmosphere and the exclusion of moisture has been essential.²⁴ The reason could be that water as a ligand often occupies metals' coordination sites. On the other hand, metal-carbon bonds are easily attacked by water either *via* proton transfer



Scheme 20 Medium- and large-ring formation by radical cyclization in water. (Reprinted with permission from ref. 19. Copyright 2000, American Chemical Society.)



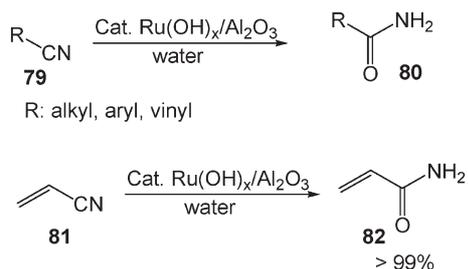
Scheme 21 Simple radical reduction in water.



Scheme 22 Isotope labelling *via* an aqueous radical reaction.

(electrophilic reaction) or *via* the oxygen (nucleophilic reaction). However, recent studies have shown that in water such catalyses are both facilitated and can be operated in open air.²⁵

Hydration of nitriles **79** to generate the corresponding amides **80** has wide application, such as as intermediates for organic synthesis and as raw materials for plastics, detergents and lubricants *etc.* Hydration of nitriles traditionally is carried out with acids or bases such as H_2SO_4 and NaOH . However, many functional groups such as carbon–carbon double bonds cannot survive this process. In addition, hydrolysis of amide products usually occurs to produce carboxylic acid by-products, especially in acidic conditions. Carefully controlled conditions with one equivalent of water with respect to starting material nitriles are necessary for the traditional hydration of nitriles to amides. However, with the easily prepared, inexpensive, and supported ruthenium hydroxide catalyst $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$, the hydration of various nitriles gives quantitatively the corresponding amide products in water.²⁶ Various functional groups such as carbon–carbon double bonds tolerate this hydration process. For example, the hydration of acrylonitrile (**81**), which is important for industry, provides acrylamide (**82**) quantitatively (Scheme 24). No side reactions, such as hydration of carbon–carbon double bonds and polymerization of acrylonitriles, occur. The water solvent also provides a way to recycle the transition metal catalyst. The $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ catalyst is easily separated from the reaction mixture by filtration. After separation of the catalyst, the catalyst can be reused at least twice with no considerable loss of activity.

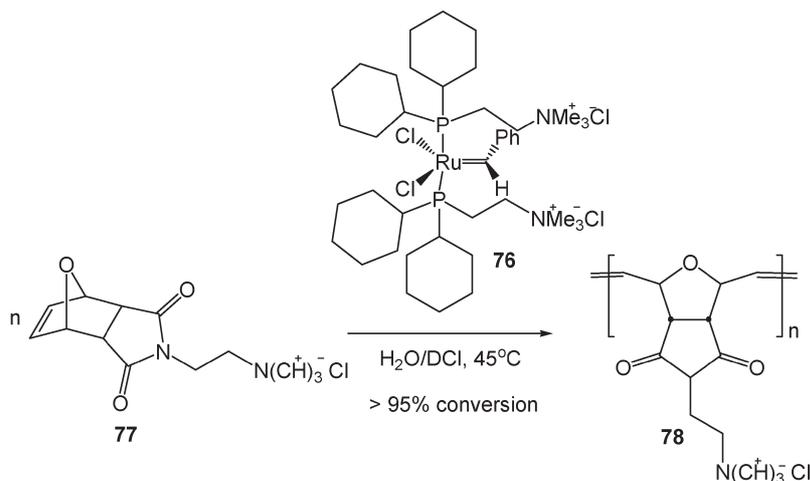


Scheme 24 Ru-catalyzed hydration of nitriles to amides in water.

