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AQUEOUS BARBIER-GRIGNARD TYPE REACTION: SCOPE, MECHANISM, AND SYNTHETIC APPLICATIONS

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I. Introduction

Since the discovery of the formation of alkylzinc compounds by Frankland from the reaction of iodoalkanes with metallic zinc,[1] the use of organometallic reagents for organic synthetic purposes has been growing in scope and in importance.[2] The successes of Reformatsky,[3] Barbier,[4] Grignard,[5] and Gilman are among the milestones in this development. More recent progress includes the use of lithium and other metals. In their most general form, these reagents serve as nucleophiles, and lead to carbon-carbon bond formations. When the reactant electrophile is a carbonyl compound, the transformations are now frequently referred to as Barbier-Grignard type reactions (Eq. 1). The generation of the organometallic reagents can be in situ (Barbier) or stepwise (Grignard). A major requisite in these cases is the strict exclusion of moisture. Such a restriction can impose limitations on synthetic design in which various acidic hydrogens in the substrates have to be protected.

(Eq. 1)

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.[6] And in the 1960's, tribenzylstannyl halide was produced in large scale in water.[7] Wurtz-type reductive coupling of allyl halides proceeded in aqueous alcohol.[8] These reports indicated the possibility of carrying out these kinds of reactions in water under special circumstances.

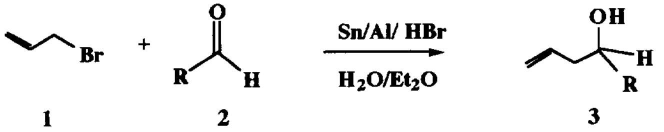
In 1977,[9] Wolinsky *et al.* observed that allylation of carbonyl compounds with allyl bromide mediated by zinc could be carried out in 95% ethanol and t-butyl alcohol. However, only a moderate yield was obtained. Since that time, significant progress has been made showing that the reaction can be carried out in aqueous medium through the use of a variety of metal mediators. These metals include zinc, tin, indium, bismuth, lead, and cadmium. It can be rationalized that these metals are relatively "soft" and are not readily affected by the "hard" solvent water.

The use of aqueous media for Barbier-Grignard type reactions offers considerable advantages:[10] There is the practical convenience of not having to handle inflammable and anhydrous organic solvents. The tedious protection-deprotection processes for certain acidic-hydrogen containing functional groups can be simplified, which contributes to the overall synthetic efficiency. Water-soluble compounds, such as carbohydrates, can be used directly without the need of derivatization. Such processes greatly reduce the burden of solvent disposal and its impact upon environment. This report summarizes developments in the use of aqueous media for Barbier-Grignard type reactions. Mechanistic considerations and stereochemistry, as well as limitations, of these reactions are also included. We hope that the review provides non-specialists with some insight into this field and serves as a helpful tool in the design of synthetic strategies in the future.

This review strived to include all relevant information in this area to the best of the author's knowledge. I apologize if any important contributions have been overlooked. In such a case, your correspondence is very much appreciated.

II. Mediated by Tin

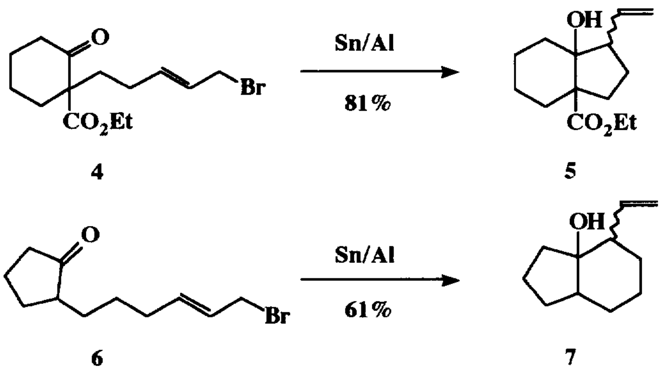
In 1983, Nokami *et al.* observed an acceleration of reaction rate during the allylation of carbonyl compounds with diallyltin dibromide in ether through the addition of water to the reaction mixture.[11] In one case, by use of a 1:1 mixture of ether/water as solvent, benzaldehyde was alkylated in 75% yield in 1.5 h, while the same reaction only gives 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 (Eq. 2). 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.



(Eq. 2)

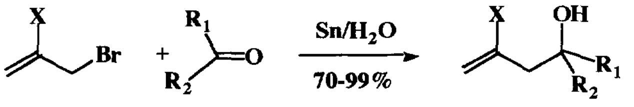
The reaction can also proceed intramolecularly. By use of the combination of tin, aluminum, and hydrobromic acid in aqueous medium, ketones having allylic halide functionality such as **4** and **6** were cyclized to form five and six membered rings (Scheme 1).[12] Similar reactions occurred with aldehydes.[13]

Scheme 1.



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.[14] 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.[15] 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.[16]

Otera *et al.* extended the tin mediated allylation to 2-substituted allyl bromides.[17] When 2-bromo and 2-acetoxy-3-bromo-1-propene were used, the allylation with tin produced the corresponding functionalized coupling products (Eq. 3). In the case 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.

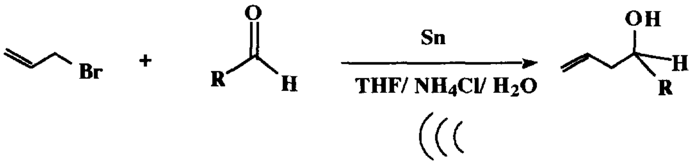


(Eq. 3)

8 9

X= Br, Cl, OAc.

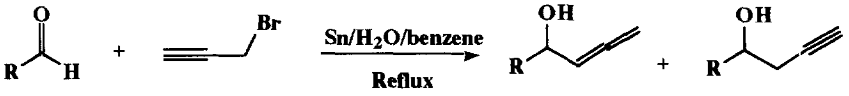
Luche found that tin mediated allylations can also be performed through ultrasonic radiation, instead of using aluminum powder and hydrobromic acid to promote the reaction (Eq. 4).[18,19] The use of a saturated aqueous NH_4Cl/THF solution, instead of water/THF, dramatically increased the yield. When a mixture of aldehyde and ketone was subjected to the reaction, highly selective allylation of the aldehyde was achieved.



(Eq. 4)

The allylation of carbonyl compounds in aqueous media with $SnCl_2$ can also employ allylic alcohols[20] or carboxylates[21] in the presence of a palladium 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.

