PART I

BARBIER-GRIGNARD TYPE REACTIONS IN AQUEOUS MEDIA

PART II

DEVELOPMENT OF A NEW TELLURIUM REAGENT FOR ORGANIC SYNTHESIS

by

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Doctor of Philosophy

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To My Wife

Chunhui

For her understanding

SUMMARY

Organometallic reactions, including allylation, alkylation, aldol and Reformatsky type reactions of carbonyl compounds in aqueous media mediated by Sn, Zn, Mn, and In were studied. The possible mechanism and stereochemistry of these reactions were investigated. The methodology has successfully been applied to the syntheses of 1,3-butadienes, vinyloxiranes, and methylenetetrahydrofurans; and the syntheses of natural products (+)-muscarine, (+)-epimuscarine, (+)-KDN and (+)-KDO.

A novel tellurium reagent, bis(triphenylstannyl)telluride, for organic synthesis was developed. Its application in the preparation of organotellurium compounds, reduction of *vic*-dihalides and α-halo ketones, desulfurization of organic trisulfides and cleavage of organic disulfides was studied. All the reactions with this reagent proceeded under very mild conditions.

RÉSUMÉ

Nous avons étudié des réactions d'allylation, d'alcoylation, d'aldolisation et la réaction de Réformatsky sur des composés carbonylés en solutions aqueuses, en utilisant différents métaux tels que : Sn, Zn, Mn et In. Nous avons exploré le mécanisme possible de ces réactions ainsi que leur stéréochimie. Cette méthodologie a été appliquée avec succès à la synthèse de butadiènes-1,3, de vinyloxiranes et de méthylènetétrahydrofurannes; en outre elle a servie à la synthèse des produits naturels suivants : (+)-muscarine, (+)-épimuscarine, (+)-KDN et (+)-KDO.

Nous avons mis au point un nouveau réactif organotelluré pour la synthèse organique, le bis(triphénylstannyl)tellure. Nous avons évalué son emploi dans la préparation de composés organotellurés, la réduction de composés *vic*-dihalogénés et d'α-halocétones, la désulfurisation de trisulfures et le clivage de disulfures. Toutes les réactions avec ce réactif s'effectuent dans des conditions très douces.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

Allylation of carbonyl compounds in aqueous media mediated by Sn, Zn, In, and Mn was developed. 1,3-Butadienes, vinyloxiranes and methylenetetrahydrofurans were conveniently synthesized by this methodology.

Alkylation of carbonyl compounds in aqueous medium was discovered with Mn/Zn or Mn/Cu bi-metallic systems. Crossed aldol and Reformatsky type reactions in aqueous media were also developed. Unusual diastereofacial selectivity was observed with indium. A single electron transfer mechanism was proposed for the aqueous medium organometallic reactions.

Anti-chelation control was discovered in the allylation of α-alkoxy aldehydes. From this, a short total synthesis of (+)-muscarine and its epimer was completed.

A novel synthesis of (+)-KDN and (+)-KDO was accomplished by the Barbier-Grignard type reaction in aqueous medium.

A novel tellurium reagent, bis(triphenylstannyl)telluride was developed for the preparation of organotellurium compounds, reduction of *vic*-dibromides, reduction of α-halo ketones, desulfurization of organic trisulfides, and cleavage of organic disulfides. All the reactions with this reagent were achieved with high selectivity and under very mild conditions.

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List of Abbreviations

AA-UTP	5-(3-amino)allyluridine-5'-triphosphate
AA-dUTP	5-(3-amino)allyldeoxyuridine-5'-triphosphate
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Bu	butyl
c-	cyclo
CD	cyclodextrin
d	doublet
DCB	2',6'-dichlorobenzyl
Dibal-H	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Eq.	equation
Et	ethyl
h	hour
Het	heteryl
KDN	3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid
KDO	3-deoxy-D-*manno*-octulosonic acid
L	large
LPS	lipopolysaccharides
M	middle
Me	methyl
mL	millilitre

m.p.	melting point
Naph	naphthyl
ORTEP	Oak-Ridge Thermal Elipsoid Plot
P	protectional group
Ph	phenyl
Pr	propyl
PSGP	polysialoglycoprotein
q	quartet
ROMP	ring-opening metathesis polymerization
s	singlet
S	small
SET	single electron transfer
t	tert or triplet
TCBOC	2,2,2-trichloro-tert-butyloxycarbonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMM	trimethylenemethane
Tol	tolyl

PART I

Barbier-Grignard Type Reactions in Aqueous Media

" Things will develop in the opposite direction when they become extreme"

--------Lao-Tse (604-531 B. C.)

Chapter 1. Introduction--A Literature Survey on Carbon-Carbon Bond Formation in Aqueous Media

Of all the inorganic substances acting in their own proper nature, and without assistance or combination, Water is the most wonderful. If we think of it as the source of all the changefulness and beauty which we have seen in clouds; then as the instrument by which the earth we have contemplated was modelled into symmetry, and its crags chiselled into grace; then as, in the form of snow, it robes the mountains it has made, with what transcendent light which we could not have conceived if we had not seen; then as it exists in the form of torrent, in the iris which spans it, in the morning mist which rises from it, in the deep crystalline pools which mirror its hanging shore, in the broad lake and glancing river; finally, in that which is to all human minds the best emblem of unwearied, unconquerable power, the wild, various, fantastic, tameless unity of the sea; what shall we compare to this mighty, this universal element, for glory and for beauty, or how shall we follow its eternal changefulness of feeling? It is like trying to paint a soul.

-----Ruskin. [1a]

The most abundant and cheapest solvent in nature--- water --- is the basis and bearer of life. All life is sustained by and in protoplasm, which is

a suspension or a solution in water. For hundreds of millions of years, water had been at work to prepare the earth for the evolution of life. It is the solvent in which numerous biochemical organic reactions (and inorganic reactions) take place. All these reactions affecting the living system have inevitably occurred in aqueous medium. On the other hand, modern organic chemistry has been developed almost on the basis that organic reactions are often to be carried out in organic solvents. For example, Barbier-Grignard type reactions, one of the most important methods to construct carbon-carbon chains discovered in the last century, are always carried out in non-aqueous solvents. Most of the studies on the Barbier-Grignard reaction after its initial discovery have tried to improve the yield by making use of other metals or solvents. All these reactions and their improvements generally require the organometallic reagents to be prepared in organic solvent previously dried thoroughly. Initiation or activation are frequently required.

Because of the high reactivity of organometallic reagents, water has been considered undesirable to these reactions and no study has been carried out concerning their reactions in aqueous medium. On the other hand, the preparation of arylmercuric chloride in aqueous medium has been known since 1905.[1b] And in the 1960's, tribenzylstannyl halide was produced in large scale in water.[1c] These reports indicate the possibility of carrying out this kind of reactions in water under some special circumstances. Thus, as the goal of part of our research, we are attempting to bring organometallic reactions into aqueous media, and to explore its potential application in organic synthesis.

Why should we consider using water as a solvent in organic reactions?

There are many reasons and advantages to use water as a reaction solvent.:

------ Cheap. Water is the cheapest solvent available on earth, using water as a solvent can make chemical industry more economical.

------ Safe. Many organic solvents are potentially explosive, mutagenic and/or carcinogenic.

------ Possible to eliminate protection and deprotection of functional groups. This will be especially useful in carbohydrate and protein chemistry.

------ Simple operation. In large industrial processes, isolation of the organic products can be performed by simple phase separation.

------ Easy to control reaction temperature, since water has the largest heat capacity.

------ Clean and easy to be recycled. It may alleviate the current serious pollution situation.

------ .....

Carbon-carbon bond formation is the essence of organic synthesis. Although the well-known Kolbe synthesis was discovered in 1849[1d] (the first observation was back up to 1834 by Faraday),[1e] for more than a century, carbon-carbon bond formation using water as a solvent has been limited nearly completely to electrochemical processes. This chapter will briefly survey some recent advances (most of them appeared in the last decade) in this area.

1.1 Diels-Alder Reactions and Claisen Rearrangement Reactions in Aqueous Solvent

1.1.1 Diels-Alder Reactions in Aqueous Media[1f]

The Diels-Alder reaction is the most important method to form cyclic structures. The Diels-Alder process is frequently used at an early stage of a synthesis to establish a structural core which can be elaborated to the more complex target structure.[2]

The Diels-Alder reaction in aqueous medium was first reported in 1939 as a patent using an aqueous detergent solution.[3] No study had been carried out afterwards until recently. In 1980, Breslow reported that Diels-Alder reactions were accelerated by using water as solvent. The acceleration is explained by the suggestion that water brings together the two nonpolar organic substrates *via* the hydrophobic effect.[4]

The hydrophobic effect is the tendency of nonpolar species to aggregate in water solution so as to decrease hydrocarbon water interfacial area. It is the principal force determining the secondary and tertiary structures of proteins and nucleic acids, the binding of substrates to enzymes, and the binding of antigens to antibodies. It causes the formation of micelles and bilayers. Substrates binding into cyclodextrin cavities and into other organic cavities in water is also driven by the hydrophobic effect. Hydrophobic acceleration of organic reaction is explained as the action of entropy as well as enthalpy.[5]

Certain agents that decrease hydrocarbon solubility in water, such as LiCl, will favor the aggregation of the nonpolar species, thus increase the hydrophobic effect, while others that increase hydrocarbon solubility lead to an decrease of hydrophobic effect. A quantitative measurement of the

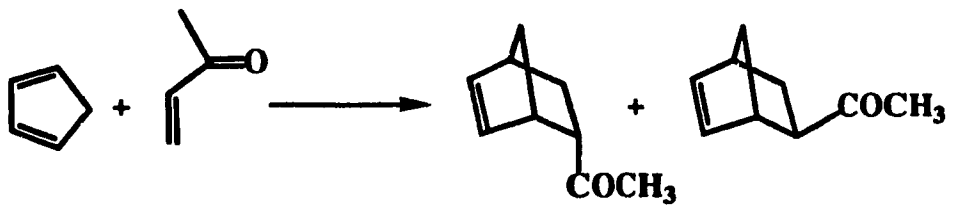
hydrophobic effect on the reaction of cyclopentadiene (1) with butenone (2) is shown in Table 1.[4]

Table 1. Rate Constants for Diels-Alder Reactions

solvent	additional component	$k_2 \times 10^5$, M^{-1} s^{-1}[a]
	Cyclopentadiene + Butenone, 20°C	
isooctane		5.94 ± 0.3
MeOH		75.5
H_2O		4400 ± 70
H_2O	LiCl (4.86 M)	10800
H_2O	$C(NH_2)_3^+ Cl^-$ (4.86 M)	4300
H_2O	β-cyclodextrin (10 mM)	10900
H_2O	α-cyclodextrin (10 mM)	2610

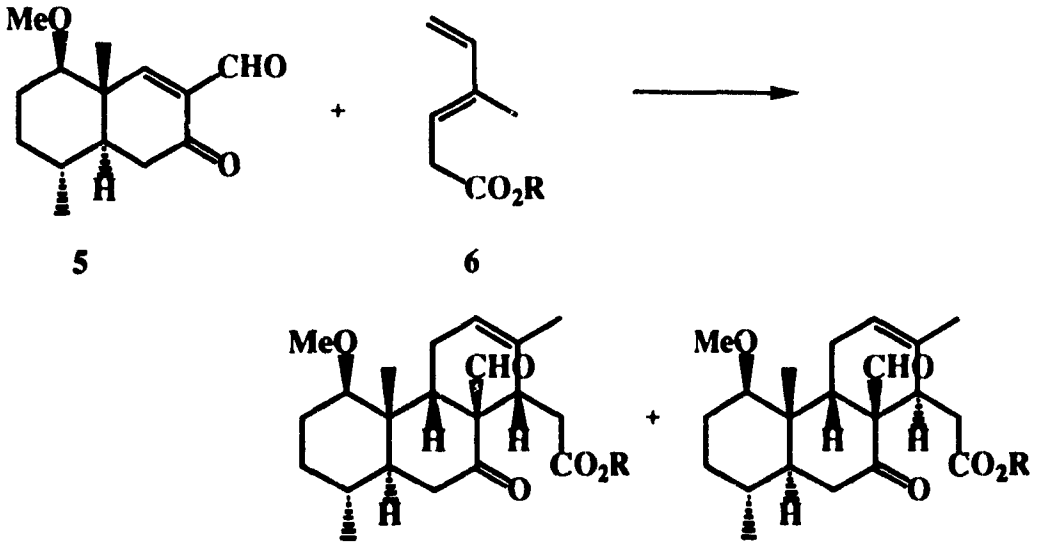
[a] Second-order rate constants.

Thus, the addition of lithium chloride increases the hydrophobic effect, i.e. it "salts out" nonpolar materials dissolved in water, and further increases the rate of the reaction.[4] The catalytic action of β-cyclodextrin and inhibition of α-cyclodextrin are explained as follows: The two reaction components can fit into the hydrophobic cavity of β-cyclodextrin but not in the smaller cavity of α-cyclodextrin (only diene binds to it).



1 2 3 4 (Eq. 1)

Water solvent also has striking effects on the selectivity of some Diels-Alder reactions. At low concentrations where both components are in true solution, reaction of cyclopentadiene with butenone gave an 21.4 ratio of endo/exo products when they were stirred at 0.15 M concentration in water, compared to only 3.85 in excess cyclopentadiene and 3.5 in ethanol as solvent.[6] Aqueous detergent solution has no effect on the ratio. The stereochemical changes are explained by the need to minimize transition state surface area in water solution, thus favouring endo stereochemistry.[7] By the same argument, addition of LiCl further increases the selectivity.



5 6 7 8

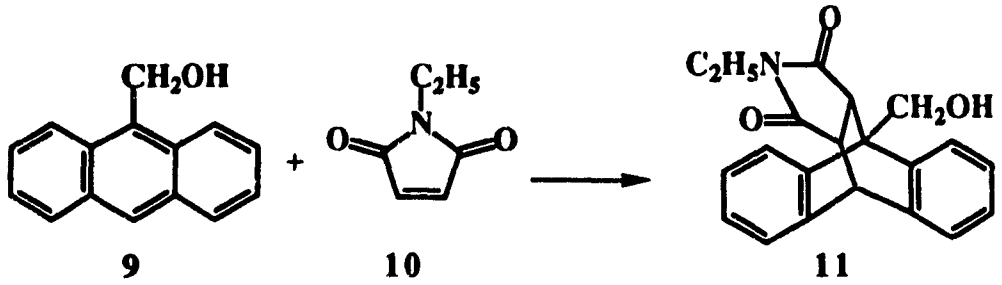
Scheme 1.

ratio **7/8** = 3:1 (in water)
1:0.85 (in benzene)

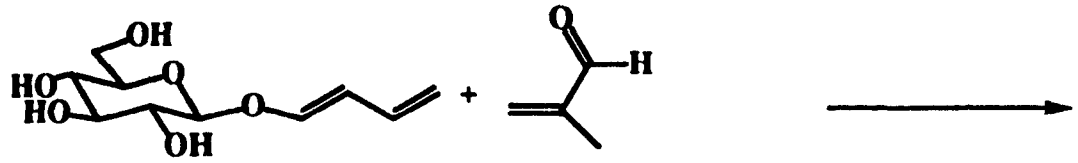
Diels-Alder reactions in aqueous media has also been studied by other authors.[8-14] Sternbach and Schneider examined the aqueous reaction catalyzed by cyclodextrin.[8,9] Gonzalez studied the Diels-Alder reaction in a mixture of water, 2-propanol and toluene in a state of micro emulsions.[10]

Grieco examined the reaction of compound **5** with diene **6** in water, and both high rate and selectivity were observed (Scheme 1).[11,12]

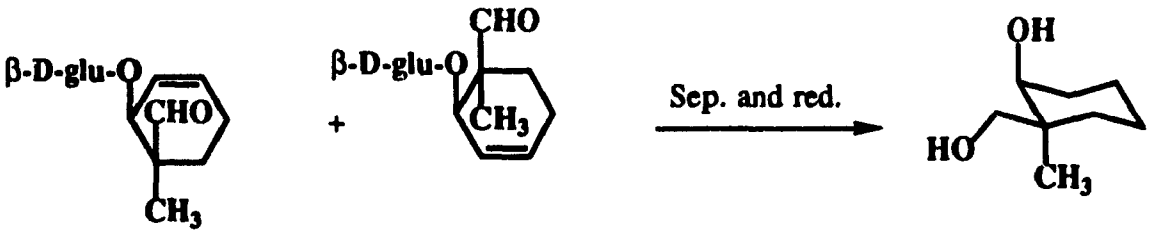
Reaction between hydroxymethylanthracene **9** and N-ethylmaleimide **10** was carried out in water at 45°C. Its second-order rate constant in water was over 200 times as large as that in acetonitrile (Eq. 2).[6]



9 **10** **11** (Eq. 2)



12 **13**



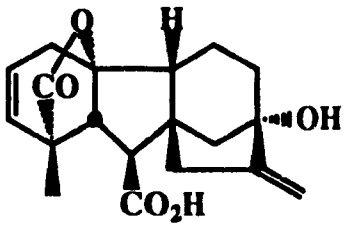
14 **15** **16** (pure enantiomer)

Scheme 2. **14/15** = 60: 40

Diels-Alder reactions of glyco-organic substrates in aqueous media were intensively studied by Lubineau *et al.*[13-15] The use of water soluble glyco-organic compounds in water achieves higher reagent concentration. The reaction also results in rate enhancement and asymmetric induction giving rise 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 2).

In synthetic applications, the aqueous Diels-Alder reaction has been used as key steps in the syntheses of Gibberellic Acid A5 (**17**),[16] Vernolepin (**18**),[17] and (±) -11-keto-testosterone (**19**).[18]



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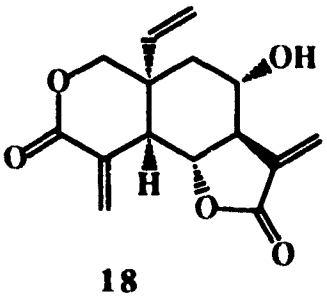

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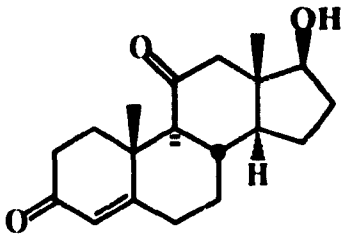

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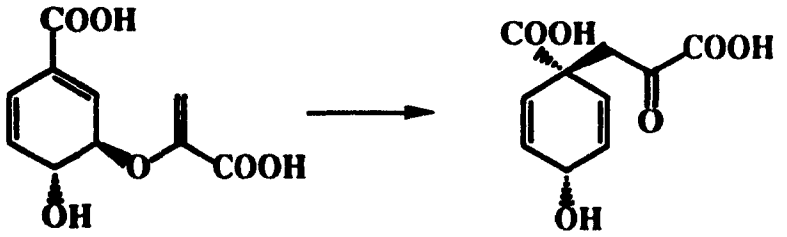
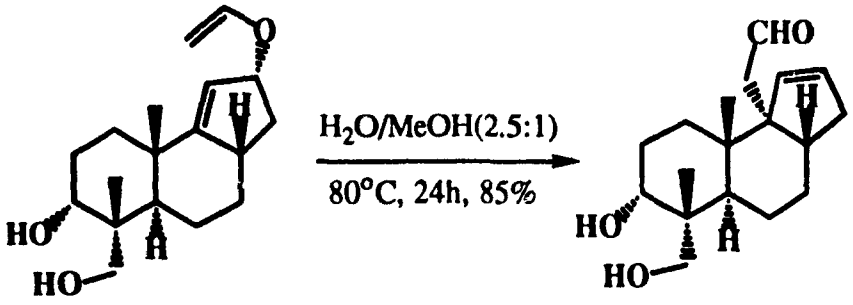
1.1.2 Claisen Rearrangement Reactions in Aqueous Media

In the early 70's, it was found that polar solvents increased the rate of Claisen rearrangements.[19] Recently, Claisen rearrangement reactions were examined thoroughly[20-25] with water as a polar solvent. Like the Diels-Alder reaction, the $\Delta V^{\neq}$ (volume change of activation) of Claisen rearrangements has a negative value,[26] therefore it should also be accelerated by water according to the hydrophobic effect. Indeed it was found that the rearrangement of chorismic acid (**20**) and related compounds in water was 100 times faster than in methanol (Eq. 3).[22]



20 **21** (Eq. 3)

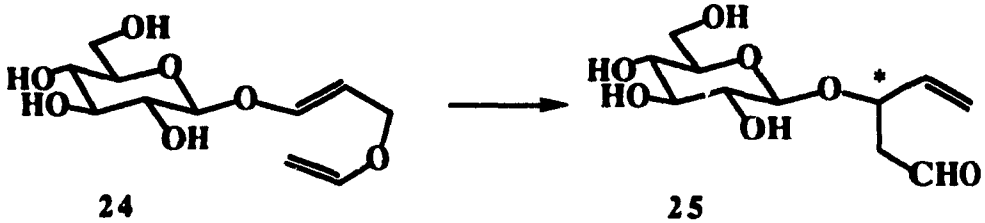
Similar results are found with other types of compounds. These studies show that this methodology has potential applications in organic synthesis. For instance, unprotected allyl vinyl ether **22**, 0.01 M in water-methanol (2.5:1) containing an equivalent of sodium hydroxide, smoothly undergoes rearrangement at ca. 80°C, affording 85% isolated yield of aldehyde **23** in 24h (Eq. 4).



22 **23** (Eq. 4)

The same rearrangement for the protected analogue under other organic Claisen conditions has considerable difficulties.[27] Elimination of acetaldehyde is often the major product.

A glucose moiety linked to an allyl vinyl ether, glyco-organic compound **24**, induces both water solubility and asymmetric induction for Claisen rearrangemcnt(Eq. 5).[25]



24 **25** (Eq. 5)

Since it can easily be removed, glucose here functions as a chiral auxiliary. After separation of the diastereomers formed, enantiomerically pure substances could be obtained.

1.2 Barbier-Grignard Type Reactions in Aqueous Media

About the same time as our study of aqueous Barbier-Grignard type reactions, several reports with the same objective have appeared in the literature. These are allylation reaction of carbonyl compounds, conjugated addition on unsaturated carbonyl compounds and pinacol coupling reactions.

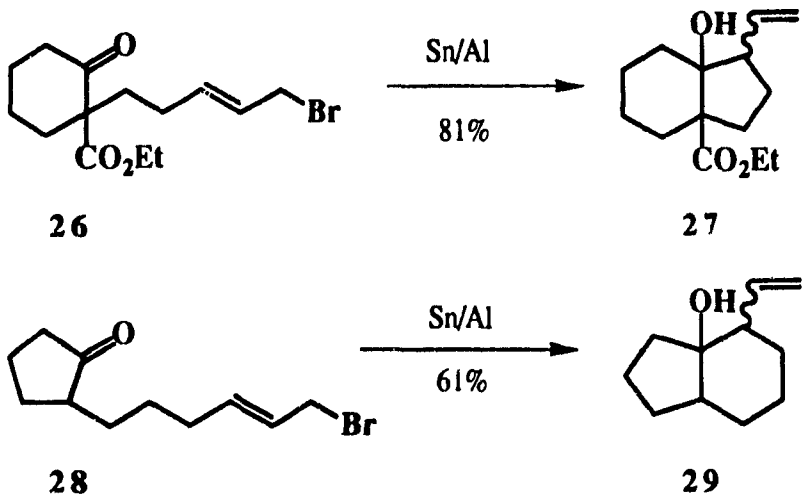
1.2.1 Allylation of Carbonyl Compounds

Being able to introduce both a hydroxyl group and a C=C bond simultaneously into a molecule, the allylation of carbonyl compounds has a wide application in organic synthesis.[28] In 1977,[29] the first allylation involving aqueous media was carried out in 95% ethanol and butanol by using activated zinc dust. However, only a moderate yield was obtained. In 1983, it was found that dialkyltin dihalide based allylation of carbonyl compounds can be accelerated by the presence of water, and the allylation can also be carried out in a mixture of ether and water with allyl bromide via metallic tin by the addition of aluminum powder or foil.[30] Addition of zinc was ineffective. Later, a similar reaction with allyl chloride was reported.[31] The reaction can also be carried out with bismuth metal as reported recently.[32]

The reaction can also proceed through an intramolecular manner. By the combination of tin and aluminum in aqueous medium, ketones

having allylic halide functionalities such as **26** and **28** were cyclized to form five and six membered rings (Scheme 3).[33]

Scheme 3.



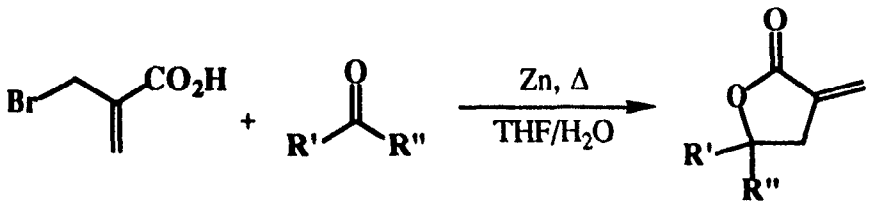
26 **27**

28 **29**

Allylation reaction in water/organic mixing solvents by an electrochemically recycled allyltin reagent has also been reported.[34]

Later, Luche found that when subjected to ultrasonic radiation, allylation reactions can be performed with metallic zinc.[35] The use of saturated NH_4Cl water/THF solution instead of water/THF, dramatically increased the yield. Under the same conditions, metal tin was also effective. When a mixture of aldehyde and ketone was subjected to the reaction, highly selective allylation of aldehyde was observed.[36] Similar chemo-selectivity was observed in compound **30** (Eq. 6).[37]

30 **31** **(Eq. 6)**

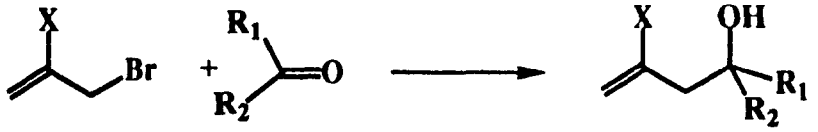


32 33 34 (Eq. 7)

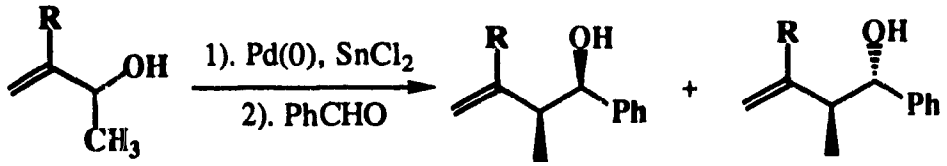
The reaction with zinc was also accelerated by silica gel.[38] Allylation or propargylation can be performed with tin by refluxing the reaction mixture.[38-40] Use of bromomethylacrylic acid instead of allyl halide gave the α-methylene-γ-butyrolactones, with zinc in saturated NH_4Cl/THF (Eq. 7).[41]

Similar products were obtained by refluxing with Sn/Al,[42] $SnCl_2$/AcOH,[43] and $SnCl_2$/ Amberlyst 15[44] in aqueous media.

When 2-bromo and 2-acetoxyl 3-bromo-1-propene were used, the allylation reaction produced the corresponding coupling products (Eq. 8).[45]



35 X= Br, OAc. 36 (Eq. 8)



37 syn 38a anti 38b (Eq. 9)

The allylation of carbonyl compounds in aqueous medium with $SnCl_2$ can also employ allylic alcohols in the presence of a palladium catalyst.[46] The diastereoselectivity of the reaction of substituted crotyl alcohols was

found to be solvation dependent (Eq. 9). Improved diastereoselectivity was found with a mixture of water and THF or DMSO instead of using organic solvent alone.

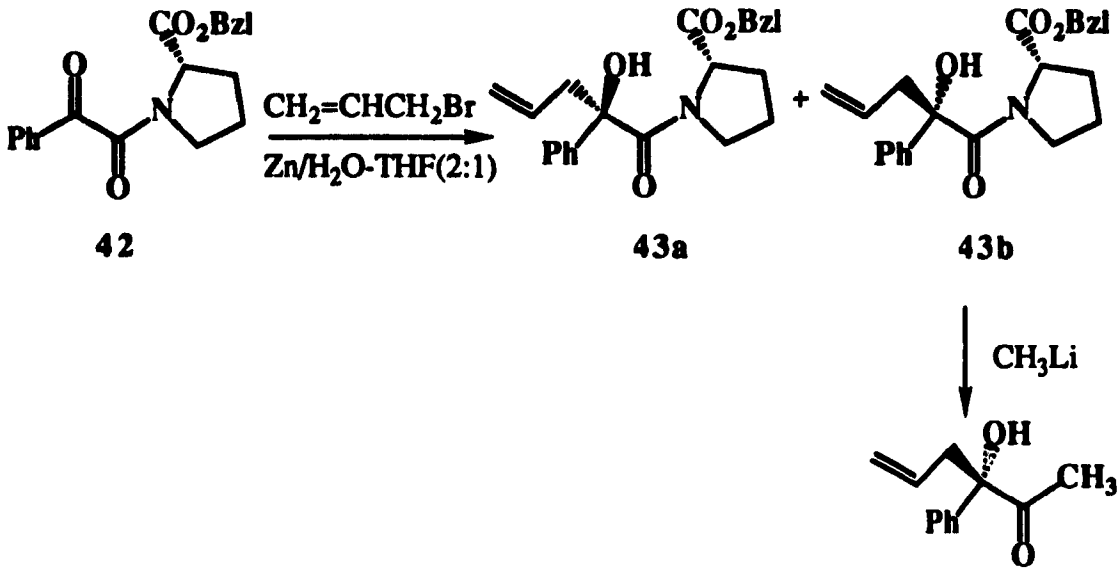
$$Bu_2RSnCl + R'COR'' + H_2O \text{ ---------> } R(HO)CR'R'' + (Bu_2SnCl)_2O \qquad \text{(Eq. 10)}$$

39 40 41

R= allyl, allenyl, acetylenyl.

Instead of using metals, allylation, allenylation, and acetylenylation of carbonyl compounds in aqueous media can also be carried out with the presumed intermediate organic tin reagents **39** (Eq. 10).[47-49]

Recently, Waldmann studied the diastereoselectivity of the reaction using proline benzyl ester as a chiral auxiliary to produce α-hydroxy amides. The diastereoselectivity was found to be as high as 4:1 (Scheme 4).[50] Separation of the diastereomers followed by reaction with methyl lithium produced the enantiomerically pure alcohol **44**.



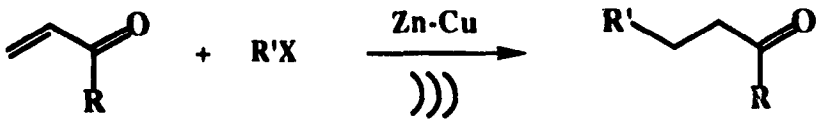
42 43a 43b 44

Scheme 4.

The reaction has also been used to prepare α, α-difluorohomoallylic alcohols from *gem*-difluoro allyl halide.[51]

1.2.2 Conjugated Addition of α,β-Unsaturated Carbonyl Compounds

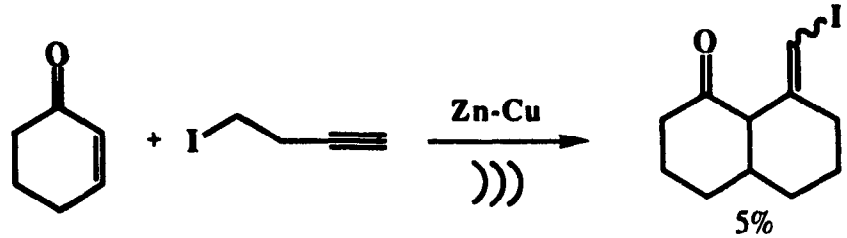
Because of the low reactivity of zinc and tin, alkylation reactions in aqueous media with unactivated alkyl halides fail to proceed. However, Luche found that when zinc-copper couple was used, alkyl halides reacted with conjugated carbonyl compounds to give 1,4-addition products in good yield under sonication conditions(Eq. 11).[52-54]



(Eq. 11)

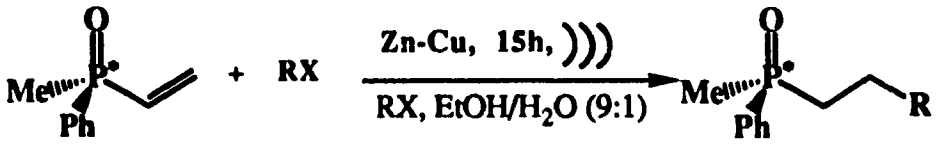
45 46

The reactivity of the halides follows the order of tertiary> secondary>> primary, and iodide> bromide (chlorides do not react). The preferred solvent system is aqueous ethanol. The process is suggested to proceed by a free radical mechanism occurring on the metal surface under sonochemical conditions. Effects to trap the intermediate by intramolecular cyclization only gave a very low yield of the cyclization product **49** (Eq. 12).[55]



(Eq. 12)

47 48 49



50 51 (Eq. 13)

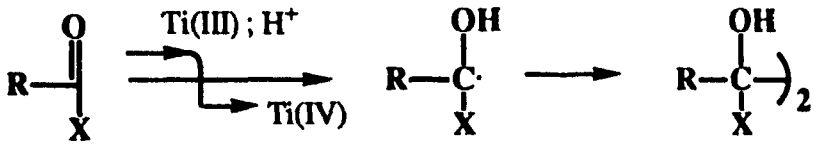
Similar additions were also found to occur on vinylphosphine oxide. When optically active vinylphosphine oxide **50** was used, P-chiral alkylphosphine oxide **51** was obtained (Eq. 13).[56]

1.2.3 Pinacol Coupling Reaction

Coupling of carbonyl compounds[57] to give 1,2-diols, known as "pinacol coupling", is one of the earliest organometallic reactions carried out in aqueous media. The use of a Zn-Cu couple to couple unsaturated aldehydes to pinacols was reported as early as 1892.[58] Early experiments also included the use of chromium and vanadium,[59] as well as some ammoniacal $TiCl_3$[60] based reducing agents. These early coupling reactions were all performed under aqueous conditions.

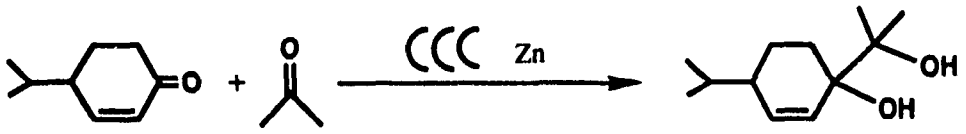
Recently, aqueous pinacol coupling by Ti(III) has been further studied by Clerici and Porta. Aromatic ketones and aldehydes were homocoupled by $TiCl_3$ in aqueous solution under alkaline conditions.[61,62] When this reagent was used in acidic solutions, aliphatic or aromatic ketones or aldehydes containing "activating" (strongly electron-withdrawing) groups have been coupled with themselves to give homo coupling products,[63] or with unactivated carbonyl compounds to give unsymmetrically cross-coupled products when the unactivated carbonyl compounds was used in excess or as solvent.[61,64-67] The activating groups

included CN, CHO, COMe, COOH, COOMe, and pyridyl. The mechanism of this reaction is suggested to be a radical process (Eq. 14).



52 53 54 (Eq. 14)

Cross coupling reactions between α,β-unsaturated carbonyl compounds and acetone was carried out under the influence of a Zn-Cu couple and ultrasonic radiation in aqueous acetone suspension (Eq. 15).[68] A similar radical mechanism was suggested.



55 56 57 (Eq. 15)

1.3 Transition Metal Catalyzed C-C Formation Reactions in Aqueous Media

The development of transition-metal reagents for use in aqueous solvent systems offers the same advantages for a wide variety of chemical processes ranging from large-scale industrial processes to laboratory organic synthesis. The advantage of aqueous methodology for large scale chemical manufacturing is in simplifying catalyst-product separation, and recycling the catalyst.

In 1973, the first unsuccessful attempt to carry out a transition metal-catalyzed hydrogenation reaction of olefins in aqueous solution in the presence of alkylphosphine was reported.[69] However, the experiment did

show that water does not interfere with the soft catalytic system. According to the hard and soft acid and base theory,[72] water, which has low energy-occupied frontier orbitals, is a "hard" base, whereas reaction intermediates in conventional organometallic catalysis often have a "soft" character.

1.3.1 Carbonylation Reactions

Hydroformylation of Olefins

Hydroformylation is a major industrial process that produces aldehydes and alcohols from olefins, carbon monoxide and hydrogen (Eq. 16).[70]

$$\underset{58}{RCH{=}CH_2} + CO + H_2 \xrightarrow{\text{"Co"}} \underset{59}{RCH_2CH_2CHO} + \underset{60}{R(CH_3)CHCHO} + \ldots \quad \text{(Eq. 16)}$$

The reaction was discovered in 1938 by Roelen,[71] who detected the formation of aldehydes from olefin, carbon monoxide, and hydrogen in the presence of a cobalt-based catalyst. Since then, a lot of improvements have been made on this process.[72] However all of them involve the tedious separation of catalyst and products from the reaction system. Later improvements were based to the attachment of a normally soluble catalyst to an insoluble support, in an attempt to combine the virtues of both homogeneous and heterogeneous catalysts.[73] Unfortunately, this approach encounters the problems of metal leaching into the solvent, lowered activity or selectivity, and facile oxidation of the ligands.[74]

Recently, another approach to the catalyst and product separation problem has been developed based on the use of transition-metal complexes with water soluble ligands (trisodium salt of tri(m-sulfophenyl)phosphine

P-(m-$PhSO_3Na)_3$,[72,75-77] $Ph_2PCH_2CH_2NMe_3^+$)[78] and water as a nonmiscible solvent for hydroformylation. Generally, the catalyst is a Rh complex. As the catalyst is practically insoluble in the aldehyde products, the recovery of the catalyst can be achieved by simple phase separation. Thus, the novel aqueous process exhibits the best performance (yield, heat recovery, etc) in hydroformylation.[72] The hydroformylation can also be performed by using methyl formate instead of carbon monoxide and hydrogen.[79]

Carbonylation of Allylic and Benzylic Halides

The transition metal-catalyzed carbonylation of allyiic and benzylic compounds offers a useful method for the synthesis of β,γ-unsaturated acids.[80] 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.[81] In 1977, it was found that carbonylation of benzyl bromide and chloride could be carried out by stirring aqueous sodium hydroxide with an organic solvent in the presence of a phase transfer agent by the catalysis of a cobalt complex.[82,83] Under high pressure and temperature, even benzylic mercaptans can react to give esters in the same way (Eq. 17).[84]

$$\underset{61}{RSH} + CO + \underset{62}{R'OH} \xrightarrow[850\text{-}900\ psi,\ 190^oC,\ 24h]{Co_2(CO)_8,\ H_2O} \underset{63}{RCOOR'} + H_2S \quad \text{(Eq. 17)}$$

Under the catalysis of nickel complexes, similar carbonylation of allyl bromide and chloride in aqueous NaOH can be carried out at atmospheric pressure.[85] The base concentration significantly influenced the yield and the product distribution.