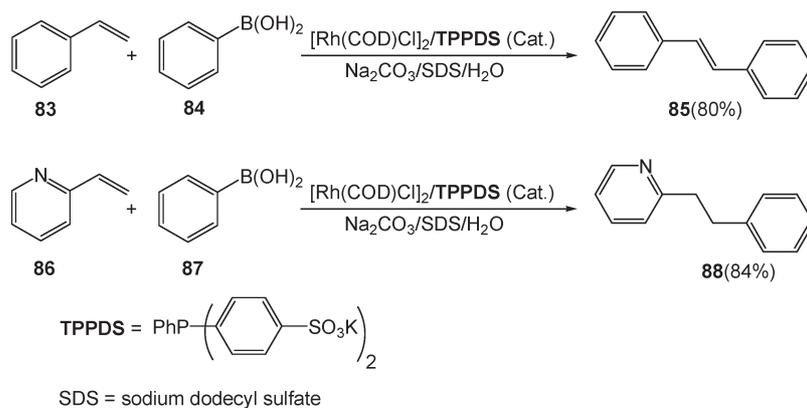
Rhodium-catalyzed addition of arylboronic acids to activated olefins (*i.e.* olefins with electron-withdrawing groups) has been significantly studied. However, a common requirement of this process is the activation of olefins with electron-withdrawing groups. The reaction substrates are expanded from activated olefins to general un-activated ones by switching organic solvents to water. With a combination of rhodium catalyst and water-soluble phosphine ligand TPPDS, a variety of un-activated styrenyl olefins **83** are reacted with arylboronic acids **84** in water to produce “Heck-type” products **85**, while the reaction of vinyl heteroaromatic compounds **86** with arylboronic acids **87** gives addition–hydrolysis products **88** (Scheme 25).²⁷ Notably, in each case, either no reaction or only sluggish reaction is observed in organic solvents with water-soluble sulfonated ligands or with triphenylphosphines.

Palladium catalyzed C–N bond formation can be carried out in water too. With a combination of a phosphine ligand **89** and a palladium catalyst, un-reactive aryl chlorides **90** are reacted with amines **91** in water smoothly to afford the corresponding amination products **92** (Scheme 26).²⁸

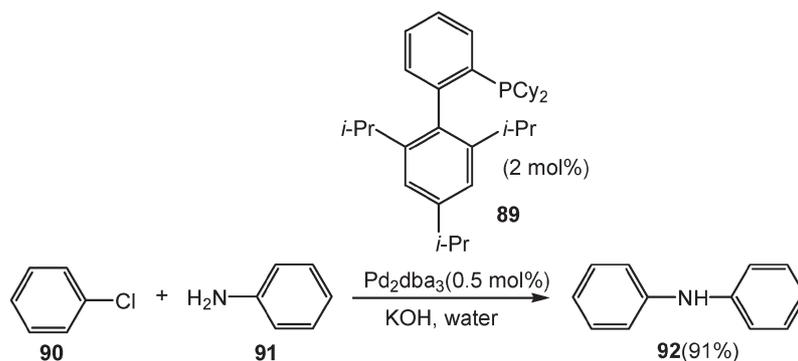
Compared to other late transition metals, gold has not been extensively explored as a catalyst. However, recent studies show gold has unique catalytic properties in several organic reactions. Gold-catalyzed organic reactions can be carried out in water too. A representative example is that the gold-catalyzed three-component reaction of aldehydes **93**, amines **94** and terminal alkynes **95** efficiently affords propargyl amine



Scheme 23 Ruthenium carbene-catalyzed aqueous polymerization. (Reprinted with permission from ref. 22. Copyright 2000, American Chemical Society.)



Scheme 25 Rh-catalyzed reaction of un-activated olefins with arylboronic acids in water.



