Organic Reactions in Aqueous Media with a Focus on Carbon–Carbon Bond Formations: A Decade Update

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Chao-Jun Li was born in 1963 and received his B.Sc. at Zhengzhou University, 1983, his M.S. at the Chinese Academy of Sciences in Beijing, 1988, and his Ph.D. at McGill University, 1992 (with T. H. Chan and D. N. Harpp). He spent 1992–1994 as a NSERC Postdoctoral Fellow in B. M. Trost's laboratory at Stanford University and became an assistant professor in 1994 at Tulane University. He was promoted to associate professor with tenure in 1998 and full professor in 2000. He was a visiting faculty member (with Robert G. Bergman) at the University of California at Berkeley, 2002. In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts are to develop innovative and fundamentally new organic reactions that will defy conventional reactivities and possess high "atom efficiency". Widely known researches include the development of Grignard-type reactions in water, transition-metal 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.

1. Introduction

Organic syntheses are composed of two main types of reactions: Carbon−carbon bond formations and functional group transformations. C−C bond formation is the essence of organic synthesis[1] and provides the foundation for generating more complicated organic compounds from simpler ones. Although enzymatic processes in nature must occur in an aqueous environment by necessity, water has been a solvent to be avoided for common organic reactions. Since the pioneering studies of Diels−Alder reactions by Breslow,[2] there has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents.[3] A decade ago, the first comprehensive review on carbon−carbon bond formations in aqueous media was reported.[4] At that time, only a few dozen references existed in the literature on this subject, with the exception of hydroformylation reactions. Since then, there has been an explosion of research activities in this field, which has been partially attributed to the development of the field of Green Chemistry. While 10 years ago, the whole field was a mere curiosity for only a few practitioners, now organic reactions in water have become some of the most exciting research endeavors. There have been many excellent reviews on specific topics in this field.[5] There has also been a great advance in understanding the reactions of organic compounds in high-temperature water, which has broad implications ranging from the origin of life and energy and fuels to chemical synthesis.[6] Several excellent reviews have been published on this subject.[7] However, the current comprehensive review updates the progress of developing carbon−carbon bond formations in aqueous media for synthetic purposes within the past decade (mostly prior to 2004). In addition, as the subject is so broad at the present time, it is necessary to rearrange the topics based on functional group transformations, which is parallel to the classical C−C bond formations in organic chemistry. More details on specific subjects can be obtained from related reviews in the references.

2. Reaction of Alkanes

The direct functionalization of alkanes is the Holy Grail of chemical synthesis and has fundamental implications in a variety of fields including chemicals, energy, medicine, and the environment. While Nature has used monohydrogenase and other enzymes to functionalize alkanes in aqueous environments at ambient conditions,[8] alkanes are generally considered nonreactive in conventional organic chemistry. Classical reactions of alkanes are all under drastic conditions. However, within the past two decades, significant progress has been made in the "activation" of alkanes under milder conditions.[9] Such activations

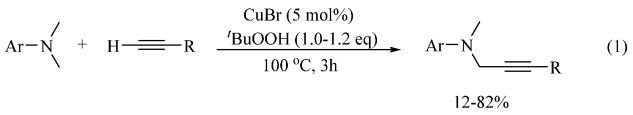
Table 1. Methane Carboxylation in Aqueous Solution[a]

CH_4	CO, Air, $NaVO_3$, 80°C, aq. sol'n, pH = 7.3	PRODUCTS (concentration/10^3 mol dm^{-3})		
		$MeCO_2H$	MeOH	HCHO
t/h	5	0.3	0.2	0.03
	15	0.6	0.4	0.1
	25	1.0	0.6	0.5

[a] Reprinted from ref 11 by permission of the Royal Society of Chemistry.

can be performed even in aqueous conditions,[10] although a detailed discussion of the field is outside the scope of the current review. By far, most research in this area has been focused on the conversion of C−H bonds in alkanes into a C−O bond. However, recently, it has been shown that it is possible to couple methane with CO to generate acetic acid in aqueous conditions by means of several catalysts (Table 1).[11]

On the other hand, significant progress has been made in the catalytic reaction of C−H bonds adjacent to heteroatoms such as nitrogen and oxygen, which are applicable in organic synthesis.[12] Li and co-workers recently found that copper could catalyze the direct alkynylation of an sp^3-hybridized C−H bond adjacent to nitrogen, and the reaction can tolerate water (eq 1). Furthermore, an asymmetric alkynyl-



(1)

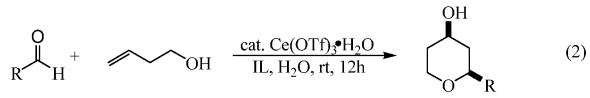
ation of prochiral sp^3-hybridized C−H bonds to generate optically active compounds (which also proceeded in water) has been reported.[13] Such couplings of C−H bond with C−H bond, which they termed as cross-dehydrogenative coupling (CDC), have been extended to sp^3 C−H with sp^3 C−H and sp^3 C−H with sp^2 C−H.[14]

Furthermore, carbon−carbon bond formation via the carbene insertion into an alkane C−H bond is possible in aqueous media under photolytic conditions.[15] Major progress has also been made recently in the reaction of α-hydrogens of carbonyl compounds and will be discussed in the carbonyl compounds section.

3. Reaction of Alkenes

3.1. Electrophilic Additions of Alkenes

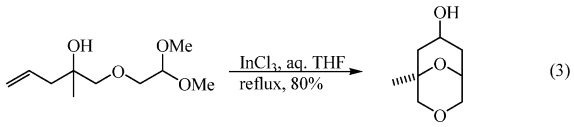
Cationic polymerization of alkenes and alkene derivatives have been carried out in aqueous media frequently.[16] On the other hand, the reaction of simple olefins with aldehydes in the presence of an acid catalyst is referred to as the Prins reaction.[17] The reaction can be carried out by using an aqueous solution of the aldehyde, often resulting in a mixture of carbon−carbon bond formation products.[18] Alternatively, Li and co-workers recently reported a direct formation of tetrahydropyranol derivatives in water using a cerium-salt-catalyzed cyclization in aqueous ionic liquids (eq 2).[19]



(2)

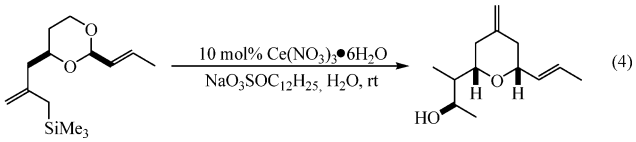
A further improvement on the tetrahydropyranol formation was made by using the Amberlite IR-120 Plus resin, an acidic resin with a sulfonic acid moiety, in which a mixture of an aldehyde and homoallyl alcohol in water, in the presence of the resin and under sonication, yielded the desired tetrahydropyranol derivatives.[20]

Cho et al. reported an indium trichloride catalyzed intramolecular Prins-type reaction of compounds having both functionalities of homoallyl alcohol and acetal moiety. The intramolecular Prins cyclizations were performed using indium trichloride in chloroform or 25% aqueous THF. Both 9-oxabicyclo[3.3.1]-nonane and 3,9-dioxabicyclo[3.3.1]nonane compounds were successfully obtained in good yields (eq 3).[21]



(3)

Aubele et al. studied the aqueous Prins cyclization using cyclic unsaturated acetals as oxocarbenium ion progenitors and allylsilanes as nucleophiles. Cyclizations proceed efficiently inside Lewis acidic micelles (of cerium salt) in water. A variety of vinyl- and aryl-substituted tetrahydropyrans with excellent stereo control were obtained (eq 4).[22]



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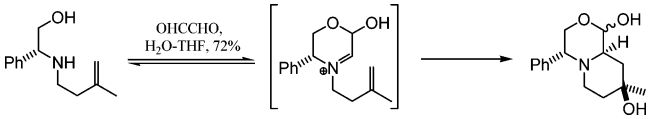
A reaction related to alkene−aldehyde coupling is the alkene−imine coupling. A one-pot cyclization involving such a reaction (Scheme 1) proceeds

Scheme 1. Cyclization in Aqueous Media[a]



[a] Reprinted with permission from ref 33. Copyright 1992 Elsevier.

smoothly in a mixture of water−THF. The reaction has been used in the asymmetric synthesis of pipecolic acid derivatives.[23]

3.2. Radical Reactions of Alkenes

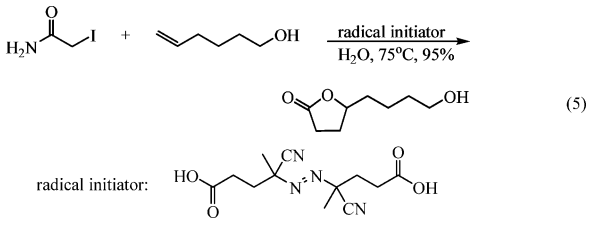
3.2.1. Radical Polymerization of Alkenes

Free radical polymerization of alkenes has been carried out in aqueous conditions.[24] Aqueous emulsion and suspension polymerization is carried out today on a large scale by free-radical routes. Polymer latexes can be obtained as a product, that is, stable

aqueous dispersions of polymer particles. Such latexes possess a unique property profile and most studies on this subject are in patent literature.[25] Atom transfer radical addition (ATRA) of carbon tetrachloride and chloroform to unsaturated compounds including styrene and 1-octene was investigated using ruthenium indenylidene catalysts. The reaction was extended to atom transfer radical polymerization (ATRP) by changing the monomer/halide ratio and can work in aqueous media. [26]

3.2.2. Radical Additions

The addition of carbon-based radicals has been shown to be successful in water. Thus, radical addition of 2-iodoalkanamide or 2-iodoalkanoic acid to alkenols using a water-soluble radical initiator in water generated γ-lactones (eq 5).[27]

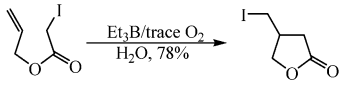


(5)

The addition of perfluoroalkyl iodides to simple olefins has been quite successful under aqueous conditions to synthesize fluorinated hydrocarbons.[28] In addition to carbon-based radicals, other radicals such as sulfur-based radicals, generated from RSH-type precursors (R = alkyl, acyl) with AIBN, also smoothly add to α-allylglycines protected at none, one, or both of the amino acid functions (NH_2, CO_2H, or both). Optimal results were obtained when both the unsaturated amino acid and RSH dissolved completely in the medium (dioxane/water or methanol/water are good solvent systems).[29] Hydroxy-bearing cyclopropenes react with allylindium reagents to undergo clean allylindation both in organic and aqueous media, and the chelation of the hydroxyl group to indium plays the central role.[30]

3.2.3. Radical Cyclization

Radical addition to alkenes has been used in cyclizations in aqueous media. Oshima and co-workers studied triethylborane-induced atom-transfer radical cyclization of iodoacetals and iodoacetates in water.[31] Radical cyclization of the iodoacetal proceeded smoothly both in aqueous methanol and in water. Atom-transfer radical cyclization of allyl iodoacetate is much more efficient in water than in benzene or hexane. For instance, treatment of **1** with triethylborane in benzene or hexane at room temperature did not yield the desired lactone. In contrast, **1** cyclized much more smoothly in water and yielded the corresponding γ-lactone in good yield (eq 6).



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Water as a reaction solvent also markedly promoted the cyclization reaction of large-membered rings. Stirring a solution of 3,6-dioxa-8-nonenyl iodoacetate in water in the presence of triethylborane at 25 °C for 10 h provided the 12-membered ring product, 4-iodo-6,9-dioxa-11-undecanolide, in 84% yield, whereas the cyclization in benzene afforded the lactone in only 22% yield. Ab initio calculation on the cyclization indicated that the large dielectrical constant of water lowers the barrier not only of the rotation from the *Z*-rotamer to the *E*-rotamer that can cyclize but also of the cyclization constructing the γ-lactone framework. Moreover, the high cohesive energy of water also affects acceleration of the cyclization because water forces a decrease in the volume of the reactant. The combination of a water-soluble radical initiator, 2,2′-azobis[2-(2-imidazolin-2-yl)propane], a water-soluble chain carrier, 1-ethylpiperidine hypophosphite, and a surfactant, cetyltrimethylammonium bromide, was found to be effective conditions for radical cyclization in water for a variety of hydrophobic substrates. [32]

3.3. Carbene Reactions

Structurally, a carbene is the smallest member of the alkene family. Because carbenes have no charge, they are expected to have a certain stability toward water. In fact, in some of the earliest work, carbenes were generated in an aqueous medium under biphasic conditions via the reaction of chloroform with a strong base such as NaOH.

3.3.1. The Generation of Carbenes in Aqueous Media

Carbenes can be generated in a variety of ways in aqueous conditions. The most common are the thermo-[33] and photodecomposition[34] of diazo compounds and the treatment of organic halides[35] with bases. Carbenes have also been generated in aqueous conditions from imidazolium salts.[36] Photolysis[37] and electrolysis[38] of organic compounds also generated transient carbene intermediates that undergo further reactions in aqueous conditions.

3.3.2. The Stability of Carbenes

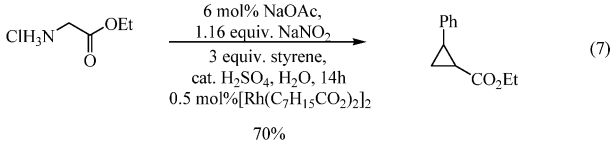
The stability of an unsubstituted methyl carbene is quite low in water. Highly correlated ab initio MO calculations have been used to study the energetics and mechanism governing the reaction between the radical $^1CH_2$ and H_2O in the gas phase and in solution. It was found that methylene reacts in a barrierless fashion to produce the ylide-like intermediate methyleneoxonium, H_2C-OH_2, which in turn undergoes a 1,2-hydrogen shift to produce CH_3OH.[39] The presence of substituents appears to stabilize carbenes toward water.[40]

Carbenes are most effectively stabilized by coordinating with transition metals, and many of these complexes are stable in water. The physical chemical properties of various transition-metal−carbene complexes in aqueous media have been studied extensively by Bernasconi[41] and others. The preparation of water-stable transition-metal−carbene complexes has been carried out in several ways: (1) by reacting

with alkynes, for example, water-soluble ruthenium carbene complexes,[42] (2) by opening unstable rings,[43] (3) by conversion of complexes through transformation of the ligands,[44] and (4) by reacting with N-heterocyclic carbenes.[45] Transition-metal−heterocyclic carbene complexes showed outstanding stability toward water and air and improved catalytic activities.

3.3.3. The Reaction of Carbenes with Alkenes in Aqueous Media

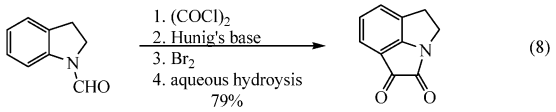
Cyclopropanation reactions involving ethyl diazoacetate and olefins proceed with high efficiency in aqueous media using Rh(II) carboxylates. Nishiyama's Ru(II)−Py-box and Katsuki's Co(II)−salen complexes that allow for highly enantioselective cyclopropanations in organic solvents can also be applied to aqueous cyclopropanations with similar results. In situ generation of ethyl diazoacetate and cyclopropanation also proceeds efficiently (eq 7).[46]



(7)

Insertions of dichlorocarbene into tertiary C−H bonds were observed even if these are not activated by neighboring phenyl or ether groups. Yields are 3−29% under the conditions used and this insertion does not require a thermo excitation of the dichlorocarbene as was assumed earlier.[47]

When N-substituted formanilides RC_6H_4NHCHO (R = H, 4-F, 4-Br, 2-, 3-, or 4-Cl, 4-OMe, 4-NO_2, or 4-Me) are treated briefly and sequentially with oxalyl chloride, Hunig's base, and bromine, isatins I are rapidly formed, many in good yields. The reaction involves deprotonation of the Vilsmeier reagent, dimerization of the carbene thus formed, and electrophilic cyclization of the dimer by bromonium ion, followed by aqueous hydrolysis (eq 8). [48]



(8)

3.4. Transition-Metal-Catalyzed Additions

Stable transition-metal−alkene complexes can be obtained readily from their salts and alkenes in water.[49]

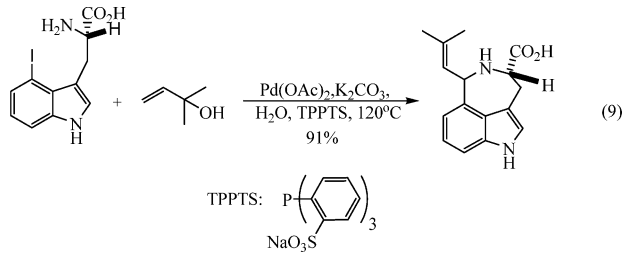
3.4.1. Polymerizations

Transition-metal-catalyzed polymerizations of alkenes in aqueous conditions have become a well-established field over the past two decades.[50] Among other advantages, the use of water as a dispersing medium is particularly environmentally friendly. A variety of high molecular weight polymers ranging from amorphous or semicrystalline polyolefins to polar-substituted hydrophilic materials have now been prepared by catalytic polymerization of olefinic monomers in water.

3.4.2. Heck Reactions and Related Vinylation/Arylation

The reaction between aryl (or alkenyl) halides and alkenes in the presence of a catalytic amount of a palladium compound to give substitution of the halides by the alkenyl group is commonly referred to as the Heck reaction.[51] Both inter- and intramolecular Heck reactions of simple alkenes have been performed in aqueous media.[52] Palladium-catalyzed reactions of aryl halides with acrylic acid or acrylonitrile gave the corresponding coupling products in high yields with a base ($NaHCO_3$ or K_2CO_3) in water. However, these reactions generally involved electron-deficient alkenes and will be discussed in detail in the section of conjugated carbonyl compounds. For simple alkenes, Parsons investigated the viability of the aqueous Heck reactions of aromatic halides coupled with styrenes under superheated conditions.[53] The reaction proceeded to approximately the same degree at 400 °C as at 260 °C. Some 1,2-substituted alkanes can be used as alkene equivalents for the high-temperature Heck-type reaction in water.[54] The Heck-type reaction can also use arenediazonium salts instead of aryl halides.[55]

The palladium-catalyzed Heck reaction of (*S*)-4-bromotryptophan with 1,1-dimethylallyl alcohol in aqueous media was applied to the synthesis of optically active clavicipitic acid. By use of $Pd(OAc)_2$ and water-soluble ligand TPPTS, the reaction could be carried out in alkaline aqueous media to give a high yield of the coupling product (up to 91%), but in organic solvent (dioxane or DMF), the reaction gave a complex mixture. The high dielectric constant of water may be responsible for the higher efficiency in aqueous conditions. The functional group in the substrate does not need to be protected in the course of palladium-catalyzed reactions. (*S*)-4-Bromotryptophan was prepared by biomimetic synthesis in two steps (eq 9).[56]

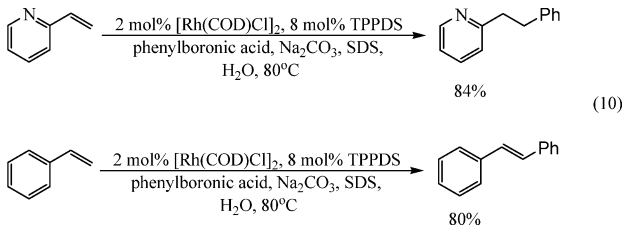


(9)

The aqueous Heck coupling reaction was also used for the synthesis of unprotected branched-chain sugar. In the media of DMF−H_2O (5:1) and with the use of $Pd(dba)_2$ and P(o-tol)$_3$, the Heck reaction proceeded smoothly to give the coupling product with high yields (up to 84%).[57] Water-soluble phosphine ligands containing *m*-guanidinium moieties and other types of moieties were synthesized and applied to aqueous Heck coupling reactions.[58] High-temperature and microwave heating appear to be beneficial for Heck-type coupling of simple alkenes in water.[59] Bulky phosphine ligands increased the rate of the reaction.[60]

Recently, a Pd/Cu-catalyzed three-component coupling reaction of aryl halides, norbornadiene, and alkynols was reported to generate 2,3-disubstituted norbornenes in high yields in the presence of aqueous NaOH and a phase-transfer catalyst in toluene at 100 °C. Guanidinium moieties were synthesized and applied to aqueous Heck coupling reactions.[61]

In addition to Heck reactions, other transition metals have also been used for arylation and vinylation of arylalkene. Lautens,[62] as well as Genet,[63] studied the addition of phenylboronic acid with alkenes in the presence of a rhodium catalyst in aqueous media. The product of the addition was found to be strongly affected by the nature of the aryl group. In the presence of a catalytic amount of $[Rh(COD)Cl]_2$ together with 3 equiv of Na_2CO_3 and a surfactant (SDS), when N-heteroarylalkenes were used the addition−hydrolysis product was formed, whereas the use of styrene derivatives generated addition−elimination products under the same reaction conditions (eq 10).



(10)

More recently, Chang reported a ruthenium-based Heck-type reaction in DME/H_2O (1:1) by using alumina-supported ruthenium catalysts.

3.4.3. Hydrovinylation

The homo- and cross-addition of alkenes catalyzed by a transition metal provided another economical way for forming C−C bonds.[64] These reactions are carried out by using nickel, palladium, or ruthenium phosphine complexes to yield vinylarenes, and some of the reactions can occur in aqueous media. By use of carbohydrate-derived ligands, asymmetric hydrovinylations can be carried out in aqueous conditions.[65]

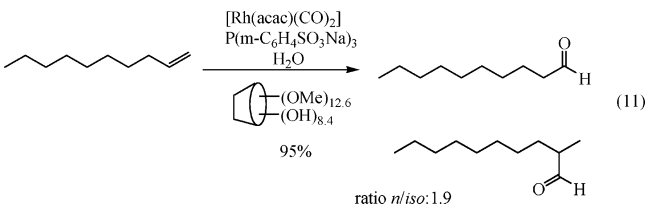
3.4.4. Reaction with Arenes

Under Lewis-acid-catalyzed conditions, electron-rich arenes can add to alkenes to generate Friedel−Crafts reaction products. This subject will be discussed in detail in the section on aromatic compounds. However, it is interesting to note that direct arylation of styrene with benzene in aqueous CF_3CO_2H containing H_2PtCl_6 yielded 30−35% *trans*-PhCH=CHR via the intermediate $PhPt(H_2O)Cl_4$.[66] Hydrophenylation of olefins can be catalyzed by an Ir(III) complex.[67]

3.4.5. Hydroformylation

Hydroformylation is a major industrial process that produces aldehydes and alcohols from olefins, carbon monoxide, and hydrogen.[68] The reaction was discovered in 1938 by Roelen,[69] who detected the formation of aldehydes in the presence of a cobalt-based catalyst. A major improvement was made by joint efforts of Ruhrchemie and Rhone-Poulenc by using rhodium in aqueous media. Extensive research has been carried out related to this process.[70] The Rh/TPPTS catalyst was employed in hydroformylation of *N*-allylacetamide in water, which proceeds at a much faster rate and in a much higher selectivity (>99%) than the Rh/PPh_3-catalyzed reaction in organic solvents. In water, at 90 °C and 50 bar H_2/CO, turnover frequencies (TOF) are >10 700 h^{-1}. The relations of regioselectivity with reaction conditions were investigated in detail.[71] By use of this method, the separation of catalyst and product is based on the use of transition-metal complexes with water-soluble phosphine ligands, and water as an immiscible solvent for the hydroformylation. Initially, the water-soluble complex $[HRh(CO)(Ph_2PPhSO_3Na)_3]$[72] was used. However, with this monosulfonated ligand, some leaching of rhodium into the organic phase was observed.[73] The highly water-soluble tris-sulfonated ligand, P(*m*-$PhSO_3Na)_3$,[74,75] was found to be highly recyclable. A variety of 1-alkenes were hydroformylated with this catalyst in high linear selectivity, generating the corresponding terminal aldehyde.[76] More effective catalysts involving the use of other sulfonated phosphine ligands have also been reported.[77] Examples include $[Rh_2(\mu\text{-}SR)_2(CO)_2(P(m\text{-}PhSO_3Na)_3)_2]$,[78] $Ph_2PCH_2CH_2NMe_3^+$,[79] *p*-carboxylatophenylphosphine,[80] and sulfoalkylated tris(2-pyridyl)phosphine.[81] The hydroformylation in aqueous acetone is significantly greater than that in acetone alone with rhodium catalyst, which was attributed to simple inhibition of the fragmentation of the catalytically active species into inactive mono- and bimetallic complexes.[82]

For long chain olefins, the hydroformylation generally proceeds slowly and with low selectivity in two-phase systems due to the their poor solubility in water. Monflier et al. recently reported a conversion of up to 100% and a regioselectivity of up to 95% for the Rh-catalyzed hydroformylation of dec-1-ene in water, free of organic solvent, in the presence of partially methylated β-cyclodextrins (eq 11).[83]



(11)

These interesting results are attributed to the formation of an alkene/cyclodextrin inclusion complex, as well as the solubility of the chemically modified cyclodextrin in both phases. Prior to this, hydroformylation in the presence of unmodified cyclodextrins had been studied by Jackson, but the results were rather disappointing.[84]

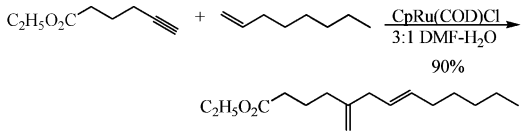
In another interesting area of hydroformylation, Davis developed the concept of supported aqueous-phase catalysis (SAP catalysis).[85] A thin, aqueous film containing a water-soluble catalyst adheres to silica gel with a high surface area. The reaction occurs at the liquid−liquid interface. Through SAP catalysis, the hydroformylation of very hydrophobic alkenes,

such as octene or dicyclopentadiene, is possible with the water-soluble catalyst [HRh(CO)tppts$_3$]. Other supported biphasic hydroformylations have also been reported. [86]

Other metal complexes containing Pd, Ru, Co, or Pt have also been used.[87] The hydroformylation reaction can also be performed by using methyl formate instead of carbon monoxide and hydrogen.[88] Hydroformylation in aqueous media has been applied in various syntheses.[89] Recently, asymmetric hydroformylation in aqueous media has also been reported through the use of a new axially chiral diphosphine ligand 2,2′-bis[(diphenylphosphino)methyl]-4,4′,6,6′-tetrachloro-1,1′-biphenyl (BIPHLOPHOS). [90]

3.4.6. Reaction with Alkynes

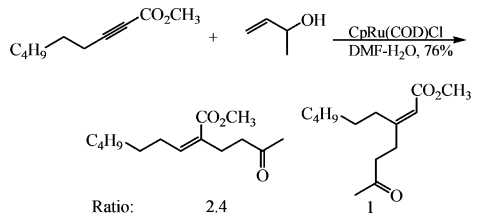
In aqueous media, addition of unactivated alkenes to unactivated alkynes to form Alder-ene products was realized by using a ruthenium catalyst (eq 12).[91]



(12)

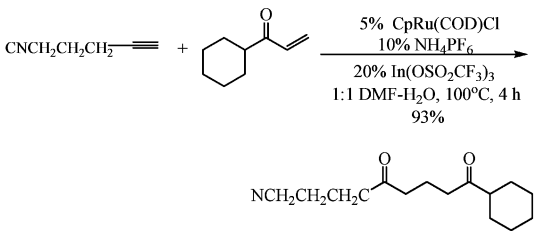
A polar media (DMF/H_2O = 1:1) favors the reaction and benefits the selectivity. The reaction was suggested to proceed via a ruthenacycle intermediate.

Mascareñas developed a synthetic method to form 1,5-oxygen-bridged medium-sized carbocycles through a sequential ruthenium-catalyzed alkyne−alkene coupling and a Lewis-acid-catalyzed Prins-type reaction. The ruthenium-catalyzed reaction can be carried out in aqueous media (DMF/H_2O = 10:1).[92] The addition of allyl alcohol to alkynes to form γ,δ-unsaturated ketones and aldehydes (eq 13) in aqueous media was developed by Trost and Dixneuf, respectively.[93]



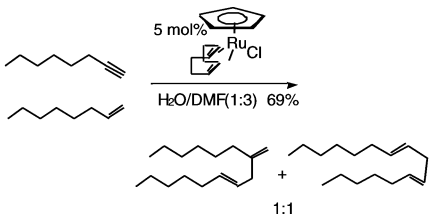
(13)

As described in section 3.1, the reaction of terminal alkynes, water, and α-vinyl ketones afforded 1,5-diketones in DMF−H_2O (eq 14). Under similar conditions, in the presence of halide, the ruthenium-catalyzed three-component coupling of alkyne, an enone, and halide ion formed vinyl halide.



(14)

Other transition metals have also been used. For example, Trost[94] reported that heating a 1:1 mixture of 1-octene and 1-octyne in DMF/water (3:1) at 100 °C with a ruthenium complex for 2 h generated a 1:1 mixture of two products corresponding to the addition of the alkene to the acetylene (eq 15). The presence of a normally reactive enolate does not interfere with the reaction (eq 16).



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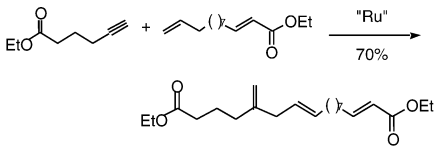


(16)

3.4.7. Carbonylation

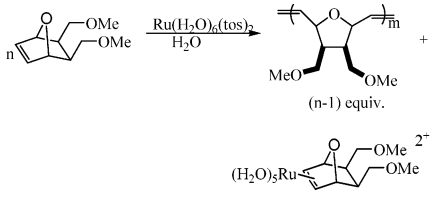
Water-soluble dicationic palladium(II) complexes, $[(R_2P(CH_2)_3PR_2)Pd(NCMe)_2][BF_4]_2$, proved to be highly active in the carbon monoxide/ethene copolymerization under biphasic conditions (water−toluene). In the presence of an emulsifier and methanol as activator, the catalytic activity increased by a factor of about three. Higher olefins could also be successfully incorporated into the copolymerization with CO and the terpolymerization with ethene and CO.[95]

3.5. Olefin Metathesis

Olefin metathesis is a useful tool for the formation of unsaturated C−C bonds in organic synthesis.[96] The most widely used catalysts for olefin metathesis include an alkoxyl imido molybdenum complex (Schrock catalyst)[97] and a benzylidene ruthenium complex (Grubbs catalyst).[98] The former is air- and moisture-sensitive and has some other drawbacks such as intolerance to many functional groups and impurities; the latter has increased tolerance to water, and many reactions have been performed in aqueous solution without any loss of catalytic efficiency. The olefin metathesis in aqueous media has been applied to the synthesis of various polymers.[99]

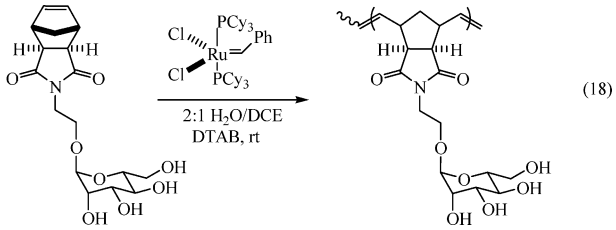
3.5.1. Ring-Opening Metathesis Polymerization (ROMP)

Novak and Grubbs reported the ring-opening metathesis polymerization (ROMP) of 7-oxanobornene derivatives initiated by $Ru(H_2O)_6(tos)_2$ in aqueous media (eq 17).[100] Compared with the same reaction carried out in organic solvent, the initiation time was greatly decreased. After the polymerization, the aqueous catalyst solution was not only reused but



(17)

also became more active in subsequent polymerizations. Living ROMP by using some well-defined ruthenium carbene complexes in aqueous media in the presence of a cationic surfactant has been used to prepare polymer latex.[101] Recent developments include the synthesis of new water-soluble ruthenium alkylidene catalysts and their application to olefin metathesis in water.[102] The addition of acid made the polymerization rate up to 10 times faster than without acid. Kiessling has extended the use of ruthenium alkylidene-catalyzed ROMP in aqueous media to give new biologically active neoglycopolymers (eq 18).[103]

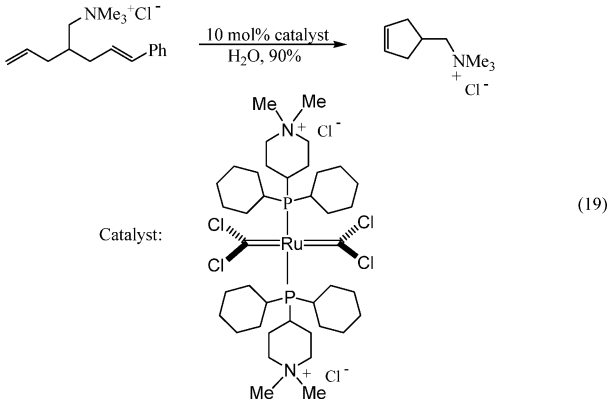


(18)

Living ring-opening metathesis polymerization (ROMP), in which the catalyst becomes active again when new starting materials are introduced, was developed by Grubbs and co-workers in water.[104] The polymerizations have been used in making a variety of materials such as dental materials and others.[105]

3.5.2. Ring-Closing Metathesis (RCM)

Whereas ROMP is an important method for making polymers, ring-closing metathesis (RCM) is an important method for construction of medium and macrocycle compounds. Ring-closing metathesis (RCM) by means of Grubb's catalyst has been used extensively in synthesis in aqueous conditions. For many biologically related substrates, the use of RCM in aqueous media can keep their important higher-order structures.[106] For example, RCM of σ,ω-dienes proceeded efficiently in aqueous media (eq 19).



(19)

More recently, a new metathesis catalyst involving a ruthenium−alkylidene complex with a sterically bulky and electron-rich phosphine ligand has been synthesized and applied to RCM in aqueous media (Figure 1).[107] This catalyst has the benefit of being soluble in almost any solvent (e.g., methanol, methanol−water, methylene chloride, and benzene) while still being an active catalyst for RCM.

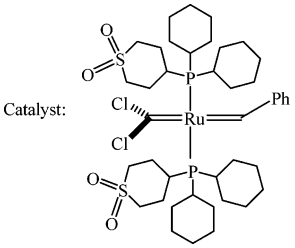


Figure 1.

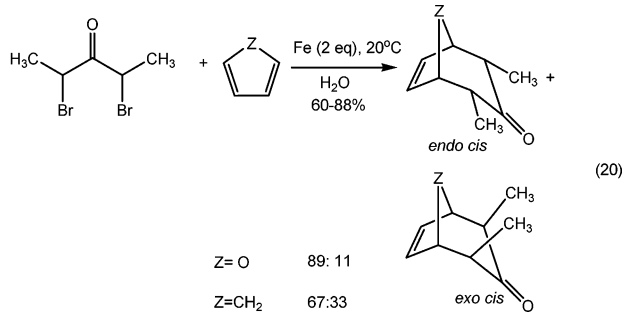
A program directed toward a general synthesis of α-methylenelactones cis- or trans-fused to larger rings was reported. The protocol originates with two ω-unsaturated aldehydes of the same or different chain length. One of these is initially transformed by way of the Baylis−Hillman reaction into a functionalized allylic bromide. Merger of the two building blocks is subsequently accomplished in aqueous solution with powdered indium metal serving as the initiator. Once the lactone ring is crafted, the end products are generated by application of ring-closing metathesis. The central issues surrounding this final step are the effects of the stereochemical disposition of the side chains, the consequences of ring strain, and the location of the double bonds on cyclization efficiency.[108] 4-Deoxy-4,4-difluoro-glycosides have been synthesized for the first time via a direct sequence involving ring-closing metathesis and indium-mediated difluoroallylation with 1-bromo-1,1-difluoropropene in water. Two protecting group strategies were explored. The first allowed protection of the primary C-6 hydroxyl group throughout the sequence, while the second was intended to allow deprotection after RCM and before dihydroxylation. The benzyl ether could be used in the first role, and pivaloyl is effective in the second. Dihydroxylations were highly stereoselective and controlled by the orientation of the glycosidic C−O bond.[109]

The synthesis and olefin metathesis activity in protic solvents of a phosphine-free ruthenium alkylidene bound to a hydrophilic solid support are reported. This heterogeneous catalyst promotes relatively efficient ring-closing and cross-metathesis reactions in both methanol and water.[110] The catalyst catalyzed cross-metathesis of allyl alcohol in D_2O to give $HOCH_2CH{:}CHCH_2OH$ in 80% yield. Other ruthenium complexes have also been used for RCM. [111]

3.6. Cycloaddition Reactions of Alkenes and Conjugated Alkenes

The thermo- and photocycloaddition of alkenes will be discussed in the section on pericyclic reactions. On the other hand, transition metals have effectively catalyzed some synthetically useful cycloaddition reactions in water. For example, Wender[112] reported a rhodium-catalyzed [5+2] cycloaddition reaction in water by using a water-soluble phosphine ligand. The use of water-soluble catalyst prevents the polymerization of the substrates, which are insoluble in water, and improves the reaction yield dramatically. The catalyst solution can be reused readily. The same catalysts can catalyze Diels−Alder reactions. Lubineau and co-workers reported a [4+3] cycloaddition

by reacting α,α-dibromo ketones with furan or cyclopentadiene mediated by iron or copper or α-chloro ketones in the presence of triethylamine (eq 20).[113]



(20)

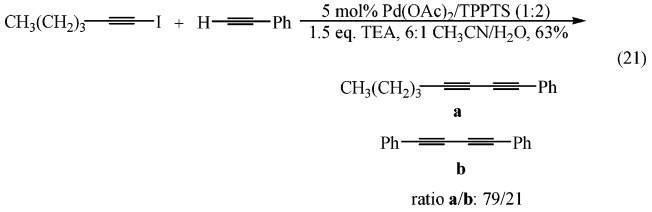
4. Reaction of Alkynes

The carbon−carbon bond formation reactions of alkynes can be classified into two categories: the reaction of the terminal C−H bond and the reaction of the carbon−carbon triple bond.

4.1. Reaction of Terminal Alkynes

4.1.1. Alkyne Oxidative Dimerization

The dimerization of terminal alkynes (known as the Glaser coupling, the Eglinton coupling, and the Cadiot−Chodkiewicz coupling) is one of the fundamental transformations in synthesis. It is especially useful in the synthesis of advanced organic materials.[114] For example, water-soluble conjugated [3]-rotaxanes and "naked" molecular dumbbells were synthesized from such couplings in water using hydrophobic interactions to direct rotaxane formation.[115] Although such couplings are mainly catalyzed by copper, other transition-metal catalysts also work for this coupling. Examples include a water-soluble palladium/TPPTS catalyzed coupling, affording diynes in moderate yields (eq 21).[116]

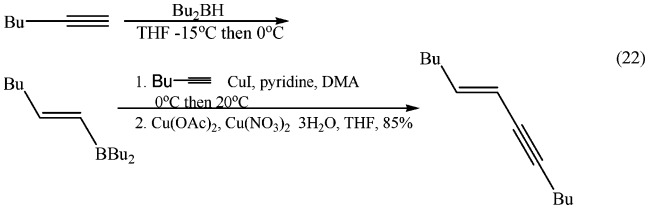


(21)

4.1.2. Alkyne Dimerization

The additive coupling of terminal alkynes catalyzed by copper is a classical reaction known as the Strauss coupling. Unfortunately, under classical conditions, a mixture of regio-isomers was obtained.[117] Recently, a rhodium-catalyzed homopolymerization and oligomerization of alkynes has been reported.[118] A major development to overcome this limitation was made by Trost, who found that using a catalytic amount of $Pd(OAc)_2$ and triphenylphosphine in dichloroethane resulted in a high yield of homocoupling of terminal alkynes.[119]

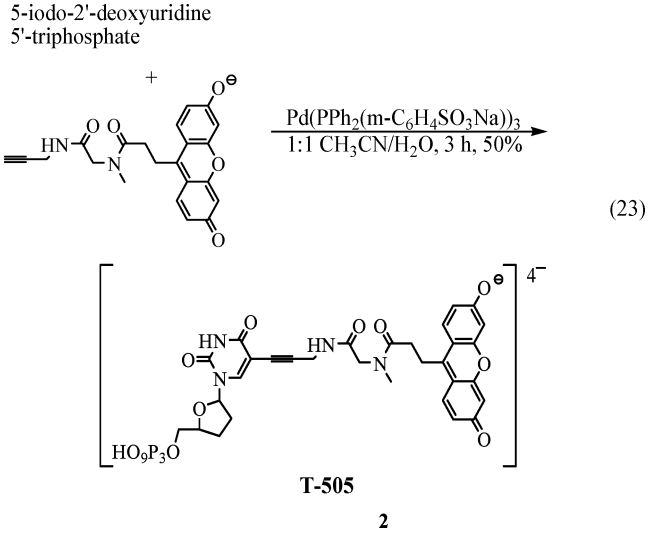
It is interesting to note that a copper(II)-mediated coupling reaction of alkenyldialkyl- or trialkylboranes with alkynylcopper compounds, generated in situ in the presence of various solvents and a small amount of water, gives (*E*)-1,3-enynes (or disubstituted alkynes) with various functional groups in reasonable yields (eq 22).[121]



(22)

4.1.3. Reaction of Alkynes with Organic Halides

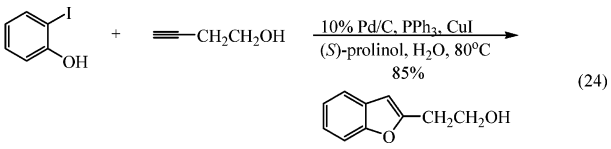
The coupling of terminal alkynes with organic halides, known as the Castro−Stephens−Sonogashira reaction, has wide applications in synthesis. The most widely used method is the Sonogashira coupling using a combination of palladium and copper as the catalyst.[122] Recently, the reaction was investigated extensively in aqueous media with some reactions without using copper as the cocatalyst. For example, when a water-soluble palladium complex is used as the catalyst, unprotected nucleosides, nucleotides, and amino acids undergo coupling with terminal acetylenes in aqueous acetonitrile.[123] Compound T-505 (**2**), part of a family of chain-terminating nucleotide reagents used in DNA sequencing and labeling, was synthesized by this route in 50% yield (eq 23).