More recently, it was found that palladium-catalyzed carbonylation of allyl chloride proceeded smoothly in two-phase aqueous NaOH/benzene medium under atmospheric pressure at room temperature (Eq. 18).[81] Catalysts either with or without phosphorus ligands gave the same result. The presence of OH^- was essential. The reaction seemed to occur at the liquid-liquid interface, since there was no phase-transfer agent being used.

$$\underset{\mathbf{64}}{CH_2{=}CHCH_2Cl} + CO + \underset{\mathbf{65}}{ROH} \xrightarrow{[Pd]} \underset{\mathbf{66}}{CH_2{=}CHCH_2COOR} + HCl \qquad \textbf{(Eq. 18)}$$

R= H, CH_3, C_2H_5, etc.

Carbonylation of Aryl Halides

Carbonylation of aryl halides in the presence of various nucleophiles and catalyzed by palladium complexes, is a convenient method for the syntheses of various aromatic carbonyl compounds, e.g. acids, esters, amides, thioesters, aldehydes and ketones. Aromatic acids bearing different aromatic fragments and having various substituents on the benzene ring have been prepared from aryl iodides at room temperature under 1 atm CO in a mixed solvent of H_2O/DMF (1/1 or 1/2, V/V), and even in water alone, depending on the solubility of the substrate (Eq. 19).[86] The palladium(II) complexes: $Pd(OAc)_2$, K_2PdCl_4, $PdCl_2(PPh_3)_2$ and $Pd(NH_3)_4Cl_2$ were used as the precursors of the catalyst, with either K_2CO_3 or NaOAc as the base.

$$\underset{\mathbf{67}}{Ar\text{-}I} \xrightarrow[-\ I^-]{CO,\ OH^-,\ \text{"Pd"}} \underset{\mathbf{68}}{ArCOO^-} \xrightarrow{H^+} \underset{\mathbf{69}}{ArCOOH} \qquad \textbf{(Eq. 19)}$$

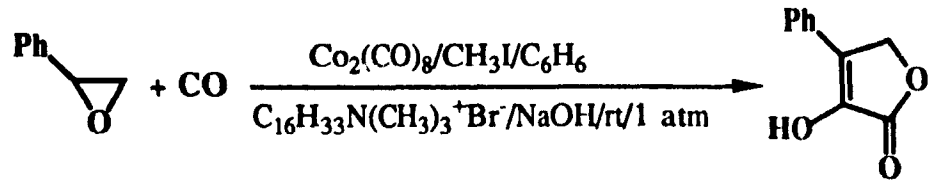
Ar= XC_6H_4, Naph, Het (het = heteryl)

Under the appropriate conditions of pressure and temperature, aryl mercaptans (thiophenols) can also be carbonylated in aqueous media .[87,88]

Other Carbonylation Reactions

Carbonylation of 1-perfluoroalkyl-substituted 2-iodoalkanes has been carried out in aqueous medium catalyzed by transition-metal complexes to give carboxylic acids with perfluoroalkyl substituent at β position.[89]

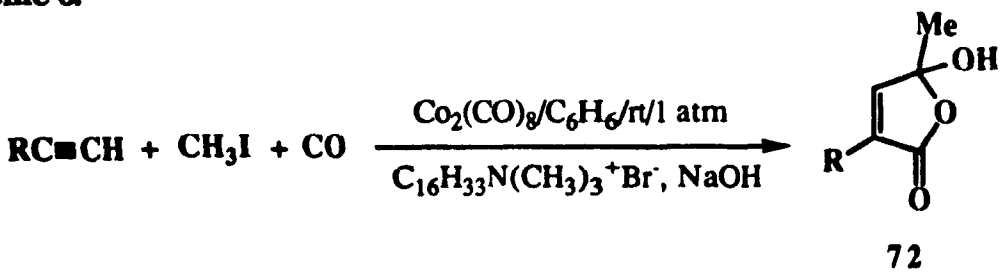
Double carbonylation in aqueous medium has also been reported. Reaction of methyl iodide with styrene oxide and carbon monoxide by the catalysis of cobalt complex resulted in the incorporation of two molecules of carbon monoxide, to give the enol **71** (Eq. 20).[90]



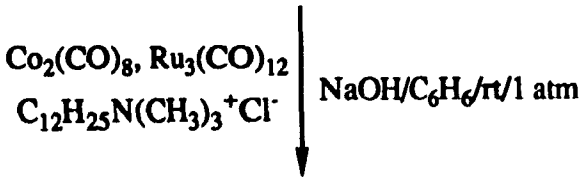
(Eq. 20)

70 **71**

Scheme 6.



72

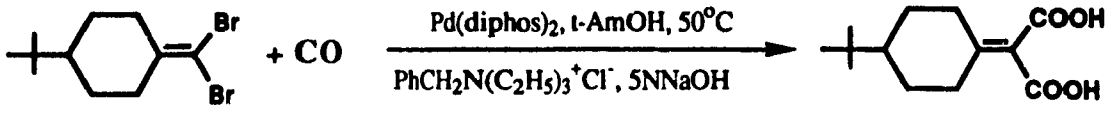


$RCHCH_2COCH_3$
|
COOH

73

Similariy, reaction of methyl iodide with alkynes and carbon monoxide resulted in the formation of 2-butenolides **72**. If the reaction mixture was first treated with the cobalt complex and then reacted with ruthenium carbonyl, the γ-keto acids **73** were obtained (Scheme 6).[91]

Under the catalysis of palladium complexes, biscarbonylation of the vinylic dibromide **74** by carbon monoxide in NaOH solution gave the unsaturated diacid **75** (Eq. 21).[92]

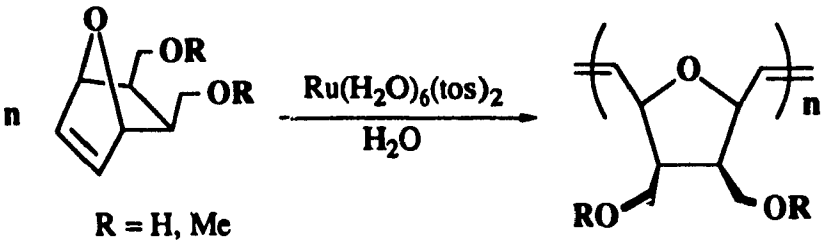


74 80% **75** **(Eq. 21)**

1.3.2 Metathesis Polymerization Reaction

The first attempt[93] of emulsion polymerization of norbornenes in aqueous solution using Ir complexes as catalyst was reported in 1965.

Recently, Novak and Grubbs reported that derivatives of 7-oxanorbornene rapidly polymerized in aqueous solution under an atmosphere of air by the catalysis of some selected group VIII coordination complexes, to provide quantitative yield of ring-opening metathesis polymerization (ROMP) polymer (Eq. 22).[94]



R = H, Me

76 **77** **(Eq. 22)**

Compared with the same reaction carried out in organic solvent, initiation time decreased from 22-24h to 30-35min. It was also found that 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 seconds. Solutions containing these aqueous catalysts had been recycled for 14 successive polymerizations without any detectable loss of activity.

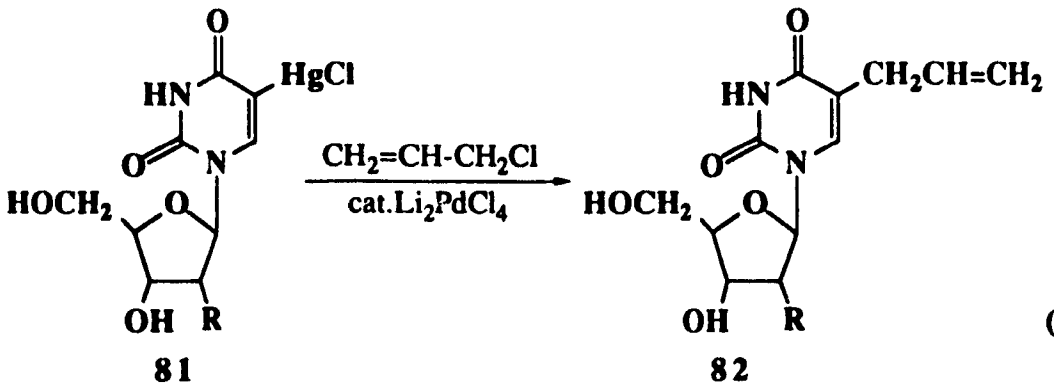
This extraordinary stability to air and water displayed by normally highly reactive organometallic intermediates (metal carbenes and metallacyclobutanes) suggests the intriguing possibility that aqueous coordination complexes might find a wider application in other established (but sensitive) catalytic processes.

1.3.3 Alkylation and Coupling Reactions

As early as in 1970, arylsulfinic acids have been coupled to biaryls with Pd(II) in aqueous solvents (Eq. 23).[95] In the presence of carbon monoxide, olefins or nitriles, insertion reactions take place leading to the carbonylation, vinylation, or acylation of arenesulfinate anions in low to moderate yields.

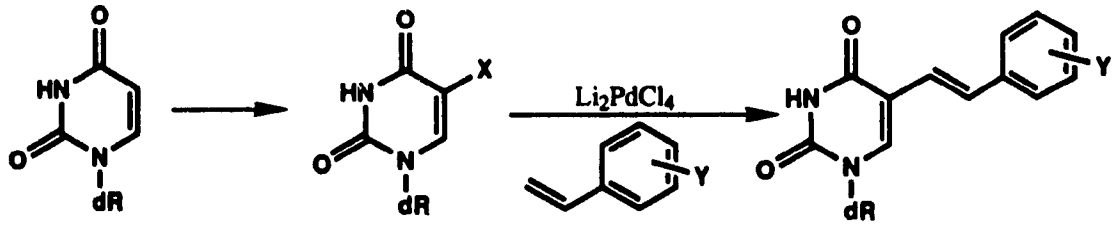
$$\underset{\textbf{78}}{2ArSO_2Na} + \underset{\textbf{79}}{Na_2PdCl_4} \xrightarrow{H_2O} \underset{\textbf{80}}{Ar\text{-}Ar} + 2SO_2 + Pd + 4NaCl \qquad \textbf{(Eq. 23)}$$

Later, synthesis of C-5 substituted pyrimidine nucleosides **82** was carried out in water *via* the mercurated intermediate **81** under the catalysis of Li_2PdCl_4 (Eq. 24).[96]



81 82 (Eq. 24)

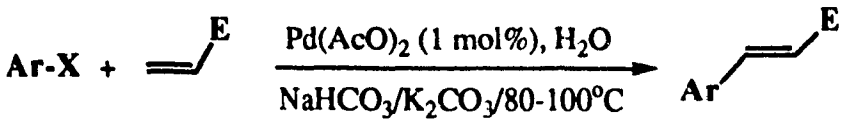
Pd(II) catalyzed coupling of the 5-mercuriuridines 84 with styrenes in aqueous media gave alkylation of the uracil nucleotides (eq. 25).[97] The reaction was not adversely affected by the presence of phosphate groups or sugar hydroxyls, and was compatible with nitro, amino, and azido substitution on the phenyl ring of the styrene.



83 84 85 86 (Eq. 25)

A similar reaction was used in the synthesis of 5-(3-amino)allyluridine and deoxyuridine-5'-triphosphates (AA-UTP and AA-dUTP).[98]

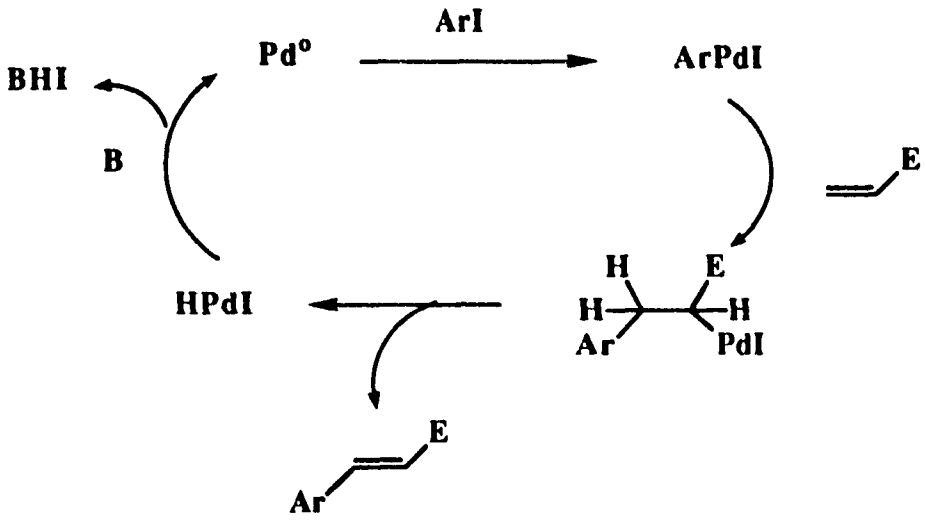
Palladium catalyzed coupling reactions of aryl halides with acrylic acid and acrylonitrile in high yields in the presence of a base ($NaHCO_3$ or K_2CO_3) in water were reported (Eq. 26).[99,100] The reaction provided a new and simple method for the synthesis of substituted cinnamic acids and cinnamonitriles.



87 88 (Eq. 26)

The catalytic cycle of this reaction is proposed as in Scheme 7 (X = COOH, CN).

Scheme 7.



Very recently, Casalnuovo and Calabrese reported that various aryl bromides and iodides coupled with aryl and vinyl boronic acids, terminal alkynes and dialkyl phosphites under the catalysis of a water soluble Pd(0) complex, $Pd(PPh_2(m\text{-}C_6H_4SO_3M)_3$ (M= Na^+, K^+), to give the cross coupling products in high yields (Eq. 27).[101]

R-X + R'-Y ----------> R-R' **(Eq. 27)**

89 90 91

X = Br, I; Y = H, $B(OR)_2$; R = aryl, heteroaromatic;
R' = aryl, vinyl, alkynyl, $P(O)(OR)_2$

The reaction can tolerate a broad range of functional groups, including those present in unprotected nucleotides and aminoacids.

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Chapter 2. Allylation of Carbonyl Compounds in Aqueous Media and Its Synthetic Applications

The importance of organometallic reactions in organic synthesis requires no elaboration. A cardinal restriction in the use of many organometallic reagents is the strict exclusion of moisture. Extreme care must be exercised to ensure that the solvents and the reagents are anhydrous. The reaction often has to be conducted under inert atmosphere, sometimes inside a dry box. A corollary to this moisture sensitivity is that organic substrates with functional groups containing labile protons must be appropriately protected during the reaction.

For some time, we have been intrigued by the possibility of conducting organometallic-type (Barbier-Grignard type) reactions in aqueous medium for the formation of carbon-carbon bond.

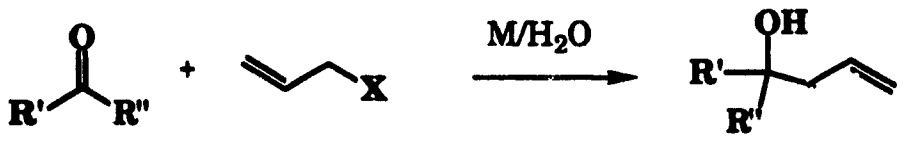
The first attempt made by us in this area was allylation reaction of carbonyl compounds by allyl halides to produce homoallyllic alcohols(Eq. 1). Initially, some reductive low valent water soluble metal salts such as $CrCl_2$, SmI_2, $SnCl_2$, $TiCl_3$ etc. were chosen as the mediator. All of them met with failure in either pure water or a mixture of water and organic solvents, although some of them could do so in dry organic solvents.

At this point, another approach was considered. It has been known that tribenzylstannyl chloride is stable in water, and it has been prepared in large scale in industry from benzyl chloride and tin metal or tin dichloride in a mixed solvent of benzene and water under refluxing conditions.[1] The stability of this organic tin compound in water suggests the possibility that upon the addition of a carbonyl compound (or other electrophiles), a

coupling reaction might take place. However, when aldehydes were mixed with benzyl chloride and tin in water under the same conditions, the reaction still gave tribenzylstannyl chloride as the only product. We suspected that the failure of the coupling reaction was possibly due to the fact that tribenzylstannyl chloride is not active enough (or it is too stable).

2.1 Allylation Reactions Promoted by Zinc and Tin in Water

In the above reaction, when the more reactive allyl bromide, instead of benzyl chloride, was used under the same conditions, the corresponding allylation product was produced almost quantitatively. Both aromatic aldehydes and aliphatic aldehydes gave good yields of the products. The exceptions to this were p-*N*,*N*-dimethylaminobenzaldehyde and p-nitrobenzaldehyde. Both of them did not react. Free hydroxyl groups somewhere in the molecule did not interfere with the reaction (Entries 8, 10, 12, Table 1). The allylation reaction usually proceeded upon heating (between 50-80°C), and failed to proceed at room temperature. α,β-Unsaturated carbonyl compounds reacted in a 1,2-fashion. Some examples are listed in Table 1. The reaction can take place with pure water as the medium. However, addition of a small amount of benzene (1 mL in 10 mL of water) often facilitated the stirring of the reaction mixture.



1 2 M= Sn, Zn 3 (Eq. 1)

Table 1. Allylation of Aldehydes With Allyl Bromide Mediated by Tin

Entry	Aldehyde	Time	Temp(°C).	3	Yield
1	PhCHO	2h	80	3a	95
2	p-ClPhCHO	2h	80	3b	86
3	p-MePhCHO	2h	80	3c	96
4	$CH_3(CH_2)_7CHO$	2h	80	3d	quant.[a]
5	$(CH_3)_3CCHO$	2h	80	3e	65
6	p-n-$C_5H_{11}OPhCHO$	2h	80	3f	97
7	p-NO_2PhCHO	3h	80		0
8	$HOCH_2C(CH_3)_2CHO$	2h	80	3g	quant.[a]
9	p-$Me_2NPhCHO$	3h	80		0
10	$HO(CH_2)_4CHO$	1.5h	80	3h	quant.[a]
11	PhCH=CHCHO	7h	50	3i	50
12	$CH_2(OH)CH(OH)CHO$	3h	80	3j	90
13	PhCH=CHCHO	1.5h	80	3k	98[a]

The yields were based on the aldehydes; a). ^1H NMR yield.

The allylation reaction was also found to be successful with zinc at a lower temperature (40°C) (Table 2). In this case, the less expensive allyl chloride was also effective. The reaction however was sensitive to the different structure of the ketones. While cyclohexanone reacted smoothly to give the corresponding homoallylic alcohol in good yield, 5-nonanone or 2-pentanone failed to react at all. In the latter two cases, the ketone was recovered but the allylic halide was consumed. This suggests that the organometallic species reacted with water faster than with the carbonyl substrate in these cases because of the steric hindrance of ketones (relative to aldehydes).

In both metal mediated allylation reactions, commercially available metallic powder can be used without pre-activation. No inert atmosphere

protection or other special apparatus is required. Thus, these simple allylation procedures are both practical and convenient.

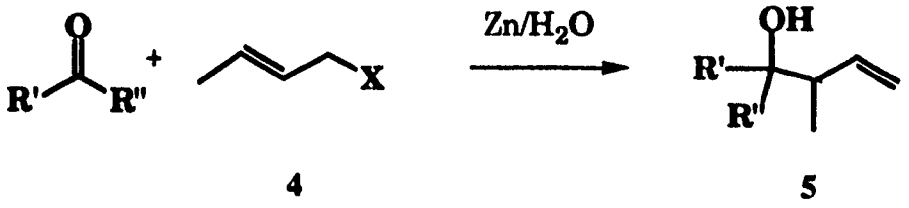
Table 2. Allylation of Aldehydes and Ketones Mediated by Zinc

Entry	Aldehyde	Time	Temp(°C).	3	Yield
1	PhCHO	4h	40	3a	98
2	$CH_3(CH_2)_3CHO$	2h	40	3l	95
3	$(CH_3)_3CCHO$	2h	40	3e	92
4	$CH_3(CH_2)_7CHO$	2h	40	3d	90
5	$C_6H_{11}CHO$	2h	40	3m	94
6	$CH_3CH=CHCHO$	4h	r.t.	3n	80
7	$(CH_3)_2CHCHO$	2h	40	3o	85
8	cyclohexanone	4h	40	3p	81
9	$CH_3(CH_2)_2COCH_3$	4h	40		0
10	$CH_3(CH_2)_3CO(CH_2)_3CH_3$	4h	40		0

Table 3. Reaction of Aldehydes With Crotyl Halide Mediated by Zinc

Entry	Aldehyde	Crotyl X	Solvent	Time	Temp.	Yield		Thre./Ery.[a]
1	PhCHO	crotyl Br	H_2O	2h	50°C	5a	90	45/55
2	PhCHO	crotyl Br	H_2O/ether[b]	2h	50	5a	98[c]	42/58
3	PhCHO	crotyl Br	H_2O/THF[b]	2h	50	5a	90[c]	40/60
4	PhCHO	crotyl Br	H_2O/Benz.[b]	2h	50	5a	92[c]	41/59
5	PhCHO	crotyl Cl	H_2O	2h	reflux	5a	85[c]	42/58
6	PhCHO	crotyl Cl	H_2O	2h	45	5a	82[c]	44/56
7	PhCHO	crotyl Cl	H_2O	14h	r.t.	5a	50[c]	50/50
8	$CH_3(CH_2)_7CHO$	crotyl Br	H_2O	2h	50	5b	87	40/60
9	$(CH_3)_2CHCHO$	crotyl Br	H_2O	2h	50	5c	85	75/25
10	$C_6H_{11}CHO$	crotyl Br	H_2O	2h	50	5d	94	71/29
11	$(CH_3)_3CCHO$	crotyl Br	H_2O	2h	50	5e	90	85/15

a): Threo/erythro ratio were determined by ^1H NMR; b): 4 mL/2 mL; c): ^1H NMR yield.



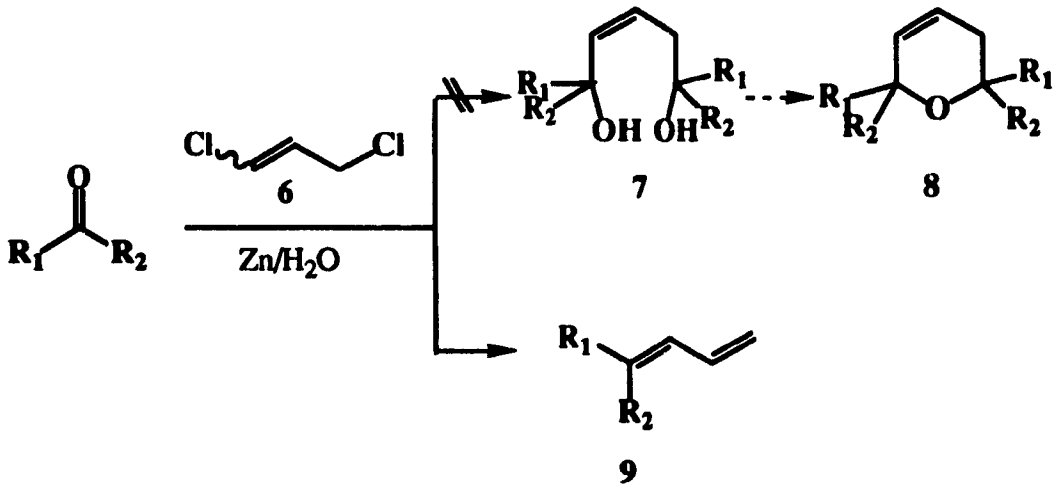
4 5 (Eq. 2)

Allylation with allylic halides bearing substituents is also effective. Reaction of carbonyl compounds with crotyl halide **4** mediated by zinc is regiospecific in giving the allylation products. However, the reaction showed no special diastereoselectivity as indicated in Table 3.

2.2 Synthesis of 1,3-Butadienes

Often, dienes were synthesized from carbonyl compounds by Wittig reaction, which has been found to suffer from competing aldol condensation,[2,3] lack of regiocontrol,[4] low yield and lack of stereoselectivity. The other conventional organometallic reactions used for diene synthesis, mediated by silicon[5] or tin,[6] pose the usual restriction of moisture sensitivity.

Scheme 1.



A simple synthesis of 1,3-butadienes from carbonyl compounds can be accomplished by immediate application of the aqueous allylation reactions. Initially, we attempted to generate dihydropyran derivatives **8** by using 1,3-dichloropropene **6** promoted by zinc powder. The reaction did not give the diol **7** (dihydropyran precursor). Instead, a compound with low polarity was produced as the major product. After characterization, the compound was found to be the conjugated 1,3-butadiene **9** (Scheme 1). The reaction was developed as a new methodology for diene synthesis.[7]

Table 4. 1-Phenyl-1,3-butadiene Prepared from Benzaldehyde and 1,3-Dichloropropene

Entry	M/ald/halide	Temp.	Solvent.	Time	Yield(**9a**)
1	2/2/1	80°C	H_2O	3h	69*
2	2/1/1	35	H_2O	4	51
3	2/1/1	20	H_2O	10	46
4	2.5/1/1.5	35	H_2O	2	47
5	2/1/1	35	H_2O/Et_2O(1:1)	6	33
6	2/1/1	reflux	Et_2O	20	0
7	2/1/1	reflux	THF	20	0

* Based on $ClCH{=}CHCH_2Cl$.

The reaction has a number of interesting features: Firstly, it is important to note that in the reaction of benzaldehyde, the yield of 1-phenylbutadiene was quite satisfactory under these conditions, but failed to proceed at all in normal organic solvents such as diethyl ether and THF. Secondly, the reaction seemed to proceed with both aldehydes and ketones. Thirdly, the butadienes were formed stereoselectively and in the case of

aldehydes, exclusively the E-isomers were obtained according to the ^1H NMR spectra of the dienes. Furthermore, unprotected hydroxy compounds such as glyceraldehyde and 5-hydroxypental underwent the diene conversion without difficulty. On the other hand, the yield of the diene was modest at best in all cases, in spite of efforts in varying the reaction temperature, time, amount of metal etc. (Tables 4 and 5).

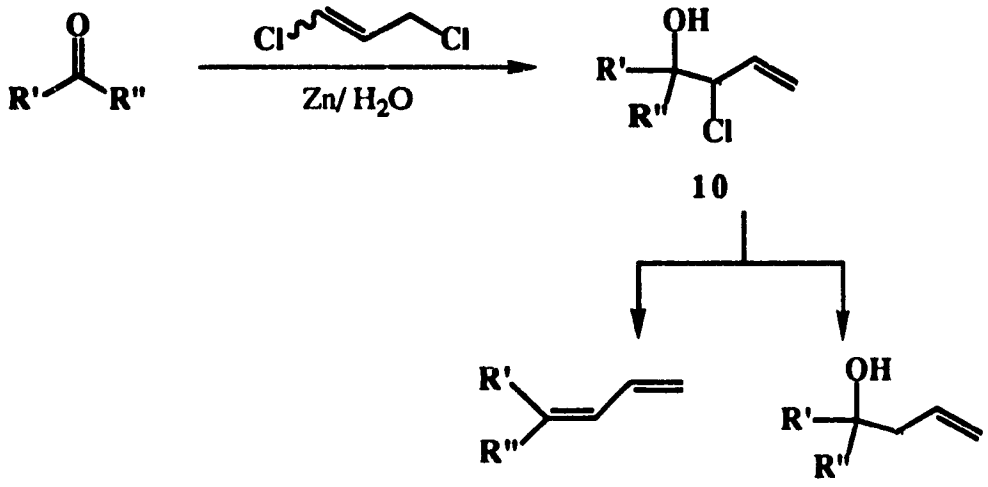
Table 5. Other Dienes Prepared with 1,3-Dichloropropene

Entry	Aldehyde	Time	Product(9)		Yield
1	$CH_3(CH_2)_8CHO$	3h	**9b**	$CH_3(CH_2)_8CH=CHCH=CH_2$	53
2	$c\text{-}C_6H_{11}CHO$	3	**9c**	$C_6H_{11}CH=CHCH=CH_2$	48
3	$C_6H_5CH=CHCHO$	3	**9d**	$C_6H_5CH=CHCH=CHCH=CH_2$	38
4	$C_6H_5COCH_3$	20	**9e**	$C_6H_5C(CH_3)=CHCH=CH_2$	22
5	$C_9H_{16}O$	3	**9f**	$C_9H_{16}=CHCH=CH_2$	36
6	$(CH_3(CH_2)_3)_2CO$	15		no reaction**	
7	$CH_3(CH_2)_8COCH_3$	6	**9g**	$CH_3(CH_2)_8C(CH_3)=CHCH=CH_2$	33
8	$HO(CH_2)_4CHO$	6*	**9h**	$THPO(CH_2)_4CH=CHCH=CH_2$	42

All the reactions were carried out with a ratio of metal/aldehyde/halide=2/1/1 at 35°C in water. The yields are based on the carbonyl compounds. * 0.5 mL of 5% HBr was added to catalyze the reaction. **20% of the product was obtained when the reaction was catalyzed by 0.5 mL 5% HBr and 0.2 mL of saturated NH_4Cl.

After careful separation and characterization of the by-product, the poor yield was traced to the formation of the homoallylic alcohol **3**, which must have been formed by the zinc mediated reduction of the intermediate chlorohydrin **10**. Thus, the yield of the diene might be increased if the reactivity of chloro and hydroxyl groups in the intermediate could be differentiated. Efforts to increase the leaving ability of hydroxyl group of **10** with HMPA or triphenylphosphine through coordination between

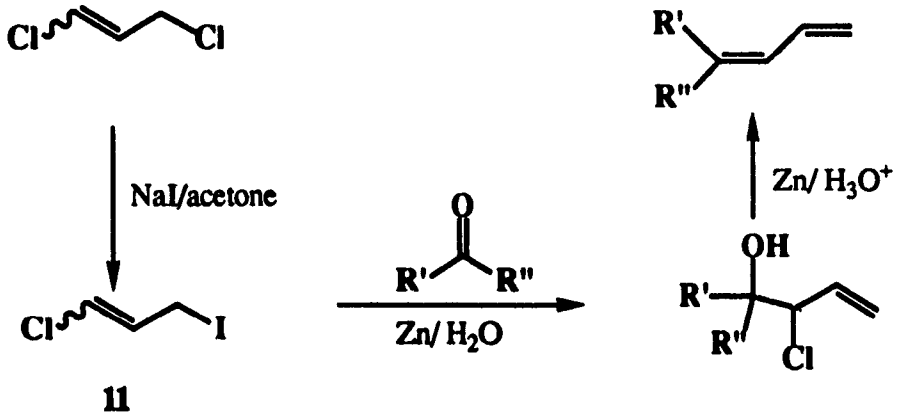
phosphorus and oxygen atoms did not succeed.



9 3

Scheme 2

Scheme 3.



Later, it was found that the aqueous reaction had a high chemoselectivity between different allyl halides. Consequently, the reaction can be manipulated to stop at the chlorohydrin stage by using 1-chloro-3-iodopropene instead of 1,3-dichlopropene. The 1-chloro-3-iodopropene can be easily obtained from the reaction of 1,3-dichloropropene and anhydrous NaI in acetone. At this stage, the leaving ability of the hydroxyl group can

be easily enhanced through protonation by a small amount of 48% HBr acid, to give the diene in high yield (Table 6).

It is interesting to note that the diastereomeric ratio of the precursor chlorohydrin is distinctly different from the E/Z ratio of the diene. This suggests that the reduction of the intermediate **10** to give the diene **9** under the experimental condition is non-stereospecific, but selective in giving the thermodynamically more stable E-isomer.

Table 6. Synthesis of 1,3-Butadienes with 1-Chloro-3-iodopropene

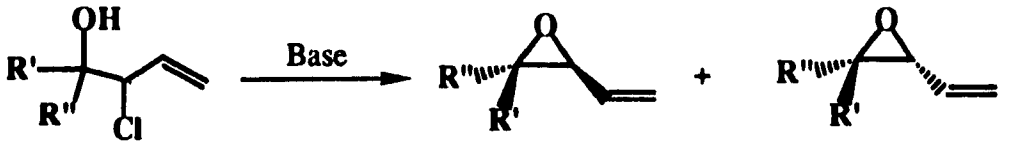
Entry	Ald.(ket.)	syn/anti(**10**)	Product(**9**)	Yield	(trans:cis)
1	C_6H_5CHO	64/36	**9a** $C_6H_5CH=CHCH=CH_2$	95	>98:2
2	ClC_6H_5CHO	64/36	**9i** $ClC_6H_5CH=CHCH=CH_2$	97	>98:2
3	MeC_6H_5CHO	64/36	**9j** $MeC_6H_5CH=CHCH=CH_2$	95	>98:2
4	$CH_3(CH_2)_8CHO$	52/48	**9b** $CH_3(CH_2)_8CH=CHCH=CH_2$	92	95:5
5	c-$C_6H_{11}CHO$	A	**9c** $C_6H_{11}CH=CHCH=CH_2$	93	>98:2
6	$C_6H_5CH=CH\text{-}CHO$	A	**9d** $C_6H_5CH=CHCH=CHCH=CH_2$	86	>98:2
7	$C_6H_5COCH_3$	A	**9e** $C_6H_5C(CH_3)=CHCH=CH_2$	80	85:15
8	cyclohexanone	A	**9k** $C_5H_{10}C=CHCH=CH_2$	95	
9	$CH_3(CH_2)_8COCH_3$	A	**9g** $CH_3(CH_2)_8C(CH_3)=CHCH=CH_2$	75	68:32

All the reactions were carried out *via* Scheme 3; A, not determined.

2.3 Synthesis of Vinyloxiranes

In the above diene synthesis, when the reaction of carbonyl compounds with 1-chloro-3-iodopropene was interrupted after the first stage by extraction with ether, the intermediate chlorohydrin was isolated. Treatment of the chlorohydrin in ethanolic NaOH gave vinyloxirane in quantitative yield (Eq. 3).[7] In this case, the trans/cis ratio of the produced vinyloxiranes was in agreement with the diastereomeric ratio of the

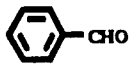
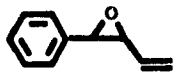
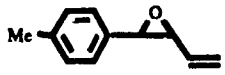
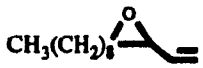
precursor chlorohydrin.



(Eq. 3)

12(a) 12(b)

Table 7. Synthesis of Vinyloxiranes

Entry	Aldehyde	Metal(method)	Product	%Yield	cis:trans
1		Sn (A)		12a 91	84:16
2		Zn (B)		12a 95	64:36
3		Sn (A)		12b 90	85:15
4		Zn (B)		12b 95	64:36
5		Sn (A)		12c 88	84:16
6		Zn (B)		12c 93	64:36
7	CH3(CH3)8CHO	Sn (A)		12d 82	80:20
8		Zn (B)		12d 92	52:48
9		Sn (A)		polymer	—
10		Zn (B)		12e 93	—

Method A, ultrasonic wave; method B, stirring; the cis/trans ratios were determined by ^{1}Hnmr according to literature.

However, while the production of 1,3-butadienes possessed high trans selectivity, the reaction gave only slight cis selection toward oxiranes. Changing the metal zinc to metal tin gave the chlorohydrin intermediate in less than 10% yield. Attempts to increase the yield by changing the reaction conditions met with failure.

It has been known that ultrasound can activate Barbier type reactions through changing the property of the metal surfaces, and ultrasound promoted allylation of carbonyl compounds by Sn with allyl chloride or bromide has been reported before.[8] When the reaction mixture of the carbonyl compounds, 1-chloro-3-iodopropene, and Sn powder was subjected to ultrasonic radiation at room temperature, the chlorohydrin intermediate was obtained in high yield. The chlorohydrin was in turn transformed to vinyloxiranes in the same way as the Zn method (Scheme 1). Interestingly, the Sn method has a much higher cis diastereoselectivity of the final vinyloxiranes than the Zn one. A comparison of the results between Zn and Sn is listed in Table 7.

The effect of ultrasonic wave on the reaction appears the same as in other reports. The addition of a small amount of ether greatly helped the dispersion of Sn powder in the solution during the sonication.

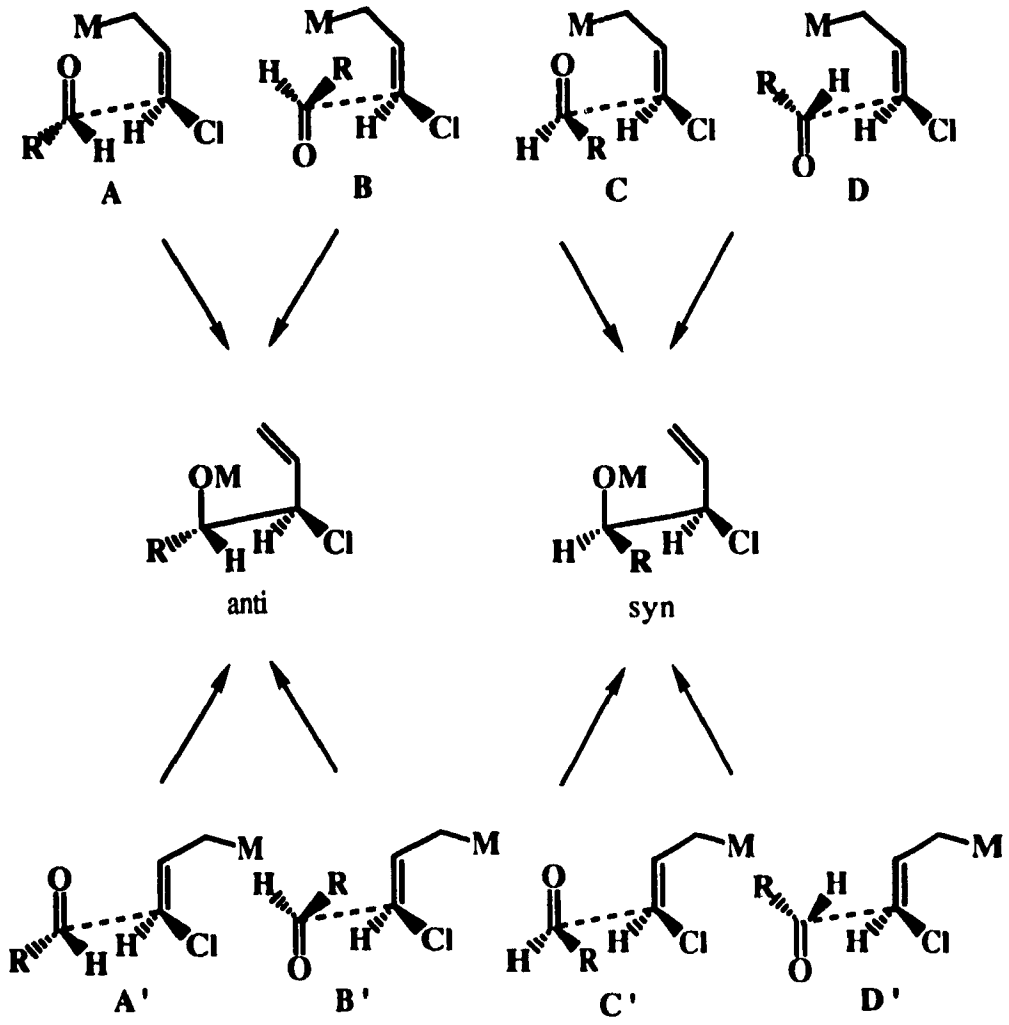
In the absence of ultrasonic radiation, a low yield (<10%) of **10** but with the same stereoselectivity was obtained. Addition of organic solvent to the reaction system did not change the cis/trans ratio of the final product. Similar selectivities were reported previously by $SnCl_2$ in organic solvent, in the preparation of vinyloxiranes,[9a] where only ca. 50% of the product was obtained.