Scheme 26 Pd-catalyzed C–N bond formations in water.

products **96** in water (Scheme 27).²⁹ Transition metal-catalyzed asymmetric organic reactions are also possible with the use of water as a solvent. With Cu(I) as a catalyst and chiral pybox (**100**) as a ligand, the addition of terminal alkynes **97** to imines **98** in water at room temperature affords the corresponding propargyl amine products **99** with a good yield and enantioselectivity (Scheme 27).³⁰

7. Oxidations–reductions

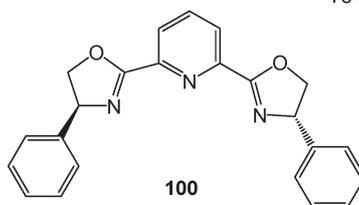
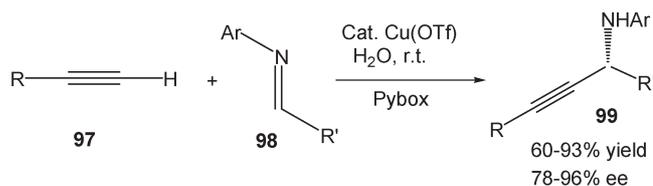
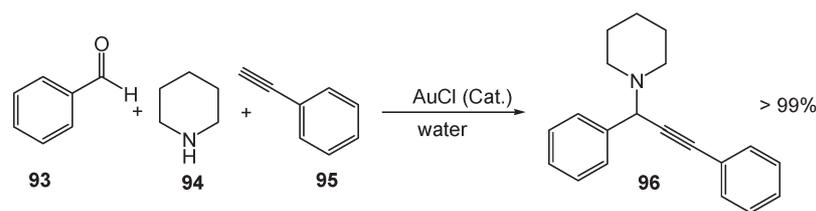
Oxidation reactions have often been conducted using stoichiometric amounts of heavy metal reagents (*e.g.* potassium permanganate, V_2O_5) or moisture-sensitive oxidants (*e.g.* oxalyl chloride, *N,N'*-dicyclohexylcarbodiimide (DCC)). Recently, new oxidative reactions have been developed in aqueous media by water-compatible oxidants, such as O_2 and H_2O_2 .

Using clean, safe, and inexpensive molecular oxygen as a sole oxidant, a variety of 2-naphthols and substituted phenols can be converted to the corresponding biaryl compounds by ruthenium catalyst $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ in moderate to excellent yields in water. Thus, in the presence of 5 mol% of $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ and 1 atm O_2 , the oxidative coupling of 2-naphthol (**101**) in water quantitatively produces 1,1'-binaphthalene-2,2'-diol (BINOL) (**102**), which is a very important building block and ligand. It is important to note, $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ catalyst can be reused without the loss of any catalytic activity even after the seventh recycling run (Scheme 28).³¹

Catalytic oxidation of alcohols can be achieved in water by molecular oxygen by using a novel amphiphilic resin-dispersion of palladium nanoparticles (ARP-Pd). In the presence of the nano-palladium catalyst, primary alcohols give the corresponding aldehydes products, and secondary alcohols give the corresponding ketones in water (Scheme 29). ARP-Pd can be reused with negligible loss of catalytic activity after several runs.³²

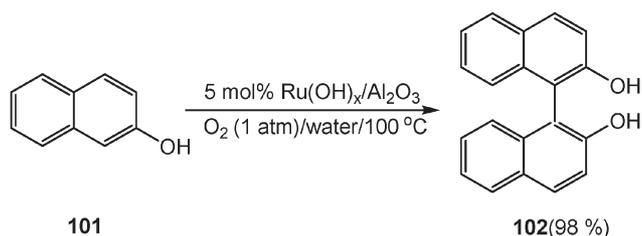
Aqueous oxidative polymerization provides a convenient way for product separation. Using molecular oxygen as an oxidant and $\text{K}_3[\text{Fe}(\text{CN})_6]$ as a catalyst, the oxidative polymerization of 2,6-dimethylphenol (DMP) **111** in aqueous NaOH solution gives poly(2,6-dimethyl-1,4-phenyleneoxide) (PPO) **112**, an important plastic in engineering (Scheme 30).³³ The DMP monomer is dissolved in aqueous NaOH solution, while the PPO polymer product is insoluble in it. The precipitated product is separated from the reaction mixture by simple distillation after the reaction and the aqueous solution can be reused for the polymerization.