The reaction of propargyl bromide with aldehydes mediated by tin in water generated a mixture of propargylation and allenylation products (Eq. 5). The selectivity in product formation is rather low.[22]



(Eq. 5)

10 11 12

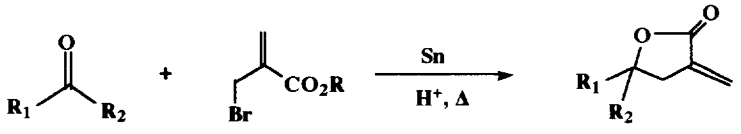
Allylations, allenylations, and propargylations of carbonyl compounds in aqueous media can also be carried out with preformed organic tin reagents, rather than by use of metals.[23, 24, 25,26] As reported by

Grieco *et al.*,[27] allylation with preformed allylstannane can be applied to immonium salts generated in situ from primary amines and formaldehyde (Eq. 6).

$$\underset{\mathbf{13}}{RNH_2.TFA} + \underset{\mathbf{14}}{Bu_3SnCH_2CH{=}CH_2} \xrightarrow[H_2O\text{-}MeOH\text{-}CHCl_3]{HCHO} \underset{\mathbf{15}}{RN(CH_2CH_2CH{=}CH_2)_2} \qquad \text{(Eq. 6)}$$

(78-100%)

The reactions of bromoacrylic acid and carbonyl compounds with Sn/Al,[28] $SnCl_2$/AcOH,[29] or $SnCl_2$/Amberlyst 15[30] in aqueous media under reflux conditions give 2-methylene-4-butyrolactones (Eq. 7) (**17**). A similar reaction occurs with the corresponding ester.[31] Normal α-halo carboxylic esters did not react under these conditions. Since substrate **16** is structurally an allylic halide, the reaction can be regarded as an allylation.



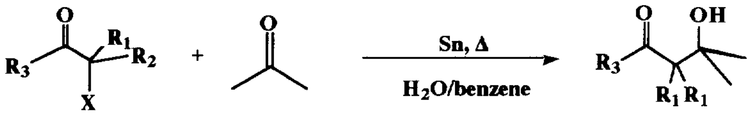
16 **17**

(Eq. 7)

Aldol reactions are well known ways to form carbon-carbon bonds.[32] However, under the classical crossed aldol conditions involving basic media, dimers, polymers, or mixtures of α,β-unsaturated carbonyl compounds often are produced as well. The formation of these products is attributed to the fact that the aldol reaction is an equilibrium process.[33] Useful modifications, especially by use of Lewis acid-promoted reactions of enol, silyl, or tin ethers with carbonyl compounds,[34,35] have been developed to alleviate these difficulties. These modifications typically include the use of an organic solvent as the reaction medium 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.[36] The crossed aldol addition products showed only a slight syn diastereoselectivity, 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.[37] Among the 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 addition product; the diastereoselectivities of these reactions were moderate. Water soluble aldehydes can be used directly, and the catalyst could be recovered and reused in this procedure.

The reaction of an α-halogen carbonyl compound with a metal and an aldehyde in water gave a direct cross-aldol product through the Barbier-Type reaction (Eq. 8).[38]



18 19

(Eq. 8)

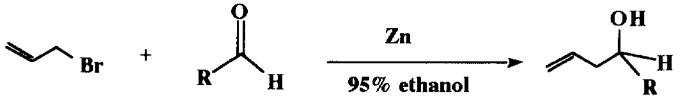
A direct Reformatsky type process occurred when an aromatic aldehyde reacted with an α-bromoester in water mediated by tin (Eq. 9).[39] However, the reaction gave only a low yield of the product, and aliphatic aldehydes failed to react.

20 21

(Eq. 9)

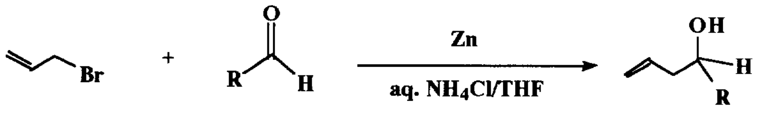
III. Mediated by Zinc

In 1977,[40] 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 or t-butyl alcohol at 78-95°C gave allylation products in yields comparable to those obtained in aprotic solvents (Eq. 10). Prior to this report, Wurtz type coupling of allyl halides was (in low yields) the normal outcome in refluxing alcohol.[41]



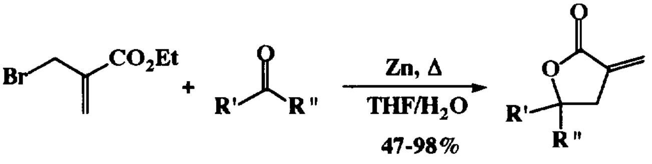
(Eq. 10)

Then, in 1985 Luche *et al.* found that allylation of aldehydes and ketones can be effected in aqueous media using zinc as the metal and THF as a cosolvent under sonication conditions (Eq. 11).[42,43] The replacement of water by aqueous saturated ammonium chloride solution enhanced the efficiency. In this case, comparable results were obtained either with or without the use of sonication.



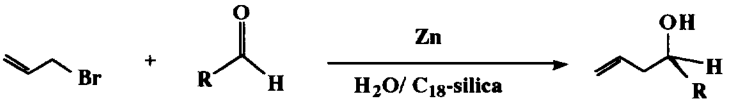
(Eq. 11)

In the same year, Benezra *et al.* reported[44] 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. 12). The same reaction 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.



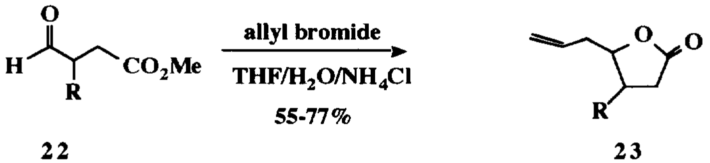
(Eq. 12)

Later, Wilson carried out a more detailed study of zinc mediated reactions in water[45] through a modification involving the use of a solid organic support instead of the cosolvent THF (Eq. 13). 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, and 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.



(Eq. 13)

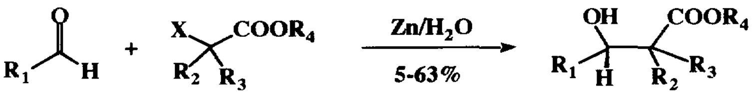
Kunz and Reißig reported[46] the zinc mediated allylation of methyl γ-oxocarboxylates **22** in a mixture of saturated aqueous ammonium chloride and THF (Eq. 14). The reaction provides a convenient synthesis of 5-allyl-substituted γ-lactone **23**.



