

# Organic Reactions in Aqueous Media—With a Focus on Carbon–Carbon Bond Formation

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## I. Introduction

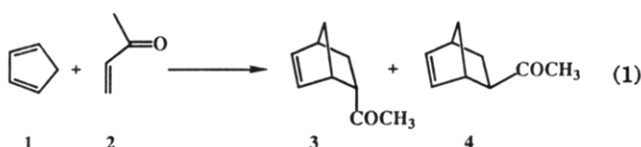
Carbon–carbon bond formation is the essence of organic synthesis. Although the well-known Kolbe synthesis was discovered in 1849<sup>1a</sup> (the first observation was made in 1834 by Faraday),<sup>1b</sup> for more than a century, carbon–carbon bond formation in aqueous media has been limited mainly to electrochemical processes and aldol condensation reactions. This is in contrast to the many enzymatic processes that by necessity must occur in an aqueous environment. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents. For example, protection and deprotection processes in organic synthesis can possibly be simplified. This review will survey this area, concentrating mainly on the last decade.

The review is organized into three main portions: nonorganometallic reactions, organometallic reactions, and transition-metal-catalyzed organic reactions in aqueous media. The conventional aldol-type and related reactions, stabilized carbanion alkylation reactions, electrochemical reactions as well as bioorganic reactions involving aqueous media and leading to carbon–carbon bond formation will not be included.

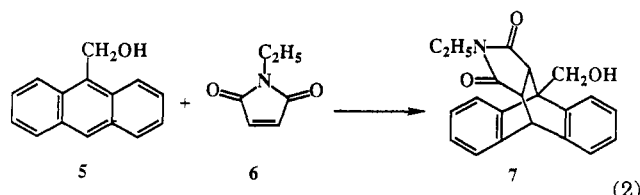
## II. Diels–Alder Reactions and Claisen Rearrangement Reactions

### A. Diels–Alder Reactions<sup>2</sup>

The Diels–Alder reaction is the most important method used to form cyclic structures. Diels–Alder reactions in aqueous media were first carried out back in the 1930s.<sup>3</sup> No further study was carried out until recently. In 1980, Breslow<sup>4</sup> and later Grieco as well as others reported that Diels–Alder reactions were accelerated by using water as solvent. Water as a reaction solvent also strikingly affected the selectivity of some Diels–Alder reactions.<sup>5</sup> 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 (eq 1). Aqueous detergent



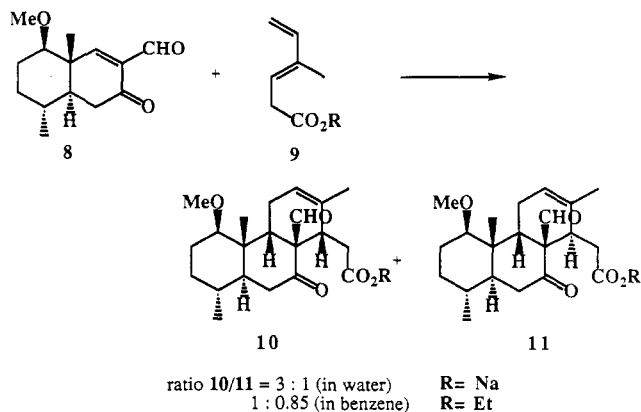
solution had no effect on the product ratio. The stereochemical changes could be explained by the need to minimize the transition-state surface area in water solution, thus favoring the more compact endo stereochemistry. The use of  $\beta$ -cyclodextrin, simultaneously forming an inclusion complex with the diene and dienophile, further enhanced the rate of aqueous Diels–Alder reactions. The reaction between (hydroxymethyl)anthracene (5) and *N*-ethylmaleimide (6) was carried out in water at 45 °C. Its second-order rate constant in water was over 200 times larger than in acetonitrile (eq 2).



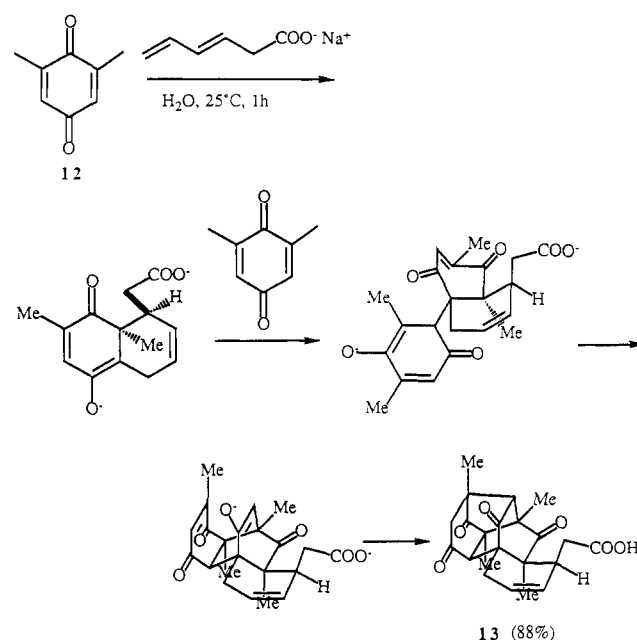
The catalytic behavior exhibited by  $\beta$ -cyclodextrin was also observed in the intramolecular Diels–Alder reaction of a furandiene in water.<sup>6a</sup> Holt studied the Diels–Alder reaction in a mixture of water, 2-propanol, and toluene as microemulsions.<sup>6b</sup> The endo/exo ratio between the reaction of cyclopentadiene and methyl methacrylate was enhanced with increasing amount of water in the presence of a surfactant.

Grieco found that when the Diels–Alder reaction in Scheme I was carried out in water, a higher reaction rate and reversal of the selectivity were observed, compared to the same reaction in a hydrocarbon solvent.<sup>7a</sup> It should be noted that, for the aqueous reaction, the sodium salt of the diene was used. Water soluble cosolvents caused a rapid reduction in rate. The best result was obtained when the reaction was conducted with a 5-fold excess of the sodium salt of diene carboxylate. The Diels–Alder reaction of the diene-carboxylate in water was also investigated with a variety of other dienophiles.<sup>7b</sup> Great enhancement of the reaction rate was also observed. Sensitive dienol ether functionality in the diene carboxylate was shown to be compatible with the conditions of the aqueous Diels–Alder reaction.<sup>8</sup> Exposure of 2,6-dimethylbenzoquinone to 1.5 equiv of a 1.0 M aqueous sodium (*E*)-3,5-hexadienoate solution, containing a catalytic amount of hydroxide, led to carboxylic acid 13 (Scheme II). The formation of 13 arose via deprotonation of the Diels–Alder adduct followed by tandem Michael ad-