(23)

Genet,[124] Beletskaya,[125] and others[126] recently carried out more detailed studies of the aqueous reaction. A variety of aryl and vinyl iodides were coupled with terminal acetylenes in aqueous media with either a water-soluble catalyst or a non-water-soluble catalyst. The reaction can also be carried out without the use of a phosphine ligand in a water−alcohol emulsion in the presence of cetyltrimethylammonium bromide (CTAB) as an emulsifier.[127] Diynes were similarly prepared by reaction of alkynyl bromide with terminal alkynes.[128] $Pd(OAc)_2$/TPPTS has been used as an efficient catalyst in a sequential two-step reaction for the coupling of 2-iodoaniline or 2-iodophenol with terminal alkynes to give the corre-

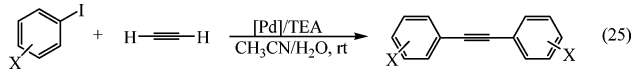
sponding indoles or benzofurans in good yield (eq 24).[129] This methodology can tolerate a number of dif-



(24)

ferent functional groups, does not require the use of a phase-transfer catalyst or water-soluble phosphine ligands, and can be performed directly in water.

Li and co-workers reported a highly efficient coupling of acetylene gas with aryl halides in a mixture of acetonitrile and water (eq 25).[130] The conditions

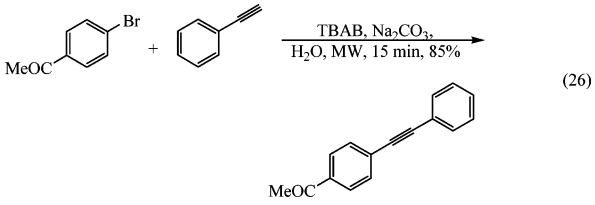


(25)

are generally milder and the yields are better than previously reported results in organic solvents. A variety of aromatic halides are coupled to give the corresponding bis-arylacetylenes. Both a water-soluble palladium catalyst (generated in situ from $Pd(OAc)_2$/TPPTS) and a water-insoluble catalyst (generated in situ from $Pd(OAc)_2/PPh_3$) can be used for the reaction.

The reaction can be carried out in water alone. The reaction proceeds equally well with or without CuI as a cocatalyst. By using the palladium-catalyzed coupling between aryl halides with acetylene gas, Li et al.[131] prepared a variety of poly(arene ethynylene)s from aryl diiodides.

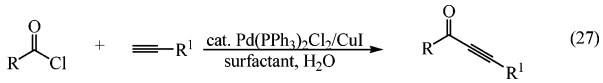
Alkenyl and aryl iodonium salts have also been coupled with terminal alkynes. The reaction of (*E*)-[*β*-(trifluoromethanesulfonyloxy)-1-alkenyl](phenyl) iodonium trifluoromethanesulfonate with terminal alkynes in the presence of catalytic amounts of dichloro(triphenylphosphine)palladium(II) and CuI in an aqueous medium proceeds stereospecifically to give the corresponding enynes in good yields.[132] $Ni(PPh_3)_2Cl_2$/CuI was also reported as a catalyst for such couplings in water.[133] An interesting development is a microwave-assisted, transition-metal-free Sonogashira-type coupling reaction (eq 26). The reac-



(26)

tions were performed in water without the use of copper(I) or a transition metal−phosphane complex. A variety of different aryl and hetero-aryl halides were reactive in water.[134]

A highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$/CuI together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base provided ynones in high yields in water (eq 27). The

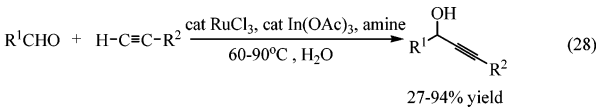


(27)

use of $PdCl_2(PPh_3)_2$/CuI as cocatalysts, together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base, provided the desired product in 98% isolated yield. No reaction was observed when either Cu(I) alone or Pd(II) alone was used as the catalyst. The use of surfactant is also critical for the success of the reaction possibly by temporarily stabilizing the acid chloride; without a surfactant/phase-transfer reagent the yield dropped from 98% to 9%.[135]

4.1.4. Reaction of Alkynes with Carbonyl Compounds

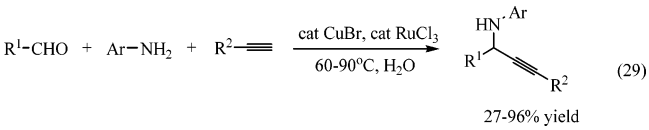
Li and co-workers developed a direct addition of terminal alkynes to aldehydes in water by using a ruthenium−indium bicatalyst system (eq 28).[136]



(28)

4.1.5. Reaction with Imines

The direct 1,2-addition of terminal alkynes to the C=N double bond in imines and their derivatives via activation of the C−H bond in the terminal alkynes is a convenient route to synthesize propargylamines. Recently, Li and co-workers reported a highly efficient A^3 coupling (aldehyde−alkyne−amine) in water or without solvent.[137] It was found that phenylacetylene can react with an arylimine in the presence of a catalytic amount of Cu(I) in aqueous media to give the desired adducts in low conversions. When $RuCl_3$ was used as a cocatalyst, the reaction was more efficient. No desired product was found with $RuCl_3$ alone as the catalyst. A broad range of substituted aromatic imines and aliphatic imines (eq 29) were converted into propargylamines by this method.

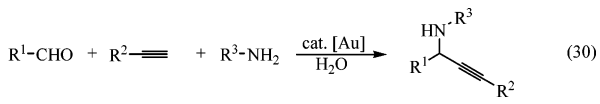


(29)

The additions were found to be highly effective under solvent-free conditions.

Li and co-workers also reported a copper-mediated coupling of alkynes with *N*-acylimines and *N*-acyliminium ions in water to generate propargyl amide derivatives.[138] *N*-Acylimines or *N*-acyliminium ions can be generated in situ from amines containing a good leaving group at the α-position, for example, α−phenylsulfonyl *N*-acylamine and α-methoxy *N*-(alkoxycarbonyl)pyrrolidine, and the products can be modified easily for various synthetic purposes. However, an excess amount of CuBr is required in this case.

Subsequently, Li and co-workers also found that the reaction is highly efficient and general with gold as the catalyst (eq 30).[139] No cocatalyst or activator

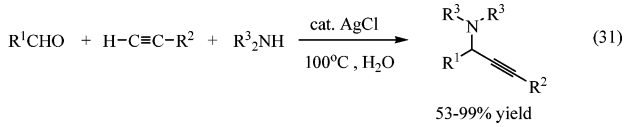


(30)

is needed for the gold-catalyzed reaction. Less than

1 mol % of catalyst is enough to generate an excellent yield of the corresponding propargylamine products. Both aromatic and aliphatic aldehydes were able to undergo this three-component coupling with alkyne and amine. Dialkylamines are good for the reaction, whereas anilines gave the corresponding products in lower yields. *N*-Alkylanilines did not form the desired products. Aromatic aldehydes reacted more efficiently, and nearly quantitative yields were obtained in most cases. Aliphatic aldehydes can also be used; however, some trimerizations of aldehydes were observed that decreased the yields of the propargylamine products. The properties of solvents significantly affect the reaction. Water is the best solvent, and the reaction process is very clean with almost quantitative yield; the use of organic solvents such as THF, toluene, and DMF resulted in low conversions and more byproducts.

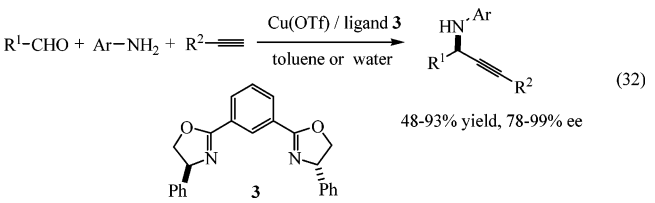
Following the success of copper and gold, it was found that AgCl, AgBr, and AgI showed good catalytic activity for the three-component coupling in water (eq 31).[140] No other additive was needed for



(31)

this reaction either. In this reaction, aromatic aldehydes decreased the reactivity of the reaction, whereas aliphatic aldehydes displayed higher reactivity and cleaner reactions compared to the reaction catalyzed by copper and gold.

Recently, Li and co-workers reported a highly efficient AA[3] coupling (asymmetric aldehyde−alkyne−amine) in water (eq 32).[141] The use of the tridentate



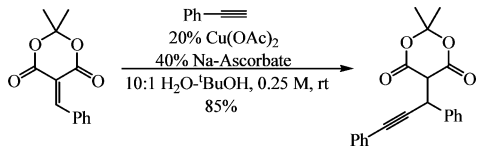
(32)

bis(oxazolinyl)pyridines (pybox) (**3**) with Cu(OTf) afforded the product with both high yield and enantioselectivity up to 99.6% ee in organic solvent and 84% ee in water. In most cases, imines were formed in situ, and the addition was very simple: mixing an aldehyde, an aniline, and an alkyne with the catalyst in one pot.

Shi and co-workers recently reported that a three-component coupling of aldehyde, alkyne, and amine via C−H activation catalyzed by CuI in water can be greatly accelerated by using microwave irradiations.[142] Using (*S*)-proline methyl ester as a chiral source, they acheived a direct and highly diastereoselective method for construction of chiral propargylamines.

4.1.6. Conjugate Addition

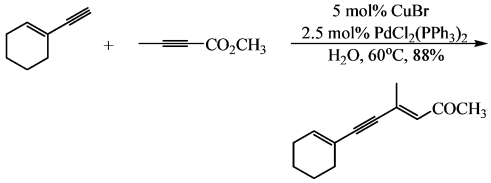
For the conjugate addition of terminal alkynes to unsaturated carbonyl compounds, Carreira reported that alkynyl copper reagents, generated from terminal alkynes and catalytic $Cu(OAc)_2$ in the presence of sodium ascorbate, undergo additions to alkylidene Meldrum's acid at room temperature in aqueous media to give the corresponding adducts (eq 33).[143]



(33)

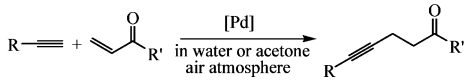
The restriction to this methodology is that it is limited to highly activated alkylidene Meldrum's acid.

On the other hand, Chen and Li reported a facile and selective copper−palladium-catalyzed addition of terminal alkynes to activated alkynes in water without the competition of the homocoupling of the terminal alkynes (eq 34).[144]



(34)

Recently, Li and co-workers also reported a simple and highly efficient Pd-catalyzed addition of a terminal alkyne to a C=C double bond such as a conjugated enone, either in water or in acetone in air (eq 35). A variety of conjugated enones are effective



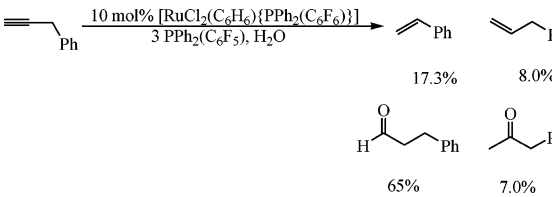
(35)

for this coupling.

4.2. Reaction of C≡C Bonds

4.2.1. Nucleophilic Additions

Unlike alkenes, simple alkynes can undergo nucleophilic additions both with and without a transition-metal catalyst.[145] Recently, the transition-metal-catalyzed addition of oxygen nucleophiles to alkynes has been studied extensively in aqueous media. Hydration of terminal alkynes catalyzed by Ru(II) complexes, for example, $[RuCl_2(C_6H_6)(PPh_2(C_6F_5))]$, in the presence of appropriate auxiliary phosphine ligands leads predominantly to the anti-Markovnikov addition of water and yields aldehydes with only a small amount of ketone (eq 36).[146]

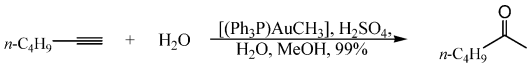


(36)

The hydration of propargylic alcohols to the corresponding aldehyde derivatives is conveniently carried out at 60 °C in an aqueous micellar environment, in the presence of 5 mol % chloro[(1,2,3,3a,7a-η)-1*H*-inden-1-yl]bis(triphenylphosphine)ruthenium, $[Ru(\eta^5\text{-}C_9H_7)Cl(PPh_3)_2]$.[147] Ruthenium catalysts can further

catalyze the breaking of carbon−carbon triple bonds by water.[148]

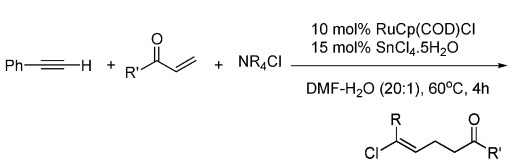
Recently, various gold catalysts have been found to be particularly effective in catalyzing the nucleophilic addition of oxygen nucleophiles to alkynes. Au(I)-catalyzed additions have high turnover frequencies for a wide range of alkynes in aqueous methanol to form the corresponding carbonyl compounds in high yields (eq 37).[149]



(37)

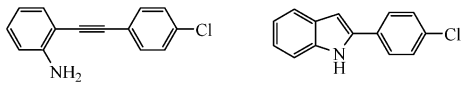
The new procedure is a valuable alternative to the Wacker oxidation. Au(III) complexes[150] and Au(I)−phosphine complexes[151] are also found effective for the addition of water and methanol to terminal alkynes.

Platinum(III) dimeric complexes of alkynes in water provide a novel approach to α-aminoketones, α-iminoketones, and α,β-diimines.[152] Ruthenium complexes are also able to catalyze the addition of halides to alkynes in water. The reaction of terminal alkynes, water, and α-vinyl ketones afforded 1,5-diketones in DMF−H_2O. Under similar conditions, in the presence of halide, ruthenium-catalyzed three-component coupling of an alkyne, an enone, and a halide ion formed vinyl halide (eq 38).[153]



(38)

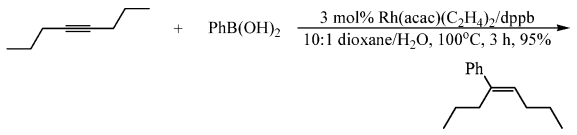
Nitrogen-based nucleophiles also add to alkynes in aqueous media. Gold(III)-catalyzed annulations of 2-alkynylanilines (e.g., **4** and **5**) in EtOH or EtOH−



4 **5**

water mixture at room temperature gave indoles and 3-haloindoles in good yields.[154]

Hayashi and co-workers reported a rhodium-catalyzed hydroarylation of alkynes with arylboronic acids or aryl boroxines to form alkenes. The hydroarylation has advantages over other methods in that it is carried out in an aqueous solvent with various functional groups such as esters, which remain intact during the reaction along with high syn selectivity (eq 39).[155]



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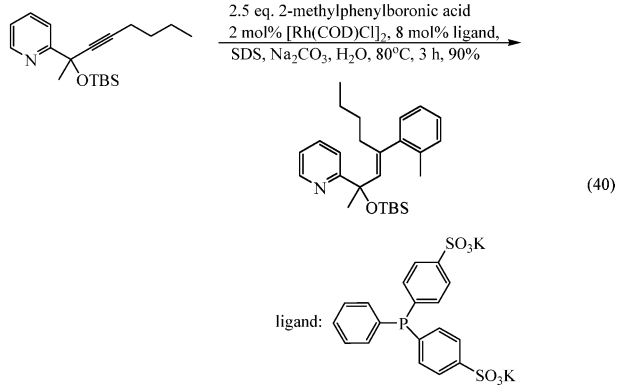
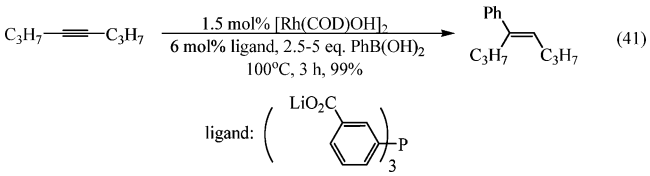
On the other hand, Lautens reported the addition of arylboronic acids to alkynes with a pyridine-substituted water-soluble phosphine ligand in aqueous media using a rhodium catalyst (eq 40).[156] As



(40)

expected for a chelation-controlled addition, only the alkynes with a nitrogen atom that is in proximity to the alkyne were converted to the corresponding alkene. This methodology provided trisubstituted alkenes with high regioselectivity from various arylboronic acids and alkynyl heteroaromatic compounds.

Genet used $[Rh(COD)OH]_2$ with the water-soluble ligand *m*-TPPTC for a Rh-catalyzed arylation of alkynes in a biphasic water/toluene system. The reaction was regioselective for alkyl arylalkynes and alkyl silylated alkynes. In addition, the Rh/*m*-TPPTC system was recycled with no loss of the activity and with excellent purity of the desired alkene (eq 41).[157]



(41)

The intramolecular cyclization of tethered allyl bromides onto terminal alkynes mediated by metallic indium proceeds smoothly and cleanly in a mixture of THF and water to give unsaturated carbocycles and heterocycles in good yields. The reaction does not proceed efficiently under rigorously anhydrous conditions.[158] An intramolecular cyclization of alkynes with furans and electron-rich arenes was catalyzed by $PtCl_2$ via platinum carbene intermediates to give dicarbonyl compounds in the presence of water.[159]

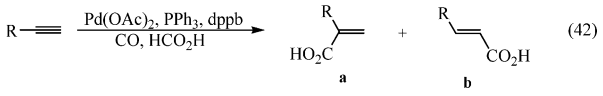
4.2.2. Electrophilic Addition

A room-temperature Kharasch reaction is catalyzed by Pd(0) in a heterogeneous aqueous system.[160] The palladium-catalyzed Kharasch reaction of alkenes and alkynes is enhanced by the use of a heterogeneous aqueous system, without the use of hydrophilic cosolvents or phase-transfer catalysts. The Pd(0)-catalyzed reaction of terminal alkenes with bromotrichloromethane in water goes to completion within 2 h at room temperature, whereas no reaction occurs in benzene under the same conditions. The Pd(0) catalyst in aqueous media also effects the radical addition of iodoperfluoroalkanes toward terminal alkenes and alkynes at room temperature.

4.2.3. Hydrocarboxylation

Alkynes are hydrocarboxylated with HCO_2H mediated by catalytic amounts of $Pd(OAc)_2$ and suitable

phosphine ligands (100−110 °C, 120 psi of CO gas pressure) to give the corresponding unsaturated carboxylic acids (eq 42). The regioselectivity of the

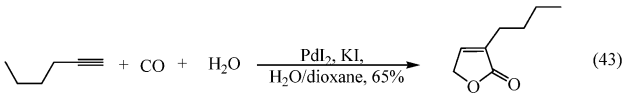


(42)

reaction is approximately 90:10 in favor of **a** when the R group is Ph or a straight chain alkyl. However, when R is *tert*-butyl, **b** is favored, and it is the exclusive product when R is Me_3Si. A reaction mechanism is proposed on the basis of experimental results and deuterated labeling studies. The OH of HCO_2H bonds to the Pd center, forming a cationic hydrido(alkyne)-palladium intermediate that undergoes a sequence of reactions including H and CO insertions to form the desired products and regenerate the catalyst.[161]

Terminal alkyne dicarbonylation can be readily effected under mild conditions by treating alkynes with carbon monoxide and alcohols or water at 25−80 °C in the presence of PdI_2, KI, and air with high catalytic efficiency.[162] Carbon dioxide was found to promote the Pd-catalyzed oxidative carbonylation of terminal alkynes to give maleic anhydrides effectively in aqueous dioxane at 60−80 °C in the presence of catalytic amounts of PdI_2 in conjunction with KI and under a 4:1:10 mixture of CO/air/CO_2 (60 atm total pressure at 25 °C). When reactions were performed in the presence of a large excess of water, maleic acids were selectively formed.[163]

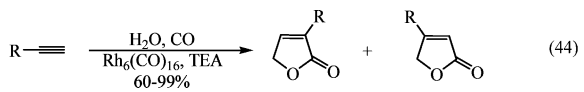
3-Alkyl- or 3-aryl-substituted furan-2(5*H*)-ones are obtained directly in fair yields by reductive carbonylation of alk-1-ynes in the presence of catalytic amounts of palladium iodide in conjunction with potassium iodide and water (eq 43).[164] The reactions



(43)

are carried out in dioxane/water under mild conditions (80 °C and 10 atm of carbon monoxide).

Rhodium complexes also catalyze the carbonylation of both terminal and internal acetylenes.[165] For example, a rhodium carbonyl cluster catalyzed the carbonylation of terminal acetylenes in water to give γ-lactones (eq 44).[166] Under water−gas shift reaction

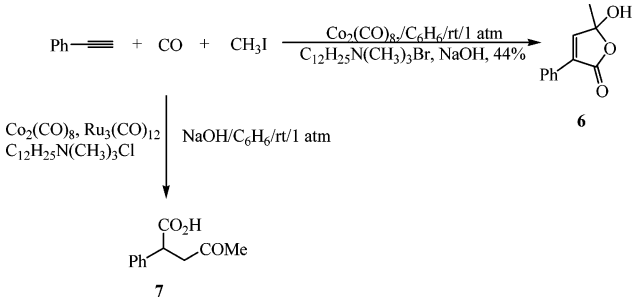


(44)

conditions, the carbonylation reaction of 2-(phenylethynyl)benzaldehyde catalyzed by $Rh_6(CO)_{16}$ gave a tricyclic lactone, indeno[2,1-*b*]furan, while the reaction of 2-(phenylethynyl)benzoate resulted in the formation of a tetracyclic lactone, indeno[1,2-*c*]isocoumarin.[167]

Rhodium-catalyzed carbonylation of 2-alkynylbenzylamines under water−gas shift reaction conditions gives a seven-membered heterocyclic product, 2,4-disubstituted 1,4-dihydrobenz[*c*]azepin-3-ones, in a good yield.[168]

Scheme 2. Carbonylation of Alkynes[a]

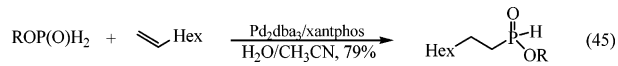


[a] Reprinted from ref 169 by permission of the Royal Society of Chemistry

Similarly, reaction of methyl iodide with alkynes and carbon monoxide resulted in the formation of 2-butenolides, **6**. However, if the reaction mixture was first treated with the cobalt complex and then reacted with a ruthenium carbonyl complex, the γ-keto acids **7** were obtained (Scheme 2).[169]

4.2.4. Hydrophosphinylation

A variety of different palladium catalysts promote the addition of hypophosphorus derivatives, $ROP(O)H_2$, to alkenes and alkynes in good yields and under mild conditions (eq 45). In particular, $Cl_2Pd(PPh_3)_2$/

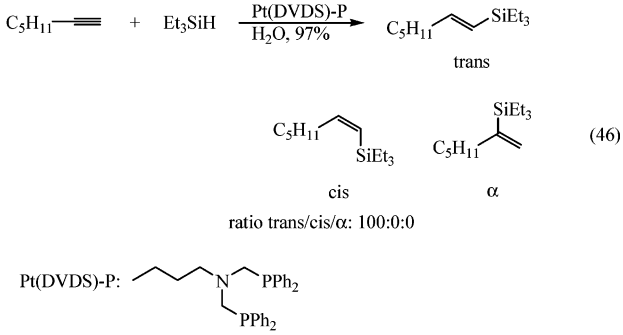


(45)

2MeLi, and Pd_2dba_3/xantphos allow for phosphorus−carbon bond formation instead of transfer hydrogenation. The methodology greatly extends upon previous routes for the preparation of H-phosphinic acids and other organophosphorus compounds.[170]

4.2.5. Hydrometalation/Coupling

A highly effective and stereoselective hydrosilylation of terminal alkynes was developed under the ambient conditions of air, water, and room temperature by using Pt(DVDS)-P as the catalyst (eq 46).[171]



(46)

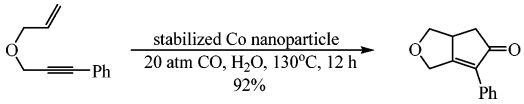
Pd(0)-catalyzed hydrogermylation of alkynes in water provides dienylgermanes efficiently with high stereo- and regioselectivity, and the reaction in water proceeds much faster than the reaction under neat conditions. [172]

By using rhodium as the catalyst and tributyltin hydride as the hydrometalating reagent, researchers developed a one-pot alkyne−hydrostannylation and conjugate addition to unsaturated carbonyl compounds.[173] Intramolecular reactions of alkynes with

furans and electron-rich arenes were catalyzed by $PtCl_2$. When the reaction is carried out in the presence of water, dicarbonyl compounds are obtained.[174]

4.2.6. Pauson–Khand-Type Reactions

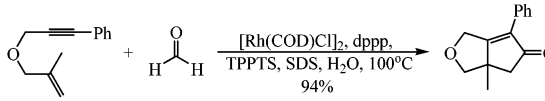
The Pauson−Khand reaction has proven to be the most effective way of forming cyclopentenone derivatives. Recently, the reaction has been studied in aqueous media, and it was found that a catalytic Pauson−Khand reaction can be promoted with a small amount of 1,2-dimethoxyethane or water.[175] Water also inhibited the formation of byproduct, possibly by modulating the reactivity of the catalyst through coordination.[176] An intramolecular Pauson−Khand reaction in water was successfully carried out by using aqueous colloidal cobalt nanoparticles as catalysts (eq 47).[177]



(47)

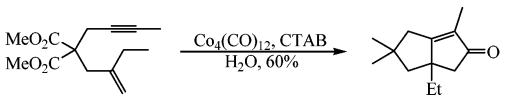
Additionally, $[Rh(COD)Cl]_2$−(*S*)-BINAP was used as the catalyst to effect an enantioselective Pauson−Khand reaction with carbon monoxide in a mixture of 1,4-dioxane and water containing sodium dodecyl sulfate (SDS). The fused cyclopentenones were prepared in 30−86% yields and in 67−93% ee.[178] The yields depended significantly upon the nature of the substrate (e.g., a 1,6-enyne with a nonterminal alkene failed to undergo the Pauson−Khand reaction with this catalyst system).

An aqueous $[RhCl(COD)]_2$-catalyzed Pauson−Khand-type reaction of enynes in the presence of formaldehyde as a water-soluble source of CO was developed by Kakiuchi and co-workers (eq 48).[179]



(48)

The decarbonylation (aqueous phase) and carbonylation (micellar phase) processes are believed to take place independently in different phases of the reaction system to result in a more efficient catalytic carbonylation reaction. When water was used as the only solvent, with the addition of surfactants, an efficient stoichiometric Pauson−Khand reaction under mild conditions was possible.[180] The use of a cationic surfactant, CTAB, provided good yields, and using $Co_4(CO)_{12}$ and CTAB provided variable results (eq 49).



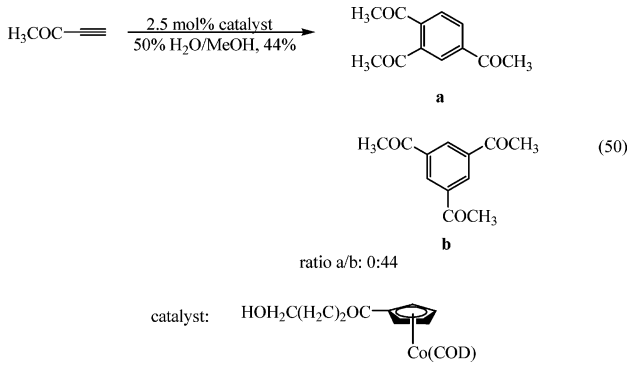
(49)

The reductive Pauson−Khand reaction (PKR) requires not only a proton source but also a polar solvent with good coordinating ability. Reductive PKR with water and $Co_2(CO)_8$ was most effective in dimethyl ether.[181]

4.2.7. Other Transition-Metal-Catalyzed Cyclization Reactions

[2 + 2 + 2] Cyclization. Parsons studied the cobalt(I) complex $CpCo(CO)_2$ catalyzed cyclotrimerizations of 1-hexyne, phenylacetylene, and 2-butyne to give their respective benzene derivatives in water at 374 °C. The hydrolysis of alkynes was observed only in the presence of acid, and water did not interfere with the cyclization. The product yields and regiochemistries were in good agreement with those reported for analogous cyclizations in organic solvents. In the absence of an added catalyst, unreacted alkyne was recovered. Pyridine synthesis via the coupling of alkynes and acetonitrile under supercritical conditions was also observed but was less effective due to relatively facile hydrolysis of the acetonitrile.[182]

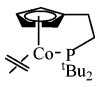
A new water-soluble cobalt catalyst that catalyzes alkyne cyclotrimerization in aqueous media under mild conditions was prepared (eq 50).[183] Additionally,



(50)

the protection of alkyne functional groups is not necessary, even for amines and carboxylic acids. The kinetic and double isotopic crossover data suggested a rate-determining dissociative coordination of the alkyne. This implies that the ligand moves to allow the alkyne access to the metal center.

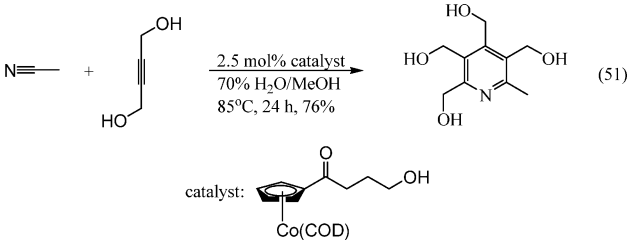
Chelate complex **8** (5 mol %) was found to catalyze



8

the [2 + 2 + 2] cyclization of terminal alkynes in good yields in a 80/20 mixture of water and ethanol at room temperature without further activation.[184] In the presence of $PdCl_2$, $CuCl_2$, and CO_2, both aryl and alkylalkynes afforded the corresponding cyclotrimerization products regioselectively in high yields.[185] Rhodium is also effective for such cyclizations in aqueous biphasic conditions.[120]

Hetero-[2 + 2 + 2] Cyclizations. Eaton and coworker reported a chemospecific cyclotrimerization of one nitrile with two alkynes for the synthesis of highly functionalized pyridines using a water-soluble cobalt(I) catalyst in aqueous media (eq 51).[186] This

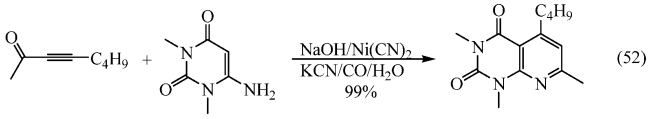


(51)

allows for the formation of highly functionalized pyridines under mild conditions without the need for

photochemical activation. Various functional groups are tolerated in this methodology, including unprotected alcohols, ketones, and amines. Various factors led the authors to suggest that there is an associative rate-determining coordination of the nitrile.

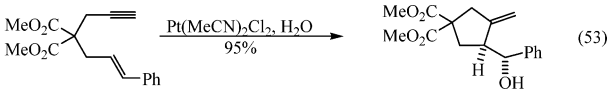
Reactions of 6-amino-1,3-dimethyluracil with substituted α-keto alkynes using homogeneous nickel catalyst in aqueous alkaline medium afforded substituted 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives in quantitative yields under very mild conditions (eq 52).[187] A mechanism has been proposed for the



(52)

reaction involving the nucleophilic attack of Ni(0) anion, formed in situ onto the triple bond of the substrate.

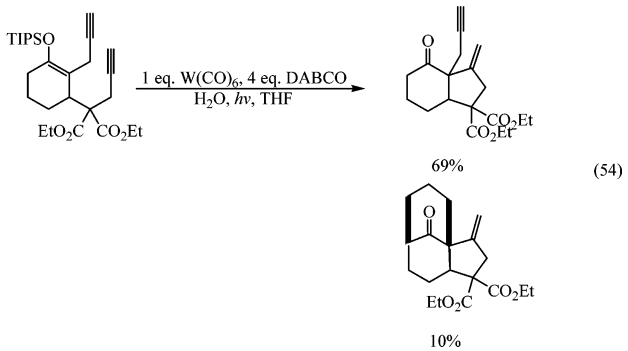
Enyne Cyclization. 1-En-6-ynes react with alcohols or water in the presence of $PtCl_2$ as catalyst to form carbocycles with alkoxy or hydroxy functional groups at the side chain (eq 53).[188]



(53)

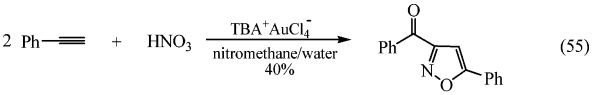
The formation of the C−C and C−O bonds takes place stereoselectively via trans addition of the electrophile derived from the alkyne and the nucleophile to the double bond of the enyne; the reaction ensues by *anti* attack of the alkene onto the (η^2-alkyne)platinum complex. The cyclization proceeds with atom economy and under relatively mild conditions. Of special interest is the alkoxy- and hydroxycyclization reactions because they allow for the simultaneous formation of C−C and C−O bonds from enynes. Based upon density functional theory (DFT) calculations, a cyclopropyl platinacarbene complex is the key intermediate, and it is formed by selective hydrogen abstraction of the *trans*-allylic substituent.

Other Cyclizations. A highly useful method for the construction of polycyclic compounds based on the amine-controlled exo- and endo-selective cyclizations of ω-alkynyl silyl enol ethers catalyzed by $W(CO)_5$-(L) was reported. When bis-alkynyl silyl enol ethers were treated with a catalytic amount of $W(CO)_6$, DABCO, and water under photoirradiation, synthetically useful tricyclic ketones were obtained in moderate yields (eq 54).[189]



(54)

Terminal alkynes react smoothly with nitric acid in 1:1 nitromethane/water and in the presence of a catalytic amount of tetrabutylammonium tetrachloroaurate to give 3,5-disubstituted isoxazoles (eq 55).[190] Some of the R groups allowed in this [2 + 2 + 1] reaction are alkyl, aryl, alkoxy, and carboxylate groups. The role of the catalyst was attributed to its attack on the triple bond of an electrophile ($AuCl_3$ or H^+) and of a nucleophile (NO_2^-) that leads to the formation of a vinyl nitrite, which is then converted into a nitrile oxide at the expense of either gold(III) or nitric acid. Subsequent 1,3-dipolar cycloaddition of a second mole of alkyne leads to the formation of the isoxazole. The same starting material is both the precursor of the nitrile oxide generated in situ and the reagent for the subsequent 1,3-dipolar cycloaddition. Additionally, nitromethane/water is a unique biphasic system for promoting this reaction.



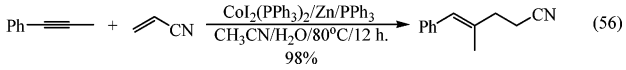
(55)

TBA: tetrabutylammonium

4.2.8. Reductive Coupling

The cathodic hydrodimerization of activated alkynes was studied under electrochemical conditions in aqueous media. Products are formed by competing hydrodimerization, hydrogenation, and nucleophilic addition to the triple bond, and their distributions depend strongly on the component of the electrolyte.[191]

In the presence of $Co(PPh_3)_2I_2$, PPh_3, water, and zinc powder, the reaction of alkynes with alkenes having an electron-withdrawing substituent proceeded smoothly in acetonitrile to give the corresponding reductive coupling products in fair to excellent yields (eq 56).[192] This reductive coupling is



(56)

highly regio- and stereoselective with only one isomer observed for each reaction.

The results of a deuterium isotope-labeling experiment support the idea that the observed regio- and stereochemistry is from the formation of a cobaltcyclopentene intermediate from cyclometalation of an alkyne and alkene to the cobalt(I) center followed by protonation of the intermediate by water. However, an alternative mechanism involving a cobalt(III) hydride generated from the protonation of cobalt(I) by water cannot be ruled out. The insertion of an acylate molecule into the metal−hydride bond gives the five-membered species, and further insertion of an alkyne and protonation provides the reductive coupling product. This pathway also explains the results of the isotope-labeling experiment and can account for the observed regioselectivity of alkynes.

Trost and Pinkerton have developed a ruthenium-catalyzed three-component coupling of an alkyne, an enone, and a halide ion to form (*E*)- or (*Z*)-vinyl halides.[193] This methodology allows for the formation of stereo-defined vinyl halides catalyzed by a cationic

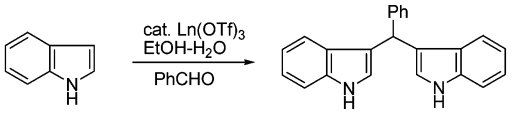
cyclopentadienyl ruthenium species. This catalyst system is the first example where either isomer of a vinyl halide can be accessed in a single catalyst system depending upon the counterion and the solvent. The optimized conditions for the formation of (*E*)-vinyl chlorides involved the use of cyclopentadienyl ruthenium(II) cyclooctadiene chloride, stannic chloride pentahydrate as a cocatalyst, and for a chloride source, either ammonium chloride in DMF/water mixtures or tetramethylammonium chloride in DMF. When alkynes with propargylic substituents are used, there is an enhanced selectivity for the (*Z*)-isomer. A mechanism involving a cis or trans halometalation is used to explain the formation of the observed products.

5. Reaction of Aromatic Compounds

5.1. Electrophilic Substitutions

The electrophilic substitution reaction is the most common reaction mode for aromatic compounds. Carbon−carbon bond formation via the electrophilic substitution of aromatic hydrogens proceeded under aqueous conditions. The most well-known example is the Friedel−Crafts-type reaction. Various indole derivatives reacted with equimolar amounts of 3% aqueous CH_2O and 33% aqueous Me_2NH at 70−75 °C for 10 min in 96% ethanol to give Mannich-type products.[194] Reactions of furan, sylvan, and furfuryl alcohol with aqueous formaldehyde in two- and three-phase systems in the presence of cation-exchange resins in their H^+-form or soluble acids gave hydroxymethylation products.[195] Both the acidity and the lipophilicity of the catalysts were found to play roles in hydroxymethylation depending on the reactivity of the substrates. Enzyme-catalyzed electrophilic aromatic substitution has been reported in prenyl-transfer reactions.[196] The substitution of heteroaromatic compounds by super-electrophilic 4,6-dinitrobenzofuroxan (DNBF) proceeded in H_2O−Me_2SO mixtures.[197]

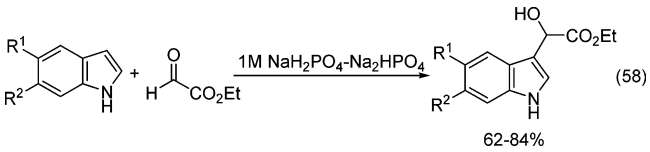
Instead of Brönsted acid, a lanthanide-catalyzed reaction of indole with benzaldehyde was reported by Wang (eq 57). The use of an ethanol/water system



(57)

was found to be the best in terms of both yield and product isolation. The use of organic solvent such as chloroform resulted in oxidized byproducts.[198]

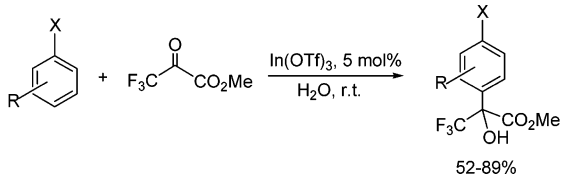
The reactions of *N*-methylindole and *N*-methylpyrrole via Friedel−Crafts reactions with $OCHCO_2Et$ in various aqueous solutions generated substituted indoles and pyrroles without using any metal catalyst (eq 58).[199]



(58)

62-84%

Bismuth tris-trifluoromethanesulfonate [$Bi(OTf)_3$] and $BiCl_3$ were found to be effective catalysts for the Friedel−Crafts acylation of both activated and deactivated benzene derivatives such as fluorobenzene.[200] Ga(III) triflate is also effective for Friedel−Crafts alkylation and acylation in alcohols and can tolerate water.[201] This catalyst is water-stable, and its catalytic activity is much higher than other metallic triflates, $M(OTf)_3$, previously reported (M = Al, Ga, Ln, or Sc). Scandium tris(dodecyl sulfate), a Lewis acid−surfactant combined catalyst, can be used for conjugate addition of indoles to electron-deficient olefins in water.[202] The 1,4-conjugate addition of indoles to nitroalkenes was efficiently carried out in aqueous media using a catalytic amount of indium tribromide (5 mol %).[203] The indium tribromide was recycled consecutively several times with the same catalyst. Rare-earth metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $Sm(OTf)_3$ work as highly effective catalysts for the chloromethylation of aromatic hydrocarbons with hydrochloric acid and trioxane.[204] They are active enough in aqueous solution at a concentration of less than 1−5% of the substrate under heterogeneous conditions of organic and aqueous phases. The triflate stays in the aqueous phase after the catalysis, and the organic products are easily separated from the catalyst. The catalyst in an aqueous solution could be recycled and used for further reactions without significant loss of activity. The catalysis occurred via the formation of a chloromethylated triflate complex and electrophilic addition to an aromatic hydrocarbon. $In(OTf)_3$-catalyzed Friedel−Crafts reaction of aromatic compounds with methyl trifluoropyruvate in water generated various α-hydroxyl esters (eq 59).[205]



(59)

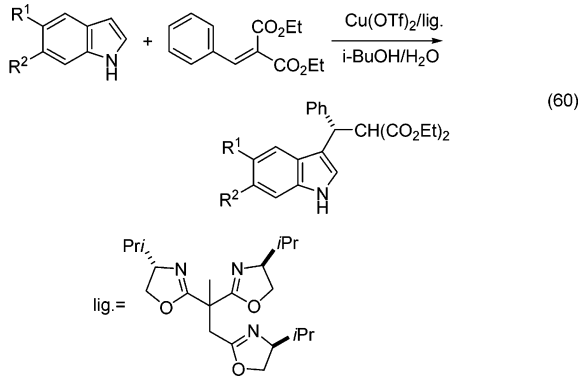
52-89%

Aqueous Friedel−Crafts reactions have also been used in polymer synthesis. The acid-catalyzed polymerization of benzylic alcohol and fluoride functionality in monomeric and polymeric fluorenes was investigated in both organic and aqueous reaction media.[206] Polymeric products are consistent with the generation of benzylic cations that participate in electrophilic aromatic substitution reactions. Similar reactions occurred in a water-insoluble Kraft pine lignin by treatment with an aqueous acid. A bisphenol A-type epoxy resin is readily emulsified in an aqueous medium with an ethylene oxide adduct to a Friedel−Crafts reaction product of styrene and 4-(4-cumyl)phenol as emulsifier.[207] A monoselective and C-specific alkylation of phloroglucinol with activated alkyl halides is reported in an aqueous buffer. [208]

Near-critical water has been used as a medium for various C−C bond formation reactions, including Friedel−Crafts alkylation and acylation.[209] In these reactions, near-critical water solubilizes the organics and acts as a source of both hydronium and hydroxide ions thereby replacing the normally required hazard-

ous solvents and catalysts that require subsequent neutralization and disposal.

