## **1993 R.U. Lemieux Award Lecture** Organometallic-type reactions in aqueous media — a new challenge in organic synthesis<sup>1</sup>

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The development of organometallic-type reactions in aqueous media is reviewed. Coupling reactions of allyl halides with carbonyl compounds mediated by zinc, or tin, or indium in aqueous media to give homoallylic alcohols are discussed. The stereochemical outcome is compared with similar reactions in organic solvents. A concise synthesis of (+)-muscarine is used to illustrate the usefulness of aqueous organometallic-type reactions in organic synthesis. The procedure to protect-deprotect hydroxy functional groups may not be necessary in these reactions. An application in the carbohydrate area is demonstrated with the synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN). The mechanistic possibilities of organometallic-type reactions in aqueous media are outlined.

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On passe en revue le développement de réactions de type organométalliques dans des milieux aqueux. On discute des réactions de couplage des halogénures allyliques et des composés carbonylés, catalysées par le zinc, l'étain ou l'indium en solutions aqueuses et conduisant à des alcools homoallyliques. On compare le résultat stéréochimique de ces réactions avec ceux de réactions semblables dans des solvants organiques. On a utilisé une synthèse concise de la (+)-muscarine pour illustrer l'utilité des réactions de type organométallique, en solutions aqueuses, en synthèse organique. Dans ces réactions, il n'est pas toujours nécessaire de protéger, puis déprotéger, les groupes hydroxyles fonctionnels. On a démontré son utilité dans le domaine des carbohydrates en procédant à la synthèse de l'acide (+)-3-désoxy-D-glycéro-D-galacto-nonulosonique. On décrit brièvement les possibilités mécanistiques des réactions du type organométallique en solutions aqueuses.

[Traduit par la Rédaction]

### Introduction

The importance of organometallic reactions in organic synthesis is well recognized. Organometallic reactions using Grignard reagents or organolithium compounds are the cornerstone of organic synthesis. In their most general form, these reagents are used to construct new carbon-carbon bonds, leading to compounds of greater complexity. A cardinal restriction in the use of many organometallic reagents is the strict exclusion of moisture. Thus, we accept, without question, the limitations imposed by these restrictions, namely, that the reactions cannot be carried out in aqueous media, and that these reagents cannot coexist with a trace of water, or with reactive hydroxy or acidic hydrogens. These inherent limitations profoundly govern our thinking about organic synthesis. We accept, first of all, that anhydrous organic solvents are required for these reactions. Furthermore, reactive hydroxy or acidic groups must be protected, and indeed, extensive protection-deprotection chemistry has been developed for that purpose. As well, we accept that compounds such as carbohydrates, insoluble in organic solvents, will have to be derivatized so that they become soluble. This has evolved to become part of the accepted way of doing synthesis in the carbohydrate field. Finally, many stereochemical formulations, e.g., Cram's rule (1) and its modifications, are based generally on conclusions reached from reactions carried out in organic solvents.

If one can perform organometallic-type reactions in aqueous media just as generally and easily as in organic solvents, such reactions may offer considerable advantages: (*i*) There is the practical convenience of not having to handle inflammable and anhydrous organic solvents. (*ii*) The tedious task of protection– deprotection chemistry for certain functional groups often encountered in organic synthesis may not be required. (*iii*) Water-soluble compounds can be reacted directly without the need of derivatization. This is a point of particular interest in carbohydrate chemistry. (*iv*) The stereochemical outcomes of organometallic reactions may well change from organic to aqueous media and thus offer new opportunities in synthesis. Several years ago, we began a program to study organometallic-type reactions in aqueous media with a view to exploring the above-mentioned possibilities.

It may be useful to examine the factors that may lead to choosing appropriate organometallic reagents for aqueous media. It is generally known that the less reactive organometalloid reagents, such as organosilicon compounds, do not react with water (2). Can they be used for organometallic-type reactions in aqueous media? The answer is negative. Precisely because silicon is less reactive, the preparation of organosilanes directly from silicon and organic halides is not as easy as the Grignard reagents or organolithiums. Furthermore, formation of a C—C bond using organosilicon reagents requires strongly acidic conditions (3). Organosilanes are not likely to be candidates.