Hydrogen peroxide, another water-compatible oxidant, is also often used in aqueous oxidative reactions. In the presence of polyoxometalate, $\text{Na}_{12}[\text{WZnZn}_2(\text{H}_2\text{O})_2(\text{ZnW}_9\text{O}_{34})_2]$, which is easily prepared in one step in water from simple salts, various alcohols are converted into the corresponding aldehyde or ketone products in water by hydrogen peroxide. The *in situ* prepared catalyst polyoxometalate could be recycled in water.³⁴



tridentate bis(oxazolonyl)pyridines (pybox)

Scheme 27 Gold- and copper-catalyzed reactions in water.

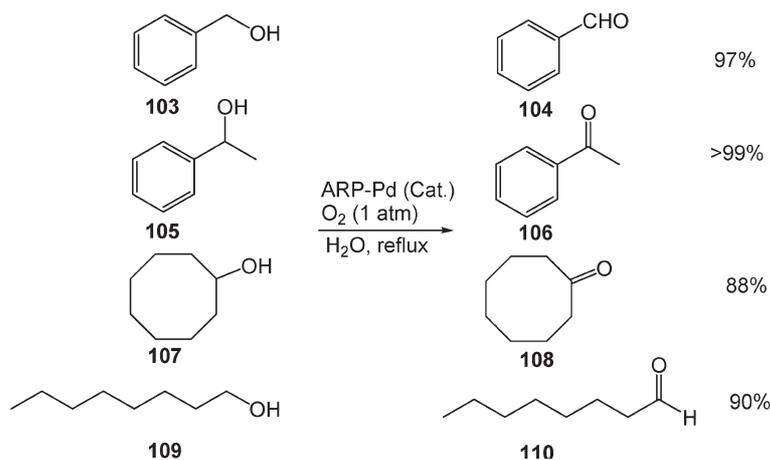


Scheme 28 Oxidative coupling of 2-naphthol in water.

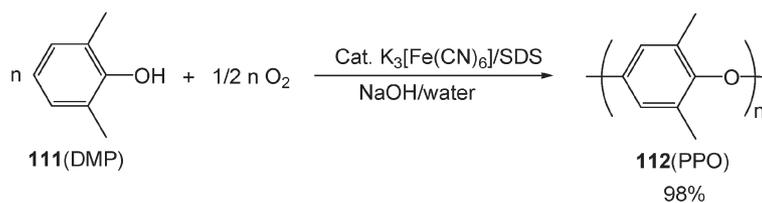
Water is rarely used as the solvent in a reduction reaction because most reducing agents are incompatible in water. However, water-compatible sodium/lithium borohydride is frequently used in water to reduce ketones or aldehydes.

When lithium borohydride (LiBH_4) is modified to the more hydrophobic reducing agent lithium pentafluorophenyl borohydride ($\text{LiC}_6\text{F}_5\text{BH}_3$), a hydrophobically directed selective reduction of ketones is observed in water. As an example, quaternized, β -keto diamines (**113**) are reduced by $\text{LiC}_6\text{F}_5\text{BH}_3$ to **114** almost exclusively in water. In contrast, the use of methanol as a solvent gives equal amounts of products **114** and **115** (Scheme 31).³⁵