Pseudo-C_3-symmetrical trisoxazoline copper(II) complexes prove to be excellent catalysts in the Friedel–Crafts alkylation of indoles with alkylidene malonates (eq 60). Water tolerance of chiral catalyst

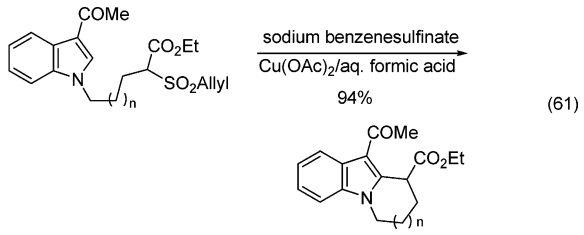


(60)

trisoxazoline/Cu(OTf)$_2$ is examined, and it is found that the addition of up to 200 equiv of water relative to the catalyst in *iso*-butyl alcohol has almost no effect on enantioselectivity but slows the reaction.[210]

5.2. Radical Substitution

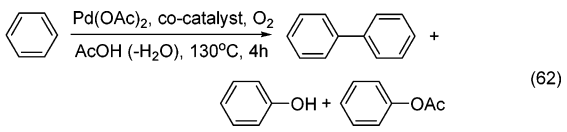
Alkyl radicals generated efficiently from allyl sulfones in 80% aqueous formic acid induced cyclization reactions on aromatic and heteroaromatic compounds to provide polycyclic aromatic and heteroaromatic derivatives (eq 61).[211]



(61)

5.3. Oxidative Coupling

The combination of Pd(OAc)$_2$/molybdophosphoric acid ($H_3PMo_{12}O_{40}$)/O_2/AcOH–H_2O (2:1) has been found to oxidize benzene to give biphenyl by oxidative dimerization with 100% selectivity and 19% yield under the conditions of 130 °C, 10 atm, and 4 h.[212] The use of $PdHPMo_{12}O_{40}$ itself as catalyst was found to be effective and gave 95% selectivity of biphenyl with a lower yield (eq 62). Poly(oxy-1,4-phenylene)



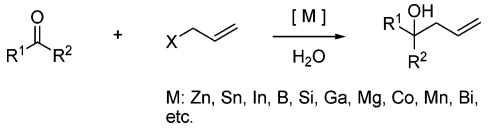
(62)

was obtained by electro-oxidative polymerization of *p*-bromophenol in aqueous NaOH solution. The yield increased when aqueous NaOH was replaced with aqueous KOH or the temperature increased. In contrast, *p*-chlorophenol dimerized to give 2,7-dichlorodibenzo[1,4]dioxin.[213]

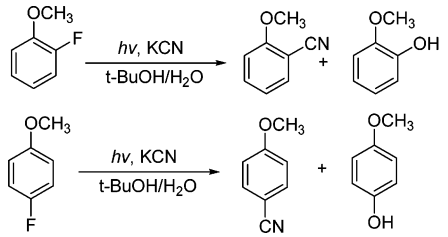
5.4. Photochemical Reactions

Interestingly, the use of water as solvent influences the chemoselectivity in photochemical substitution

Scheme 3



reactions. For example, while the photochemical aromatic substitution of fluorine by the cyano group in *ortho*-fluoroanisole gives predominantly the hydoxylation product, the same reaction with *para*-fluoroanisole generates the cyanation product preferentially (eq 63).[214] The hydrogen bonding between



(63)

water and the methoxyl group was attributed to the hydroxylation reaction in *ortho*-fluoroanisole. The effect of such hydrogen bonding on the product distribution is much less in the latter case.

6. Reaction of Carbonyl Compounds

6.1. Nucleophilic Additions

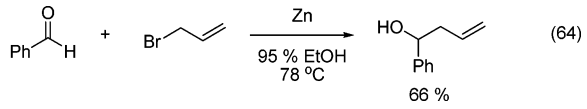
The nucleophilic addition of organometallic reagents to carbonyl compounds is among the most important methods for forming C–C bonds. However, a major requisite in these reactions is the strict exclusion of moisture. On the other hand, some classes of organometallics remain viable in the presence of water. For example, the preparation of arylmercuric chlorides in aqueous media has been known since 1905.[215] And in the 1960s, tribenzylstannyl halide was produced on a large scale in water.[216] Wurtz-type reductive coupling of allyl halides proceeded in aqueous alcohol.[217] These reports indicated the possibility of carrying out these kinds of reactions in water under special circumstances. Indeed, within the past two decades, extensive research has been carried out on developing organometallic-type nucleophilic additions in aqueous media. Although a large amount of the research has been on allylation reactions, the reaction has been extended to all types of substrates.

6.1.1. Allylation

Among all the nucleophilic addition reactions of carbonyl compounds, the allylation reaction has been the most successful, partly due to the relatively high reactivity of allyl halides. Various metals have been found to be effective in mediating such a reaction (Scheme 3). Among them, indium came out as the most popular metal for such a reaction.

Mediated by Zinc. In 1977,[218] Wolinsky et al. reported that slow addition of allyl bromide to a stirred slurry of "activated" zinc dust and an aldehyde or a ketone in 95% ethanol at 78 °C gave allylation

products in yields comparable to those obtained in aprotic solvents (eq 64). Then, in 1985 Luche et al.



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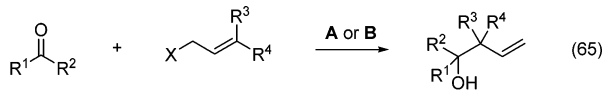
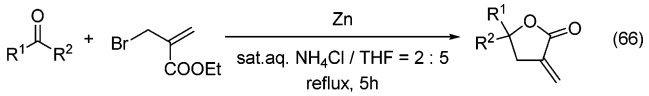
found that allylation of aldehydes and ketones can be effected in aqueous media using zinc as the metal and THF as a cosolvent under magnetic stirring or sonication conditions (eq 65).[219,220] The replacement



(65)

A: Zn, sat.aq. NH_4Cl / THF = 5 : 1, r.t., stirring;
B: Sn, H_2O / THF =5 : 1, sonication.

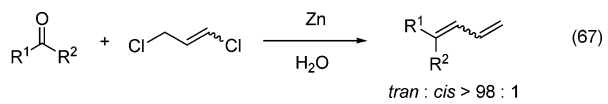
of water by an aqueous saturated ammonium chloride solution enhanced the efficiency due to both the increased acidity of the media and the formation of complexes between the metal ion and ammonia. In this case, comparable results were obtained either with or without the use of sonication. In the same year, Benezra et al. reported[221] that ethyl (2-bromomethyl)acrylate can couple with carbonyl compounds, mediated by metallic zinc, in a mixture of saturated aqueous $NH_4Cl-THF$ under reflux to give α-methylene-γ-butyrolactones (eq 66). The same re-



(66)

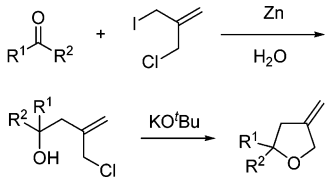
action in THF alone gives only a low yield (15%) of the product within the same time range and under the same conditions. Although it is much less effective, (2-bromomethyl)acrylic acid could also be used directly upon neutralization with triethylamine. Later, Wilson carried out a more detailed study of zinc-mediated reactions in water[222] through a modification involving the use of a solid organic support instead of the cosolvent THF. The solid organic supports included reverse-phase C-18 silica gel, biobeads S-X8, which is a spherical porous styrene divinylbenzene copolymer with 8% cross-links, GC column packing OV-101 on Chromosorb, etc. The reactions proceed at about the same rate as reactions with THF as a cosolvent. Both allyl bromide and allyl chloride can be used. Kunz and Reissig reported[223] the zinc-mediated allylation of methyl γ-oxocarboxylates in a mixture of saturated aqueous ammonium chloride and THF. The reaction provides a convenient synthesis of 5-allyl-substituted γ-lactone.

Chan and Li reported that conjugated 1,3-butadienes were produced in moderate yields when carbonyl compounds reacted with 1,3-dichloropropene and zinc in water (eq 67).[224] The use of 3-iodo-1-



(67)

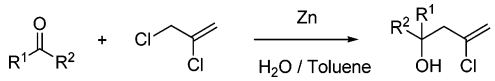
chloropropene instead of 1,3-dichloropropene greatly improved the yields. When the reactions were interrupted after their initial allylations, subsequent base treatment of the intermediate compounds produced vinyloxiranes in high yields. Similarly, reactions of carbonyl compounds with 3-iodo-2-chloromethyl-1-propene followed by base treatment produced 2-methylenetetrahydrofurans (eq 68).[225] Thus, the 3-iodo-



(68)

2-chloromethyl-1-propene here served as a novel trimethylenemethane equivalent.[226]

Oda et al. reported that under reflux conditions, the zinc-promoted reaction of 2,3-dichloro-1-propene with aldehydes and ketones in a two-phase system of water and toluene containing a small amount of acetic acid gave 2-chloroallylation products (eq 69).[227]



(69)

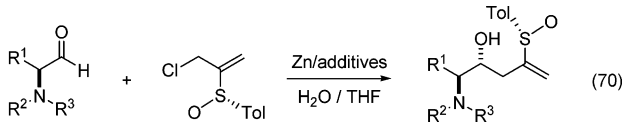
No conversion occurred when tin was used as the promoter. The absence of water completely shuts down the reaction. Interestingly, the action of 2,3-dichloropropene plus zinc powder in aqueous ethanol gives the dechlorination product, allene.[228]

Reisse used "activated" zinc for aqueous Barbier-type reactions.[229] Submicromic zinc powder produced by pulsed sono-electroreduction is about three times more effective than the commercial variety. The stereochemical course of the allylation and propargylation of several aldehydes with crotyl and propargyl halides using zinc powder as the condensing agent in cosolvent/water(salt) media have been extensively studied.[230] The Zn-mediated reactions of cinnamyl chlorides with aldehydes and ketones in $THF-NH_4Cl(aq)$ give both α- and γ-addition products, as well as phenylpropenes and dicinnamyls, indicating the presence of radical intermediates in the reaction.[231] Enolizable 1,3-dicarbonyl compounds can be allylated by zinc.[232]

An efficient route for the synthesis of the Phe-Phe hydroxyethylene dipeptide isostere precursors, utilized for the design of potential inhibitors of renin and HIV protease, was developed. The key step is the zinc-mediated stereoselective allylation of N-protected α-amino aldehydes in aqueous solution.[233] $NaBF_4/M$ (M = Zn or Sn) showed facilitating allylation of a variety of carbonyl compounds in water; α- and γ-addition products of crotylations could be alternatively obtained under the control of this novel mediator.[234]

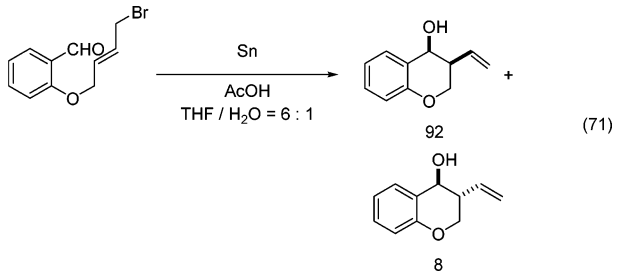
The aqueous medium Barbier–Grignard-type reaction has also been used in the synthesis of various compounds. Chan and Li used the zinc-mediated allylation as a key step in a total synthesis of (+)-muscarine.[235] The strategy was based on the observation that the diastereoselectivity of the allylation reaction in water can be reversed through protection of the α-hydroxyl group. Diastereoselective allylation

under aqueous Barbier conditions of α-amino aldehydes with the chiral building block (*S*)-3-chloro-2-(*p*-tolylsulfinyl)-1-propene gave enantiomerically pure sulfinyl amino alcohol in good yields and diastereoselectivity (eq 70).[236]



(70)

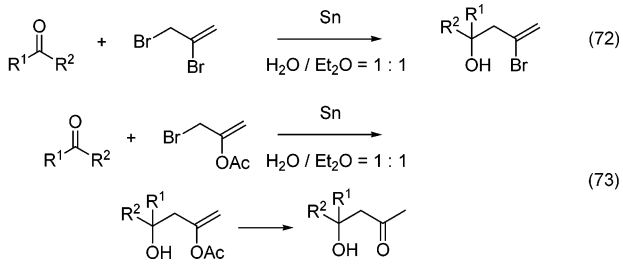
Mediated by Tin. In 1983, Nokami et al. observed an acceleration of the reaction rate during the allylation of carbonyl compounds with diallyltin dibromide in ether through the addition of water to the reaction mixture.[237] In one case, through the use of a 1:1 mixture of ether/water as solvent, benzaldehyde was alkylated in 75% yield in 1.5 h, while the same reaction only gave less than 50% yield in a variety of organic solvents, such as ether, benzene, or ethyl acetate, even after a reaction time of 10 h. The reaction was equally successful with a combination of allyl bromide, tin metal, and a catalytic amount of hydrobromic acid. In the latter case, the addition of metallic aluminum powder or foil to the reaction mixture dramatically improved the yield of the product. The use of allyl chloride for such a reaction, however, was not successful. The reaction can also proceed intramolecularly. When the combination of tin, aluminum, and hydrobromic acid in an aqueous medium was used, ketones having allylic halide functionality were cyclized to form five- and six-membered rings.[238] Similar reactions occurred with aldehydes.[239] The intramolecular allylation of carbonyl compounds promoted by metallic tin proceeds in a stereo-controlled manner to give cyclic products with high diastereoselectivity (eq 71).



(71)

Later, Torii et al. found that the tin−aluminum-mediated allylation can be carried out with the less expensive allyl chloride, instead of allyl bromide, when a mixture of alcohol−water−acetic acid was used as the solvent.[240] When combined with stoichiometric amounts of aluminum powder, both stoichiometric and catalytic amounts of tin are effective. As reported by Wu et al., higher temperatures can be used instead of aluminum powder.[241] Under such a reaction condition, allyl quinones were obtained from 1,4-quinones, followed by oxidation with ferric chloride. Allylation reactions in water/organic solvent mixtures were also carried out electrochemically with the advantage that the allyltin reagent could be recycled.[242]

Otera et al. extended the tin-mediated allylation to 2-substituted allyl bromides.[243] When 2-bromo and 2-acetoxy-3-bromo-1-propene were used, the allylation with tin produced the corresponding functionalized coupling products (eqs 72 and 73). In the case



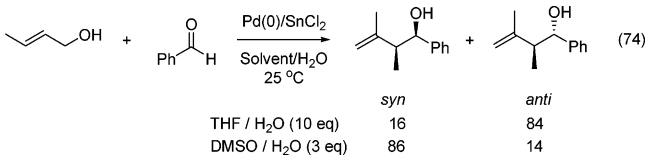
(72)

(73)

of 2,3-dibromopropene, the reaction occurred exclusively through allylation in the presence of the vinyl bromo group. The presence of other electrophiles, such as a nitrile (−CN) or an ester (−COOR), did not interfere with the reaction.

Luche found that tin-mediated allylations can also be performed through ultrasonic radiation, instead of using aluminum powder and hydrobromic acid (possibly cleaning the metal surface and increasing the acidity of the medium) to promote the reaction.[244,245] The use of a saturated aqueous NH_4Cl/THF solution instead of water/THF dramatically increased the yield. When a mixture of aldehyde and ketone was subjected to the reaction, highly selective allylation of the aldehyde was achieved.

The allylation of carbonyl compounds in aqueous media with $SnCl_2$ can also employ allylic alcohols (eq 74)[246] or carboxylates[247] in the presence of a pal-

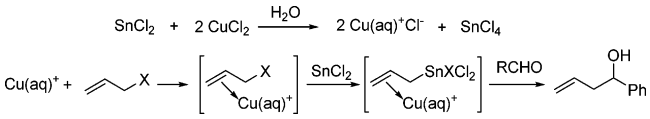


(74)

ladium catalyst. The diastereoselectivity of the reactions with substituted crotyl alcohols was solvent-dependent. Improved diastereoselectivity resulted when a mixture of water and THF or DMSO was used instead of the organic solvent alone.

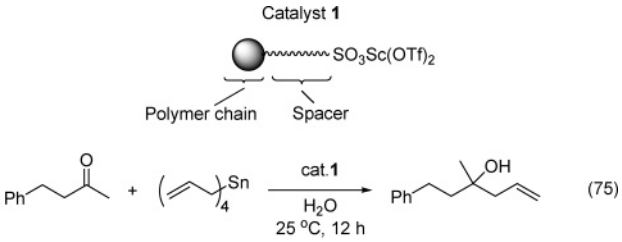
Allylations, allenylations, and propargylations of carbonyl compounds in aqueous media can also be carried out with preformed organic tin reagents, rather than through the use of metals.[248−250] For example, the allylation reaction of a wide variety of carbonyl compounds with tetraallyltin was successfully carried out in aqueous media by using scandium trifluoromethanesulfonate (scandium triflate) as a catalyst.[251] A phase-transfer catalyst (PTC) is found to help the allylation mediated by tin at room temperature without any assistance.[252] Recently, nanometer tin-mediated allylation of aldehydes or ketones in distilled or tap water gave rise to homoallyl alcohol in high yield without any other assistance such as heat or ultrasound or acidic media.[253] Allylation of β-keto aldehydes and functionalized imines by diallyltin dibromide was carried out to generate skipped and conjugated dienes.[254] Aldehydes are allylated with CH_2:$CHCH_2SnBu_3$ using Sn catalysts in acidic aqueous media. Exclusive aldehyde selectivity was observed for competitive reactions of

Scheme 4



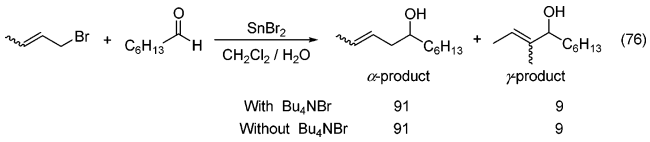
aldehydes and ketones in the presence of 5 mol % of $(CH_2{:}CHCH_2)_4Sn$ or $SnCl_4$ in a mixture of aqueous HCl and THF.[255]

Methyltin trichloride and indium(III) chloride promote the addition of aldehydes to cyclic allylic stannanes, providing good yields of the corresponding homoallylic alcohols.[256] Bu_4NBr/PbI_2 acts as an effective catalyst for the allylation of aldehydes with allylic tin reagents in water.[257] High *syn* selectivity was achieved in water without any aprotic solvents in the reaction of the aromatic aldehydes with crotyltri-*n*-butyltin irrespective of their *E*/*Z* geometry. A Lewis acid−surfactant combined catalyst (LASC) has been developed and applied to Lewis-acid-catalyzed allylation by allyltin reagents in water.[258] $PhSO_3Sc(O_3SCF_3)_2$, attached to divinylbenzene-cross-linked polystyrene by a pentylphenylpentyl spacer, was prepared. The catalyst is active in water and several C−C bond-forming reactions proceeded smoothly and in high yields with this catalyst (eq 75).[259]



(75)

1-Bromobut-2-ene in a dichloromethane−water biphasic system at 25 °C causes α-regioselective addition to aldehydes with $SnBr_2$ to produce 1-substituted pent-3-en-1-ols and causes γ-regioselective addition to aldehydes with $SnBr_2-Bu_4NBr$ to produce 1-substituted 2-methylbut-3-en-1-ols (eq 76).[260]

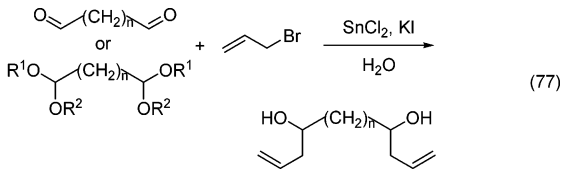


(76)

The allylation of aldehydes using stannous chloride and catalytic cupric chloride or copper was reported in aqueous media.[261] In situ probing experiments provided indirect (NMR, CV) and direct (MS) evidence for the copper(I)-catalyzed formation of an allyltrihalostannane intermediate at a very high concentration in water (Scheme 4). A hydrophilic palladium complex also efficiently catalyzes the allylation of carbonyl compounds with allyl chlorides or allyl alcohols and $SnCl_2$ under aqueous−organic biphase conditions, which allow the separation of the product and recovery of the organic solvent from the reaction mixture easily.[262] A combination of $TiCl_3$ and $SnCl_2$ is also effective for the allylation.[263]

A solid-phase version of the palladium-catalyzed carbonyl allylation of aldehydes by allylic alcohols was also reported. Allylation of resin-bound aldehyde (P = Merrifield resin) with allylic alcohols (e.g., $MeCH{:}CHCH_2OH$) in the presence of $SnCl_2$ afforded the homoallylic alcohols under different solvent conditions, in DMSO and aqueous DMSO.[264]

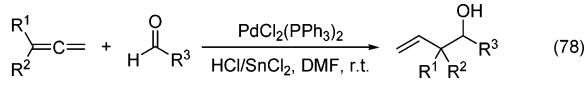
Bis-homoallylic alcohols were prepared in good yields by allylation of dialdehydes or their acetals with allyl bromide, tin(II) chloride, and potassium iodide in water or water/THF (eq 77).[265] Under



(77)

ultrasonication, $SnCl_2$ could efficiently mediate the aqueous Barbier reactions between carbonyl compounds and allyl bromide to give the corresponding homoallylic alcohols in high yields without using any additional Lewis acid catalyst.[266]

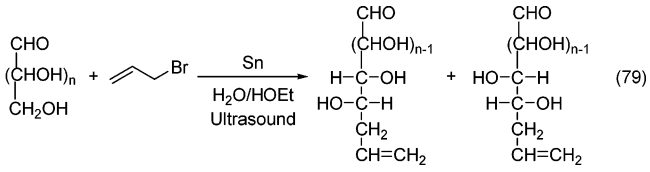
Highly regio- and stereoselective allylation of aldehydes by allenes proceeds smoothly in aqueous/organic media in the presence of $PdCl_2(PPh_3)_2$, HCl, and $SnCl_2$. For example, reaction of 1,1′-dimethylallene with $SnCl_2$ and PhCHO, under the above named conditions, gave the corresponding carbonyl allylation product in 95% isolated yield (eq 78). The reaction



(78)

likely occurs via hydrostannylation of allenes and allylation of aldehydes by the in situ generated allyltrichlorotins to afford the final products.[267]

In 1991, Whitesides et al. reported the first application of the aqueous Barbier−Grignard reaction to carbohydrate synthesis through the use of tin in an aqueous/organic solvent mixture (eq 79).[268] The

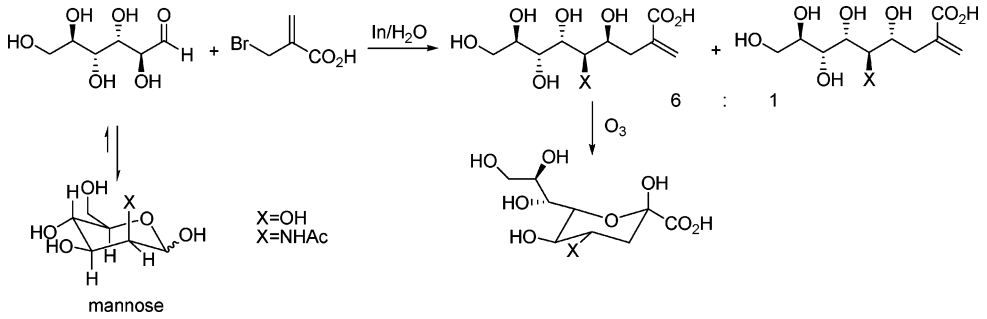


(79)

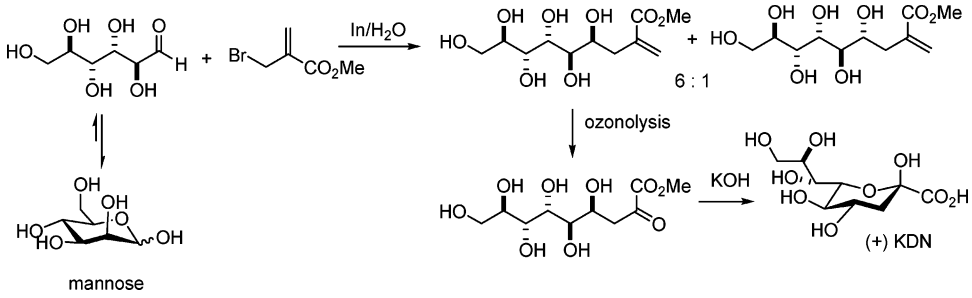
adducts were converted into higher carbon aldoses by ozonolysis of the deprotected polyols followed by suitable derivatization. The reaction showed a higher diastereoselectivity when there was a hydroxyl group present at C-2. However, no reaction was observed under the reaction conditions when there was an *N*-acetyl group present at the C-2 position.

Mediated by Indium. In 1991, Li and Chan reported the use of indium to mediate Barbier−Grignard-type reactions in water.[269] The work was designed on the basis of the first ionization potentials of different elements,[270] in which indium has the lowest first ionization potential relative to the other metal elements near it in the periodic table. On the other hand, indium metal is not sensitive to boiling water or alkali and does not form oxides readily in air. Such special properties of indium indicate that it is perhaps a promising metal for aqueous Barbier−Grignard-type reactions. Indeed, it appears that

Scheme 5

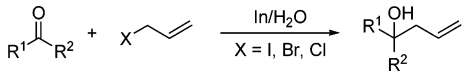


Scheme 6. Synthesis of Sialic Acids[a]



[a] Reprinted from ref 279 by permission of the Royal Society of Chemistry.

indium is the most reactive and effective metal for such reactions (eq 80). When the allylation was



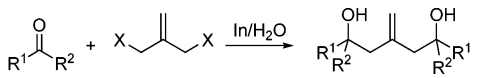
(80)

mediated by indium in water, the reaction went smoothly at room temperature without any promoter, whereas the use of zinc and tin usually requires acid catalysis, heat, or sonication. Furthermore, the coupling of ethyl 2-(bromomethyl)acrylate with carbonyl compounds proceeds equally well under the same reaction conditions, which makes the synthesis of sialic acids possible.

Later, Araki et al. found that the allylation of aldehydes and ketones can be carried out by using catalytic amounts of indium(III) chloride in combination with aluminum or zinc metal.[271] This reaction was typically performed in a THF−water (5:2) mixture at room temperature, although the conversion is much slower relative to the same reaction mediated by use of a stoichiometric amount of indium, and it requires days to complete. When the reaction was carried out in anhydrous THF, the yield dropped considerably, while side-reactions (such as reducing to alcohol) increased. The combinations of Al−$InCl_3$ or Zn−$InCl_3$ gave comparable results.

Whitesides et al. examined the effect of substituents on the allylic moiety on the indium-mediated reactions in water and found that the use of indium at room temperature gave results comparable to those of tin-mediated reactions carried out at reflux.[272] Replacement of the aqueous phase with 0.1 N aqueous HCl further increased the rate of the reaction by increasing the acidity of the medium. The transformation can also be carried out with preformed allylindium chloride.

The carboxylic acid functionality on allyl halides is compatible with the indium-mediated reactions (Scheme 5).[273,274] Thus, when the 2-(bromomethyl)-acrylic acid, instead of the ester, was treated directly with carbonyl compounds and indium in water, the corresponding γ-hydroxyl-α-methylenecarboxylic acids were generated in good yields. The combination of 2-halomethyl-3-halo-1-propene with carbonyl compounds mediated by indium in water generates bis-allylation products (eq 81).[275] The bis-allylation of 1,3-



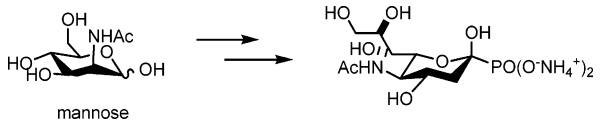
(81)

dibromo-propene with carbonyl compounds mediated by indium in water gave predominately the 1,1-bisallylation product.[276]

The indium-mediated allylation carried out with allylstannanes in combination with indium chloride in aqueous media was reported by Marshall et al.[277] Allyl indium was proposed as the reaction intermediate. Various aldehydes can be very efficiently alkylated with 3-bromo-2-chloro-1-propene mediated by indium in water at room temperature. Subsequent treatment of the compound with ozone in methanol followed by a workup with sodium sulfite provided the desired hydroxyl ester in high yield.[278]

Because of its superior reactivity, the indium-mediated reaction in water has found wide applications in natural product synthesis. Chan and Li reported[279] an efficient synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) (Scheme 6) using the indium-mediated alkylation reaction in water. A similar synthesis of 3-deoxy-D-manno-octulonate led primarily to the undesired diastereomer. However, through the disruption of the newly generated stereogenic center,[280] a formal synthesis[281] of KDO was completed. In contrast to the tin-mediated reactions, the indium-mediated reaction also occurred on a substrate with an *N*-acetyl group present at C-2. Whitesides et al. reported the synthesis of *N*-acetyl-

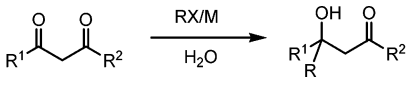
Scheme 7



neuraminic acid,[282] as well as other sialic acid derivatives, based on this strategy. The use of indium is essential for the carbon−carbon bond formation step in these sialic acid syntheses. KDO was synthesized via indium-mediated allylation of 2,3:4,5-di-*O*-isopropylidene-D-arabinose.[283] In this case, the desired product became the major product due to the protection of the α-hydroxyl group. Subsequently, Chan et al. further shortened the already concise sialic acid synthesis to two steps through the indium-mediated reaction of α-(bromomethyl)acrylic acid with sugars. Both KDN and *N*-acetyl-neuraminic acid have been synthesized in such a way.[58] The indium-mediated allylation reaction was applied by Schmid et al. to the elongation of the carbon chain of carbohydrates in forming higher analogues[284] and to deoxy sugars.[285]

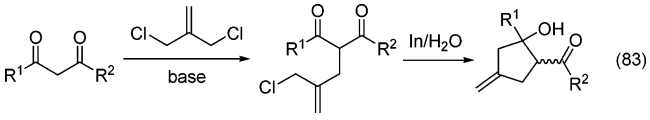
Phosphonic acid analogues of both KDN and *N*-acetyl-neuraminic acid have been synthesized using the indium-mediated coupling of the lower carbohydrates with dimethyl 3-bromopropenyl-2-phosphonate in water (Scheme 7).[286]

Loh reported the reaction of the glucose-derived aldehyde with allyl bromide mediated by indium.[287] The reaction again gives a nonchelation product as the major diastereomer. The use of an organic cosolvent increases the diastereoselectivity. The addition of ytterbium trifluoromethanesulfonate [Yb(OTf)$_3$] enhances both the reactivity and the diastereoselectivity. Enolizable 1,3-dicarbonyl compounds undergo efficient carbonyl allylation reactions in aqueous media (eq 82).[288] A variety of 1,3-dicarbonyl com-



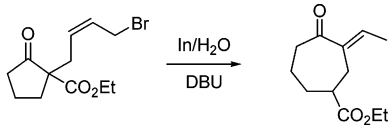
(82)

pounds have been alkylated successfully using allyl bromide or allyl chloride in conjunction with either tin or indium. The reaction can be used readily for the synthesis cyclopentane derivatives (eq 83).[289] The



(83)

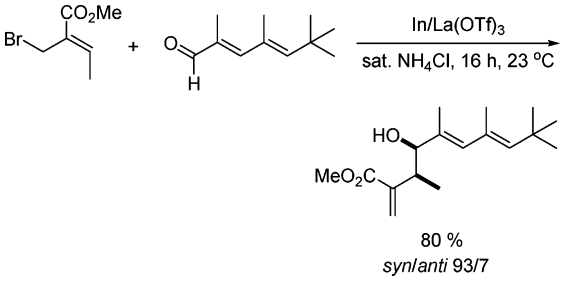
allylation reaction in water could also be used to prepare α,α-difluorohomoallylic alcohols from *gem*-difluoro allyl halides.[290] Application of the aqueous Barbier-type reaction in a carbocycle ring enlargement methodology was developed by Li and coworkers (eq 84).[291] By use of the indium-mediated



(84)

Barbier-type reaction in water, five-, six-, seven-, eight-, and twelve-membered rings are enlarged by two-carbon atoms into seven-, eight-, nine-, ten-, and fourteen-membered ring derivatives, respectively. The use of water as a solvent was found to be critical for the success of the reaction. Similar ring expansion in organic solvents was not successful. The ring expansion has also been applied to the synthesis of heterocyclic medium rings.[292] One-carbon ring expansion was similarly reported.[293]

Indium-mediated allylation of an unreactive halide with an aldehyde[294] was used to synthesize an advanced intermediate in the synthesis of antillatoxin,[295] a marine cyanobacterial (*Lyngbya majuscula*) toxin that is one of the most ichthyotoxic compounds isolated from a marine plant to date. In the presence of a lanthanide triflate, the indium-mediated allylation of (*Z*)-2-bromocrotyl chloride and aldehyde in saturated aqueous NH_4Cl under sonication yielded the desired advanced intermediate in a 1:1 mixture of diastereomers in 70% yield. Loh et al.[296] then changed the halide compound to methyl (*Z*)-2-(bromomethyl)-2-butenoate and coupled it with aldehyde under the same conditions to yield the desired homoallylic alcohol in 80% yield with a high (93:7) *syn*/*anti* selectivity (eq 85).

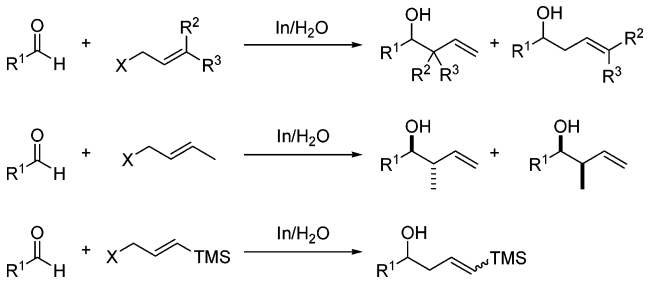


(85)

The indium-mediated allylation of trifluoroacetaldehyde hydrate (R = H), trifluoroacetaldehyde ethyl hemiacetal (R = Et), or dihydropyran and dihydrofurans with an allyl bromide in water yielded the homoallyl alcohols.[297] Lanthanide triflate-promoted indium-mediated allylation of aminoaldehyde in aqueous media generated β-amino alcohols stereoselectively.[298] Indium-mediated intramolecular carbocyclization in aqueous media generated fused α-methylene−γ-butyrolactones.[299] Forsyth and co-workers applied the indium-mediated allylation in the synthesis of an advanced intermediate for azaspiracids.[300] Other potentially reactive functionalities, such as azide, enone, and ketone, did not compete with the aldehyde for reaction with the in situ generated organo-indium intermediate.

Chemo-, Regio-, and Stereoselectivity. The regioselectivity of indium-mediated coupling has been examined (Scheme 8).[303] The following conclusions can be drawn: (1) In general, the reaction gives the regioisomer where the substituent is α to the carbon−carbon bond to be formed. (2) The regioselectivity is governed by the steric size of the substituent but not by the degree of substitution. When the substituent is sterically bulky (e.g., *tert*-butyl or silyl), the preferred regioisomer formed has the substituent away (at the γ-position) from the carbon−carbon bond being created. (3) Regioselectivity is not governed by the conjugation of the double

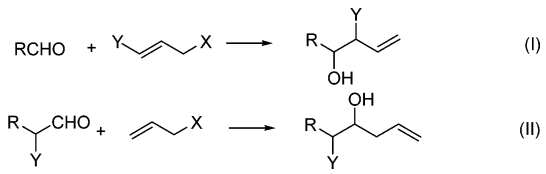
Scheme 8[a]



[a] Reprinted with permission from ref 303. Copyright 1995 Elsevier.

bond with the substituent. (4) Regioselectivity is independent of the geometry of the double bond and either *E*- or *Z*-cinnamyl bromide coupled with *i*-butanal to give the same regioisomer. (5) Regioselectivity is independent of the initial location of the substituent on the double bond.

The stereochemistry of the reaction in aqueous media is somewhat analogous to that in organic solvents. In terms of diastereoselectivity, two types of situations prevail (type I and type II). Within the type I situation, the reaction can favor either syn or anti diastereoselectivity, depending on the properties of the α-substituents. The presence of a strong α-chelating group, such as a hydroxyl, leads to syn product, whereas a non-α-chelating group, such as a methyl, produces anti product. However, when a weak α-chelating group (e.g., alkoxyl) is present, allylation in an organic solvent usually favors a chelation-controlled product. In contrast, the presence of an α-alkoxyl group will generate the non-chelating product through the aqueous reactions.[301] Thus, it is possible to reverse the diastereoselectivity of an allylation simply either by using a free hydroxyl group or by protecting it as an alkoxyl. In the type I situation, the stereogenic center can be farther away from the carbonyl group. Such an example can be found in Waldmann's studies of the diastereoselectivity of allylations using proline benzyl ester as a chiral auxiliary to produce α-hydroxyl amides. The diastereoselectivity was around 4−5:1.[302] Separation of the diastereomers followed by reaction with methyllithium produced the enantiomerically pure alcohol.

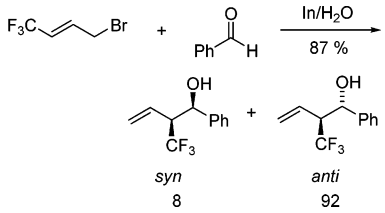


The type II situation usually gives an anti diastereoselectivity that is independent of the stereochemistry of the double bond in the allyl bromide moiety. The diastereoselectivity (anti/syn ratio) is governed by the steric size of the substituent on the aldehydes. Anti/syn ratio increases as the size of the aldehyde R group increases.

Normally, the addition of C-nucleophiles to chiral α-alkoxyaldehydes in organic solvents is opposite to the Cram's rule. The anti-Cram selectivity has been rationalized on the basis of chelation control.[304] The same anti preference was observed in the reactions of α-alkoxyaldehydes with allyl bromide/indium in water.[305] However, for the allylation of α-hydroxyaldehydes with allyl bromide/indium, the syn isomer is the major product. The syn selectivity can be as high as 10:1 (syn/anti) in the reaction of arabinose. It is argued that in this case, the allylindium intermediate coordinates with both the hydroxy and the carbonyl function, leading to the syn adduct.

The same coordination is used to account for the observed anti preference in the allylation of β-hydroxybutanal with allyl bromide/indium in water. The intermediate leads to the anti product. In support of the intramolecular chelation model, it is found that if the hydroxy group is converted into the corresponding benzyl or *tert*-butyldimethylsilyl ether, the reaction is not stereoselective at all and gives nearly equal amounts of syn and anti products.