22 **23**

(Eq. 14)

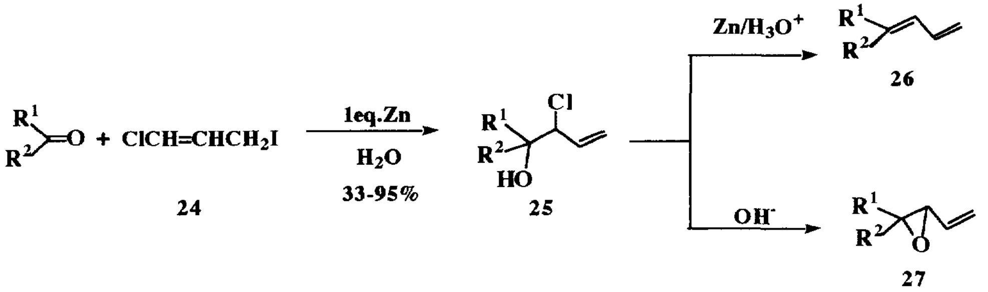
The combination of an α-halogen carbonyl compound with zinc and an aldehyde in water gave a direct cross-aldol addition product.[47] A direct Reformatsky type conversion occurred when an aromatic aldehyde reacted with an α-bromo ester in water mediated by zinc (Eq. 15).[48] Similar to the case of tin, the reaction gave only a low yield of the product, and aliphatic aldehydes failed to react.



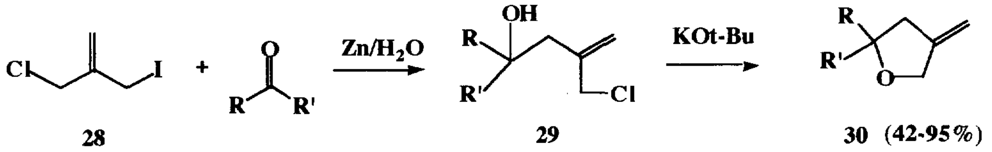
(Eq. 15)

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.[49] The use of 3-iodo-1-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 (Scheme 2). Similarly, reactions of carbonyl compounds with 3-iodo-2-chloromethyl-1-propene followed by base treatment produced 2-methylenetetrahydrofurans (Scheme 3).[50] Thus, the 3-iodo-2-chloromethyl-1-propene here served as a novel trimethylenemethane equivalent.[51]

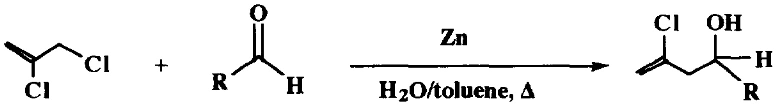
Scheme 2.



Scheme 3.



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 small amount of acetic acid gave 2-chloroallylation products (Eq. 16).[52] The reaction has been applied to large scale industrial synthesis.[53] 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.[54]

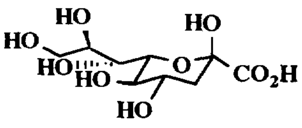


31 **32** **(Eq. 16)**

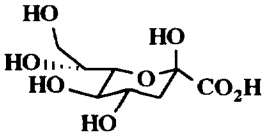
Very recently, Reisse used "activated" zinc for aqueous Barbier-type reactions.[55] Zinc powder produced by pulsed sono-electro reduction is about three times more effective than the commercial variety.

IV. Mediated by Indium

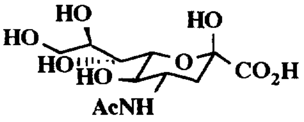
In 1990, Li and Chan reported the use of indium to mediate Barbier-Grignard type reactions in water.[56] The work was an outgrowth of developing an aqueous strategy toward the synthesis of sialic acids, *e.g.* (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **33**), 3-deoxy-D-manno-octulosoic acid (KDO, **34**) and N-acetyl-neuraminic acid (**35**), through the coupling of a sugar with ethyl (2-bromomethyl)acrylate. While the reactions of carbonyl compounds with (2-bomomethyl)acrylate mediated by zinc and tin were known, they are not suitable for the sialic acid synthesis owing to the harsh conditions associated with these reactions. Hence, a more reactive metal was needed.



33 (+) KDN



34 (+) KDO



35 (+) neuraminic acid

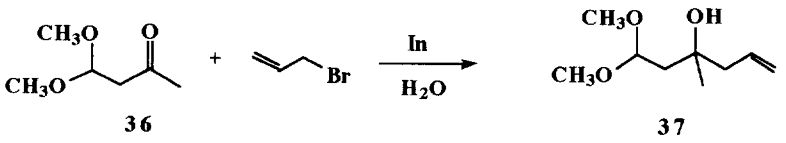
By examining the first ionization potentials of different elements,[57] they found that indium has the lowest first ionization potential relative to the other metal elements near it in the periodic table. In fact, the ionization potential of indium is on the same level with the most active alkali metals and was much lower than that of zinc or tin, or even of magnesium (Table 1). 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 indium is the most reactive and effective metal for such reactions.

Table 1. First Ionization Potential of Some Metals

Metal	Indium	Magnesium	Zinc	Tin	Lithium	Sodium
First Ionization Potential (ev)	5.79	7.65	9.39	7.43	5.39	5.12

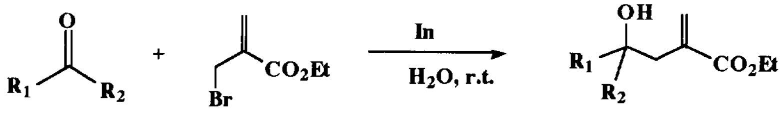
Obtained from *CRC Handbook of Chemistry and Physics*. 75th ed., CRC Press, 1994.

When the allylation was 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. An organic cosolvent is not necessary either. The mildness of the reaction conditions make it possible to use the indium method to allylate a methyl ketone **36** in the presence of an acid sensitive acetal functional group (Eq. 17). Attempts to achieve such transformations with zinc and tin have not been successful. 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 (Eq. 18).



(Eq. 17)

M	Yield, %
Zn	0 and destruction of starting materials
Sn	10 (under sonication)
In	70

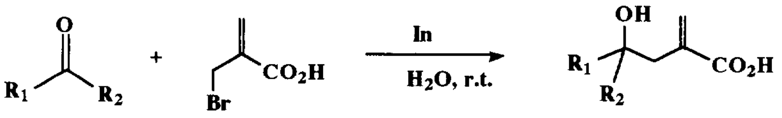


(Eq. 18)

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.[58] This reaction was typically performed in a THF-water (5:2) mixture at room temperature. However, with this method, the conversion is much slower, relative to the same reaction mediated by use of a stoichiometric amount of indium; it requires days to complete. When the reaction was carried out in anhydrous THF, the yield dropped considerably, while side-reaction (such as reducing to alcohol) increased. The combinations of Al-$InCl_3$ or Zn-$InCl_3$ gave comparable results.