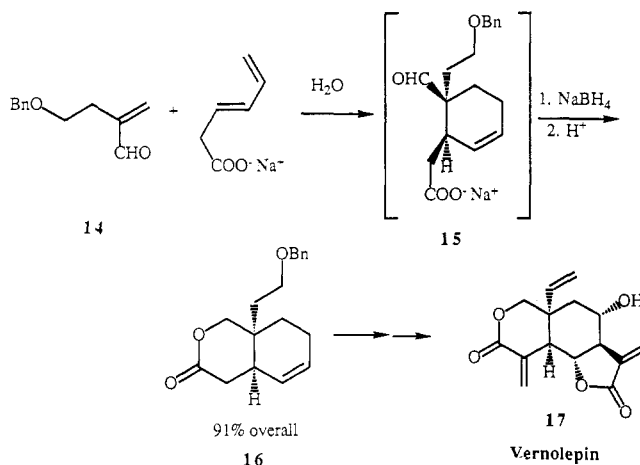
#### Scheme I



#### Scheme II

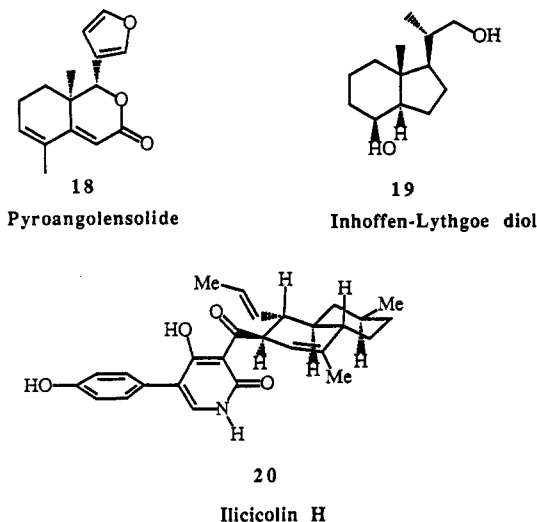


#### Scheme III



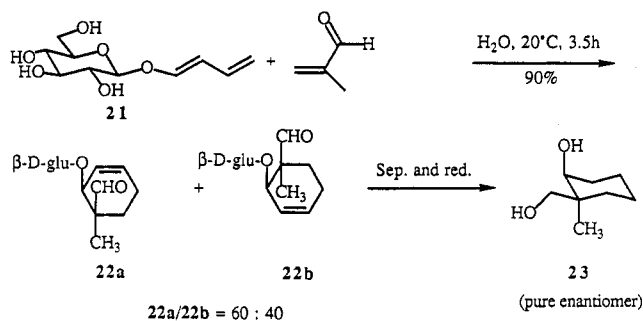
dition reactions.<sup>9</sup> Similar results were obtained with sodium (*E*)-4,6-heptadienoate. Cycloaddition of sodium (*E*)-3,5-hexadienoate with the  $\alpha$ -substituted acrolein 14 in water followed by direct reduction of the intermediate Diels–Alder adduct 15, gave 16 in excellent yield in one pot.<sup>10</sup> This compound constituted the basic AB ring system of the sesquiterpene lactone, vernolepin (17, Scheme III). Similar reactions were applied to the syntheses of *dl*-*epi*-pyroangolensolide, *dl*-pyroangoenolide (18)<sup>11</sup> and the Inhoffen–Lythgoe diol (19).<sup>12</sup> Sodium (*E*)-4,6,7-octatrienoate reacted smoothly with a variety of dienophiles to give conjugated diene products.<sup>13</sup> An intramolecular version of the Diels–Alder reaction with a diene carboxylate was used in the synthetic study of antibiotic ilicicolin H (20).<sup>14</sup>

The dienes in the Diels–Alder reactions can also bear other water-solubilizing groups, such as the sodium salt of phosphoric acid or a dieny ammonium chloride.<sup>2b,15</sup> A diene bearing a chiral water-soluble glyco hydrophilic moiety was studied extensively by Lubineau.<sup>16</sup> The use of water soluble glyco organic compounds in water achieved higher reagent concentration. The reaction also resulted in rate enhancement and asymmetric induction. Even though the diastereoselectivity was

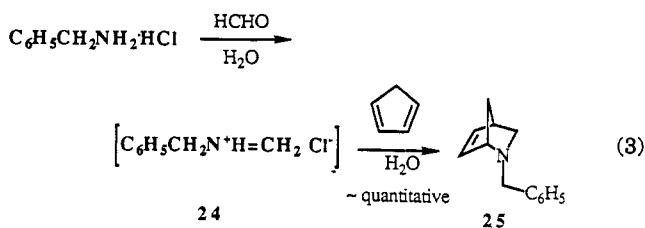


modest (20% de), separation of the diastereomers led to chiral adducts in pure enantiomeric form after cleavage of the sugar moiety by acidic hydrolysis, or by using glycosidase in neutral conditions at room temperature (Scheme IV).

#### Scheme IV

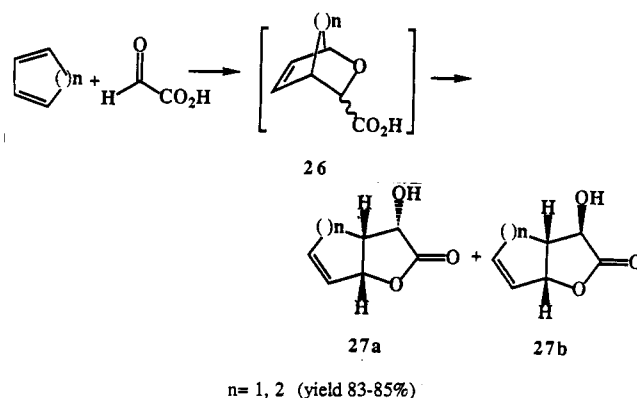


Hetero-Diels-Alder reactions also proceeded in aqueous media. Grieco reported that simple iminium salts, generated in situ under Mannich-like conditions, reacted with dienes in water to give aza-Diels-Alder reaction products with the potential for alkaloid synthesis (eq 3).<sup>17</sup> C-Acyl iminium ions reacted similarly



with cyclopentadienes.<sup>18</sup> Retro-aza-Diels-Alder reactions also occurred readily in water.<sup>19,20</sup> This reaction provided a novel method for the N-methylation of dipeptides and amino acid derivatives. Waldmann used (*R*)- and (*S*)-amino acid methyl esters and chiral amines as chiral auxiliaries in analogous aza-Diels-Alder reactions.<sup>21</sup> The diastereoselectivity of these reactions ranged from moderate to excellent. Cyclopentadiene or cyclohexadiene reacted with an aqueous solution of glyoxylic acid to give  $\alpha$ -hydroxy  $\gamma$ -lactones arising from the rearrangement of the cycloadducts (Scheme V).<sup>22</sup> Water as a solvent allowed direct use of the inexpensive

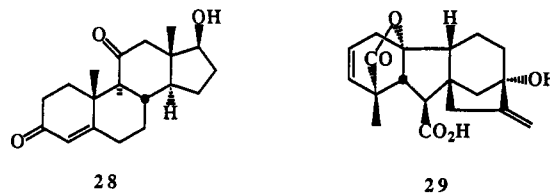
#### Scheme V



aqueous solution of glyoxylic acid for cycloaddition, and it also enhanced the rate of the hetero-Diels-Alder reaction relative to the dimerization of cyclopentadiene.

The acceleration of the Diels-Alder reaction in water has been explained by the suggestion that water brings together the two nonpolar organic substrates via the hydrophobic effect, which is the tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon-water interfacial area.<sup>2a</sup> This effect is the principal force determining the secondary and tertiary structures of proteins and nucleic acids and the binding of substrates to receptors. Certain agents that decrease hydrocarbon solubility in water, such as LiCl, will favor the aggregation of the nonpolar species, thus increasing the hydrophobic effect, while others that increase hydrocarbon solubility lead to a decrease of the hydrophobic effect. Breslow has studied the influence of the hydrophobic effect on the aqueous Diels-Alder reactions in detail.<sup>23,24</sup> Schneider has reported a quantitative correlation between solvophobicity and rate enhancement of aqueous Diels-Alder reactions.<sup>25,26</sup> The acceleration may also be explained by the high internal pressure of water, which would affect the reaction in the same way as external high pressure would. Enforced hydrophobic interactions between diene and dienophile have also been suggested to account for the acceleration in water.<sup>27</sup> A computer simulation study of such acceleration has been carried out.<sup>28</sup>

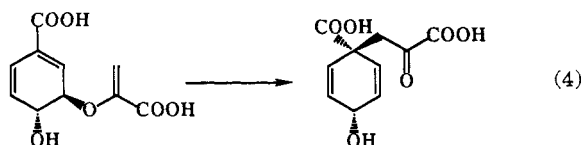
Aqueous Diels-Alder reactions have also been used as key steps in the syntheses of ( $\pm$ )-11-ketotestosterone (28)<sup>29</sup> and ( $\pm$ )-gibberellin A<sub>5</sub> (29).<sup>30</sup>



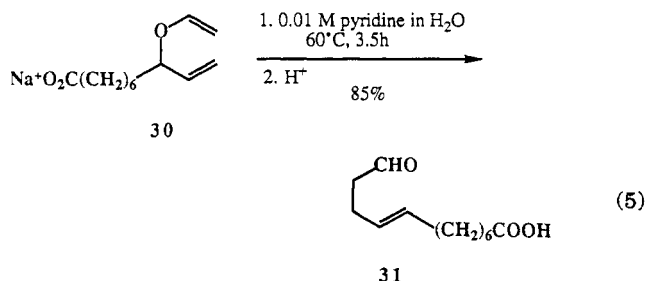
#### B. Claisen Rearrangement Reactions

Polar solvents have been known to increase the rate of Claisen rearrangement reactions.<sup>31</sup> Recently, it was observed that Claisen rearrangement reactions were accelerated on going from nonpolar to aqueous solvents.<sup>32</sup> For instance, the rearrangements of chorismic acid and related compounds in water were 100 times faster than in methanol (eq 4).<sup>33a</sup> Because the  $\Delta V^\ddagger$  (volume change of activation) of Claisen rearrangements