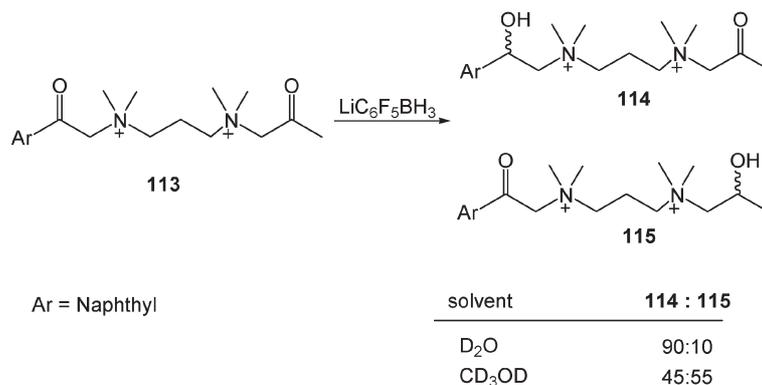
A new water-soluble ruthenium complex of β -cyclodextrin-modified amino alcohols **116** serves as a supramolecular catalyst in the selective reduction of ketones. In the presence of NaCOOH , this Ru-base catalyst reduces conjugated (**117**) and non-activated unconjugated ketones (**118**) to the corresponding alcohols with good yields and enantioselectivities in water (Scheme 32).³⁶



Scheme 29 Catalytic oxidative reaction of alcohols in water.



Scheme 30 Polymerization of DMP in water.



Scheme 31 Hydrophobically directed selective reduction of ketones. (Reprinted with permission from ref. 35. Copyright 2003, American Chemical Society.)

8. Synthetic applications

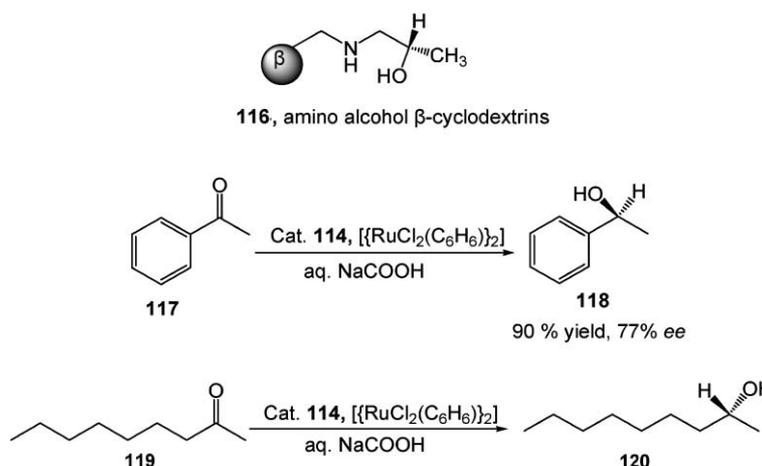
Because of its unique properties, aqueous organic chemistry has found wide applications in organic synthesis, life science and chemical biology.

8.1. Carbohydrate chemistry

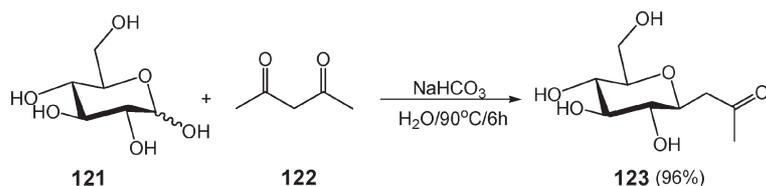
One of the most important advantages of aqueous organic reactions in organic synthesis is that water-soluble hydroxyl-containing molecules can be used directly without the need of tedious protection–deprotection processes. Thus, the most important application for carrying out organic reactions in water is carbohydrate chemistry where the protection–deprotection processes are involved most extensively. C-Glycosides have wide applications used as a variety of

building blocks for total synthesis of natural products and as potential enzyme inhibitors. Traditionally, C-Glycosidic ketones are prepared from a protected sugar by addition of a suitable nucleophile in anhydrous conditions. A new protocol using water as a solvent eliminates tedious protection–deprotection processes, and thus it greatly increases the overall yields. With commercially available D-glucose (**121**) and pentane-2,4-dione (**122**) as starting substrates, β-C-glycosidic ketone **123** is obtained in one step with almost a quantitative yield in aqueous NaHCO₃ solution (Scheme 33). In a sharp contrast, in organic solvents the β-C-glycosidic ketone **123** is prepared from benzylated D-glucose, a protected sugar, in seven steps in an overall low yield.³⁷

Polyhydroxylated N-heterocycles, or azasugars, which show broad biological activities, are among the most attractive



Scheme 32 Enantioselective reduction of ketones in water.