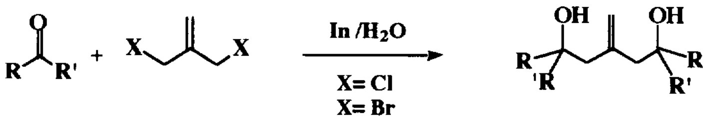
Recently, Whitesides *et al.* examined the effect of substituents on the allylic moiety on the indium mediated reactions in water and found that the use of indium at room temperature gave results comparable to those of tin-mediated reactions carried out at reflux. Replacement of the aqueous phase with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

More recently, Chan *et al.* reported that the carboxylic acid functionality on allyl halides is compatible with the indium-mediated reactions (Eq. 19).[59,60] 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. In some cases in which the indium powder and organic substrate clumps and makes the mixture difficult to stir, the addition of some ethanol is helpful. Interestingly, the addition of aprotic solvents, such as THF, completely shuts down the reaction.



(Eq. 19)

Li reported that combination of 2-halomethyl-3-halo-1-propene with carbonyl compounds mediated by indium in water generates bis-allylation products (Eq. 20).[61] The bromo compound is more effective here than the chloro analog. Such a system effectively constitutes a trimethylenemethane dianion (**40**) equivalent in water.

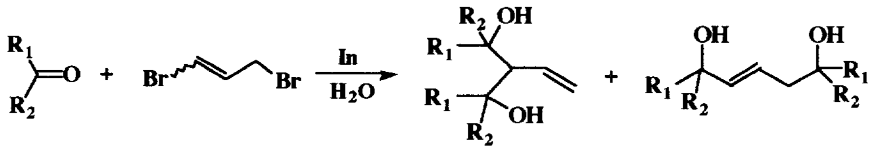


38 **39**

(Eq. 20)

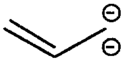
40

An unusual regioselectivity was observed by Li *et al.* during the bis-allylation of 1,3-dibromo-propene with carbonyl compounds mediated by indium in water (Eq. 21).[62] The reaction gave predominately 1,1-bisallylation product. Such a selectivity provides an allyl dianion (**44**) equivalent in water.



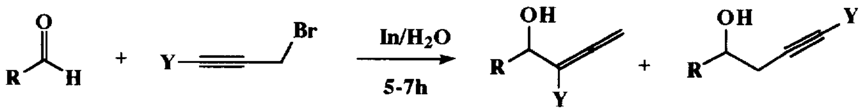
(Eq. 21)

41 **42** Major **43** Minor



44

Chan *et al.* reported the behavior of aldehydes with propargyl bromides in aqueous medium mediated by indium (Eq. 22).[63] 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.



(Eq. 22)

45 **46** **47**

Y= H	Minor	Major
Y= alkyl, aryl, or silyl	Major or exclusive	Minor

The indium mediated allylation carried out with allylstannanes in combination with indium chloride in aqueous medium was reported by Marshall *et al.*[64] Allyl indium was proposed as the reaction intermediate.

V. Mediated by Other Metals

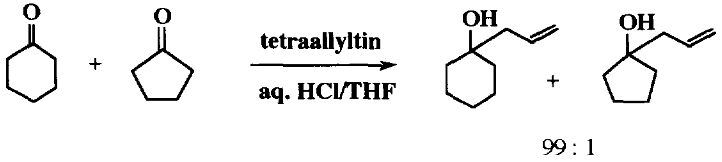
In addition to the those discussed above, other metals have been found to mediate the Barbier-Grignard type conversions in water, but investigations on these metals are very limited. Wada reported[65] that metallic bismuth can also be used for allylation in aqueous medium in a way similar to that of tin, in which aluminum powder and hydrobromic acid were used as the promoter. 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)/$BiCl_3$, and Fe(0)/$BiCl_3$. Later, Katritzky *et al.* found that the bismuth(III)-aluminum system also mediated the allylation of immonium cations to give amines.[66] 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.*[67] Lead and cadmium powder can also be used in such cases, but these metals are much less reactive than ones discussed previously.[57]

VI. Limitations

Although allylations in aqueous media have been very successful, attemted alkylations of carbonyl compounds in aqueous media with non-activated alkyl halides usually failed. Such results are presumably due to the higher ionization potentials of non-activated alkyl halides. Acyclic ketones other than methyl ketones are relatively unreactive under aqueous conditions.

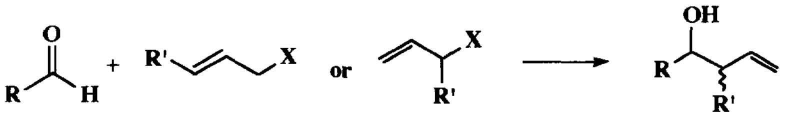
VII. Chemo, Regio, and Stereoselectivity

In a comparison of Barbier-Grignard type reactions in aqueous medium and in organic solvents, one of the most striking differences is the former's high chemoselectivity. Ordinarily, an aldehyde can be alkylated selectively in the presence of a ketone. As shown by Yamamoto [68]*et al.*, the selectivity is usually higher than 99%. Even a cyclohexanone can be selectively allylated in the presence of cyclopentanone (Eq. 23).



(Eq. 23)

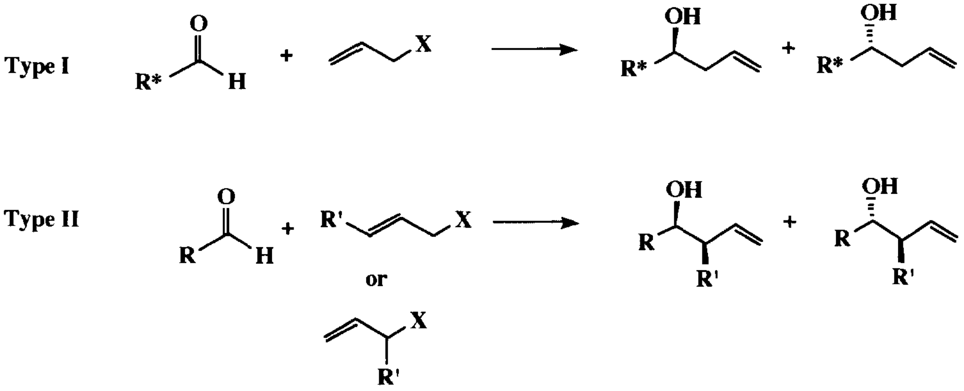
The second special aspect of the aqueous medium reaction is its regiochemistry of the allylic moiety. Both electronic and steric effects operate here. Usually, the carbon-carbon bond forms at the more substituted carbon of the allyl halide, irrespective of the position of halogen in the starting material (Eq. 24). However, the carbon-carbon bond forms at the less substituted carbon when the γ-substituents of allyl halides are large enough (e.g., trimethylsilyl or tert-butyl) as shown by Chan *et al.*[69] They have studied the regioselectivity in detail and have invoked a cyclic transition state to explain the results.