What about the somewhat more reactive organotin compounds? It was known as early as 1961 that tin reacts with benzyl chloride directly to form the corresponding organotin compounds 1 and 2 (Scheme 1) (4). What is interesting, and was little exploited at that time, is the fact that the reaction could be carried out in a number of solvents, including water. It was reported that the yield of tribenzyltin chloride (2) was quite respectable when the reaction was carried out in aqueous medium. Even though the tin-chlorine bond was partially hydrolysed, the tin-carbon bond survived in water to a large extent in spite of the fairly high temperature. It was in the 70s, and then increasingly so in the 80s, that the use of tin, and zinc as well, to mediate the allylation of aldehydes and ketones in water to give the corresponding homoallylic alcohols (3) (Scheme 2) was reported, first by Wolinsky and co-workers in

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1977 (5), then by Nokami et al. in 1983 (6), later on more systematically by Luche and co-workers in France (7), and more recently by Wilson and Guazzaroni in the U.S. (8). The metal used can be either Sn or Zn, and the solvent used can be water, with or without organic cosolvents. The yields are in general good to excellent. But there is always an induction period of indefinite time, and the use of catalyst, ammonium chloride or hydrobromic acid, appears to promote the reaction. The use of heat or ultrasound radiation has also been found to facilitate the reaction. The side products most often reported are the reduced carbonyl compounds, the alcohols **4**, and (or) the pinacols **5** 



from the reductive coupling of the precursor carbonyl compounds.

#### **Results and discussion**

When we began our work in this area, the first question we posed was a very simple one: can one extend the known reactions to synthesize compounds other than homoallylic alcohols?

Indeed, we found (9) that aldehydes and ketones could be converted to 1,3-butadienes 6 or vinylepoxides 7 by reaction with 1-chloro-3-iodopropene (8). Powdered zinc metal was used (Scheme 3). The intermediate chlorohydrin 9 could be isolated, which on further reaction with zinc in water gave the diene 6 in good to excellent yields. Alternatively, treatment of the chlorohydrin with base gave the vinylepoxide 7. The results of this reaction are summarized in Table 1. The following features of the reaction are noteworthy. The carbonyl compound can contain an unprotected hydroxy group, and the reaction proceeds equally well. While this is not surprising in view of the fact that the reaction is carried out in water, one can hardly expect an hydroxy group to prevent the reaction if water is present everywhere. This is nevertheless quite contrary to conventional organometallic reactions: namely, the hydroxy group would first have to be protected, and then deprotected after the reaction. Secondly, the reaction seems to proceed in a 1,2-addition fashion. With cinnamaldehyde, the corresponding triene is obtained. Thirdly, the butadienes 6 are formed stereoselectively and, in the case of aldehydes, exclusively as the E isomers. On the other hand, the vinylepoxides 7 are formed as a mixture of cis/trans diastereomers, and the ratio is in agreement with the diastereomeric ratio of the precursor chlorohydrins 9. This suggests that the reduction of 9 to give 6 under the experimental conditions is non-stereospecific but selective in giving the thermodynamically more stable E isomer. This is contrary to the usual trans elimination under metal/dihalide reduction conditions (10).

Another simple modification is to use 2-chloromethyl-3iodopropene (10) as the allylic halide. This provides a synthesis of methylenetetrahydrofurans 11 from the carbonyl precursors in good to excellent yields (Scheme 4) (11). The reaction can be looked upon as providing a trimethylenemethane equivalent 12, the 1,3-dipolar species. The conventional trimethylenemethane