Scheme 33 One-step synthesis of β -C-glycosidic ketone in water.

synthetic targets. The most commonly employed methods for the synthesis of azasugars have involved starting from commercially available carbohydrates because their structures are similar to those of sugars. However, their asymmetric synthesis usually requires lengthy procedures and produces low yields. With the use of water as a solvent for all the steps, an extremely efficient asymmetric synthesis of a pyrrolidine azasugar has been developed in only four steps, without any protection–deprotection process, and in 60% overall yield. At first, a modified Sharpless asymmetric dihydroxylation of achiral and cheap 1,6-dibromodiene **124** gives the chiral bis-electrophilic diol **125** in a good yield and enantioselectivity (70% yield, 97% ee). Notably, it has unique and useful reactivity in water (Scheme 34) because of the instability of **124** and **125** in organic solvents. The following selective hydrolysis of **125** affords triol **126** in 98% yield. Then, with dinuclear peroxotungstate $K_2[W_2O_3(O_2)_4(H_2O)_2]$ as a catalyst and H_2O_2 as an oxidant, a novel water-compatible epoxidation of **126** affords the desired epoxy alcohol **127** in 99% yield (92% ds). Finally, following the nucleophilic displacement of the bromide by ammonia, an intramolecular ring opening of the epoxide gives azasugar **128** in 88% yield. The overall yield of **128** is thus 60%.³⁸

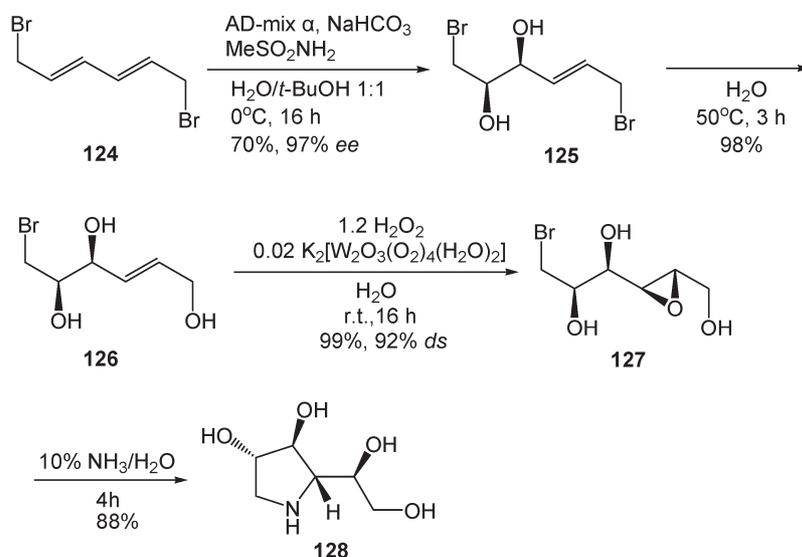
8.2. Chemical modification of biomolecules

Aqueous organic chemistry is essential for the emerging field of chemical biology, which uses chemical tools to study biology. Since life constructs chemical bonds in aqueous