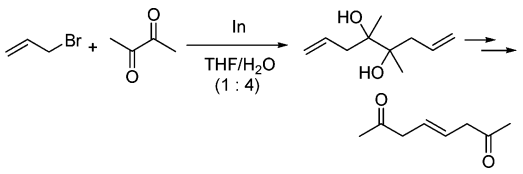
It is possible to combine both type I and type II situations in the coupling of a chiral aldehyde with a substituted allylic halide. Such is the case in the coupling of unprotected aldoses (e.g., glyceraldehyde) with cinnamyl bromide. In such a coupling, two new stereogenic centers are created. It has been found that the syn,syn isomer is formed preferentially. To account for the syn,syn stereochemistry, chelation of the allylindium species with the hydroxyaldehyde function with intramolecular attack through a cyclic transition state is postulated. The stereochemistry of the adduct is then dependent on the geometry of the attacking allylindium species. The In-mediated allylation of aldehydes with $BrCH_2CH{:}CHCF_3$ in water afforded α-trifluoromethylated homoallylic alcohols in high yields (eq 86).[306]



(86)

Allylation reactions of racemic and optically pure 4-oxoazetidine-2-carbaldehydes were investigated both under anhydrous conditions and in aqueous media. Indium-promoted allylation showed a reverse diastereofacial preference, although the observed selectivity is not synthetically useful.[307] Indium-mediated allylation of *gem*-diacetates gave excellent yields of the corresponding homoallylic acetates in aqueous media.[308] Allyl addition to α-diketones by treatment with allyl bromide and indium in water/THF gives diallyl diols such as $H_2C{:}CHCH_2CPh(OH)CH(OH)$-$CH_2CH{:}CH_2$ with moderate stereoselectivities. Ring-closing metathesis of the diallyl diols with Grubbs' ruthenium olefin metathesis catalyst, followed by

catalytic hydrogenation and diol cleavage with leadtetraacetate, gave *cis*-alkenediones (eq 87).[309] The allyl-

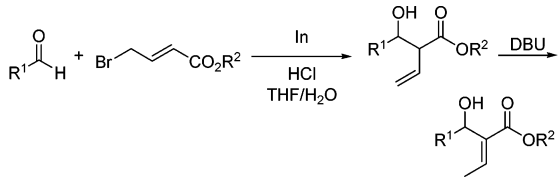


(87)

ation was applied in the total asymmetric synthesis of the putative structure of the cytotoxic diterpenoid (−)-sclerophytin and of the authentic natural sclerophytins.[310]

Allylation of the C-3 position of the cephem nucleus was accomplished by either indium-mediated or indium trichloride promoted tin-mediated allylation reactions in aqueous media. Both methods gave 3-allyl-3-hydroxycephams in moderate to excellent yields.[311]

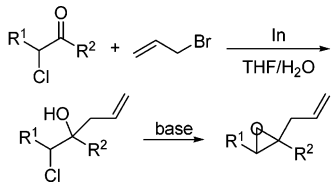
A new method has been developed for the synthesis of (*E*)-*β*-methyl Baylis−Hillman adducts with high *E*−*Z* (>93%) selectivity in modest to good yields. The process consists of two steps: an indium-mediated allylation reaction and a simple base-catalyzed isomerization step (eq 88). Various aldehydes were allylated



(88)

with allyl bromides using indium under very mild conditions in aqueous media.[312]

C-branched sugars or C-oligosaccharides are obtainable through indium-promoted Barbier-type allylations in aqueous media.[313] Indium-mediated allylation of α-chlorocarbonyl compounds with various allyl bromides in aqueous media gave the corresponding homoallylic chlorohydrins, which could be transformed into the corresponding epoxides in the presence of a base (eq 89).[314] An excellent three-step,

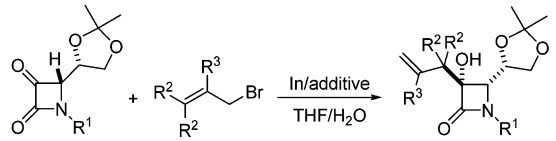


(89)

two-pot asymmetric synthesis of polyfunctionalized tetrahydrofuran was recently reported by Lindström and co-workers via the asymmetric dihydroxylation followed by the indium mediated reaction of 1,6-dibromodiene with aldehyde in water.[315] The substrates polymerized rapidly in organic solvents, and water effectively retarded the polymerization.

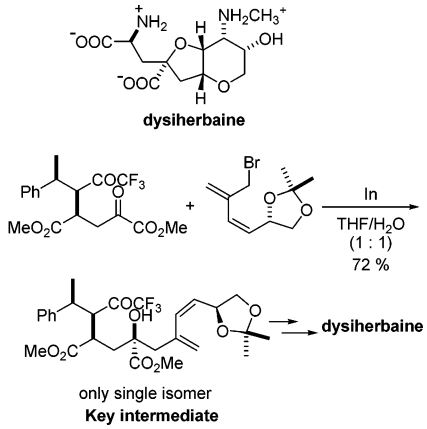
Linear α-homoallylic alcohol adducts were obtained with high regioselectivities in moderate to good yields using allylic indium reagents in the presence of water.[316] A new mechanism is proposed for the α-regioselective indium-mediated allylation reaction in water based on the results and observations obtained from an NMR study, a crossover experiment, and the complete inversion of the stereochemistry of *β*,*γ*-adduct (homoallylic sterols to the α,α-adduct homoallylic sterols). It is suggested that the initially formed *γ*-adduct undergoes a bond cleavage to generate the parent aldehyde in situ followed by a concerted rearrangement, perhaps a retro-ene reaction followed by a 2-oxonia [3,3]-sigmatropic rearrangement, to furnish the α-adduct.[317]

Various nitrobenzaldehydes were simultaneously allylated and reduced using indium in the presence of HCl in aqueous media to give compounds having both homoallylic alcohol and aromatic amine functionalities.[318] Reactions of racemic as well as optically pure carbonyl *β*-lactams with stabilized organoindium reagents were investigated in aqueous media. The regio- and stereochemistry of the processes were generally good, offering a convenient asymmetric approach toward densely functionalized hydroxy-*β*-lactams (eq 90).[319]



(90)

Palladium-catalyzed allylation of carbonyl compounds with various allylic compounds used In−$InCl_3$ in aqueous media.[320] Various allylic compounds can be effectively applied to palladium-catalyzed allylation of carbonyl compounds via the formation of *π*-allylpalladium(II) intermediates and their transmetalation with indium in the presence of indium trichloride in aqueous media. The indium-mediated allylation reaction in aqueous media was also used in the synthesis of dysiherbaine (eq 91).[321]



(91)

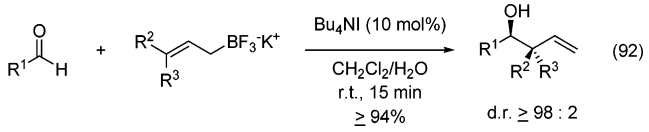
Metal-mediated allylation of difluoroacetyltrialkylsilanes with various allyl bromides in aqueous media formed homoallylic alcohols exclusively. The common Brook rearrangement, carbon to oxygen-silyl migration, was totally suppressed with no detectable formation of silyl enol ether.[322] The reaction afforded high syn selectivity regardless of the allylic bromide geometry. The enantioselective indium-mediated allylation was attempted and found to give the desired products in moderate yields with high syn selectivity and enantioselectivity.[323] Indium trichloride-catalyzed indium-mediated allylation of dihydropyrans and dihydrofurans was reported in water. This

catalytic system afforded the allylated diols in moderate to high yields.[324]

Mechanistic Discussion. For the mechanism of the metal-mediated allylation reaction in aqueous media, Li proposed a carbanion−allylmetal−radical triad in which the specific mechanism of the reaction is dependent on the metal being used. Recently, detailed mechanistic study of the allylation has been carried out. Secondary deuterium kinetic isotope effects in the metal-mediated allylation of benzaldehyde in aqueous media were detected.[325] The inverse SDKIE observed for the indium and tin cases are consistent with the polar addition mechanism. For magnesium and antimony, normal SDKIE were observed. These were interpreted as single-electron-transfer processes on a metal surface in the magnesium case, or between the allylmetal and the carbonyl compound in the antimony case.

Mediated by Other Metals. In addition to those discussed above, other metals have been found to mediate the Barbier−Grignard-type conversions in water. However, investigations on these metals are rather limited.

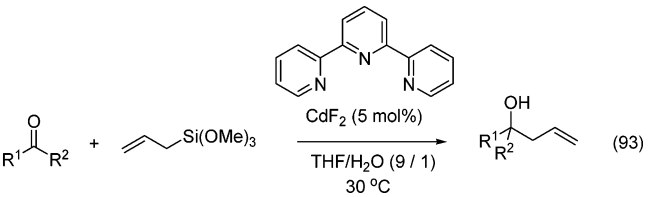
Boron. Potassium allyl- and crotyltrifluoroborates undergo addition to aldehydes in biphasic media as well as water to provide homoallylic alcohols in high yields (>94%) with excellent diastereoselectivity (dr > 98:2). The presence of a phase-transfer catalyst (e.g., Bu_4NI) significantly accelerates the rate of the reaction, whereas fluoride ion retards the reaction (eq 92).[326] The method was applied to the asymmetric



(92)

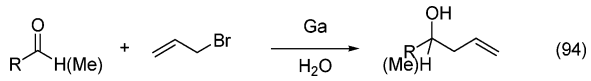
total synthesis of the antiobesity agent tetrahydrolipstatin (orlistat).[327]

Silicon. Tris(pentafluorophenyl)boron was found to be an efficient, air-stable, and water-tolerant Lewis acid catalyst for the allylation reaction of allylsilanes with aldehydes.[328] $Sc(OTf)_3$ catalyzed the allylations of hydrates of α-keto aldehydes and glyoxylates and activated aromatic aldehydes with allyltrimethylsilane in H_2O-CH_3CN. α-Keto and α-ester homoallylic alcohols and aromatic homoallylic alcohols were obtained in good to excellent yields.[329] Allylation reactions of carbonyl compounds such as aldehydes and reactive ketones using allyltrimethoxysilane in aqueous media proceeded smoothly in the presence of 5 mol % of a CdF_2−terpyridine complex (eq 93).[330]



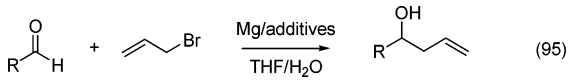
(93)

Gallium. Gallium was used to allylate carbonyl compounds in water.[331] The reaction can also be carried out by using preformed allylgallium reagents.[332] The corresponding homoallyl alcohols were obtained in high yields without the assistance of either acidic media or sonication (eq 94).



(94)

Magnesium. Li and co-workers reported magnesium-mediated Barbier−Grignard allylation of benzaldehyde in water (eq 95).[333] Recently, some water-

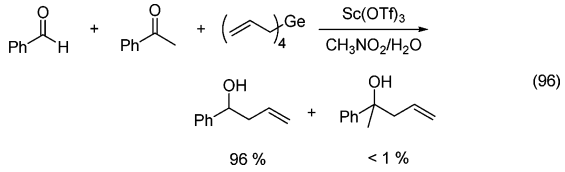


(95)

tolerant allylating agents prepared in situ from allylmagnesium chloride and various metallic salts reacted with aldehydes in $THF-H_2O$ to afford the desired homoallylic alcohols.[334]

Cobalt. In the presence of cobalt(II) chloride−metallic aluminum, allylic halides react with aldehydes at room temperature in tetrahydrofuran−water to afford the corresponding alcohols in high yields.[335]

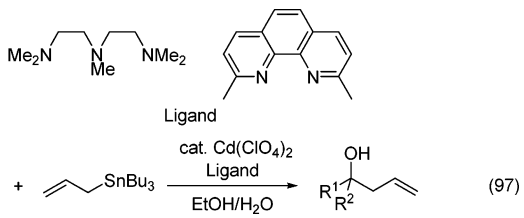
Germanium. Scandium(III) triflate-catalyzed allylation of carbonyl compounds with tetraallylgermane proceeded readily in aqueous nitromethane to afford homoallyl alcohols in good to excellent yields.[336] The presence of H_2O is indispensable for the allylation of aldehydes to proceed smoothly. Aldehydes were allylated exclusively in the presence of ketone moieties (eq 96).



(96)

Lead. Homoallylic alcohols can be obtained from allylation of aldehydes and ketones with allyl bromide promoted by metallic lead in aqueous media.[337]

Cadmium. Cadmium perchlorate was found to catalyze allylation reactions using allyltributyltin in aqueous media very efficiently.[338] These cadmium-catalyzed allylation reactions are accelerated by ligands such as *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine or 2,9-dimethylphenanthroline (eq 97).



(97)

This accelerated catalytic system gave allylation products of various aldehydes and ketones in high yields.

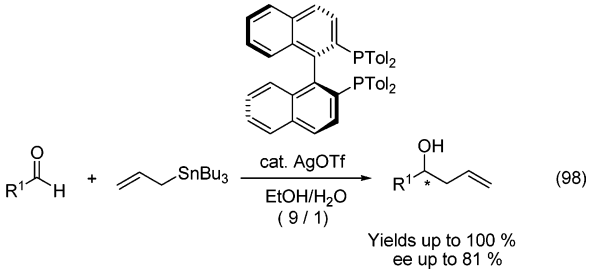
Manganese. Manganese is also effective for mediating aqueous carbonyl allylations and pinacol-coupling reactions. Manganese offers a higher reactivity and complete chemoselectivity toward allylation of aromatic aldehydes.[339]

Antimony. Commercial antimony metal reacts with allyl bromide and aldehydes in aqueous 1 M HCl or DCl solution to give the corresponding homoallylic alcohols in good yields. The reaction proceeds through the formation of allylstibine intermediates.[340]

Bismuth. Wada reported[341] that metallic bismuth can be used for allylation in aqueous media in a way similar to that of tin, in which aluminum powder and hydrobromic acid were used as the promoters. Again, the reaction is more effective than the same one conducted in an organic solvent. As a comparison, the allylation of phenylacetaldehyde carried out in a mixture of THF/water at room temperature gave the corresponding alcohol in 90% yield. Under the same conditions, the use of THF as solvent led to decreased yields and irreproducible results. Other metal promoters are also effective under the same conditions. Such combinations include Al(0)/$BiCl_3$, Zn(0)/$BiCl_3$, Fe(0)/$BiCl_3$, and Mg/$BiCl_3$.[342] Bismuth-mediated allylation was found to be promoted by the presence of a fluoride ion,[343] sonication,[344] or ammonium ions.[345] Katritzky et al. found that the bismuth(III)−aluminum system also mediated the allylation of immonium cations to give amines.[346] In this case, even methylation with iodomethane took place smoothly. Allylation of aldehydes carried out by electrochemically regenerated bismuth metal in an aqueous two-phase system was reported by Tsuji et al.[347] Nanobismuth was also used for the allylation. [348]

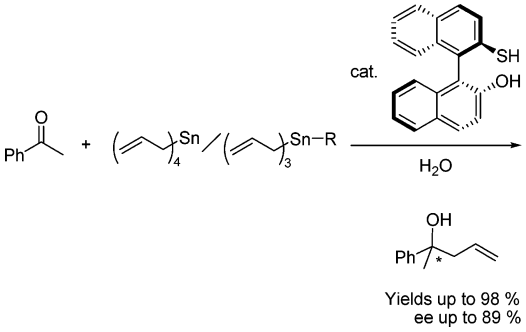
Asymmetric Allylation. One of the recent new developments on this subject is the asymmetric allylation reaction. It was found that native and trimethylated cyclodextrins promote enantioselective allylation of 2-cyclohexenone and aldehyde, using Zn dust and alkyl halides in 5:1 H_2O−THF. Moderate optically active products with ee up to 50% were obtained.[349] The results can be rationalized in terms of the formation of inclusion complexes between the substrates and the CDs and of their interaction with the surface of the metal.

A (s)-Tol−BINAP/$AgNO_3$ was successfully applied to a catalytic enantioselective allylation reaction of aldehydes in an aqueous system. The reactions with aromatic aldehydes afforded the desired products in high yields with good stereoselectivities and up to 81% ee (eq 98).[350] In the presence of the monothio-



(98)

binaphthol (MTB) ligand aryl ketones are allylated by a mixture of $Sn(CH_2CH{=}CH_2)_4$/$RSn(CH_2CH{=}CH_2)_3$ (R = Et, Bu) in high ee. The presence of water suppresses the racemic background allylation. Allylation using the pure components alone were rather ineffective. The (1*R*)-2-mercapto[1,1′-binaphthalen]-2-ol-mediated allylation of acetophenone using a mixture of tetra(2-propenyl)stannane/ethyltri(2-propenyl)stannane/butyltri(2-propenyl)stannane gave (α*R*)-α-methyl-α-(2-propenyl)benzenemethanol in >98% yield and in 86−89% ee (eq 99). Aliphatic ketones



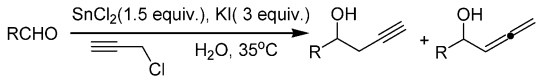
(99)

gave complex mixtures of products; a similar reaction using cyclohexyl methyl ketone gave α-methyl-α-(2-propenyl)cyclohexanemethanol with only 59% enantiomeric excess. *tert*-Butyl methyl ketone did not react.[351] Catalytic asymmetric allylation of aldehydes with allyltributyltin in aqueous media has been realized using combinations of cadmium bromide and chiral diamine ligands. These ligands were found to accelerate the reactions significantly.[352]

A chemoenzymatic methodology has been developed using indium-mediated allylation of heterocyclic aldehydes under aqueous conditions followed by *Pseudomonas cepacia* lipase-catalyzed enantioselective acylation of racemic homoallylic and homopropargylic alcohols in organic media.[353]

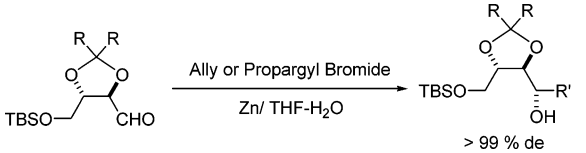
6.1.2. Propargylation

The reaction of propargyl bromide with aldehydes mediated by tin in water generated a mixture of propargylation and allenylation products. The selectivity in product formation is rather low.[354] Allenylations and propargylations of carbonyl compounds in aqueous media could also be carried out with the preformed organic tin reagents, instead of using metals.[355−358] The combination of $SnCl_2$ and KI was found to be more effective for the reaction (eq 100).[359]



(100)

The zinc-mediated propargylation of 3-formylcephalosporins was also studied in aqueous media.[360] Zn-mediated propargylation (and allylation) of a chiral aldehyde in the presence of water proceeded efficiently with a very high diastereoselectivity (>99%) to give homopropargylic alcohols (eq 101).[361] Chan et

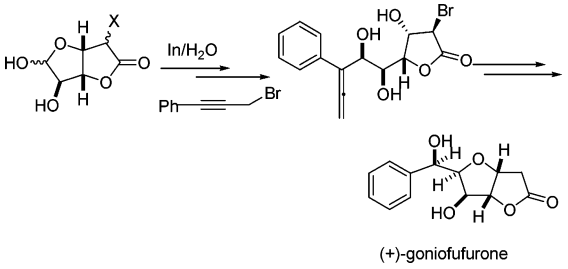


(101)

al. studied the behavior of aldehydes with propargyl bromides in an aqueous medium mediated by indium.[362] They found that simple prop-2-yn-1-yl bromide reacted with both aliphatic and aromatic aldehydes in water to give mainly the homopropargyl

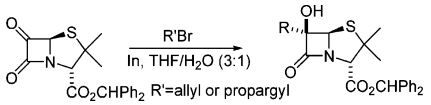
alcohols. In contrast, when propargyl bromide is γ-substituted, the coupling products were predominantly or exclusively the allenylic alcohols. Such couplings also proceed with α-chloropropargyl phenyl sulfide.[363]

In synthetic applications, Li et al. examined the propargylation−allenylation of carbonyl compounds by using a variety of metals including Sn, Zn, Bi, Cd, and In.[364] By using the indium-mediated allenylation reaction, Li and co-workers developed the synthesis of the antiviral, antitumor compound (+)-goniofufurone[365] (a key component isolated from the Asian trees of the genus *Goniothalamus*)[366] and other styryl lactone derivatives (eq 102).



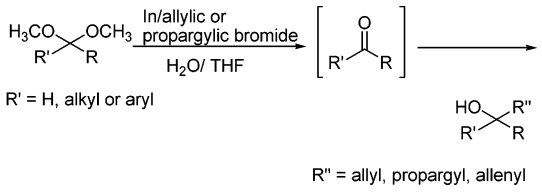
(102)

Propargylation (allylation) of diphenylmethyl 6-oxopenicillanate and 7-oxocephalosporanate was accomplished by reacting with the corresponding bromides in the presence of indium or zinc in moderate yields in aqueous conditions (eq 103).[367]



(103)

In-mediated propargylation of acetals and ketals with various allyl or propargyl bromides in aqueous media successfully provided the corresponding or homopropargylic (and allenylic) alcohols (eq 104).[368]

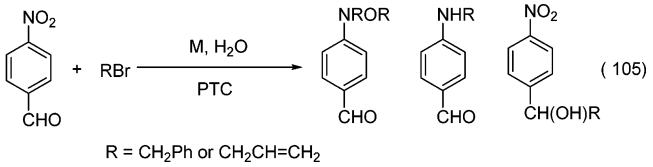


(104)

Metal-mediated carbonyl allylation, allenylation, and propargylation of optically pure azetidine-2,3-diones were investigated in aqueous environments.[369] Different metal promoters showed varied regioselectivities on the product formation during allenylation/propargylation reactions of the keto-β-lactams. The stereochemistry of the newly generated C3-substituted C3-hydroxy quaternary center was controlled by placing a chiral auxiliary at C4. The process led to a convenient entry to densely functionalized hydroxy-β-lactams.

6.1.3. Benzylation

Zinc-mediated benzylation of carbonyl compounds in aqueous media was reported by Bieber.[370] The benzylation of 4-nitrobenzaldehyde could be controlled chemoselectively by using different phase-transfer catalysts and different metal reductants in water (eq 105).[371] Water as a solvent was found to

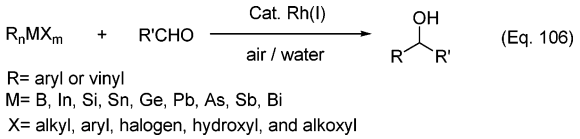


(105)

accelerate the indium-mediated Barbier-type allylation and benzylation of γ,β,-unsaturated piperidinium ion.[372] Facile benzylation of 1,3-diketones is mediated by n-Bu_4NF in THF−water. [373]

6.1.4. Arylation/Vinylation

Miyaura reported the rhodium-catalyzed addition of aryl or alkenylboronic acids to aldehydes.[374] Li and co-workers studied the addition of various aryl- and vinylorganometallic reagents to aldehydes in air and water. It was found that aryl- and vinyltin compounds added to aldehydes smoothly, which is catalyzed by either $Rh_2(COD)_2Cl_2$ or $Rh(COD)_2BF_4$ (eq 106).[375] Arylboron and arylbismuth reagents reacted

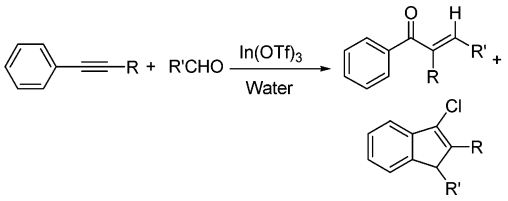


(Eq. 106)

equally well to generate the aldehyde addition products. A strong electronic effect due to the groups attached to the metal center was discovered by Li and co-workers: whereas no reaction was observed with arylmetal halides under neutral conditions, the replacement of halide by alkyl, aryl, alkoxyl, or hydroxyl groups provided the product efficiently.[376] Thus, aryltriethoxysilanes can add to aldehydes in high yield in the presence of a Rh(I) catalyst and aqueous NaOH.[377] On the other hand, treatment of α,β-acetylenic ketones with chromium(II) in the presence of aldehydes, Me_3SiCl, and water in THF gives 2,5-disubstituted furans in good to excellent yields.[378]

6.1.5. Alkynylation

An indium chloride-catalyzed coupling of alkynes to aldehydes was also successful and gave α,β-unsaturated carbonyl compounds in water in low yields (eq 107).[379] Also see section 4.0, Reactions of Alkynes.

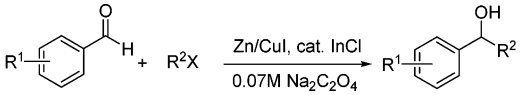


(107)

6.1.6. Alkylation

The direct addition of simple alkyl groups onto aldehydes is the most challenging in water. Mitzel

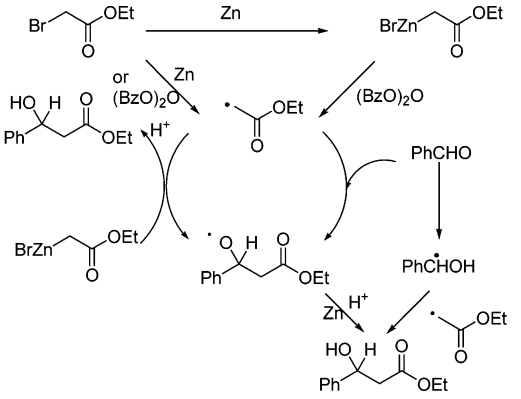
reported the indium-mediated alkylation of carbonyl compounds with α-sulfur-stabilized systems.[380] Recently, Li and co-workers reported an efficient addition of simple alkyl halides to aldehydes in water (eq 108).[381] A one-carbon carbocycle ring expansion reaction has been developed by using zinc- and indium-mediated reaction of various α-halomethyl cyclic β-keto esters and α-halomethyl benzocyclic β-keto esters. [382]



6.1.7. Reformatsky-Type Reaction

The reaction of an α-halogen carbonyl compound with zinc, tin, or indium together with an aldehyde in water gave a direct cross-aldol reaction product.[383] A direct Reformatsky-type reaction occurred when an aromatic aldehyde reacted with an α-bromo ester in water mediated by zinc in low yields.[384] Recently, it was found that under sonications such a reaction mediated by indium is successful.[385] The combination of $BiCl_3-M$,[386] $CdCl_2-Sm$,[387] and $Zn-Et_3B-Et_2O$[388] are also effective mediators. Bismuth metal, upon activation by zinc fluoride, effected the crossed aldol reaction between α-bromo carbonyl compounds and aldehydes in aqueous media. The reaction was found to be regiospecific and syn diastereoselective.[389]

Bieber reported that the reaction of bromoacetates is greatly enhanced by catalytic amounts of benzoyl peroxide or peracids and gives satisfactory yields with aromatic aldehydes. A radical chain mechanism initiated by electron abstraction from the organometallic Reformatsky reagent is proposed (eq 109).[390]

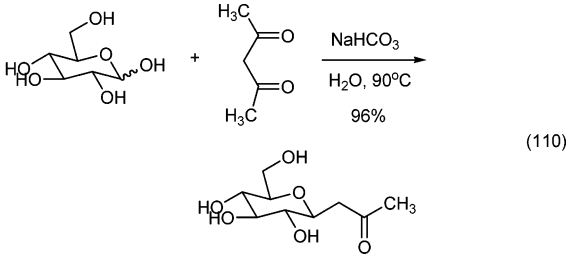


However, an alternative process of reacting aldehydes with 2,3-dichloro-1-propene and indium in water followed by ozonolysis provided the Reformatsky product in practical yields.[391] An electrochemical Reformatsky reaction in an aqueous medium and in the absence of a metal mediator has also been reported.[392]

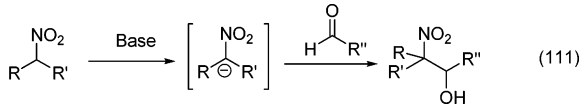
The indium-mediated aqueous Reformatsky reaction was used in the synthesis of α,α-difluoro-β-hydroxy ketones.[393]

6.1.8. Direct Aldol Reaction

Classical Aldol. The aldol reaction is an important reaction for creating carbon−carbon bonds. The condensation reactions of active methylene compounds such as acetophenone or cyclohexanone with aryl aldehydes under basic or acidic conditions gave good yields of aldols along with the dehydration compounds in water.[394] The presence of surfactants led mainly toward the dehydration reactions. The most common solvents for aldol reactions are ethanol, aqueous ethanol, and water.[395] The two-phase system using aqueous sodium hydroxide−ether has been found to be excellent for the condensation reactions of reactive aliphatic aldehydes.[396] High-temperature water has also been used successfully for cross-aldol reactions.[397] Recently, Rodrigues et al. reported a convenient, one-step synthesis of β-*C*-glycosidic ketones via the condensation of pentane-2,4-dione with different unprotected sugars in alkaline aqueous media (eq 110).[398]

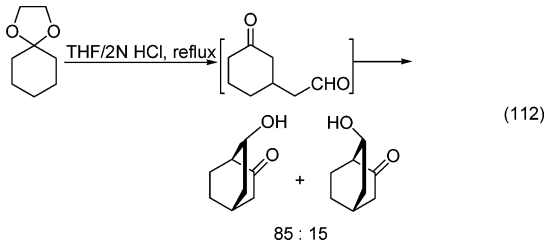


The Henry (nitroaldol) reaction was reported under very mild reaction conditions in aqueous media using a stoichiometric amount of a nitroalkane and an aldehyde in NaOH 0.025 M and in the presence of cetyltrimethylammonium chloride (CTACl) as cationic surfactant (eq 111).[399] Good to excellent yields



of β-nitroalkanol were obtained. Under these conditions, several functionalities are preserved, and side-reactions such as retro-aldol reaction or dehydration of 2-nitro alcohol were avoided.

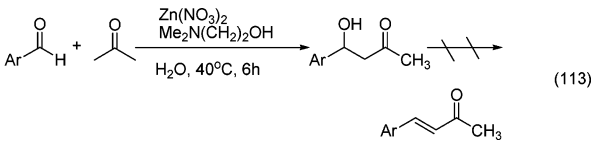
Base-catalyzed aldol reactions have been carried out intramolecularly.[400] The aqueous acid-catalyzed intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes proceeded diastereoselectively (eq 112).[401]



Selective retro-aldol has also been reported by using aqueous HCl in THF.[402] Recently, catalytic aldol reactions in aqueous media have generated great interest due to the atom economy related to the reaction. Reaction of 2-alkyl-1,3-diketones with aqueous formaldehyde using aqueous 6−10 M potassium

carbonate as base afforded aldol reaction products, which are cleaved by the base to give vinyl ketones.[403]

Lewis-Acid-Catalyzed Aldol Reactions. Recently, various Lewis acids have been examined as catalysts for aldol reactions. In the presence of complexes of zinc with aminoesters or amino alcohols, the dehydration can be avoided, and the aldol addition becomes essentially quantitative (eq 113).[404] A

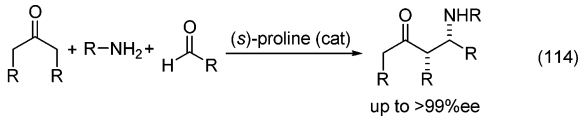


(113)

microporous coordination polymer obtained by treating anthracenebis(resorcinol) with La(O*i*Pr)$_3$ possessed catalytic activity for ketone enolization and aldol reactions in pure water at neutral pH.[405] The La network was stable against hydrolysis and maintained microporosity and reversible substrate binding, which mimics an enzyme. Zn complexes of proline, lysine, and arginine were found to be efficient catalysts for the aldol addition of *p*-nitrobenzaldehyde and acetone in an aqueous medium to give quantitative yields and up to 56% enantiomeric excesses with 5 mol % of the catalysts at room temperature.[406]

Enzyme-Catalyzed Aldol Reactions. The enzyme aldolases are the most important catalysts for catalyzing carbon−carbon bond formations in nature.[407] A multienzyme system has also been developed for forming C−C bonds.[408] Recently, an antibody developed by Schultz and co-workers has been found to catalyze the retro-aldol reaction and Henry-type reactions.[409]

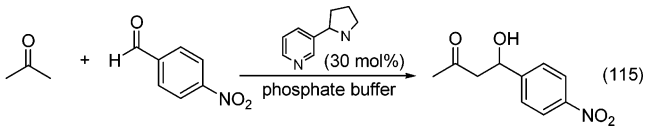
Organic-Base-Catalyzed Aldol Reactions. Asymmetric direct aldol reactions and related reactions possess atom economical and biomimetic features, which have received considerable attention (eq 114).[410] Direct asymmetric catalytic aldol reactions



(114)

have been successfully performed using aldehydes and unmodified ketones together with chiral cyclic secondary amines as catalysts.[411] L-Proline and 5,5-dimethylthiazolidinium-4-carboxylate (DMTC) were found to be the most powerful amino acid catalysts for the reaction of both acyclic and cyclic ketones as aldol donors with aromatic and aliphatic aldehydes to afford the corresponding aldol products with high regio-, diastereo-, and enantioselectivities. Reactions employing hydroxyacetone as an aldol donor provide *anti*-1,2-diols as the major product with ee values up to >99%. The observed stereochemistry of the products was explained by a metal-free Zimmerman−Traxler-type transition state and involved an enamine intermediate. The reactions tolerate a small amount of water (<4 vol %) but do not require inert reaction conditions or preformed enolate equivalents and can be conveniently performed at room temperature in various solvents.

Quite recently, Janda reported that the aqueous direct aldol reaction can be catalyzed by a nicotine metabolite enantiomerically. This is the only exampleof a metabolite capable of being used as a catalyst (eq 115).[412] Direct cross-aldol reactions can also be

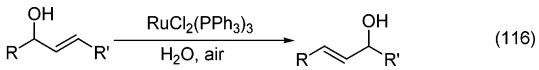


(115)

catalyzed by organoamine in buffered aqueous media. Various aldehydes and ketones including carbohydrate derivatives can be chosen as the substrates. The synthetic method is predicted to get further attention as a prebiotic route to sugar.[413] A proline-catalyzed aldol reaction of nitrobenzaldehydes with various ketones was investigated in aqueous anionic micelles.[414] High pressure, induced by water freezing, has been successfully applied to the direct catalytic asymmetric aldol reaction, in which higher yield and better enantioselectivity can be realized (likely due to the conformational confinement in ice) than in the reaction at room temperature under 0.1 MPa. [415]

Aldol Reactions with No Catalyst. High-intensity ultrasound was employed to reinvestigate the aldol reaction in water without any catalyst.[416] Within 15−30 min, acetophenone reacted with non-enolizable aldehydes to afford the aldol exclusively, while under conventional heating conditions, the same compounds either failed to react or gave, after several hours, the enone, often in complex product mixtures. Benzaldehyde reacted with a series of 1,3-dicarbonyl compounds to afford the corresponding bis(benzylidene) adducts. Preparative organic synthesis was investigated in aqueous media at temperature up to 300 °C. An intramolecular aldol condensation (and other reactions) in superheated water has been scaled up.[417]

Other Aldols. Alternatively, Li and co-workers reported that a $RuCl_2(PPh_3)_3$-catalyzed rearrangement of functional groups of homoallylic alcohols in water (eq 116)[418] led to an aldol-type reaction. This

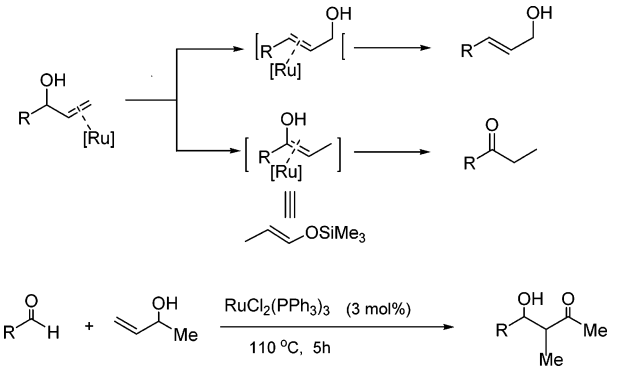


(116)

was developed by reacting allyl alcohols with aldehyde (Scheme 9).[419] The presence of In(OAc)$_3$ promoted the aldol reaction with α-vinylbenzyl alcohol and aldehyde.[420] An indium hydride-promoted reductive aldol reaction of unsaturated ketones in aqueous media was developed.[421] The use of water and methanol as solvent dramatically reversed stereochemistry from anti to syn. Boron enolates have been used for aldol reactions in water using catalytic amounts of boron reagents.[422]

Synthetic Applications. By the condensation of an arylaldehyde in an alkaline aqueous medium with an arylmethyl ketone followed by oxidation with hydrogen peroxide, 7- and 3′,4′-substituted flavonols were synthesized under one-pot conditions.[423] Other examples of synthetic applications of aqueous aldol

Scheme 9. Aldol Reaction via Allylic Isomerization[a]

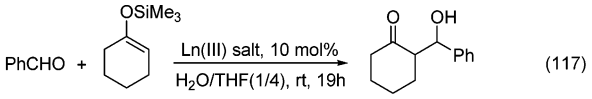


[a] Reprinted with permission from ref 419. Copyright 2002 Elsevier.

reactions include carminic acid[424] and various sugar derivatives. [425]

6.1.9. Mukaiyama Aldol Reaction

The crossed aldol reaction of silyl enol ethers with carbonyl compounds (Mukaiyama aldol) was studied by Lubineau and co-workers in aqueous solvents without any acid catalyst. However, the reaction took several days to complete.[426] A major development is the use of water-tolerant Lewis acids for such reactions, pioneered by Kobayashi and co-workers.[427] Adding a catalytic amount of lanthanide triflate (a stronger Lewis acid) greatly improved the rate and the yield of such reactions (eq 117).[428] Among the

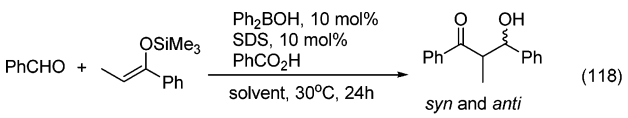


(117)

8-91% yield, $Yb(OTf)_3$: 91%

lanthanide triflates, ytterbium triflate ($Yb(OTf)_3$), gadolinium triflate ($Gd(OTf)_3$), and lutetium triflate ($Lu(OTf)_3$) generally gave better yields of the aldol condensation product; the diastereoselectivities of these reactions were moderate. Water-soluble aldehydes were applicable, and the catalyst could be recovered and reused in this procedure. Since then, various Lewis acids have been used for such reactions. The catalytic activities of Lewis acids in water were related to hydrolysis constants and exchange-rate constants for substitution of inner-sphere water ligands.[429]

Lewis-Acid-Catalyzed Reactions. Other metals used with some success as catalysts in aqueous aldol reactions are $Bi(OTf)_3$,[430] $Cu(OTf)_2$,[431] $FeCl_3$,[432] and $InCl_3$.[433] The formation of syn aldol products is predominant in the water-based aldol reactions, which is in contrast to the analogous reactions run under anhydrous conditions where the anti isomer is usually the major product. Boron has been shown to be an efficient mediator of stereoselective aldol reactions (eq 118).[434] The reaction between aldehydes



(118)

syn and *anti*

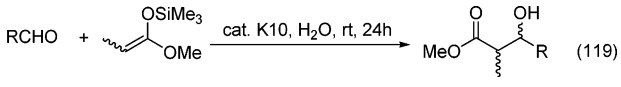
in H_2O, 93% yield, *syn* : *anti* = 94 : 6

and silyl enol ethers in a water/SDS mixture was catalyzed by 10 mol % Ph_2BOH to give syn-substituted β-hydroxy ketones in high diastereomeric excesses (80−94% de). In organic solvents (Et_2O, CH_2Cl_2), the reaction was almost completely thwarted. The accelerating effect of water was proposed via a boron enolate intermediate generated by a silicon-metal exchange. $CeCl_3$ and $InCl_3$ were found to work best in *i*-PrOH/H_2O (95:5), and no reaction was observed in pure water, which was attributed to the destruction of the starting silyl enol ether.[435]

Scandium triflate-catalyzed aldol reactions of silyl enol ethers with aldehyde were successfully carried out in micellar systems[436] and encapsulating systems.[437] While the reactions proceeded sluggishly in water alone, strong enhancement of the reactivity was observed in the presence of a small amount of a surfactant. The effect of surfactant was attributed to the stabilization of enol silyl ether by the surfactant. Versatile carbon−carbon bond-forming reactions proceeded in water without using any organic solvents. Cross-linked Sc-containing dendrimers were also found to be effective, and the catalyst could be readily recycled without any appreciable loss of catalytic activity.[438] Aldol reaction of 1-phenyl-1-(trimethylsilyloxy)ethylene and benzaldehyde was also conducted in a gel medium of fluoroalkyl end-capped 2-acrylamido-2-methylpropanesulfonic acid polymer.[439] A nanostructured, polymer-supported Sc(III) catalyst (NP-Sc) functions in water at ambient temperature and can be efficiently recycled. It also affords stereoselectivities different from isotropic solution and solid-state scandium catalysts in Mukaiyama aldol and Mannich-type reactions.[440]

LiOAc-catalyzed aldol reaction between trimethylsilyl enolates and aldehydes in a DMF−H_2O (50:1) solvent proceeded smoothly to afford the corresponding aldols in good to high yields.[441] In the presence of $CaCl_2$, dimethylsilyl enolates reacted smoothly with aldehydes to give aldol adducts in good to high yields in pure water. This catalytic system was applicable to the aldol reaction with aqueous aldehydes such as formalin.[442]

Montmorillonite K10 was also used for the reaction in water.[443] Hydrates of aldehydes such as glyoxylic acid can be used directly. Thermal treatment of K10 increased the catalytic activity. The catalytic activity is attributed to the structural features of K10 and its inherent Brönsted acidity. The aldol reactions of more reactive ketene silyl acetals with reactive aldehydes proceed smoothly in water to afford the corresponding aldol products in good yields (eq 119).[444]

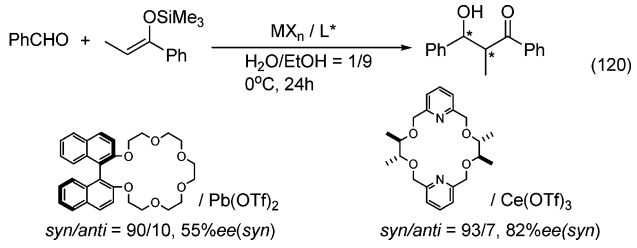


(119)

Polar polyoxyethylene−polyoxypropylene (POE-POP) resin, derivatized with a 4-hydroxymethyl phenoxy linker, was used as a solid support for lanthanide triflate-catalyzed Mukaiyama-type solid-phase aldol reactions.[445] The use of an aqueous solvent was found to be crucial. The reactions on an

N-terminal peptide aldehyde substrate proceeded in very high yields.