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Entry	Aldehyde	Halide	Product	% Yield (method) <sup>a</sup>	trans:cis
1	СНО	CICH = CHCH <sub>2</sub> CI		53 (A)	>98
2		CICH=CHCH <sub>2</sub> I	_/	95 (B)	>98
3		CICH CHCH <sub>2</sub> I	$\overline{\lambda}_{\underline{A}}$	95 (C)	36:64
4	СІСНО	CICH=CHCH <sub>2</sub> I		97 (B)	>98
5		CICH — CHCH <sub>2</sub> I		95 (C)	36:64
6	Ме-СНО	CICH=CHCH <sub>2</sub> I	Me	95 (B)	>98
7		CICH — CHCH <sub>2</sub> I	Me	93 (C)	36:64
8	CH <sub>3</sub> (CH <sub>3</sub> ) <sub>3</sub> CHO	CICH=CHCH <sub>2</sub> CI	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH=CH-CH=CH <sub>2</sub>	53 (A)	95:5
9		CICH=CHCH <sub>2</sub> I	0	92 (B)	95:5
10		CICH=CHCH <sub>2</sub> I	СН <sub>3</sub> (СН <sub>2</sub> ) <sub>3</sub> СН—СН—СН=СН <sub>2</sub>	92 (C)	48:52
11	Срсно	CICH=CHCH2Cl	CH=CH-CH=CH <sub>2</sub>	48 (A)	>98
12		CICH=CHCH <sub>2</sub> I		93 (B)	>98
13	⟨¯⟩−сн=сн−сно	CICH=CHCH <sub>2</sub> CI	СН=СН-СН=СН-СН=СН2	38 (A)	>98
14		CICH=CHCH2I	_	86 (B)	>98
15		CICH=CHCH <sub>2</sub> CI	C(CH <sub>3</sub> )=CH-CH=CH <sub>2</sub>	53 (A)	85:15
16		CICH — CHCH <sub>2</sub> I		80 (B)	85:15
17		CICH == CHCH <sub>2</sub> Cl	CH-CH=CH2	36 (A)	
18	─=0	CICH — CHCH <sub>2</sub> I		95 (B)	
19		CICH=CHCH2I		93 (C)	
20	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	CICH == CHCH <sub>2</sub> Cl	$CH_{3}(CH_{2})_{3}$ $C=CH-CH=CH_{2}$ $CH_{3}(CH_{2})_{3}$	20 (A)	
21	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COCH <sub>3</sub>	CICH=CHCH <sub>2</sub> CI	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> C(CH <sub>3</sub> )=CH-CH=CH	I <sub>2</sub> 33 (A)	70:30
22		CICH=CHCH <sub>2</sub> I		75 (B)	68:32
23	HO(CH₂)₄CHO	CICH=CHCH <sub>2</sub> CI		42 (A)	88:12
	он он 		он он 		
24	ĊHĊHCHO	CICH=CHCH <sub>2</sub> CI	снснсн=сн-сн=сн <sub>2</sub>	33 (A)	>98

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<sup>a</sup>Method: (A) A mixture of the carbonyl compound (1 mmol), 1,3-dichloropropene (1 mmol), and zinc powder (2 mmol) in 10 mL of water was heated to  $35^{\circ}$ C with vigorous stirring for 3–4 h. The reaction mixture was cooled and quenched with ether. The organic product was isolated from the ether phase and purified by flash column chromatography. (B) A mixture of the carbonyl compound (1 mmol), 1-chloro-3-iodopropene (1.5 mmol), and zinc powder (1.5 mmol) in 10 mL of water was stirred at room temperature until the zinc almost disappeared (in cases where the reaction did not start properly, 2–3 drops of hydrobromic acid or saturated ammonium hydrochloride solution could be added to initiate the reaction). To the reaction mixture was then added 2 mL of hydrobromic acid (48%) and zinc powder (10 mmol) over a period of 5 h. The reaction mixture was then extracted with ether to give, after purification by flash column chromatography, the diene. (C) The reaction was interrupted after the first stage of method (B) by extraction with ether. The intermediate chlorohydrin was isolated, and treated in ethanolic NaOH (0.4 g/10 mL) to give the vinylepoxide in quantitative yield.

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equivalents usually require balanced reactive ends, for example, compound 13 with a less reactive silyl or stannyl nucleophilic end, but a more reactive acetate electrophilic end (12), or compound 14 with a more reactive zinc or magnesium halide end



### 14 MX=ZnBr or MgCl

together with a less reactive phenoxy end (13). Such a balance in reactivity of the two polar centers is required to prevent self-cyclization, or di- and polymerization. In the case of the present reaction, what is the possible mechanism? Is a true organozinc intermediate actually formed, in the presence of water, with a reactive allylic halide as the other polar center?