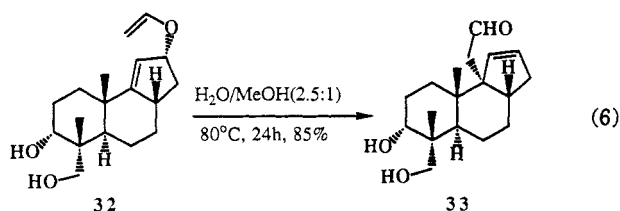
also has a negative value, as in the Diels–Alder reactions, therefore the Claisen rearrangement reaction is expected to be accelerated by water according to the same effect.<sup>33b,c</sup>



Grieco observed a facile [3,3]-sigmatropic rearrangement of allyl vinyl ether **30** in water, giving rise to aldehyde **31** (eq 5). The corresponding methyl ester underwent the facile rearrangement similarly. A solvent

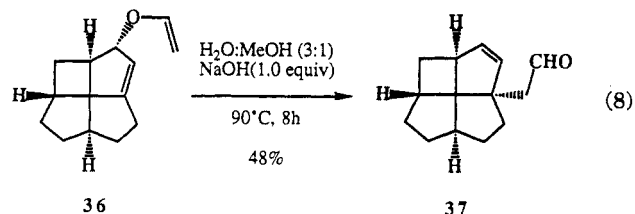
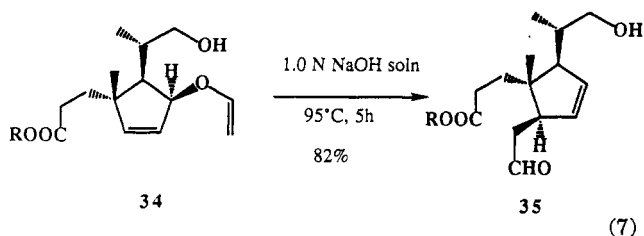


polarity study on the rearrangement rate of allyl vinyl ether **30** was conducted in solvent systems ranging from pure methanol to water at 60 °C.<sup>34</sup> The first-order rate constant for the rearrangement of **30** in water was  $18 \times 10^{-5} \text{ s}^{-1}$ , compared to  $0.79 \times 10^{-5} \text{ s}^{-1}$  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. For instance, unprotected allyl vinyl ether **32**, as a 0.01 M solution in water–methanol (2.5:1) containing 1 equiv of sodium hydroxide, smoothly underwent rearrangement at ca. 80 °C, affording 85% isolated yield of aldehyde **33** in 24 h (eq 6).<sup>35</sup> The same rearrangement for the protected

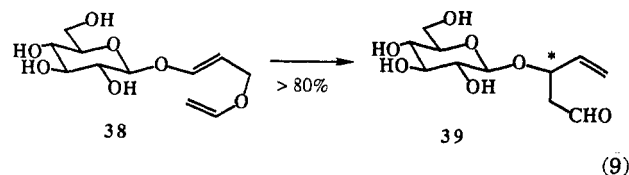


analog under organic Claisen reaction conditions had considerable difficulties and often resulted in the elimination of acetaldehyde.<sup>36</sup> The rearrangement of allyl vinyl ether **34** occurred smoothly in water (eq 7), while the corresponding methyl ester only led to recovered starting material upon prolonged heating in decalin.<sup>35</sup> A surprisingly facile rearrangement of fenestrene **36** took place to give fenestrene **37**, which possessed a trans ring fusion between the two five-membered rings (eq 8).<sup>35</sup> Previous attempts to synthesize such a ring fusion and to employ Claisen rearrangements within the carbon framework of a fenestrene system had been unsuccessful.

The use of the glucose chiral auxiliary led to moderate asymmetric induction in the Claisen rearrangement of compound **38** (20% de). Both compounds **38** and **39**



were water soluble due to the high polarity of the glucose moiety (eq 9).<sup>37</sup> Since it could be removed easily, glucose functioned here as a chiral auxiliary. After separation of the diastereomers, enantiomerically pure substances could be obtained. A self-consistent-field solvation model was applied to the aqueous medium Claisen rearrangement.<sup>38</sup> The aqueous acceleration of the Claisen rearrangement was suggested to be due to electric polarization and first-hydration-shell hydrophilic effects.



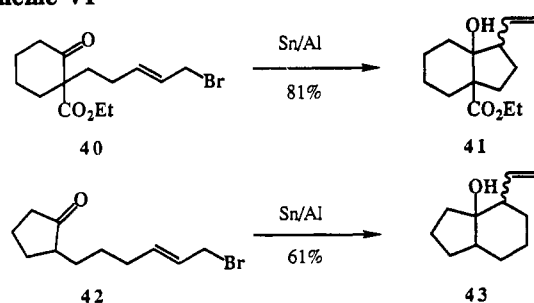
### III. Barbier-Type Reactions and Pinacol-Coupling Reactions

Because of the high reactivity of organometallic reagents, water has been considered undesirable for Barbier-type reactions and limited study has been carried out only recently concerning their reactions in aqueous media. On the other hand, the preparation of arylmercuric chloride in aqueous media has been known since 1905.<sup>39</sup> In the 1960s, tribenzylstannyl halide was produced in large scale in water.<sup>40</sup> These reports indicated the possibility of carrying out these kinds of reactions in water under special circumstances. Recently, there has been a tremendous effort to study organometallic reactions in water. These reactions include the allylation reaction of carbonyl compounds, conjugated addition to unsaturated carbonyl compounds, crossed aldol and Reformatsky-type reactions, and pinacol-coupling reactions.

#### A. Allylation of Carbonyl Compounds

Introducing both a hydroxyl group and a C=C bond simultaneously into a molecule, the allylation of carbonyl compounds has wide application in organic synthesis.<sup>41</sup> Allylations are by far the most successful Barbier type reactions in aqueous media. The presence of a metal surface seems to be critical in these reactions. In 1977,<sup>42</sup> the first allylation reaction involving aqueous media was carried out in 95% ethanol and butanol by using activated zinc dust. However, only a moderate

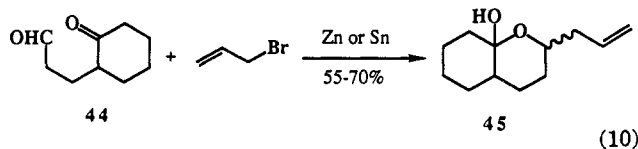
## Scheme VI



yield was obtained. In 1983, it was found that diallyltin dihalide-based allylation of carbonyl compounds could be accelerated by the presence of water. The allylation could be carried out in a mixture of ether and water by using allyl bromide and metallic tin with the addition of aluminum powder or foil.<sup>43</sup> However the addition of zinc was ineffective. Later, allylation with allyl chloride was also successful.<sup>44</sup> A similar reaction occurred with bismuth metal or bismuth(III) chloride together with either aluminum, zinc, or iron.<sup>45a</sup> The bismuth(III)-aluminum system also mediated the allylation of immonium cations to give amines.<sup>45b</sup> In this case, even methylation with iodomethane took place smoothly.

The reaction can also proceed intramolecularly. By using the combination of tin and aluminum in aqueous medium, ketones having allylic halide functionality such as 40 and 42 were cyclized to form five and six membered rings (Scheme VI).<sup>46</sup> Allylation reactions in water/organic solvent mixtures also utilized an electrochemical process, with the advantage that the allyltin reagent could be recycled.<sup>47</sup>

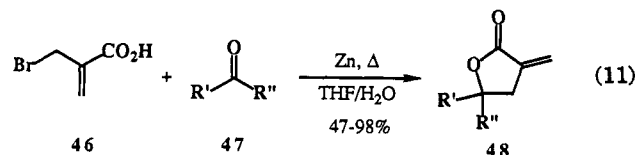
Later, Luche found that allylation reactions, when subjected to ultrasonic radiation, could be performed with metallic zinc.<sup>48,49</sup> The use of saturated aqueous  $\text{NH}_4\text{Cl}/\text{THF}$  solution, instead of water/THF, dramatically increased the yield. Under the same conditions, metallic tin was also effective. When a mixture of aldehyde and ketone was subjected to the reaction, highly selective allylation of the aldehyde was achieved. Similar chemoselectivity occurred in compound 44 (eq 10).<sup>50</sup>