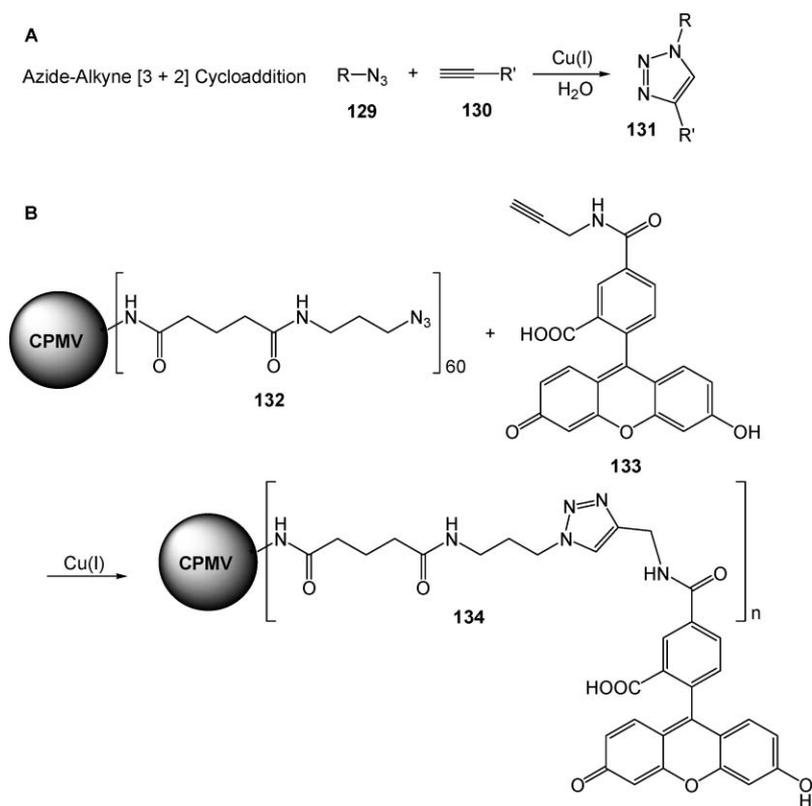
environments, selective chemical reactions designed to modify biomolecules are now recognized as powerful tools in chemical biology. They provide insight into cellular processes and inspire new strategies for protein engineering. To achieve this goal, the participating functional groups must have a narrow distribution of reactivity and must be inert toward biological molecules. In addition, the selective chemical reactions must occur at room temperature and in aqueous physiological environments.

Azides and alkynes are highly energetic functional groups and nearly inert to biomolecules. The Huisgen cycloaddition of azides **129** and alkynes **130** is irreversible and thermodynamically more favorable by approximately 30–35 kcal mol⁻¹. However, the reaction requires elevated temperature. A copper(I)-catalyzed version, recently developed by Sharpless and co-workers, occurs readily at physiological temperatures and in aqueous solutions (Scheme 35A). This reaction enables the selective modification of various biological molecules such as virus particles, nucleic acids, and proteins. An example is the cowpea mosaic virus (CPMV) which has 60 identical copies of a two-protein unit around a single-stranded RNA genome. In the presence of Cu(I) catalyst, the virus CPMV (**132**), decorated with azides, is efficiently coupled with the dye-alkyne **133** (Scheme 35B).³⁹

The modified Staudinger reaction is another chemoselective reaction designed to modify biomolecules. The Staudinger reaction occurs between phosphines and azides to produce azalides. In the presence of water, the phosphines and azides



Scheme 34 Total synthesis of azasugar in water. (Reprinted with permission from ref. 38. Copyright 2005, The Royal Society of Chemistry.)