At this point, it might be profitable to speculate on the possible mechanism of this kind of organometallic-type reaction in aqueous media. In the case where metallic zinc is used, the actual formation of the allylzinc intermediate is considered unlikely, because such organozincs are known to react instantaneously with water (14). The involvement of the less reactive allyltin intermediate may also be unlikely, while it has been known that allylic bromide does react with tin in organic sol-



vents to give the corresponding diallyltin dibromide (15). In water, the same reaction gives propene, presumably because the allyltin intermediate reacts with water under the reaction conditions (Scheme 5) (15). One possible mechanism is that the metal reacts with the carbonyl compound by a single electron transfer (SET) process to give the radical anion intermediate 16. The ketyl radical anion couples with the allylic halide to give the alkoxy radical, which on further reduction by the metal in another single electron transfer step gives the alkoxide anion, which is then protonated by water to the homoallylic alcohol product (Scheme 6). This mechanism can account not only for the product, but also for the side product of the reaction, namely, the pinacol 5, because of the coupling of the ketyl radical anion.

Another equally likely mechanism is the following: it is the allylic halide that reacts with the metal in an SET step to give the radical anion 17. The radical anion then couples with the carbonyl compound to give the alkoxy radical species, which on further reduction by the metal gives the product (Scheme 7). In support of this mechanism, the self-coupling product 18 of the allylic halide 10 can also be found in the reaction mixture as a side product.



Irrespective of the real mechanism (a question that may take a long time to resolve), if a single electron transfer step is indeed involved, one may ask: can other metals perform the same function equally well or even better? This led us to search for other possibilities. If one looks at what is required of this metal, one



SCHEME 6



TABLE 2. First to	o fourth	ionization	potential	of	some	metals
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	Ionization potential (eV)						
Metal	I	II	III	IV			
Indium	5.785	18.86	28.03	54.4			
Aluminum	5.984	18.82	28.44	119.96			
Magnesium	7.646	15.035	80.143	109.29			
Zinc	9.39	17.96	39.7				
Tin	7.34	14.63	30.49	40.72			

realizes that the metal itself must not react with water. This removes from consideration metals such as sodium, potassium, cesium, magnesium, etc., or similarly reactive metals. Furthermore, the metal must not react in air to form water-insoluble oxides. This eliminates metals such as titanium or aluminium whose oxides are water insoluble. Another consideration is that the metal must be somewhat more reactive than silicon and germanium, or perhaps even tin.

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In this connection, indium metal offers some intriguing possibilities. Compared to other metals, indium has not been much explored in organometallic reactions (16). It is only recently that indium has been used in Reformatsky reactions (17), allylations (18), and cyclopropanations (19) of carbonyl compounds. While these results are interesting, the use of indium in organic solvents offers no obvious advantages over other conventional organometallic reactions. On the other hand, it is known that indium is unaffected by boiling water! It does not readily form oxide in air. Most interestingly, its first ionization potential is much lower than zinc. In Table 2, we compare the ionization potentials of five metallic elements. Indium has the lowest first ionization potential among them, but it has the highest second ionization potential. If the mechanism of the aqueous



organometallic reactions is indeed initiated by a single electron transfer step and not a two-electron transfer reaction, then indium should be a reasonable candidate.

Sure enough, when allylic halide and carbonyl compounds are stirred with indium in aqueous media, the reaction proceeds very well to give the corresponding homoallylic alcohols (Scheme 8) (20). The yields are usually good to excellent (Table 3). There are few side products of alcohols or pinacols. In contrast to the zinc- and tin-mediated reactions, where some acidic initiators are usually required, the indium reaction can be applied to carbonyl compounds with acid-labile groups. An example is found by comparing the three metals in the same reaction with the substrate **19** where there is a labile acetal group. With zinc as the metal, the reaction fails with destruction of the starting materials. Using tin, the yield is very poor, but with indium the reaction proceeds normally to give the desired product in 70% yield (Scheme 9).

A useful variation on the same theme is to use the allylic halide **20** with the ester functional group. The reaction can be mediated by indium in water to give the coupled product in very good yield. This can serve, of course, as a facile route to  $\alpha$ -methylene- $\gamma$ -lactones **21** (Scheme 10).