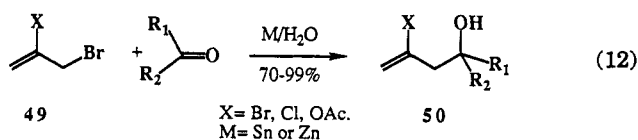
The reaction with zinc was also accelerated by C-18 silica gel.<sup>51</sup> Allylations or propargylations could be performed with tin at refluxing temperature.<sup>52,53</sup> An interesting result was found with indium. The metal was not sensitive to boiling water or alkali and did not form oxides readily in air. Its first ionization potential was much lower than that of zinc or tin, or even magnesium. When indium was used in the allylation of carbonyl compounds instead of zinc or tin, the reaction proceeded smoothly at room temperature.<sup>54a</sup> Compared to the use of zinc and tin where acid catalysis, heat, or sonication was often required, the reaction with indium did not require any promoter. In this case, selective allylation of a methyl ketone in the presence

of an acid-sensitive acetal was achieved. Only a catalytic amount of indium was required when the allylation was carried out with the combination of  $\text{In(III)-Al}$  or  $\text{In(III)-Zn}$ .<sup>54b</sup>

The use of ethyl 2-(bromomethyl)acrylate, instead of allyl halide, with zinc or tin in saturated aqueous  $\text{NH}_4\text{Cl}/\text{THF}$  under refluxing conditions, followed by treatment with acid, gave  $\alpha$ -methylene- $\gamma$ -butyrolactones (eq 11).<sup>55</sup> Similar coupling reactions of methyl ester mediated by indium proceeded smoothly at room temperature in water alone.<sup>54a</sup> The same products were obtained under much stronger conditions by refluxing bromoacrylic acid and carbonyl compounds with  $\text{Sn-Al}$ ,<sup>56</sup>  $\text{SnCl}_2\text{-AcOH}$ ,<sup>57</sup> and  $\text{SnCl}_2\text{-Amberlyst 15}$ <sup>58</sup> in aqueous media.

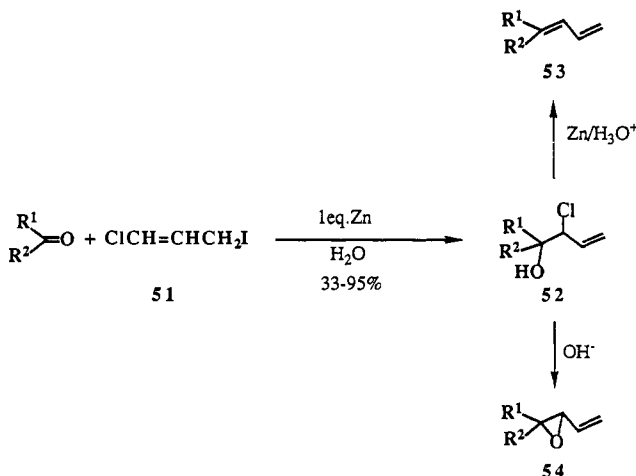


When 2-bromo- and 2-acetoxy-3-bromo-1-propene were used, the allylation reaction with tin<sup>59</sup> produced the corresponding functionalized coupling products (eq 12). 2,3-Dichloro-1-propene reacted similarly by using zinc.<sup>60</sup>

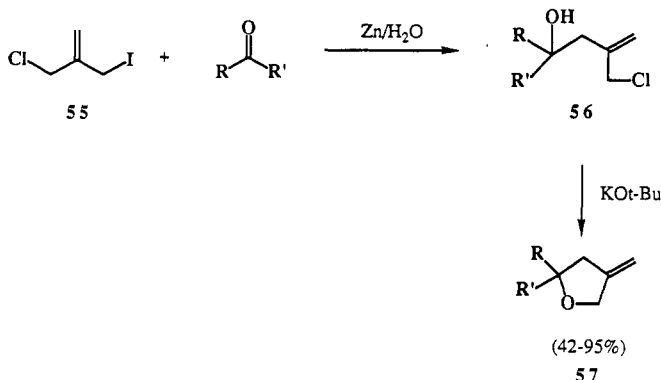


Conjugated 1,3-butadienes were produced in moderate yields when carbonyl compounds reacted with 1,3-dichloropropene and zinc in water.<sup>61</sup> The use of 3-iodo-1-chloropropene instead of 1,3-dichloropropene greatly improved the yields of the reactions. When the reactions were interrupted after their initial allylations, subsequent base treatment of the intermediate compounds produced vinyloxiranes in high yields (Scheme VII). Similarly, reactions of carbonyl compounds with 3-iodo-2-(chloromethyl)-1-propene followed by base treatment produced 2-methylenetetrahydrofurans (Scheme VIII).<sup>62</sup> Thus, the 3-iodo-2-(chloromethyl)-

## Scheme VII

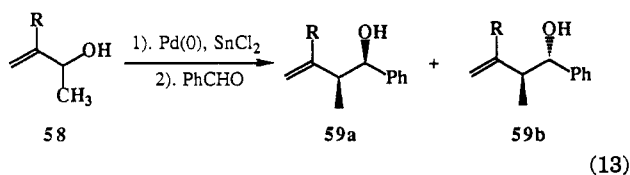


## Scheme VIII

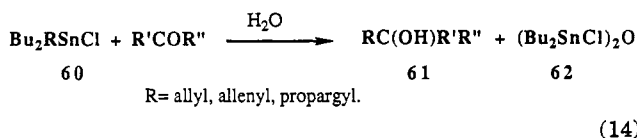


1-propene here served as a novel trimethylenemethane equivalent.<sup>63</sup>

The allylation of carbonyl compounds in aqueous media with  $\text{SnCl}_2$  can also employ allylic alcohols<sup>64</sup> or carboxylates<sup>65</sup> in the presence of a palladium catalyst. The diastereoselectivity of the reactions with substituted crotyl alcohols was solvation dependent (eq 13). Improved diastereoselectivity was obtained with a mixture of water and THF or DMSO instead of using the organic solvent alone.



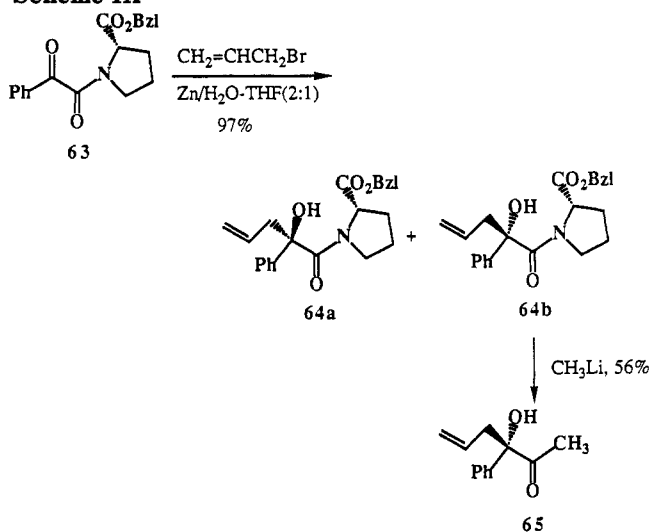
Allylations, allenylations, and propargylations of carbonyl compounds in aqueous media could also be carried out with the presumed intermediate organic tin reagents 60, instead of using metals (eq 14).<sup>66-68</sup> Reactions of  $\alpha,\beta$ -unsaturated carbonyl compounds generally gave 1,2-addition products.<sup>69</sup>



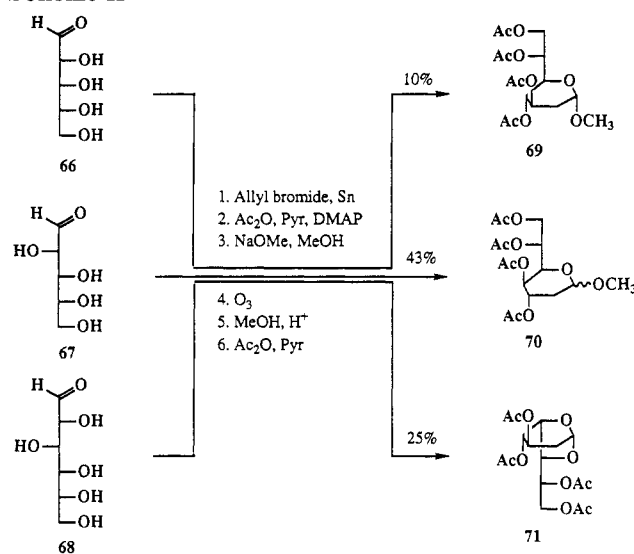
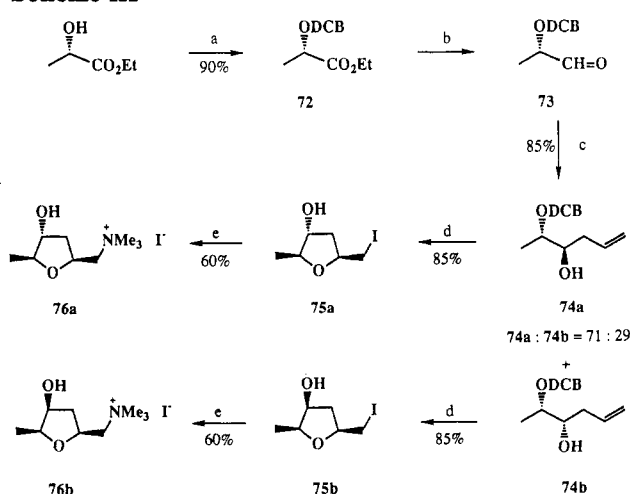
Recently Waldmann studied the diastereoselectivity of allylation reactions using proline benzyl ester as a chiral auxiliary to produce  $\alpha$ -hydroxy amides. The diastereoselectivity was around 4-5:1 (Scheme IX).<sup>70</sup> Separation of the diastereomers followed by reaction with methyl lithium produced the enantiomerically pure alcohol 65.