The ^1H NMR and GC analysis of the starting 1-chloro-3-iodopropene showed the presence of a mixture of cis and trans isomers in a ca. 5:3 ratio.

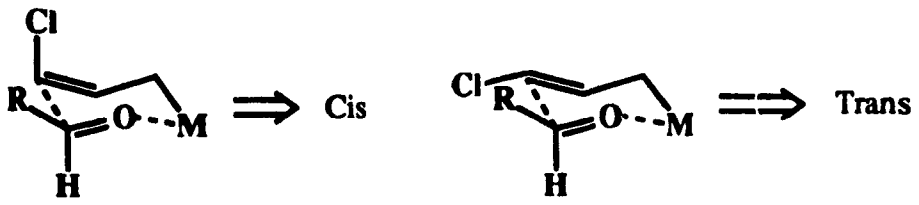
Thus, the reaction was not stereospecific and it also depended on the metal used. The cis stereoselectivity (cis:trans > 4:1) with tin indicated that both cis and trans starting material favoured the cis product.

The stereoselectivity could not be explained by the usually proposed cyclic chair form transition state for allylations with organometallic reagents,[9b] because it would have predicted different stereochemistries with cis or trans starting material. A reasonable explanation for the stereochemistry is that the chelation between Sn and the carbonyl oxygen was not important here, and the reaction proceeded *via* non cyclic transition states (A, B, C, D, and A', B', C', D'). Therefore, the product formation is mainly determined by steric reasons. Scheme 4a shows the possible transition states leading to syn (cis product) and anti (trans product) chlorohydrins based on this assumption. Because the transition states A, A' and C, C' have the eclipsed conformations and the transition states B, B' have the R group in gauche relation to both vinyl and chloro groups. It is easy to decide that among the eight possible geometries, two (D and D') are favoured. A similar explanation was used for the stereoselectivities, regardless of the stereochemistry of starting material, of the allylation of aldehydes by crotyltin[9d] and γ-alkoxallyltin[9c] reagents in organic solvent.

When the allyl organometallic reagent has greater ionic properties between the carbon-metal bond, it is conceivable that the propensity for a cyclic transition state will be increased. Therefore, the cis selectivity with zinc is decreased. Indeed, the cis/trans ratio of the chlorohydrin intermediate reflected the cis/trans ratio of starting iodide. Thus, the reaction with zinc is better explained by the cyclic transition states in Scheme 4b.



Scheme 4a



Scheme 4b

2.4 Synthesis of Methylenetetrahydrofurans

Initially postulated by a theoretician,[10] trimethylenemethane (TMM) has been a favorite molecule for quantum mechanical calculations. TMM was invoked as a possible intermediate in methylenecyclopropane

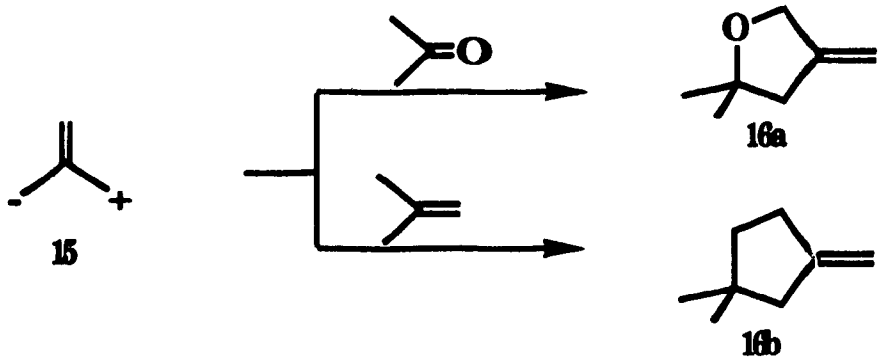
rearrangement[11] and in the decomposition of pyrazoline in gas phase.[12] The triplet state of TMM was identified by ESR spectroscopy[13] and subsequently shown to be the ground state of the diradical.[14] The chemistry of TMM has been reviewed several times in the literature.[11]

13 14 (Eq. 4)

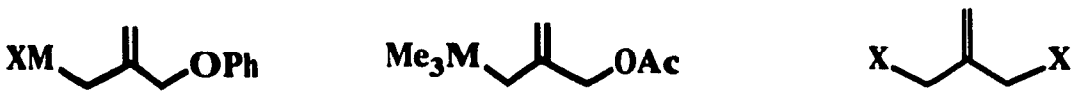
Sporadic reports of intermolecular reactions of TMM and its derivatives, generated from a variety of precursors, appeared in the 1960's,[11] but the yields of the products were usually low. The principal reaction was cyclization to methylenecyclopropane. This cyclization is extremely fast in the singlet manifold, even the more stable triplet form only requires an activation barrier of 7.7 kcal/mol for cyclization.[15,16] Thus, application of TMM itself in organic synthesis is limited.

TMM Equivalent

Scheme 4c

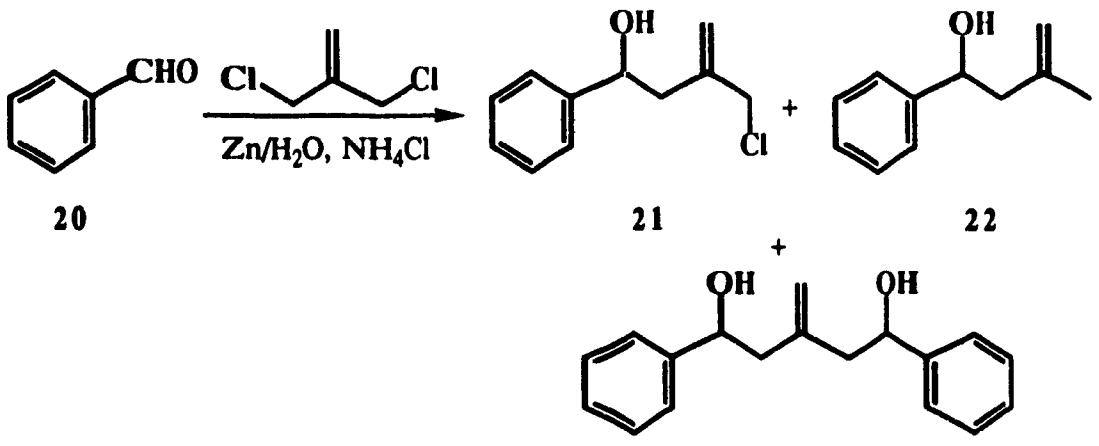


15 16a 16b



17 18 19

On the other hand, a TMM equivalent, the 1,3-dipolar species **15**[16] which bears a nucleophilic and an electrophilic center, is quite useful in synthesis since it can react with a carbonyl functionality (or its equivalent) in 3+2 fashion to yield a 5-membered ring product (Scheme 4c). Methods developed for the generation of a TMM equivalent include the use of precursors **18** (M= Sn or Si) where the nucleophilic component contains a stable organometalloid function rather than the more reactive conventional organometallic function.[17] Alternatively, for reagents (e. g. **17**, M= Zn or Mg) containing the more nucleophilic organozinc[18] or organomagnesium[19] moiety, the electrophilic center tends to be the less reactive ether function. Such a balance of reactivity of the two polar centers is necessary to prevent self cyclization or di- and polymerization.

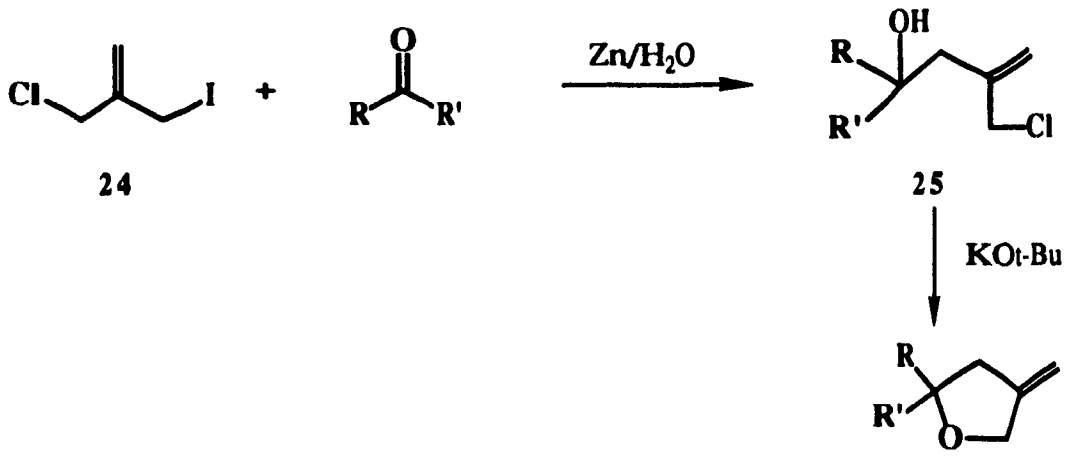


20 **21** **22** **23**

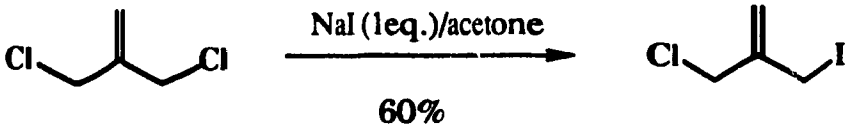
Scheme 5

As part of our study on the area of organometallic reactions in aqueous media, we have developed a simple TMM equivalent reaction. Considering the above diene and vinyloxirane synthesis, other functionalised allylic halides, such as **19**, should be amenable to the same

type of reactions. When benzaldehyde was allowed to react with 2-chloromethyl-3-chloropropene, three products, **21**, **22** and **23** were produced (Scheme 5).



Scheme 6



(Eq. 5)

By taking advantage of the same selectivity between the allylic chloro and the allylic iodo group, the reactions of 2-chloromethyl-3-iodo-1-propene **24** with carbonyl compounds gave selectively the monoallylation product **25**. Methylenetetrahydrofuran **26** was obtained from compound **25** upon reaction with KOt-Bu (Scheme 6).[20] The reagent 2-chloromethyl-3-iodo-1-propene can be easily prepared by the reaction of 2-chloromethyl-3-chloro-1-propene with 1 equivalent of sodium iodide in acetone followed by vacuum distillation to isolate the product (Eq. 5).

For the success of the reaction, the presence of water is critical. When the reaction of benzaldehyde with **24** was carried out in diethyl ether or tetrahydrofuran, there was no or little formation of **25**. Addition of water

to the organic solvent led to the formation of **25** accompanied by the reduction product benzyl alcohol.

Table 8. Synthesis of Methylenetetrahydrofurans from RCOR'

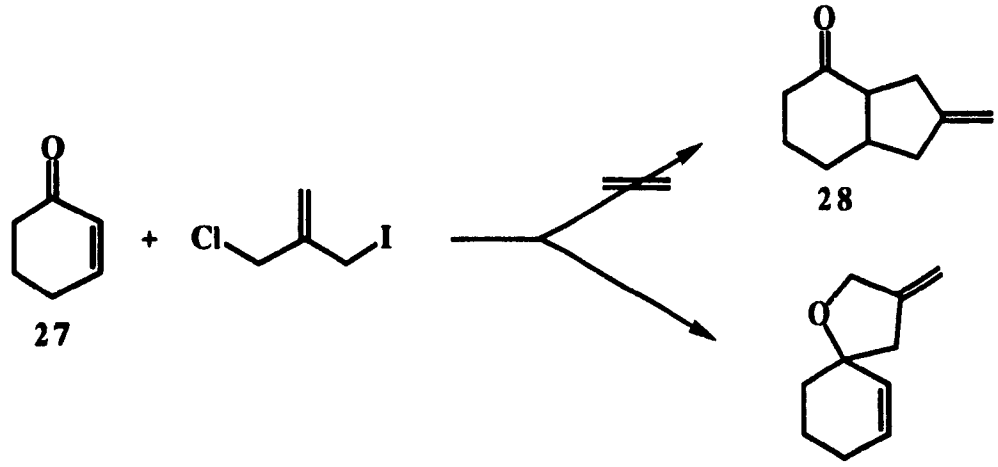
Entry	Carbonyl compound	Solvent/Initiator	Yield(**25**)	Cyclization	Yield(**26**)
1	PhCHO	H_2O/A	**25a** 92	C	**26a** 92
2		Et_2O/---	**25a** 0	---	---
3		THF/---	**25a** 0	---	---
4		(H_2O:Et_2O=1:20) +	**25a** 65 $PhCH_2OH$(5%)	---	---
5		(H_2O:THF=1:20) +	**25a** 40 $PhCH_2OH$(30%)	---	---
6	PhCHO+$(C_4H_9)_2CO$	H_2O/A	**25a** 90 **25k** 0		
7	p-ClPhCHO	H_2O/A	**25b** 93	C	**26b** 92
8	p-MePhCHO	H_2O/A	**25c** 85	C	**26c** 85
9	$CH_3(CH_2)_8CHO$	H_2O/A+B	**25d** 92	C	**26d** 90
10	c-$C_6H_{11}CHO$	H_2O/A+B	**25e** 88	D	**26e** 88
11	PhCH=CHCHO	H_2O/A	**25f** 95	C	**26f** 95
12	cyclohexanone	H_2O/A+B	**25g** 88	D	**26g** 88
13	PhCOMe	H_2O/A+B	**25h** 65	D	**26h** 65
14	2-cyclohexenone	sat. NH_4Cl(aq.)	**25i** 45	D	**26i** 42
15	$PhCH(CH_3)CHO$	H_2O/A	**25j** 85	D	**26j** 82*

A: 2-3 drops of saturated NH_4Cl water solution was added; B: 2-3 drops of 48% HBr was added; C: KOt-Bu/iopropanol; D: KOt-Bu/hexane; * syn:anti=2:1 by ^1H NMR.

Other carbonyl compounds reacted similarly with **24** to give the coupled products and subsequently the methylenetetrahydrofurans in good yields. It is interesting to note that the chloro group in entry 7 was not affected. Ketones were converted to **25** as well as aldehydes. Attempts to do

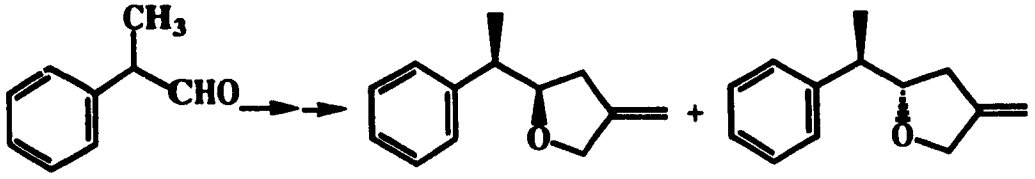
a 2+3 carbon cyclo addition to conjugated carbonyl compounds according to Scheme 7 was not successful. The conjugated carbonyl compounds reacted in a 1,2-fashion as demonstrated by cinnamaldehyde and cyclohexenone.

Scheme 7.



When a mixture of benzaldehyde and 5-nonanone was subjected to the reaction conditions, a highly selective reaction of benzaldehyde was found. Similar high selectivity has been found by Luche,[21] during the ultrasound promoted allylation of a mixture of aldehyde and ketone.

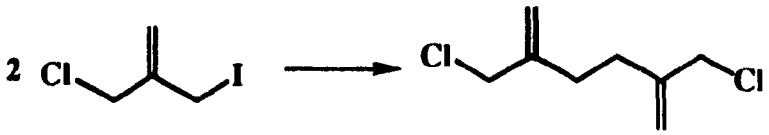
Using α-phenylpropanal (**29**) as the typical α-chiral aldehyde, the reaction gave two diastereomeric products (syn/anti) in 2:1 ratio. The major isomer was found to agree with Cram's rule or Felkin's model.[46,47]



(Eq. 6)

29 30 (major) 31 (minor)

When **24** alone was allowed to reacted with zinc under identical conditions in the absence of a carbonyl compound, the dimer **32** was obtained as the product.



24 **32** **(Eq. 7)**

2.5 Allylation of Carbonyl Compounds Promoted by Indium and Manganese (and Other Metals)

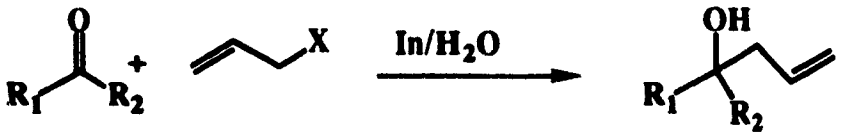
In spite of the advantages of carrying out organometallic reactions in aqueous media, the choice of metals, however, is still very limited. The reactive alkali and alkaline earth metals cannot be used because of their vigorous reactions with water itself. Metals which form water insoluble oxides readily are also unlikely candidates. Instead of using tin and zinc however, indium metal offers some intriguing possibilities. Compared to other metals, indium has not been much explored in organometallic reactions.[22] It was only recently that indium has been used in Reformatsky reactions,[23] allylations[24] and cyclopropanations[25] of carbonyl compounds. While these results are interesting, the use of indium in organic solvents offered no obvious advantages over conventional organometallic reactions. On the other hand, it is known that indium is unaffected by boiling water or alkali.[26] It does not form oxides readily in the air. Furthermore, its first ionization potential (Table 9) is much lower than that of zinc or tin, and for that matter, even magnesium. If aqueous organometallic reactions proceed by a single electron transfer mechanism, as we suspected,[27]

indium may well be effective in such reactions. These considerations led us to examine the use of indium as a metal to mediate the aqueous organometallic reactions.

Table 9. First to Fourth Ionization Potential of Some Metals

Metal	Ionization Potential (Volt)			
	I	II	III	IV
Indium (In)	5.785	18.86	28.03	54.4
Aluminum (Al)	5.984	18.82	28.44	119.96
Magnesium (Mg)	7.646	15.035	80.143	109.29
Zinc (Zn)	9.39	17.96	39.7	
Tin (Sn)	7.34	14.63	30.49	40.72
Manganese (Mn)	7.43	15.63	33.690	52
Lithium (Li)	5.39			
Sodium (Na)	5.12			
Potasium (K)	4.32			
Rubidium (Rb)	4.16			
Cesium (Cs)	3.87			

Obtained from *CRC Handbook of Chemistry and Physics*, 53rd ed.



(Eq. 8a)

Table 10. Allylation of Carbonyl Compounds in Water Mediated by Indium

Entry	R^1	R^2	X	Metal	A/allylX/M	Time(hrs)	Yield	Syn:anti
1	Ph	H	Br	In	1/1.5/1	3	97	
2	Ph	H	I	In	1/1.5/1	3	95	
3	Ph	H	Cl	In	1/1.5/1	5	60	
4	Ph	H	Cl	Sn	1/1.5/1	5	0[a,b]	
5	ClPh	H	Br	In	1/1.5/1	1	94	
6	CH_3CHOH	H	Br	In	1/1.5/1	3	85	67:33
7	$CH_3CH(ODCB)$	H	Br	In	1/1.5/1	3	75	24:76
8	$CH_3(CH_2)_2CH(OBn)$	H	Br	In	1/1.5/1	3	80	24:76
9	$PhCH(CH_3)$	H	Br	In	1/1.5/1	3	90	78:22
10	Ph	CH_3	Br	In	1/1.5/1	5	72	
11	Ph	CH_3	Br	Zn	1/1.5/1	5	18[c]	
12	Ph	CH_3	Br	Sn	1/1.5/1	3	0[a]	
13	$-(CH_2)_5-$		Br	In	1/1.5/1	6	68	
14	$-(CH_2)_5-$		Br	Sn	1/1.5/1	6	0[a]	
15	$HOCH_2C(CH_3)_2$	H	Br	In	1/1.5/1	3	85	
16	$HO(CH_2)_4$	H	Br	In	1/1.5/1	3	95	
17	$(CH_3O)_2CHCH_2$	CH_3	Br	In	1/2/1.5	6	70	
18	$(CH_3O)_2CHCH_2$	CH_3	Br	Zn	1/2/2	6	0	
19	$(CH_3O)_2CHCH_2$	CH_3	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, otherwise mentioned; [a]mediated by tin at 80^0C, [b]promoted by sonication; [c]mediated by zinc with sonication; [d]by ^{1}Hnmr.

We found that indium can indeed effect allylation of aldehydes and ketones in water at room temperature in high yield (Table 10).[28a] The reaction required no protection of inert atmosphere. Allyl bromide

appeared to be as good as allyl iodide in undergoing the reaction. Even the less reactive allyl chloride can be used, but (the reaction) required a longer reaction time. Reactions with indium metal need no promoter. In this case, it is different from zinc and tin where acid catalysts, heat or sonication were often required.

In the presence of an acid sensitive group such as an acetal (entry 17), reaction by indium gave cleanly the allylation of the carbonyl group without affecting the acetal. The same reaction with zinc under all the usual conditions (entry 18) did not give any allylation product and little recovery of the starting acetal ketone, whereas allylation with tin promoted by saturated NH_4Cl gave less than 10% yield of the product (entry 19). Addition of HBr (or other acids) and use of ultrasonic radiation to catalyze the Sn reaction led to a mixture of several products.

The indium itself seemed converted to In^{+3}, since indium compounds of lower valencies are known to be unstable. The halides InX and InX_2 disproportionate in the presence of water as follows:[28b]

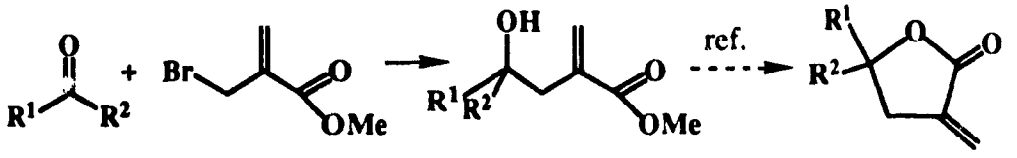
$$3\,InX \longrightarrow 2\,In + InX_2$$

$$3\,InX_2 \longrightarrow In + 2\,InX_3$$

Furthermore, addition of potassium ferrocyanide to the reaction mixture produced a white deposit which was soluble in HCl aqueous solution, a typical property of In^{3+} ion.[28b] Similar In(III) valency species $R_3In_2X_3$ was the reaction product between indium and alkyl halide in organic solvent.[28c]

The allylation with indium can be extended to the reactions of carbonyl compounds with methyl (2-bromomethyl)acrylate (33) to give the

corresponding hydroxy acrylic esters **34**, a precursor for 2-methylene-γ-lactone **35** which is an important structural unit in a variety of natural products. The reactions proceeded smoothly with indium at room temperature in a few hours (Table 11). The same reaction with zinc has not been reported and gave only low yields in our hands with all the usual reaction conditions including catalysts and sonication. Reactions with tin required long reaction times of refluxing in acid and gave poorer yields.[29]



(Eq. 8b)

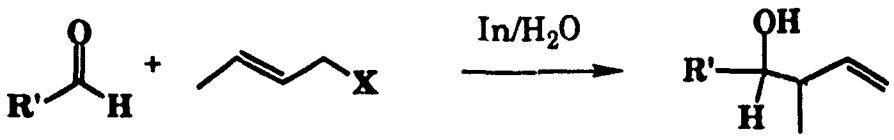
33 **34** **35**

Table 11. Reaction of Aldehydes with Methyl (2-bromomethyl)acrylate

Entry	RCHO	halide	Metal	Temp.	Time	Yield
1	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	In	r.t.	5	34a 96
2	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	Zn	US[a]	5	34a 26
3	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	Zn	r.t.[b]	6	34a 52
4	$HOCH_2(CH_3)_2CHO$	$BrCH_2C(CH_2)CO_2CH_3$	In	r.t.	5	34b 85
5	$HOCH_2(CH_3)_2CHO$	$BrCH_2C(CH_2)CO_2CH_3$	Zn	US[a]	5	34b 17

All the reactions were performed at 1 mmol scale in water with RCHO/halide/M = 1: 1: 1; a: sonication; b: catalysed by NH_4Cl.

The reaction of carbonyl compounds with crotyl halide promoted by indium was also studied. However, as in the cases of Zn and Sn, while the yields of the products were acceptable, no significant diastereoselectivity was observed.



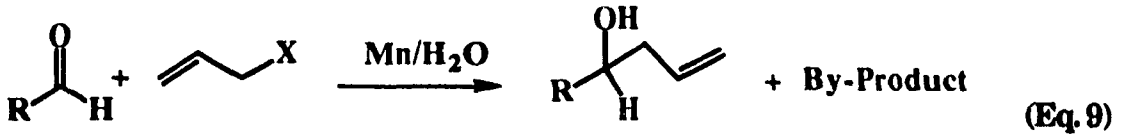
R'= Ph- Erythr.threo= 50:50

R'= n-C_7H_{15} =50:50

From Table 9, it would seem that another potential metal for the aqueous organometallic reactions is manganese. Ever since the discovery of large amounts of manganese nodule on the ocean floor, increasing attention has been drawn to the use of manganese in organic chemistry. In view of its natural abundance, manganese is expected to play an important role in future organic synthesis. In the past, manganese compounds were mainly used as oxidizing reagents.[30] Only recently, it was found that low valent manganese or metallic manganese can be used for Grignard-type carbonyl addition[31], conjugated addition of alkyl halide to unsaturated carbonyl compounds[32] and reaction with carboxylic acid chlorides to form ketones.[33] Yet, all these reactions were carried out in organic solvent under inert gas, such as nitrogen or argon. The manganese reagent was usually prepared in situ from organolithium or magnesium compounds.

The first report of using metallic manganese directly in organic reactions was the allylation of carbonyl compounds in THF. The reaction required a large excess of manganese (7 eq.) and allylic halide (6 eq.). The manganese also has to be activated by the addition of one equivalent of iodine.[34] A recent report improved the procedure by refluxing the reaction mixture in ethyl acetate.[35]

We tried to apply manganese to the allylation reactions in aqueous media. The product, homoallylic alcohol, was obtained in low yield (~23%) (Eq. 9).



(Eq. 9)

The low yield of the reaction seemed to be due to the formation of oxide crust on the metal surface thus blocking the progress of further reaction. When NH_4Cl was added, it broke the crust presumably via the formation of water soluble complexes. Even under these conditions, most of the product was the reduction of aldehyde, giving the corresponding alcohol. The use of a basic buffer solution of (NH_4Cl+NaOH) (pH= 9) improved the yield of allylation and depressed the reduction. Lowering the reaction temperature (-5 to 0°C) further improved the yield. The use of other buffer such as Na_2HPO_4 gave essentially the same result as the reaction in pure water. The results are shown in Table 12.

Table 12. Allylation of Benzaldehyde Mediated by Manganese according to Eq. 9

Entry	R	X	Ald/allylX/Mn	Solvent	Temp.	Time	Yield	Recov(ald.)
1	Ph-	Br	1/1.5/1.5	H_2O	r.t.	15h	23	72
2	Ph-	Br	1/1.5/1.5	sat.NH_4Cl	r.t.	20min	35	0
3	Ph-	Br	1/1.5/1.5	sat.Na_2HPO_4	r.t.	15h	30	70
4	Ph-	Br	1/1.5/1.5	sat.NaCl	r.t.	15h	20	75
5	Ph-	Br	1/1.5/1.5	NH_4Cl (pH=7))	r.t.	20min	38	0
6.	Ph-	Br	1/1.5/1.5	NH_4Cl(pH=8.5)	r.t.	20min	40	0
7.	Ph-	Br	1/1.5/1.5	NH_4Cl (pH=9)	-5°C	30min	70	0

The NH_4Cl buffer was obtained from titration of NaOH (1N) to the saturated water solution of NH_4Cl.

Instead of using a single metal to promote the reaction, we found that the allylation reaction can be successfully conducted in water with a mixture of manganese-copper bi-metallic system.

Generally, in organic reactions, a metal can be activated by the addition of a Lewis acid, or iodine,[34] a more active metal,[36] or a salt of a less active metal.[37] The higher reactivity of the well known Zn/Cu couple than Zn itself is still not fully understood.[38a]

When a mixture of Mn/Cu powder, instead of Mn alone, was used, surprisingly, the reaction proceeded smoothly to give the desired product. Some results of the allylation mediated by Mn/Cu was listed in Table 13a.

Table 13a. Allylation of Aldehydes Mediated by Manganeses/Copper

Entry	R	X	Ald/allylX/Mn	Solvent	Temp.	Time	Yield	Recov(ald.)
1	Ph-	I	1/2/2+1 Cu	H_2O	r.t.	2h	40	1
2	Ph-	Br	1/2/2+1 Cu	H_2O	r.t.	2h	55	1
3	Ph-	Br	1/2/2+1 Cu	ether	r.t.	2h	0	100
4	Ph-	Cl	1/2/2+1 Cu	H_2O	r.t.	2h	92	6
5	ClPh-	Cl	1/2/2+1 Cu	H_2O	r.t.	2h	90	8
6.	MePh-	Cl	1/2/2+1 Cu	H_2O	r.t.	2h	50	49
7.	MePh-	Cl	1/2/2+1 Cu	H_2O	r.t.	8h	90	8
8.	C_6H_{11}-	Cl	1/2/2+1 Cu	H_2O	r.t.	5h	0	100

One interesting feature of the reaction is that although allyl iodide and allyl bromide are much more active than allyl chloride, yet the best allylation was obtained by using allyl chloride. The former two halides (entries 1 and 2) led to ca 50% of by-products (reduced product, benzylic alcohol and pinacol coupled product), whereas with allyl chloride, there

were nearly no by-products. A possible explanation for this was that the organometallic intermediate generated from the more reactive allyl iodide (or bromide) tended to react with another molecule of allyl iodide (or bromide) to give the Wurtz coupling product, whereas the intermediate generated from allyl chloride was stable enough to add to carbonyl double bond.

The structure of the aldehyde seemed critical to the reaction. Slight change in the structure of the aldehyde changed the reactivity. For instance, while allyl chloride reacted with benzaldehyde smoothly the reaction with 4-methylbenzaldehyde was much slower, and there was no reaction at all with aliphatic aldehydes. The reason for the failure of the reaction with aliphatic aldehyde was not clear. It might be due to the higher reduction potential of aliphatic aldehydes.[38b]

CH_3CH_2CHO and higher homologues	$E_{1/2}$ -1.76 eV
PhCHO	-0.96 eV

The influence of the amount of additional Cu on the yield of allylation of benzaldehyde was examined. The total conversion of the aldehyde versus the ratio of the copper addition under a fixed reaction condition(r.t./2 h) is shown in Figure 1. The most effective combination of Mn:Cu was around 2:1.

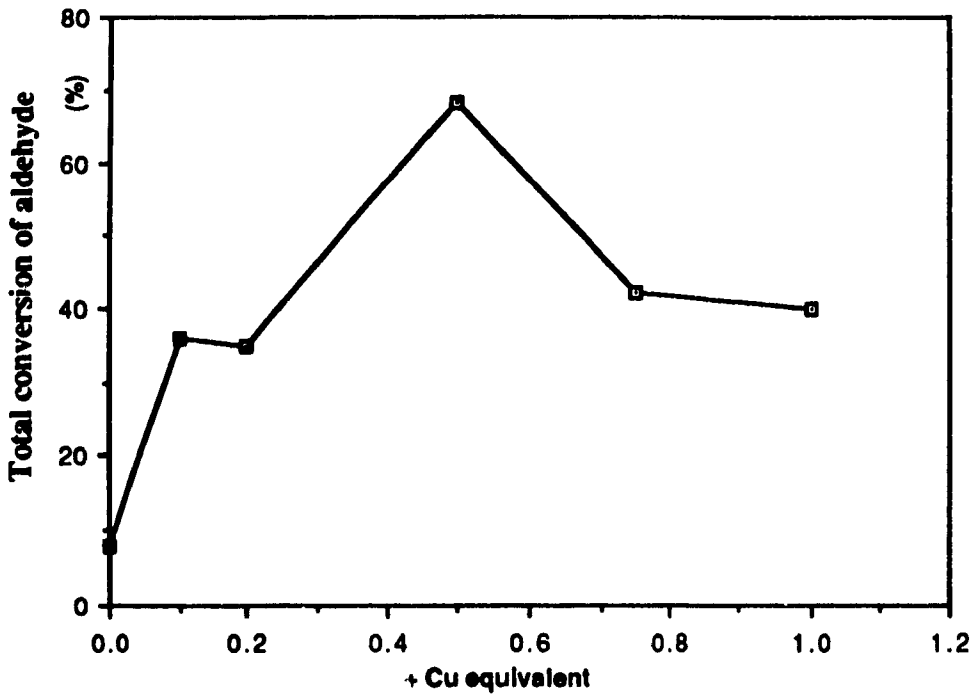


Figure 1. All the reactions were carried out on a 1 mmol scale in 10 mL pure water at r.t. with allyl bromide/Mn/benzaldehyde in 1/1/1 ratio, in two hours .

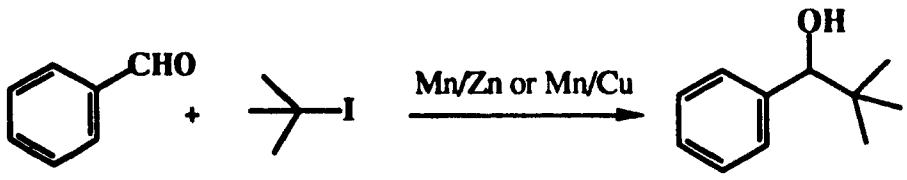
In addition to the above mentioned Zn, In, Sn and Mn, allylation reaction can also mediated by other metals such as Cd, Ti, and Bi. Allylation with Cd is as effective as Zn except that it is less reactive. Allylation with titanium alone does not proceed. However, the reaction succeeded by using KF as a catalyst. This might be because a complex between titanium and fluoride ion dissolved the oxide crust much in the same way as ammonium chloride in the cases of Zn, Sn and Mn. Also in this case, reduction of the aldehyde to the alcohol was a major side reaction. Like indium, bismuth can also mediate the aqueous allylation of benzaldehyde at room temperature without any promoter. However, bismuth is less reactive thanindium. A comparison of these results is listed in Table 13b.

Table 13b. Allylation of Benzaldehyde with CH_2:$CHCH_2Br$ Mediated by other Metals (Metal/allyl bromide/benzaldehyde= 1.5:1.5:1) at R.T.

Entry	Metal	Promoter	Time(h)	Yield	Reduced
1	Ti	no	2	0	0
2	Ti	KF(3 eq.)	3	43	11
3	Cd	NH_4Cl(sat.)	2	75	--
4	Bi	no	3	61	--

2.6 Attempted Alkylation of Carbonyl Compounds in Aqueous Media

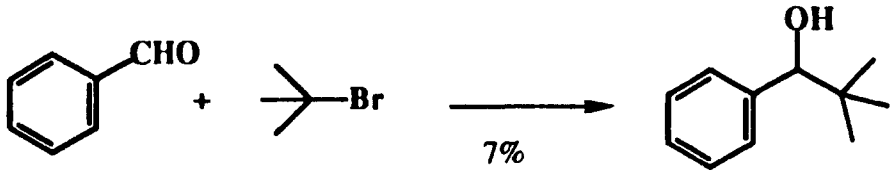
For the aqueous Grignard reaction, it would be most desirable if alkylation of carbonyl compounds with non-activated alkyl halides could also be carried out in aqueous medium in the same way as allylation. To accomplish this purpose, we examined a variety of metals such as Zn, Sn, Ti, Al, Mg and Mn etc. with different alkyl halides. All of them failed to give the alkylation product.



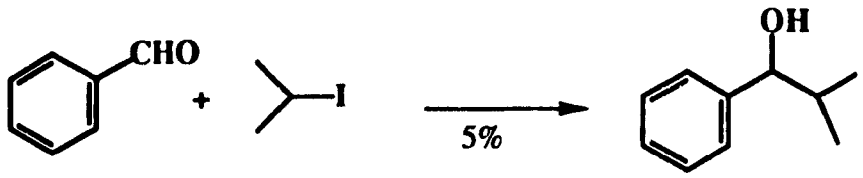
36 37 (Eq. 10)

When a mixture of benzaldehyde with t-butyl iodide was subjected to a mixture of Mn-Zn powder at room temperature in water, the corresponding alkylation product (6-33%) was obtained together with the reduced and pinacol coupled products of benzaldehyde. A similar result was obtained with a mixture of Mn-Cu. The Mn-Zn and Mn-Cu mixture were prepared by simply mixing together the two metallic powders. A Mn-

Cu couple, prepared in situ from Mn and CuCl, gave the same result as the Mn-Cu mixture.



38 (Eq. 11)



39 40 (Eq. 12)

The reaction can also take place between benzaldehyde and t-butyl bromide or isopropyl iodide. However, both of these gave only low yields. Under the same conditions, other aromatic aldehydes can also react. Alkylation of aliphatic aldehydes failed to proceed under these conditions, including the use of the usual activation methods. Alkyl chlorides, secondary or primary bromides and primary iodides also failed to react.