In 1990, we reported on crossed aldol-type condensation reactions in aqueous media. Aldehydes and  $\alpha$ -halo-carbonyl compounds condense in water with zinc or tin to give the crossed aldol-type products **22** (Scheme 11) in reasonably good yields (21). The distinctive feature of this reaction is that there does not appear to be the normal complication of crossed aldol reaction in organic solvents in that there are few elimination products, poly-aldol condensations, or self-aldol products. The major side products appear to be owing to the reductive coupled products, for example, the 1,4-diketone **23** from the bromoketone **24**. The diastereoselectivity of the reaction is between

# PhCO-C(Me)<sub>2</sub>Br $[PhCO-C(Me)_2]_2$ 24 23

1:1 and 2:1, not much different from the normal diastereoselectivity of this type of reaction performed in organic solvents.

When the same crossed aldol-type reaction is carried out



TABLE 3. Allylation of aldehydes and ketones mediated by indium in aqueous media

Entry	$\mathbb{R}^1$	$R^2$	x	Metal	A/allylX/M	Time (h)	Yield	syn:anti
1	Ph	Н	Br	 In	1/1.5/1	3	97	
2	Ph	Н	Ι	In	1/1.5/1	3	95	
3	Ph	Н	Cl	In	1/1.5/1	5	60	
4	Ph	Н	Cl	Sn	1/1.5/1	5	$0^{a,b}$	
5	ClPh	H	Br	In	1/1.5/1	1	94	
6	CH <sub>3</sub> CHOH	Н	Br	In	1/1.5/1	3	85	67:33
7	$CH_{3}CH(ODCB)$	Н	Br	In	1/1.5/1	3	75	24:76
8	$CH_3(CH_2)_2CH(OBn)$	Н	Br	In	1/1.5/1	3	80	24:76
9	$PhCH(CH_3)$	Н	Br	In	1/1.5/1	3	90	78:22
10	Ph	CH <sub>3</sub>	Br	In	1/1.5/1	5	72	
11	Ph	CH <sub>3</sub>	Br	Zn	1/1.5/1	5	18 <sup>c</sup>	
12	Ph	$CH_{3}$	Br	Sn	1/1.5/1	3	$0^a$	
13	-(CH <sub>2</sub> ) <sub>5</sub> -	5	Br	In	1/1.5/1	6	68	
14	-(CH <sub>2</sub> ) <sub>5</sub> -		Br	Sn	1/1.5/1	6	$0^a$	
15	$HOCH_2C(CH_3)_2$	Н	Br	In	1/1.5/1	3	85	
16	$HO(CH_2)_4$	Н	Br	In	1/1.5/1	3	95	
17	(CH <sub>3</sub> O) <sub>2</sub> CHCH <sub>2</sub>	CH <sub>3</sub>	Br	In	1/2/1.5	6	70	
18	(CH <sub>3</sub> O) <sub>2</sub> CHCH <sub>2</sub>	CH <sub>3</sub>	Br	Zn	1/2/2	6	0	
19	(CH <sub>3</sub> O) <sub>2</sub> CHCH <sub>2</sub>	CH <sub>3</sub>	Br	Sn	1/2/2	6	$10^d$	•

All the reactions were performed at 1 mmol scale at room temperature in water by stirring the reaction mixture for the proper time, unless otherwise mentioned. <sup>a</sup>Mediated by tin at 80°C.

<sup>b</sup>Promoted by sonication.

"Mediated by zinc with sonication.

<sup>d</sup>By <sup>1</sup>H nmr.

TABLE 4. Crossed aldol reactions mediated by indium in water

Entry	RCHO	Halide	RCHO/halide/In	Time (h)	erythro:threo	Yield
1	PhCHO	BrC(CH <sub>3</sub> ) <sub>2</sub> COPh	1/1.5/1	3		88
2	PhCHO	BrCH(CH <sub>3</sub> )COPh	1/1.5/1	3	12:1	85
3	PhCHO	BrCH(CH <sub>3</sub> )COPh	1/1/1	3	12:1	56 <sup>a</sup>
4	p-MePhCHO	BrCH(CH <sub>3</sub> )COPh	1/1/1	5	12:1	72
5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CHO	BrCH(CH <sub>3</sub> )COPh	1/1/1	5	4:1	64
6	PhCHO	BrCH <sub>2</sub> COPh	1/1/1	5		15
7	PhCHO	BrCH(CH <sub>3</sub> )COCH <sub>3</sub>	1/1/1	5	3:1	48

<sup>a</sup>In methanol/water 1:1; All reactions were performed at 1 mmol scale in water by stirring the reaction mixture for the corresponding time.