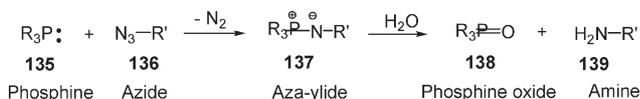
Scheme 35 Chemical modification of CPMV by azide-alkyne [3 + 2] cycloaddition.

react efficiently at room temperature to produce amines and phosphine oxides (Scheme 36A). Both phosphines and azides are nearly inert to biological molecules. Therefore, the classical

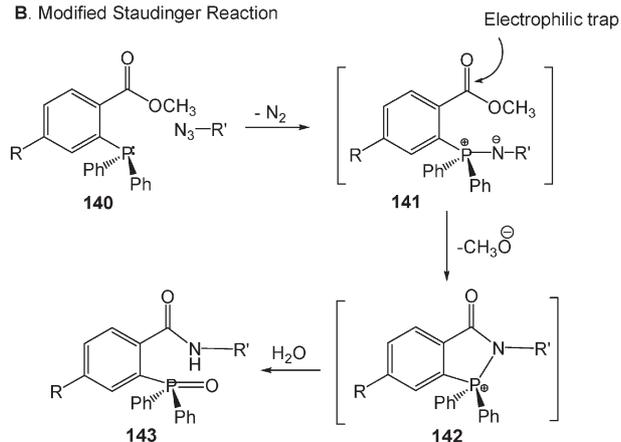
Staudinger reaction is a good candidate for the chemical modification of bio-molecules.

However, the aza-ylides are not stable in water which limits their application for constructing a new and useful covalent bond under physiological conditions. Using an electrophilic trap, Bertozzi and co-workers developed an aqueous Staudinger reaction that would ultimately produce a stable amide bond (Scheme 36B). With this modified Staudinger reaction, the water-soluble biotinylated phosphine **145** couples with azides installed within cell surfaces to produce stable cell-surface adducts **146** (Scheme 37).⁴⁰

A. Classical Staudinger Reaction



B. Modified Staudinger Reaction



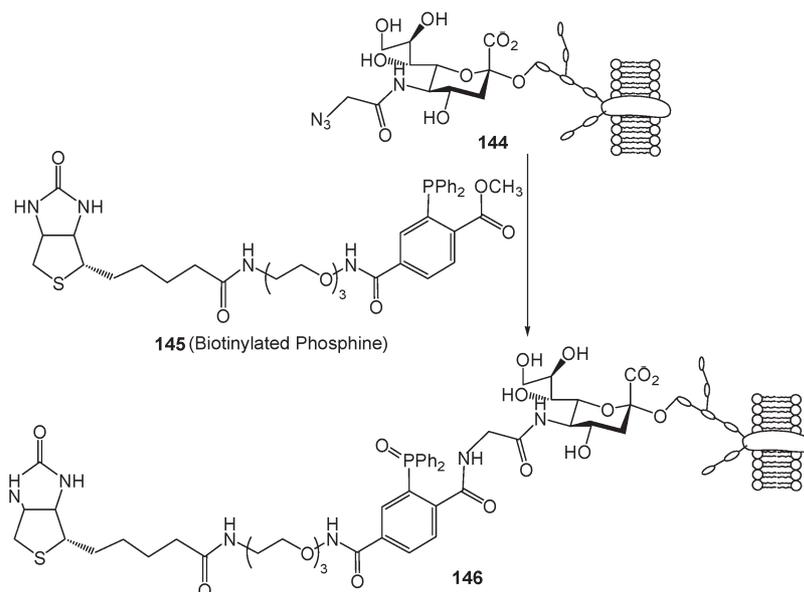
Scheme 36 Classical and modified Staudinger reactions. (Reprinted with permission from ref. 40. Copyright 2000, American Association for the Advancement of Science.)

9. Conclusion and outlook

Extraordinary attention has been paid to organic reactions in water in the past decade and research and development in this area is still increasing exponentially.⁴¹ This review provides an introductory overview of this field. The types of organic reactions in water are now as diverse as those in organic solvents. It is worthy of note that completely new reactivities of reactions have been discovered in water. The wide application of aqueous organic reactions also provides a driving force for the future development of this area.

Acknowledgements

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Scheme 37 Reaction of biotinylated phosphine with cell surface azido sialic acid. (Reprinted with permission from ref. 40. Copyright 2000, American Association for the Advancement of Science.)

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