In order to improve the yield of the reaction, factors which might influence the alkylation were studied. We first examined the effect of the composition of the metal mixture on the yield of the alkylation product. The result is shown in Fig. 2. From Figure 2, it appears that the bi-metallic mixture is more effective than one metal alone. The highest alkylation yield was obtained when the content of Zn in the mixture was in the range of 70% to 90%.

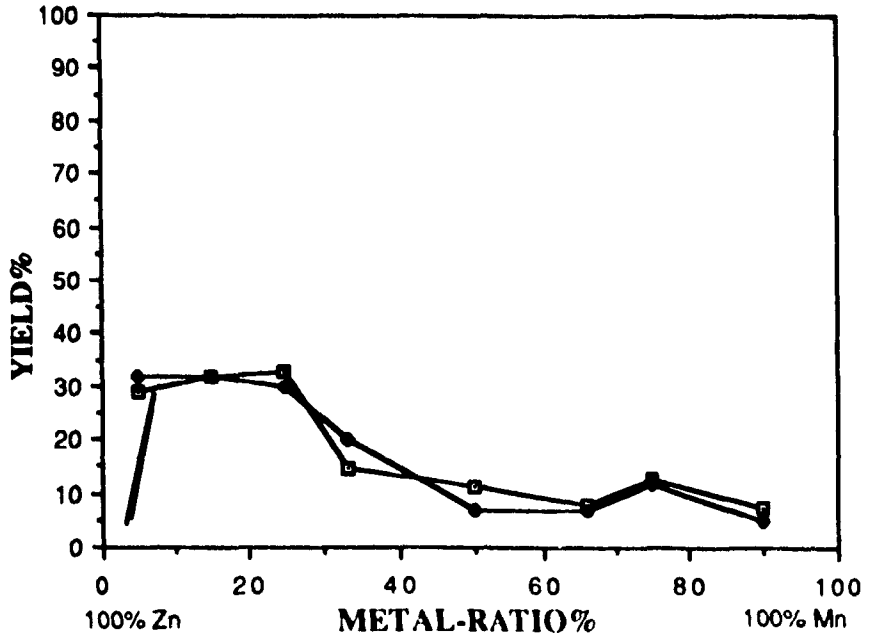


Figure 2. Dark ♦ : H NMR result; White ◘ : GLC result. The reactions were performed on 1 mmol scale with iodide/aldehyde/metal(total)=2:1:2.

The choice of solvent also seemed to be important. The addition of a small amount (10% V/V) of some organic solvent such as hexane, benzene, ethyl acetate or ether led to failure of the reaction. The presence of a small amount of ethanol or HMPA did not change the yield of the reaction. The reaction also failed to proceed in either pure ethanol or a 1:1 mixture of water/ethanol.

Changing the amount of alkyl iodide and metal relative to the amount of benzaldehyde gave some interesting results. The yield of the alkylation product increased as the relative amount of alkyl iodide and metal increased, which was to be expected. However, it reached a maximum point when the ratio of benzaldehyde/alkyl iodide (and metal) was around 2 to 3. After that, the yield dropped to the same level as when the ratio was 1:1. Thus, a large excess of the t-butyl iodide did not seem to

favor the reaction.

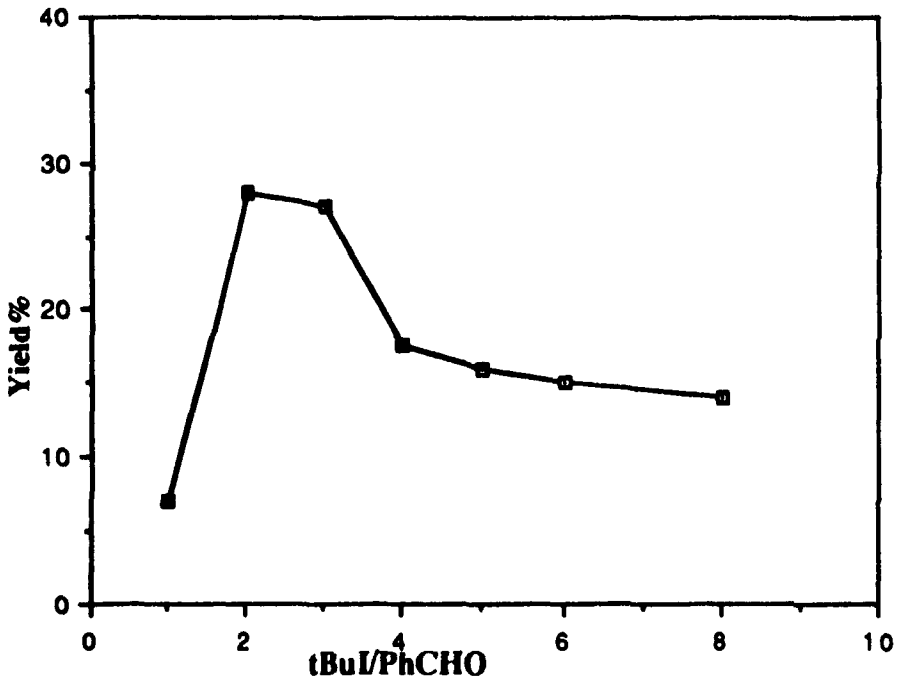


Figure 3. The reactions were performed on 1 mmol scale with aldehyde/metal(total)=1:3 and Mn:Zn = 1:3.5

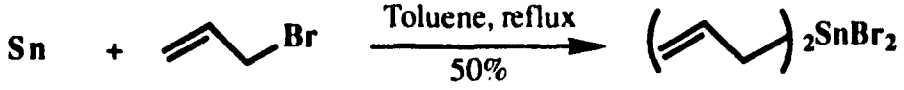
In all cases, there was always some starting benzaldehyde that did not react. Applying ultrasonic radiation to the reaction did not improve the yield.

2.7 Mechanistic Consideration

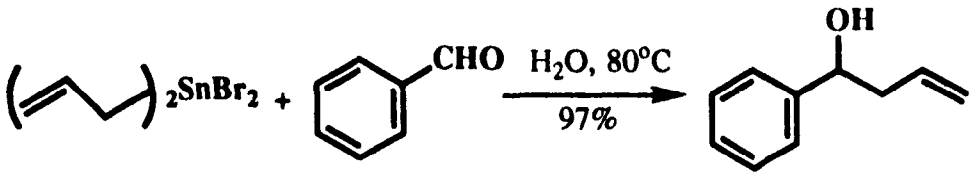
In spite of the considerable amount of literature reports on organometallic type reactions in aqueous media, the mechanism of these reactions is not clear. In view of the reactivity of organometallic reagents in water, it is unlikely that actual organometallic intermediates were formed during the reaction. Luche[21] suggested that this type of reaction may go through a radical mechanism.

In order to determine whether an organic tin compound was formed

or not during the reaction, an allyl tin reagent was prepared *via* a literature procedure (Eq. 13).[40a] When the allyl tin reagent **41** was stirred with benzaldehyde in water under the same conditions, the allylation product was obtained similarly. This result suggests that the allyltin species **41** may be stable enough to survive aqueous conditions without being hydrolyzed. It also indicated the possible involvement of this species as an intermediate in the allylation in water in the same way as in organic solvent.



41 (Eq. 13)

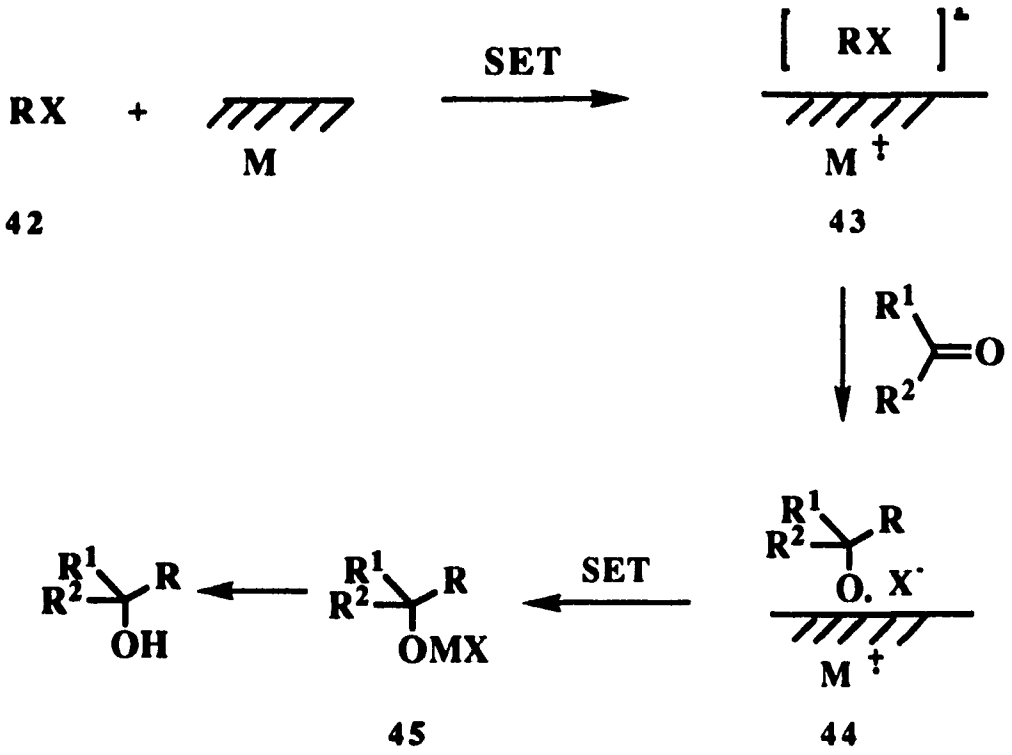


(Eq. 14)

However, the more reactive allylzinc compound was not likely to have been formed. Furthermore, water soluble low valent metal salts (e.g. $CrCl_2$) with similar reductivity as metal Zn or Sn failed to mediate the reaction to any extent. Thus it is likely that the metal surface is as critical a requirement for the success of the reaction as the choice of the metal itself.

The hydrophobic effect might be another important factor influencing the reaction. The hydrophobic effect can help the aqueous Barbier-Grignard reaction by bringing the organic species onto the metal surface. Water might also further lower the ΔG of the reaction through solvation of the MX_n ionic salt produced.

Based on these arguments, the reaction mechanism is proposed to be a single electron transfer process on the metal surface (Scheme 8).

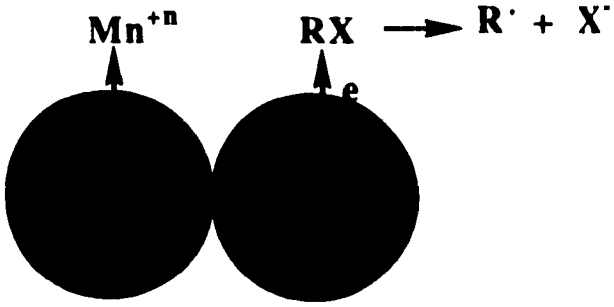


Scheme 8. SET = Single Electron Transfer

In the case of allylation, it is possible that both reactants are activated on the metal surface by coordination with the surface atoms through d-p Π bonding. This coordination lowers the activation energy of the reaction. Thus, it can be expected that a large metal surface will increase the rate of the reaction. This expectation is consistent with the experimental result that the reaction can only take place with fine metal powder and can not take place or only very slowly with metal lumps because of the smaller surface available. The observation that the Wurtz type coupling products produced from allyl halides and the reactivity difference among different

carbonyl compounds, possibly due to their coordination difference, also supported the mechanism.

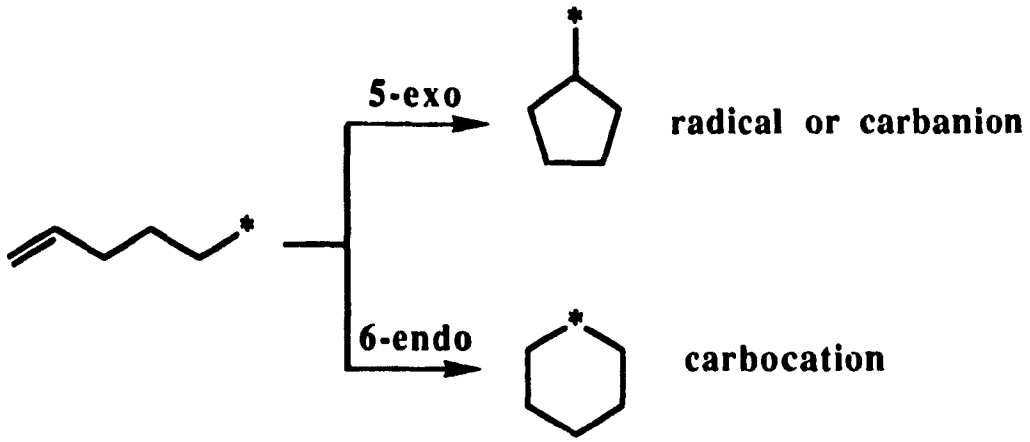
Reactions mediated by the manganese-copper system are somewhat different from the previous ones. The activation of manganese by copper seemed likely to be coming from a micro-cell single electron transfer process, where Mn (the negative pole) of the electric cell was consumed according to Scheme 9.[40b]



Scheme 9.

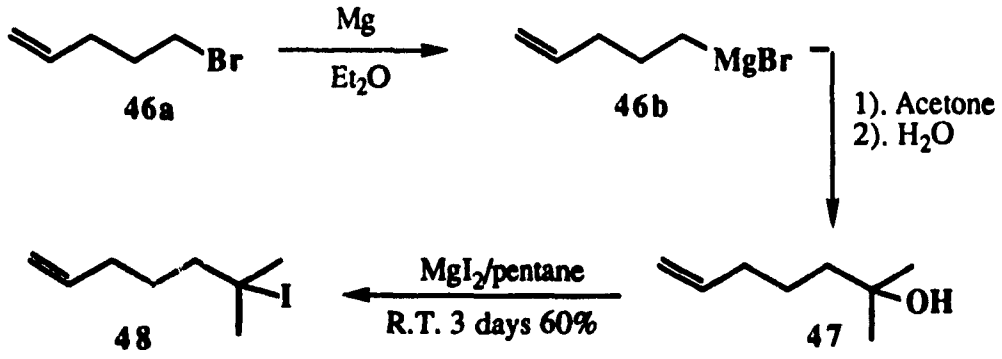
In such a system, it is conceivable that the d-p Π coordination between the halide and the metal is less important. Thus, even alkyl halides without Π bonding, e.g. t-butyl iodide or bromide and i-propyl iodide, can react under the same reaction conditions. In this case, a designed probe was used to study the possible mechanism.

It is known that reactions involving different reactive intermediates give different cyclization products with the 5-hexenyl probe depending on the nature of the intermediate according to Scheme 10.



Scheme 10.

Reactions involving radical and carbanion intermediates cyclized to give 5-membered ring products because of the entropy effect and the induction effect (for carbanions) (5-exo), and those involving carbocation intermediates gave 6-membered ring products due to the stability of the final carbocation (secondary>primary) (6-endo).

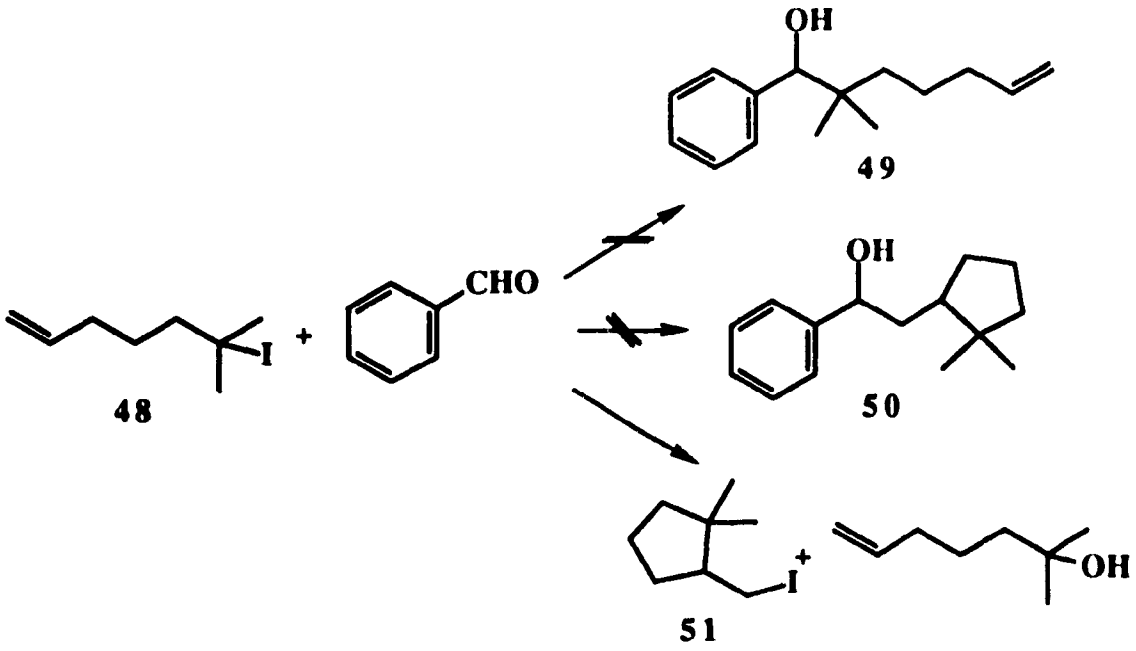


Scheme 11.

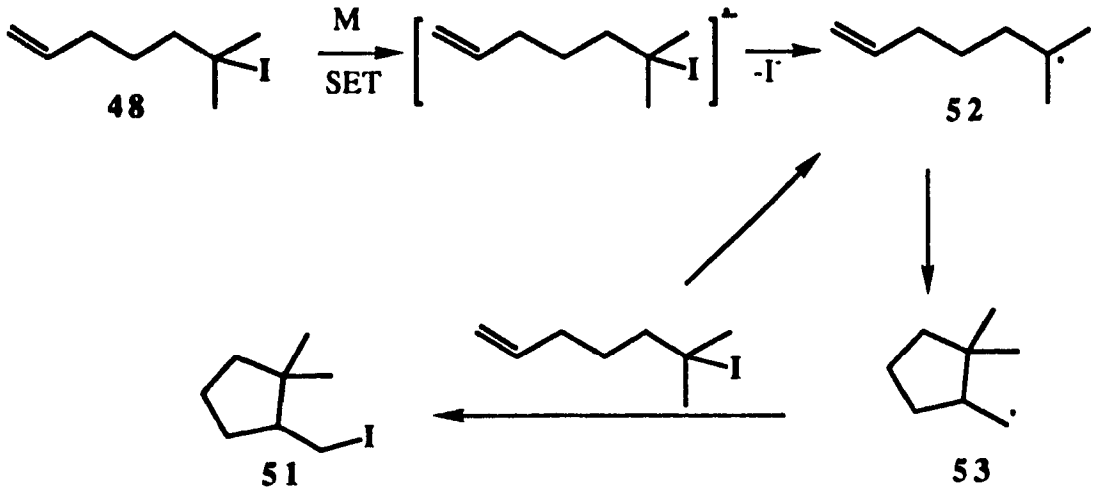
In order to examine the alkylation process, a radical probe was prepared in the following way. Commercially available 5-bromo-1-pentene (**46a**) was transformed to the corresponding Grignard reagent **46b**. It

reacted with acetone to produce the tertiary alcohol **47**. Treatment of the alcohol **47** with magnesium iodide in pentane for three days gave iodide **48**.[40c] The synthesis was later improved by treating the alcohol **47** with trimethylsilyl iodide in chloroform for 1h.[40d]

When the iodide **48** was allowed to react with benzaldehyde under the alkylation reaction conditions with Mn/Zn (1:4), the alkylation product (**49** or **50**) was not obtained. Instead, a cyclized 5-membered ring iodide **51** was isolated in 55% yield from the reaction mixture. The formation of this product has often been interpreted as evidence of a radical mechanism known as "iodine atom transfer reaction".[41] Thus, this result indicated the presence of some sort of radical species and it provided a direct evidence into the mechanism for this kind of reactions.



Scheme 12.



Scheme 13.

The explanation for the iodine transfer reaction is as follows: action of the metal on the iodide **48** produced the tertiary radical **52**, which immediately cyclized to give the primary radical **53**. The primary radical **53** then picked up an iodine from another molecule of **48** to complete the iodine transfer process and regenerate another radical **52**.

As demonstrated by Fraser-Reid and others recently,[42] radicals can add to a carbonyl double bond in the same way as to a carbon-carbon double bond, although this is less frequent. The failure of the alkylation with this probe may be attributed to the fact that the intramolecular cyclization process of the radical is faster than its addition to a carbonyl double bond.

In the case of t-butyl iodide, the intramolecular competing process was absent and the alkylation product was obtained.

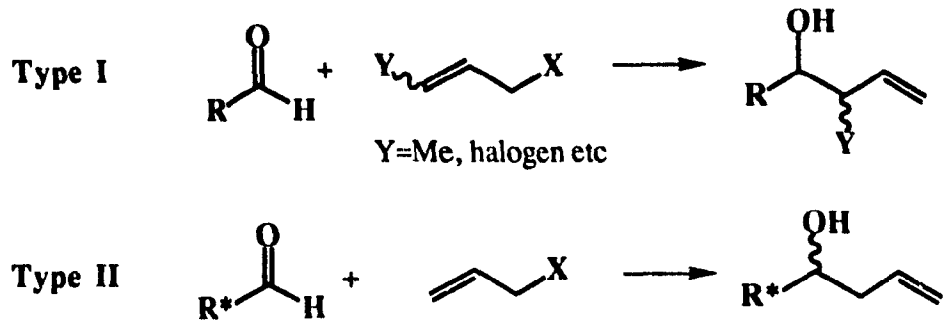
We should mention, however, that when the same probe **48** was subjected to other metal (Zn, In, Sn) mediated reactions, no reaction was observed.

2.3 Stereochemistry of the Allylation Reactions

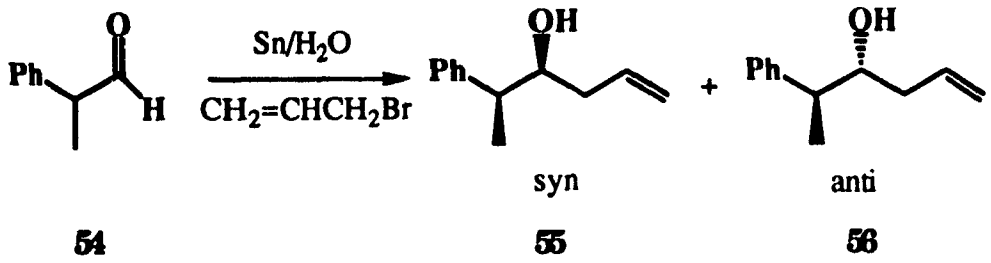
In recent years, there has been extensive investigation of the

stereochemistry of the addition of allylic organometallic reagents to aldehydes, which included diastereoselective addition to achiral aldehydes (Type I), and diastereoselective addition to chiral aldehydes (Type II).[43,44,45]

Scheme 14.



Controlling the stereochemistry of reactions between aldehydes and substituted allyl metal compounds has attracted much research interest recently. As mentioned previously, we have examined the addition of crotyl halides to aldehydes. Under the experimental conditions, the reaction did not show significant selectivity. When the methyl moiety was replaced by a chloro group, moderate selectivity was observed with zinc and fairly high selectivity was observed with tin. Both the addition of organic solvent and the application of ultrasonic waves did not change the selectivity.



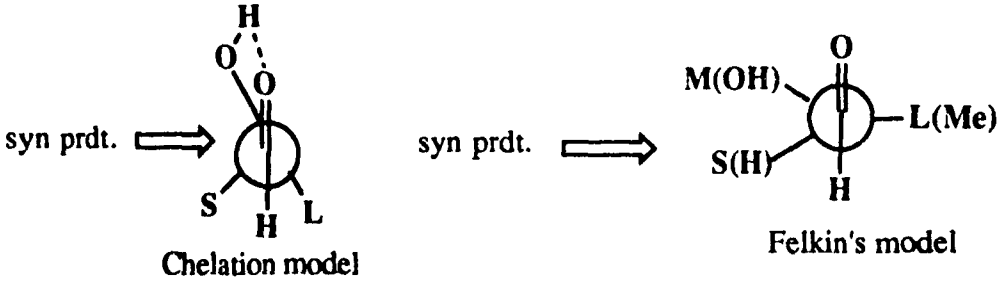
54 **55** **56**

The selectivity of the Type II reaction is normally rationalized via Cram's rule[46] or Felkin's model.[47] Allylation of α-phenylpropanal with tin

and allyl bromide in water produced a mixture of diastereomers (**55** and **56**) in 1.8:1 (syn:anti) ratio which also agreed with Felkin's model.

We are interested in reactions between α-hydroxyl or alkoxyl aldehydes and allyl halide, since this can produce compounds with two adjacent oxygenated functional groups which have potential application in natural product synthesis.

In the case of α-hydroxyl aldehydes, diastereoselectivity is usually explained by the chelation model as in Scheme 15. Felkin's model predicates the same result if the hydroxy group is considered to be medium size. However, if Felkin's model is due to the $\sigma^*-\pi$ interaction as in Scheme 17, then anti product would be formed.

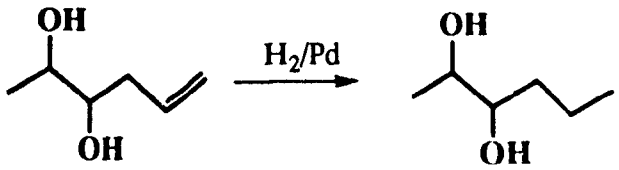


Scheme 15. **57**

When the α-hydroxyl aldehyde **57** was allowed to react with allyl bromide and zinc, syn selectivity of product **58** was observed as expected. Tin and indium gave the same results (Table 14). The determination and assignment of the diastereomers was performed according to a literature procedure (Eq. 15),[45a] which was confirmed later by its iodocyclization product (Section 2.9). The same trend of syn selectivity was found by Whitesides in aqueous medium allylation of sugars with tin.[70]

Table 14. Allylation of α-Hydroxyl Aldehyde

Entry	Aldehyde	Metal	Yield	Syn:anti
1	$CH_3CH(OH)CHO$	Zn	85	67:33
2	$CH_3CH(OH)CHO$	Sn	88	70:30
3	$CH_3CH(OH)CHO$	In	88	67:33

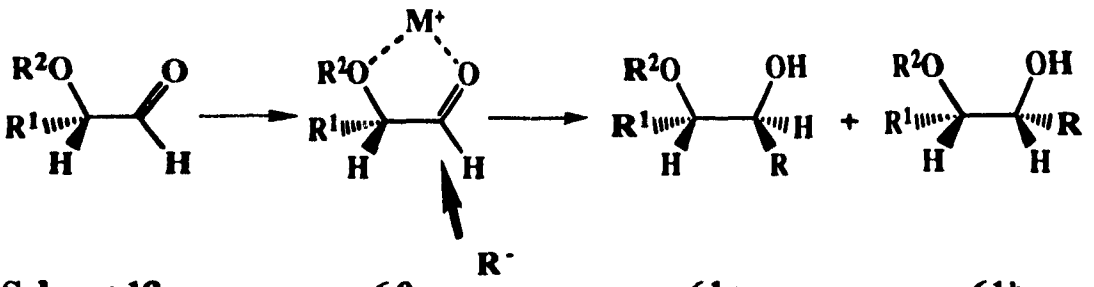


58 59 (Eq. 15)

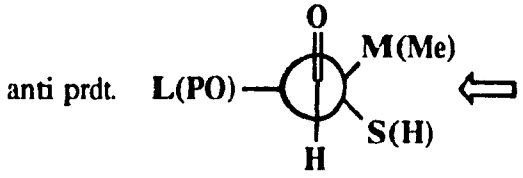
The addition of C-nucleophiles to α-alkoxyl aldehydes (and ketones) in organic solvents follows the same chelation model (Cram's rule). That is the aldehyde forms the chelate **60**. The C-nucleophile (R-) attacks from the less hindered side as indicated by the arrow, giving the chelation-controlled product **61a** preferentially over the non-chelation product **61b** (Scheme 16). This chelation-control approach serves as a useful and convenient synthesis of **61a**. On the other hand, it is important in organic synthesis to be able to obtain both syn and anti selectively. Yet, selective formation of the non-chelation product **61b** is not an easy task since there is no general way to avoid chelation of the α-alkoxyl aldehyde with conventional organometallic (Grignard, organolithium, zinc or copper) reagents in organic solvents.[48]

We envisioned that in aqueous solution the chelation might be reduced. This predicted that the anti product **61b** should be formed, if OR^2 is considered sterically larger than R^1 according to Cram's rule. If

Felkin's model is due to the $\sigma^*-\pi$ interaction, the same anti product would still be formed.

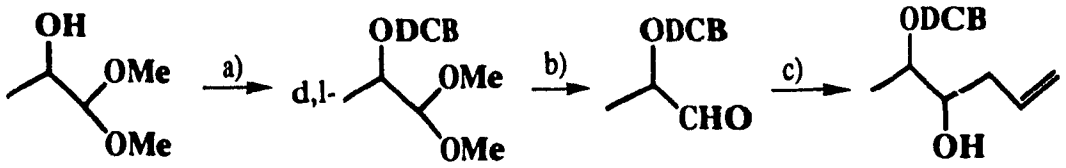


Scheme 16. **60** **61a** **61b**



Scheme 17.

In contrast to the chelation-controlled additions obtained in organic solvents and the previous aqueous allylation with α-hydroxyl aldehydes, reversed stereoselectivity was observed in the zinc-mediated allylation of chiral α-2',6'-dichlorobenzoxy-propanal, prepared from compound **62**, in aqueous media (Scheme 18).



62 **63** **64a** **64b**

Scheme 18. a). 2,6-Dichlorobenzyl bromide/NaH/DMSO/r.t.;
b). Dowex-50 $H^+/H_2O/70^oC$;
c). Allyl bromide /Zn/H_2O/r.t.

Other α-protected aldehydes show a similar behavior. The diastereofacial selectivity results are summarized in Table 15. The three α-benzoxyaldehydes all reacted with allyl Grignards in ether (-78°C) to give preferentially the chelation-controlled products. Similar reaction with

diallylzinc in ether[72] resulted in a complicated mixture. On the other hand, allylations of the aldehydes with allylbromide and zinc in water at room temperature gave, in all cases, the non-chelation-controlled product preferentially. The same reaction in ether[71] resulted in the polymerization of the aldehyde. Similar reversal of stereoselection was observed for α-2,6-dichlorobenzyloxy (ODCB) propanal. However, no reversal of diastereofacial selection was observed in the reactions of α-phenylpropanal (entries 5a and 5b), the typical chiral α-substituted aldehydes. Thus the change in stereoselection may be ascribed to an absence of chelation in the critical carbon-carbon bond formation step in aqueous media. However, non-chelation-controlled product was also obtained with zinc in DMF(entry 4c).[73] Irrespective of the origin of the anti chelation behavior, the anti selectivity provides a useful method for the selective preparation of anti related oxygenated functional groups.

Table 15. Stereoselective Allylation of Chiral α-Substituted Aldehydes

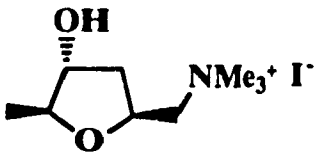
Entry	R^1	R^2O	Method	Syn:Anti	Yield(%)
1a	Ph	BnO	O(Mg)	67:33	75
1b	Ph	BnO	A(Zn)	43:57	50
2a	Bu	BnO	O(Mg)	60:40	60
2b	Bu	BnO	A(Zn)	24:76	80
3a	Me	BnO	O(Mg)	65:35	50
3b	Me	BnO	A(Zn)	35:65	85
4a	Me	DCBO	O(Mg)	60:40	45
4b	Me	DCBO	A(Zn)	29:71	85
4c	Me	DCBO	DMF(Zn)	33:67	88
5a	Ph	Me	O(Mg)	60:40	90
5b	Ph	Me	A(Zn)	68:32	85

O, organic; A, aqueous.

This observation also generated a convenient route to the synthesis of the natural product (+)-muscarine.

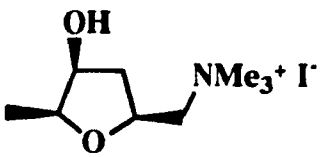
2.9 Total Synthesis of (+)-Muscarine and (+)-Epimuscarine

To find useful applications of a methodology is as important as to develop it. Following the methodology studies, we tried to apply them to natural product synthesis. Our first target molecule was the widely studied alkaloid, (+)-muscarine.



(+) Muscarine

65



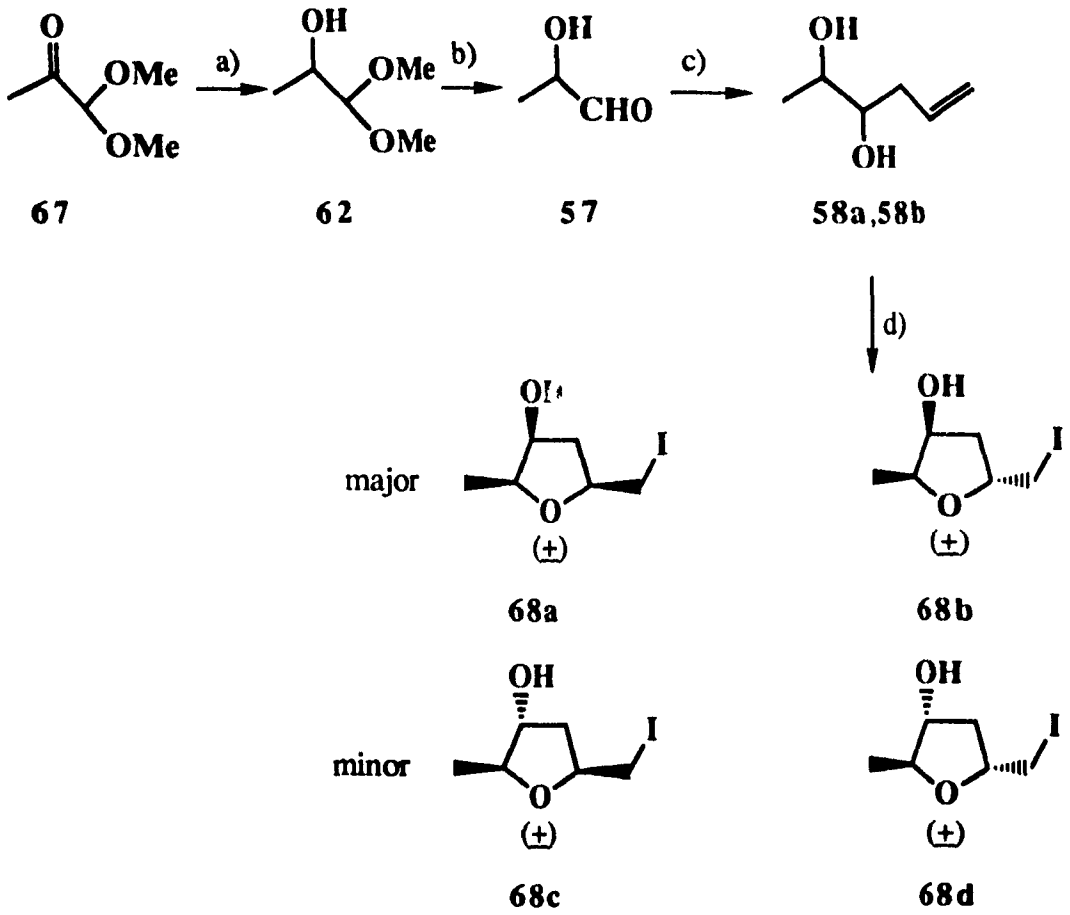
(+) Epimuscarine

66

(+)-Muscarine[49] (**65**, $I^- = OH^-$), an alkaloid present in a variety of poisonous mushrooms, e.g. *Amanita muscaria* (fly agaric), has gained renewed interest because of the implication of the various subtypes of muscarinic receptors in the study of Alzheimer's disease.[50] The synthesis of muscarine has been accomplished a number of times from different precursors.[51] However, a very efficient enantiomerically pure synthesis of this compound is still a challenge for organic chemists. By applying our previously developed method, we found an efficient synthesis of (+)-muscarine (**65**) and (+)-epimuscarine (**66**) from readily available s-(-)-ethyl lactate (**69**)[52] in a very straight forward manner.

The initial study of the synthesis was carried out according to Scheme 19. (±)-2-Hydroxypropanal dimethyl acetal (**62**) was prepared by $LiAlH_4$ reduction of a commercially available pyruvaldehyde dimethyl

acetal (**67**) in ether. Treatment of the 2-hydroxypropanal dimethyl acetal (**62**) with Dowex-50 (H^+) in water at 70°C for 1.5h resulted in the formation the racemic 2-hydroxypropanal (**57**) which reacted without isolation with allyl bromide and zinc in water to give a mixture of the corresponding diols **58a** and **58b** (syn:anti= 2;1) (Scheme 19).



Scheme 19. a). $LiAlH_4/Et_2O$;
b). Dowex 50-H^+/H_2O/70°C;
c) allyl bromide /Zn/H_2O/r.t.;
d) I_2/acetonitrile/0°C.

Iodo induced cyclisation of the diols **58a** and **58b** in acetonitrile gave a mixture of four pairs of racemic iodo compounds **68a-d** as shown. ^1H NMR

spectrum of the crude mixture shows the presence of two major racemic compounds (**68a** and **68b**) coming from cyclization of the syn diol **58a** and two minor compounds **68c** and **68d** coming from the anti diol **58b**. They can be transformed to the desired muscarines directly by reaction with trimethylamine, if they are separated.

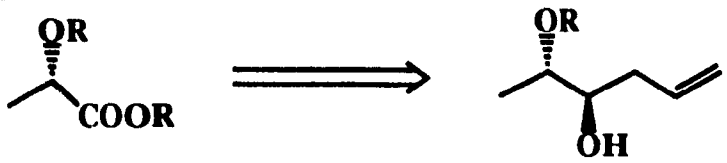
The foregoing study proved the feasibility of the synthetic plan. However, the syn:anti ratio of **58** showed that the allylation of the aldehyde **57** gave the undesired diastereomer **58a** preferentially, resulting in **68c** as the minor cyclized product.