The allylation reaction could also be used to prepare  $\alpha,\alpha$ -difluorohomoallylic alcohols from *gem*-difluoroallyl halides.<sup>71</sup> Whitesides recently applied the tin-mediated allylation to the carbonyl moieties of carbohydrates in an aqueous/organic solvent mixture.<sup>72</sup> The adducts were converted to higher carbon aldoses by ozonolysis of the deprotected polyols followed by suitable derivatization (Scheme X). 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 C-2 position. In synthetic applications, Chan and Li used the zinc mediated allylation as a key step in a total synthesis of (+)-

## Scheme IX



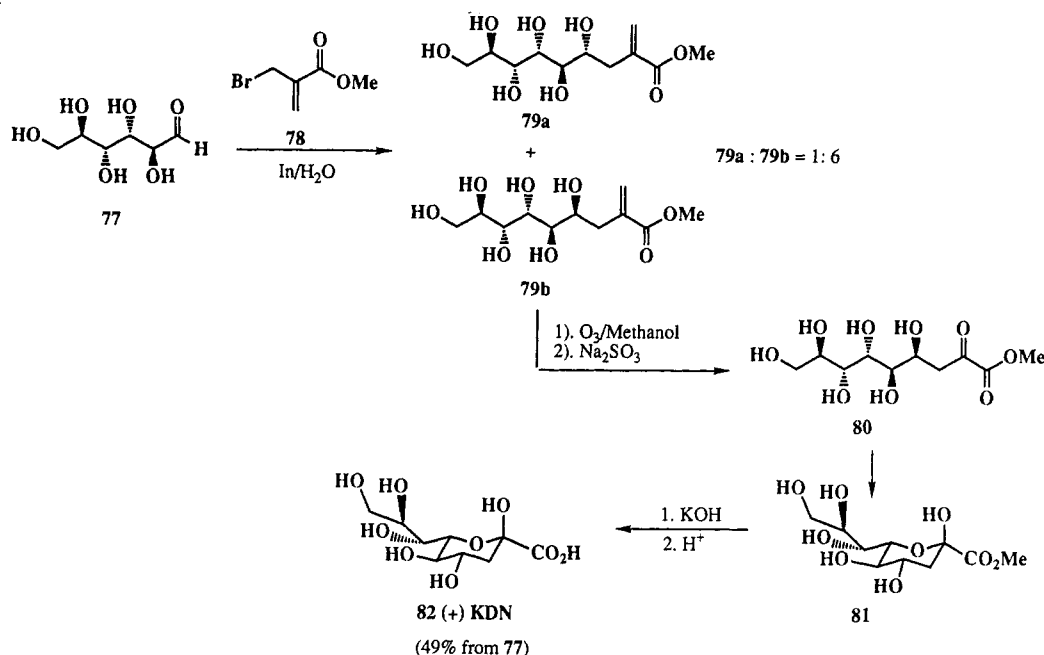
## Scheme X

Scheme XI<sup>a</sup>

<sup>a</sup> (a) DCBB/Ag<sub>2</sub>O/Et<sub>2</sub>O/reflux/6 h; (b) DIBAL-H/Et<sub>2</sub>O/-78 °C/2 h; (c) CH<sub>2</sub>=CHCH<sub>2</sub>Br/Zn/H<sub>2</sub>O/NH<sub>4</sub>Cl/3 h; (d) I<sub>2</sub>/CH<sub>3</sub>CN/0 °C/3 h; (e) NMe<sub>3</sub>/EtOH/80 °C/4 h.

muscarine (76a) (Scheme XI).<sup>73</sup> They used the indium-mediated allylation in a concise synthesis of (+)-3-deoxy-*glycero*-D-*galacto*-nonulosonic acid (KDN, 82)

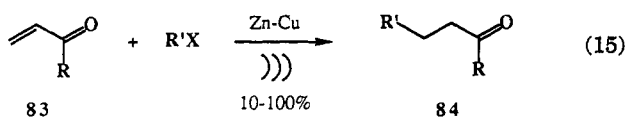
## Scheme XII



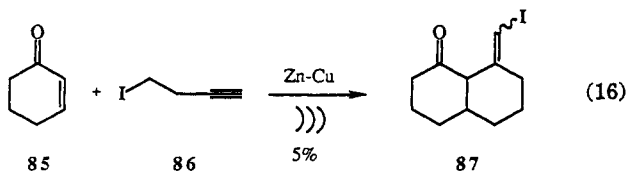
(Scheme XII).<sup>74a</sup> In contrast to the tin-mediated reactions, the indium-mediated reaction also occurred on substrates with an *N*-acetyl group present at C-2.<sup>74b</sup> This could serve as a useful entry to the synthesis of neuraminic acids.

B. Conjugated Addition Reactions<sup>75</sup>

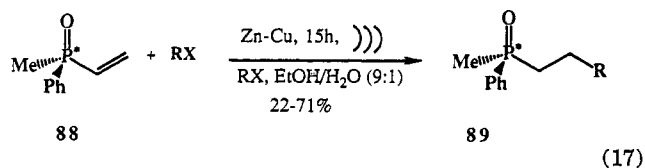
Although the allylation reactions in aqueous media were very successful, alkylation reactions in aqueous media with nonactivated alkyl halides usually failed to proceed, presumably due to the higher ionization potential of these compounds. However, Luche found that when the zinc-copper couple was used, the less reactive alkyl halides reacted with conjugated carbonyl compounds and nitriles to give 1,4-addition products in good yields under sonication conditions (eq 15).<sup>76</sup> A moderate diastereoselectivity was observed in these reactions when a mixture of diastereomers could be generated.<sup>77</sup>



The reactivity of the halides followed the order of tertiary > secondary >> primary, and iodide > bromide (chlorides do 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. Efforts to trap the intermediate intramolecularly only gave a very low yield of the cyclization product 87 (eq 16).<sup>78</sup>



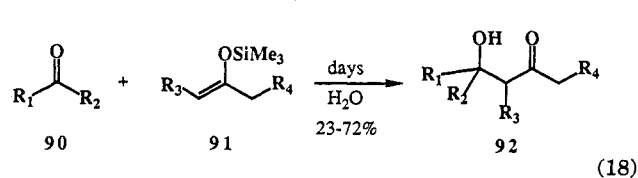
Similar additions also occurred on vinylphosphine oxides. When the optically active vinylphosphine oxide 88 was used, *P*-chiral alkylphosphine oxide 89 was obtained with retention of configuration (eq 17).<sup>79</sup>



## C. Crossed Aldol and Reformatsky-Type Reactions

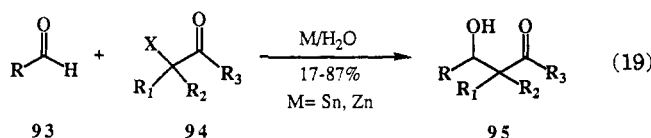
The aldol condensation is another important reaction for forming carbon-carbon bonds.<sup>80</sup> However, under the classical aldol reaction conditions involving basic media, dimers, polymers, self-condensation products, or  $\alpha,\beta$ -unsaturated carbonyl compounds often are formed as well. The formation of these products is attributed to the fact that the aldol condensation is an equilibrium process.<sup>81</sup> Useful modifications of the classical aldol condensation, especially using Lewis acid-promoted reactions of enol, silyl, or tin ethers with carbonyl compounds,<sup>82,83</sup> have been developed to alleviate these difficulties. These modifications typically include the use of an organic solvent as the reaction media and require the exclusion of moisture.