 $\begin{array}{c} R \\ H \end{array} = 0 + \begin{array}{c} 0 \\ X \end{array} \begin{array}{c} M \\ H_2 O \end{array} \begin{array}{c} R \\ H_2 O \end{array} \begin{array}{c} R \\ H_0 \end{array} \begin{array}{c} R \\ H_0 \end{array} \begin{array}{c} 22 \\ 22 \end{array}$ 

example of benzaldehyde reacting with  $\alpha$ -bromopropiophenone (25), when the reaction is carried out in water with zinc as the metal, the yield is 82% with the ratio of the two diastereomeric products 26, erythro to threo, being 2.5 to 1. Using tin as the metal for the same reaction, the yield is slightly poorer, and the ratio of the two diastereomers, erythro to threo, becomes 1 to 1.1. But when the same reaction is carried out with indium in water, the yield is good at 85% but, more dramatically, the ratio of the two diastereomers is now 12 to 1 in favour of the erythro compound (Scheme 12). While one cannot give a logical explanation at this time for the stereochemical differences, the improved diastereoselectivity renders the indium-mediated crossed aldol condensation reactions synthetically useful.

with indium instead of zinc or tin in aqueous media, the yield of the reaction is slightly improved (Table 4) (22). But the most interesting change is that the diastereoselectivity appears to have improved to between 2:1 and 12:1. Using the specific

Not surprisingly, Reformatsky-type condensation reactions can also be carried out with indium in water.  $\alpha$ -Haloesters (27)



LABLE 5.	Reformatsky	v reactions	mediated	by	indium	in	water <sup>a</sup>
				- /			

Entry	α-Halocarbonyl (equiv.)	Aldehyde (equiv.)	In (equiv.)	erythro:threo <sup>b</sup>	% yield
1	$BrCMe_2CO_2Et (1.0)$	PhCHO (1.0)	1.0		52
2	BrCHMeCO <sub>2</sub> Et (1.0)	PhCHO (1.0)	1.0	2.2:1	35
3	PhCHBrCO <sub>2</sub> Me (1.5)	PhCHO (1.0)	1.0		0
4	MeCHBrCO <sub>2</sub> H (1.5)	PhCHO (1.0)	1.5	2.2:1	40
5	MeCHBrCO <sub>2</sub> Na (1.5)	PhCHO (1.0)	1.5	2.2:1	35
6	$nBuCHBrCO_{2}H$ (1.5)	PhCHO (1.0)	1.5	2.2:1	5
7	PhCHBrCO <sub>2</sub> H (1.5)	PhCHO (1.0)	1.5	1.7:1	37
8	(-)-MeCHBrCO <sub>2</sub> H (1.5)	PhCHO (1.0)	1.5	2.2:1	37
9	PhCHBrCO <sub>2</sub> Na (1.5)	$C_3H_7CHO(1.0)$	1.0		0

<sup>*a*</sup>Reaction time = 6 h.

<sup>b</sup>Analyzed by <sup>1</sup>H nmr.

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react with carbonyl compounds to give the corresponding  $\beta$ -hydroxyesters (28) in moderate yields (Scheme 13). The reaction appears to be chemoselective in that only aromatic aldehydes participate in this kind of reaction. Aliphatic aldehydes are recovered unchanged under identical reaction conditions (Table 5). The major products obtained in these situations are the reduced esters 29. The diastereoselectivity observed is unexceptional, in the range of 2 to 1.