Asymmetric Lewis-Acid-Catalyzed Reactions. Another important advance in aqueous Mukaiyama aldol reactions is the recent success of asymmetric catalysis.[446] In aqueous ethanol, Kobayashi and coworkers achieved asymmetric inductions by using $Cu(OTf)_2$/chiral bis(oxazoline) ligand,[447] $Pb(OTf)_2$/chiral crown ether,[448] and $Ln(OTf)_3$/chiral bis-pyridino-18-crown-6 (eq 120).[449]



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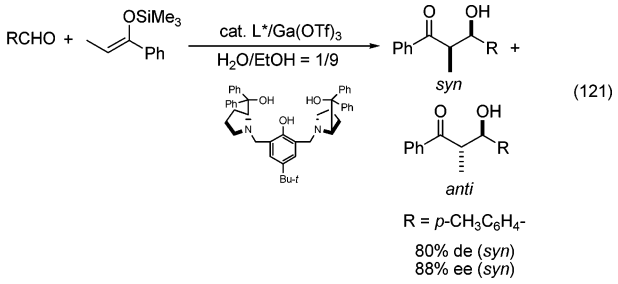
On the other hand, Wang and Li recently developed a highly efficient asymmetric Mukaiyama reaction by using chiral gallium catalysts with Trost's chiral semi-crown ligands (eq 121).[450] Such a system can



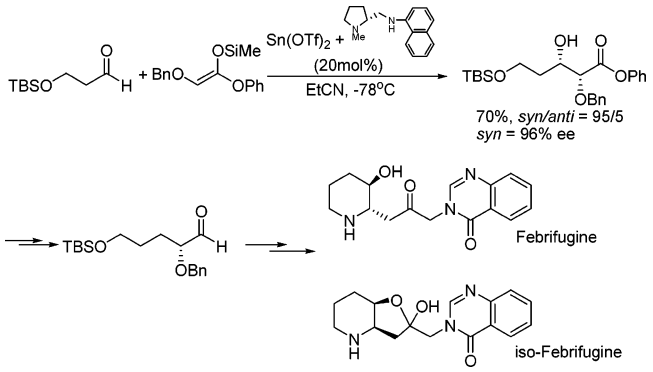
(121)

achieve high enantioselectivity even in pure water. The combination of $Ga(OTf)_3$ and the chiral ligand made the aqueous reaction to proceed smoothly with good yield (89%), diastereoselectivity (syn/anti 89:11), and enantioselectivity of syn product (ee 87%).

A chiral zirconium catalyst generated from $Zr(OCMe_3)_4$ and (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol [(*R*)-3,3′-I_2BINOL] catalyzes the aldol reaction in high yields under mild conditions. Anti adducts were obtained in high diastereo- and enantioselectivities.[451] Sulfonate derivatives of chiral 1,1′-binaphthol were used as chiral anionic surfactants in asymmetric aldol-type reactions in water to give aldol adducts with moderate to good diastereo- and enantioselectivities; $Ga(OTf)_3$ and $Cu(OTf)_2$ provided better results than $Sc(OTf)_3$ as Lewis acid catalysts in this system.[452] The aldol reaction of trimethylsilyl enol ethers with aqueous CH_2O proceeded moderately well using tetrabutylammonium fluoride as an activator. Asymmetric hydroxymethylation of trimethoxysilyl enol ethers using (*R*)-BINAP−AgOTf as Lewis acid and KF as Lewis base has been achieved in aqueous media (up to 57% ee).[453]

Chiral bis(oxazoline) ligands disubstituted at the carbon atom linking the two oxazolines by Frechet-type polyether dendrimers coordinated with copper(II) triflate were found to provide good yields and moderate enantioselectivities for Mukaiyama aldol reactions in water, which are comparable with those

Scheme 10[a]



[a] Reprinted with permission from ref 456. Copyright 1999 Elsevier.

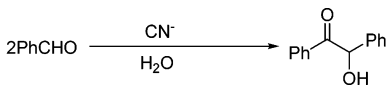
resulting from the corresponding smaller catalysts.[454] $AgPF_6$−BINAP is very active in this reaction and the addition of a small amount of water enhanced the reactivity.[455]

A tin(II)-catalyzed catalytic asymmetric aldol reaction and lanthanide-catalyzed aqueous three-component reaction have been used as the key steps for the synthesis of febrifugine and isofebrifugine (Scheme 10).[456]

6.1.10. Hydrogen Cyanide Addition

The addition of HCN to carbon−heteroatom multiple bonds, such as cyanohydrin formation reactions[457] and C=N or C≡N addition reactions,[458] has been performed in aqueous media. In particular, synthesis of higher sugars through cyanohydrin formation, the Kiliani−Fischer synthesis, is a classical reaction and probably is the earliest carbohydrate chemical synthesis without the use of a protecting group.[459] The reaction is governed by the acidity of the media. The addition of cyanide to simple aldoses is essentially quantitative at pH 9.1, whereas the reaction is much slower at a lower pH. The rate difference is most likely due to the different effective concentrations of cyanide ion. The cyanohydrins are not isolated but are converted into the corresponding lactones. Reduction of the lactones by sodium amalgam, by catalytic hydrogenation, or by reduction with sodium borohydride at pH 3−4 in aqueous solution generates the higher aldoses. By controlling the counterion of cyanide, one can change the proportions of diastereomers, originated from the creation of a new stereogenic center. The synthesis of, essentially, a single diastereomer is also possible.[460] Enzyme-catalyzed asymmetric formation of (*S*)-cyanohydrins derived from aldehydes and ketones has been reported in a biphasic solvent system.[461]

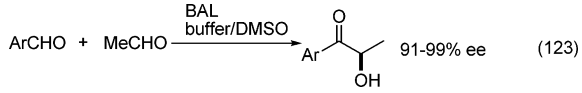
Benzoin Condensation. The benzoin condensation is a related reaction that consists of treating an aromatic aldehyde with potassium cyanide or sodium cyanide, usually in an aqueous ethanolic solution. Breslow studied the effects of inorganic salts on the rate of the cyanide-catalyzed benzoin condensation in aqueous media (eq 122).[462] The reaction is 200



(122)

times faster in water than in ethanol. Through the use of a quantitative antihydrophobic effect as a probe for transition-state structures, it was postulated that the acceleration of benzoin condensation in water was related to the amount of hydrophobic surfaces that are solvent-accessible in the transition states compared with the initial state.[463] Thus, the addition of salts, increasing the hydrophobic effect, further increased the rate of the reaction. The addition of γ-cyclodextrin (in which both substrates can fit) also accelerates the reaction, whereas the addition of β-cyclodextrin (with a smaller cavity) inhibits the condensation. The cyanide-catalyzed benzoin condensation is comparable to the benzoin condensation catalyzed by thiamine in the biological systems, elucidated by Breslow.[464] Recently, Breslow has prepared several γ-cyclodextrin thiazolium salts that mimic the action of thiamine and catalyze the benzoin condensation very effectively.[465]

(*R*)-Benzoins and (*R*)-2-hydroxypropiophenone derivatives are formed on a preparative scale by benzaldehyde lyase (BAL)-catalyzed C−C bond formation from aromatic aldehydes and acetaldehyde in aqueous buffer/DMSO solution with remarkable ease in high chemical yield and high optical purity (eq 123).[466] Less stable mixed benzoins were also gener-

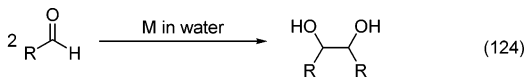


(123)

ated via reductive coupling of benzoyl cyanide and carbonyl compounds by aqueous titanium(III) ions.[467]

6.2. Pinacol Coupling

The coupling of carbonyl compounds[468] to give 1,2-diols, known as the "pinacol coupling", has been carried out in aqueous media.[469] Clerici and Porta extensively studied the aqueous pinacol coupling reactions mediated by Ti(III).[470] Schwartz reported a stereoselective pinacol coupling with a cyclopentadienetitanium complex.[471] Pinacol-type couplings were also developed by using a Zn−Cu couple,[472] Mg,[473] Mn,[474] Zn,[475] In,[476] Sm,[477] Al/NaOH (or KOH),[478] Al/F$^-$,[479] Ga,[480] Cd,[481] and other metals in aqueous media (eq 124). Under sonication, Kim and co-workers[482]



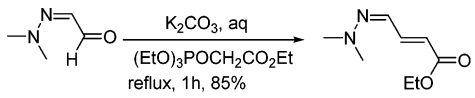
(124)

found that aromatic aldehydes homocoupled to generate pinacol-type products. Pinacol-coupling of benzaldehyde in an aqueous medium mediated by magnesium, zinc, iron, nickel, and tin was studied under the effect of ultrasound on these reactions with magnesium providing the best results.[483] The reaction occurred in neutral aqueous media over 8−22 h. In the absence of sonication, the reaction was much slower and the yield of the product was decreased by a factor of 2−3. Interestingly, the reaction did not proceed under nitrogen protection. Water alone or a 1:1 mixture of water and *t*-BuOH were used in these reactions. Aliphatic aldehydes and ketones are inert under the reaction conditions. Solid aldehydes resulted in poor yield of the product or no product.

A cross-coupling reaction of aldehydes with α-diketones proceeded in the presence of water to give the corresponding adducts in moderate to good yields. It is possible to use substrates such as phenylglyoxal monohydrate, aqueous methylglyoxal, formalin, and aqueous α-chloroacetaldehyde for this reaction.[484]

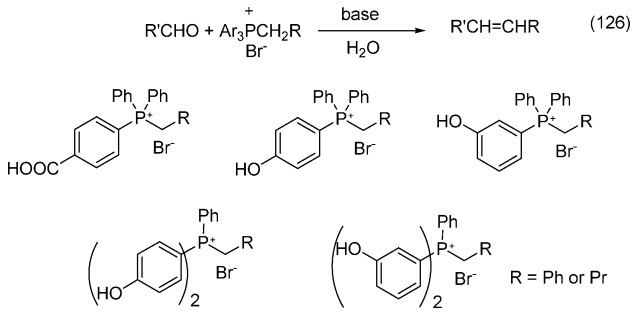
6.3. Wittig Reactions

The Wittig reaction has been investigated in aqueous conditions.[485] Wittig olefination reactions with stabilized ylides (known as the Wittig−Horner or Horner−Wadsworth−Emmons reaction) are sometimes performed in an organic/water biphase system.[486] Very often, a phase-transfer catalyst is used. Recently, the use of water alone as solvent has been investigated.[487] The reaction proceeds smoothly with a much weaker base such as K_2CO_3 or $KHCO_3$. No phase-transfer catalyst is required. Compounds with base- and acid-sensitive functional groups can be used directly. For example, under such a condition, β-dimethylhydrazoneacetaldehyde can be olefinated efficiently (eq 125).[488]



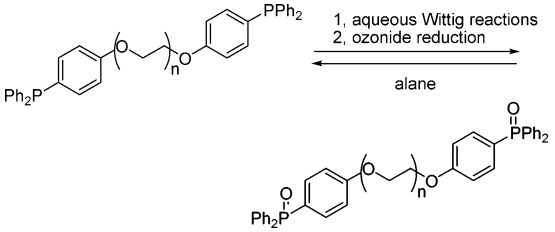
(125)

Recently, water-soluble phosphonium salts were synthesized, and their Wittig reactions were studied in water (eq 126).[489]



(126)

A tandem enzymatic aldol−intramolecular Horner−Wadsworth−Emmons reaction has been used in the synthesis of a cyclitol.[490] The one-pot reaction takes place in aqueous solution at slightly acidic (pH 6.1−6.8) conditions. The aqueous Wittig-type reaction has been investigated in DNA-templated synthesis.[491] The use of water-soluble reagents and catalysts allows reactions to be performed in aqueous buffered solutions. PEG-functionalized triarylphosphine has been used in a Wittig reaction under mildly basic aqueous conditions (eq 127).[492] The aqueous Wittig



(127)

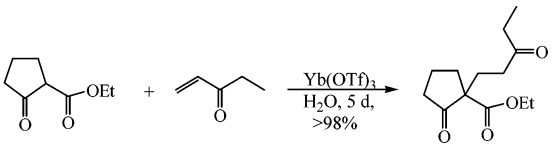
reaction has also been used in the synthesis of picenadol and analogues.[493]

7. Reaction of α,β-Unsaturated Carbonyl Compounds

7.1. Conjugate Additions

7.1.1. Addition of α-Carbonyl Compounds

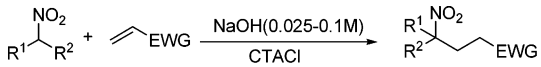
In the 1970s, Hajos[494] and Wiechert[495] independently reported that the Michael addition of 2-methylcyclopentane-1,3-dione to vinyl ketone in water gives the corresponding conjugate addition product without the use of a basic catalyst. The Michael-addition product further cyclizes to give a 5−6 fused ring system. The use of water as solvent is much superior both in terms of yield and the purity of the product in comparison with the same reaction in methanol with base. A similar enhancement of reactivity was found in the Michael addition of 2-methyl-cyclohexane-1,3-dione to vinyl ketone, which eventually led to optically pure Wieland−Miescher ketone.[496] The reaction, however, proceeds under more drastic conditions. Deslongchamps extended the aqueous Michael addition to acrolein.[497] The study has been applied to the total synthesis of 13-α-methyl-14α-hydroxysteroid. The addition of ytterbium triflate ($Yb(OTf)_3$) further enhances the rate of the Michael-addition reactions in water (eq 128).[498]



(128)

A significant acceleration of Michael addition was reported by Lubineau in the reaction of nitroalkanes with buten-2-one when going from nonpolar organic solvents to water.[499] Additives such as glucose and saccharose further increase the rate of the reaction. The Michael-addition reaction between ascorbic acid and acrylic enones was effectively carried out in water in the presence of an inorganic acid, rather than a base, as catalyst.[500]

The Michael reaction of benzylidene acetophenone and benzylidene acetone with ethyl acetoacetate, nitromethane, and acetylacetone was studied by Musaliar and co-workers in the presence of a cetyltrimethylammonium bromide-containing aqueous micellar medium.[501] The Michael reaction of various nitro alkanes with electrophilic alkenes is performed in NaOH (0.025−0.1 M) without any organic solvent (eq 129).[502]

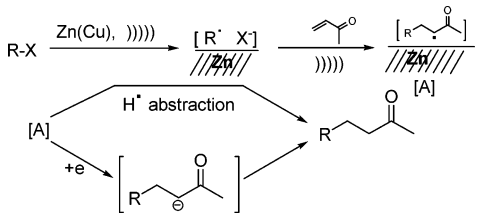


(129)

EWG= COMe, CN, SO_2Ph

Jenner investigated the kinetic pressure effect on some specific Michael and Henry reactions and found that the observed activation volumes of the Michael reaction between nitromethane and methyl vinyl ketone are largely dependent on the magnitude of the electrostriction effect, which is highest in the lanthanide-catalyzed reaction and lowest in the base-catalyzed version. In the latter case, the reverse reaction is insensitive to pressure.[503] Recently, Kobayashi and co-workers reported a highly efficient Lewis-acid-catalyzed, asymmetric Michael addition in water.[504]

Scheme 11[a]



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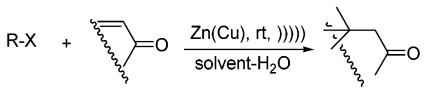
7.1.2. Addition of Allyl Groups

It was reported that indium-mediated Michael addition of allyl bromide to 1,1-dicyano-2-arylethenes proceeded well in an aqueous medium.[505]

7.1.3. Addition of Alkyl Groups

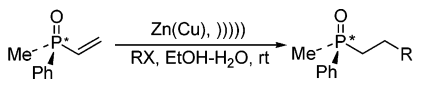
Luche reported that when a zinc−copper couple was used, alkyl halides reacted with conjugate carbonyl compounds and nitriles to give 1,4-addition products in good yields under sonication conditions (eq 130).[506]



(130)

A moderate diastereoselectivity was observed in reactions where a mixture of diastereomers could be generated.[507] The reactivity of the halides followed the order of tertiary > secondary ≫ primary and iodide > bromide (chlorides did not react). The preferred solvent system was aqueous ethanol. The process was suggested to proceed by a free radical mechanism occurring on the metal surface under sonochemical conditions (Scheme 11). Efforts to trap the intermediate intramolecularly gave a very low yield of the cyclization product.[508]

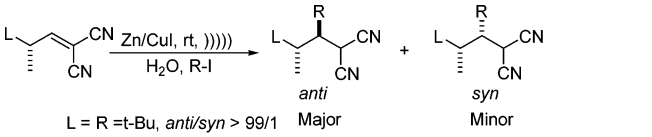
Similar additions also occurred on vinylphosphine oxides. When the optically active vinylphosphine oxide was used, P-chiral alkylphosphine oxide was obtained with retention of configuration (eq 131)[509]

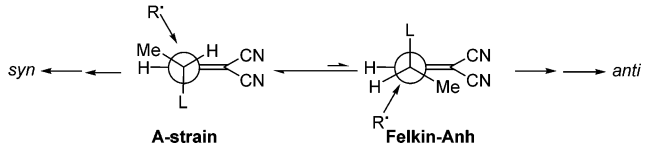


(131)

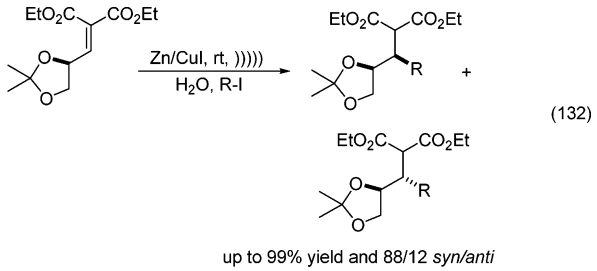
Giese studied the diastereoselectivity associated with such a conjugate addition in water.[510] The anti isomer was found to be the major product if the attacking radical is bulky, which was explained by the argument that the more stable "A-strain" conformer of the alkene reacts slower with bulky

alkyl radical than the less stable "Felkin−Anh"conformer. The diastereoselective, ultrasonically induced





zinc−copper 1,4-addition of alkyl iodides to chiral α,β-unsaturated mediated systems in aqueous media was studied by Suares and co-workers: the *Z*-isomer gives good diastereoselectivities, while reactions with the *E*-isomer are nonstereoselective.[511] The 1,4-addition to chiral γ,δ-dioxolanyl-α,β-unsaturated esters also proceeds with good yields (51−99%) (eq 132).[512]



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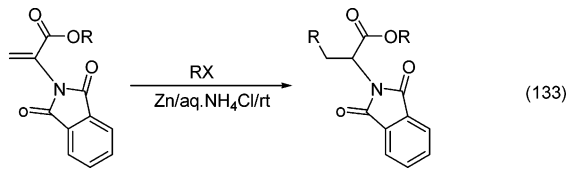
Li and co-workers reported the conjugate addition of the alkyl group to enamides mediated by zinc in aqueous NH_4Cl to generate α-amino acid derivatives (eq 133).[513] Miyabe et al.,[514] as well as Jang and

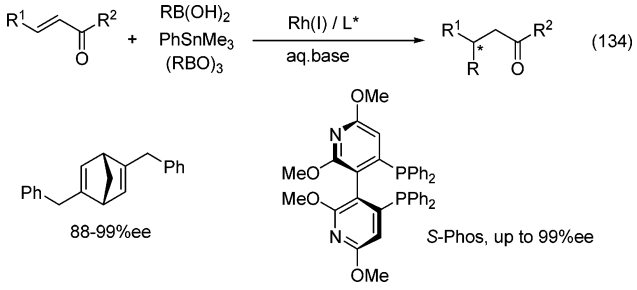


(133)

Cho,[515] reported the addition of alkyl radicals from alkyl iodide to α,β-unsaturated ketones, esters, and nitriles mediated by indium in aqueous media.

7.1.4. Addition of Vinyl and Aryl Groups

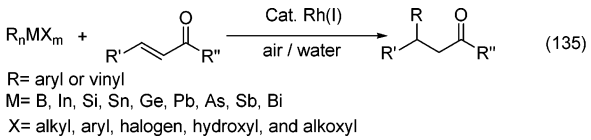
Miyaura and co-workers[516] reported the Rh(I)-catalyzed conjugate addition of aryl- or 1-alkenylboronic acids, $RB(OH)_2$, to enones in high yields at 50 °C in an aqueous solvent. A combination of (acac)-$Rh(CO)_2$ and dppb was highly effective for the addition to acyclic and cyclic enones. For example, a 96% yield of 2-phenyl-4-octanone was obtained from $PhB(OH)_2$ and 2-octen-4-one in aqueous MeOH in the presence of $(acac)Rh(CO)_2$ and dppb. Since then, extensive studies have been carried out on the boronic acid chemistry largely related to conjugate additions, including asymmetric conjugate additions most noticeably by Hayashi and co-workers.[517] For example, reactions of α,β-unsaturated ketones with excess arylboronic acids in the presence of a rhodium catalyst generated in situ from $Rh(acac)(C_2H_4)$ and (3*S*)-4,4′-bis(diphenylphosphino)-2,2′,6,6′-tetramethoxy-3,3′-bipyridine ((*S*)-P-Phos), in dioxane/water at 100 °C gave high yields of the corresponding products in up to 99% ee.[518] As an example, 2-cyclohexenone was reacted with phenylboronic acid in the presence of $Rh(acac)(C_2H_4)$ and (*S*)-P-Phos giving 3-phenylcyclohexanone in >99% yield and 99% ee (eq 134). Aryl-



(134)

boronate esters bearing a pendant Michael-acceptor alkene can add to norbonene and cyclize to give indane systems in yields ranging from 62% to 95% with high diastereomeric excess (>20:1).[519] The reaction is accelerated by bases and ligands.[520]

Li and co-workers examined the addition of various aryl and vinyl organometallic reagents to α,β-unsaturated carbonyl compounds in air and water. It was found that both $Rh_2(COD)_2Cl_2$ and $Rh(COD)_2BF_4$ are effective.[521] The organometallic reagents include organotin,[522] organoindium, organobismuth,[523] organolead,[524] and organosilicon compounds (arylhalosilanes and aryl silanols) (eq 135),[525] in addition to



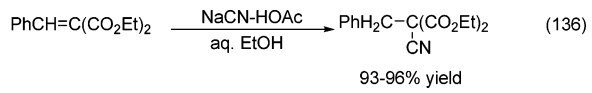
(135)

organoboron compounds. For the conjugate addition, both ketones (linear and cyclic) and esters were effective as the electron-withdrawing groups. When either a mono- or a disubstituted unsaturated C=C was involved, the reaction proceeded rapidly. In some cases, a mixture of several products including both the conjugate addition and Heck-type reaction products were observed for the monosubstituted derivatives. Either no reaction was observed or very low yields of the products were obtained with trisubstituted derivatives. A novel synthesis of α-amino acids was developed by the method in air and water.[526] The conjugate addition of organosiloxanes to α,β-unsaturated carbonyl compounds catalyzed by a cationic rhodium complex (2 mol % $[Rh(cod)(MeCN)_2]BF_4$) in water-containing solvent (dioxane/H_2O = 10:1) gives arylation products in yield 72−97%.[527]

7.1.5. Other Conjugate Additions

The hydrocyanation of conjugated carbonyl compounds is a related reaction.[528] Very often such a conjugate addition is carried out under an aqueous condition. For example, in the pioneer work of Lapworth, hydrocyanation of activated olefins was car-

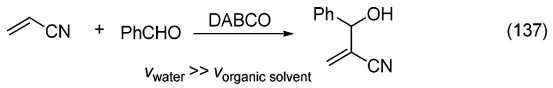
ried out with KCN or (NaCN) in aqueous ethanol in the presence of acetic acid (eq 136).[529]



(136)

7.2. Baylis–Hillman Reactions

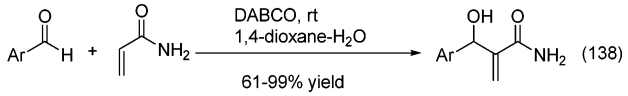
For Michael addition with nitrogen nucleophiles, a quantitative study of the Michael addition of activated olefins by using substituted pyridines as nitrogen nucleophiles in water was also reported.[530] In this report, the rate-determining step was investigated. A related reaction between activated olefins with aldehydes in the presence of tertiary amines, the so-called Baylis−Hillman reaction, generates synthetically useful allyl alcohols.[531] In some cases, an aqueous medium was used for the reaction. The reaction, however, is generally very slow, requiring several days to complete. Recently, Augé et al. studied the reaction in an aqueous medium in detail.[532] A significant increase in reactivity has been observed when the reaction is carried out in water (eq 137). The addition of lithium or sodium iodide



(137)

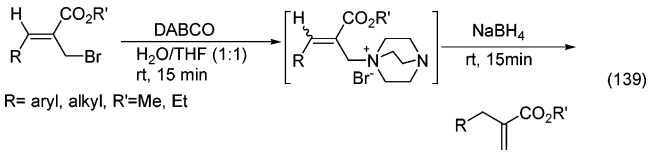
further increases the reactivity. These results suggested that the increased reactivity in water could be due to the hydrophobic effect. Most studies were done with DABCO as the catalyst.

A practical and efficient set of conditions were developed using stoichiometric base catalyst 1,4-diazabicyclo[2,2,2]octane (DABCO) and an aqueous medium to overcome problems commonly associated with the Baylis−Hillman reaction, such as low reaction yields and long reaction time.[533] Acrylamide reacted with aromatic aldehydes to give the corresponding 3-hydroxy-2-methylenepropionamides in 61−99% yield (eq 138).[534]



(138)

A convenient synthesis of 2-methylenealkanoates and alkanenitriles is accomplished via the regioselective nucleophilic addition of hydride ion from $NaBH_4$ to (2*Z*)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)alk-2-enenitriles, respectively, in the presence of DABCO in aqueous media (eq 139).[535] The

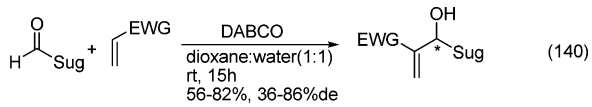


(139)

reaction of the in situ generated DABCO [1,4-diazabicyclo[2.2.2]octane] salt of Baylis−Hillman acetate and tosylamide in aqueous THF gave the Baylis−Hillman adduct of *N*-tosylimine in good yield. [536] The reaction of the DABCO salts, generated in situ from the Baylis−Hillman acetates, and KCN in aqueous THF gave ethyl 3-cyano-2-methylcinnamates and 3-cyano-2-methylcinnamonitriles in good yields.

Other catalysts have also been used. In aqueous media, imidazole and azoles were found to catalyze Baylis−Hillman reactions of cyclopent-2-enone with various aldehydes to afford the desired adducts in high yields.[537] The reaction of 2-cyclohexenones with aqueous formaldehyde, catalyzed by DMAP in THF, affords the corresponding 2-(hydroxymethyl)-2-cyclohexenone in good yields.[538] For example, 2-(hydroxymethyl)-2-cyclohexenone was prepared in 82% yield from 2-cyclohexenone. Trimethylamine-mediated Baylis−Hillman coupling of alkyl acrylates with aldehydes also proceeds in aqueous media.[539] In a homogeneous H_2O/solvent medium, the reaction rate of aromatic aldehydes and acrylonitrile or acrylate was greatly accelerated, which led to shorter reaction time, lower reaction temperature, and higher yield.[540] High pressure (ca. 200 MPa), generated by freezing H_2O in a sealed autoclave, was successfully applied to the Baylis−Hillman reaction, in which an efficient rate enhancement was observed. [541] The dominant role in Baylis−Hillman reaction is recently attributed to hydrogen bonding rather than a hydrophobic effect.[542] The reactivity of a variety of quinuclidine-based catalysts in the Baylis−Hillman reaction has been examined and a straightforward correlation between the basicity of the base and the reactivity has been established, without exception. The following order of reactivity was established with pK_a's of the conjugate acids (measured in water) given in parentheses: quinuclidine (11.3), 3-hydroxyquinuclidine (9.9), DABCO (8.7), and 3-acetoxyquinuclidine (7.2).[543] The Baylis−Hillman reaction of cyclic enones was greatly accelerated in basic water solution with imidazoles as catalysts. [544]

The asymmetric Baylis−Hillman reaction of sugar-derived aldehydes as chiral electrophiles with an activated olefin in dioxane/water (1:1) proceeded with 36−86% de and in good yields of the corresponding glycosides (eq 140).[545]



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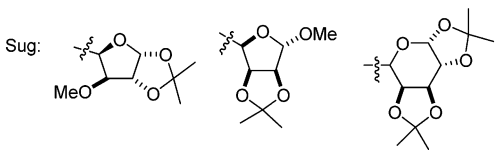
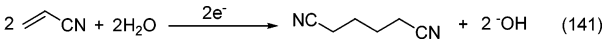


It should be noted that a catalytic amount of bis-arylureas and bis-arylthioureas greatly accelerated the DABCO-promoted Baylis−Hillman reaction of aromatic aldehydes with methyl acrylate in the absence of a solvent. These robust organocatalysts were better mole-per-mole promoters of the reaction than either methanol or water and were recovered in high yields.[546]

7.3. Reductive Coupling

The production of adiponitrile is an important industrial process involving the electro-hydrodimerization (EHD) of acrylonitrile. Adiponitrile is used as

an important precursor for hexamethylenediamine and adipic acid, the monomers required for the manufacture of nylon-66 polymer. The annual production of adiponitrile is about a million tons.[547] Although it was initially studied in the 1940s,[548] the electroreductive coupling of acrylonitrile to adiponitrile was only commercialized more than a decade later after Baizer (at Monsanto) developed the supporting electrolyte. It was found that a 90% yield of adiponitrile could be achieved when a concentrated solution of certain quaternary ammonium salts (QAS), such as tetraethylammonium-*p*-toluenesulfonate, is used together with lead or mercury cathodes (eq 141).[549] Initially, Monsanto employed a divided cell



(141)

EHD process, which was soon replaced by an undivided-cell process because of several shortcomings with the former process.[550] The undivided-cell system involves electrolysis of a dilute solution of acrylonitrile in a mixed sodium phosphate−borate electrolyte using a cadmium cathode and a carbon steel anode. The presence of a quaternary ammonium salt is essential for the adiponitrile selectivity.

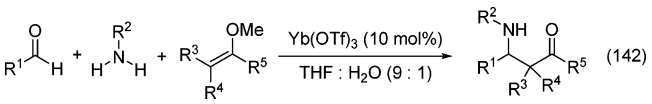
Zinc-mediated reductive dimerization cyclization of 1,1-dicyanoalkenes occurs to give functionalized cyclopentenes in good yields under saturated aqueous NH_4Cl−THF solution at room temperature. The trans isomers are the major products.[551]

8. Reaction of C═N, C–N, and C≡N Compounds

8.1. Nucleophilic Additions

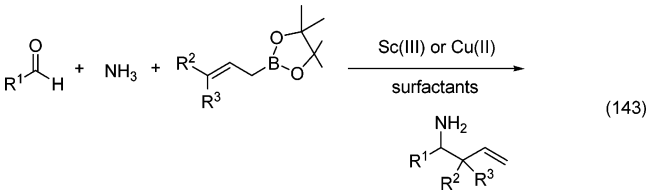
8.1.1. Mannich-Type Reactions

Mannich-type reactions are useful for the synthesis of β-aminocarbonyl compounds. The rate of Mannich-type reactions of phenols and ketones with secondary amines is greatly increased in aqueous compared with alcoholic or hydrocarbon solvents.[552] Recently, Mannich-type reactions catalyzed by various Lewis acids have been studied extensively. Under an aqueous condition of THF−water (9:1), Kobayashi reported the reaction of an aldehyde with an amine and a vinyl ether to give the Mannich-type product in the presence of 10 mol % of ytterbium triflate, Yb(OTf)$_3$.[553] On the other hand, Loh reported a one-pot Mannich-type reaction between aldehydes, amines, and silyl enol ethers catalyzed by indium trichloride in water to give β-amino ketones and esters in moderate to good yields.[554] Suitable silyl enol ethers were $MeOC(:CMe_2)OSiMe_3$ and CH_2:$CPhOSiMe_3$. The catalyst can be recycled when the reaction is complete. In the presence of a catalytic amount of Ln(OTf)$_3$ or Cu(OTf)$_2$, Kobayashi found that the three component Mannich-type reactions of aldehydes, amines, and silyl enolates proceeded smoothly in micellar systems to afford the corresponding β-amino ketones and esters in high yields (eq 142).[555] They



(142)

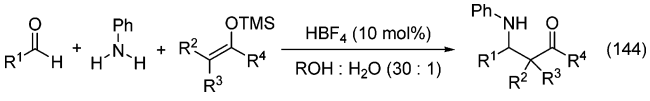
also found that a Lewis acid−surfactant combined catalyst (LASC), composed of water-stable Lewis acidic metal cations such as scandium(III) and copper(II) and anionic surfactants such as dodecyl sulfate and dodecanesulfonate, is highly successful for a Mannich-type reaction and other Lewis-acid-catalyzed C−C bond formations in water (eq 143).[556]



(143)

Furthermore, the results of aldol reactions in various solvents show that water is the best for the LASC-catalyzed reactions. The LASCs were found to form stable colloidal dispersions rapidly in the presence of reaction substrates in water, even when the substrates are solid. Mannich-type reaction between *N*-pyrrolecarboxylates, CH_2O, and hydrochlorides of primary amines is catalyzed by $Y(O_3SCF_3)_3$ to afford a monoaminoalkylation product in good yield in aqueous media.[557] Zinc tetrafluoroborate and other Lewis acids are also highly effective for such couplings in aqueous THF.[558] Kobayashi also reported Mannich-type reactions of imines with silicon enolates catalyzed by neutral salts such as sodium triflate in water as a suspension medium. Unusual kinetic behavior indicates that the presence of the Mannich adduct facilitates the rate of its formation.[559]

Brönsted acids have also been quite effective in catalyzing Mannich-type reactions in aqueous media. Following their studies on the BF_3·OEt_2-catalyzed Mannich-type reaction in aqueous media,[560] Akiyama reported that HBF_4-catalyzed Mannich-type reactions of aldehydes, amines, and silyl enolates took place smoothly in water in the presence of a surfactant to afford β-amino carbonyl compounds in high yields.[561] One-pot synthesis of β-amino carbonyl compounds from aldehydes and amines also worked well (eq 144).[562] The diastereoselectivity on the HBF_4-

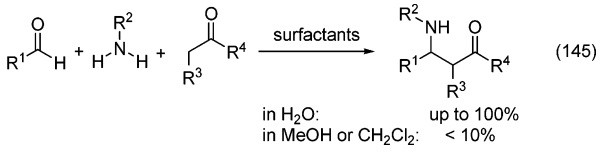


(144)

catalyzed Mannich-type reaction of ketene silyl acetal derived from α-oxy esters with aldimines showed that the use of ketene silyl acetal derived from aryl ester in aqueous 2-propanol gave anti β-amino-α-siloxy ester with excellent stereoselectivity and the use of ketene silyl acetal derived from methyl ester in water in the presence of sodium dodecyl sulfate gave the syn isomer preferentially.[563]

On the other hand, Kobayashi has developed a Brönsted acid combined catalyst for aqueous Mannich-type reactions. Three-component Mannich-type reactions of aldehydes, amines, and ketones, for example, benzaldehyde, *p*-anisidine, and cyclohexanone, were efficiently catalyzed by dodecylbenzenesulfonic acid at ambient temperature in water to give various β-amino ketones in good yields, whereas the

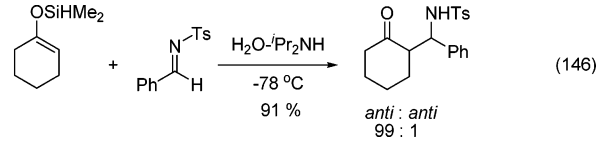
same reaction proceeded sluggishly in organic solvents (eq 145).[564] The catalyst is also effective for the



(145)

reactions of aldehydes, amines, and silyl enolates in water.[565] The Brönsted acid and surfactant can be used separately.[566] For example, the HBF_4 (0.1 equiv)-catalyzed Mannich-type reactions of ketene silyl acetals with aldimines proceeded smoothly in water in the coexistence of as low as 1 mol % of SDS. Hydrophobic polystyrene-supported sulfonic acid (PS–SO_3H) has also been used for such couplings in water.[567]

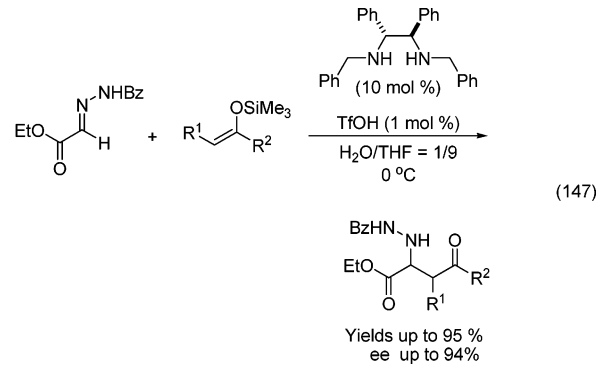
It has been shown that dimethylsilyl enolates can be activated by diisopropylamine and water and exhibited a high reactivity toward *N*-tosyl imines to give Mannich-type reaction product in the absence of Lewis acid or Brönsted acid.[568] For example, the reaction of [(1-cyclohexen-1-yl)oxy]dimethylsilane with 4-methyl-*N*-(phenylmethylene)benzenesulfonamide gives the anti isomer in 91% yield stereoselectively (99:1 anti/syn) (eq 146). On the other hand, Li and



(146)

co-workers reported a ruthenium-catalyzed tandem olefin migration/aldol and Mannich-type reaction by reacting allyl alcohol and imine in protic solvents.[569]

More recently, the asymmetric Mannich-type reaction has been studied in aqueous conditions. Barbas and co-workers reported a direct amino acid-catalyzed asymmetric aldol and Mannich-type reaction that can tolerate a small amount of water (<4 vol %).[570] Kobayashi found that a diastereo- and enantioselective Mannich-type reaction of a hydrazono ester with silyl enol ethers in aqueous media can be successfully achieved with ZnF_2, a chiral diamine ligand, and trifluoromethanesulfonic acid (eq 147).[571]



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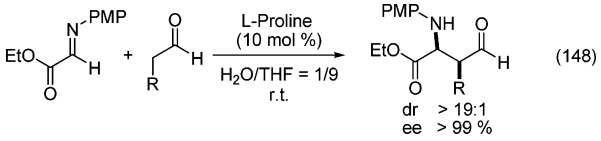
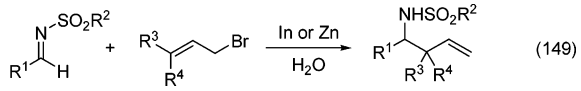
Diastereoselective Mannich-type reactions of chiral aldimines with 2-silyloxybutadienes in the presence of zinc triflate and water led to products with 74–90% de.[572] Cordova and Barbas reported a direct organocatalyzed asymmetric Mannich-type reaction in aqueous media using L-proline as catalyst. The reaction between protected α-imino ethyl glyoxylate and aldehydes provides β-formyl-substituted α-amino acid derivatives with excellent diastereoselectivities (up to 19:1, syn/anti) and high enantioselectivities (ee between 72% and >99%). By combination of the proline-catalyzed Mannich-type reactions with indium-promoted allylation in aqueous media, a one-pot asymmetric synthesis of cyclic γ-allyl-substituted α-amino acid derivatives (up to >99% ee) was accomplished (eq 148).[573]



(148)

8.1.2. Addition of Allyl Groups

As reported by Grieco et al.,[574] immonium salts generated in situ from primary amines and formaldehyde can be allylated with preformed allylstannane under aqueous conditions. Chan reported that the allylation of sulfonimines in water can be mediated by either indium[575] or zinc (eq 149).[576]



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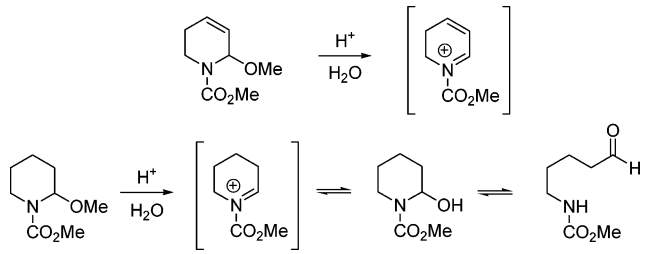
Allylation of acyloyl-imidazoles, pyrazoles, and glyoxylic acid oxime ethers[577] with allyl halide mediated by indium in aqueous media provides a facile regioselective synthesis of β,γ-unsaturated ketones, which has been applied to the synthesis of the monoterpene artemesia ketone. The same product can be obtained by indium-mediated allylation of acyl cyanide.[578] Samarium, gallium, and bismuth can be used as mediators for the allylation of hydroxylamine and hydrazides in aqueous media in the presence of Bu_4NBr.[579] The reaction rate with gallium and bismuth can be increased dramatically under microwave activation.