Recently, the crossed aldol reaction of silyl enol ethers with carbonyl compounds was carried out in aqueous solvents without any acid catalyst. However, the reaction took several days to complete (eq 18).<sup>84</sup> The crossed aldol products showed only a slight syn dias-

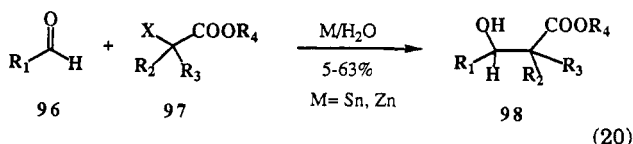


tereoselectivity, which was the same as when this reaction was carried out in organic solvent under high pressure. Adding a catalytic amount of lanthanide triflate greatly improved the yields of such reactions.<sup>85</sup> Among the lanthanide triflates, ytterbium triflate [Yb(OTf)<sub>3</sub>], gadolinium triflate [Gd(OTf)<sub>3</sub>], and lutetium triflate [Lu(OTf)<sub>3</sub>] 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.

The reaction of an  $\alpha$ -carbonyl compound with a metal and an aldehyde in water gave a direct crossed aldol reaction product (eq 19).<sup>86</sup> Either tin or zinc could be used to mediate the reaction, depending on the reaction temperature. The reaction was explained as a radical anion process occurred on the metal surface.



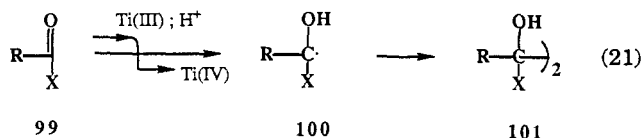
Reformatsky-type reactions in aqueous media first were reported in 1985,<sup>55</sup> using (bromomethyl)acrylic acid (46) and metallic zinc to prepare  $\alpha$ -methylene- $\gamma$ -butyrolactones (section III.A). Normal  $\alpha$ -halo carboxylic esters did not react under these conditions. Since the substrate 46 structurally was an allylic halide, the reaction should be regarded as an allylation. A direct Reformatsky-type reaction occurred when an aromatic aldehyde reacted with an  $\alpha$ -bromo ester in water mediated by either tin or zinc (eq 20).<sup>87</sup> However, the reaction gave only a low yield of the product, and aliphatic aldehydes failed to react.



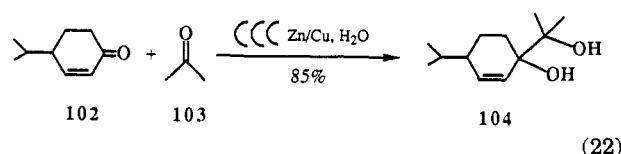
#### D. Pinacol-Coupling Reactions

The coupling of carbonyl compounds<sup>88</sup> to give 1,2-diols, known as the "pinacol coupling", has been carried out in aqueous media. The use of a Zn-Cu couple to couple unsaturated aldehydes to pinacols were reported as early as 1892.<sup>89</sup> Early experiments also included the use of chromium and vanadium,<sup>90</sup> as well as some ammoniacal titanium trichloride<sup>91</sup>-based reducing agents.

Recently, Clerici and Porta extensively studied the aqueous pinacol-coupling reactions mediated by Ti(III). Aromatic ketones and aldehydes were homocoupled by TiCl<sub>3</sub> in aqueous solution under alkaline conditions.<sup>92</sup> When this reagent was used under acidic conditions, aliphatic or aromatic ketones or aldehydes containing "activating" (strongly electron-withdrawing) groups reacted to give homocoupling products.<sup>93,94</sup> With nonactivated carbonyl compounds, cross-coupled products were obtained when the nonactivated carbonyl compounds were used in excess or as a solvent.<sup>92,95-98</sup> The activating groups included CN, CHO, COMe, COOH, COOMe, and pyridyl. The mechanism of this reaction was suggested to be a radical process (eq 21).



Cross-coupling reactions between  $\alpha,\beta$ -unsaturated carbonyl compounds and acetone were carried out by using a Zn-Cu couple and ultrasonic radiation in an aqueous acetone suspension (eq 22).<sup>99</sup> A similar radical mechanism was suggested. The large excess of acetone was intended to alleviate the self-coupling of the  $\alpha,\beta$ -unsaturated substrates.



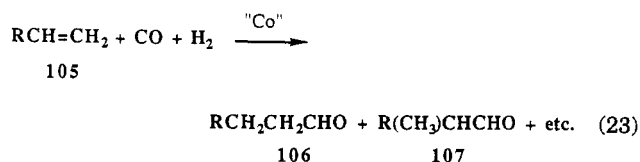
#### IV. Transition-Metal-Catalyzed C-C Formation Reactions

The development of transition-metal reagents for use in aqueous solvent systems offers the same advantages for a wide variety of chemical reactions ranging from large-scale industrial processes to laboratory organic synthesis. The advantage of using water-soluble transition-metal catalysts for a large-scale chemical manufacturing lies in simplifying product isolation and recycling the catalyst. In 1973, the first attempt was reported to carry out a transition-metal-catalyzed hydrogenation reaction of olefins in aqueous solution with a water-soluble phosphine ligand.<sup>100</sup> No exceptional property was observed with the catalyst. However, the experiment showed that water did not interfere with the soft catalytic system. According to the hard and soft acid and base theory, water is considered a "hard" base, whereas the intermediates in conventional organometallic catalyzed reactions often have a "soft" character.<sup>101</sup>

#### A. Carbonylation Reactions

##### 1. Hydroformylation of Olefins

Hydroformylation is a major industrial process that produces aldehydes and alcohols from olefins, carbon monoxide, and hydrogen (eq 23).<sup>102</sup> The reaction was



discovered in 1938 by Roelen,<sup>103</sup> who detected the formation of aldehydes from olefins, carbon monoxide, and hydrogen in the presence of a cobalt-based catalyst. In the 1950s, it was found that rhodium was much more active than cobalt, and the use of rhodium complexed with phosphorous ligands was more effective. Since then, many improvements have been made on this process.<sup>101</sup> However, all of them involve the tedious separation of the catalyst and products from the reaction system. Later improvements were based on the attachment of a normally soluble catalyst to an

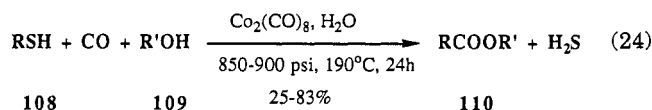


insoluble support, attempting to combine the virtues of both homogeneous and heterogeneous catalysts.<sup>104</sup> Unfortunately, this approach encountered the problems of metal leaching into the solvent, lowered activity or selectivity, and facile oxidation of the ligands.<sup>105</sup>

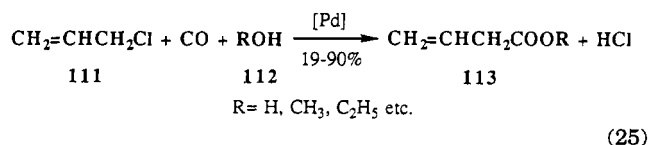
Recently, another approach to the catalyst and product separation has been developed based on the use of transition-metal complexes with water-soluble phosphine ligands [ $\text{Ph}_2\text{PPhSO}_3\text{Na}$ ,<sup>106</sup>  $\text{P}(m\text{-PhSO}_3\text{Na})_3$ ,<sup>101,107,108</sup> and  $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{NMe}_3^+$ <sup>109</sup>] and water as an immiscible solvent for the hydroformylation. Generally, the catalyst is a rhodium complex. Other metal complexes containing Pd, Ru, or Pt are also used occasionally. As the catalyst is practically insoluble in the aldehyde products, its recovery can be achieved by a simple phase separation. The hydroformylation reaction can also be performed by using methyl formate instead of carbon monoxide and hydrogen.<sup>110</sup>

## 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  $\beta,\gamma$ -unsaturated acids.<sup>111</sup> The requirements of a high carbon monoxide pressure and the low yield of the products limit the usefulness of the conventional carbonylation method in organic synthesis.<sup>112</sup> 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 and a cobalt catalyst.<sup>113,114</sup> Under high pressure and temperature, even benzylic mercaptans reacted similarly to give esters (eq 24).<sup>115</sup>



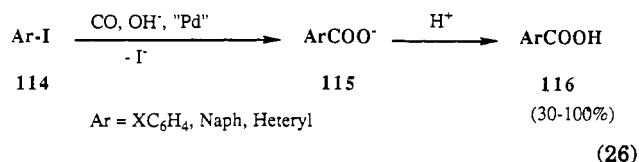
In the presence of a nickel catalyst, similar carbonylations of allyl bromide and chloride in aqueous NaOH could be carried out at atmospheric pressure.<sup>116</sup> The base concentration significantly influenced the yield and the product distribution. More recently, it was found that the palladium-catalyzed carbonylation of allyl chloride proceeded smoothly in a two-phase aqueous NaOH/benzene medium under atmospheric pressure at room temperature (eq 25).<sup>112</sup> Catalysts either with or without phosphorus ligands gave the same result, and the presence of hydroxide was essential. The reaction seemed to occur at the liquid-liquid interface, because no phase-transfer agent was used.