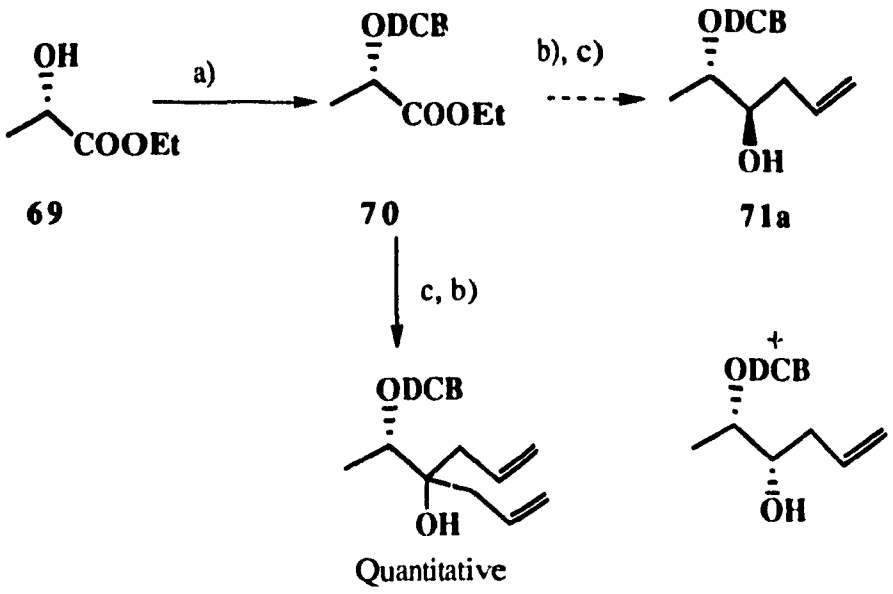
In order to synthesize enantiomerically pure muscarine, the three chiral centers in the molecule have to be controlled by one way or another *via* chiral starting material and stereocontrolled reactions.

Currently, the most efficient method for the synthesis of muscarine from acyclic precursor is *via* the stereoselective iodocyclization of the mono 2,6-dichlorobenzyl protected diol (**71a**),[53] which can give stereospecifically the cis 2,5- relationship of muscarine. However, the synthesis of this precursor usually is fairly tedious.[53]

To achieve the anti selection in the formation of diols, we have tried also a recently reported procedure,[45e] which can selectively give either syn or anti product from α-alkoxyaldehyde by changing the order of "H⁻" and "R⁻" addition (Scheme 20a). However, in the present case, the diallylation product **72** was always obtained as the major product instead of the anti product **71a** (Scheme 20b).

Scheme 20a.





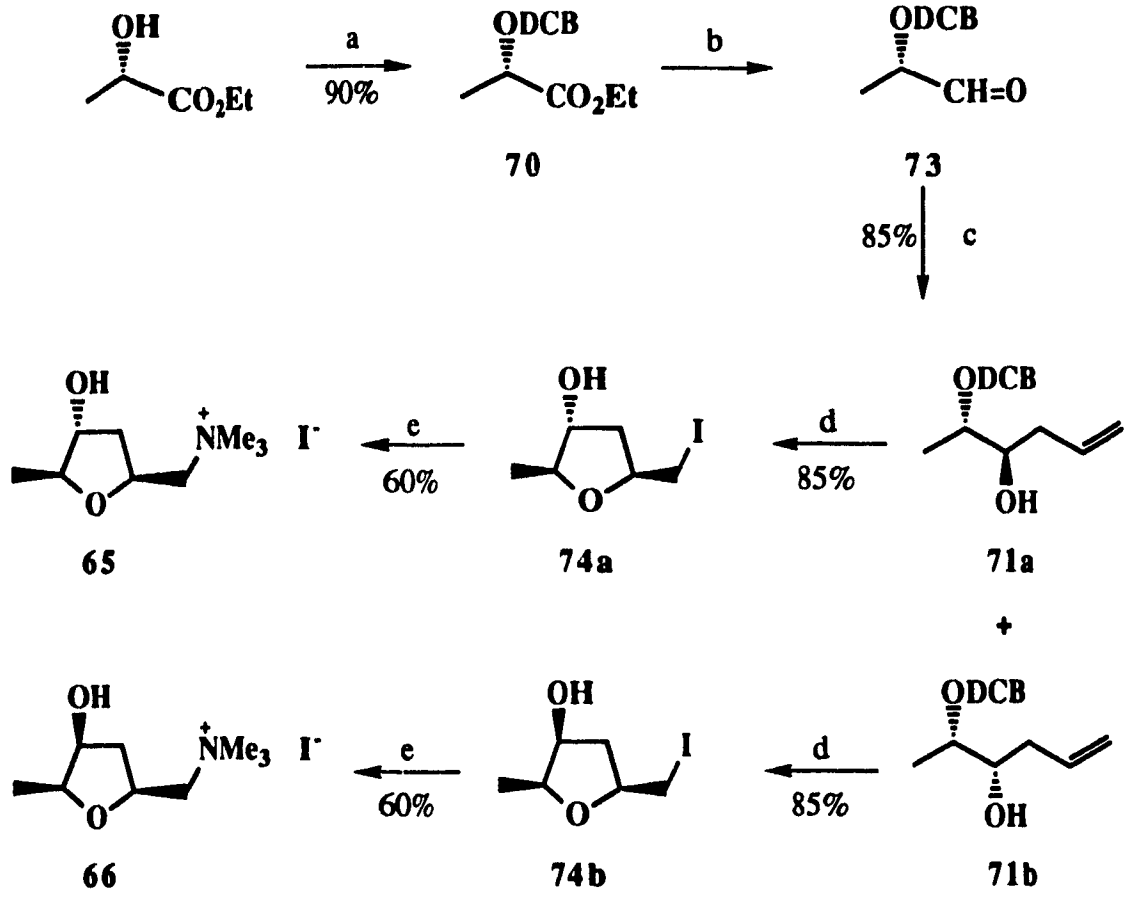
Scheme 20b.

a). 2,6-Dichlorobenzyl bromide/Ag_2O/Et_2O/reflux;
b). Dibal/ether/-78°C;
c). CH_2=$CHCH_2MgBr$/ether/-78°C.

By applying the aqueous allylation reaction to the α-alkoxyaldehyde **73**, the desired anti product **71a** was obtained selectively. Consequently, an enantiomerically pure synthesis of (+)-muscarine was completed (Scheme 21).[52]

S-(-)-Ethyl lactate is a commercially available compound with high optical purity. Treatment of the lactate with 2,6-dichlorobenzyl bromide in the presence of silver oxide afforded the benzyl ether **70** (90%) with retention of configuration.[54] DIBAL reduction of the ester gave the aldehyde **73**.[55] Treatment of the crude aldehyde with allyl bromide and zinc powder in H_2O by the catalysis of NH_4Cl produced a mixture of diastereomers **71a** and **71b** in a 71:29 (Anti: Syn) ratio in 85% combined yield. The two diastereomers can be easily separated by flash chromatography (eluent: hexane/ethyl acetate= 20/1). Iodocyclization of the **71a** in CH_3CN at 0°C gave the product

74a stereospecifically in 85% yield. Finally, treatment of **74a** with excess trimethylamine in ethanol provided (+)-muscarine **65** (2S, 4R, 5S).



Scheme 21. a). 2'6'-Dichlorobenzyl bromide/Ag_2O/Et_2O/reflux;
b). DIBAL/ether/-78°C;
c). Allyl bromide /Zn/H_2O/r.t.;
d). I_2/Acetone/0°C;
e). Me_3N/ethanol/80°C.

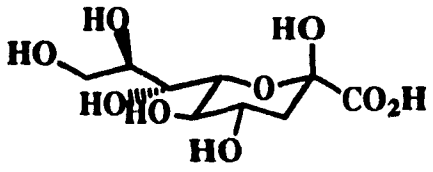
Via the same sequence, the minor syn mono protected diol **71b** was converted to iodo alcohol **74b** and subsequently to (+)-epimuscarine **66**.

This highly efficient synthesis allows us to easily obtain (+)-muscarine and (+)-epimuscarine. Large scale synthesis is also possible. Furthermore, by simply changing the chirality of the starting lactate, this synthesis could also be used to obtain enantiomerically pure (-)-muscarine

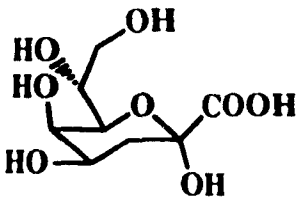
and (-)-epimuscarine. This work also demonstrated that the aqueous allylation reaction can make a meaningful difference in synthesis.

3.10 Synthesis of (+)-KDN and (+)-KDO

Another application of the aqueous Grignard reaction is the syntheses of (+)-KDN and (+)-KDO. 3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **75a**) was recently isolated from polysialoglycoprotein (PSGP) of rainbow trout eggs.[56] Structural analysis has shown that the KDN residues were exclusively located at the non-reducing termini in PSGP. Terminal capping of oligo(poly)sialyl chains by the KDN residues protects these chains from exosialidases, and thereby helps them to perform some required, but as yet unidentified functions during egg activation or early development. 3-Deoxy-D-*manno*-octulosonic acid (KDO, **76b**) is a characteristic sugar component of lipopolysaccharides (LPS) and capsular polysaccharides which occur in the cell surface of Gram negative bacteria.[57] Incorporation of KDO is vital for the growth and proliferation of these bacteria.



75a (+)-KDN

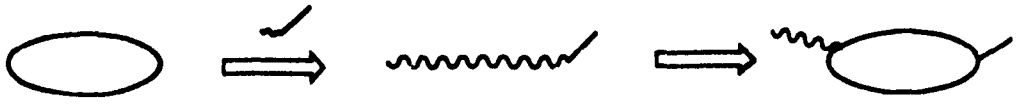


76b (+)-KDO

The synthesis of KDO has been reported many times with different methodologies.[58] KDN, on the other hand was only synthesized once as a mixture without isolation[59a] and once via enzyme immobilized aldolase[59b], and prepared twice by modification of the corresponding neuraminic

acid.[56,60]

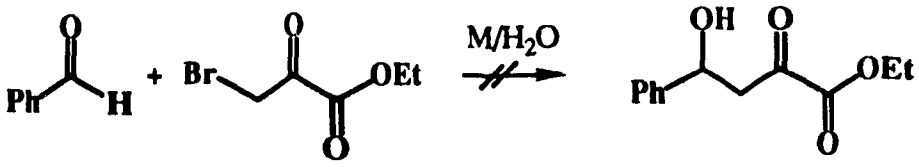
Our synthetic plan can be illustrated by the following cartoon:



close open close

The attempted synthesis starts from a sugar (most of it exists in a cyclic form). Opening of the closed form and a coupling reaction of the sugar by a proper reaction in water produce a polyhydroxylated open chain product. Then, closing of the open chain at the expected positions forms the final closed form product with a head (COOR) and a tail ($HO(CH_2)(CHOH)_n$-) .

Initially, we tried to couple a sugar with ethyl bromopyruvate directly to produce the α-keto carboxylic ester. This attempt did not succeed with the model compound benzaldehyde under a variety of conditions (Eq. 16).



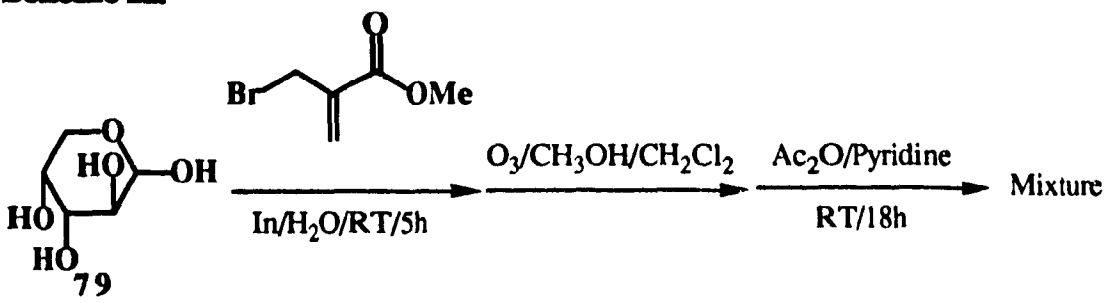
(Eq. 16)

77 78

Then, another approach to the target molecules was considered. Since indium can efficiently mediate the coupling of aldehydes with methyl (2-bromomethyl)acrylate, a similar reaction should occur on sugars. When arabinose was subjected to the reaction conditions, the coupling reaction produced a mixture of products. Ozonolysis of the crude material, followed by the protection of the hydroxyl groups with acetic anhydride/pyridine catalyzed by DMAP resulted in a mixture which was difficult to separate. Furthermore, the diastereoselectivity around the newly generated chiral

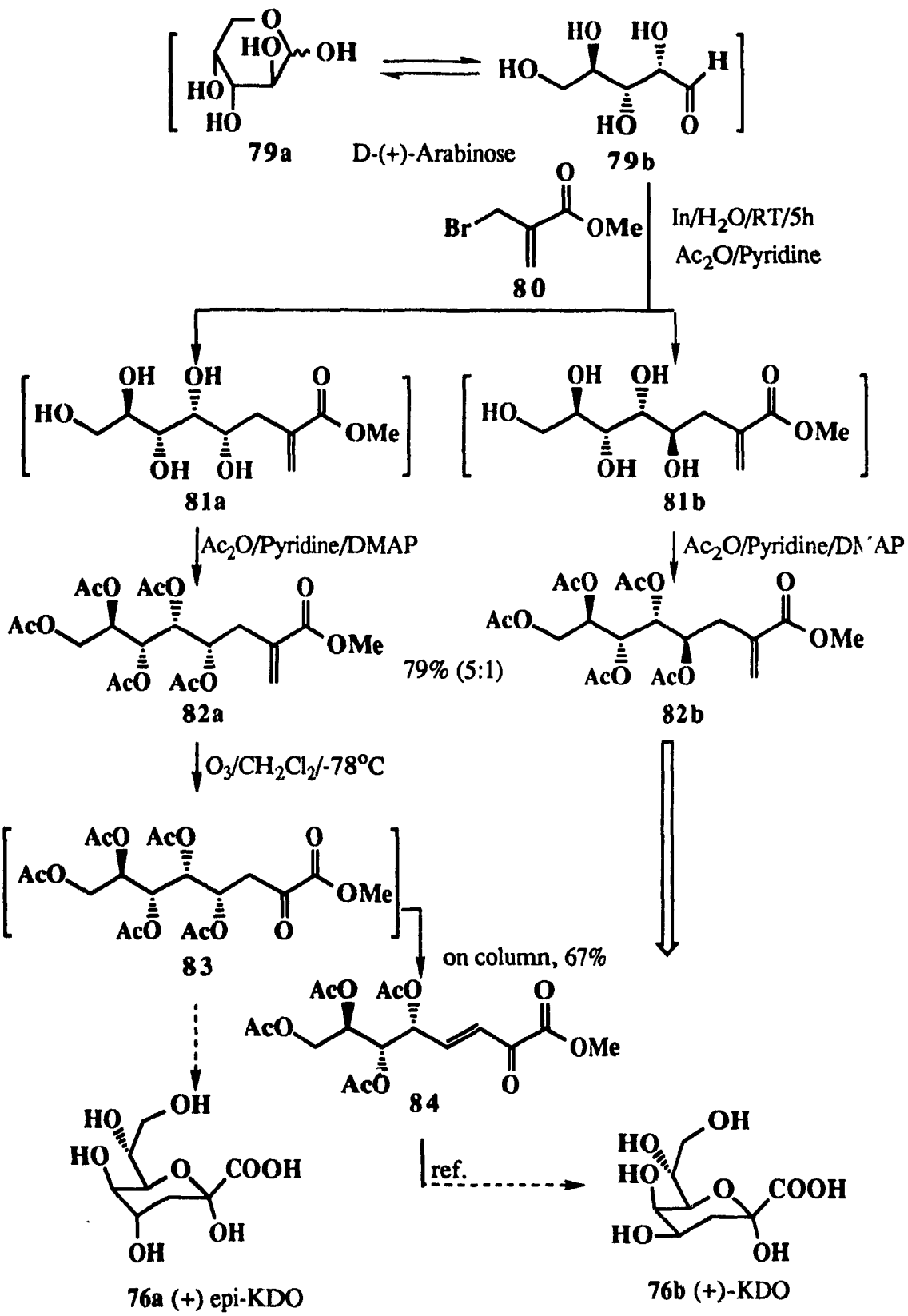
center could not be determined (Scheme 22).

Scheme 22.

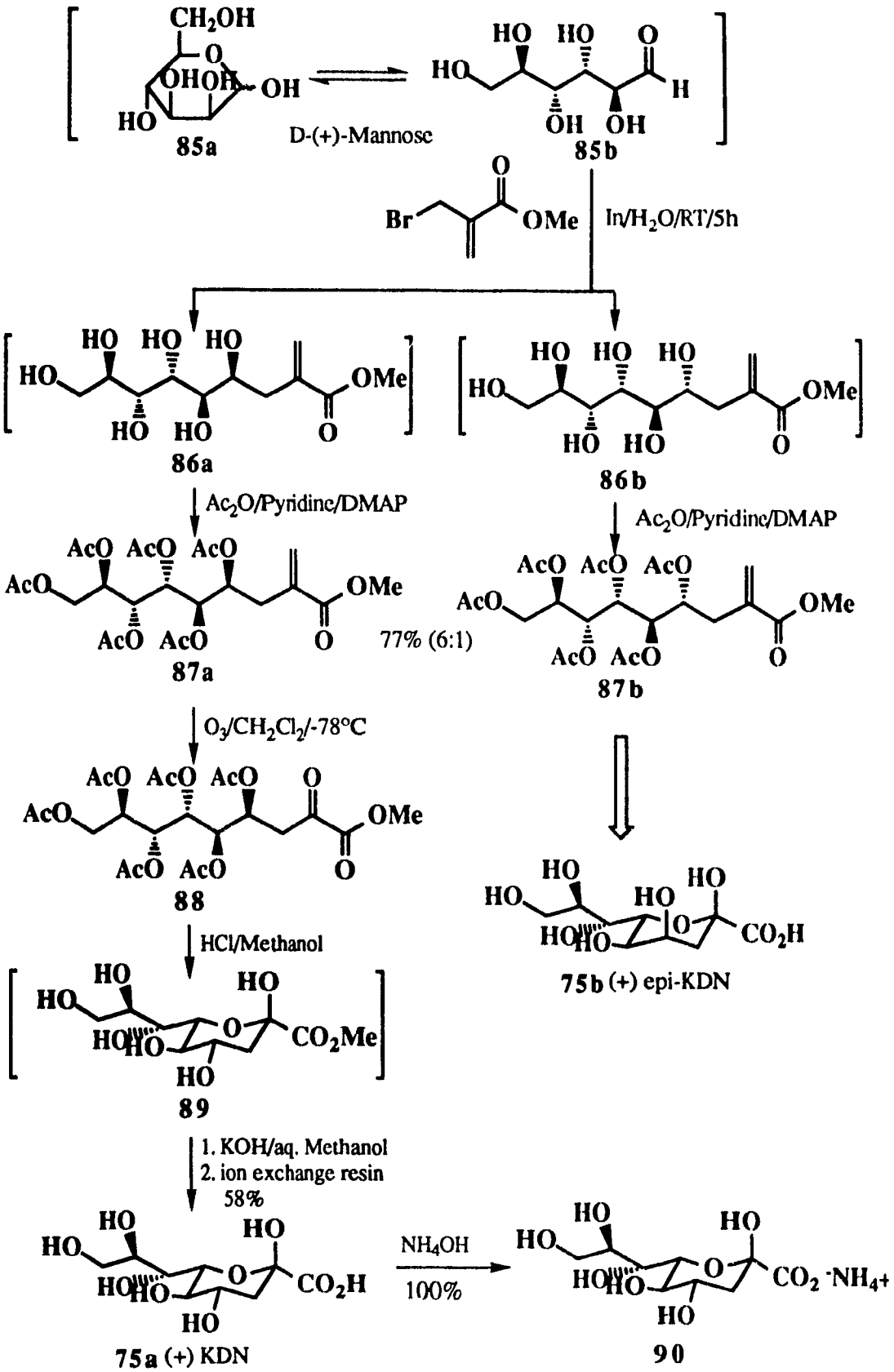


In order to solve this problem, the sequence of ozonolysis and acetylation was exchanged according to Scheme 23. D-(+)-Arabinose (**79**) was coupled efficiently with methyl (2-bromomethyl)acrylate **80** and indium in water to give the compounds (**81a**, **81b**) which were converted to the peracetates **82a** and **82b**. In this case, the diastereofacial selectivity at the new chiral center was 5:1 favoring the syn diastereomer **81a**. The major acetate isomer, **82a** leading to the formation of epi-KDO (D-*gluco*-KDO), was isolated in pure form through flash column chromatography. Subsequent ozonolysis of this compound produced the crude α-keto ester **83**. Purification of the keto ester **83** on silica gel column furnished completely the elimination product **84**, which had been used as a precursor of KDO synthesis before.[61] The reaction sequence is therefore a formal synthesis of KDO.

A similar coupling reaction from D-mannose (**85**), as outlined in Scheme 24, followed by acetylation of the hydroxy groups in **86** gave a mixture of diastereomers **87a** and **87b** in 6:1 ratio. In this case, the preferred diastereomer **87a** has the same syn stereochemistry as KDN. The major isomer **87a** was isolated in pure form by flash chromatography. Ozonolysis of the compound **87a** gave the corresponding keto ester **88**.



Scheme 23. Synthesis of KDO



Scheme 24. Synthesis of KDN

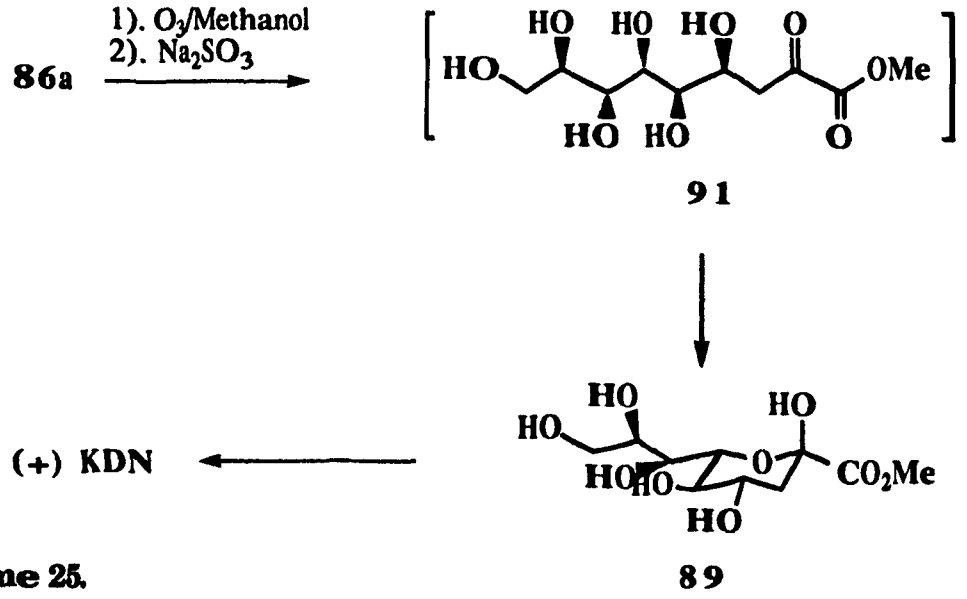
Attempts to remove the acetate groups of the crude keto ester to give KDN directly by KOH or other weaker bases, such as Na_2CO_3, gave a complicated mixture.

The failure of the reaction is because the α-keto ester **88** is too labile to bases. On the other hand, when the keto ester **88** was treated with dilute HCl in methanol for 24 h according to a recent report,[69] the corresponding KDN methyl ester **89** was obtained, which has been transformed in one step to the corresponding (+)-KDN in the literature.[58] Thus, a formal synthesis of (+)-KDN was also completed.

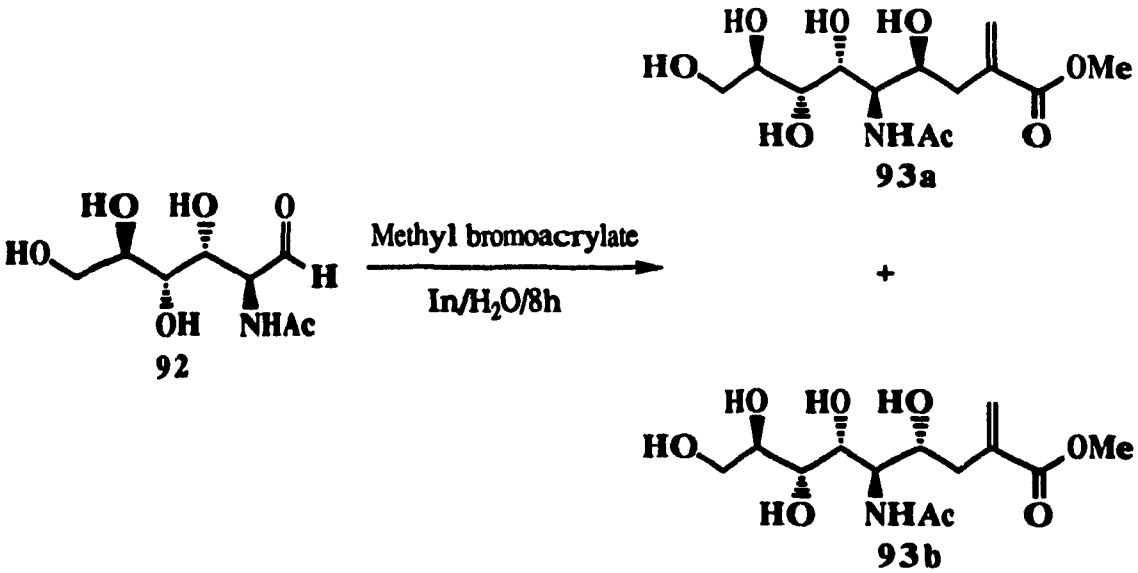
However, decomposition of the ester was observed on long standing. In order to avoid the decomposition, the methyl ester **89** was saponified directly with dilute KOH in aqueous methanol, followed by passing the produced potassium salt through an ion-exchange resin eluted with dilute formic acid and lyophilized to give KDN (**75a**) in pure form. The KDN was then transformed into its ammonium salt **90** by treatment with dilute NH_4OH. The NMR spectrum was in agreement with literature reports.[58,59]

After the success of the synthesis, a more concise route was also developed. The protection and deprotection process in the above sequence could be completely eliminated. The major alkylation product **86a** (62%) was easily obtained and purified by recrystalization from methanol/EtOAc. Ozonization of **86a** directly in methanol for 25 min followed by the treatment with Na_2SO_3 afforded the corresponding α-keto ester **91** which immediately cyclized to give the (+) KDN methyl ester **89**. The same procedure of saponification and ion exchange chromatography produced the (+) KDN (79% from **86a**) which was also characterized through its ammonium salt **90**. The new procedure produced the (+) KDN essentially in three steps in excellent yield (overall 49%). The spectra of the ammonium salt from these

two procedures are identical in any aspect. The same reaction sequence from D-arabinose should give the corresponding epi-KDO conveniently.



Scheme 25.



Scheme 26.

The coupling reaction also occurred on N-acetyl-β-D-mannosamine 92 (Scheme 26) gave 93b. This should give an easy entry to the synthesis of neuraminic acids. Further study is still in progress.

2.11 Experimental Section

The zinc powder was obtained from Anachemia Chemical Company as dust; tin powder was obtained from Fisher Scentific Limited as 325 mesh; indium and manganese were obtained from Aldrich Chemical Company as 150 and 325 mesh respectively. All the metal powders were used directly without any previous treatment. Solvents were dried prior to use: THF and hexane were dried over sodium metal/benzophenone, methylene chloride was dried over phosphorus pentoxide, pyridine was dried and distilled over KOH, and acetonitrile was dried over CaH_2. Melting points were taken with a Gallenkamp apparatus and are uncorrected. Nuclear magnetic resonance spectra were taken with Varian XL-200, or XL-300, Gemini-200 or Jeol CPF-270 instruments. Infrared spectra were obtained from films on NaCl plates for liquids and as a KBr pellets for solids on an Analect FTIR AQS-18 spectrophotometer and reported in cm^{-1}. Optical rotations were measured on a JASCO DID-140 Polarimeter. Column chromatography was performed on silica gel 60 (Merck or EM Science). Low Resolution Mass Spectra were determined on a DuPont 21-492B spectrometer, High Resolution Mass Spectra were performed on a VG ZAB-HS instrument at the Biomedical Mass Spectrometry Unit, McGill University.

General Procedure for the Allylation of Carbonyl Compounds Mediated by Zinc and Tin:

A mixture of allyl bromide (1.5 mmol), the aldehyde (1 mmol), tin powder or zinc powder (1 mmol and 1.5 mmol respectively) and 10 mL of water in a 50 mL flask was heated with magnetic stirring to 80°C (40°C for zinc) for 2 h. The reaction mixture was cooled and 1 mL of 1N HCl was added followed by stirring for 10 min. The reaction mixture was poured into a separatory funnel and was extracted three times with ether. The combined organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel chromatography.

General Procedure for the Allylation of Carbonyl Compounds Mediated by Indium:

A mixture of carbonyl compound (1 mmol), allyl halide (1.5 mmol) and indium powder (1 mmol) in water (15 mL) was stirred at room temperature in a stoppered 25 mL flask for 1-6 h. Then, 1 mL of 1N HCl was added followed by stirring for 10 min. The product was extracted with ether and purified by flash chromatography.

General Procedure for the Allylation of Carbonyl Compounds Mediated by Manganese:

A mixture of carbonyl compound (1 mmol), allyl halide (1.5 mmol) 10 mL of water was stirred at room temperature. While stirring, a pre-mixed powder of Mn/Cu was added in one portion and the mixture was stirred for the corresponding time. Then, 1 mL of 1N HCl was added followed by stirring for 5 min. The product was extracted with ether and purified by flash chromatography.

General Procedure for the Preparation of 1,3-Butadienes:

Method A:

A mixture of carbonyl compound (1 mmol), 1,3-dichloropropene (1 mmol), and zinc powder (2 mmol) in 10 mL of water was heated to 35-40°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 to give the corresponding 1,3-butadiene.

Method B:

A mixture of carbonyl compound (1 mmol), 1-chloro-3-iodo-propene (1.5 mmol) and zinc powder (1.5 mmol) in 10 mL of water was stirred at room temperature until the zinc powder almost disappeared (in case where the reaction did not start properly, 2-3 drops of hydrobromic acid (48%) or saturated NH_4Cl 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) sporadically during a period of 5 h. The reaction mixture was then extracted with ether, dried and evaporation of the solvent gave, after purification, the diene.

General Procedure for the Preparation of Vinyloxiranes:

Method A:

After the first stage of 1,3-diene synthesis (method B), the reaction was interrupted by extraction with ether, the intermediate chlorohydrin was isolated by column chromatography. The chlorohydrin was treated with NaOH in ethanol (0.4 g/10 mL) to give the vinyloxirane in quantitative yield.

Method B:

A mixture of carbonyl compound (1 mmol), 1-chloro-3-iodo-propene (1.5 mmol) and tin powder (1.5 mmol) in 10 mL of water and 2 mL ether was processed with a ultrasonic processor for 1h. The reaction mixture was extracted with ether and the intermediate chlorohydrin was isolated by column chromatography. The chlorohydrin was treated as above to give the vinyloxirane in quantitative yield.

Dienes:

1-Chloro-3-iodo-propene (11):[6]

A mixture of 1,3-dichloro-propene (11.1 g, 0.1 mol) and NaI (30 g, 0.2 mol) in 100 mL of acetone was stirred at room temperature under nitrogen for 4h. The solid was filtered off. Vacuum distillation of the liquid mixture gave the title compound , b.p. 42°C/15 mmHg. ^{1}H NMR ($CDCl_3$), δ=3.90 (m, 2H), 6.15(m, 2H); IR: 3155, 1793, 1473, 1381cm^{-1}. Both ^{1}H NMR and GC indicated the presence of a mixture of cis and trans (5:3). The assignment of the stereochemistry was based on the general trend that cis compound has a lower boiling point and a smaller coupling constant between the two adjacent =CH protons.

1-Phenyl-1,3-butadiene (9a):

The title compound was prepared from the general procedure, either method A or method B, from benzaldehyde. ^{1}H NMR($CDCl_3$): δ= 5.1-5.4(m, 2H), 6.4-6.9(m, 3H), 7.35(br, 5H)ppm; IR: 3081, 1620, 1327, 1159cm^{-1}; MS(EI): 130(M, 100%), 129(92), 115(75), 102(32), 89(21), 77(39), 63(37), 51(35), 39(37), 27(26).[6]

4-Phenyl-1,3-pentadiene (9e):

The title compound was prepared by the general procedure, either method A or method B, from acetophenone. ^{1}H NMR($CDCl_3$): δ=

2.12(minor, s, 3H), 2.12(major, s, 3H), 5.25(m, 2H), 6.47(m, 1H), 6.8(m, 1H), 7.3(m, 5H)ppm; IR: 3065, 3058, 3029, 2948, 1628, 1596, 1496, 1448cm^{-1}; MS(EI): 144(M, 48%), 129(100), 115(27), 103(10), 91(21), 77(23), 65(22), 63(25), 51(28), 39(48), 27(9).[5]

1-Phenyl-1,3,5-hexatriene (9d):

The title compound was prepared by the general procedure (either method A or method B) from cinnamaldehyde. ^{1}H NMR($CDCl_3$): δ= 5.1-5.4(m, 2H), 6.4-6.9(m, 5H), 7.35(br, 5H)ppm; IR: 3155, 1793, 1656, 1615, 1473, 1361cm^{-1}; MS(EI): 156(M, 12%), 129(87), 115(33), 105(31), 91(41), 83(100), 77(50), 47(56), 39(14), 35(48), 28(55).[6]

1-(4-Chlorophenyl)-1,3-butadiene (9i):

The title compound was prepared by the general procedure method B from 4-chloro-benzaldehyde. ^{1}H NMR($CDCl_3$): δ= 5.18-5.4(m, 2H), 6.4-6.6(m, 2H), 6.7-6.83(m, 1H), 7.3(m, 5H)ppm; IR: 3089, 3042, 3015, 1635, 1603, 1591cm^{-1}.[64]

1-(4-Methylphenyl)-1,3-butadiene (9j):

The title compound was prepared by the general procedure method B from p-tolualdehyde. ^{1}H NMR($CDCl_3$): δ= 2.35(s, 3H), 5.18-5.4(m, 2H), 6.4-6.6(m, 2H), 6.7-6.83(m, 1H), 7.3(m, 4H)ppm; IR: 3020, 2943, 1635, 1601, 1458 cm^{-1}; MS(EI): 144(M, 49.6%), 129(100), 115(23.5), 105(10.8), 91(18.8), 83(62.5), 75(34), 65(10), 47(14), 39(20), 28(18).[65]

1,3-Tridecadiene (9b):

The title compound was prepared by the general procedure (either method A or method B) from decyl aldehyde. ^{1}H NMR($CDCl_3$): δ= 0.9(t, 3H), 1.3(br, 14H), 2.1(m, 2H), 5.0(m, 2H), 5.7(m, 1H), 6.05(m, 1H), 6.4(m, 1H)ppm; IR: 3034, 2927, 1653, 1604cm^{-1}; MS(EI): 180(M, 41%), 152(3.2), 138(2.6), 109(15,1), 95(62.4), 81(76.2), 67(86.6), 54(100), 41(89), 27(71).[5]

4-Methyl-1,3-tridecadiene (9g):

The title compound was prepared by the general procedure (either method A or method B) from 2-undecanone. ^{1}H NMR($CDCl_3$): δ= 0.9(t, 3H), 1.3(br, 14H), 1.75(s, 3H), 2.05(major, t, 2H), 2.15(minor, t, 2H), 5.0(m, 2H), 5.75(d, J= 11Hz, 1H), 6.6(m, 1H)ppm; IR: 3085, 2928, 1653, 1598, 1466, 1458cm^{-1}; MS(EI): 194(M, 40%), 123(32), 109(20), 95(77), 82(100), 68(87), 55(68), 43(66), 29(65).[66]

1-Cyclohexyl-1,3-butadiene (9c):

The title compound was prepared by the general procedure (either method A or method B) from cyclohexanecarboxaldehyde. ^{1}H NMR($CDCl_3$): δ= 1.2(br, 6H), 1.7(br, 4H), 2.0(m, 1H), 5.05(m, 2H), 5.65(dd, J=6.7, 6.0Hz, 1H), 6.05(m, 1H), 6.3(dt, J=10.0, 16.8Hz, 1H)ppm; MS(EI): 136(M, 67%), 121(22), 107(41), 94(57), 82(87), 67(100), 54(86), 41(64), 39(71), 29(27), 27(36).[5]

2-Propenylidenecyclohexane (9k):

The title compound was prepared by the general procedure method B from cyclohexanone. ^{1}H NMR($CDCl_3$): δ= 1.5(br, 6H), 2.2(m, 4H), 5.05(m, 2H), 5.7(m, 1H), 6.6(m, 1H)ppm; IR: 3065, 2931, 1629, 1448cm^{-1}; MS(EI): 136(M, 67%), 121(21), 107(41), 94(57), 82(87), 67(100), 54(86), 41(64), 39(71), 29(27), 27(36).[5]

2-Propenylidenecyclononane (9f):

The title compound was prepared by the general procedure method A from cyclononanone. ^{1}H NMR($CDCl_3$): δ= 1.3-1.8(m, 12H), 2.15-2.35(m, 4H), 5.0(m, 2H), 5.95(d, J=11.4Hz, 1H), 6.6(dt, Ja=10.3, Jb=17Hz, 1H)ppm; MS(EI): 164(M, 33%), 149(4), 135(15), 123(10), 95(51), 81(80), 67(82), 55(53), 39(48), 28(100).

4-Butyl-1,3-octadiene (9l):

The title compound was obtained by the general procedure method A

from 5-nonanone. ^{1}H NMR($CDCl_3$): δ= 0.9(t, 6H), 1.3(br, 8H), 2.05(t, 1H), 2.15(t, 1H), 5.0(m, 2H), 5.9(d, J= 10.4Hz, 1H), 6.5(dt, Ja= 10.4, Jb=16.7Hz, 1H)ppm; MS(EI): 167(M+1, 18), 149(21), 129(32), 111(30), 97(25), 85(43), 71(52), 57(100), 43(85), 29(44).