# رياً 0R' **29**

## **31** (R'=H)

Somewhat surprising is the observation that the free  $\alpha$ -haloacids **30** can also undergo the same Reformatsky-type condensation reactions with aromatic aldehydes in water in more or less the same modest yields (Scheme 13). Again, the side product is the reduced acid **31** and the diastereoselectivity is uneventful (Table 5). An interesting aspect of the experimental result is that when optically active (S)-(-)-bromopropionic acid (88% ee) is reacted with benzaldehyde and



indium in water, the condensation product 32 is obtained in about 50% yield. Two diastereomers are formed, in the ratio of 2.2 to 1 in favour of the *erythro* isomer. The two diastereomers have been separated as the methyl esters 33, and both are found to be optically inactive (Scheme 14). This allows us to draw some limited conclusions about the possible mechanism of this reaction. If the reaction proceeds by first forming a radical anion with the carbonyl compound (path a), then the lack of optical activity in 33 would rule out a direct displacement of the halide by the radical anion in an  $S_N^2$ -type process because this would have given an optically active 33. On the other hand, if the reaction proceeds by first forming a radical anion with the  $\alpha$ -haloacid (path b), the result of the

Path a

optical activity would imply that the carbon-halogen bond must have dissociated sufficiently, leading to racemization prior to reaction with the carbonyl compound (Scheme 15). A similar dissociation of the carbon-halogen bond on a magnesium metal surface, leading to racemization, was recently advanced to account for the stereochemical observations of Grignard reactions (23).

One can take advantage, in synthesis, of the change in stereoselectivity in organometallic-type reactions in aqueous media. We recently reported a concise synthesis of (+)-muscarine (34)by using the zinc-mediated allylation reaction (24). Normally, the stereoselectivity observed in the addition of C-nucleophiles such as organometallic reagents to chiral a-alkoxyaldehydes (and ketones) is opposite to Cram's rule. The anti-Cram stereoselectivity has been rationalized on the basis of chelation control. The carbonyl compound 35 forms the chelate 36 as shown in Scheme 16. The C-nucleophile (R-) attacks from the less hindered side as indicated by the arrow, giving the chelation-controlled product 37 in preference to the non-chelation product 38 (25). One would expect the formation of the chelate 36 in aqueous media to be much diminished or even disrupted. In Table 6, the allylation of a number of  $\alpha$ -alkoxyaldehydes with allylmagnesium bromide in ether is compared with the reaction with allyl bromide/zinc in water. In all cases where the reaction is conducted in organic solvent, the syn isomer is obtained as the major isomer, in agreement with the chelation model. But in cases where the reaction is conducted in water, a reversal of stereoselectivity is observed, now with the anti isomer as the major product. While it is possible that the observed stereoselectivity in aqueous organometallic-type reactions may be due to factors associated with the metal surface in such heterogenous reactions, it is interesting to note that in the case of





Scheme 16

TABLE 6. Stereoselective allylation of  $\alpha$ -substituted aldehydes



Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	Method (M)	Yield (%)	syn:anti <sup>a</sup>
1	Me	ODCB	A(Zn)	85	29:71
2	Me	ODCB	B(Mg)	45	60:40
3	Me	OBn	A(Zn)	85	35:65
4	Me	OBn	B(Mg)	50	65:35
5	Bu	OBn	A(Zn)	80	24:76
6	Bu	OBn	B(Mg)	60	60:40
7	Ph	OBn	A(Zn)	58	43:57
8	Ph	OBn	B(Mg)	75	67:33
9	Ph	Me	A(Zn)	85	68:32
10	Ph	Me	B(Mg)	90	60:40

A: Aqueous medium, Zn, RT, catalyzed by NH<sub>4</sub>Cl; B: allylmagnesium bromide, ether, -78°C. <sup>a</sup>Determined by <sup>1</sup>H nmr.

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(a) DCBBr/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 Scheme 17

 $\alpha$ -methylphenylacetaldehyde (39), where there is no possibility of chelation, there is no significant difference in the diastereoselectivity between allylations in organic or aqueous media.



(+)-Muscarine is synthesized from (S)-(-)-ethyl lactate in five steps with the application of the zinc-mediated allylation reaction in aqueous media (Scheme 17). In the critical step in which compound 40 is transformed into the two diastereomers 41*a* and 41*b*, the aqueous reaction gives the desired diastereomer 41*a* as the major product whereas the same reaction with allylmagnesium bromide in ether gives 41*b* as the major product.