Allylation of the nitro group on nitrobenzene derivatives proceeded under similar reaction conditions.[580] Allylation reactions of various benzoylhydrazones with tetraallyltin were carried out in the presence of scandium triflate as a Lewis acid catalyst in aqueous media.[581] Three-component reactions of aldehydes, benzoylhydrazine, and tetraallyltin were also catalyzed by scandium triflate in the same media. The reaction was used to prepare oxazolidinone derivatives.[582] Allylation and propargylation of glyoxylic oxime ether in the presence of a catalytic amount of palladium(0) complex and indium(I) iodide were studied. A three-component synthesis of homoallylic amines starting from aldehyde, amine, and allyltributylstannane were realized by using tin(II) chloride dihydrate in H_2O in the presence of SDS surfactant.[583]

Iminium ions, generated in aqueous solution from secondary amines and formaldehyde, undergo a Bar-

Scheme 12[a]



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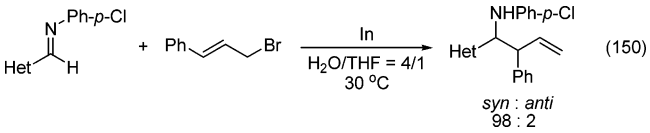
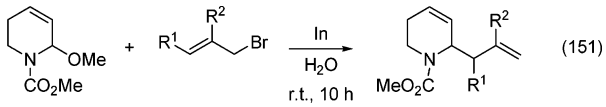
bier-type allylation mediated by tin, aluminum, and zinc (eq 150). The reaction is catalyzed by copper and



(150)

produces tertiary homoallylamines in up to 85% yield.[584] The imines, generated in situ from 2-pyridinecarboxaldehyde/2-quinolinecarboxaldehyde and arylamines, undergo indium-mediated Barbier allylation in aqueous media to provide homoallylic amines.[585] Crotyl and cinnamyl bromides lead to diastereoselective allylation with the diastereomeric ratio up to 98:2.

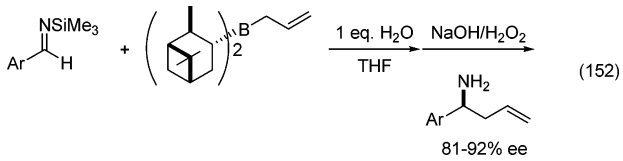
The allylation reaction of electron-deficient imines with allylic alcohol derivatives in the presence of a catalytic amount of palladium(0) complex and indium(I) iodide was studied in the presence of water.[586] Homoallylic *o*-methylhydroxylamines are prepared by indium-mediated addition of allylic bromides to oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid (eq 151). γ-Substituted allylic



(151)

bromides undergo bond formation at the most substituted termini; when the allylic bromide is γ-substituted, the syn stereoisomers of the hydroxylamine products predominate. The reaction does not occur if the oxime ether does not possess a chelating group in close proximity. The use of water as a solvent was found to accelerate the indium-mediated Barbier-type allylation and benzylation of β,γ-unsaturated piperidinium ion, which was generated from β,γ-unsaturated α-methoxy-*N*-methoxycarbonylpiperidine, while the ring-opened allylation product was obtained when β,γ-saturated α-methoxy-*N*-methoxycarbonylpiperidine was used. Solvents other than water resulted in low yields of the allylation and benzylation products, suggesting that water is essential to generate the piperidinium ion intermediate from β,γ-saturated α-methoxy-*N*-methoxycarbonylpiperidine (Scheme 12).[587]

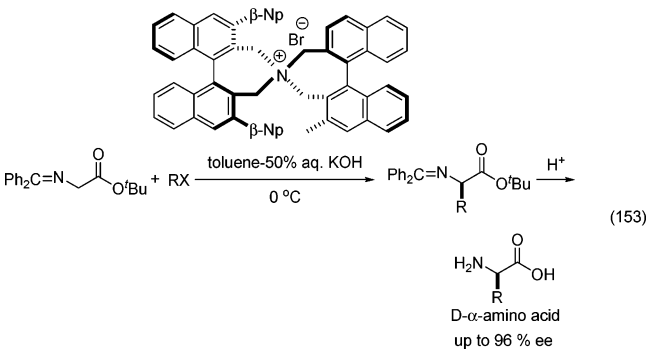
The stereoselective allylation of carbon−nitrogen multiple bonds has also been studied. The addition of allylzinc bromide to aromatic imines derived from (*S*)-valine esters was affected by reversibility, which caused the lowering of the diastereoisomeric ratio with increasing reaction time. The retro-allylation reaction could be avoided by performing the reaction in the presence of a trace amount of water or by using $CeCl_3 \cdot 7H_2O$ as the catalyst with a decreased reaction rate.[588] Hanessian reported the synthesis of enantiomerically pure or highly enriched allylglycine and its chain-substituted analogues from the reaction of the sultam derivatives of *o*-benzyl glyoxylic acid oxime with allylic bromides in the presence of powered zinc in aqueous ammonium chloride.[589] Brown noticed the critical importance of water in the asymmetric allylboration of *N*-trimethylsilylbenzaldimines with *B*-allyldiisopinocampheylborane.[590] The reaction required 1 equiv of water to proceed (eq 152).



(152)

Indium-mediated allylation reactions of α-keto imides derived from Oppolzer's sultam proceeded in aqueous THF in good yields and excellent diastereoselectivity.[591] The indium-mediated allylation of the Oppolzer camphorsultam derivatives of glyoxylic oxime ether proceeded with excellent diastereoselectivity in aqueous media, providing a variety of enantiomerically pure α-amino acids.[592]

More recently, catalytic asymmetric allylations of imines and imine derivatives in aqueous media have been studied. An *N*-spiro C_2-symmetrical chiral quaternary ammonium salt (*S,S*)-I-Br [(*S,S*)-β-Np-NAS-Br] has been evaluated in the allylation of glycine *tert*-butyl ester benzophenone Schiff base $Ph_2C{:}NCH_2COOCMe_3$ for synthesis of both natural and unnatural α-amino acids (eq 153).[593]



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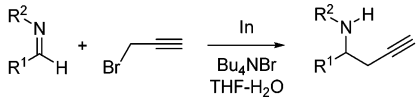
A formal enantioselective synthesis of antibiotic L-azatyrosine was developed. The asymmetric allylation of hydrazono esters with allylsilanes in the presence of a catalytic amount of ZnF_2-chiral diamines in aqueous media generated (benzoyl)hydrazino-4-pentenoates in high enantioselectivity.[594]

8.1.3. Reaction with Propargyl Groups

The indium-mediated coupling of propargyl bromide with a variety of imines and imine oxides afforded homo-propargylamine derivatives in aqueous media under mild conditions (eq 154).[595] Propargylation of glyoxylic oxime ether in the presence of a catalytic amount of palladium(0) complex and

indium(I) iodide in aqueous media was also studied.[596]



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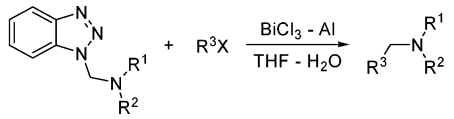
8.1.4. Addition of Alkyl Groups

Katrizky[597] reported that in the presence of bismuth(III) chloride−metallic aluminum, alkyl (as well as allyl) halides react with *N*-(alkylamino)benzotriazoles at 20 °C in THF−water to give the corresponding homoalkylated amines in high yields (eq 155).



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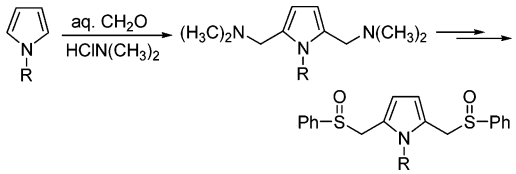
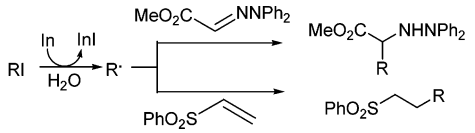
Competitive addition of $^{-}CCl_3$ anions to *N*-alkylpyridinium salts was studied in a two-phase system, chloroform/concentrated aqueous NaOH, and in a homogeneous medium.[598] Aminomethylation of 1-alkylpyrroles by aqueous formaldehyde and dimethylamine hydrochloride, followed by reaction with iodomethane, affords the 1-alkyl-2,5-bis[(trimethylammonio)methyl]pyrrole diiodide (eq 156).[599]



(156)

Clerici and Porta reported that phenyl, acetyl, and methyl radicals add to the C_α atom of the iminium ion, $PhN^{+}Me{:}CHMe$, formed in situ by the titanium-catalyzed condensation of *N*-methylaniline with acetaldehyde to give PhNMeCHMePh and PhNMeCHMeAc in 80% overall yield.[600] Recently, Miyabe and co-workers studied the addition of various alkyl radicals to imine derivatives. Alkyl radicals generated from alkyl iodide and triethylborane added to imine derivatives, such as oxime ethers, hydrazones, and nitrones, in an aqueous medium.[601] The reaction also proceeds on solid support.[602] *N*-Sulfonylimines are also effective under such reaction conditions.[603] Indium is an effective mediator (eq 157).[604] A tandem



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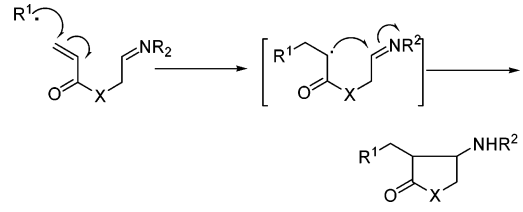
radical addition−cyclization reaction of oxime ether and hydrazone was also developed (eq 158).[605] The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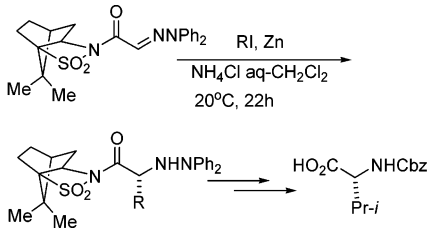
zinc-mediated radical reaction of the hydrazone bearing a chiral camphorsultam provided (with good diastereoselectivities) the corresponding alkylated products, which can be converted into enantiomerically pure α-amino acids (eq 159).[606]



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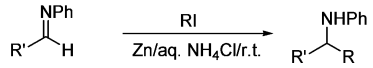
Li and co-workers reported the synthesis of α-amino acid derivatives and amines via the addition of simple alkyl halides to imines and enamides mediated by zinc in water (eq 160).[607]



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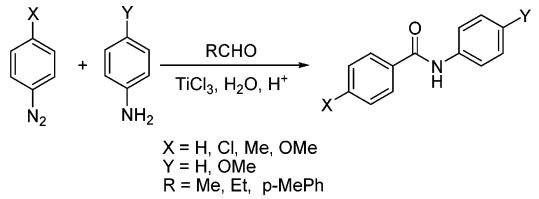
8.1.5. Addition of Vinyl and Aryl Groups

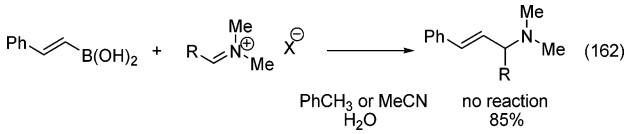
The reaction of aromatic radicals, generated by decomposition of diazonium salts, with iminium salts in the presence of $TiCl_3$ in aqueous media produced secondary amines (eq 161).[608] The iminium salts are



(161)

formed in situ from aromatic amines and aldehydes.

Petasis reported an efficient addition of vinyl boronic acid to iminium salts.[609] While no reaction was observed when acetonitrile was used as solvent, the reaction went smoothly in water to give allylamines (eq 162). The reaction of the boron reagent



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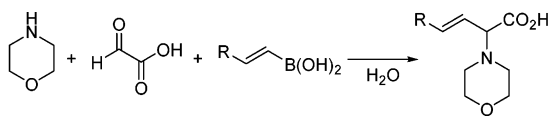
with iminium ions, generated from glyoxylic acid and amines, affords novel α-amino acids (eq 163). Car-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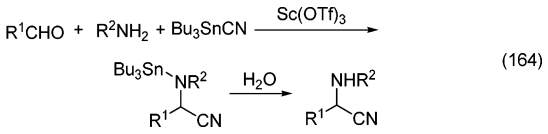
boalumination of alkynes in the presence of catalytic Cp_2ZrCl_2 and H_2O affords vinylalane intermediates, which serve as nucleophiles in the subsequent addition to generate enantiomerically enriched (*tert*-butyl)- and (*p*-tolyl)sulfinimines. Chiral allylic sulfinamides are obtained in high diastereoselectivity and in good yield.[610]

Miyaura and co-workers reported the rhodium-catalyzed reaction of arylboronic esters with *N*-

sulfonylaldeimines under aqueous conditions.[611] Recently, Wang and Li[612] reported that in the presence of a rhodium catalyst, imines react with phenyltrimethyltin or phenyltrimethyllead in air and water under ultrasonic irradiation at 35 °C to give the corresponding diarylmethylamines in good yields.

8.1.6. Other Nucleophilic Additions

In the presence of a catalytic amount of $Yb(O_3SCF_3)_3$, imines reacted with Me_3SiCN to afford α-amino nitriles in excellent yields. Although some imines are difficult to prepare and purify, three-component reactions of aldehydes, amines, and Me_3SiCN proceeded smoothly.[613] Strecker-type reactions were successfully carried out by simply mixing aldehydes, amines, and tributyltin cyanide in aqueous media (eq 164).[614] The presence of a small amount of water was

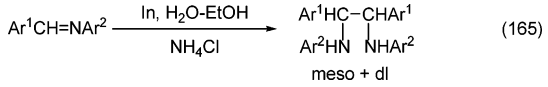


(164)

found to be crucial for the asymmetric addition of Reformatsky-type reagent to imines utilizing diisopropyl tartrate as a chiral auxiliary.[615]

8.2. Reductive Coupling

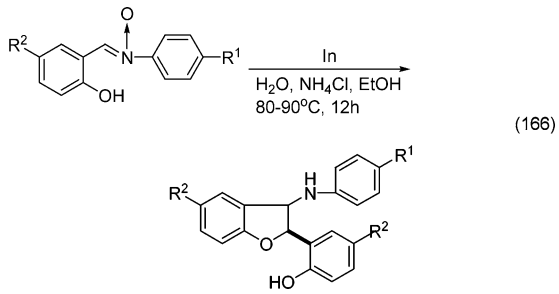
Reductive coupling of aldimines, obtained from aromatic aldehydes and aromatic amines, generated vicinal diamines mediated by indium in aqueous ethanol (eq 165).[616] Small indium rods were used in



(165)

this study. No side product due to unimolecular reduction was observed. The presence of NH_4Cl was found to accelerate the reaction, while the reaction fails completely in CH_3CN, DMF, or wet DMF. The use of nonaromatic substrates also resulted in the failure of the reaction.

Reductive coupling of aldimines into vicinal diamines has been performed using zinc powder in 10% NaOH aqueous solution without using any organic solvent at ambient temperature in high yields.[617] Additives such as NH_4Cl and L-tyrosine can be used in lieu of 10% NaOH.[618] Vicinal disulfonamides were generated by reductive coupling of *N*-sulfonylimines in Sm/HCl/THF,[619] whereas reductive coupling of aldimines and ketimine was examined using Sm(II)-based reagents (SmI_2, SmI_2–HMPA, $SmBr_2$, Sm-$\{N[Si(CH_3)_3]_2\}_2$, and SmI_2/triethylamine) in water.[620] Nitrones, for example, 2-HOC_6H_4CH:N(O)Ph, undergo deoxygenative reductive coupling and subsequent cyclization to give 3-arylamino-2,3-dihydrobenzofuran derivatives in the presence of indium under aqueous conditions at ambient temperature in good yields (eq 166).[621] The reductive coupling cyclization



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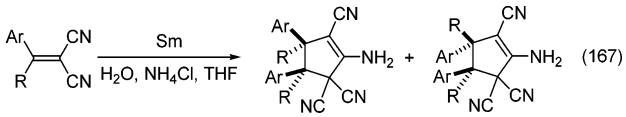
of 1,1-dicyanoalkenes was performed with metallic samarium in saturated aqueous NH_4Cl–THF solution at room temperature (eq 167).[622]



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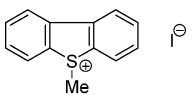
9. Reaction of Organic Halides

9.1. Nucleophilic Substitution

For carbon–carbon bond formation purposes, SN_2 nucleophilic substitutions are frequently used. Simple SN_2 nucleophilic substitution reactions are generally slower in aqueous conditions than in aprotic organic solvents, which has been attributed to the solvation of nucleophiles in water. However, Breslow and coworkers have found that cosolvents such as ethanol increase the solubility of hydrophobic molecules in water and provide interesting results for nucleophilic substitutions. In alkylations of phenoxide ions by benzylic chlorides, SN_2 substitutions can occur both at the phenoxide oxygen and at the ortho and para positions of the ring. In fact, carbon alkylation occurs in water but not in nonpolar organic solvents, and this reactivity is observed only when the phenoxide bears at least one methyl substituent (ortho, meta, or para). The effects of phenol substituents and of cosolvents on the rates of the competing alkylation processes indicate that in water the carbon alkylation involves a transition state with hydrophobic packing of the benzyl group onto the phenol ring.[623]

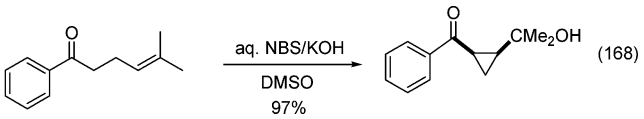
Methylation of relatively acidic ($pK_a < 13$) carbon nucleophiles occurs at neutral pH in aqueous media when substituted methylsulfonium and -selenonium salts are used as electrophiles (e.g., **9**).[624] The formation of C–C and C–O bonds by the reaction of enolate intermediates with organic halides in aqueous sodium hydroxide at moderate temperatures was reported.[625]



9

A simple one-pot preparation of (*Z*)-cyclopropanes from γ,δ-ketoalkenes used intramolecular alkylation under aqueous conditions. Sequential treatment of γ,δ-ketoalkenes with aqueous *N*-bromosuccinimide

(NBS) in DMSO and then with solid KOH provides (*Z*)-cyclopropanes in good overall yields with a diastereoselective excess >99% (eq 168).[626]



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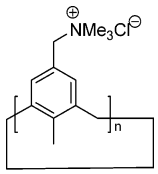
Quantum mechanical/molecular mechanical (QM/MM) study on the Favorskii rearrangement in aqueous media has been carried out.[627] The results obtained by QM/MM methods show that of the two accepted molecular mechanisms for the Favorskii rearrangement, the semibenzilic acid mechanism is favored over the cyclopropanone mechanism for the α-chlorocyclobutanone system. However, the study of ring size effects reveals that the cyclopropanone mechanism is the energetically preferred reactive channel for the α-chlorocyclohexanone ring, probably due to the straining effects on the bicyclic cyclopropanone, an intermediate that appears on the semibenzilic acid pathway. These results provide new information on the key factors responsible for the behavior of reactant systems embedded in aqueous media.

The water-soluble calix[*n*]arenes **10** ($n = 4$, 6, and 8) containing trimethylammoniomethyl groups act as



10

efficient inverse phase-transfer catalysts in the nucleophilic substitution reaction of alkyl and arylalkyl halides with nucleophiles in water.[628] In the presence of various surfactants (cationic, zwitterionic, and anionic), the reaction of different halides and ketones shows that the amount of ketone alkylation is much higher and that the reactions are faster in the presence rather than in the absence of surfactant aggregates,[629] as the hydrolysis of the halide is minimized in the presence of cationic or zwitterionic surfactants. Nucleophilic aromatic photosubstitution reactions in aqueous solutions and in micellar media have been investigated extensively.[630] An allylgallium reagent is found to be effective for radical allylation of α-iodo or α-bromo carbonyl compounds in aqueous conditions. [631]

9.2. Reductive Coupling

9.2.1. Wurtz-Type Coupling

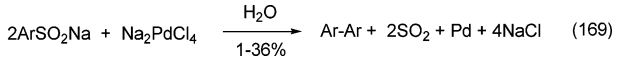
Homocoupling of alkyl halides in aqueous media can be mediated by manganese/cupric chloride to give the dimerization products in good yield. Cross-coupling can also be controlled to give the desired product.[632] Wurtz-type coupling of allyl halides was (in low yields) the normal outcome in refluxing alcohol.[633] Organic halides undergo reductive dimerization (Wurtz-type coupling) promoted by zinc at room temperature in an aqueous medium.[634] The reaction yields are strongly enhanced by a catalytic amount of copper. This coupling procedure provides an efficient and simple method for the homocoupling of benzylic and allylic bromides and primary alkyl iodides. An allylgallium reagent is found to be effective for radical allylation of α-iodo or α-bromo carbonyl compounds. Treatment of benzyl bromoacetate with allylgallium, prepared from allylmagnesium chloride and gallium trichloride, in the presence of triethylborane in THF provided benzyl 4-pentenoate in good yield. The addition of water as a cosolvent improved the yields of allylated products. [635] It was suggested that the acceleration was due to either a decrease of the total volume of the reactants or the transformation of allygallium into the more reactive allylgallium hydroxide.

The Wurtz-type reductive coupling reaction of primary alkyl iodides or allyl halides and haloorganotins in cosolvent/$H_2O(NH_4Cl)$/Zn media provides a route to mixed alkyl and allylstannanes. For example, mixed tetraalkylstannanes R_3SnR' (R = Et, *n*-Pr, or *n*-Bu and R′ = Me, Et, *n*-Pr, *n*-Bu, or *n*-Pent) and $R_2SnR'_2$ (R = *n*-Bu and R′ = Me, Et, *n*-Pr, or *n*-Bu) can be easily prepared in a one-pot synthesis via a coupling reaction of alkyl iodides R′I with R_3SnX (X = Cl, I) and R_2SnCl_2 compounds in a cosolvent−$H_2O(NH_4Cl)$ medium mediated by zinc dust. Coupling also occurs with $(Bu_3Sn)_2O$. Secondary alkyl iodides did not couple under the same reaction conditions.[636]

9.2.2. Ullmann-Type Coupling and Related Reactions

It is noteworthy to mention that the Ullmann−Goldberg condensation of aryl halides with phenols and anilines worked efficiently in the presence of copper in water.[637] For example, coupling of 2-chlorobenzoic acid with 4-chlorophenol (K_2CO_3/pyridine/copper powder) gave 2-(4-chlorophenoxy)carboxylic acid.[638] The CuI-catalyzed transformation of 2-bromobenzoic acid into salicylic acid has also been studied in aqueous media.[639]

Ullmann-Type Coupling. The homocoupling of aryl halide to diaryl compounds is a synthetically useful reaction and has wide applications in materials research. Such couplings have been studied in aqueous conditions. In 1970, arylsulfinic acids were coupled with Pd(II) in aqueous solvents to biaryls (eq 169).[640] However, the reaction requires the use of a



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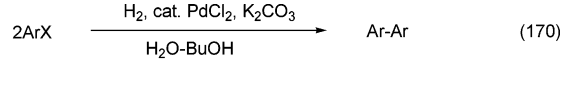
stoichiometric amount of palladium. In the presence of hydrogen gas, aryl halides homocoupled to give biaryl compounds in moderate yields (30−50%) in an aqueous/organic microemulsion (eq 170).[641]

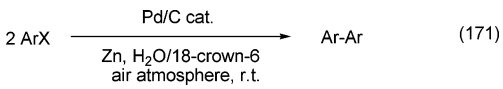


(170)

X=I, Br; Ar=Ph, p-MePh, p-MePPh, p-ClPh, m-CF_3Ph

In 1999, Venkatraman and Li reported a facile coupling of aryl halides via a palladium-catalyzed

reductive coupling using zinc in air and aqueous acetone at room temperature by using Pd/C as a catalyst (eq 171).[642] Various aryl iodides and aryl



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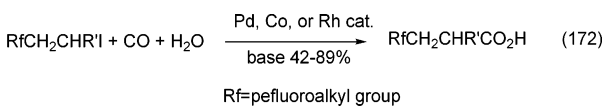
bromides coupled effectively under these conditions. Subsequently, they found that the addition of a surfactant or a crown ether in water alone provided better isolated yields of the product.[643] Sasson and co-workers further developed this reaction by using PEG as an additive and by increasing the reaction temperature. In this case, aryl chloride also worked effectively.[644] Reductive homocoupling of chlorobenzenes to biphenyls affords high yields (93−95%) in the presence of catalytic PEG-400 and 0.4 mol % of a recyclable, heterogeneous trimetallic catalyst (4% Pd, 1% Pt, and 5% Bi on carbon). The competing reduction process is minimized.[645] They believe that dihydrogen is generated in situ. In addition to Pd/C, Rh/C is also effective as the catalyst.[646] Carbon dioxide was found to promote the palladium-catalyzed zinc-mediated reductive Ullmann coupling of aryl halides. In the presence of carbon dioxide, Pd/C, and zinc, various aromatic halides including less reactive aromatic chlorides were coupled to give the corresponding homocoupling products in good yields.[647]

9.3. Carbonylation of Organic Halides

9.3.1. Carbonylation of Alkyl Halides

Transition-metal-catalyzed carbonylation of 1-perfluoroalkyl-substituted 2-iodoalkanes has been carried out in aqueous media to give carboxylic acids with a perfluoroalkyl substituent at the β position (eq 172).[648] The carbonylation of representative alkyl,



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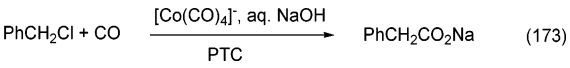
allyl, benzyl, aryl, and vinyl halides catalyzed by complexes of group VIII metals proceeded in the presence of water or alcohols in *N*,*N*,*N*′,*N*′-tetraalkylurea in the absence of an added base to give the corresponding carboxylic acids or esters, respectively, in good to excellent yields.[649]

9.3.2. Carbonylation of Allylic and Benzylic Halides

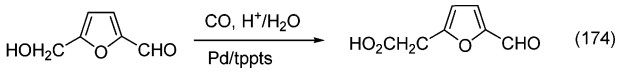
The transition-metal-catalyzed carbonylation of allylic and benzylic compounds offers a useful method for the synthesis of β,γ-unsaturated acids.[650] The requirement of high carbon monoxide pressure and the low yield of the products limited the usefulness of the method in organic synthesis.[651] In 1977, it was found that the carbonylation of benzyl bromide and chloride could be carried out by stirring aqueous sodium hydroxide and an organic solvent using a phase-transfer agent together with a cobalt catalyst (eq 173).[652,653] Under high pressure and temperature,



(173)

even benzylic mercaptans reacted similarly to give esters.[654] In the presence of a nickel catalyst, similar carbonylations of allyl bromide and chloride in aqueous NaOH can be carried out at atmospheric pressure.[655] The base concentration significantly influenced the yield and the product distribution. More recently, it was found that the palladium-catalyzed carbonylation of allyl chloride proceeded smoothly in a two-phase aqueous NaOH/benzene medium under atmospheric pressure at room temperature.[656] Catalysts with or without phosphorus ligands gave similar results and the presence of hydroxide was essential. The reaction seemed to occur at the liquid−liquid interface because no phase-transfer agent was used. However, the addition of surfactants such as n-$C_7H_{15}SO_3Na$ or n-$C_7H_{15}CO_2Na$ does accelerate the reactions.[657]

When a water-soluble palladium catalyst is used, 5-hydroxymethylfurfural is selectively carbonylated to the corresponding acid at 70 °C, together with reduced product (eq 174).[658]



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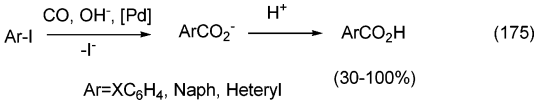
9.3.3. Carbonylation of Aryl Halides

The palladium-catalyzed carbonylation of aryl halides in the presence of various nucleophiles is a convenient method for synthesizing various aromatic carbonyl compounds (e.g., acids, esters, amides, thioesters, aldehydes, and ketones). Aromatic acids bearing different aromatic fragments and having various substituents on the benzene ring have been prepared from aryl iodides at room temperature under 1 atm CO in a mixed solvent of H_2O/DMF (1/1 or 1/2, v/v) and even in water alone, depending on the solubility of the substrate (eq 175).[659] The palladium(II) com-



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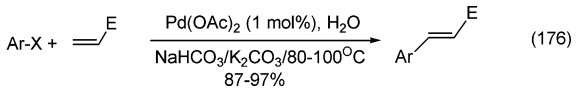
plexes $Pd(OAc)_2$, K_2PdCl_4, $PdCl_2(PPh_3)_2$, and $Pd(NH_3)_4Cl_2$ are used as the precursors of the catalyst using either K_2CO_3 or NaOAc as the base. Iodoxyarenes can be carbonylated in water alone due to its solubility in the solvent.[660] Recent work was done on the use of water-soluble catalysts.[661] Under the appropriate conditions of pressure and temperature, aryl mercaptans (thiophenols) can also be carbonylated in aqueous media with cobalt carbonyl as the catalyst.[662]

9.4. The Heck Coupling

The reaction between aryl (or alkenyl) halides and alkenes in the presence of a catalytic amount of a palladium compound to give substitution of the halides by the alkenyl group is commonly referred

to as the Heck reaction.[663] Both inter- and intramolecular Heck reactions have been performed in aqueous media. Palladium-catalyzed reactions of aryl halides with acrylic acid or acrylonitrile gave the corresponding coupling products in high yields in the presence of a base in water (eq 176).[664] The reaction



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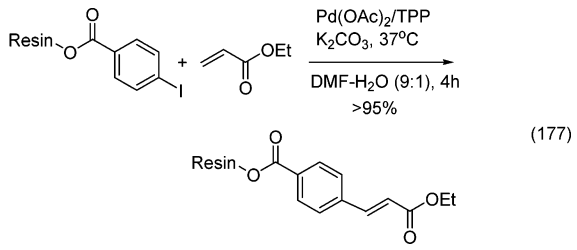
provides a new and simple method for the synthesis of substituted cinnamic acids and cinnamonitriles. Recently, such reactions were carried out using a water-soluble phosphine ligand.[665] Polymer-supported carbene ligands[666] and dendrimer-encapsulated nanoparticle catalysts[667] were also used for Heck couplings in water. Iodobenzoic acid can be used directly to couple with acrylic acid. Diaryliodonium salts react similarly.[668] Jeffery studied the reaction under phase-transfer conditions.[669] It was found that the presence of water is the determinant for the efficiency of quaternary ammonium salt in the palladium-catalyzed vinylation of organic halides using an alkaline metal carbonate as the base, possibly due to the increased solubility of the metal carbonate. The phase-transfer procedure can be performed without the organic cosolvent.

In aqueous DMF, the reaction can be applied to the formation of C−C bonds in a solid-phase synthesis (eq 177).[670] The reaction proceeds smoothly and leads

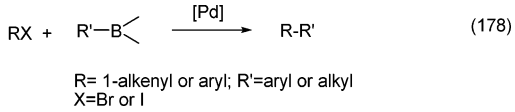


(177)

to moderate or high yields of the product under mild conditions. The optimal conditions involve the use of a 9:1 mixture of DMF−water. Parsons investigated the viability of the aqueous Heck reactions under superheated conditions.[671] A series of aromatic halides were coupled with styrenes under these conditions. The reaction proceeded to approximately the same degree at 400 °C as at 260 °C. Some 1,2-substituted alkanes can be used as alkene equivalents for the high-temperature Heck-type reaction in water.[672] A mixture of pyrrolidinium and piperidinium tetrafluoroborate melt with water has been examined as solvent for Heck and Suzuki reactions.[673] The aqueous Heck reaction has been used in various syntheses.[674]

9.5. The Suzuki Coupling

The cross-coupling reaction of alkenyl and aryl halides with organoborane derivatives in the presence of a palladium catalyst and a base, known as the "Suzuki reaction", has often been carried out in an organic/aqueous mixed solvent (eq 178).[675] The



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reaction was initially carried out in a mixture of benzene and aqueous Na_2CO_3.[676] However, the reaction proceeds more rapidly in a homogeneous medium (e.g., aqueous DME). This condition works satisfactorily in most aryl−aryl couplings.[677] Thus, dienes are conveniently prepared from the corresponding alkenylborane and vinyl bromide in refluxing THF in the presence of $Pd(PPh_3)_4$ and an aqueous NaOH solution.[678] The use of aqueous TlOH instead of NaOH or KOH significantly increased the rate of the coupling. In Kishi's palytoxin synthesis, the cross-coupling between the alkenylboronic acid and the iodoalkene was accomplished stereoselectively at room temperature.[679] The TlOH promoted coupling has also been used effectively in Roush's synthesis of kijanimicin,[680] Nicolaou's synthesis of (12*R*)-hydroxyeicosatetraenoic acid (HETE),[681] and Evans' synthesis of rutamycin B.[682] Multigram-scale synthesis of a biphenyl carboxylic acid derivative used a Pd/C-mediated Suzuki-coupling approach.[683] The Suzuki reaction in an aqueous medium has also been used in other applications such as the synthesis of monosubstituted arylferrocenes,[684] insulated molecular wires (conjugated polyrotaxanes),[685] cyclodextrin [2]rotaxanes,[686] unprotected halonucleosides,[687] 6-substituted *N*-Boc 3,4-dihydro-2*H*-pyridines,[688] heteroarylbenzoic acids,[689] alkenylpurines,[690] 6-alkyl-*N*-alkoxycarbonyl-3,4-dihydro-2*H*-pyridines,[691] coumarinic derivatives,[692] and biaryl colchicinoids.[693] The reaction has been used in synthesizing a combinatorial library of biaryls.[694]

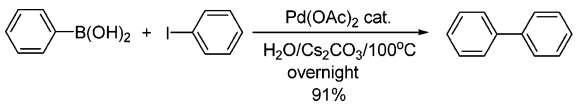
Casalnuovo and Calabrese reported that by using the water-soluble palladium(0) catalyst $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_4$ ($M = Na^+, K^+$) various aryl bromides and iodides reacted with aryl and vinyl boronic acids, terminal alkynes, and dialkyl phosphites to give the cross-coupling products in high yields in water.[695] This reaction can tolerate a broad range of functional groups, including those present in unprotected nucleotides and amino acids. Cross-coupling of boronic acids or esters with alkenyl iodides was conducted similarly, generating functionalized dienes.[696] Polyfunctional biaryls are prepared by a modified Suzuki cross-coupling reaction between arylboronic acids or sodium tetraphenylborate and aryl halides in aqueous solvents or neat water using a phosphine-free palladium catalyst and in the presence of bases with high catalytic efficiency (250 000 catalytic cycles). All four Ph groups of Ph_4BNa participate in the reaction.[697] The poly(ethylene glycol) esters of bromo, iodo, and triflate para-substituted benzoates are smoothly cross-coupled with aryl boronic acids (Suzuki reaction) under "ligand-less" palladium acetate catalysis in water. The reaction proceeds without an organic cosolvent under conventional thermal conditions (70 °C, 2 h) and under microwave irradiation (75 W, 2−4 min). Whereas conventional thermal

conditions induced ester cleavage (up to 45%), this side reaction is suppressed when microwave conditions are employed.[698] The Suzuki coupling can be done without any organic cosolvent.[699]

Pd nanoparticles are efficient catalysts for the Suzuki reactions in an aqueous medium.[700] The initial rate depends linearly on the concentration of Pd catalyst, suggesting that the catalytic reaction occurs on the surface of the Pd nanoparticles. The role of capping materials on the catalytic activity and the stability of transition metal nanoparticles used in catalysis in solution was studied.[701] The particles were used as catalysts in Suzuki reactions in an aqueous medium to study the effects of these stabilizers on the metallic nanoparticle catalytic activity and stability. The stability of the Pd nanoparticles was measured by the tendency of nanoparticles to give Pd black powder after the catalytic reaction. The Suzuki reactions between arylboronic acids and bromoarenes, catalyzed by Pd nanoparticles, result in byproducts due to the homocoupling of bromoarenes. The two properties were found to be anticorrelated, that is, the most stable is the least catalytically active. The Pd/CD clusters were found to exhibit an excellent catalytic activity toward the Suzuki−Miyaura cross-coupling reactions in water between iodophenols and phenylboronic acid.[702] Reverse-phase glass beads have been employed in Suzuki reactions to provide, in aqueous media, a route to diverse polar substrates in good yields and with low levels of palladium leaching. [703] Pd(II)-exchanged NaY zeolite showed high activity in the Suzuki cross-coupling reactions of aryl bromides and iodides without added ligands. The DMF/water ratio and the type and amount of base were found to be critical for the efficiency of the reaction. The catalyst is reusable after regeneration. Addition of phosphine additives, such as dimethylphenylphosphine and 3-methylbenzothiazolium iodide brought the reaction to a halt.[704] Cyclodextrins or calixarenes possessing extended hydrophobic host cavities and surface-active properties were found to be very efficient as mass-transfer promoters for the palladium-mediated Suzuki cross-coupling reaction of 1-iodo-4-phenylbenzene and phenylboronic acid in an aqueous medium. The cross-coupling rates were up to 92 times higher than those obtained without addition of any compound.[705] Other supported palladium catalysts have also been used for Suzuki reactions in water. [706]

Sterically demanding, water-soluble alkylphosphines as ligands showed high activity in Suzuki coupling of aryl bromides in aqueous solvents.[707] Turnover numbers up to 734 000 mmol/mmol of Pd have been achieved under such conditions. Glucosamine-based phosphines were found to be efficient ligands for Suzuki cross-coupling reactions in water.[708]

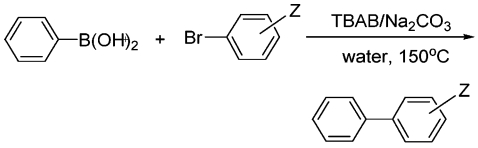
Recently, Suzuki-type reactions in air and water have also been studied for the first time by Li and co-workers.[709] They found that the Suzuki reaction proceeded smoothly in water under an atmosphere of air with either $Pd(OAc)_2$ or Pd/C as catalyst (eq 179). Interestingly, the presence of phosphine ligands



(179)

prevented the reaction. Subsequently, Suzuki-type reactions in air and water have been investigated under a variety of systems. These include the use of oxime-derived palladacycles[710] and tuned catalysts (TunaCat).[711] A preformed oxime−carbapalladacycle complex covalently anchored onto mercaptopropyl-modified silica is highly active (>99%) for the Suzuki reaction of *p*-chloroacetophenone and phenylboronic acid in water; no leaching occurs and the same catalyst sample was reused eight times without decreased activity.[712] By utilization of a solid support-based tetradentate *N*-heterocyclic carbene−palladium catalyst, cross-couplings of aryl bromides with phenylboronic acid were achieved in neat water under air.[713] A high ratio of substrate to catalyst was also realized.

The use of microwave heating is a convenient way to facilitate the Suzuki-type reactions in water.[714] It is possible to prepare biaryls in good yield very rapidly (5−10 min) on small (1 mmol) and larger (10−20 mmol) scales from aryl halides and phenylboronic acid using water as solvent and palladium acetate as catalyst. Recently, Leadbeater[715] found that the Suzuki reaction can be carried out in water at high temperature without using any transition metal catalyst (eq 180).[716] At 150 °C in a sealed tube,



(180)

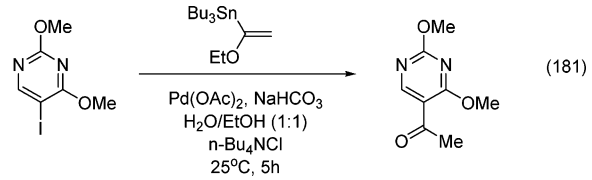
Z=Me, OMe, Cl, NH_2, NO_2, CHO, COMe, CO_2H, CO_2R etc.

optimum yields of the product were obtained when the ratio of aryl bromide to boronic acid was 1:1.3. The required excess amount of boronic acid was attributed to some protodeboronation of the boronic acid, which gave benzene. Various aryl bromides bearing both electron-donating and electron-withdrawing groups proceeded readily. Aryl bromides provided better yields than aryl iodides or aryl chlorides; the latter showed no reactivity under the reaction conditions. Sterically demanding aryl bromides were also coupled in good yields. The reaction also proved to be regiospecific with respect to both the aryl bromide and the boronic acid, and the reaction of 4-bromoacetophenone with 4-methylbenzeneboronic acid obtained the desired coupling product in excellent yield. Microwave heating for 5 min provided comparable yields to conventional heating for 5 h with 4-bromoacetophenone. With unactivated and deactivated aryl bromides, conventional heating is not sufficient even after 16 h. To show that the reaction was truly metal-free, new glassware, apparatus, and reagents were used. No palladium was detected down to 0.1 ppm Pd by analysis of the crude

reaction mixture. Subsequently, it was found that a trace amount of Pd in commercial Na_2CO_3 was responsible for the reaction.[717] A nonracemic axially chiral bridged antimitotic agent was prepared using the enantioselective Suzuki coupling reaction in the presence of (*R*)-BINAP in 1,4-dioxane/water (9:1). [718]

9.6. The Stille Coupling

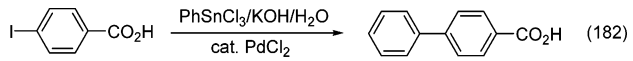
The coupling between alkenyl and aryl halides with organostannanes in the presence of a palladium catalyst is referred to as the Stille reaction.[719] Although it was known that in the palladium-catalyzed coupling reaction of organostannanes with vinyl epoxides addition of water to the organic reaction medium increased yields and affected the regio- and stereochemistry,[720] the Stille coupling reaction in aqueous media was extensively investigated only recently. Davis[721] reported a coupling in aqueous ethanol (eq 181). The reaction gave a high yield of



(181)

the coupled product, which hydrolyzed in situ.