## 3. Carbonylation of Aryl Halides

The palladium-catalyzed carbonylation of aryl halides in the presence of various nucleophiles, is a convenient method to synthesize various aromatic carbonyl compounds (e.g., acids, esters, amides, thioesters, aldehydes, and ketones). Aromatic acids bearing different aromatic fragments and having various substituents on

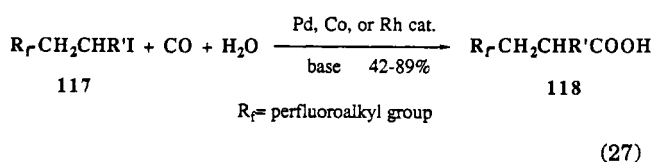
the benzene ring have been prepared from aryl iodides at room temperature under 1 atm of CO in a mixed solvent of H<sub>2</sub>O/DMF (1/1 or 1/2, v/v), and even in water alone, depending on the solubility of the substrate (eq 26).<sup>117</sup> The palladium(II) complexes,  $\text{Pd}(\text{OAc})_2$ ,  $\text{K}_2\text{PdCl}_4$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ , and  $\text{Pd}(\text{NH}_3)_4\text{Cl}_2$ , are used as the precursors of the catalyst, using either  $\text{K}_2\text{CO}_3$  or  $\text{NaOAc}$  as the base.



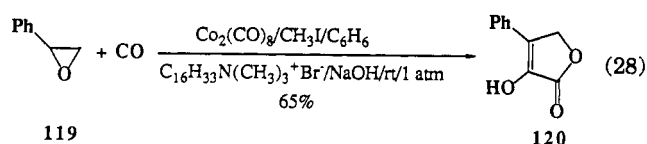
Under the appropriate conditions of pressure and temperature, aryl mercaptans (thiophenols) can also be carbonylated in aqueous media with cobalt carbonyl as the catalyst.<sup>118</sup>

## 4. Other Carbonylation Reactions

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  $\beta$  position (eq 27).<sup>119</sup> Rhodium complexes also catalyze the carbonylation of both terminal and internal acetylenes.<sup>120</sup>

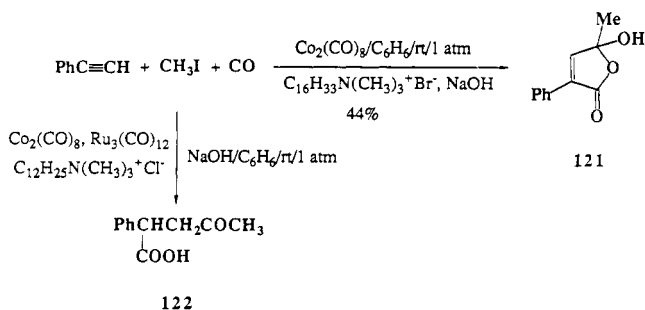


Biscarbonylation in aqueous media has also been reported. The reaction of methyl iodide with styrene oxide and carbon monoxide catalyzed by a cobalt complex resulted in the incorporation of two molecules of carbon monoxide, giving the enol 120 (eq 28).<sup>121</sup>

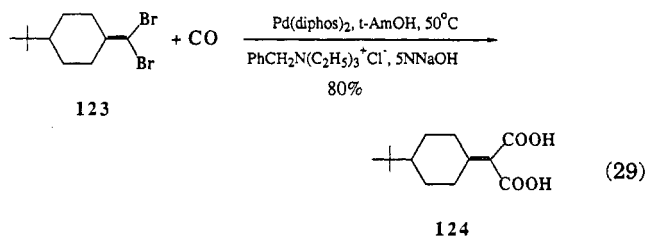


Similarly, reaction of methyl iodide with alkynes and carbon monoxide resulted in the formation of 2-butenolides 121. If the reaction mixture was first treated with the cobalt complex and then reacted with a ruthenium carbonyl complex, the  $\gamma$ -keto acids 122 were obtained (Scheme XIII).<sup>122</sup>

## Scheme XIII

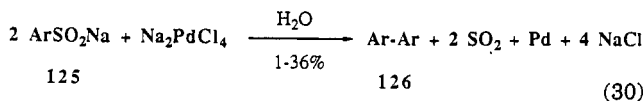


Biscarbonylation of the vinylic dibromide **123** by carbon monoxide in NaOH solution gave the unsaturated diacid **124** in the presence of a palladium catalyst (eq 29).<sup>123a</sup> By using palladium chloride as a catalyst in a water/THF mixture, biscarbonylation products were also formed from the carbonylation of terminal alkynes with formic acid.<sup>123b</sup>

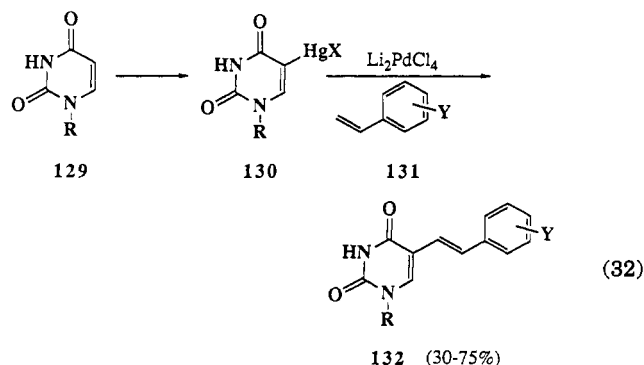
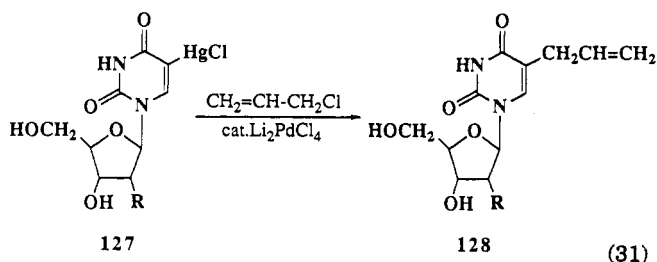


## B. Alkylation and Coupling Reactions

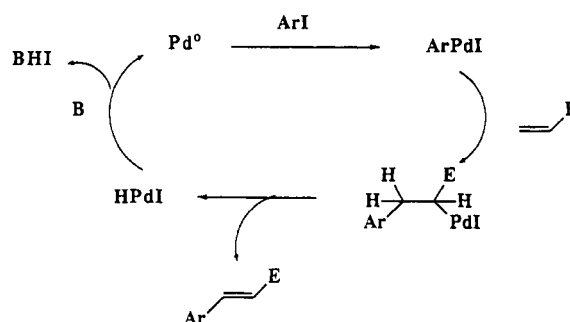
As early as in 1970, arylsulfonic acids were coupled to biaryls with Pd(II) in aqueous solvents (eq 30).<sup>124</sup> In the presence of carbon monoxide and olefins or nitriles, insertion reactions took place leading to the carbonylation, vinylation, or acylation of arenesulfinate anions in low to moderate yields.