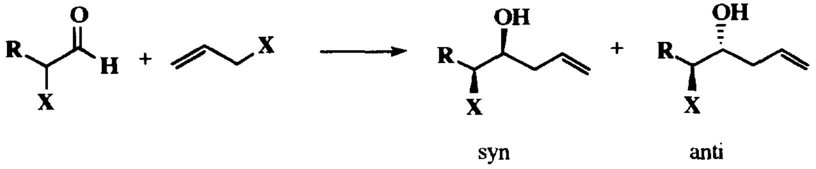
(Eq. 24)

The stereochemistry of the reaction in aqueous medium is somewhat analogous to that in organic medium. In terms of diastereoselectivity, two types of situation prevail (Type I and Type II) (Scheme 4). 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 (Scheme 5). However, when a weak α-chelating group (e.g., alkoxyl) is present, allylation in an organic solvent usually favors a chelation-controlled product. However the presence of an α-alkoxyl group will generate the non-chelating product through the aqueous reactions.[70] Thus, it is possible to reverse the diastereoselectivity of an allylation simply by use of either a free hydroxyl group or by protecting it as an alkoxyl. An application of such a selectivity change is utilized in the synthesis of muscarine, carried out by Chan and Li (see Section IX synthetic applications). A similar strategy was later used by Whitesides in a 3-deoxy-D-manno-octulosoic acid (KDO) synthesis (see synthetic applications).

Scheme 4.



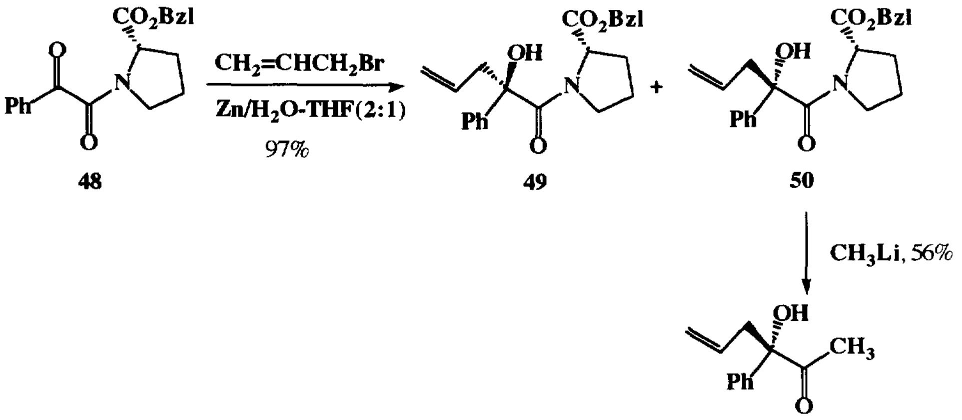
Scheme 5.



	syn	anti
X= strong α-chelating	major	minor
X= non- or weak α-chelating	minor	major

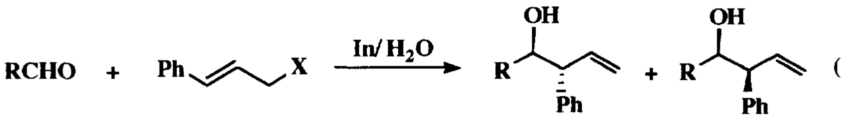
In the Type I situation, the stereogenic center can be farther away from the carbonyl group. Such an example can be found in Waldmann's studies of the diastereoselectivity of allylations using proline benzyl ester as a chiral auxiliary to produce α-hydroxyl amides. The diastereoselectivity was around 4~5:1 (Scheme 6).[71] Separation of the diastereomers followed by reaction with methyl lithium produced the enantiomerically pure alcohol **51**.

Scheme 6



48 **49** **50** **51**

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 (Eq. 25).[69]



52 **53a** **53b**

(Eq. 25)

	anti/syn
R= n-C_8H_{17},	69: 31
R= i-Propyl,	96: 4

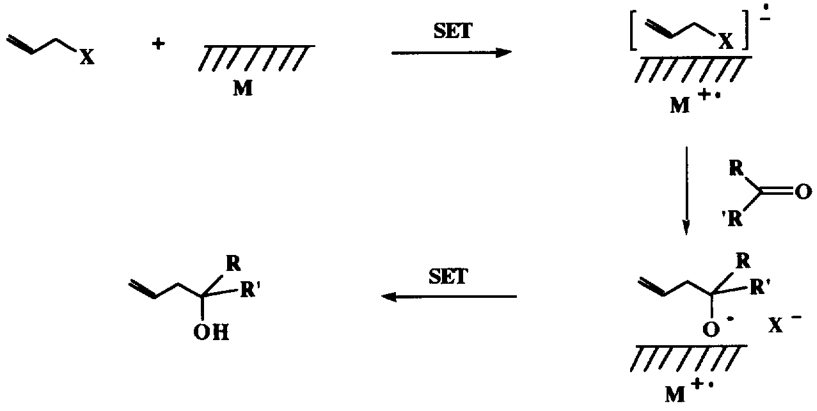
VIII. Mechanistic Discussion

Despite the successes of aqueous Barbier-Grignard reactions, their mechanisms are intriguing, since most organometallic reagents react violently with water. Luche *et al.* proposed that a radical pair process could be involved and has suggested that a radical derived from the halide attacks the carbonyl group. Wilson *et al.* investigated such a mechanism by the use of a radical probe, but they did not observe any radical intermediate (Scheme 7). Furthermore, the proposed free-radical mechanism also contradicts the chemoselectivity associated with the allylation of α,β-unsaturated carbonyl compounds, in which exclusive 1,2-addition products are obtained, whereas radicals tend to undergo conjugated additions.

Scheme 7.

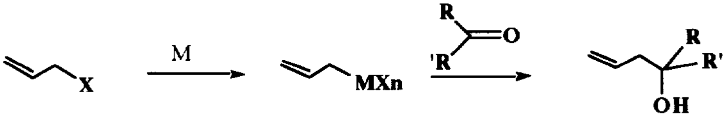
Chan and Li have proposed a mechanism involving a radical anion that is coordinated on the metal surface. In this pathway, a single electron transfer (SET) process is involved (Scheme 8).

Scheme 8.



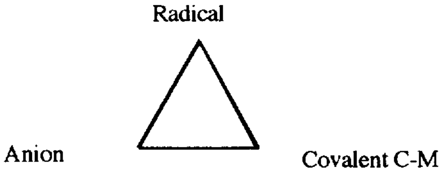
On the other hand, work by Whitesides, by Grieco, by Marshall, and by others has shown that it is possible to carry out alkylations in water with preformed allylmetal reagents (Scheme 9). Such results raise the possibility of a third mechanism involving a discrete organometallic intermediate.

Scheme 9.



In reality, an element of validity can be found in each of the proposed mechanisms. Possibly one mechanism might reflect the actual detail more than the others, depending on the metal, the substrates, and the reaction conditions. From these analyses, we can generalize the mechanism as a radical-anion-covalent (C-M) triangle (Scheme 10). In any given case the prefered pathway is within the triangle at an exact location determined by the substrates, the metal being used, and the reaction conditions. The three corners only represent extreme situations.