Vinyloxiranes:

4-Phenyl-3,4-oxo-1-butene (12a):

Using the general procedure from either method A or method B and starting from benzaldehyde and 1-chloro-3-iodo-propene, a mixture of 1-phenyl-2-chloro-3-buten-1-ol diastereomers was obtained: ^{1}H NMR($CDCl_3$): δ= (major) 2.85(d, J=3.4Hz, 1H), 4.55(m, 1H), 4.73(dd, J= 3.6, 7.3Hz, 1H), 5.2(m, 2H), 5.7(m, 1H), 7.3(m, 5H)ppm; (minor) 2.62(d,J=3.4Hz,1H), 4.55(m, 1H), 4.95(m, 1H), 5.2(m, 2H), 5.7(m, 1H), 7.3(m, 5H)ppm; IR: 3431(OH), 3005, 1640, 1455cm^{-1}. The chlorohydrin diastereomeric mixture was transformed to the title compound upon treatment with sodium hydroxide in ethanol. ^{1}H NMR($CDCl_3$): (cis) δ= 3.67(dd, Ja=4.3Hz, Jb=7.2Hz, 1H), 4.26(d, J=4.2Hz 1H), 5.2-5.85(m, 3H), 7.35(br, 5H)ppm; (trans) δ= 3.35(dd, Ja=1.9Hz, Jb=7.2Hz, 1H), 3.78(d, J=1.8Hz, 1H)ppm.[6, 62]

4-(4-Chlorophenyl)-3,4-oxo-1-butene (12b):

From 4-chloro-benzaldehyde, using the general procedure (either method A or method B), 1-(4-chlorophenyl)-2-chloro-3-buten-1-ol was produced. ^{1}H NMR($CDCl_3$): δ= (major) 2.85(d, J=3.4Hz, 1H), 4.5(m, 1H), 4.70(dd, J= 3.6, 7.3Hz, 1H), 5.2(m, 2H), 5.7(m, 1H), 7.3(m, 5H)ppm; (minor) 2.62(d,J=3.4Hz,1H), 4.5(m, 1H), 4.9(m, 1H), 5.2(m, 2H), 5.7(m, 1H), 7.3(m, 5H)ppm; IR: 3016, 1521, 1421cm^{-1}. Treatment of this chlorohydrin by NaOH/ethanol gave the title compound. ^{1}H NMR($CDCl_3$): δ= (cis) 3.68(dd, Ja=4.3Hz, Jb=7.2Hz, 1H), 4.20(d, J=4.2Hz, 1H), 5.2-5.85(m, 3H), 7.30(m, 4H)ppm; (trans) δ= 3.31(dd, Ja=1.9Hz, Jb=7.2Hz, 1H), 3.74(d, J=1.8Hz, 1H),

5.2-5.85(m, 3H), 7.30(m, 4H)ppm. [62]

4-(4-Methylphenyl)-3,4-oxo-1-butene (12c):

From p-tolualdehyde, using the general procedure (either method A or method B), 1-(4-methylphenyl)-2-chloro-3-buten-1-ol was produced. ^{1}H NMR($CDCl_3$): δ= (major) 2.35(s, 3H), 2.75(d, J=3.4Hz, 1H), 4.55(m, 1H), 4.70(dd, J= 3.6, 7.3Hz, 1H), 5.2(m, 2H), 5.8(m, 1H), 7.3(m, 4H)ppm; (minor) 2.45(s, 3H), 2.5(d,J=3.4Hz,1H), 4.5(m, 1H), 4.9(m, 1H), 5.2(m, 2H), 5.8(m, 1H), 7.3(m, 4H)ppm; IR: 3016, 1520, 1421cm^{-1}. Treatment of the chlorohydrin by NaOH/ethanol gave the title compound. ^{1}H NMR($CDCl_3$): δ= (cis) 2.34(s, 3H), 3.65(dd, Ja=4.4Hz, Jb=7.0Hz, 1H), 4.21(d, J=4.4Hz, 1H), 5.2-5.85(m, 3H), 7.2(m, 4H)ppm; (trans) δ= 3.35(dd, Ja=1.8Hz, Jb=7.0Hz, 1H), 3.74(d, J=1.8Hz, 1H), 5.2-5.85(m, 3H), 7.2(m, 4H)ppm. MS(EI), 160(M^+, 15.9%), 159(8.4), 145(19.3), 131(100), 116(16.0), 103(31.0), 91(33.0), 78(21.0), 65(9.2), 51(7.5), 39(11.5), 28(26.0). [63]

3,4-Oxo-1-tridecene (12d):

The title compound was prepared by the general procedure (method A or method B) from decyl aldehyde. ^{1}H NMR($CDCl_3$): δ= (cis) 0.9(t, 3H), 1.2-1.7(br, 16H), 3.07(m, 1H), 3.38(dd, Ja=4.1Hz, Jb=7.0Hz, 1H), 5.2-5.8(m, 3H)ppm; (trans) 0.9(t, 3H), 1.2-1.7(br, 16H), 2.41(dt, Ja=1.9Hz, Jb=7.2Hz, 1H), 2.81(dt, Ja=2Hz, Jb=5.6Hz, 1H), 5.2-5.85(m, 3H), 7.35(br, 5H)ppm. MS(CI), 197(M+1, 19.9%), 179(29.2), 155(100), 137(24.8), 123(29.9), 109(44.4), 95(57.4), 83(52.3), 71(38.7), 69(37.2).[63]

2-Vinyl-1-oxaspiro[2, 5]octane (12e):

The title compound was prepared from method A. ^{1}H NMR($CDCl_3$): δ= 1.4-1.8(br, 10H), 3.19(d, J=7.2Hz, 1H), 5.3-5.9(m, 3H)ppm.[63]

General Procedure for the Preparation of 2-Methylene-tetrahydrofuran Derivatives:

A mixture of the carbonyl compound (1 mmol), 2-chloromethyl-3-iodo-propene (1.5 mmol) and zinc powder (1.5 mmol) in 10 mL of water was stirred vigorously at room temperature. Very often, 2-3 drops of saturated aqueous NH_4Cl solution or 48% hydrobromic acid was added to initiate the reaction. The mixture was stirred until the zinc almost disappeared (usually in 3-4 h). The reaction mixture was then extracted with ether to give the alcohol intermediate in good yield. With or without purification, the alcohol was converted to methylene-tetrahydrofurans by treatment with KO-t-Bu/isopropanol (3 mmol/20 mL) or KO-t-Bu/hexane (2 mmol/20 mL). The final product was isolated by flash chromatography.

2-(Chloromethyl)-3-iodo-propene (24):

A mixture of 1-chloro-2-(chloromethyl)-propene (30 g, 0.242 mol), sodium iodide (36 g, 0.242 mol) in 200 mL of acetone was stirred under nitrogen at room temperature until no further solid came out from the solution (~3 h). The solid was filtered off and the liquid mixture was separated by vacuum distillation to obtain the title compound, (29 g, 59%): b.p. 51°C/1.1 mmHg, ^1H NMR($CDCl_3$): δ= 4.06(s, 2H), 4.25(s, 2H), 5.25(s, 1H), 5.4(s, 1H)ppm; ^{13}C NMR($CDCl_3$): δ= 5.6, 45.7, 117.6, 142.49ppm; MS(EI): 218(M+2, 31%), 216(M, 93%), 181(19), 127(15), 89(100), 53(53).

2,5-Bis(chloromethyl)-1,5-hexadiene (32):

This compound was obtained by stirring 2-chloromethyl-3-iodo-propene (214 mg, 1 mmol) with Zn powder (130 mg, 2 mmol) in 10 mL of water under the catalysis of 1 mL of saturated NH_4Cl solution. The compound was isolated by column chromatography (hexane:EtOAc=30:1) ^1H NMR($CDCl_3$): δ= 2.37(s, 4H), 4.06(s, 4H), 5.0(s, 2H), 5.16(s, 2H)ppm; ^{13}C

NMR($CDCl_3$): δ= 30.66, 48.31, 114.99, 144.26ppm; IR: 3153, 2988, 1815, 1561cm^{-1}; MS(EI): 143(M-35, 6.0%), 141(5.8), 129(45), 107(43), 93(100), 79(27), 67(22), 53(65), 39(29), 27(7).

2-Phenyl-4-methylenetetrahydrofuran (26a):

Reaction of benzaldehyde (105 mg, 1 mmol) with 2-chloromethyl-3-iodo-propene in water by the general procedure gave the coupled product 3-chloromethyl-1-phenyl-3-buten-1-ol, which was purified by column chromatography (hexane/EtOAc=20/1), (180 mg, 92%): ^1H NMR($CDCl_3$): δ= 2.1(br, 1H), 2.6(m, 2H), 4.06(s, 2H), 4.9(br, 1H), 5.1(s, 1H), 5.27(s, 1H), 7.3(br, 5H)ppm. Treatment of this compound with potassium t-butoxide in isopropyl alcohol gave the title compound quantitatively. ^1H NMR($CDCl_3$): δ= 2.6(m, 1H), 2.95(m, 1H), 4.5(m, 2H), 5.0(m, 3H), 7.37(m, 5H)ppm; IR: 3085, 3075, 3063, 3028, 2959, 1669cm^{-1}.[19]

2-(4-Chlorophenyl)-4-methylenetetrahydrofuran (26b):

The general procedure of the coupling reaction afforded the compound 3-chloromethyl-1-(4-chlorophenyl)-3-buten-1-ol, which was purified by column chromatography (hexane/EtOAc= 20/1): ^1H NMR($CDCl_3$): δ= 2.2(br, 1H), 2.55(m, 2H), 4.06(s, 2H), 4.85(m, 1H), 5.1(s, 1H), 5.27(s, 1H), 7.3(br, 4H)ppm; IR: 3363(OH), 3065, 2948, 1646, 1596cm^{-1}. Treatment of the coupled product with potassium t-butoxide in isopropyl alcohol gave the title compound quantitatively. ^1H NMR($CDCl_3$): δ= 2.5(m, 1H), 2.95(m, 1H), 4.5(m, 2H), 5.0(m, 3H), 7.37(m, 4H)ppm; IR: 3082, 2910, 1669, 1599, 1493cm^{-1}.

2-(4-Methylphenyl)-4-methylenetetrahydrofuran (26c):

The general procedure of the synthesis from 4-methylbenzaldehyde produced the title compound. ^1H NMR($CDCl_3$): δ= 2.35(s, 3H), 2.55(m, 1H), 2.95(m, 1H), 4.5(m, 2H), 5.0(m, 3H), 7.37(m, 4H)ppm; IR: 3025, 2913, 1668,

1517cm^{-1}.

2-(2'-Phenylvinyl)-4-methylenetetrahydrofuran (26f):

From cinnamaldehyde, using the general procedure of the synthesis, the title compound was produced. ^{1}H NMR($CDCl_3$): δ= 2.47(m, 1H), 2.80(m, 1H), 4.5(m, 3H), 5.0(m, 2H), 6.25(dd, J= 6.7, 16Hz, 1H), 6.6(d, J= 16Hz, 1H), 7.3(m, 5H)ppm; IR: 3062, 3059, 3027, 2852, 1668, 1600cm^{-1}.[67]

2-Nonyl-4-methylenetetrahydrofuran (26d):

Using the general procedure of the coupling reaction, 2-chloromethyl-1-tridece-4-ol was obtained followed by purification with column chromatography (hexane/EtOAc=20/1). ^{1}H NMR($CDCl_3$): δ= 0.85(t, 3H), 1.2-1.6(br, 16H), 1.6(s, 1H), 2.2(m, 1H), 2.45(m, 1H), 3.8(m, 1H), 4.1(s, 2H), 5.07(d, J= 1.1Hz, 1H), 5.26(d, J= 1.1Hz, 1H)ppm. Treatment of the coupled product with pctassium t-butoxide in isopropyl alcohol gave the title compound, which was purified through a short column chromatography (hexane/EtOAc= 40/1). ^{1}H NMR($CDCl_3$): δ= 0.86(t, 3H), 1.2-1.8(br, 16H), 2.2(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.3(m, 2H), 4.9(dt, J= 2.4, 14Hz, 2H)ppm; IR: 3076, 2921, 2854, 1671, 1465cm^{-1}.[67]

2-Cyclohexyl-4-methylenetetrahydrofuran (26e):

General procedure of the coupled reaction from cyclohexanecarboxaldehyde afforded 3-chloromethyl-1-cyclohexyl-3-buten-1-ol, which was purified by column chromatography (hexane/EtOAc=20/1). ^{1}H NMR($CDCl_3$): δ= 1.0-1.9(br, 11H), 2.19(m, 1H), 2.5(m, 1H), 3.5(m, 1H), 4.1(s, 2H), 5.07(s, 1H), 5.25(s, 1H)ppm. Treatment of the coupled product by potassium t-butoxide in hexane gave quantitatively the title compound. ^{1}H NMR($CDCl_3$): δ= 0.9-2.0(br, 11H), 2.25(m, 1H), 2.55(m, 1H), 3.6(m, 1H), 4.3(m, 2H), 4.9(m, 2H)ppm; IR: 3076, 2924, 1666, 1449cm^{-1}.[68]

Spirocyclohexane-1,2'-(4-methylenetetrahydrofuran) (26g):

General procedure of the synthesis from cyclohexanone produced the title compound. ^1H NMR($CDCl_3$): δ= 1.2-1.8(br, 10H), 2.35(d, J=1.3Hz, 2H), 4.3(d, J= 1.6Hz, 2H), 4.9(m, 2H)ppm; IR: 3076, 2933, 1667, 1448cm^{-1}.[19]

2-Methyl-2-phenyl-4-methylenetetrahydrofuran (26h):

General procedure of the synthesis from acetophenone produced the title compound. ^1H NMR($CDCl_3$): δ= 1.56(s, 3H), 2.85(q, 2H), 4.45(q, 2H), 4.9(dm, 2H), 7.35(m, 5H)ppm; IR: 3063, 3061, 2927, 1668, 1431cm^{-1}.[19]

Spiro(2-cyclohexene)-1,2'-(4-methylenetetrahydrofuran) (26i):

General procedure of the coupling reaction from 2-cyclohexenone afforded the compound 1-(2-chloromethyl-2-propenyl)-2-cyclohexen-1-ol, which was purified by column chromatography (hexane/EtOAc=20/1): ^1H NMR($CDCl_3$): δ= 1.6(br, 1H), 1.7(br, 4H), 2.0(br, 2H), 2.45(s, 2H), 4.2(s, 2H), 5.05(d, J=1.5Hz, 1H), 5.3(d, J=1.5Hz, 1H), 5.75(m, 2H)ppm. Treatment of the coupled product by potassium t-butoxide in hexane gave the title compound. ^1H NMR($CDCl_3$): δ= 1.2-2.2(br, 6H), 2.45(d, J=1.6Hz, 2H), 4.3(d, J= 1.6Hz, 2H), 4.9(m, 2H), 5.8(m, 2H)ppm; IR: 3076, 2933, 1667, 1448cm^{-1}.[19]

2-(1-Phenylethyl)-4-methylenetetrahydrofuran (26j):

The title compound was prepared by the general procedure from 2-phenylpropanal and purified by column chromatography (hexane/EtOAc= 40/1). ^1H NMR ($CDCl_3$): δ= (major) 1.4(d, 3H), 2.0-3.0(m, 3H), 4.0-4.5(m, 3H), 4.85(br, 2H), 7.3(m, 5H); (minor) 1.35(d, 3H)ppm; IR: 3076, 2963, 1687, 1453, 1055cm^{-1}.

Mechanism:

Diallylstannyl dibromide (41):

To a suspension of tin powder (1.78g, 0.015 mol) in 15 ml of toluene

was added mercuric chloride (0.05 g, 0.2 mol). The resulting mixture was refluxed for 30 min with stirring. After cooling, triethylamine (0.02 g, 0.2 mol) was added and the mixture was heated to reflux again. Then, allyl bromide (1.82 g, 0.015 mol) was added dropwise to the reaction mixture with efficient stirring. Stirring was continued for 1.5 h. The reaction apparatus was cooled down. Unchanged tin together with some other solid were filtered off and the filtrate was evaporated under reduced pressure. The residue oil was distilled in vacuo yielding 1.8 g (50%) of diallyl tin dibromide b.p. 100-102°C/ 8 mmHg. ^{1}H NMR($CDCl_3$): δ= 2.8(d, 4H), 5.0-5.4(m, 4H), 5.8-6.1(m, 2H)ppm.[40]

Preparation of magnesium iodide:

A mixture of Mg (2.4 g, 0.1 mol) and 50 mL dry ether in a 250 mL flask was heated to reflux under nitrogen. To the refluxing suspension, a solution of Iodine (25.4 g, 0.1 mol) in 150 mL of ether was added dropwise. The reflux was continued for another 3h after the completion of the addition. Evaporation of the solvent in vacuo left a solid, which can be used directly.

2-Methyl-6-hepten-2-ol (47):

Mg (1.8 g, 73.7 mmol) and 50 mL of dry ethyl ether was mixed in a 250 mL flask. To the mixture, 5-bromo-1-pentene(10 g, 67 mol) in 50 mL ether (a few crystals of iodine were added to initiate the reaction) were added. Following the addition, the mixture was stirred for 2 h. Afterwards, a solution of acetone (4.7 g, 83.8 mmol) in 40 mL ether was added dropwise, and stirring was continued for another 2 h following the addition. Then 40 mL of water was added. The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude material. The desired 2-methyl-6-hepten-2-ol (47) was isolated by vacuum distillation (35-

37°C/1.1 mmHg) , yield 75%; ^{1}H NMR ($CDCl_3$) δ= 1.21(s, 6H), 1.47(m, 4H), 2.07(m, 2H), 5.0(m, 2H), 5.08(m, 1H); IR: υ= 3370, 3010, 2973, 1641, 909cm^{-1}.

6-Iodo-6-methyl-1-heptene (48):

(Method A): MgI_2 (3.614 g, 13 mmol) was added into a solution of **47** (3.2 g, 25 mmol) in 20 mL of pentane. The reaction mixture was stirred under nitrogen for 3 days. Evaporation of the solvent gave a sticky liquid. Distillation (vacuum, 1 mmHg) resulted in an inseparable mixture of 6-iodo-6-methyl-1-heptene and the starting alcohol.

(Method B): A solution of **47** (2.56 g, 20 mmol) in 100 mL molecular sieve dried chloroform was stirred under a stream of nitrogen. Then iodotrimethylsilane(5.70 mL, 20 mmol) was added dropwise at 0°C. After the addition, the reaction mixture was stirred at r.t. for 1 h. The chloroform was removed in vacuo and 50 mL of pentane was added. The solution was washed with 10 mL of water and dried over anhydrous $MgSO_4$. Vacuum distillation of the crude mixture gave 2.9 g of 6-iodo-6-methyl-1-heptene (**48**, 60%) (40°C/1.0 mmHg); ^{1}H NMR ($CDCl_3$) δ= 1.58(m, 4H), 1.90(s, 6H), 2.07(m, 2H), 5.0(m, 2H), 5.08(m, 1H)ppm. [41]

2-Dimethyl-1-iodomethyl cyclopentane (51):

^{1}H NMR ($CDCl_3$): δ= 0.76(s, 3H), 1.02(s, 3H), 1.2-1.6(m, 5H), 1.8-2.2(m, 2H), 2.94(dd, J=9.4, 11.4 Hz, 1H), 3.3(dd, J= 3.7, 9.3 Hz, 1H)ppm; ^{13}C NMR ($CDCl_3$) δ= 8.93, 19.98, 20.99, 27.97, 32.39, 41. 77, 42.66, 52.84ppm. [41]

Muscarine:

D, L-2-Hydroxypropanal dimethyl acetal (62):

Into a dry 250 mL three-neck flask containing $LiAlH_4$ (3.6 g, 95 mmol) in 75 mL of anhydrous ether under nitrogen, dimethyl acetal pyruvaldehyde (10.2 g, 86 mmol) was added dropwise. When the addition

was complete, an additional 75 mL of ether was added. The reaction mixture was refluxed for 1h, cooled and quenched with dropwise addition of saturated aqueous NaCl solution. To the mixture, Na_2SO_4 was added to absorb water, and the slurry was filtered. The solid was washed with ether, and all organic solution were combined and concentrated under vacuum. Distillation of the residue gave 8.4 g (83%) of the title compound. b.p. 65°C/28 mmHg; ^1H NMR($CDCl_3$): δ= 1.16 (d, J= 6.4, 3H), 2.13(s, br, 1H), 3.43(d, J= 6.4, 6H), 3.74(m, 1H), 4.06(d, J= 6.0, 1H)ppm.

D, L-2-Dichlorobenzyoxypropanal dimethyl acetal (63):

To a dispersion of NaH (48 mg, 2 mmol) in 10 mL of dry DMSO, D, L-2-hydroxyl propanal dimethyl acetal (240 mg, 2 mmol) was added dropwise. The resulting mixture was stirred for 30 min and DCBBr(480 mg, 2 mmol) was added. After stirring at room temperature for 12h, the reaction mixture was quenched with water and extracted with ether. The ethereal layer was washed with NH_4Cl aqueous solution and water, dried over $MgSO_4$. After evaporation of the solvent, the residue was run through a short column (hexane/EtOAc =10/1) to give the title compound. Yield (490 mg, 89%).

1-Hexen-4,5-diol(syn:anti) (58):

D, L-Lactaldehyde dimethyl acetal(120 mg, 1 mmol) was dissolved in 10 mL of distilled water. The solution was heated with Dowex-50-H^+ at 70°C for 5h. The reaction mixture was cooled down, allyl bromide (240 mg, 2 mmol) and 2 mmol of M (Zn, Sn, In) was added. The reaction mixture was stirred at room temperature (75°C for Sn) for 2 h, after work up and purification to give the title diol as a mixture. major(syn): ^1H NMR($CDCl_3$) δ= 1.2(br 3H), 2.2(br, 4H), 3.41(br, 1H), 3.62(m, 1H), 5.2(m, 2H), 5.85(m, 1H)ppm; minor(anti): ^1H NMR ($CDCl_3$): δ= 3.62(br, 1H), 3.85(m, 1H)ppm.

2, 3-hexandiol(syn:anti) (59):

The hydrogenation was carried out according to a literature procedure to give the saturated diol. Major (syn): ^1H NMR($CDCl_3$): δ= 0.92(t, 3H), 1.1-1.3(br, 3H), 1.3-1.6(br, 4H), 2.7(br, OH, 2H), 3.35(br, 1H), 3.58(m, 1H)ppm; minor(anti): ^1H NMR($CDCl_3$): δ= 3.61(br, 1H), 3.79(m, 1H)ppm.[45a]

Ethyl S-(-)-2-(2',6'-dichlorobenzyl)oxy-propionate (70):

Dry powdered silver oxide (1.3 g, 5.25 mmol) was added to a solution of ethyl S-(-)-lactate (559 mg, 5 mmol) and 2,6-dichlorobenzyl bromide (1.2 g, 5 mmol) in 50 mL dry ether over a period of 40 min. with stirring. The reaction was kept refluxing for 6 h until TLC showed complete disappearance of the starting lactate. Then the reaction mixture was filtered through celite. Evaporation of the solvent resulted in a crude material, which was purified by flash chromatography (hexane : ethyl acetate= 20: 1) to give 1.25 g (90%) colorless oil. ^1H NMR($CDCl_3$): δ= 1.30(t, J= 7.1, 3H), 1.41(d, J=6.9, 3H), 4.1(q, J=7.1, 1H), 4.2(q, J=7.1, 2H), 4.7(d, J= 10.6, 1H), 5.02(d, J=10.61, 1H), 7.25(m, 3H)ppm; IR(neat): υ= 2986, 2901, 2886, 1746, 1581, 1564, 1436, 1373, 1268, 1197, 1139, 1116, 766cm^{-1}; HRMS: $C_{12}H_{14}O_3Cl_2+H^+$, calc. 277.03988, found 277.03983.

(2S, 3R)-2-(Dichlorobenzyloxyl)-5-hexen-3-ol (71a):

To a solution of the lactate (556 mg, 2 mmol) in 20 mL ethyl ether under argon, diisobutyl aluminium hydride 2.2 mL (1.0 M in hexane) was added dropwise with a syringe over 40 min at -78°C. After stirring for 2h, saturated ammonium chloride solution 10 mL was added to quench the reaction, followed by the addition of 2 mL 10% HCl. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent afforded a crude material, which was directly used without purification. The crude

aldehyde was transferred into a 100 mL of flask and mixed with 50 mL of H_2O. To the suspension was added (360 mg, 3 mmol) allyl bromide and zinc powder (192 mg, 3 mmol) and 2 mL of saturated ammonium chloride solution to catalyze the reaction. The reaction was followed until the aldehyde disappeared. Then, the reaction mixture was extracted with ether. The ethereal extraction was dried over $MgSO_4$. Evaporation of the solvent gave a mixture of diastereomers (2~ 3 : 1). Separation of the diastereomers is possible by flash chromatography (hexane : ethyl acetate = 20 : 1). The major isomer was proved to be (2S, 3R)-2-(dichlorobenzyloxyl)-5-hexen-3-ol 302 mg (55%). ^1H NMR($CDCl_3$): δ= 1.21(d, J=6.3, 3H), 2.21(br, 3H), 3.50(m, 1H), 3.71(m, 1H), 4.75(dd, J= 10.2, 17.5, 2H), 5.1(m, 2H), 5.8(m, 1H), 7.25(m, 3H)ppm; ^{13}C NMR($CDCl_3$): δ= 13.96, 36.75, 65.3, 72.2, 77.65, 117.31, 128.28, 129.81, 133.31, 134.86, 136.62ppm.[53]

(2S, 3S)-2-(Dichlorobenzyloxyl)-5-hexen-3-ol (71b):

The above minor product proved to be (2S,3S)-2-(dichlorobenzyloxyl)-5-hexen-3-ol 126 mg (yield 23%); ^1H NMR($CDCl_3$) δ= 1.23(d, J=6.0, 3H), 2.21(br, 2H), 2.77(d, OH, J=2.6, 1H), 3.41(m, 2H), 4.80(dd, J= 10.2, 43.1, 2H), 5.1(m, 2H), 5.8(m, 1H), 7.25(m, 3H)ppm; ^{13}C NMR($CDCl_3$): δ= 15.2, 37.1, 65.2, 74.2, 77.95, 116.91, 128.3, 129.94, 133.1, 134.6, 136.6ppm.[53]

(2S, 4R, 5S) 2-Iodomethyl-5-methyl-tetrahydrofuran-4-ol (74a):

(2S, 3R)-2-(Dichlorobenzyloxyl)-5-hexen-3-ol (266 mg, 0.97 mmol) in 15 mL acetonitrile was treated in small portions under the protection of nitrogen at -5°C with iodine (254 mg, 1.0 mmol). After stirring for 3h at 0°C, the mixture was diluted with ether and washed with water and thiosulfate. After short drying ($MgSO_4$), (2S, 4R, 5S) 2-iodomethyl-5-methyl-furan-4-ol was isolated by flash chromatography (hexane: EtOAc = 2: 1) as a colorless oil 234 mg (85%); ^1H NMR($CDCl_3$): δ= 1.21(d, J=6.4, 3H), 1.88(m,

1H), 2.0(m, 1H), 2.6(s, br, 1H), 3.25(m, 2H), 3.9-4.2(m, 3H)ppm; ^{13}C NMR($CDCl_3$): 10.41, 19.72, 40.79, 76.99, 77.21, 83.16ppm; IR (neat): υ= 3399 (br, OH), 2970, 2930, 1733, 1445, 1358, 1249, 1096, 1063, 984, 992, 905cm^{-1}.[53]

(2S, 4S, 5S) 2-Iodomethyl-5-methyl-furan-4-ol (74b):

The compound was obtained from (2S, 3S)-2-(Dichlorobenzyloxyl)-5-hexen-3-ol by the same procedure as described above as colorless needle crystals, m.p. 62°C (lit.[53d] 62-63); ^1H NMR($CDCl_3$): δ= 1.28(d, J=6.4, 3H), 1.75(br, 2H), 2.4(m, 1H), 3.35(m, 2H), 3.8-4.0(m, 2H), 4.16(m, 1H)ppm; ^{13}C NMR($CDCl_3$): 79.85, 76.68, 73.39, 41.41, 14.07, 11.8ppm; IR(KBr): υ= 3435(br, OH), 2885, 1716, 1539, 1179, 1164, 1065, 1039, 1013cm^{-1}.[53]

(+)-Muscarine iodide (65):

The iodoalcohol (170 mg, 0.7 mmol) and excess of trimethylamine (~ 500mg) was put in ethanol, heated to 80°C in an ampoule for 4h. On cooling, (+)-muscarine iodide crystallized from solution as colorless needles. Recrystallization of the crude material, twice from 2-propanol, furnished colorless crystals, yield 60%. m.p. 141-143°C; (lit.[53c] 138-142°C, 149.22°C[2]); $[\alpha]^{20}D$ + 6.3° (c 1.0, EtOH), (lit.[50b] $[\alpha]^{20}D$ +6.36° (c 0.346, EtOH); ^1H NMR(D_2O): δ= 1.23(d, J= 6.5, 3H), 2.1(m, 2H), 2.9(br, 1H), 3.25(s, 9H), 3.55(m, 2H), 4.15(m, 2H), 4.65(m, 1H)ppm; IR(KBr): υ= 3374(br, OH), 3016, 2969, 2923, 2906, 2741, 1651, 1486, 1465, 1183, 1100, 1008, 970, 929cm^{-1};

(+)-Epimuscarine iodide (66):

By the same procedure as described above, (+)-epimuscarine was obtained as colorless needle crystals, m.p. 169-170°C (lit.[53d] 175°C); $[\alpha]^{20}D$ + 41.9° (c 0.34, EtOH), (lit.[50b] $[\alpha]^{20}D$ + 43.23° (c 0.636, EtOH); ^1H NMR(D_2O): δ= 1.25(d, J= 6.4, 3H), 1.65(m, 1H), 2.65(m, 1H), 3.20(s, 9H), 3.55(m, 2H), 3.96(m, 1H), 4.25(m, 1H), 4.45(m, 1H)ppm.

KDN and KDO Syntheses

Methyl 4,5,6,7,8-penta-*O*-acetyl-3-deoxy-2-methylene-octonate (*manno and gluco*) (82a, 82b):

Indium powder (230 mg, 2 mmol) was added to a stirring mixture of D-(-)-arabinose (150 mg, 1 mmol) and methyl bromomethylacrylate (358 mg, 2 mmol) in 20 mL of water. The reaction mixture was stirred at room temperature for 7h. Dowex-50 (H^+) was added to neutralize the water solution. Filtration of the resin and evaporation of water left a crude residue. The crude material was then dissolved in 5 mL of pyridine and 3 mL of acetic anhydride. DMAP (10 mg) was added to the solution and the resulting mixture was stirred at r.t. for 18h. Evaporation of the solvents produced a crude material. Extraction of the crude material with hexane/EtOAc (3:1) left a yellow solid. The extraction was concentrated to give a yellow syrup. Column chromatography (eluent: hexane/ethyl acetate = 3/1) of the syrup give 363 mg (79%) of a mixture of diastereomers (5:1). The major component was isolated in pure form through another column chromatography (eluent: CH_2Cl_2/Et_2O = 9/1). ^1H NMR ($CDCl_3$): δ= 1.95(s, 3H), 2.02(s, 3H), 2.03(s, 3H), 2.05(s, 3H), 2.2(s, 3H), 2.2-2.4(m, 1H), 2.7-2.8(dd, 1H), 3.7(s, 3H), 4.0-4.12(dd, J= 5.3, 12.5, 1H), 4.16-4.25(dd, J= 3.5, 12.5, 1H), 5.0-5.1(m, 1H), 5.25(m, 2H), 5.45(dd, J= 3.2, 7.3, 1H), 5.55(br, 1H), 6.12(br, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ= 20.5, 34.1, 51.9, 61.4, 68.4, 70, 71, 128, 135.2, 166.3, 169.8, 169.9, 170, 170.5 ppm.

Methyl 4,5,6,7,8-penta-O-acetyl-3-deoxy-octulosonate (*gluco*) (83, crude):

The above compound (230 mg, 0.5 mmol) was dissolved in 15 mL of CH_2Cl_2. The solution was cooled down to -78°C and subjected to ozonization until a blue color appeared. The reaction mixture was allowed to come to r.t. after treatment with an excess amount (~ 5 mmol) of dimethyl sulfide,

and stirring was continued at r.t. for 12h. Evaporation of the solvents under vacuum left a crude product. ^{1}H NMR($CDCl_3$): δ= 2.0(m, 15H), 2.8-3.0(dd, 1H), 3.15-3.25(dd, 1H), 3.82(s, 3H), 4.0-4.25(m, 2H), 5.0-5.5(br, 4H)ppm.

Methyl 5,6,7,8-tetra-*O*-acetyl-octulosonen-3-ate (84):

Column chromatography on silica gel of the above compound afforded the title compound (154 mg, 67%). ^{1}H NMR($CDCl_3$): δ= 2.0-2.2(m, 12H), 3.86(s, 3H), 4.1-4.3(m, 2H), 5.15-5.25(m, 1H), 5.4-5.5(m, 1H), 5.75(br, 1H), 6.7-6.8(dd, J= 1.6, 15.9, 1H), 6.96-7.05(dd, J= 4.3, 15.9, 1H)ppm.[61a]

Methyl 4,5,6,7,8,9-hexa-*O*-acetyl-3-deoxy-2-methylene-D-nonanonate (87a, 87b):

The same reaction sequence as in the KDO synthesis from D-mannose (360 mg, 2 mmol) produced a mixture of diastereomers (820 mg, 77%) in 6:1 ratio. The major one leading to the formation of KDN was isolated in pure form by flash column chromatography (eluent: CH_2Cl_2/Et_2O = 9:1). ^{1}H NMR ($CDCl_3$): δ= 1.95(s, 3H), 2.02(s, 6H), 2.04(s, 3H), 2.08(s, 3H), 2.12(s, 3H), 2.1-2.2(m, 1H), 2.6-2.7(dd, J= 2.9, 13.8, 1H), 3.72(s, 3H), 3.95-4.05(dd, J=5.1, 12.5), 4.15-4.25(dd, J=2.9, 12.7, 1H), 4.9-5.0(m, 1H), 5.15-5.23(m, 2H), 5.26-5.33(m, 1H), 5.38-5.45(m, 1H)5.5(br, 1H), 6.1(br, 1H)ppm. ^{13}C NMR ($CDCl_3$): δ= 20.1, 34, 51, 61, 66.9, 67.4, 68.1, 68.4, 69, 127.6, 135.8, 166.6, 169.7, 169.9, 170.1, 170.3, 170.6 ppm.

Methyl 4,5,6,7,8,9-hexa-*O*-acetyl-3-deoxy-D-nonulsonate (crude) (88):

The same procedure of ozonolysis of the above compound (267 mg, 0.5 mmol) produced the crude title compound. ^{1}H NMR ($CDCl_3$): δ= 2.0-2.1(m, 18H), 2.68-2.8(dd, 1H), 3.04-3.17(dd, 1H), 3.82(s, 3H), 3.92-4.02(dd, 1H), 4.1-4.2(dd, 1H), 4.8-5.0(m, 5H)ppm.

(+)-KDN (75a) (and its ammonium salt, 90)

Method A: The above crude material was treated with 40 mL of dilute HCl in methanol (~ 0.05 M) for 24 h at room temperature. TLC indicated the disappearance of the starting material. Evaporation of the solvent produced the cyclized KDN methyl ester **89**. The ester was then treated with 5 mL 0.1M KOH in aqueous methanol for 6 h at room temperature providing the (+)-KDN sodium salt, which was passed through ion exchange resin (AG 50W-8A, formate form equiliberated with NaCl water solution) by elution with dilute formic acid (0.05 M in water) and lyophilised to yield (+)-KDN (80 mg, 58%). Treatment of the KDN with dilute NH_4OH (3 mL, 0.5 M) followed by lyophilization to give the (+)-KDN ammonium salt (**90**) (82 mg, 100%). ^1H NMR (D_2O): δ= 1.75(t, J=12 Hz, 1H), 2.15(dd, J=5, 13Hz, 1H), 3.5-4.05(m, 7H)ppm; ^{13}C NMR (D_2O): δ= 39.2, 63.5, 68.5, 69.2, 70.2, 70.5, 72.0, 96.8, 176.9 ppm. They are in agreement with literature report.[58a,58b,59]

Method B: Compound **86a** (118 mg, 0.42 mmol) was dissolved in 15 mL of methanol. The solution was subjected to ozone for 25 min at -78°C and followed by treatment with Na_2SO_3(53 mg, 0.42 mmol). After stirring at room temperature for 15 h, the reaction mixture was filtered and the filtrate was concentrated to give a syrup. ^1H NMR spectrum of this syrup was identical to the KDN methyl ester in Method A. The same saponification and lyophilization procedure as above produced the KDN (89 mg, 79%) which was then quantitatively transformed to the ammonium salt **90**.

Methyl 4,5,6,7,8,9-Hexahydroxy-3-deoxy-2-methylene-D-nonanonate (86a):

Coupling reaction between D-mannose and methyl (2-bromomethyl)-acrylate followed by treatment with Dowex-50 (H^+) and lyophilization gave a

white solid mixture. Extraction of the mixture with methanol and evaporation of the solvent afforded another white solid. Recrystallization of the solid from methanol/ethyl acetate produced the pure title compound. ^{1}H NMR (D_2O): δ= 2.5(d, J=6.7Hz, 2H), 3.4-3.8(m, 6H), 3.66(s, 3H), 3.97(t, J=6.9Hz, 1H), 5.69(s, 1H), 6.17(s, 1H)ppm; ^{13}C NMR (D_2O): δ= 31.8, 65.9, 71.1, 71.6, 73.4, 73.5, 80.2, 125.2, 137.1, 176.6 ppm.