Finally, organometallic-type reactions in aqueous media may offer a unique opportunity in carbohydrate chemistry. We have demonstrated this with the syntheses of the two carbohydrate molecules, KDO (42), an eight-carbon sugar, with a carboxylic acid end, and KDN (43), a nine-carbon compound of similar structure. They belong to a family of compounds called sialic acids, which are now known to play some critical role in many cell-surface glycoproteins (26). Chemical syntheses of these two compounds have been reported in the literature (27), very often involving the protective group chemistry that is standard in carbohydrate chemistry.

Using the indium-mediated reaction, D-mannose can be coupled in water with allyic halide **20** bearing a methyl ester group to give the two diastereomers **44** and **45** in a ratio of 6:1. The major isomer **44** can be conveniently crystallized out. Ozonolysis of the double bond (in methanol) gives the ketone **46**, which spontaneously cyclizes to the methyl ester **47** of KDN (28). Saponification with KOH in aqueous methanol according to literature procedure (29) gives KDN (Scheme 18). This synthesis is concise, and offers the distinct advantage that the mannose does not need to be derivatized, but is used directly in water.

The same approach can be carried out starting with D-arabinose (Scheme 19). Coupling with 20 by indium in water gives the two diastereomers 48 and 49, in a ratio of 1 to 5 with the wrong isomer 49 predominating. The major epimer 49 can be acetylated and ozonolyzed to give the unsaturated keto-ester 50, which was converted to KDO (42) (30).

It is perhaps instructive to compare these syntheses with the enzymic syntheses of both KDN and KDO recently reported by Wong and co-workers (31). With the sialic acid aldolase from Escherichia coli as the enzyme, D-mannose couples with pyruvate in water to give D-KDN (Scheme 20). However, when Lmannose is used as the substrate, L-KDN is obtained as the product. This represents a reversal of stereoselectivity at the new stereogenic center, a situation that is normally not the case for enzymic reactions. Similarly, when D-arabinose is used as a substrate (which is not a natural substrate of the enzyme), D-KDO and the 4-epimer (51) are obtained in a ratio of between 1:2.6 and 1:1.5, also with the wrong epimer predominating (Scheme 21). What is interesting is that in both the enzymic reactions, and in the chemical synthesis using indium in aqueous media, the same syn selectivity (anti-Cram) is observed in the critical C-C bond formation step. Normally, anti-Cram selectivity in the reaction of  $\alpha$ -hydroxyaldehydes with nucleophiles in organic solvents is explained by chelation control. Since both the enzymic and the chemical coupling are carried out in aqueous solution, the chelation control explanation may be invalid, as we have demonstrated for the zinc-mediated allylation of  $\alpha$ -alkoxyaldehydes in water. At present, we explain the syn selectivity for  $\alpha$ -hydroxyaldehydes by the Felkin model (32), which predicts the syn stereochemical outcome if the hydroxy group is considered to be of medium size.



CO<sub>2</sub>Me



D-arabinose

rt/5 h



20





CO<sub>2</sub>H

OH

**43** (D)-KDN

CO<sub>2</sub>H





D-mannose

aldolase

 $H_2O$ 

лон Он но́он CO<sub>2</sub>Me

D-arabinose





SCHEME 21

.CO<sub>2</sub>Me

,CO<sub>2</sub>Me

,CO<sub>2</sub>Me

49

HQ

HOmy

HO

HO,

SCHEME 20

ОĤ

ĥ

### Conclusion

We have demonstrated that certain organometallic-type reactions can be carried out in aqueous media. The reactions offer the following advantages. Anhydrous organic solvents are no longer needed. We have shown that reactive hydroxy or acidic groups need not be protected, and therefore much of the protection-deprotection chemistry in synthesis may become unnecessary. In some cases there are different stereochemical outcomes from reactions in organic solvents. These can be exploited in organic synthesis. Finally, as demonstrated in the synthesis of KDN, water-soluble compounds can be used as such without the need to be derivatized. There remain many challenges. The types of reactions for forming the carbon-carbon bond are still quite limited, and one would like to extend the scope of aqueous organometallic-type reactions. The mechanism of the reactions is far from having been established. Nevertheless, there is no doubt that organometallic-type reactions in aqueous media can play a useful role in organic synthesis.

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