Scheme 10.

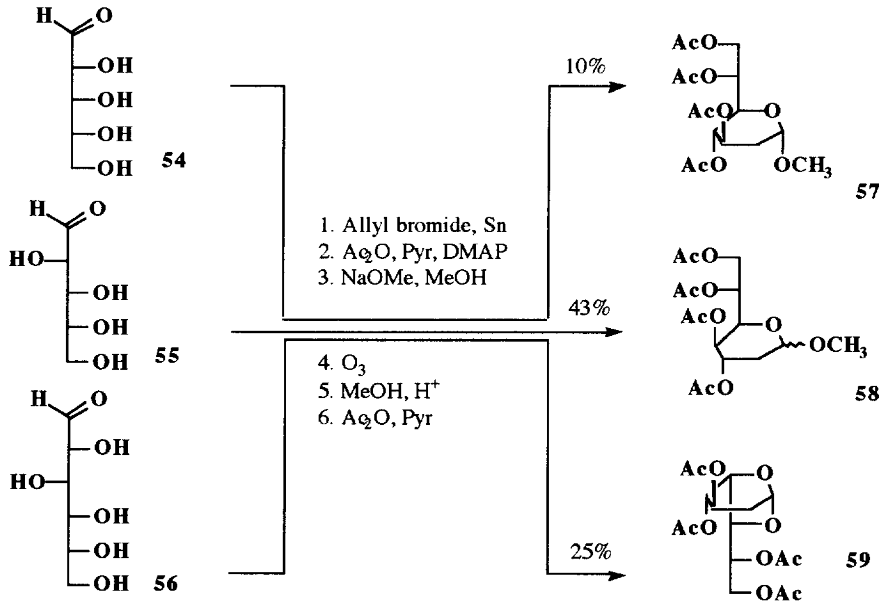


IX. Synthetic Applications

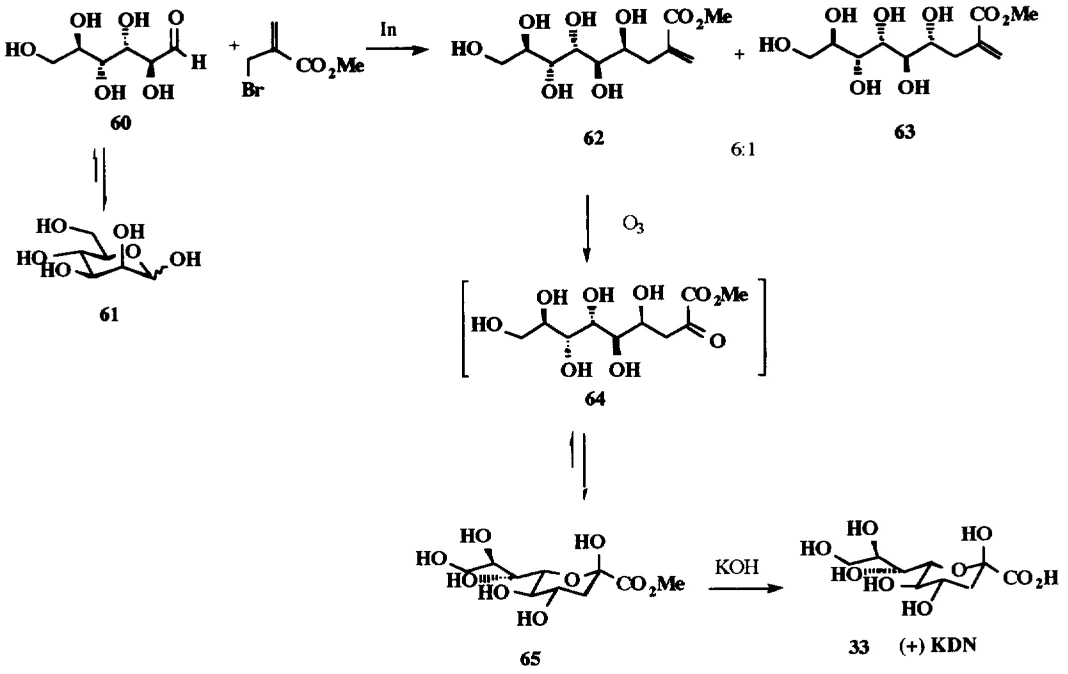
Because of its higher reactivity, the indium-mediated reaction in water developed by Li and Chan has found the widest applications in natural product synthesis so far. Synthetically, one of the most important features of carrying out organic reactions in water is that water-soluble hydroxyl-containing molecules can be used directly without involvement of protection-deprotection processes. As such, the most important application of aqueous Barbier-Grignard type reactions in organic synthesis are where the most extensive protection-deprotection processes are involved. A typical such area is in carbohydrate chemistry. Indeed, in 1991, Whitesides *et al.* reported the first application of aqueous medium Barbier-Grignard reaction to carbohydrate synthesis through the use of tin in an aqueous/organic solvent mixture.[72] The adducts were converted to higher carbon aldoses by ozonolysis of the deprotected polyols followed by suitable derivatization (Scheme 11). The reaction showed a higher diastereoselectivity when a hydroxyl group was present at C-2. However, no reaction was observed when an N-acetyl group was present at C-2.

Shortly afterwards, Chan and Li reported[73] an efficient synthesis of (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **33**)(Scheme 12), the first application of the aqueous medium reactions to synthesis of sialic acids, following their success in accomplishing the indium-mediated alkylation reaction in water. A similar attempt toward 3-deoxy-D-manno-octulonate (KDO, **34**) led primarily to the undesired diastereomer. However, through the disruption of the newly generated stereogenic center,[74] they completed a formal synthesis[75] of KDO (Scheme 13). In contrast to the tin mediated reactions, the indium mediated one also succeeded on a substrate with a C-2 N-acetyl group, which later led to the efficient synthesis of N-acetyl-neuraminic acid (neu5NAc, **35**).[57]