Collum[722] reported that while the Stille coupling can proceed without using a phosphine ligand, the addition of a water-soluble ligand improved the yield of the reaction. Water-soluble aryl and vinyl halides were coupled with alkyl-, aryl-, and vinyltrichlorostannane derivatives in this way (eq 182).



(182)

no ligand 81%

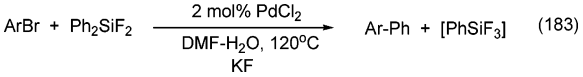
with PhP(*m*-C_6H_4-SO_3Na)$_2$ 95%

Arenediazonium chlorides and hydrogen sulfates react with tetramethyltin in aqueous acetonitrile in the presence of a catalytic amount of palladium acetate to give high yields of substituted toluenes.[723] One-pot hydrostannylation/Stille couplings with catalytic amounts of tin were performed by syringe-pump addition of 1.5 equiv of various Stille electrophiles to a 37 °C ethereal mixture of alkyne, aqueous Na_2CO_3, polymethylhydrosiloxane, Pd_2dba_3, tri-2-furylphosphine, $PdCl_2(PPh_3)_2$, and 0.06 equiv of Me_3SnCl over 15 h to give the cross-coupled products in 75−91% yield.[724] An efficient Stille cross-coupling reaction using a variety of aryl halides in neat water has been developed.[725] Employing palladium−phosphinous acid catalyst $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$ allows formation of biaryls from aryl chlorides and bromides in good to high yields.

Li and co-workers reported a Stille-type coupling in water under an atmosphere of air.[726]

9.7. Other Couplings

Biaryls were obtained in good yields by reacting diphenyldifluorosilane or diphenyldiethoxysilane with aryl halides in aqueous DMF at 120 °C in the presence of KF and a catalytic amount of $PdCl_2$ (eq 183).[727] Phosphine ligands are not required for the

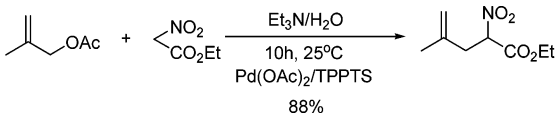


(183)

reaction. Li and co-workers reported a highly efficient palladium-catalyzed coupling of aryl halides with arylhalosilanes in open air in water in the presence of a base or fluoride ion. Both $Pd(OAc)_2$ and Pd/C are effective as catalysts. [728]

9.8. The Trost–Tsuji Reaction

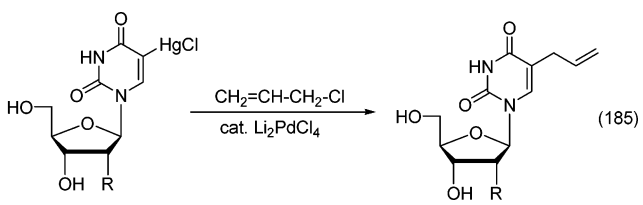
Coupling reactions involving π-allyl palladium intermediates have recently been investigated in aqueous media.[729] For example, by using a water-soluble palladium catalyst, allyl acetates couple with α-nitroacetate in water in the presence of triethylamine (eq 184). Other compounds bearing an active



(184)

hydrogen can be used as well in place of α-nitroacetate. Heteroatom nucleophiles can also be used for this reaction. The reaction of an amine with allyl acetate generated the *N*-allylation product.[730] Nucleophiles such as azide and toluenesulfinate reacted similarly to give quantitative yields of the corresponding allyl azide and allylsulfone.[731] The reaction can also be used for the removal of allyloxy carbonyl protected functional groups.[732] The method has been successfully used for deprotection of a wide range of secondary amines. Both homogeneous aqueous acetonitrile and the biphasic diethyl ether/water system are suitable for the removal of the alloc moiety from nitrogen- and oxygen-based functional groups.

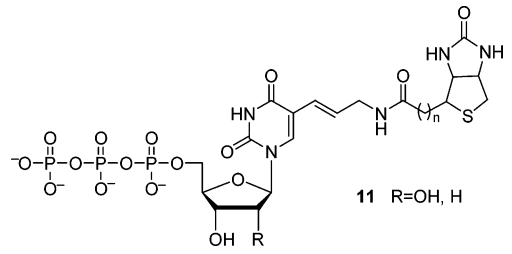
Examples involving the use of organomercury reagents as nucleophiles in aqueous medium are also known. Bergstrom studied the synthesis of C-5-substituted pyrimidine nucleosides in aqueous media via a mercurated intermediate using Li_2PdCl_4 as a catalyst (eq 185).[733] Mertes investigated the coupling



(185)

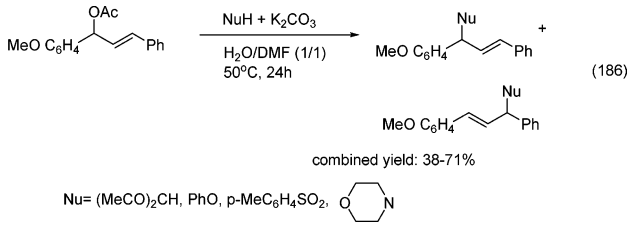
of the 5-mercuriuridines with styrenes in aqueous media, resulting in alkylation of the uracil nucleotides.[734] Carbon alkylation of the C-5 of the uracil ring in the ribo- and deoxyribonucleosides and nucleotides was obtained in high yields by this method. A similar reaction was used by Langer et al. in the synthesis of 5-(3-amino)allyluridine and

deoxyuridine-5′-triphosphates (AA-UTP and AA-dUTP) (**11**).[735]



Asymmetric palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with carbon and nitrogen nucleophiles occurs in water in the presence of a surfactant, a base, and BINAP as the chiral ligand.[736] Enantioselectivities of up to 91% were obtained using carbon nucleophiles, and 93% using nitrogen nucleophiles, in the presence of $CTHASO_4$ as the surfactant. While the efficiency of the catalyst was higher in water in the presence of the surfactant in the case of carbon nucleophiles, no micellar effects were observed using the nitrogen nucleophiles.

Recently, a water-mediated transition-metal-free Tsuji−Trost-type reaction has been reported.[737] The treatment of 1-acetoxy-1,3-diphenylpropene by C-, O-, S- and N-nucleophiles in basic aqueous media produced the corresponding substitution products in the absence of a transition-metal catalyst (eq 186).



(186)

Mechanistic studies led to the proposal of a BAL_1 cleavage of the ester function leading to a stabilized allylic carbocation as intermediate.

10. Pericyclic Reactions

10.1. Diels–Alder Reactions

10.1.1. Diels–Alder Reactions Promoted by Water

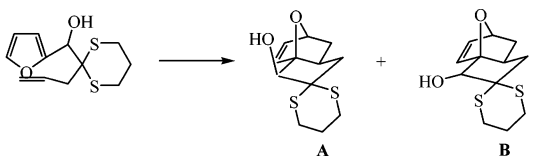
The Diels−Alder reaction is one of the most important methods used to form cyclic structures and is one of the earliest examples of carbon−carbon bond formation reactions in aqueous media.[738] Diels−Alder reactions in aqueous media were first carried out back in the 1930s,[739] but no particular attention was paid to this fact until 1980, when Breslow[740] made the dramatic observation that the reaction of cyclopentadiene with butenone in water was more than 700 times faster than the same reaction in isooctane; whereas the reaction rate in methanol is comparable to that in a hydrocarbon solvent. Such an unusual acceleration of the Diels−Alder reaction by water was attributed to the "hydrophobic effect",[741] in which the hydrophobic interactions brought together the two nonpolar groups in the transition state.

In addition, the hydrophobic binding of the diene and dienophile into a cyclodextrin cavity in water largely replaces the association because of the hydrophobic interaction. Therefore, the catalysis of the Diels−Alder reactions with cyclopentadiene occurs by mutual binding of the reagents in the cyclodextrin cavity, relative to the unassociated molecules. The use of β-cyclodextrin, which simultaneously forms an inclusion complex with the diene and dienophile, and the use of 4.86 M LiCl aqueous solution as solvent, which salts out nonpolar materials dissolved in water,[742] further enhanced the rate of aqueous Diels−Alder reactions.

On the other hand, the use of α-cyclodextrin decreased the rate of the reaction. This inhibition was explained by the fact that the relatively smaller cavity can only accommodate the binding of cyclopentadiene, leaving no room for the dienophile. Similar results were observed between the reaction of cyclopentadiene and acrylonitrile. The reaction between hydroxymethylanthracene and *N*-ethylmaleimide in water at 45 °C has a second-order rate constant over 200 times larger than in acetonitrile. In this case, the β-cyclodextrin became an inhibitor, rather than an activator, due to the even larger transition state, which cannot fit into its cavity. A slight deactivation was also observed with a salting-in salt solution, e.g., quanidinium chloride aqueous solution.

The stereoselectivity of some Diels−Alder reactions was also strongly affected in water.[743] At low concentrations, where both components were completely dissolved, the reaction of cyclopentadiene with butenone gave a 21.4 ratio of endo/exo products when they were stirred at 0.15 M concentration in water, compared to only a 3.85 ratio in excess cyclopentadiene and an 8.5 ratio in ethanol as the solvent. Aqueous detergent solution had no effect on the product ratio. The stereochemical changes were explained by the need to minimize the transition-state surface area in water solution, thus favoring the more compact endo stereochemistry. The results are also consistent with the effect of polar media on the ratio.[744]

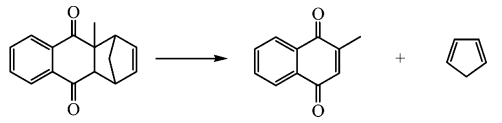
The catalytic behavior exhibited by β-cyclodextrin was also observed by Sternbach in the intramolecular Diels−Alder reaction of a furan-ene in water (eq 187).[745] In water alone, the cyclization proceeded in



(187)

20% yield with an epimeric selectivity of 1:2 (A/B) at 89 °C after 6 h. The same reaction gave 91% of the cyclized product when 1 equiv of β-cyclodextrin is present. In this case, the epimeric selectivity is also changed to 1:1.5 (A/B). However, no significant change of reactivity was observed with either α-cyclodextrin or the nonionic detergent Brij-35 present. A similar enhancement of reactivity by β-cyclodextrin was observed in the cyclization of the amine derivative.

Roskamp reported[746] a similar intramolecular Diels–Alder reaction accelerated by silica gel saturated with water. The reaction led to the ready construction of the bicyclo[6.2.1] ring systems. Intramolecular Diels–Alder reaction has also been investigated by Keay.[747] The Diels–Alder reaction of 2,5-dimethylpyrrole derivatives with dimethyl acetylenedicarboxylate in water generated the corresponding cyclization products.[748] The retro-Diels–Alder (RDA) reaction of anthracenedione (eq 188) proceeds con-



(188)

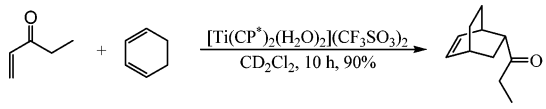
siderably faster in aqueous solution than in organic solvents.[749] Addition of organic solvents to water retards the reaction, whereas glucose induces a modest acceleration.

Holt studied the Diels–Alder reaction in a mixture of water, 2-propanol, and toluene as microemulsions.[750] The endo/exo ratio between the reaction of cyclopentadiene and methyl methacrylate was enhanced with increasing amounts of water in the presence of a surfactant.

Utley et al. were able to perform Diels–Alder reactions in aqueous solution via electrogenerated *ortho*-quinodimethanes.[751] They cathodically generated the *ortho*-quinodimethanes in aqueous electrolyte in the presence of *N*-methylmaleimide, which is both the redox mediator and the dienophile. Competition from the electrohydrodimerization of *N*-methylmaleimide is suppressed, allowing for the efficient formation of the endo adduct.

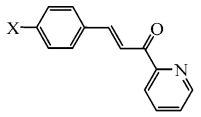
10.1.2. Lewis-Acid-Catalyzed Reactions

Recently, the effect of water-tolerating Lewis acids has been used to catalyze various Diels–Alder reactions in aqueous media. An important aspect of the Diels–Alder reaction is the use of Lewis acids for the activation of the substrates. While most Lewis acids are decomposed or deactivated in water, Bosnich reported that $[Ti(Cp^*)_2(H_2O)_2]^{2+}$ is an air-stable, water-tolerant Diels–Alder catalyst.[752] A variety of different substrates were subjected to the conditions to give high yields and selectivity (eq 189).



(189)

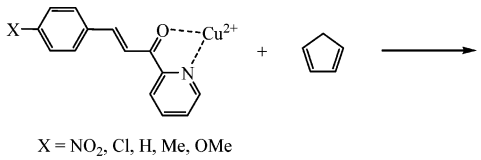
Kobayashi has found that scandium triflate, $Sc(OTf)_3$,[753] and lanthanide triflates, $Ln(OTf)_3$, are stable and can be used as a Lewis catalyst under aqueous conditions. Many other Lewis acids have also been reported to catalyze Diels–Alder reactions



X = NO_2, Cl, H, Me, OMe, $CH_2SO_3^-Na^+$, $CH_2N^+(CH_3)_3Br^-$

Figure 2. Various 3-(*para*-substituted phenyl)-1-(2-pyridyl)-2-propen-1-ones.

in aqueous media. For example, Engberts reported[754] that the following cyclization reaction (eq 190)



X = NO_2, Cl, H, Me, OMe

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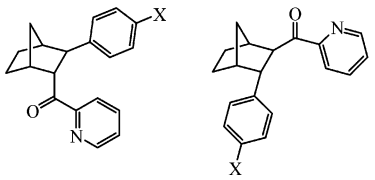


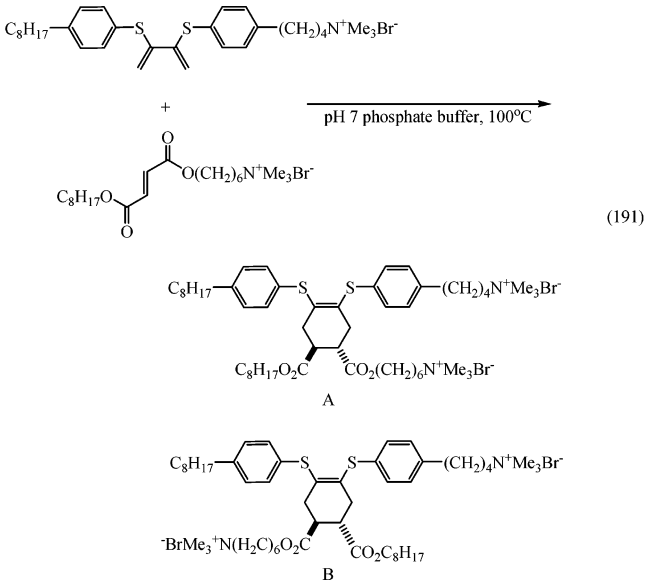
in an aqueous solution containing 0.010 M $Cu(NO_3)_2$ is 250 000 times faster than that in acetonitrile and ca. 1000 times faster than that in water alone. Other salts, such as Co^{2+}, Ni^{2+}, and Zn^{2+}, also catalyze the reaction but not as well as Cu^{2+}. However, water has no effect on the endo–exo selectivity for the Lewis acid-catalyzed reaction.

Tris(pentafluorophenyl)boron was found to be an efficient, air-stable, and water-tolerant catalyst for Diels–Alder reactions.[755] Other Lewis acids[756] effective for catalyzing Diels–Alder reactions in aqueous conditions include $InCl_3$,[757] methylrhenium trioxide (MTO),[758] $In(OTf)_3$,[759] $Bi(OTf)_3$,[760] and others.[761] A comparative study of specific acid catalysis and Lewis acid catalysis of Diels–Alder reactions between dienophiles and cyclopentadiene in water and mixed aqueous media was carried out. At equimolar amounts of copper(II) nitrate as the Lewis acid catalyst and hydrochloric acid (0.01 M) as the specific acid catalyst and under the same reaction conditions, the reaction rate of a dienophile with cyclopentadiene is about 40 times faster with copper catalysis than with specific acid catalysis.[762] The stereoselectivity of the Diels–Alder reaction of (*E*)-γ-oxo-α,β-unsaturated thioesters with cyclopentadiene is greatly enhanced in the presence of Lewis acids favoring the endo acyl isomers. In the absence of Lewis acid, the reaction at 25 °C gave two adducts, endo acyl isomers and exo acyl isomers in a ratio of 1:1. In the presence of Lewis acids, the reaction gave the two products in ratios of 75:26–94:6. The stereoselectivity was enhanced to ratios of 95:5–98:2 with lower reaction temperature.[763]

It has been found that the combination of Lewis acids and surfactants is particularly effective for catalyzing Diels–Alder reactions in water. The effect of micelles of SDS, CTAB, dodecyl heptaoxyethylene ether ($C_{12}E_7$), and copper and zinc didodecyl sulfate [$M(DS)_2$] on the Diels–Alder reaction of 3-(*para*-substituted phenyl)-1-(2-pyridyl)-2-propen-1-ones (Figure 2) with cyclopentadiene was studied.

In the absence of catalytically active transition-metal ions, micelles impede the reaction. In contrast to SDS, CTAB, and $C_{12}E_7$, $Cu(DS)_2$ micelles catalyze the Diels–Alder reaction with extremely high efficiency, leading to rate enhancements up to 1.8×10^6 compared to the uncatalyzed reaction in acetonitrile.[764] This is primarily due to the complete complexation of the dienophiles to the copper ions at the micellar surface. When the dienophile does not bind to the micelle, the reaction is repressed because the uptake of the diene in the micelle lowers its concentration in the aqueous phase. The researchers contend that the retardation of the reaction results from a significant difference in the binding location of the diene and dienophile with the dienophile preferring the outer regions of the micelle and the diene the interior.

The use of aqueous surfactant aggregates to control the regiochemistry of Diels–Alder reactions was investigated extensively by Jaeger and co-workers (eq 191).[765] They have shown that a Diels–Alder reaction



(191)

of a surfactant 1,3-diene with a surfactant dienophile with a short tether between their functional groups and headgroups can proceed with high regioselectivity.

Under various reaction conditions, the isomer ratio of A was consistently higher than that of B. Isomer A is the expected regioisomer if the diene and dienophile react in their preferred orientation within a mixed micelle in which the quaternary ammonium groups are at the aggregate–water interface and the rest of the molecule is extended into the micelle interior (Figure 3). Isomer B comes about from the misalignment of the diene and dienophile within the mixed micelles.

The Diels–Alder reactions of benzoquinones with penta-1,3-diene and isoprene were also studied in aqueous cyclodextrin solutions giving highly enhanced ortho and meta regioselectivities.[766]

In contrast to Lewis acids, Diels–Alder reactions in aqueous media are also catalyzed by bovine serum albumin,[767] enzymes,[768] antibodies,[769] amines,[770] and specific acids. [771]

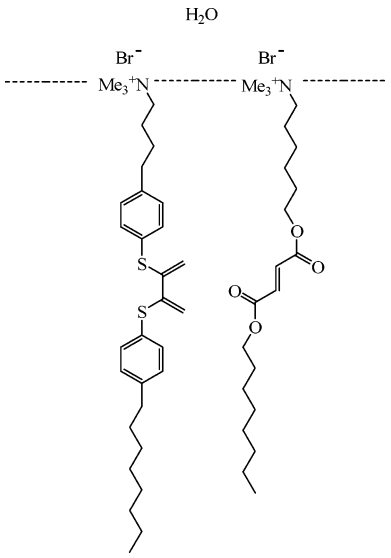
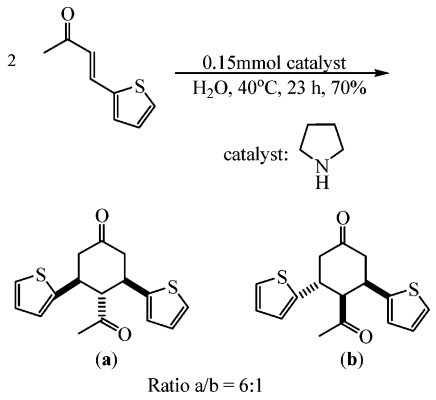


Figure 3. Preferred orientation of diene and dienophile at a surfactant aggregate–water interface.

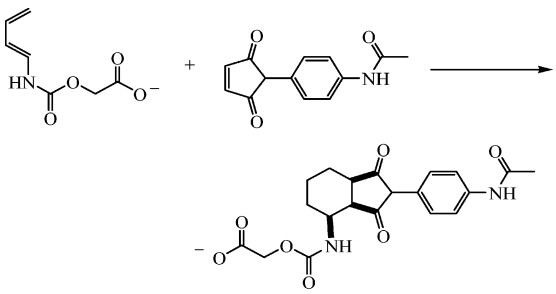
The amine-catalyzed self-Diels–Alder reaction of α,β-unsaturated ketones in water was developed by Barbas et al. to form cyclohexanone derivatives (eq 192). They believe that the reaction proceeds via the



(192)

in situ formation of 2-amino-1,3-butadiene and iminium-activated enone, as the diene and dienophile, respectively.

The antibody-catalyzed Diels–Alder reaction developed by Schultz utilized a "Diels–Alderase" enzyme-like catalyst evolved from an antibody combining site (eq 193). The idea is that the generation of

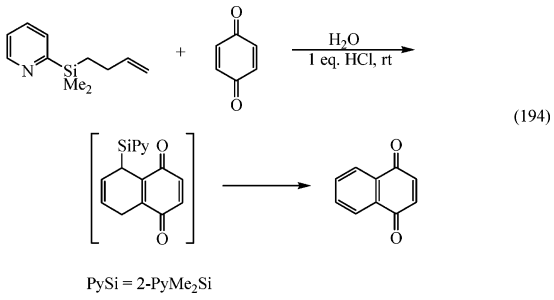


(193)

antibodies to a structure that mimics the transition state for the Diels–Alder reaction should result in an antibody combining site that lowers the entropy of activation by binding both the diene and dienophile in a reactive conformation.

A self-assembled coordination cage[772] and micelles[773] were found to accelerate Diels–Alder reactions in an aqueous medium. The catalysis of Diels–Alder reactions via noncovalent binding by synthetic, protein, and nucleic acid hosts has been surveyed and compared to explore the origin of the noncovalent catalysis. These catalysts consist of binding cavities that form complexes containing both the diene and the dienophile with the reaction occurring in the cavity. The binding requires no formation of covalent bonds and is driven principally by the hydrophobic (or solvophobic) effect.[774]

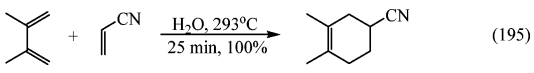
Yoshida and co-workers developed the concept of a "removable hydrophilic group" using 2-pyridyldimethylsilyl (2-PyMe$_2$Si) for aqueous organic reactions including Diels–Alder reactions, hetero Diels–Alder reactions, Claisen rearrangement, radical reactions, and transition-metal-catalyzed reactions. Although the low solubility of organic molecules in water has been a bane in aqueous organic reactions, the incorporation of hydrophilic groups into the substrate structure can overcome the solubility problem and at the same time enhance the hydrophobic effect.[775] The Diels–Alder reaction of 2-PyMe$_2$Si-substituted 1,3-dienes with *p*-benzoquinone occurs at room temperature in water (eq 194). There is a simultaneous



(194)

desilylation and aromatization to afford naphthoquinones quantitatively, which also means that there is no need for an additional step to remove the 2-PyMe$_2$Si group.

Diels–Alder reactions in supercritical water have also been investigated.[776] Kolis has shown that Diels–Alder reactions of dienes with various electron-poor dienophiles can be performed in supercritical water with high yields of the desired product without the addition of any catalysts (eq 195).



(195)

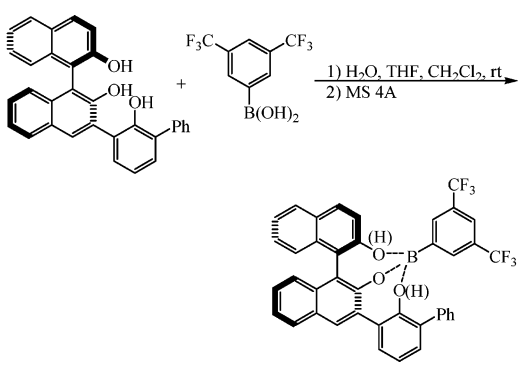
Metal-free, noncovalent catalysis of Diels–Alder reactions by neutral hydrogen bond donors was studied in water.[777] The researchers examined the catalytic activity of substituted thioureas in Diels–Alder and 1,3-dipolar cycloadditions. They conclude from their kinetic data that the observed accelerations in the relative rates are more dependent upon the thiourea substituents than on the reactants or solvent. However, even though the catalytic efficacy is highest in a noncoordinating, nonpolar solvent such as cyclohexane, it is also present in a highly coordinating polar solvent such as water meaning that both hydrophobic and polar interactions can coexist, making the catalyst active even in highly coordinating solvents. These catalysts increase the reaction rates along with the endo selectivities of Diels–Alder reactions in a manner similar to weak Lewis acids but without the associated product inhibition.

It should be noted, however, that despite many examples of acceleration of Diels–Alder reactions by the use of aqueous media, Elguero[778] reported that the Diels–Alder reaction between cyclopentadiene and methyl (and benzyl) 2-acetamideacrylates proceeded better in toluene than in water both in yield and in exo/endo selectivity. Additionally, ultrasonic irradiation did not improve the yield.

10.1.3. Asymmetric Diels–Alder Reactions in Water

The use of aqueous Diels–Alder reactions for generating optically active compounds is one of the recent efforts on the subject. A diene bearing a chiral water-soluble glyco hydrophilic moiety was studied extensively by Lubineau.[779] The use of water-soluble glyco-organic compounds in water achieved higher reagent concentration and resulted in rate enhancement and asymmetric induction. Even though the diastereoselectivity was modest (20% de), separation of the diastereomers led to chiral adducts in pure enantiomeric form after cleavage of the sugar moiety by acidic hydrolysis or by using glycosidase in neutral conditions at room temperature. A variety of substrates bearing other glyco-derivatives were also studied. Chiral dienophiles, prepared from an aldehyde and asparagine in water followed by reacting with acryloyl chloride, reacted with cyclopentadiene at room temperature in water or ethanol–water to provide cycloadducts diastereoselectively and to lead to chiral products upon separation and hydrolysis (47–64% ee for the endo isomers; endo/exo 82:18).[780]

Recently, catalytic asymmetric Diels–Alder reactions have been investigated. Yamamoto reported a Brönsted acid assisted chiral (BLA) Lewis acid prepared from (*R*)-3-(2-hydroxy-3-phenylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl and 3,5-bis(trifluoromethyl)benzeneboronic acid, which is effective in enantioselective Diels–Alder reaction between both α-substituted and α-nonsubstituted α,*β*-enals and various dienes.[781] The interesting aspect is the role of water, THF, and MS 4 Å in the preparation of the catalyst (eq 196). To prevent the trimerization of the boronic



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acid during the preparation of the catalyst, the chiral triol and the boronic acid were mixed under aqueous conditions and then dried. When the catalyst pre-

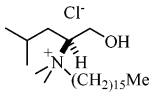
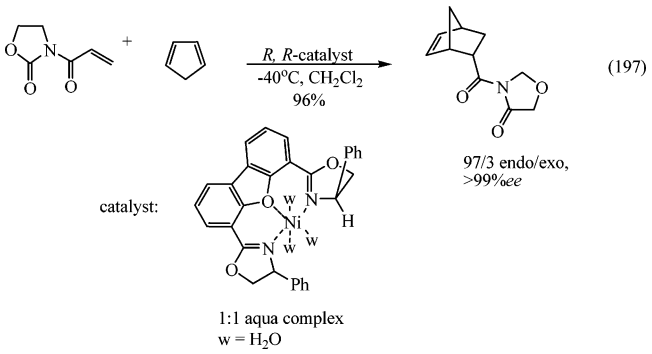


Figure 4. (*S*)-Leucine-derived surfactant.

pared in this manner was used, a 99% ee was obtained in the Diels−Alder reaction of methacrolein and cyclopentadiene, while preparing the catalyst in the presence of activated MS 4 Å under anhydrous conditions reduced the enantioselectivity for the same reaction to less than 80% ee.

Kanemasa et al.[782] reported that cationic aqua complexes prepared from the trans-chelating tridentate ligand (*R,R*)-dibenzofuran-4,6-diyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph) and various metal(II) perchlorates are effective catalysts that induce absolute chiral control in the Diels−Alder reactions of 3-alkenoyl-2-oxazolidinone dienophiles (eq 197). The nickel(II), cobalt(II), copper(II), and zinc(II) complexes are effective in the presence of 6 equiv of water for cobalt and nickel and 3 equiv of water for copper and zinc.



Desimoni et al. have shown that the use of magnesium perchlorate or magnesium triflate, three chiral bis(oxazolines) and 2 equiv of achiral auxiliary ligands such as water or tetramethylurea induces a strong change of the enantiofacial selectivity with >94% ee.[783]

Chiral surfactants have been used in the aqueous chiral micellar catalysis of a Diels−Alder reaction using a (*S*)-leucine-derived surfactant (Figure 4) to catalyze the reaction between cyclopentadiene and nonyl acrylate.[784]

In 1998, Engberts and co-workers reported the first enantioselective Lewis-acid-catalyzed Diels−Alder reaction in pure water.[785] In the presence of 10% copper(II), complexes of α-amino acids with aromatic side chains (e.g., L-phenylalanine, L-tyrosine, L-tryptophan, and L-abrine) as ligands coordinated to copper(II) induced up to 74% ee in the Diels−Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene. For the copper−L-abrine-catalyzed reaction, an enantiomeric excess of 74% can be achieved, which is considerably higher than that in organic solvents (17−44% ee) and shows that water significantly enhances enantioselectivity. Since significant enantioselectivity was observed exclusively for α-amino acids containing aromatic side groups, the interaction between the aromatic ring of the α-amino acid and the pyridine ring of the dienophile during the activation process was proposed to be responsible for the observed enantioselectivity. In addition, Engberts also investigated the influence of a series of diamine ligands and α-amino acid ligands on the rate and enantioselectivity of the nickel(II)- and copper(II)-catalyzed Diels−Alder reaction between 3-phenyl-1-(2-pyridyl)-2-propen-1-ones and cyclopentadiene in water.[786] However, they found that the diamine ligands did not improve the catalytic efficiency and it was the binding of the aromatic α-amino acid ligands to copper(II) that led to the overall rate increase of the reaction.

Optically active Diels−Alder adducts were also prepared by a one-pot preparative method and enantioselective Diels−Alder reaction with optically active hosts in a water suspension medium.[787]

10.1.4. Theoretical Studies

The effect of water on Diels−Alder reactions has been studied extensively by various theoretical and experimental methods. Breslow studied the influence of the hydrophobic effect on the aqueous Diels−Alder reactions in detail,[788,789] while the volumes of activation for catalyzed Diels−Alder reactions was examined by Isaacs et al.[790]

Recent studies show that the concept of internal pressure cannot be used to explain the strong rate enhancement of Diels−Alder reactions when carried out in water with respect to common organic solvents.[791] Schneider reported a quantitative correlation between solvophobicity and rate enhancement of aqueous Diels−Alder reactions.[792,793] Enforced hydrophobic interactions between diene and dienophile and hydrogen bonding have also been suggested by Engberts to account for the acceleration in water.[794] It was found that an increase in the hydrophobicity close to the reaction center in the diene has a much more pronounced effect on the rate acceleration in water than a comparable increase in hydrophobicity in the dienophile further away from the reaction center. [795]

Density functional theory study of aqueous-phase rate acceleration and endo/exo selectivity of the butadiene and acrolein Diels−Alder reaction[796] shows that approximately 50% of the rate acceleration and endo/exo selectivity is attributed to hydrogen bonding and the remainder is attributed to bulk-phase effects, including enforced hydrophobic interactions and cosolvent effects. A pseudo-thermodynamic analysis of the rate acceleration in water relative to 1-propanol and 1-propanol−water mixtures indicates that hydrogen-bond stabilization of the polarized activated complex and the decrease of the hydrophobic surface area of the reactants during the activation process are the two main causes of the rate enhancement in water.[797]

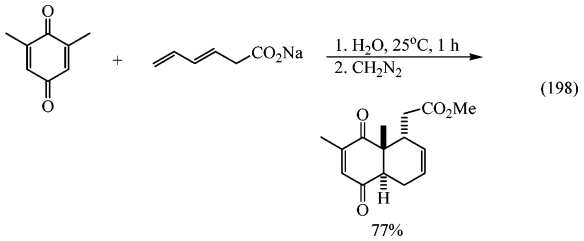
Studies of Diels−Alder reactions under high pressure by Jenner revealed that water can alter kinetics and chemo- and enantioselectivity through polarity and hydrophobic effects.[798] The weight of these two, however, depends on the use of specific reaction partners. By studying the reaction in dilute aqueous ethanol, Smith[799] and Griesbeck[800] pointed out that the concentration of the reaction substrates is important for rate enhancement. The rate shows a maximum at 0.5 M under the aqueous ethanol condi-

tion. The effect of salt and cosolvent on the stereoselectivity and rate of aqueous Diels–Alder reactions were studied extensively by Kumar.[801] The low yield of the endo products of a Diels–Alder reaction in aqueous $LiClO_4$ can be enhanced by a simple solvent manipulation.[802] The endo/exo selectivity was found to be mainly dependent upon the solvophobic and hydrogen bond donor properties of the solvent, and regioselectivity almost exclusively depends on the hydrogen bond donor ability of the solvent.[803]

Ab initio molecular orbital (MO) calculation by Jorgensen revealed enhanced hydrogen bonding of a water molecule to the transition states for the Diels–Alder reactions of cyclopentadiene with methyl vinyl ketone and acrylonitrile, which indicates that the observed rate accelerations for Diels–Alder reactions in aqueous solution arise from the hydrogen-bonding effect in addition to a relatively constant hydrophobic term.[804] Ab initio calculation using a self-consistent reaction field continuum model shows that electronic and nuclear polarization effects in a solution are crucial to explain the stereoselectivity of nonsymmetrical Diels–Alder reactions.[805] Using a combined quantum mechanical and molecular mechanical (QM/MM) potential, Gao carried out Monte Carlo simulations to investigate the hydrophobic and hydrogen-bonding effects on Diels–Alder reactions in aqueous solution. Enhanced hydrogen-bonding interaction and the hydrophobic effect were found to contribute to the transition-state stabilization.[806] The number of hydrogen bonds was found to cause strong Coulomb interactions and discriminate heats of formation of transition states for exo/endo products.[807] On the other hand, the aqueous Diels–Alder reaction between 2-methylfuran and maleic acid in water is found to be 99.9% stereospecific.[808] The results suggest that a large portion of the Diels–Alder reaction occurs via diradical intermediates.

10.1.5. Synthetic Applications

Much effort has been directed at developing aqueous Diels–Alder reactions toward the syntheses of a variety of complex natural products. Grieco employed micellar catalysis[809] in pure water as the solvent using dienecarboxylate with a variety of dienophiles.[810] He reported a higher rate and selectivity using aqueous media relative to hydrocarbon solvents. For example, the reaction of 2,6-dimethylbenzoquinone with sodium (*E*)-3,5-hexadienoate (generated in situ by the addition of 0.95 equiv of sodium bicarbonate) proceeded in water for 1 h to give a 77% yield (eq 198),



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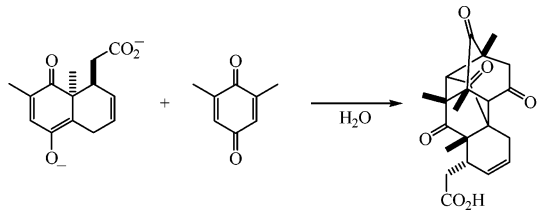
while the same reaction performed in toluene provided only trace amounts after the reaction was stirred for 1 week at room temperature.

However, when 2,6-dimethylbenzoquinone was reacted with sodium (*E*)-3,5-hexadienoate (generated in situ by the addition of 1.5 equiv of sodium hydroxide) in water in the presence of a catalytic amount of sodium hydroxide, pentacyclic adducts were formed via deprotonation of the Diels–Alder adduct followed by tandem Michael-addition reactions (eq 199).[811]

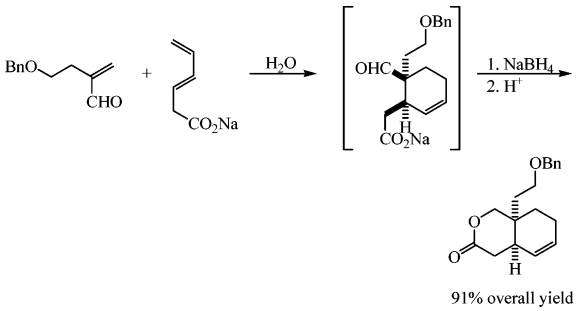


(199)

Similar results were obtained with sodium (*E*)-4,6-heptadienoate.

Sensitive dienol ether functionality in the diene carboxylate was shown to be compatible with the conditions of the aqueous Diels–Alder reaction.[812] The dienes in the Diels–Alder reactions can also bear other water-solubilizing groups such as the sodium salt of phosphoric acid and dienylammonium chloride.[813] The hydrophilic acid functionality can also be located at the dienophile.[814]

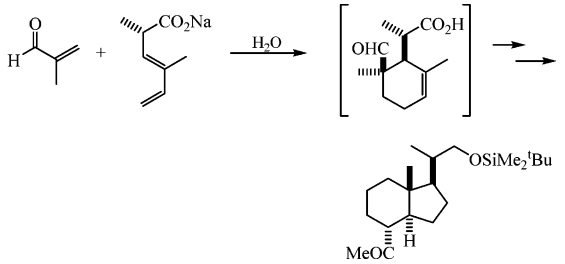
Grieco utilized an aqueous intermolecular Diels–Alder reaction as the key step in forming the AB ring system of the potent cytotoxic sesquiterpene vernolepin.[815] Cycloaddition of sodium (*E*)-3,5-hexadienoate with an α-substituted acrolein in water, followed by direct reduction of the intermediate Diels–Alder adduct, gave the desired product in 91% overall yield (eq 200).



(200)

91% overall yield

Similar reactions were applied to the syntheses of *dl*-epi-pyroangolensolide and *dl*-pyroangoensolide[816] and the formal synthesis of the Inhoffen–Lythgoe diol (eq 201).[817] The key step in the formal synthesis

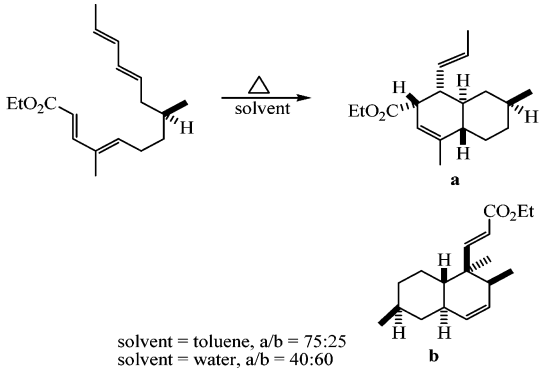


(201)

of the Inhoffen–Lythgoe diol is the aqueous Diels–Alder reaction between the sodium salt of the diene and methacrolein to form the cycloadduct, which then undergoes subsequent reactions to form the known hydrindan. Sodium (*E*)-4,6,7-octatrienoate reacted

smoothly with a variety of dienophiles to give conjugated diene products.[818]

An intramolecular version of the Diels−Alder reaction with a dienecarboxylate was used by Williams et al. in the synthetic study of the antibiotic ilicicolin H.[819] The interesting aspect of this work is that under aqueous conditions, there is an observed reversal of regioselectivity (eq 202). In toluene, there is a 75:25



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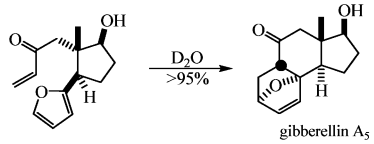
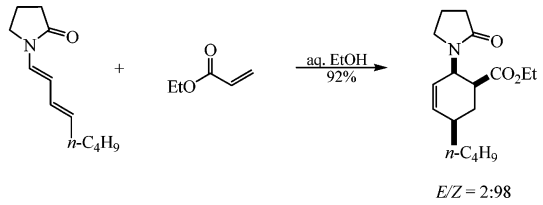
ratio of **a/b** while in degassed water, the ratio of **a/b** is 40:60.