2.12 References

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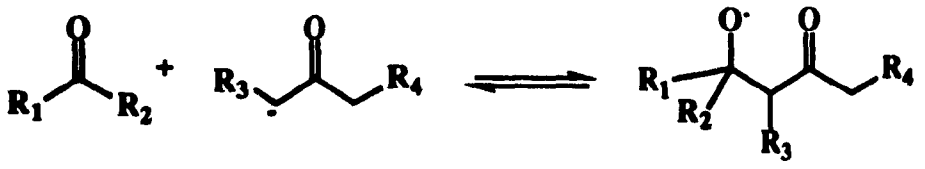
Chapter 3. Cross Aldol Type Condensation and Reformatsky Reactions in Aqueous Media

The aldol condensation is another important reaction for forming carbon-carbon bonds.[1] However, under the classical aldol reaction conditions involving basic media, dimers, polymers, self-condensation products, or α,β-unsaturated carbonyl compounds are often formed as well. The formation of these products is attributed to the fact that the aldol condensation is an equilibrium process (Eq. 1).[2] Useful modifications of the classical aldol condensation, especially using Lewis acid promoted reactions of enol silyl, or tin ethers with carbonyl compounds,[3,4] 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. Because of the structural similarity between α-halo carbonyl compounds and allyl halides, we suspected that similar coupling reactions might take place. Before carrying out the reaction, we first examined the reactivity of some α-halo ketones with metals under aqueous conditions.



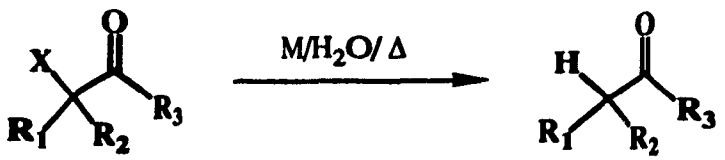
(Eq. 1)

1 2 3

3.1 Reduction of α-halo Carbonyl Compounds

Reduction of α-halo carbonyl compounds is one of the basic procedures which are often encountered in organic synthesis. A variety of new methods have been developed recently in this aspect.[5] In order to check

out the reactivity of α-halo ketones in the aqueous organometallic reaction conditions, we first examined the reduction of α-halo carbonyl compounds.[6] It was found that in water alone, under mild neutral condition, α-bromo and chloro ketones were effectively hydrodehalogenated to the parent ketones by tin or zinc powder (Eq. 2). Some experimental results with tin are listed in Table 1. Both aromatic and aliphatic bromo ketones can be reduced. The reaction temperature seems to be critical to the reduction. The steric factor also affects the reduction as shown in entries 1 and 3. α-Chloro ketones was reduced as well as α-bromo ketones, but higher reaction temperature and longer reaction time had to be applied.



4 M=Sn, Zn 5 (Eq. 2)

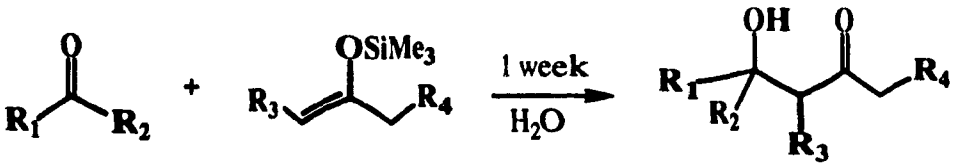
Table 1. Dehalogenation of α-Halo Ketones by Tin in Aqueous Media

Entry	α-halo ketone(4)	Temp.	Time		Product(5)	Yield
1	$PhCOCBr(CH_3)_2$	75°C	3h	5a	$PhCOCH(CH_3)_2$	38%
2	$PhCOCBr(CH_3)_2$	85	3h	5a	$PhCOCH(CH_3)_2$	91
3	$PhCOCHBrCH_3$	75	3h	5b	$PhCOCH_2CH_3$	100
4	$PhCOCH_2Br$	75	3h	5c	$PhCOCH_3$	100
5	$PhCOCH_2Cl$	75	3h	5c	$PhCOCH_3$	6
6	$PhCOCH_2Cl$	90	4h	5c	$PhCOCH_3$	77
7	2-Cl-cyclohexanone	90	3h	5d	cyclohexanone	53

These results demonstrated that α-halo carbonyl compounds are reactive enough under the aqueous organometallic reaction conditions. Thus, it suggested the possibility of carrying out crossed aldol type condensation reactions in aqueous medium in the presence of another carbonyl compound.

3.2 Cross Aldol Type Condensation Reactions with Tin or Zinc in Aqueous Media

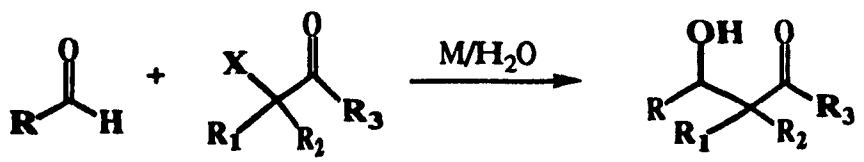
Recently, it was reported that the aldol reaction of silyl enol ethers with carbonyl compounds could be carried out in aqueous solvents without any acid catalyst. However, the reaction took several days to complete (Eq 3).[7,8] The cross-aldol products showed a slight syn diastereoselectivity, the same as the reactions in organic solvent under high pressure.



(Eq. 3)

6 7 8

We found that in aqueous medium direct cross aldol type reaction products were obtained when α-carbonyl compounds, a metal and an aldehyde were reacted together (Eq. 4). Either tin or zinc can be used to mediate the reaction, depending on the reaction temperature. The results are summarized in Table 2.



(Eq. 4)

9 10 M= Sn, Zn 11

Table 2. Cross Aldol Type Reactions in Aqueous Media.

Entry	Halide(equiv.)	Aldehyde(equiv.)	Metal/temp./time	Yield(11)		Ery/thr
1	$PhCOCMe_2Br$(1)	PhCHO(1)	Sn(1eq.)/70°C/4(h)	11a	41	
2	$PhCOCMe_2Br$(1)	PhCHO(1)	Sn(1)/85/4	11a	0	
3	$PhCOCMe_2Br$(1.5)	PhCHO(1)	Zn(4)/r.t./2	11a	76	
4	$PhCOCMe_2Br$(1)	n-$C_8H_{17}CHO$(1)	Sn(1)/75/3	11b	57	
5	PhCOCHMeBr(1.5)	PhCHO(1)	Zn(4)/r.t./2	11c	82	71/29
6	PhCOCHMeBr(1.5)	Me_2CHCHO(1)	Zn(4)/r.t./2	11d	74	45/55
7	PhCOCHMeBr(1.5)	c-$C_6H_{11}CHO$(1)	Zn(4)/r.t./2	11e	83	40/60
8	PhCOCHMeBr(1.5)	n-$C_8H_{17}CHO$(1)	Zn(4)/r.t./2	11f	87	64/36
9	PhCOCHMeBr(1.5)	n-C_3H_7CHO(1)	Zn(4)/r.t./2	11g	80	68/32
10	PhCOCHMeBr(1)	PhCHO(1)	Sn(1)/80/4	11c	67	47/53
11	PhCOCHMeBr(1)	c-$C_6H_{11}CHO$(1)	Sn(1)/80/4	11e	83	64/36
12	$PhCOCH_2Br$(1)	PhCHO(1)	Sn(1)/80/4	11h	64	
13	$PhCOCH_2Br$(1.5)	PhCHO(1)	Zn(4)/r.t./2	11h	85	
14	MeCOCHMeBr(1.5)	PhCHO(1)	Zn(4)/35/2	11i	71	61/39
15	$MeCH_2COCH_2Br$(1.5)	PhCHO(1)	Zn(4)/35/2	11j	72	
16	MeCOCHMeBr(1)	PhCHO(1)	Sn(1)/80/4	11i	84	77/23
17	$MeCH_2COCH_2Br$(1)	PhCHO(1)	Sn(1)/80/4	11j	17	
18	MeCOCHMeBr(1.5)	n-$C_8H_{17}CHO$(1)	Zn(4)/35/2		0	
19	MeCOCHMeBr(1)	n-$C_8H_{17}CHO$(1)	Sn(1)/80/4		0	
20	$MeCOCH_2Cl$(1.5)	PhCHO(1)	Zn(4)/35/2	11k	63	

The reactions were carried out on 1 mmol scale. The ratio of erythro/threo was determined by ^1H NMR.

The reaction has several interesting features; firstly, the aldol product is not accompanied by the usual side products from self-condensation of the aliphatic aldehydes expected from metal enolate chemistry in aqueous media. Secondly, the reactions of 1-bromobutan-2-one or its regioisomer 3-bromobutan-2-one with benzaldehyde were regiospecific (entries 14 and 15) in giving the appropriate crossed aldol type products

without a trace of the regioisomers. A metal enolate intermediate would be expected to equilibrate in aqueous medium to give the various regioisomeric enolates.

Thirdly, the reduction product, which is more likely to be derived from the metal enolate, was formed by a pathway apparently different from that giving the crossed aldol product. For example, in the reaction of 2-bromo-2-methyl-1-phenylpropan-1-one with benzaldehyde and tin at 70°C, the aldol product was formed together with the reduction product (entry 1). On the other hand, when the same reaction was carried out at a temperature of 85°C, only the reduced product was obtained (entry 2).

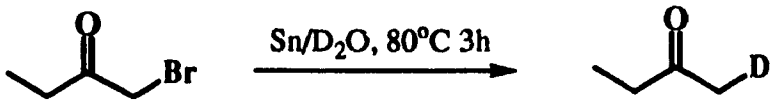
It was found that aromatic aldehydes can smoothly react with different α-halo ketones. However, aliphatic aldehydes only reacted with aromatic halo ketones.

As in the reduction, the yield of the aldol condensation product was dependant on both the reactivity and the steric effect of the α-halo carbonyl compounds. Under similar conditions, secondary halide gave the higher yield relative to primary or tertiary halides, presumably because of a balance of these two effects. In the cases of secondary halide, a mixture of diastereomers was produced. The diastereofacial selectivity was different with different reactants and different metals. Yet, the diastereoselectivity was not significant enough to be synthetically useful.

In the case of simple α-halo aliphatic ketones, since the boiling point of both the halo ketones and their reduced product were relatively low, it

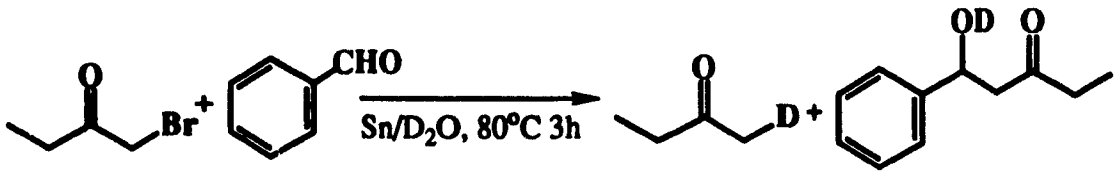
was uncertain whether the halo ketones had been reduced to their corresponding ketones or simply not recovered. In order to resolve this question, 1-bromo-2-butanone was used as a probe to check the reaction in deuterium water.

First, the same aldol reaction was carried out in deuterated water instead of water. After the reaction was complete, the ^1H NMR spectrum of the reaction mixture was taken directly (Eq. 6). Then, the same reaction was performed with the same conditions but without benzaldehyde in deuterated water (Eq. 5). Comparing ^1H NMR spectra of these two reaction mixtures, it was found that all the 1-bromo-2-butanone has either reacted with benzaldehyde in giving the aldol product or reduced to 1-deutero-2-butanone. Therefore, no bromobutanone remained unreacted under the reaction conditions.



(Eq. 5)

12 13



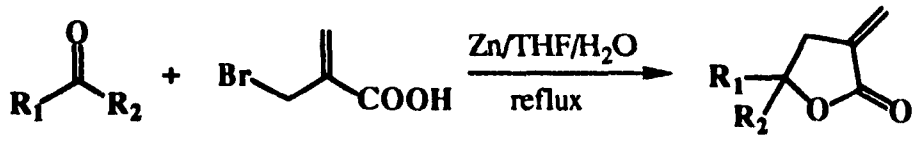
(Eq. 6)

12 14 13 15

3.3 Reformatsky Reactions with Tin and Zinc

Reformatsky type reactions in aqueous media were first reported in 1985,[9] using bromomethylacrylic acid and metallic zinc to prepare α-methylene-γ-butyrolactones (Eq. 7). Normal α-halo carboxylic esters did not

react under these conditions. The substrate was structurally an allylic halide. Therefore, the reaction most likely took place *via* allylation reaction similar to the allylation reactions of the previous chapter.



(Eq. 7)

16 17 18

Table 3. Reformatsky Reactions Mediated by Zinc and Tin

Entry	RCHO	Halide	RCHO/halide/M	Temp/Time	Ery:thr[a]	Yield
1	PhCHO	$BrC(CH_3)_2CO_2Et$	1/1/(Sn)1	80°C/4(h)		**20a** 63
2	PhCHO	$BrCH(CH_3)CO_2Et$	1/1/(Sn)1	80/4	61:39	**20b** 15[a]
3	PhCHO	$BrCH_2CO_2Et$	1/1/(Sn)1	80/4		0
4	n-C_8H_{17}CHO	$BrC(CH_3)_2CO_2Et$	1/1/(Sn)1	80/4		0
5	PhCHO	$BrC(CH_3)_2CO_2Et$	1/1/(Zn)1	45/4		**20a** 66
6	PhCHO	$BrCH(CH_3)CO_2Et$	1/1/(Zn)1	45/4	55:45	**20b** 15[a]
7	PhCHO	$BrCH_2CO_2Et$	1/1/(Zn)1	45/4		0
8	n-C_8H_{17}CHO	$BrC(CH_3)_2CO_2Et$	1/1/(Zn)1	45/4		0

a: Determined by ^1H NMR.

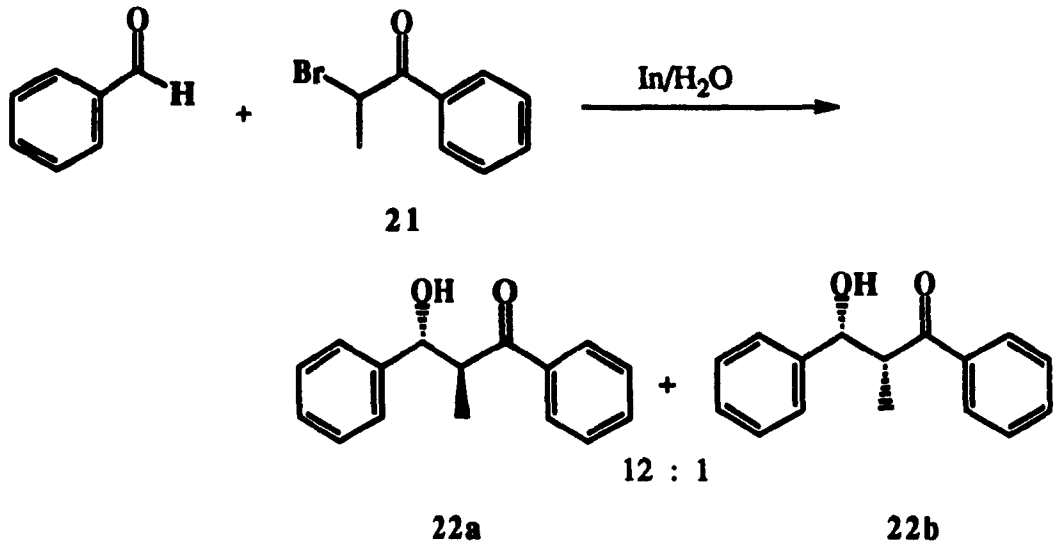
When benzaldehyde was allowed to react with alkyl α-halocarboxylic esters and tin powder in water, the corresponding Reformatsky reaction product was obtained (Eq. 7 and 8). Other aromatic aldehydes reacted similarly. The reaction was however strongly influenced by the structure of both carbonyl compounds and the halo esters. As in the case of aldol condensation, aliphatic aldehydes failed to react. Tertiary halo esters gave the highest yield and no reaction was found with primary halo esters. Similar reactions were found with zinc in water. Yet, all the reactions only

gave moderate yields of the products and slight diastereoselectivity for secondary halo esters.

19 20 (Eq. 8)

3.4 Aldol and Reformatsky Reactions with Indium

In the previous chapter, we described the intriguing character of indium in allylation reactions. The high reactivity of indium powder on the allylation reaction suggested the possibility of mediating other reactions such as cross aldol type condensation reactions. It was found that cross aldol type reactions with indium in aqueous medium also occurred smoothly at room temperature in good yields (Table 4), in contrast to the above Sn and Zn methods which required heating. However, as in the cases of Sn and Zn, aliphatic aldehydes did not react with aliphatic α-halo ketones.



Scheme 1.

The diastereoselectivity of the aldol products produced from secondary α-halo ketones with indium was quite high. For example, reaction of benzaldehyde and 2-bromopropiophenone with indium in water gave a mixture of diastereomers in 12:1 ratio favoring the erythro isomer **22a** (Scheme 1), whereas in the cases of Zn and Sn, only a slight excess of one diastereomer was observed (Table 2).

Table 4. Cross Aldol and Reformatsky Type Reactions Mediated by Indium

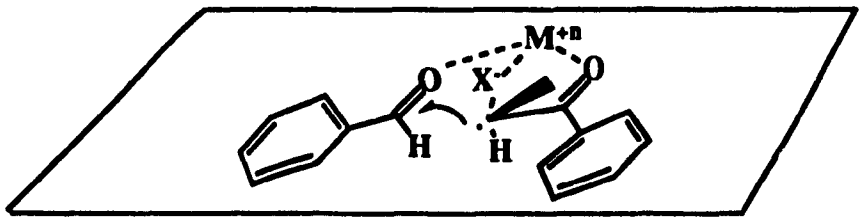
Entry	RCHO	Halide	RCHO/halide/In	Time	Ery:thr		Yield
1	PhCHO	$BrC(CH_3)_2COPh$	1/1.5/1	3(h)		**11a**	88
2	PhCHO	$BrCH(CH_3)COPh$	1/1.5/1	3	12:1	**11c**	85
3	PhCHO	$BrCH(CH_3)COPh$	1/1/1	3	12:1	**11c**	56[a]
4	MePhCHO	$BrCH(CH_3)COPh$	1/1/1	5	12:1	**11l**	72
5	$CH_3(CH_2)_7CHO$	$BrCH(CH_3)COPh$	1/1/1	5	4:1	**11f**	64
6	PhCHO	$BrCH_2COPh$	1/1/1	5		**11h**	15
7	PhCHO	$BrCH(CH_3)COCH_3$	1/1/1	5	3:1	**11i**	48
8	PhCHO	$BrC(CH_3)_2CO_2Et$	1/1/1	4			52
9	PhCHO	$BrCH(CH_3)CO_2Et$	1/1/1	5	2.2:1		35
10	PhCHO	$BrCH_2COCH_2CH_3$	1/1/1	15		**11j**	~10

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

The high reactivity of indium may also be ascribed to the low ionization potential of the metal as in the case of allylation. Yet the exact origin of the high stereoselectivity is not clear. The lower reaction temperature might have been a factor, but it should not be very significant, since not much diastereoselectivity difference was observed between zinc and tin. Therefore, we postulate that the selectivity may be attributed to the coordination of the reactants on the surface of indium metal as in **23**, which

blocks one face of the reaction. This postulation agrees with our previous proposed single electron transfer mechanism. The reaction gave higher selectivity when both the carbonyl compound and the halide were aromatic. This may be because the aromatic ring has a better coordination ability than an aliphatic chain. Addition of methanol to the reaction system slightly increases the yield but does not change the stereoselectivity. Chloro substitution on the benzene ring of benzaldehyde also made no difference to the stereoselectivity.

The coordination model explaining the diastereoselectivity in the reaction of benzaldehyde with **21** is shown in Scheme 2. Both of the aromatic reactants are lying flat on the metal surface. The most favorable alignment for the α-halo ketone **21** is that the methyl points away from the metal surface. The two oxygen atoms of the carbonyl groups together with the halogen are coordinated with the newly generated metal ion on the metal surface. The radical anion intermediate from **21** adds to the aldehyde from the top face. This analysis predicts erythro as the major product, in agreement with the experiment result. From this model, it can also be anticipated that replacing the methyl with another more steric hindered group may increase the diastereoselectivity .



Scheme 2. **23**

Reaction of 2-bromoisobutylphenone with benzaldehyde gave the condensation product in very high yield. It was also different from the Sn

and Zn reaction in that in this case, no reduction of either benzaldehyde or the halide was observed. The by-product in the In reaction was almost exclusively the coupling of the halide. In the absence of carbonyl compounds, however, there was no reaction between the halide and indium. The reason for this is not clear at present.

3.5 Aldol Reactions with Manganese

Attempts to perform crossed aldol reaction with manganese gave products in low yield. As in the allylation, the reaction was induced to proceed by the addition of NH_4Cl. It could also proceed by using a Mn-Cu bimetal mixture. Some results are listed in Table 5. Aliphatic aldehydes failed to react under the same conditions. The reaction was not further explored.

Table 5. Aldol Reactions Mediated by Manganese in Water

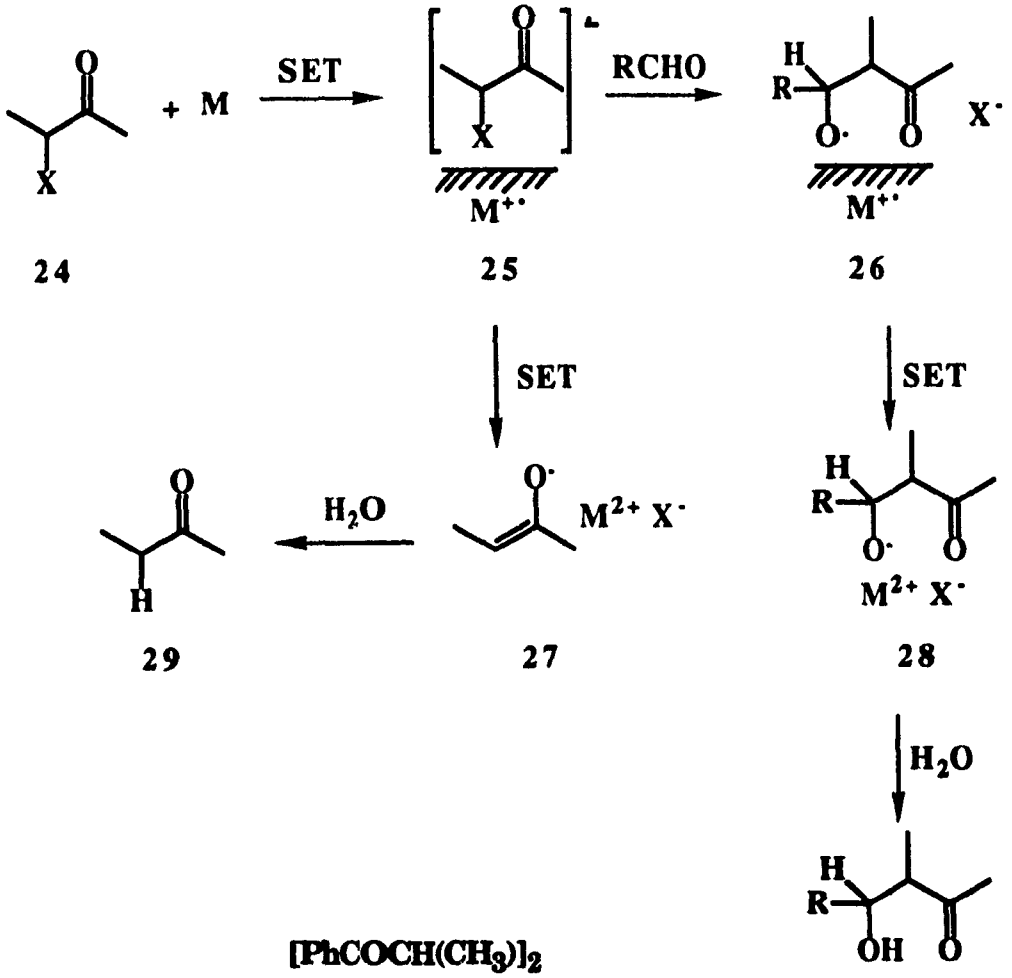
Entry	α-Halo Ketone	Condition	Time	Ery./Thr.	Yield
1	$(CH_3)_2CBrCOPh$	Mn/H_2O	15h		25
2	$(CH_3)_2CBrCOPh$	Mn/NH_4Cl(sat. aq.)	20min		71
3	$(CH_3)_2CBrCOPh$	$Mn/Cu/H_2O$*	2h		79
4	$CH_3CHBrCOPh$	$Mn/Cu/H_2O$*	2h	74:26	47

All the reaction were performed with benzaldehyde; * Mn/Cu= 2:1.

3.6 Mechanistic Consideration

As in the allylation reaction, a similar single electron transfer reaction mechanism invoking the intermediate of a radical anionic species is proposed for the crossed aldol and Reformatsky reactions (Scheme 3). In the reaction process, the critical carbon-carbon bond formation occurs prior

to the formation of the free metal enolate **27**, possibly on the metal surface. In support of this mechanism, compound **31** was obtained as a minor product in the reaction of 2-bromo-2-methyl-1-phenylpropan-1-one with benzaldehyde. Compound **31** is most likely derived from the coupling of the radical intermediate.



24 **25** **26**

29 **27** **28**

30

[PhCOCH(CH$_3$)]$_2$

31

Scheme 3.

3.7 Experimental Section

General Procedure for the Aqueous Aldol and Reformatsky Type Reactions:

The metal powder (Zn, Sn or In, 1 mmol scale) was added to a mixture of an α-halocarbonyl compound and an aldehyde in 15 ml of water. The reaction mixture was stirred at the appropriate temperature for the corresponding period of time, then quenched with ether. The ether solution was dried, evaporated, and the crude product was purified by flash chromatography on silica gel to give the corresponding product (for specific conditions, see the tables in the text).

3-Hydroxy-2,2-dimethyl-1,3-diphenylpropan-1-one (11a)

^{1}H NMR ($CDCl_3$): δ= 1.18 (d, J=22.4Hz, 6H) , 3.0 (br, 1H) , 5.12 (s, 1H) , 7.40 (m, 8H) , 7.57(m, 2H) ppm; MS (%): 253 (M^+-1, 0.2), 236 (M^+-18, 1.7), 148(69.3), 133(38.8), 122(31.0), 115(20.1), 105(98.0), 91(38.2), 77(100).[10]

3-Hydroxy-1,3-diphenylpropan-1-one (11h)

^{1}H NMR ($CDCl_3$): δ= 3.70(m, 2H), 3.90(s, 1H), 5.03(m, 1H), 7.20-7.65(m, 8H), 7.92(m, 2H)ppm; MS (%): 226(M^+, 0.1), 225(0.6), 134(2.9), 120(19.5), 105(100), 94 (32.2), 77(56).[10]

3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (11c)

^{1}H NMR ($CDCl_3$): δ= *Threo-isomer*: 1.05(d, J=7.2Hz, 3H), 3.08(d, J=4.0Hz, 1H), 3.83(p, J=7.4Hz, 1H), 4.98(dd, J=8.0, 4.0Hz, 1H), 7.45(m, 8H), 7.98(m, 2H)ppm; *Erythro-isomer*: 1.20(d, J=7.1Hz, 3H), 3.72(qd, J=7.2, 4.0Hz, 1H), 3.96(br., 1H), 5.17(d, J=4.0Hz, 1H), 7.37(m, 8H), 7.90(d, J=7.0Hz, 2H)ppm; MS (%): 240(M^+, 0.5), 222(1.5), 134 (36.0), 108(51.5), 105(55.0),

86(61.4), 77 (53.5), 43 (100). IR (neat): 3500, 3016, 1675, 1598, 1215, 1001, 751 cm^{-1}.[10]

3-Hydroxy-2-methyl-1-phenyl-3-(4'-methylphenyl)propan-1-one (11l)

^1H NMR ($CDCl_3$): δ= *Threo-isomer*: 1.03(d, 3H), 2.4(s, 3H), 3.85(m, 1H), 5.0(m, 1H), 7.45-8.0(m, 9H)ppm; *Erythro-isomer*: 1.20(d, J=5.2Hz, 3H), 2.3(s, 3H), 3.70(m, 1H), 5.2(d, J=3.1Hz, 1H), 7.1-8.0(m, 9H) .[10,13]

4-Hydroxyl-4-phenyl-3-methylbutan-1-one (11i)

^1H NMR ($CDCl_3$): δ= *Threo-isomer*: 0.87(dd, J=7.2, 1.8Hz, 3H), 2.18(s, 3H), 2.90(p, J=7.2Hz, 1H), 4.08 (m, 1H), 4.70(dd, J=8.6, 1.4Hz, 1H), 7.30(m, 5H)ppm; *Erythro-isomer*: 1.06 (d, J=7.6Hz, 3H), 2.09(s, 3H), 2.81(qd, J=7.2, 4.2Hz, 1H), 3.74(m, 1H), 5.04(dd, J=4.2, 1.5Hz, 1H), 7.29(m, 5H)ppm; MS(%): 160(M^+-18, 0.5), 122(8.0), 106(70.1), 105(56.4), 77(58.6), 43(100). IR(neat): 3400, 3060, 3029, 2978, 2942, 1704, 1453, 1358, 1023cm^{-1}.[11]

1-Hydroxy-1-phenylpentan-3-one (11j)

^1H NMR ($CDCl_3$): δ= 1.05(t, J=7.3Hz, 3H), 2.44(q, J=7.2Hz, 2H), 2.79(m, 2H), 3.50(br., 1H), 5.13(m, 1H), 7.33(m, 5H)ppm; MS(%): 160(M^+-18, 2.0), 131(18.3), 106(55.1), 105(53.0), 77(58.3), 72(38.0), 57 (24.6), 51(39,9), 43(100). IR(neat): 3400, 3035, 2983, 2942, 2901, 1701, 1453, 1028cm^{-1}.[11]

3-Hydroxyl-2-methyl-1-phenyl-1-undecanone (11f)

^1H NMR ($CDCl_3$): δ= 0.83(t, J=6.2Hz, 3H), 1.23(m, 15H), 1.48(m, 2H), 3.11(br., 1H), 3.43(qd, J=7.1,3.3Hz, *Erythro*), 3.53(p, J=7.1Hz, *Threo*), 3.83(m, *Threo*), 3.97(m, *Erythro*), 7.46(m, 3H), 7.93(m, 2H)ppm; MS (%): 276 (M^+, 0.1), 134(38.4), 105(89.9), 84(62.4), 77(56.8), 71(56.1), 57(88.9), 43(100). IR(neat): 3450, 3065, 2938, 2909, 1686, 1598, 1458, 1448, 1375, 1214cm^{-1}.

3-Hydroxyl-2,2-dimethyl-1-phenyl-1-undccanone (11b)

^{1}H NMR ($CDCl_3$): δ= 0.9(t, 3H), 1.2-1.7(br, 20H), 2.7(br, 1H), 3.85(d, 1H), 7.4-7.7(m, 5H) ppm; IR(neat): 3500, 2925, 2855, 1669, 1458, 1265, 1074 cm^{-1}.

3-Cyclohexyl-3-hydroxy-2-methyl-1-phenyl-1-propanone (11e)

^{1}H NMR ($CDCl_3$): δ= 0.90-2.15(m, 14H), 3.15(br., 1H), 3.50-3.80(m, 2H), 7.45(m, 3H), 7.92(m, 2H)ppm; MS (%): 246(M^+, 0.3), 228(2.4), 163(37.8), 134(50.7), 133(20.7), 105(95.2), 83(51.6), 77(70.8), 55(92.7), 43(100). IR(neat): 3463, 2936, 2850, 1669, 1597, 1450, 1373, 1210cm^{-1}.[13]

Ethyl 2,2-Dimethyl-3-hydroxy-3-phenyl-propionate (20a)

^{1}H NMR ($CDCl_3$): δ= 1.11(d, J=5.4, 6H), 1.25(t, J=7.1, 3H), 4.15(q, J=7.1, 2H), 4.9(s, 1H), 7.3(br, 5H)ppm. IR(neat): 3470, 2985, 1733, 1473, 1365, 1263, 1262, 1126cm^{-1}.[12]

Ethyl 2-Methyl-3-hydroxy-3-phenyl-propionate (20b)

^{1}H NMR ($CDCl_3$): δ= IR(neat): 3500, 2968, 2875, 1735, 1717, 1436, 1363, 1265, 1232, 1195, 1167, 1039, 1026cm^{-1}.[12]

3.8 References

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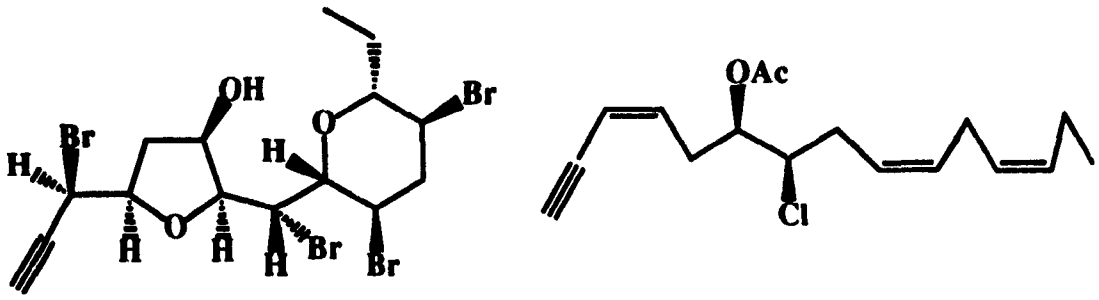
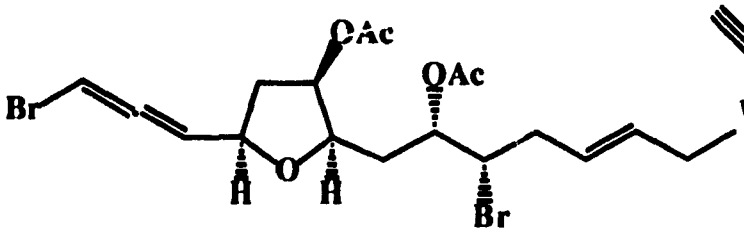
Chapter 4. Outlook for Future Development

In conclusion, we have studied and developed Barbier-Grignard allylation, alkylation, aldol and Reformatsky reactions in aqueous solution mediated by Zn, Sn, In and Mn metals etc. The reaction mechanism has been examined briefly. The aqueous methodology has successfully been used in the synthesis of 1,3-butadienes, methylenetetrahydrofurans, (+)-muscarine, (+)-KDN and KDO.

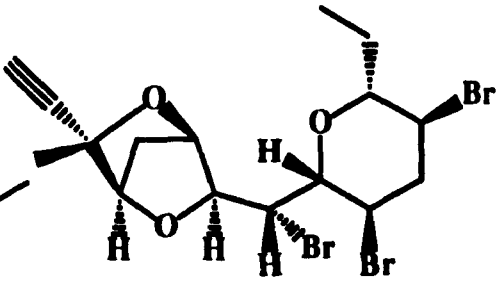
In terms of the future development of this project, a lot of interesting research can be continued. The yield of aqueous Grignard alkylation, which is still very important, needs to be improved. The mechanism study on allylation and aldol reactions still needs to be examined in greater detail.

These methodologies should also find other important applications in organic synthesis. For example, there is a large number of marine natural products recently isolated from the widely distributed red algae of the genus *Laurencia*.[1] Most of these metabolites possess a characteristic five membered tetrahydrofuran ring with cis side chains, which are in a trans or cis relationship to an oxygen substituent at C(3) as in the structures of muscarine or epimuscarine. A representative selection of metabolites of this common type is shown as follows (1-12):





3 Graciosallene



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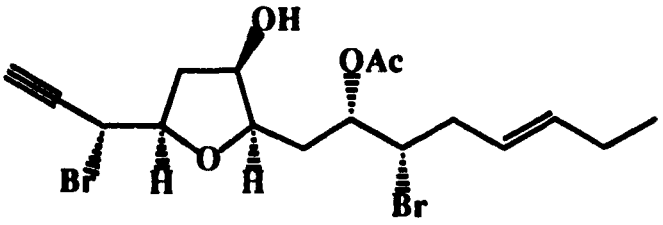
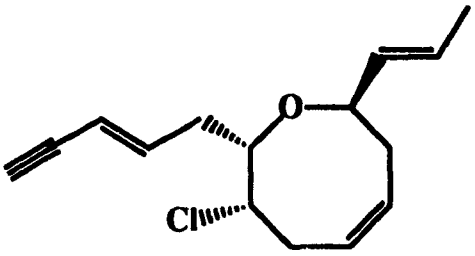
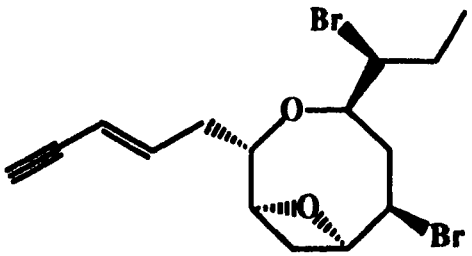


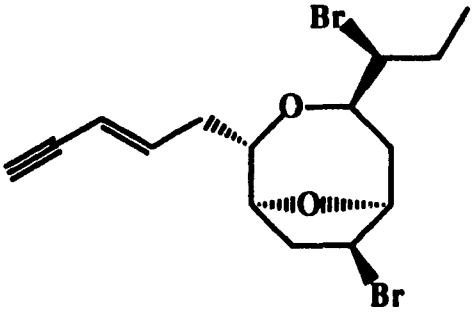
5 Graciosin



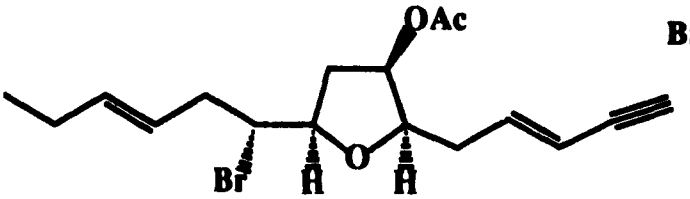
6 (-)-Laurenyne



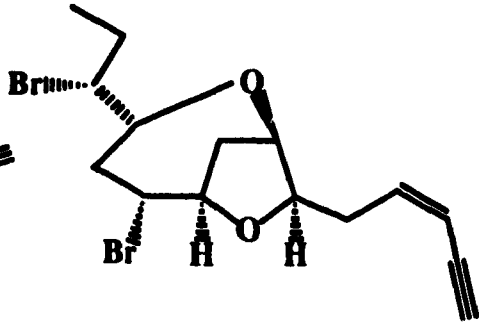
7 (3E)-Laureatin



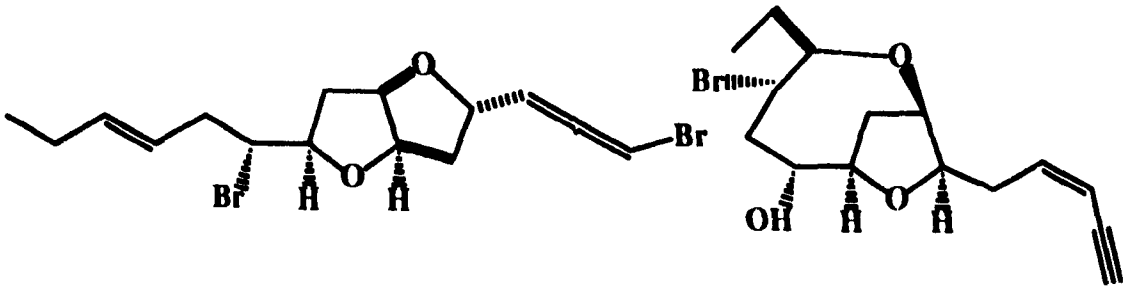
8 (3E)-iso-Laureatin



9 trans-Kumausyne



10 is-Prelaurefucin



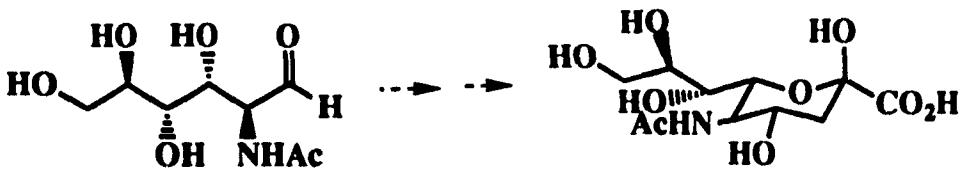
11 Kumausallene 12 Laurefucin

The previous muscarine synthesis may provide a convenient general entry into the synthesis of these compounds. A similar methodology may also be used in the synthesis of 6-membered ring compounds and other hetero cyclic compounds. Those structures also exist widely in natural products.