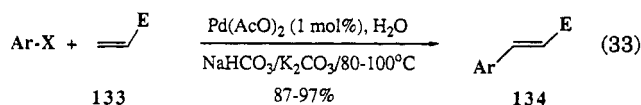
Recently, C-5-substituted pyrimidine nucleosides **128** were synthesized in aqueous media via the mercurated intermediate **127** using  $\text{Li}_2\text{PdCl}_4$  as a catalyst (eq 31).<sup>125</sup> Palladium(II)-catalyzed coupling of the 5-mercuriuridines **130** with styrenes in aqueous media resulted in alkylation of the uracil nucleotides (eq 32).<sup>126</sup> The reaction was not affected adversely by the presence of phosphate groups or sugar hydroxyls and was compatible with nitro, amino, and azido substitution on the phenyl ring of the styrene. A similar reaction was used in the synthesis of 5-(3-aminoallyl)uridine and deoxyuridine-5'-triphosphates (AA-UTP and AA-dUTP).<sup>127</sup>



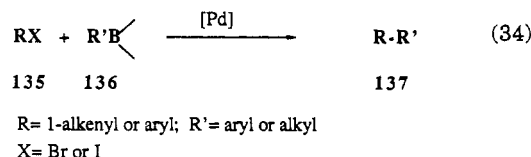
## Scheme XIV



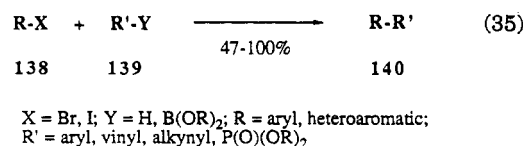
Palladium-catalyzed reactions of aryl halides with acrylic acid and acrylonitrile gave the corresponding coupling products in high yields with a base ( $\text{NaHCO}_3$  or  $\text{K}_2\text{CO}_3$ ) in water (eq 33).<sup>128</sup> The reaction provided a new and simple method for the synthesis of substituted cinnamic acids and cinnamionitriles. The catalytic cycle of this reaction was proposed as in Scheme XIV. Recently, such reactions were carried out by using a water-soluble phosphine ligand.<sup>129</sup>



The cross-coupling reaction of 1-alkenyl and aryl halides with organoboranes 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 34).<sup>130</sup> Very recently,



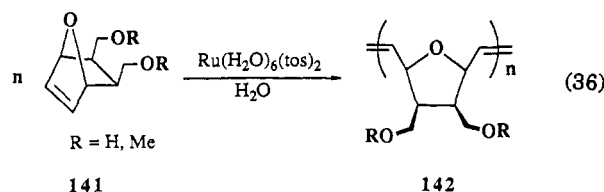
Casalnuovo and Calabrese reported that by using the water-soluble palladium(0) catalyst  $\text{Pd}(\text{PPh}_2(m\text{-C}_6\text{H}_4\text{-SO}_3\text{M}))_3$  ( $\text{M} = \text{Na}^+, \text{K}^+$ ) various aryl bromides and iodides reacted with aryl and vinyl boronic acids, terminal alkynes, and dialkyl phosphites to give the cross-coupling products in high yields in water (eq 35).<sup>131</sup> The reaction could tolerate a broad range of functional groups, including those present in unprotected nucleotides and amino acids. Terminal alkynes were also coupled with allyl bromides using a copper(I) and phase-transfer catalyst.<sup>132</sup>



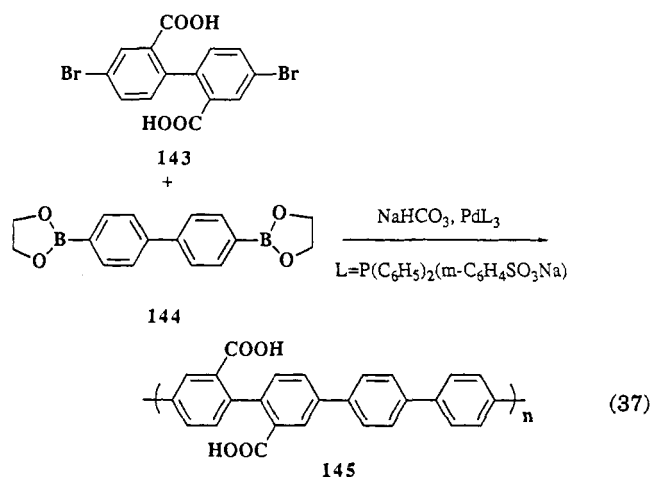
## C. Polymerization Reactions

The first attempt<sup>133</sup> at emulsion polymerization of norbornenes in aqueous solution was reported in 1965 using iridium complexes as catalysts. Recently, Novak and Grubbs reported that 7-oxanorbornene derivatives rapidly polymerized in aqueous solution under an air atmosphere using some selected group VIII coordination complexes as catalysts, providing a quantitative yield of a ring-opening metathesis polymerization (ROMP)

product (eq 36).<sup>134a</sup> A similar ring-opening metathesis polymerization reaction occurred with norbornene.<sup>134b</sup>



Compared with the same reaction carried out in organic solvent, the initiation time decreased from 22–24 h to 30–35 min. After the polymerization, the aqueous catalyst solution not only could be reused but also became more active in subsequent polymerizations and the initiation period dropped to only 10–12 s. Solutions containing these aqueous catalysts have been recycled for 14 successive polymerizations without any detectable loss of activity. This extraordinary stability to air and water displayed by the normally highly reactive organometallic intermediates (metal carbenes and/or metallacyclobutanes) suggested the intriguing possibility that aqueous coordination complexes might find a wider application in other established (but sensitive) catalytic processes. A hydrocarbon nonmetallic conducting polymer with a rigid rod of benzene rings was synthesized recently from two biphenyl compounds via the Suzuki reaction in water.<sup>135</sup> The reaction was catalyzed by a water-soluble palladium catalyst (eq 37).



## V. Miscellaneous Reactions

In addition to the reactions surveyed above, there are still other reactions that are frequently carried out in aqueous media.<sup>136</sup> Addition reactions of HCN to carbon-hetero multiple bonds, such as cyanohydrin formation reactions,<sup>137</sup> the Strecker synthesis,<sup>138</sup> and C=N or C≡N addition reactions,<sup>139</sup> have all been performed in aqueous media. The addition of an olefin to formaldehyde, namely the Prins reaction, has often been carried out in water in the presence of an acid catalyst.<sup>140a</sup> An ene-iminium one-pot cyclization proceeds smoothly in aqueous media. The reaction has been used in the asymmetric synthesis of pipercolic acid derivatives.<sup>140b</sup> Wittig olefination reactions with stabilized ylides are sometimes performed in an organic/water biphasic system.<sup>141</sup> Diazo-carbonyl compounds react with trialkylboranes in aqueous media to produce

the coupled products. The benzoin condensation reaction consists of treating an aromatic aldehyde with potassium cyanide or sodium cyanide usually in an aqueous ethanolic solution.<sup>136</sup> Recently, Breslow studied the effects of inorganic salts on the rate of the cyanide-catalyzed benzoin condensation in aqueous media.<sup>142</sup> Acceleration of the reaction by hydrophobic effect was observed.

## VI. Conclusion

This article provides the first general review of organic reactions in aqueous media. The review has shown the diversity and potential usefulness of carrying out organic reactions in aqueous media. The exact role of water in these reactions is still not well understood. Nevertheless, the advantages of using water as solvent for organic reactions are numerous. An aqueous media is both economical and avoids usage of inflammable organic solvents. Protection-deprotection processes, product isolation, and catalyst recycling are simplified. With the present growing concern about our environment and our future resources, the use of water in organic reactions thus will become more applicable in the future of organic chemistry. Rapid development of this field could therefore be envisioned.

## VII. Acknowledgments

The author is deeply grateful to Prof. T. H. Chan for his advice and help during the preparation of this manuscript. Thanks are also given to McGill University and NSERC for the Fellowships as well as to Profs. B. M. Trost and D. N. Harpp for their encouragement.

## Notes Added in Proof

Aqueous Diels-Alder reactions were recently used for the syntheses ofazole antifungals (Saksena, A. K.; Girijavabhan, V. M.; Chen, Y. T.; Jao, E.; Pike, R. E.; Desai, J. A.; Rane, D.; Ganuly, A. K. *Heterocycles* **1993**, *35*, 129) as well as for the syntheses of 3-deoxy-D-manno-2-octulosonic acid (KDO), 2-deoxy-KDO, and thioglycoside of KDO (Lubineau, A.; Auge, J.; Lubin, N. *Tetrahedron* **1993**, *49*, 4639). Aqueous Diels-Alder reactions were catalyzed by scandium trifluoromethanesulfonate (Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitan, H. *Tetrahedron Lett.* **1993**, *34*, 3755). Aldimines were coupled by indium under aqueous conditions (Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, *34*, 1647). A ruthenium-catalyzed addition of alkenes to acetylenes was recently reported in a mixture of DMF and water (Trost, B. M.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 4361). Palladium-mediated coupling reactions of aryl and vinyl halides with olefins were further studied (Zhang, H. C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499; Genet, J. P.; Blart, E.; Sarignac, M. *Synlett* **1992**, 715).

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