De Clercq has shown that aqueous Diels−Alder reactions can be used as key steps in the syntheses of (±)-11-keto-testosterone,[820] (±)-gibberellin A_5 (eq 203),[821] and (+)-biotin. [822]



(203)

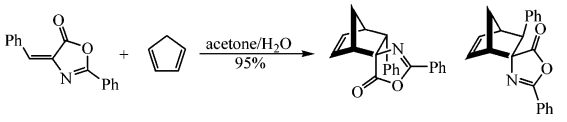
The reaction of dienes bearing an *N*-dienyl lactam moiety with activated olefins was examined by Smith.[823] The lactams were excellent enophiles and provided exclusively the ortho regioisomer with good selectivity for the endo (*Z*) product (eq 204).



(204)

In the synthesis of 2,2,5-trisubstituted tetrahydrofurans, a novel class of orally active azole antifungal compounds, Saksena[824] reported that the key step of the Diels−Alder reaction in water led to the desired substrate virtually in quantitative yield, while the same reaction in organic solvent resulted in a complicated mixture with only less than 10% of the desired product being isolated. This success made the target compounds readily accessible.

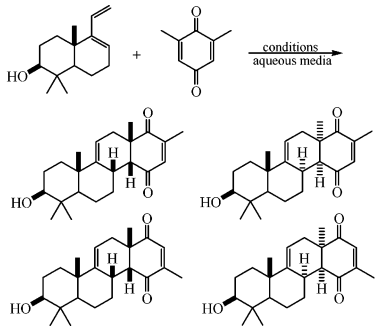
The Diels−Alder reaction between oxazolone and cyclopentadiene was investigated by Cativiela in water (eq 205).[825] Although the reaction is very slow,



(205)

the (*E*)-5(4*H*)-oxazolone reacted with cyclopentadiene in an aqueous media for 6 days at room temperature to form the corresponding spiroxazolones in a 95% yield. The cycloadducts are then readily converted into amino-norbornane carboxylic acids.

In the synthesis of the tetracyclic intermediates for the synthesis of isoarborinol and its CDE-antipode fernenol, the stereochemistry of the Diels−Alder reaction can be varied using various Lewis acid catalysts in aqueous media (eq 206).[826] The results

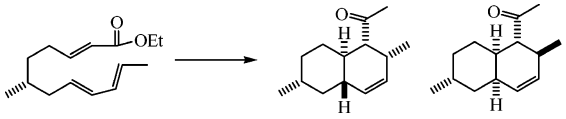


(206)

show that the hydrophobic effects play an important role in enhancing reaction rate and can control product distribution.

Aqueous Diels−Alder reactions of halogenated 2-arylfurans with acetylenedicarboxylates made available 2,2,5-trisubstituted tetrahydrofurans, which were successfully elaborated in a general stereocontrolled route to a novel class of orally active azole antifungals.[827] Novel 2,4-dialkyl-1-alkylideneamino-3-(methoxycarbonylmethyl)azetidines were obtained from aldazines and methyl 3-(alkylidenehydrazono)-propionates in an aqueous solution of sodium periodate.[828]

A Diels−Alder cyclization was proposed to occur during polyketide synthase assembly of the bicyclic core of lovastatin by *Aspergillus terreus* MF 4845.[829] In vitro Diels−Alder cyclization of the corresponding model compounds generated two analogous diastereomers in each case under either thermal or Lewis acid-catalyzed conditions (eq 207). As expected, the



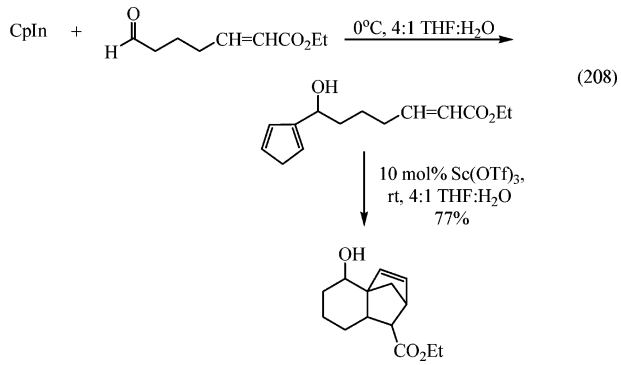
(207)

Diels−Alder reaction occurred faster in aqueous media. The cyclization half-life in chloroform at room temperature is 10 days, while the half-life in aqueous media at either pH 5 or 7 drops to 2 days.

An efficient one-pot synthesis of mikanecic acid derivatives was accomplished from allylic phosphonates, $ClCO_2Et$, and aqueous H_2CO.[830] The overall process involves a cascade sequence linking together metalation−alkoxycarbonylation, Horner−Wadsworth−Emmons, and Diels−Alder reactions.

Cyclopentadienylindium(I) has been shown to be effective in the reaction with aldehydes or electron-deficient alkenes to form highly functionalized cyclopentadienes in aqueous media.[831] This reaction with the appropriate substrates can be followed by an intramolecular Diels−Alder reaction in the same

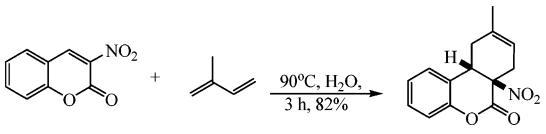
pot to provide complex tricyclic structures in a synthetically efficient manner (eq 208).



(208)

The aqueous Diels−Alder reaction has also been used for bioconjugate studies. A Diels−Alder reaction of diene oligonucleotides with maleimide dieneophiles was used to prepare oligonucleotide conjugates in aqueous media under mild conditions.[832] A Diels−Alder-type cycloaddition of an electronically matched pair of saccharide-linked conjugated dienes and a dienophile equipped with protein was the first method to create a carbon−carbon bond in the bioconjugation step between a saccharide and a protein. These neoglycoproteins were formed at room temperature in pure water and have a reaction half-life of approximately 2 h.[833]

The one-pot synthesis of (*E*)-2-aryl-1-cyano-1-nitroethenes[834] and an approach to the synthesis of nitrotetrahydrobenzo[*c*]chromenones and dihydrodibenzo[*β*,*δ*]furans were developed on the basis of aqueous Diels−Alder reactions.[835] Once again, it was found that the reaction occurred faster in water under heterogeneous conditions relative to those performed in toluene and methylene chloride (eq 209).

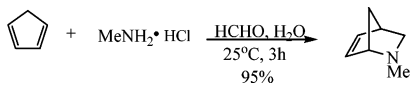


(209)

10.2. Hetero-Diels−Alder Reactions

10.2.1. Water-Promoted and Acid-Catalyzed Reactions

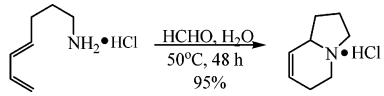
For the synthesis of heterocyclic compounds, hetero-Diels−Alder reactions with nitrogen- or oxygen-containing dienophiles are particularly useful. Such reactions have been studied extensively in aqueous media.[836] In 1985, Grieco reported the first example of hetero-Diels−Alder reactions with nitrogen-containing dienophiles in aqueous media. (eq 210).[837]



(210)

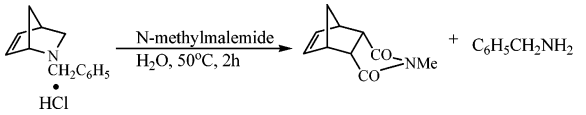
Simple iminium salts, generated in situ under Mannich-like conditions, reacted with dienes in water to give aza-Diels−Alder reaction products. The use of alcoholic solvents led to a decrease in the reaction rate, while the use of THF as a cosolvent did not affect the rate of the reaction.

This methodology has the potential to be generally applicable to the synthesis of various alkaloids that have a bridgehead nitrogen via the intramolecular aza-Diels−Alder reaction (eq 211).[838]



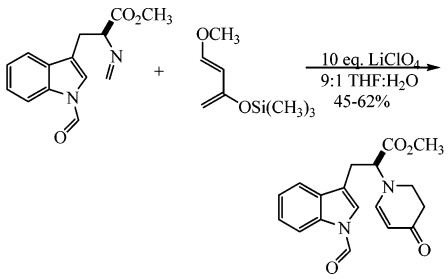
(211)

Retro-aza-Diels−Alder reactions also readily occurred in water.[839] As shown in eq 212, the 2-azanorbornene undergoes acid-catalyzed retro-Diels−Alder cleavage in water. The produced iminium derivative then reacts with the trapping reagent, *N*-methylmaleimide, or is reduced to give primary amines. No reaction was observed in a variety of organic solvents, such as benzene, THF, or acetonitrile under similar or more drastic conditions. This means that water accelerates hetero-Diels−Alder reactions in both the forward and reverse directions by lowering the energy of the transition state. This reaction provided a novel method for the N-methylation of dipeptides and amino acid derivatives.[840]



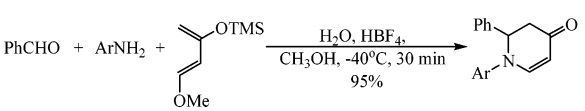
(212)

Waldmann used (*R*)- and (*S*)-amino acid methyl esters and chiral amines as chiral auxiliaries in analogous aza-Diels−Alder reactions with cyclodienes.[841] The diastereoselectivity of these reactions ranged from moderate to excellent and the open-chain dienes reacted similarly. Recently, the aza-Diels−Alder reaction was used by Waldmann in the asymmetric synthesis of highly functionalized tetracyclic indole derivatives (eq 213), which is useful for the synthesis of yohimbine and reserpine-type alkaloids.[842]



(213)

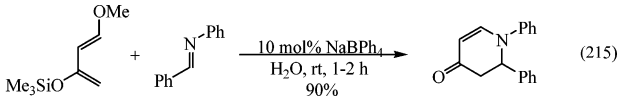
As in the case of Diels−Alder reactions, aqueous aza-Diels−Alder reactions are also catalyzed by various Lewis acids such as lanthanide triflates.[843] Lanthanide triflate catalyzed imino Diels−Alder reactions of imines with dienes or alkenes were developed. Three-component aza-Diels−Alder reactions, starting from aldehyde, aniline, and Danishefsky's diene, took place smoothly under the influence of HBF_4 in aqueous media to afford dihydro-4-pyridone derivatives in high yields (eq 214).[844]



(214)

The montmorillonite K10-catalyzed aza-Diels–Alder reaction of Danishefsky's diene with aldimines, generated in situ from aliphatic aldehydes and *p*-anisidine, proceeded smoothly in H_2O or in aqueous CH_3CN to afford 2-substituted 2,3-dihydro-4-pyridones in excellent yields.[845] Also, complex $[(PPh_3)Ag(CB_{11}H_6Br_6)]$ was shown to be an effective and selective catalyst (0.1 mol % loading) for a hetero-Diels–Alder reaction with Danishefsky's diene and showed a striking dependence on the presence of trace amounts of water.[846] The acceleration effect was rationalized by the resulting Lewis-assisted Brønsted acid due to silver-bound water molecules in the catalytic process.

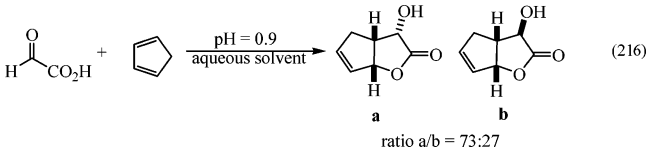
Two-component or three-component aza-Diels–Alder reactions of Danishefsky's diene with imines or aldehydes and amines in water took place smoothly under neutral conditions in the presence of a catalytic amount of an alkaline salt such as sodium triflate to afford dihydro-4-pyridones in high yields (eq 215).[847]



(215)

Antibodies have also been found to catalyze hetero-Diels–Alder reactions.[848]

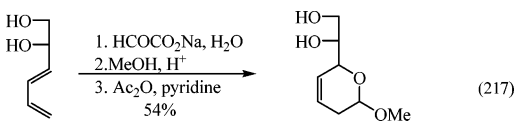
For hetero-Diels–Alder reactions with an oxygen-containing dienophile, cyclopentadiene or cyclohexadiene reacted with an aqueous solution of glyoxylic acid to give α-hydroxyl-γ-lactones arising from the rearrangement of the cycloadducts. The reaction was independently studied by Augé[849] and Grieco.[850] Augé showed that using water as the solvent allowed for the direct use of the inexpensive aqueous solution of glyoxylic acid for the Diels–Alder reaction (eq 216).



(216)

Using water as the solvent enhanced the rate of the hetero-Diels–Alder reaction relative to the dimerization of cyclopentadiene. In addition, the reaction is much faster at low pH, which implies that the reaction is acid-catalyzed. The 5,5-fused system generated has been used in the total synthesis of several bioactive compounds, including the anti-HIV agent (−)-carbovir[851] and the hydroxylactone moiety of mevinic acids.[852]

Acyclic dienes react via a Diels–Alder reaction to give dihydropyran derivatives (eq 217). An excellent



(217)

application of the oxo-Diels–Alder reaction is reported by Lubineau et al. in the synthesis of the sialic acids 3-deoxy-D-manno-2-octulosonic acid (KDO) and 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN).[853]

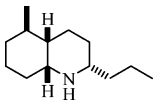
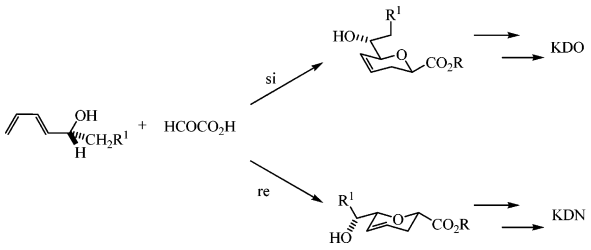


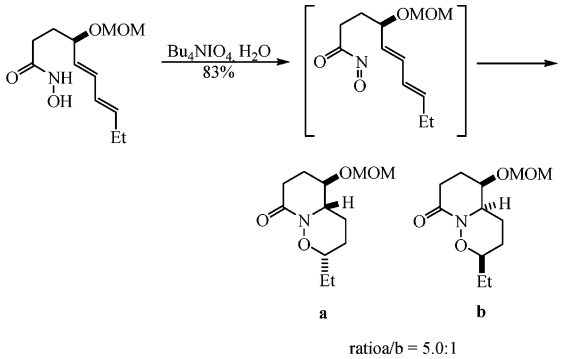
Figure 5. (−)-Pumiliotoxin C.

As shown in eq 218, with glyoxylate as the dienophile, if the attack is on the *si* face of the diene, it would lead to the skeleton of KDO; if the attack is on the *re* face, it would lead to the skeleton of KDN. C-disaccharide analogues of trehalose were prepared using an aqueous Diels–Alder reaction as a key step.[854]



(218)

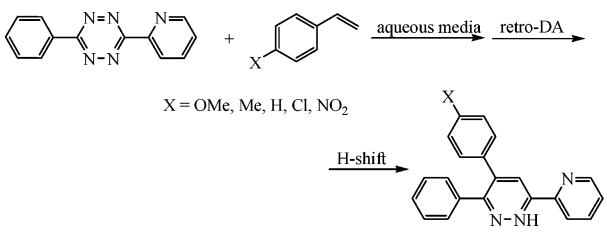
The hetero-Diels–Alder reaction has also utilized dienophiles in which both reactive centers are heteroatoms. Kibayashi reported that the intramolecular hetero-Diels–Alder cycloaddition of chiral acylnitroso compounds, generated in situ from periodate oxidation, showed a marked enhancement of the trans selectivity in an aqueous medium compared with the selectivity in nonaqueous conditions (eq 219).[855] The



(219)

reaction was readily applied in the total synthesis of (−)-pumiliotoxin C (Figure 5).[856]

The hetero-Diels–Alder reaction can also employ dienes containing heteroatoms. Cycloaddition of substituted styrenes with di-(2-pyridyl)-1,2,4,5-tetrazine was investigated by Engberts (eq 220).[857] Again, the

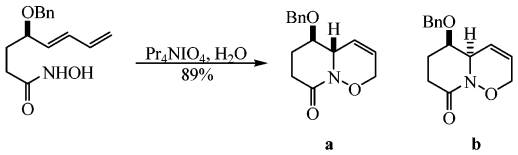


(220)

rate of the reaction increased dramatically in water-rich media. Through kinetic studies, they showed that the solvent effects on the kinetics of hetero-

Diels−Alder reactions are very similar to homo-Diels−Alder reactions in aqueous solvent.

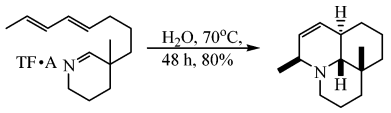
A new noncarbohydrate-based enantioselective approach to (−)-swainsonine was developed in which the key step was an aqueous intramolecular asymmetric hetero-Diels−Alder reaction of an acylnitroso diene under aqueous conditions (eq 221).[858] Under



(221)

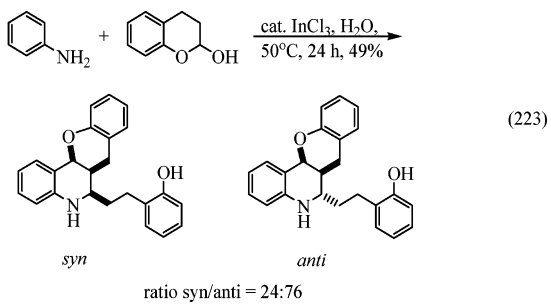
aqueous conditions there was a significant enhancement of the trans stereoselectivity relative to the reaction under conventional nonaqueous conditions.

Grieco investigated the intramolecular Diels−Alder reaction of iminium ions in polar media such as 5.0 M lithium perchlorate−diethyl ether and in water[859] to form carbocyclic arrays. Water as the solvent provided good to excellent yields of tricyclic amines with excellent stereocontrol (eq 222).



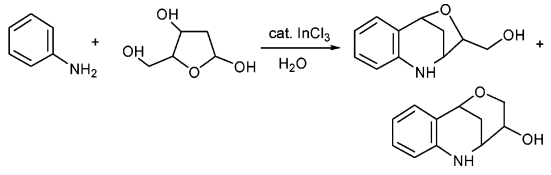
(222)

By reacting aniline with 2,3-dihydrofuran or dihydropyran and a catalytic amount of Lewis acid such as indium chloride, Li obtained various tetrahydroquinoline derivatives via an in situ hetero-Diels−Alder reaction in water.[860] Alternatively, similar compounds were synthesized from anilines and 2-hydroxyltetrahydrofuran or 2-hydroxyltetrahydropyran and a catalytic amount of indium chloride in water (eq 223).[861]



(223)

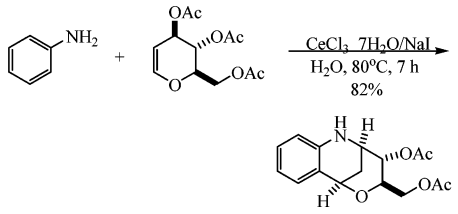
One notable result is the treatment of a 2-hydroxy cyclic ether analogue, 2-deoxy-D-ribose, with aniline in water catalyzed by $InCl_3$ to afford the novel tricyclic tetrahydroquinoline compounds (eq 224). The



(224)

reaction can also be catalyzed by a recoverable cation-exchange resin instead of indium chloride.[862] When a stoichiometric amount of indium metal is used, a domino reaction of nitroarenes with 2,3-dihydrofuran generates the same products.[863]

Yadav et al. explored the reaction of substituted anilines with 3,4,6-tri-*O*-acetyl-D-glucal to offer the tetrahydroquinoline moieties.[864] Most yields are around 80% with excellent distereoselectivity, and the reaction was carried out in water (eq 225). The



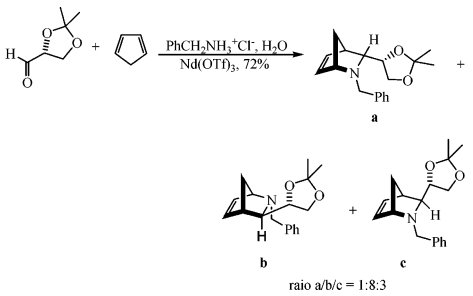
(225)

primary disadvantage is that both $CeCl_3$ and NaI are required in stoichiometric amounts.

10.2.2. Asymmetric Hetero-Diels–Alder Reactions

The presence of a small amount of water was found to be beneficial to several asymmetric hetero-Diels−Alder reactions. The asymmetric catalysis of a hetero-Diels−Alder reaction with Danishefsky's diene by chiral lanthanide bis(trifluoromethanesulfonyl)amide (bis-trifylamide) complexes showed a significant effect of water as an additive in increasing both the enantioselectivity and the chemical yield.[865] The addition of chiral auxiliaries have also been used in hetero-Diels−Alder reactions.[866] Fringuelli et al. reacted (*E*)-2-aryl-1-cyano-1-nitroalkenes with both achiral and enantiopure vinyl ethers in pure water. In addition, using (−)-*N*,*N*-dicyclohexyl-(1*S*)-isoborneol-10-sulfonamide as the chiral auxiliary, they observed asymmetric cycloadditions.

Aqueous aza-Diels−Alder reactions of chiral aldehydes prepared from carbohydrates with benzylamine hydrochloride and cyclopentadiene were promoted by lanthanide triflates (eq 226).[867] The nitrogen-



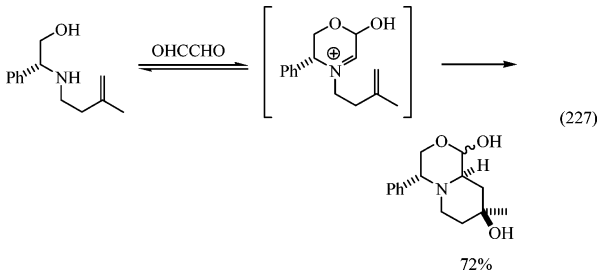
(226)

containing heterocyclic products were further transformed into aza sugars, which are potential inhibitors against glycoprocessing enzymes.

10.3. Other Cyclization Reactions

10.3.1. Alder-ene Reactions

An ene-iminium one-pot cyclization proceeds smoothly in a mixture of water−THF (eq 227).[868] The



(227)

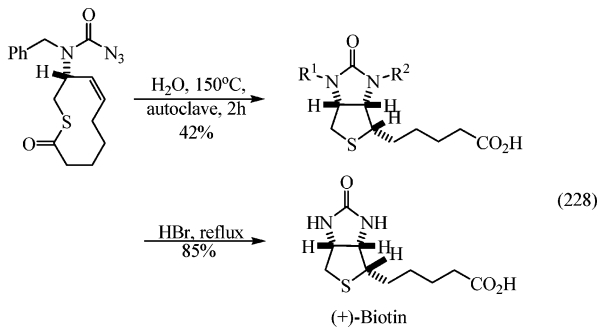
reactivity of the ene-iminium substrates is highly dependent upon the substitution pattern of the ethylenic double bond. This methodology can be used to form homochiral pipecolic acid derivatives.

10.3.2. 1,3-Dipolar Cycloaddition Reactions

The 1,3-dipolar cyclization of nitrile oxide with dipolarophiles generates structurally important heterocycles. As shown by Lee,[869] the reaction can be carried out in an aqueous−organic biphase system in which the nitrile oxide substrates can be generated from oximes or hydrazones in situ. The method provides a convenient one-pot procedure for generating a variety of heterocyclic products.

Reaction of preformed aromatic nitrile *N*-oxides with alkyl disubstituted benzoquinones gives the 1,3-dipolar cyclization product in aqueous ethanol.[870] The effect of the polarity of solvents on the rate of the reaction was investigated. While the reaction is usually slower in more polar solvents than in less polar ones, the use of water as the solvent increases the reactivity. The nitrile oxide reaction has also been catalyzed by baker's yeast[871] and β-cyclodextrin.[872] Reaction of an azomethine ylide, generated in situ from methyl *N*-methylglycinate and formaldehyde with activated olefins, generated the corresponding dipolar products.[873] The reaction rate of 1,3-dipolar cycloaddition of nitrone derivative with dibutyl fumarate increases dramatically in aqueous solution relative to other solvents.[874] The catalytic activity of substituted thioureas in a series of Diels−Alder reactions and 1,3-dipolar cycloadditions was studied. The kinetic data reveal that the observed accelerations in the relative rates are more dependent on the thiourea substituents than on the reactants or solvent. [875]

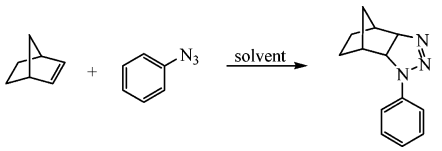
An elegant application of 1,3-dipolar cyclization of an azide derivative in water was reported by De Clercq in the synthesis of (+)-biotin (eq 228).[876] Upon



(228)

thermolysis of the azide compound, a mixture of (+)-biotin and its benzylated derivative was formed directly. The use of water is necessary as the nucleophile and to accelerate the cyclization via betaine stabilization.

The kinetics of 1,3-dipolar cycloaddition of phenyl azide to norbornene in aqueous solutions was studied (eq 229).[877] As shown in Table 2, when the reaction



(229)

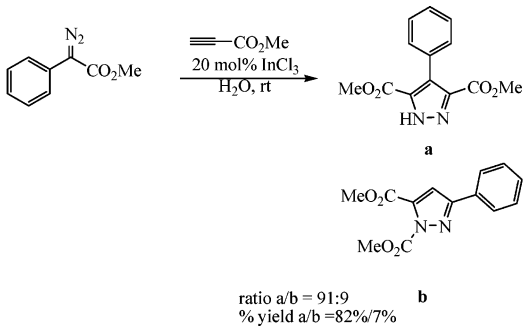
Table 2. Second-Order Constants for Cycloaddition

solvent	$10^5 \times k_2$ (M^{-1} s^{-1})
n-hexane	4.7
EtOH	7.4
2-PrOH	8.2
DMSO	17.5
4:1 H_2O/EtOH	37
92:8 H_2O/2-PrOH	83
99:1 H_2O/NCP[b]	250

[a] Reprinted with permission from ref 877. Copyright 1995 Elsevier. [b] NCP = 1-cyclohexyl-2-pyrrolidinone.

was performed in organic solvents, the reaction showed very small solvent effect, while in highly aqueous media, significant accelerations were observed. The influence of water on the kinetic and synthetic 1,3-dipolar cycloaddition reactions of phthalazinium-2-dicyanomethanide and pyridazinium dicyanomethanide with a wide range of dipolarophiles is reported. Water enhanced the rates of all reactions. [878]

An intermolecular 1,3-dipolar cycloaddition of diazocarbonyl compounds with alkynes was developed by using an $InCl_3$-catalyzed cycloaddition in water. The reaction was found to proceed by a domino 1,3-dipolar cycloaddition−hydrogen (alkyl or aryl) migration (eq 230).[879] The reaction is applicable to various



(230)

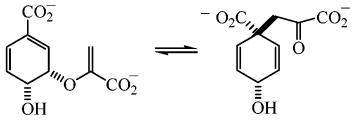
α-diazocarbonyl compounds and alkynes with a carbonyl group at the neighboring position, and the success of the reaction was rationalized by decreasing the HOMO−LUMO of the reaction. The effect of water on the 1,3-dipolar cycloaddition reaction of nitrilimines to alkenes was studied by Hartree−Fock (HF) and DFT ab initio calculations. It was concluded that (i) the effect of water is in general rather small and (ii) therefore water is not directly responsible for the large acceleration of the 1,3-dipolar cycloaddition reaction of nitrilimines to alkenes.[880]

10.4. Sigmatropic Rearrangements

10.4.1. Claisen Rearrangements

The enzyme chorismate mutase was found to accelerate the Claisen rearrangement of chorismic

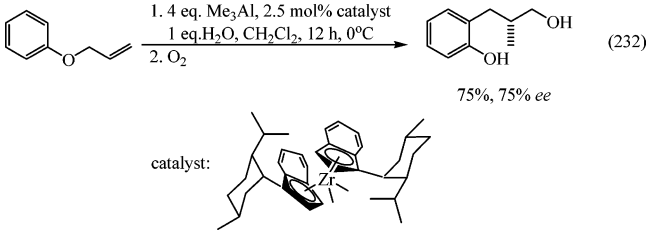
acid.[881] For many years, the origin of the acceleration perplexed and intrigued chemists and biochemists. Polar solvents have been known to increase the rate of the Claisen rearrangement reactions.[882] Claisen rearrangement reactions were found to be accelerated going from nonpolar to aqueous solvents.[883] For instance, the rearrangements of chorismic acid and related compounds in water were 100 times faster than those in methanol (eq 231).[884]



(231)

Due to the $\Delta V^{\ddagger}$ (volume change of activation) of Claisen rearrangements having a negative value, as in the Diels–Alder reactions, the Claisen rearrangement reaction is expected to be accelerated by water according to the same effect.[885,886]

Allyl aryl ethers undergo accelerated Claisen and [1,3] rearrangements in the presence of a mixture of trialkylalanes and water or aluminoxanes. The addition of stoichiometric quantities of water accelerates both the trimethylaluminum-mediated aromatic Claisen reaction and the chiral zirconocene-catalyzed asymmetric carboalumination of terminal alkenes. These two reactions occur in tandem and, after oxidative quenching of the intermediate trialkylalane, result in the selective formation of two new C–C bonds and one C–O bond (eq 232).[887] Antibodies



(232)

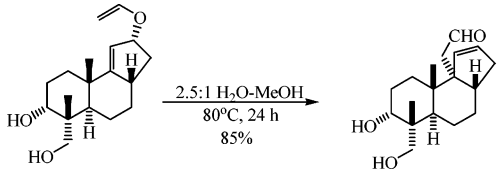
have also been found to catalyze Claisen[888] and oxy-Cope[889] rearrangements.

Grieco observed a facile [3,3]-sigmatropic rearrangement of an allyl vinyl ether in water, giving rise to an aldehyde (eq 233). The corresponding methyl

(233)

ester similarly underwent the facile rearrangement. A solvent polarity study on the rearrangement rate of the allyl vinyl ether was conducted in solvent systems ranging from pure methanol to water at 60 °C.[890] The first-order rate constant for the rearrangement of the allyl vinyl ether in water was 18×10^{-5} s^{-1} compared to 0.79×10^{-5} s^{-1} in pure methanol.

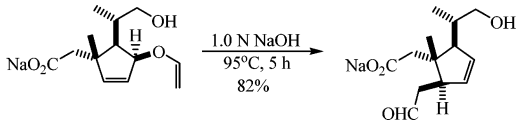
The accelerating influence of water as a solvent on the rate of the Claisen rearrangement has also been demonstrated on a number of other substrates. These studies showed that this methodology has potential applications in organic synthesis. In eq 234, the



(234)

unprotected vinyl ether in a 2.5:1 water–methanol solvent with an equivalent of sodium hydroxide underwent rearrangement to give the aldehyde in 85% yield.[891] The same rearrangement for the protected analogue under organic Claisen reaction conditions had considerable difficulties and often resulted in the elimination of acetaldehyde.[892]

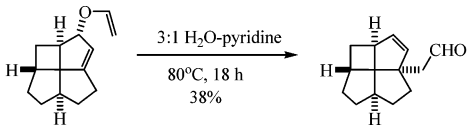
Water also had an effect on the [3,3]-sigmatropic shift of the allyl vinyl ether in the synthesis of the Inhoffenn–Lythgoe diol (eq 235). The rearrangement



(235)

occurred in only 5 h at 95 °C in 0.1 N NaOH solution to give the aldehyde in 82% yield, while the corresponding methyl ester only led to recovered starting material upon prolonged heating in Decalin.

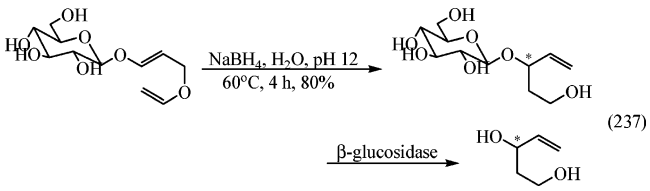
It is interesting to note that all previous attempts to utilize the Claisen rearrangement within the carbon framework of the fenestrane system, as well as all efforts to prepare a fenestrane in which one of the ring fusions is trans, had not been successful. In eq 236, a facile rearrangement of fenestrene took



(236)

place in aqueous pyridine to form a fenestrene aldehyde with a trans configuration between the two five-membered rings common to the acetaldehyde unit.

The use of the glucose chiral auxiliary by Lubineau et al. led to moderate asymmetric induction in the Claisen rearrangement (20% de; eq 237).[893] Since it



(237)

could be removed easily, glucose functioned here as a chiral auxiliary. After separation of the diastereomers, enantiomerically pure substances could be obtained.

The origin of the rate acceleration in Claisen rearrangement has been studied extensively by various methods.[894] A self-consistent-field solvation model was applied to the aqueous medium Claisen rearrangement.[895] The aqueous acceleration of the Claisen rearrangement was suggested to be a result of solvent-induced polarization and first-hydration-shell

hydrophilic effects.[896] Theoretical studies by Jorgensen[897] and Gajewski[898] suggested that increased hydrogen bonding in the transition state is responsible for the observed acceleration. On the other hand, studies by Gajewski on the secondary deuterium kinetic isotope effects argue against the involvement of an ionic transition state.[899] A combined quantum mechanical and statistical mechanical approach used by Gao indicated that different substrates have different degrees of acceleration.[900] The effects of hydration on the rate acceleration of the Claisen rearrangement of allyl vinyl ether were investigated by a hybrid quantum mechanical and classical Monte Carlo simulation method.[901] A number of continuum models, combined with ab initio wave functions, have been used to predict the effect of solvation by water on the Claisen rearrangement of allyl vinyl ether.[902] Monte Carlo simulations have been used by Jorgensen to determine changes in free energies of solvation for the rearrangement of chorismate to prephenate in water and methanol.[903] The calculation reproduces the observed 100-fold rate increase in water over methanol. The origin of the rate difference is traced solely to an enhanced population of the pseudodiaxial conformer in water, which arises largely from a unique water molecule acting as a double hydrogen bond donor to the C_4 hydroxyl group and the side-chain carboxylate.

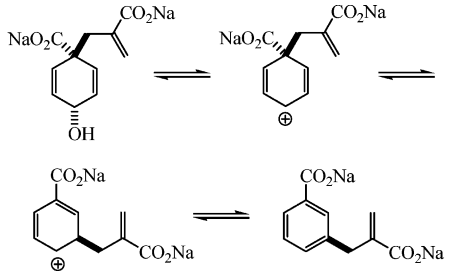
The differences in the rate constant for the water reaction and catalyst reactions reside in the mole fraction of substrate present as near attack conformers (NACs).[904] These results and knowledge of the importance of transition state stabilization in other cases suggest a proposal that enzymes utilize both NAC and transition-state stabilization in the mix required for the most efficient catalysis. When a combined QM/MM Monte Carlo/free-energy perturbation (MC/FEP) method was used, 82%, 57%, and 1% of chorismate conformers were found to be NAC structures (NACs) in water, methanol, and the gas phase, respectively.[905] The observation that the reaction occurs faster in water than in methanol was attributed to greater stabilization of the transition state in water by specific interactions with first-shell solvent molecules. The Claisen rearrangements of chorismate in water and at the active site of *Escherichia coli* chorismate mutase have been compared.[906] It follows that the efficiency of formation of NAC (7.8 kcal/mol) at the active site provides approximately 90% of the kinetic advantage of the enzymatic reaction as compared to the water reaction.

Isotope effects on the rearrangement of allyl vinyl ether have been studied.[907] Secondary deuterium kinetic isotope effects in the aqueous Claisen rearrangement are found to be against an ionic transition state.[908]

A thio-Claisen rearrangement[909] was used for the regioselective synthesis of thiopyrano[2,3-*b*]pyran-2-ones and thieno[2,3-*b*]pyran-2-ones. A convenient method for the aromatic amino-Claisen rearrangement of *N*-(1,1-disubstituted-allyl)anilines led to the 2-allylanilines cleanly and in high yield by using a catalytic amount of *p*-toluenesulfonic acid in acetonitrile/water.[910]

10.4.2. Cope Rearrangements

Cope rearrangement has also been studied in aqueous media. Both enzymatic and nonenzymatic Cope rearrangements of carbaprephenate to carbachorismate were investigated.[911] Carbaprephenate and its epimer undergo spontaneous acid-catalyzed decarboxylation in aqueous solution. Only at high pH does the Cope rearrangement compete with the decarboxylation, and at pH of 12 at 90 °C, carbaprephenate slowly rearranges to carbachorismate, which rapidly loses water to give 3-(2-carboxyallyl)-benzoic acid as the major product (eq 238). An ene-



(238)

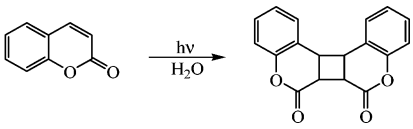
iminium intermediate resulting from the condensation of a homoallylic amino alcohol and glyoxal (water or formic acid solution) undergoes a cationic aza-Cope rearrangement leading to a new ene-iminium compound. The diastereoselective transformation led ultimately to enantiomerically pure α-amino acids.[912]

A chelation-assisted Pd-catalyzed Cope rearrangement was proposed in the reaction of phenanthroline to generate isoquinolinone derivatives.[913] The use of aqueous media and ligands enable a double Heck reaction on a substrate favoring alkene insertion over *β*-hydride elimination.

10.5. Photochemical Cycloaddition Reactions

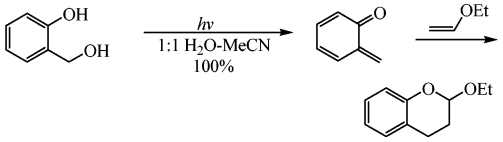
An excellent review on organic photochemistry in organized media, including aqueous solvent, has been reported.[914] The quantum efficiency for photodimerization of thymine, uracil, and their derivatives increased considerably in water compared with other organic solvents. The increased quantum efficiency is attributed to the preassociation of the reactants at the ground state.

Organic substrates having poor solubilities in water, such as stilbenes and alkyl cinnamates, photodimerize efficiently in water. The same reaction in organic solvents, such as benzene, mainly leads to cis−trans isomerizations.[915] As in the case of Diels−Alder reaction, the addition of LiCl (increasing hydrophobic effect) increases the yield of dimerizations. On the other hand, the addition of quanidinium chloride (decreasing the hydrophobic effect) lowers the yield of the product. The photodimerization of stilbenes is more efficient in a hydroxylic solvent such as methanol or water than in a non-hydroxylic solvent such as hexane, benzene, or acetonitrile.[916] The proposed accelerated photodimerization originates from a formation of a fluorescent solute−solute aggregate. Similarly, coumarin dimerized more efficiently in water than in organic solvents (eq 239).[917]



(239)

The quantum yield of the dimerization in water is more than 100 times higher than that in benzene and methanol. When a surfactant is added in water, it will aggregate forming micelles. The formation of such micelles has also been found to have a significant effect on the regio- and stereoselectivity of photochemical reactions. In the micellar case, the hydrophobic interior of micelles provides a hydrophobic pocket within the bulk water solvent. An analogous situation of hydrophobic cage effect is the use of cyclodextrin. Thus, a selectivity in product formation could be expected also in this case. Indeed, while four isomers are generated for the photodimerization of anthracene-2-sulfonate, the same reaction gives only one isomer when β-cyclodextrin is present.[918] When an appropriately substituted *o*-hydroxybenzyl alcohol precursor is used, a photogenerated *o*-quinone methide undergoes efficient intramolecular Diels−Alder cycloaddition in aqueous CH_3CN to generate the hexahydrocannabinol ring system (eq 240).[919]



(240)

The dienophile tether must be sufficiently electron-rich, having at least three alkyl groups. Laser flash photolysis studies show the intermediacy of an *o*-quinone methide that has a lifetime >2 ms. Quantum yields for reaction and fluorescence parameters depend strongly on the proportion of water in the H_2O−CH_3CN solvent mixture.

11. Conclusion

This review demonstrates how it is being recognized that water as a medium can promote various old and new reactions. The types of reactions that can be carried out in water are as diverse as those in nonaqueous conditions. The proceeding of such aqueous reactions implies that many protection−deprotection procedures in classical nonaqueous conditions may be curtailed. Most importantly, completely new reactivities have been discovered by using water as a solvent. Thus, organic synthesis in water can significantly reduce the number of steps when designed properly. Ultimately, the combination of shortening synthetic routes, increasing product selectivity, and reducing volatile organic consumption will provide economical, health, and environmental benefits. The opportunities of pursuing unconventional chemical reactivities provide the driving force for future innovation of the field and in chemistry as a whole.

12. Acknowledgment

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13. Note Added in Proof

A recent prominent development in the field is the development of organic reactions "on-water" by Sharpless and co-workers, see: Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

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