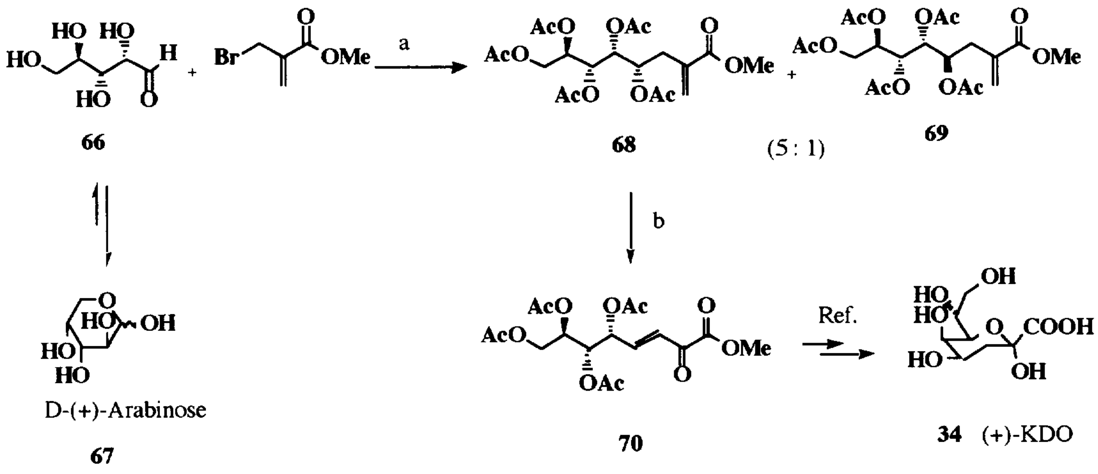
Scheme 11.



Scheme 12.



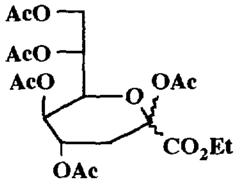
Scheme 13.



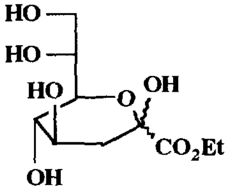
a). In/ H_2O, vigorous stirring, then Ac_2O/pyridine/4-dimethylaminopyridine, 79%; b). O_3/methylene chloride -78°C to r.t., then column chromatography; 67%.

Later, Whitesides *et al.* reported the synthesis of N-acetyl-neuraminic acid (**35**),[76] as well as other sialic acid derivatives (**71** and **72**) based on a similar strategy.[77] The use of indium is essential for the carbon-carbon bond forming step in these sialic acid syntheses. KDO was synthesized *via* indium mediated allylation of 2,3:4,5-di-O-isopropylidene-D-arabinose (Scheme 14).[78] In this case, the desired product predominated due to the protection of α-hydroxyl group.

35

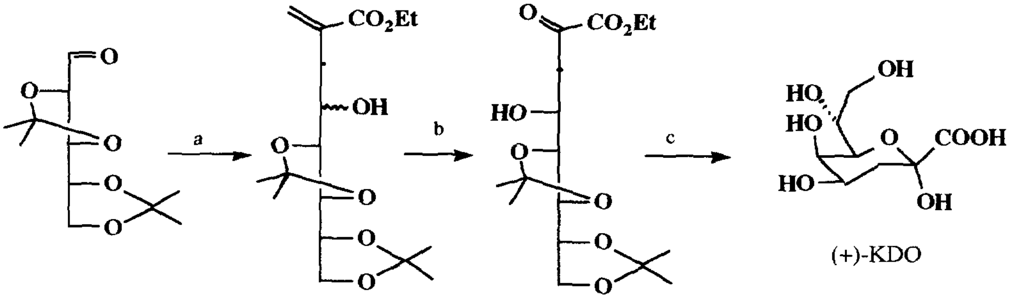


71



72

Scheme 14.

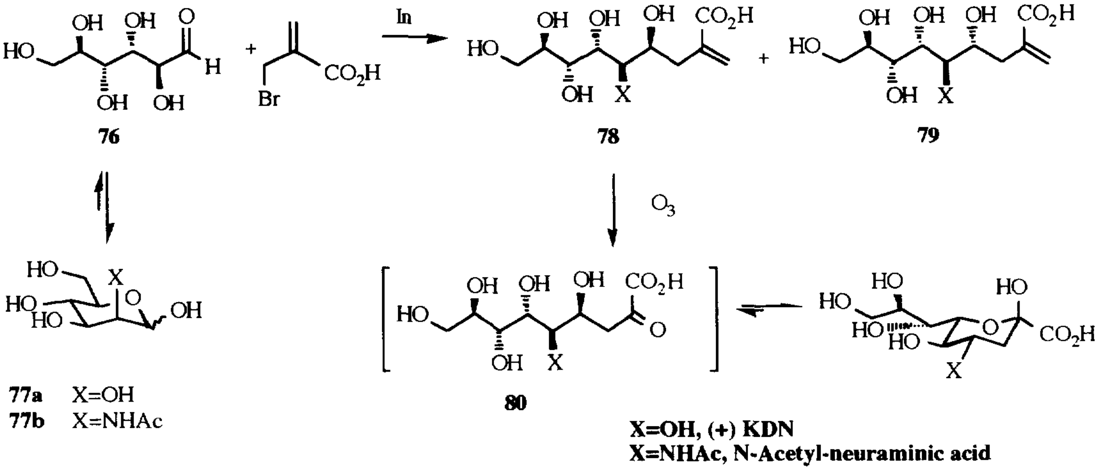

(+)-KDO

73 **74** erythro: threo = 2: 1 **75**

a). In/ethyl α-(bromomethyl)acrylate, 10% formic acid, aqueous MeCN, 61%; b). O_3, MeOH, -78°C to r.t. 92%, c). Trifluoroacetic acid, NH_4OH, 55%.

Recently, Chan *et al.* made more progress in sialic acid synthesis and have further shortened the already short route to two steps through the indium mediated reaction of α-(bromomethyl)acrylic acid with sugars (Scheme 15). Both KDN and N-acetyl-neuraminic acid were synthesized in this way.[79]

Scheme 15.



76 78 79

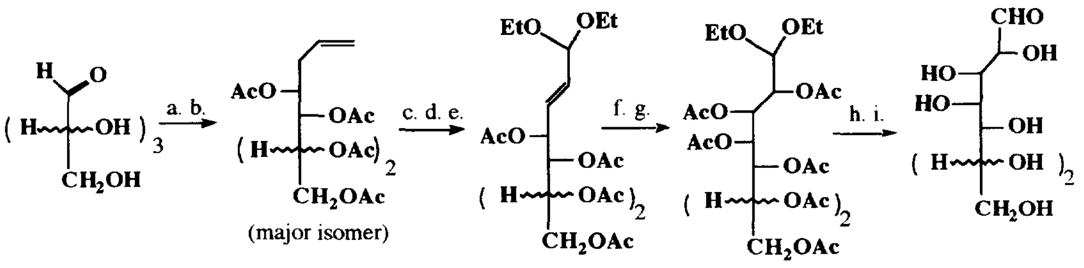
77a X=OH
77b X=NHAc

80

X=OH, (+) KDN
X=NHAc, N-Acetyl-neuraminic acid

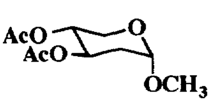
The indium mediated allylation was recently applied by Schmid *et al.* to elongation of the carbon chain of carbohydrates to produce higher analogs (Scheme 16)[80] and to deoxy sugars (**86-89**).[81]

Scheme 16.

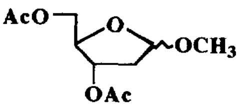


81 **82** **83** **84** **85**

a. In/allyl bromide, ultrasound; b. Ac_2O/pyridine/4-dimethylaminopyridine; c. OsO_4, KIO_4; d. TBAF; e. $H^+/HC(OEt)_3$; f. OsO_4, N-methylmorpholine N-oxide; g. Ac_2O/pyridine/4-dimethylaminopyridine; h. NaOMe/MeOH; i. H^+.



86



87

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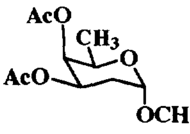
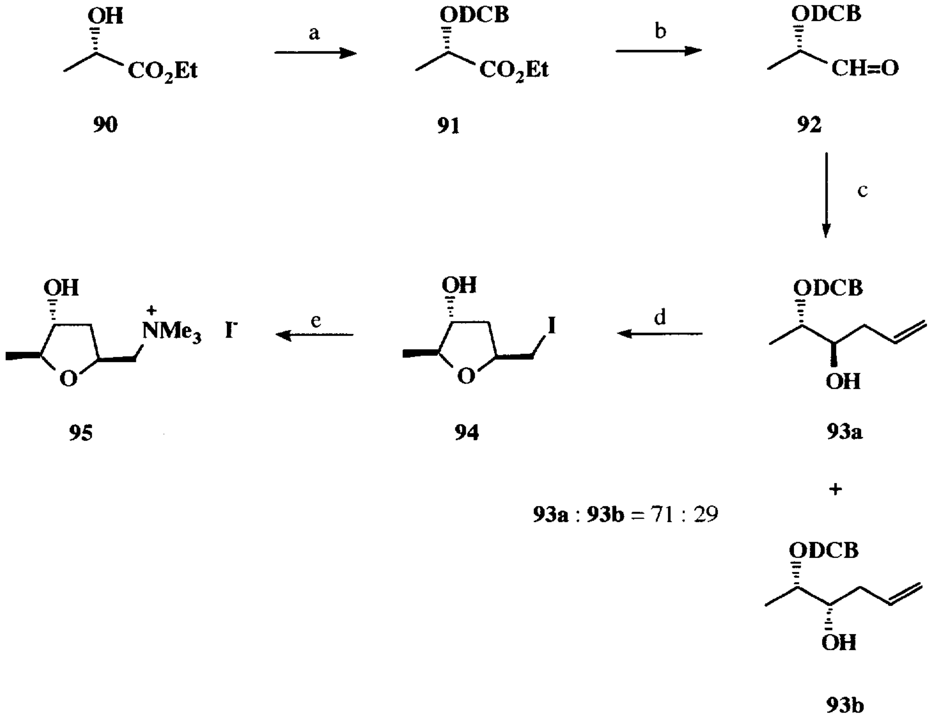


89

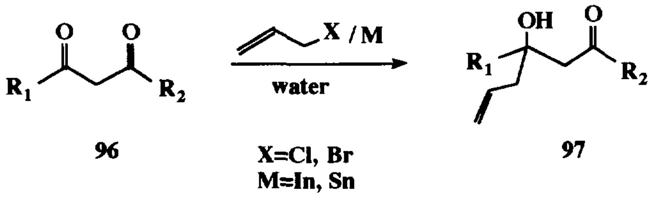
The aqueous Barbier-Grignard type reaction has also been employed in non-carbohydrate synthesis. Chan and Li used zinc mediated allylation as a key step in a total synthesis of (+)-muscarine (**95**)(Scheme 17).^{82,83} The strategy was based on the discovery that the diastereoselectivity of the allylation in water can be reversed through protection of the α-hydroxyl group.

As reported by Li *et al.*, enolizable 1,3-dicarbonyl compounds undergo efficient carbonyl allylation in aqueous medium through such a reaction (Eq. 26).^{84} The transformation is general and a variety of 1,3-dicarbonyl compounds have been alkylated successfully by use of allyl bromide or allyl chloride in conjunction with either tin or indium. The allylation in water can also be used to prepare α,α-difluorohomoallylic alcohols from *gem*-difluoro allyl halides as reported by Burton *et al.*^{85}

Scheme 17



(a). 2,6-Dichlorobenzyl bromide/ Ag_2O/ Et_2O/ reflux/ 6h (90%); (b) DIBAL-H / Et_2O/ -78°C/ 2h; (c) allyl bromide/ Zn/ H_2O/ NH_4Cl/ 3h (85%, two steps); (d) I_2/ CH_3CN/ 0°C/ 3h (85%); (e) NMe_3/ EtOH/ 80°C/ 4h (60%).



(Eq. 26)

X. *Conclusion*

In spite of their synthetic power as demonstrated in this review, the study and application of Barbier-Grignard type reactions in water are still at their infancy. Since their history is only a decade old, the full synthetic potential of such reactions is still waiting to be explored and they need to be extended to non-activated alkyl halides. For this, more active and more efficient mediators than indium and other currently used metals have to be discovered. Factors that affect the stereochemistry of the reactions need to be tailored in order to control stereoselectivity. Enantioselective synthesis through such aqueous reactions has yet to be explored and certainly will be one of the most important developments for the future. In this respect, promising progress is already underway in several laboratories.[86] Thus, it can be expected that the use of aqueous solvents for Barbier-Grignard type reactions will be an important chapter in the history of organometallic reactions.

XI. *Acknowledgments*

The author is particularly grateful to Prof. T. H. Chan for stimulating and cultivating his interests in this special field. Our research contributions in this area are attributed to a group of dedicated co-workers including Dr. D. Wang, Messieurs J. X. Haberman, Y. Q. Lu, D. L. Chen, W. Slavern, X. H. Yi, and D. T. Tran. We are grateful to our colleagues at Tulane, to Tulane University's Committee on research, to the Eli Lilly Teaching Committee, and to the U.S. Department of Energy for their support of our programs in various forms. Finally, the author would like to thank Profs. A. Nickon, T. H. Chan, S. R. Wilson and L. A. Paquette for many comments and corrections.

Notes Added in Proof.

Paquette recently reported a highly selective allylation of α-and β-hydroxyaldehydes in aqueous medium promoted by indium (Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863). More detailed information will be available shortly (Paquette, L. A.; Mitzel, T. M. in preparation and Paquette, L. A.; Lobben, P. C. in preparation). Katritzky reported an efficient N-derivatization of L-proline and pipecolinic esters using benzotriazole as a synthetic auxiliary in aqueous medium mediated by bismuth chloride (Katritzky, A. R.; Allin, S. M. *Synth. Commun.* **1995**, *25*, 2751).

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