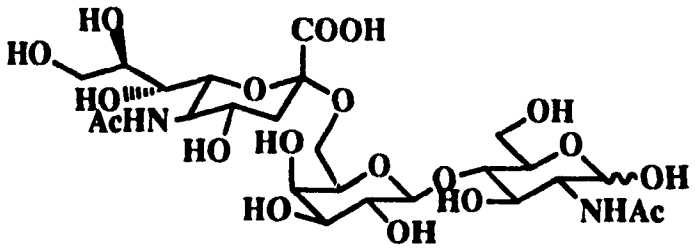
The aqueous organometallic reactions should find the most valuable application in carbohydrate chemistry, because of the possibility of avoiding protection and deprotection procedures. In the synthesis of KDN and KDO, if the 2-hydroxy group of the starting sugar was changed to a protected amino group, the same procedure can be used for the synthesis of another type of very important natural products, neuraminic acids, a characteristic structural fragment of different kinds of influenza virus receptors.

These compounds can be further manipulated to more complicated molecules such as sialyl oligosaccharide Neuα-2,6Galβ1,4GlcNAc (**15**), a higher structural unit of the receptor and inhibitor of human influenza virus,[2] and its analogues.

Scheme 1.

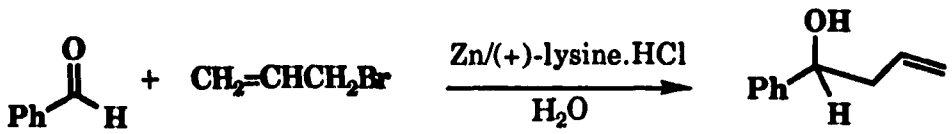


13 14



15

Another important continuation of this project is asymmetrical synthesis. We have shown that about 10% ee was obtained in the product in the allylation reaction when lysine·HCl was present in the aqueous media.



16 17

Although the degree of chiral induction is not very significant at this moment, it may be possible to use some other water soluble natural chiral materials to obtain better chiral inductions. The use of water as solvent in these reactions can also make the recycling of the chiral axillary easier by simply adjusting the pH value of the post-reaction mixture to precipitate the chiral auxiliary.

The most promising continuation of this research is probably the indium metal induced reactions. Their intriguing reactivity and diastereoselectivity are worth exploring further.

Finally, the aldol type condensation reactions should also find significant applications in natural product synthesis.

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1. For reviews see: a). Faulkner, D. J. *Nat. Prod. Reports* **1990**, 269;
b). Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378.
2. Sabesan, S.; Duns, J. Ø.; Domaille, P.; Kelm, S.; Pauson, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 5865.

PART II

Development of a New Tellurium Reagent for Organic Synthesis

Chapter 1. Introduction to Organotellurium Chemistry

Tellurium[1] is located in the same group in the periodic table as oxygen, sulfur and selenium; they are collectively known as chalcogens. Tellurium has the electronic structure $[Kr]4d^{10}5S^25P^4$ and an atomic number of 52. The element tellurium was discovered (and appropriately named metallum problematicum) by Franz Joseph Mueller von Rechenstein in 1782 from a Transylvanian ore which had previously been thought to be some kind of alloy of antimony and bismuth, although neither of these were in reality constituents of the mineral. The present name tellurium, derived from the Latin tellus, earth, is by Kloproth in 1789.[1] The abundance of tellurium in the earth's crust has been determined to be 2×10^{-7} percent by weight. Native tellurium is uncommon, usually occurring in conjunction with native sulfur. Its minerals are rare, the most abundant ones are tellurides of lead, copper, silver, gold and antimony. Tellurium minerals however do not form large deposits and tellurium has often been obtained as a by-product of mining and processing operations of other ores, such as in electrolytic copper refining. The anode sludge can contain up to 8 percent tellurium. Crystalline tellurium is a silver-white substance with a metallic luster. It melts at 449.8°C to a dark liquid and boils at 1390°C. Tellurium alloys have been used as additives to copper, copper alloys and to lead. Small quantities of tellurium have been used to color glass and ceramics. Tellurium has also found some application as secondary vulcanizing agents for natural rubber.

The first organic tellurium compounds, dialkyl tellurides, were prepared by Woehler in 1840.[2] In the decade of the 1910's, Lederear enriched the knowledge in this area of chemistry. His synthetic efforts produced a large number of aromatic tellurium derivatives. Starting in the 1960's, research in organotellurium chemistry expanded rapidly. The recent tremendous interest in the application of tellurium compounds in organic synthesis began after Barton's procedure for the preparation of sodium hydrogen telluride (NaHTe).[23] Therefore, although organic tellurium chemistry is almost as old as organic chemistry, it is only in the last two decades that it has drawn special attention. The most widely explored area is telluration (introducing tellurium into organic molecules) and sodium hydrogen telluride-based organic transformations. Organotellurium compounds have found important applications also in the organic semiconductor area and in chemical therapy. For example, heat-resistant telluro-polymers with controllable band gaps, intrinsic electronic and optical properties and other electronic properties characteristic of insulators, semiconductors, or conductors are prepared by polycondensation of tellurophene with an aliphatic, aromatic or heterocyclic aldehydes.[3] Tellurapyrylium dyes have been considered as potential photochemotherapeutic agents.[4]

* *The recommended maximum permissible concentration of tellurium in air is 0.1 mg/m^3, which is 2 orders of magnitude lower than hydrogen cyanide (10 mg/ m^3). Therefore, all tellurium compounds should*

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* SAx, I. Dangerous Properties of Industrial Materials, Reinhold Publishing Corporation, New York, N. Y. (1975).

be handled with care. However, these compounds, apart from hydrogen telluride, are less toxic than those of selenium.

1.1 Methods for the Introduction of Tellurium into Organic Molecules

Introducing tellurium into organic molecules and the preparation of many kinds of organotellurium compounds is the entire study of early organic tellurium chemistry.[5a] A number of organic tellurium compounds can be synthesized directly from elemental tellurium. The inorganic tellurium compounds most often employed as starting materials are tellurium tetrahalides and alkali metal telluride. Diphosphorus pentatelluride, aluminum telluride, tellurium dioxide, hydrogen telluride, tetramethoxy tellurium and hexamethoxy tellurium have found very limited application. Certain organic tellurium compounds can react further with organic reagents to yield compounds with more organic groups bonded to the tellurium atom than in the starting material.

1.1.1 From Elemental Tellurium

Reactions with Organic Halides

Among the methods for introducing tellurium into organic molecules, only a few organic iodides have been used. They react with elemental tellurium to produce dialkyl tellurium diiodides in moderate yields. (Eq. 1).[5]

$$\underset{1}{2RI} + \underset{2}{Te} \dashrightarrow \underset{3}{R_2TeI_2} \qquad \text{(Eq. 1)}$$

($R = CH_3, C_2H_5, C_6H_5CH_2, C_6F_5$)

Organic dihalides, $X-(CH_2)_n-X$, combine with tellurium to form telluracycloalkane 1,1-dihalides.[6] The reactivity of the dihalides seems to decrease with decreasing atomic mass of the halogen atom.

Insertion Reactions into Carbon-metal Bonds

Elemental tellurium inserts into the carbon-metal bonds of compounds of the type RMgBr,[7] RLi[8] and $R-C\equiv C-Na$[9] (Eq. 2-4) to form unstable adducts which are therefore not isolated but treated immediately with the appropriate reagent to form tellurides, ditellurides, diorgano tellurium dihalides and tellurols. The reactions, however, are often more complicated than they seem.

R-MgBr + Te ----------> R-Te-MgBr **(Eq. 2)**

4 **5**

R-Li + Te ----------> R-Te-Li **(Eq. 3)**

6 **7**

R-C≡C-Na + Te ----------> R-C≡C-Te-Na **(Eq. 4)**

8 **9**

Reactions with Organic Radicals

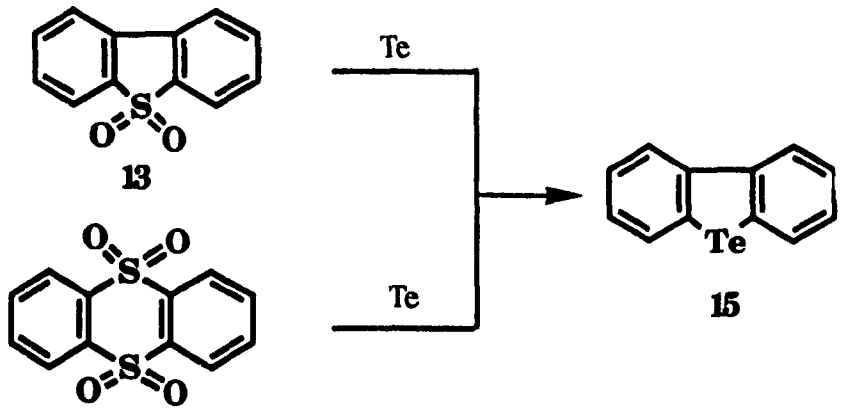
Mirrors of elemental tellurium are removed by radicals like $CH_3\cdot$, $CF_3\cdot$, $C_3H_7\cdot$ and CH_2: generated by the thermal decomposition of variety of compounds.[10] These reactions are unimportant as synthetic methods, since the organic tellurium compounds formed can be prepared much easier and in higher yields by other methods.

Replacement of Mercury, SO_2 Groups and Hydrogen

Diaryl mercury[11] reacts with tellurium upon heating in the absence of a solvent according to equation 5. The yields range from 53-100%.

$$\underset{\textbf{10}}{R_2Hg} + 2\,Te \dashrightarrow \underset{\textbf{11}}{R_2Te} + \underset{\textbf{12}}{HgTe} \qquad \textbf{(Eq. 5)}$$

Tellurium replaces the SO_2 group in biphenylene sulfone (**13**)[12] and thianthrene 5,5,10,10-tetroxide (**14**)[13] upon heating, to give in both cases dibenzotellurophene (**15**) (Eq. 6).



13 **14** **15** **(Eq. 6)**

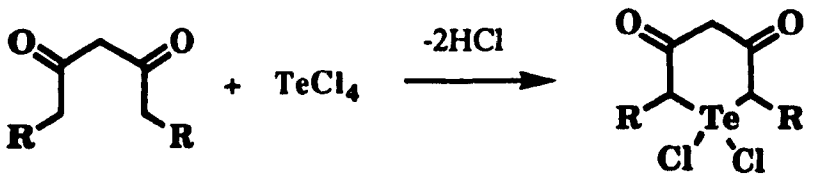
1.1.2 From Tellurium Halides

Among the tellurium tetrahalides, the tetrachloride is used almost exclusively.

Condensation Reactions of Tellurium Tetrachloride with Elimination of Hydrogen Chloride

Tellurium tetrachloride combines with substances containing activated hydrogen atoms to form cyclic and linear condensation products. 1,3-Diketones condense with tellurium tetrachloride producing 1-tellura-

3,5-cyclohexanedione-1,1-dichlorides (Eq. 7). Most of the work in this area was done by Morgan and coworkers in the 1920's.[14] Some of this work was reinvestigated later in the 1960's.[15]



16 17 18 (Eq. 7)

Monoketones,[16] carboxylic acid anhydrides,[17] dimethyl sulfite[18] and substituted aromatic compounds[19] have also been investigated as organic compounds for the condensation. Tellurium tetrabromide and tetraiodide do not undergo condensation reactions to the same extent as the tetrachloride.

Reactions of Tellurium Halides with Organometallic Compounds

Tellurium tetrahalides have been reacted with Grignard reagents, organomercury chlorides, organic lithium compounds, diethyl zinc and bis(pentafluorophenyl)thallium bromide.[20] Tellurium tetrabromide and tetraiodide give the same yields in reactions with Grignard reagents as tellurium tetrachloride; these reactions give complicated results as they will always give mixtures under these conditions. Aryl mercury chlorides are employed to form the carbon-tellurium bond when a direct condensation between tellurium tetrachloride and an aromatic compounds is not possible. Equimolar quantities of aryl mercury chlorides and tellurium tetrachloride give exclusively the aryl tellurium trichloride in yields ranging from 60-90% (Eq. 8).

$$\underset{19}{RHgCl} + TeCl_4 \dashrightarrow \underset{20}{RTeCl_3} + \underset{21}{HgCl_2} \qquad \text{(Eq. 8)}$$

Organic lithium compounds combine with tellurium tetrachloride with the elimination of lithium chloride. The reaction proceeds to form organotellurium trichloride, diorganotellurium dichloride, triorganotellurium chloride and tetraorganotelluride depending on the molar ratios employed.

1.1.3 From Alkali Metal Tellurides and Other Inorganic Tellurium Compounds

Alkali metal tellurides are easily alkylated by organic chlorides, bromides and iodides (Eq. 9, 10).

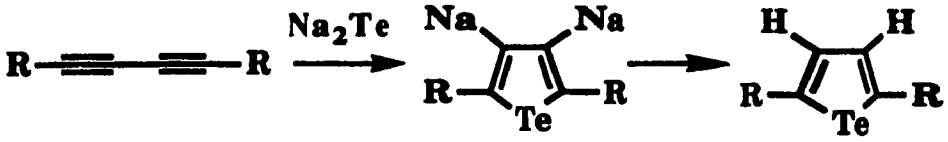
$$\underset{22}{Na_2Te} + \underset{23}{2RX} \dashrightarrow \underset{24}{R_2Te} + 2NaX \qquad \text{(Eq. 9)}$$

$$\underset{25}{Na_2Te_2} + 2RX \dashrightarrow \underset{26}{R_2Te_2} + 2NaX \qquad \text{(Eq. 10)}$$

The alkylation reactions are carried out either in an aqueous medium, when the telluride were prepared according to Tschugaeff and Chlopin,[21] or in liquid ammonia,[22] when the telluride was synthesized from the alkali metal and elemental tellurium. Although the aqueous systems are easier to handle, liquid ammonia is the appropriate solvent for higher alkyl halides which are not appreciably soluble in an aqueous medium. Diorganotellurides and some diorganyl ditellurides are prepared in this way. Recently, Barton modified the preparation by stirring a

mixture of tellurium and sodium borohydride in water/ethanol making this method much more popular for the preparation of organic tellurium compounds.[23]

Sodium telluride also reacts with diacetylenes (**27**) in methanol at room temperature to form the dianion intermediate (**28**), which is hydrolyzed to produce tellurophenes (**29**) (Eq. 11).[24]



(Eq. 11)

27 28 29

Aluminum telluride, Al_2Te_3, was also employed in some of the telluride preparations.[25]

1.1.4 From Other Organic Tellurium Compounds

Further manipulation of organic tellurium compounds can lead to the formation of additional carbon-tellurium bonds. Alkylation of naphthyl tellurium iodide with Grignard reagents was used to synthesize unsymmetrical tellurides.[26] Organomercury chlorides react with organyl tellurium trichlorides to produce dialkyl tellurium dichlorides which can also be obtained by addition of trichlorides[27] to carbon-carbon double bonds. Organotellurium trichlorides and tribromides condense with acetone, acetophenone, alkoxyl or dialkylamino or 2,4-dihydroxylbenzene to form diorganotellurium dihalides. Reaction of organotellurium trichlorides with ditellurides gave diorganyl tellurium dichlorides and tellurium (Eq.12).[28]

$$2R_2Te_2 + 2RTeCl_3 \dashrightarrow 3R_2TeCl_2 + 3Te \qquad \text{(Eq. 12)}$$

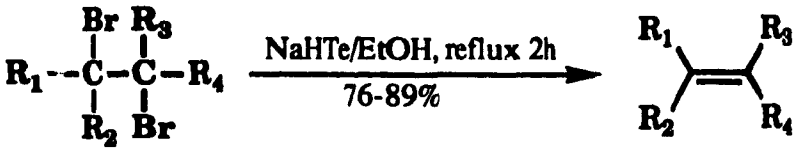
30

Diorganotellurides combine with organic halides to give triorganotellurium halides. Diorganyl ditellurides are cleaved by methyl iodide to give diorgano methyl telluronium iodide and organo methyl tellurium diiodide.[29] *Vic*-dibromides[28] transform ditellurides into diorganyl tellurium dibromides with the elimination of tellurium. Ditellurides decompose thermally to tellurides and tellurium.[28]

1.2 Sodium Telluride (NaHTe or Na_2Te) as a Versatile Reagent in Organic Synthesis

Sodium telluride is not only the most important and widely used reagent for the introduction of elemental tellurium into organic molecules, but also the most widely used tellurium reagent in organic synthesis. New applications in organic transformations by this reagent have been emphasized after Barton developed a new procedure for its preparation.[23] The reagent formed by the new procedure was called sodium hydrogen telluride. However, the existing species in the reagent was found to be Na_2Te,NaHTe or Na_2Te_2 depending on the ratio of reactants and the pH of the solution.[30] Sodium telluride is used in a variety of organic functional group transformations.[31]

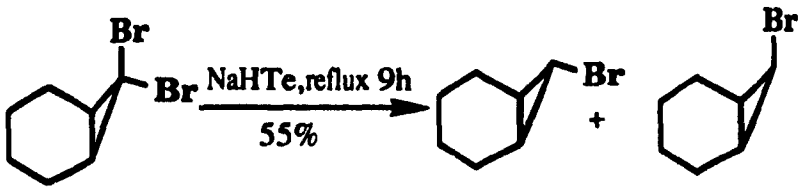
Sodium hydrogen telluride is recognized as a useful reagent for debromination *vic*-dibromides to olefins (Eq. 13).[32] The debromination occurs by an anti E_2 β-elimination as determined by the stereochemical results.



(Eq. 13)

31 32

gem-Dibromocyclopropanes are reduced to monobromocyclopropanes by NaHTe.[33] This reduction was found to be faster and more selective than $NaBH_4$ (Eq. 14).

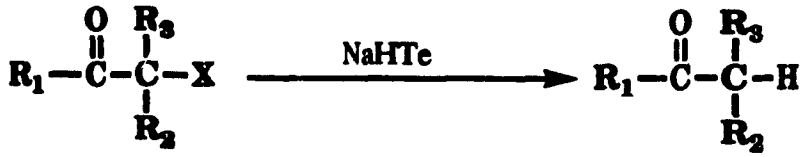


(Eq. 14)

33 34 35

Sodium hydrogen tellluride is also effective for the selective removal of halogen atoms adjacent to carbonyl groups (Eq. 15).[34,35] The method seems to be general, chemoselective, and free from side reactions.

The mechanism of this reaction was not studied in detail but was assumed to involve a nucleophilic attack of telluride ion on halogen leading to the formation of an enolate.

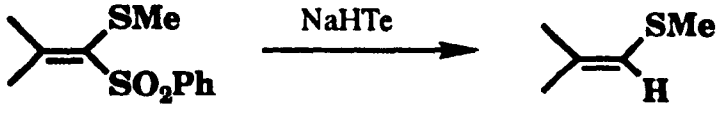


(Eq. 15)

36 37

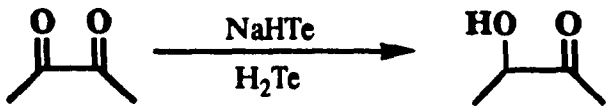
X=halogen, sulfonyl

Under the same conditions, the sulfonyl group at the α-position of the carbonyl was also removed.[36,37] Similarly, α-methylthio-α,β-unsaturated sulfones (38) were also desulfonylated (Eq.16).[38]



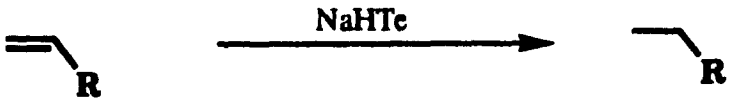
38 39 (Eq. 16)

α-Diketones are partially reduced to the corresponding α-hydroxyketones in the presence of acetic acid. or trifluoroacetic acid (Eq.17).[39] The reactive species here seems to be hydrogen telluride rather than sodium hydrogen telluride.



40 41 (Eq. 17)

Sodium hydrogen telluride is also able to reduce carbon-carbon double bonds in high yields without affecting the carbonyl or aromatic ring (Eq. 18).[40-46] Later, the reaction mechanism was also studied and a hydride transfer process was proposed.[47]

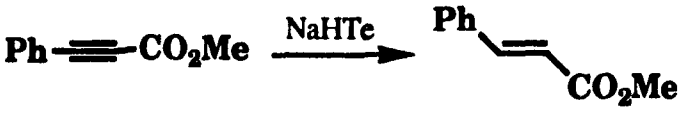


42 43 (Eq. 18)

The action of NaHTe on non-electrophilic carbon-carbon double bonds was also investigated.[48,49] The reaction is very sensitive to the substituents on the ethylenic linkage. The reagents add to isolated mono and

disubstituted double bonds leading to organotellurium derivatives and with *gem*-disubstituted ones it leads to a mixture of reduction and addition products. These results are interpreted in terms of a radical mechanism involving hydrogen atom transfer from HTe^- to the double bond.

A limited amount of the reagent can reduce activated carbon-carbon triple bonds to carbon-carbon double bonds (Eq. 19). When the reagent is in excess, the double bond produced is reduced to a saturated carbon-carbon bond.[50]

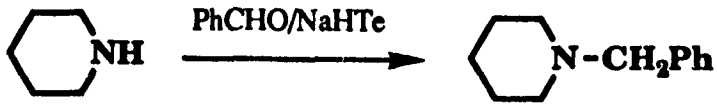


(Eq. 19)

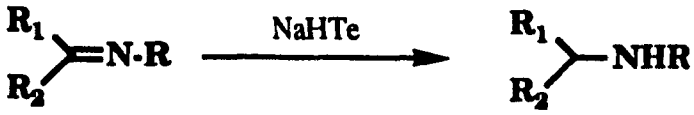
44 45

The reagent was also found to reduce a variety of nitrogen containing compounds. The reagent reduces secondary amines with carbonyl compounds to tertiary amines under mild conditions.[51] Thus, refluxing piperidine with benzaldehyde and NaHTe in ethanol gave N-benzylpiperidine (47) (Eq. 20).

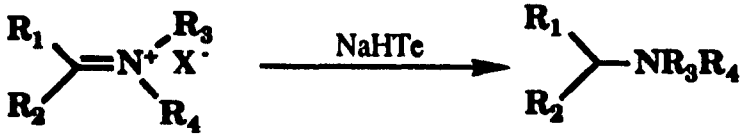
The action of sodium hydrogen telluride on imines was also reported (Eq. 21).[52,53] The reaction mechanism has been studied.[53] The reagent also reduced quaternary ammonium salts[54] and imonium salts (Eq. 22).[55] The products of the latter depend upon the pH value of the solution. Under alkaline pH, only dihydro derivatives are formed. Alkyl and aryl azides was reduced by NaHTe to the corresponding primary amines (Eq. 23).[56] For α-azido ketones, the produced amines self-condensed followed by aerobic oxidation to give pyrazines.[57]



46 47 (Eq. 20)



48 49 (Eq. 21)

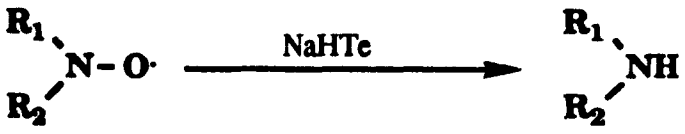


50 51 (Eq. 22)

52 53 (Eq. 23)

Various nitro compounds were effectively reduced to the corresponding amines in good yield (Eq. 24).[58-60] Under the same conditions, N-oxides were reduced to secondary amines (Eq. 25), but sulfoxides were not reduced.[60]

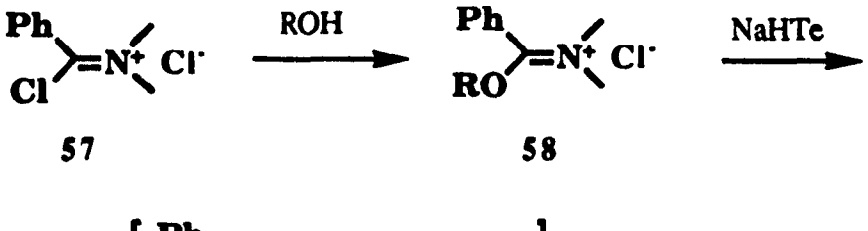
54 (Eq. 24)



55 56 (Eq. 25)

Alcohols can be converted into the corresponding benzyl ethers by reaction with the Vilsmeier salt, chloro(phenylmethylene)-dimethyl

ammonium chloride **57** (prepared from dimethylbenzamide and phosgene), giving the imidate salts **58**, followed by reduction with sodium hydrogen telluride (Eq. 26).[61] The reaction proceeds under mild conditions, most probably *via* the tellurobenzoate and hydrogen atom transfer.

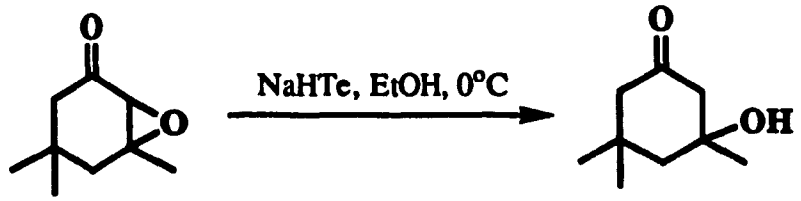


57 **58** **59** **60** (Eq. 26)

Reductive cleavage of disulfides with NaHTe gives the corresponding thiol in 65-98% yield (Eq. 27).[62]

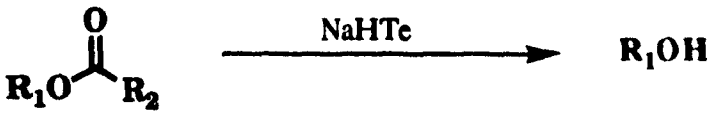
61 **62** (Eq. 27)

α,β-Epoxy ketones were chemo- and regioselectively reduced to β-hydroxy ketones by the NaHTe (Eq. 28).[63] The reaction also opens unactivated epoxides cleanly by an S_N2 process to give telluro-alcohols, which by reduction with borohydride afford alcohols.[54]



63 **64** (Eq. 28)

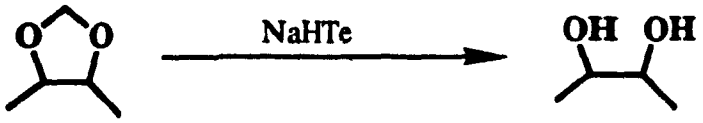
The reagent has also been used in the deprotection of alcohols or acids by the formation of different esters through cleavage of the ester bond (Eq. 29).[64-69] Five-membered cyclic acetals were also cleaved by this reagent to give the corresponding diols (Eq. 30).[71]



(Eq. 29)

65 66

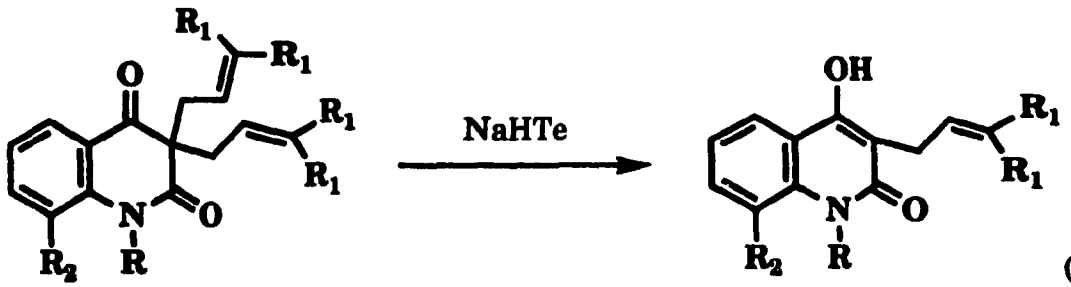
R_1=Ar, Phenyacyl, Benzyl, Alkyl, CH_2CH_2X
R_2= Me, Et, Pr, iPr, Benzyl, Ar



(Eq. 30)

67 68

Diallyltetrahydroquinolinediones (69) undergo partial dealkylation to give allylhydroxyquinolines (70) on treatment with NaHTe in boiling ethanol (Eq. 31).[71]



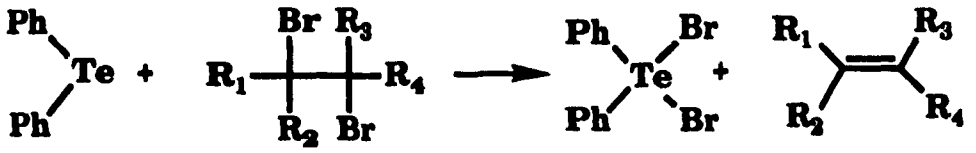
(Eq. 31)

69 70

1.3 Other Tellurium Compounds as Alternatives of NaHTe in Organic Synthesis

In addition to the widely used NaHTe, some other tellurium compounds have been used as alternatives to this reagent in different reactions. Among them, most frequently used are diaryl telluride, diaryl ditelluride and bis(2-thienyl)ditelluride.

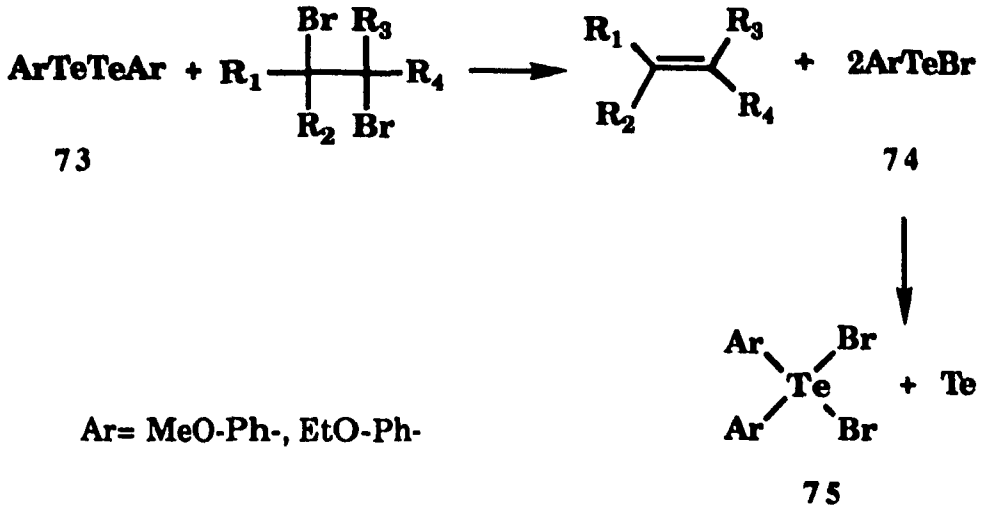
The dehalogenation of *vic*-dibromides with diphenyl telluride giving diphenyl dibromide and the corresponding olefin is the first reported transformation of an organic molecule by means of organotellurium compounds (Eq. 32).[72] The conversion occurs by heating the reaction mixture for several hours. The stereospecificity of the anti-elimination is supported by the formation of trans olefins from meso dibromides.



(Eq. 32)

71 72

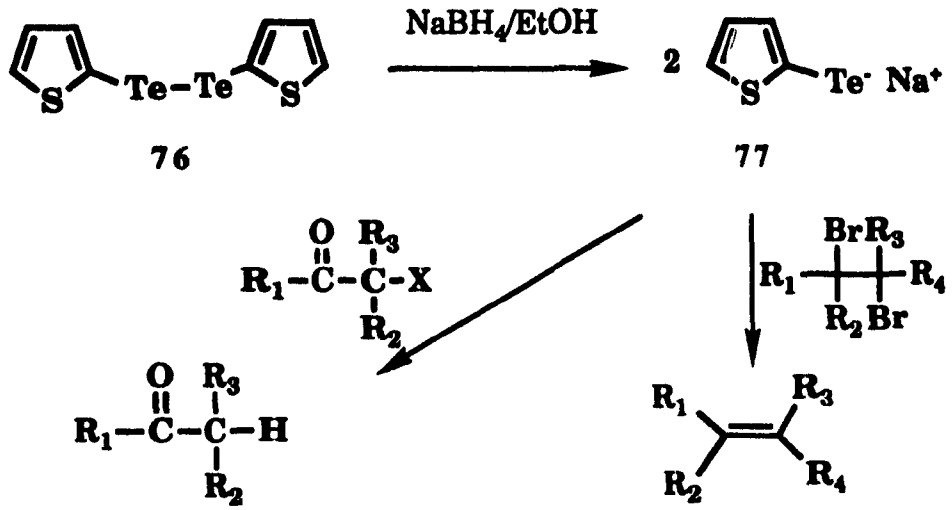
Similar to diaryl tellurides, diaryl ditellurides (73) also reduce *vic*-dibromides to olefins. The reaction involves the corresponding aryltellurenyl bromide (74) which is then converted into a 1:1 mixture of diaryltellurium dibromide and elemental tellurium. In the reaction however, half of the tellurium is lost. Similar stereochemistry is observed with this reagent as with diaryltelluride mediated reductive elimination.[73-75]



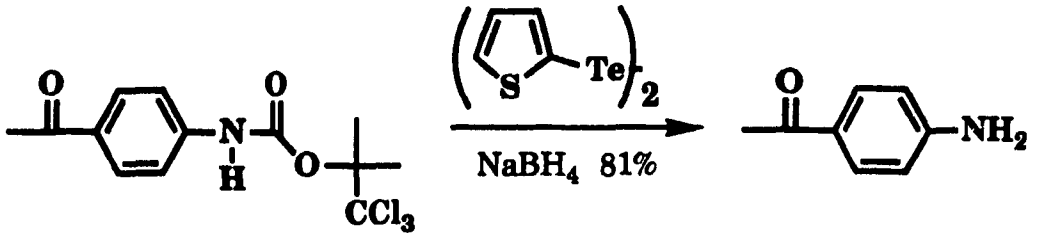
Scheme 1.

A recently reported method for the debromination of *vic*-dibromides employs sodium borohydride together with a catalytic amount of bis(2-thienyl) ditelluride (**76**). The ditelluride is reduced to the corresponding sodium telluride (**77**) which debrominates *vic*-dibromides to olefins through attack on bromine. The ditelluride is regenerated by the successive reaction of the formed tellurenyl bromide with another molecule of telluroate ion.[76,77] 1,4-Dibromo-2-olefins and 1,2,3,4-tetrabromoalkanes are reduced to 1,3-dienes by this methodology.[78]

Scheme 2.



The 2-thiophenetelluroate anion **77** produced from the reduction of bis(2-thienyl) ditelluride with sodium borohydride also reduces a number of α-halo, α-acetoxyl, α-mesyloxyl-, and α-thiophenyl-ketones in good yields.[79] It reacts with 2,2,2-trichloro-tert-butyloxycarbonyl (TCBOC) protected amine derivatives **78** to give the deprotected amines **79** (Eq. 33).[80]



(Eq. 33)

78 **79**

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Chapter 2. Bis(triphenylstannyl)telluride (1) as a New Tellurium Reagent for Organic Synthesis

The previous summary has shown the versatility and importance of sodium hydrogen telluride in the introduction of tellurium into organic compounds and its useful application in organic transformations. However, there are still several critical limitations of this reagent:

1. The reagent itself is not stable enough and cannot be stored for a long period; each time when it is used, it has to be freshly prepared. Thus, the use of this reagent is not convenient.
2. All the preparation procedures of this reagent, including Barton's modification, involve the use of a protic solvent (ethanol, water, or liquid ammonia). These solvents are not always desired in organic synthesis.
3. From the preparation procedure, the reagent was obtained by the reaction of tellurium with an excess amount of sodium borohydride under reflux. Thus, the reagent mixture is both a strong base and a strong reducing agent. This may induce side reactions in organic synthesis, especially for complicated molecules.
4. Because of the preparation method, it is difficult to carry out very small scale quantitative reactions with this reagent. This limits its application in fine organic synthesis involving small amounts reactants (mmol reactions).

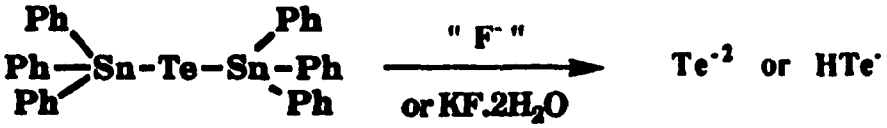
In order to overcome the above limitations as the purpose of this section of the thesis, we intend to develop a new tellurium reagent which can be prepared, stored and used very easily in virtually any solvent system.

In addition, it should be mild and effective for nearly any scale reaction.

2.1 Preparation and Physical Properties of Bis(triphenylstannyl)telluride (1)

Following earlier studies on the series of bis(triphenylstannyl and silyl)chalcogenides and on fluorodestannylation in this laboratory,[1] we wished to exploit the chemical reactions of telluride 1. We suspected that it might be a good candidate for the new tellurium reagent through the following fluorodestannylation procedure.

Scheme 1.



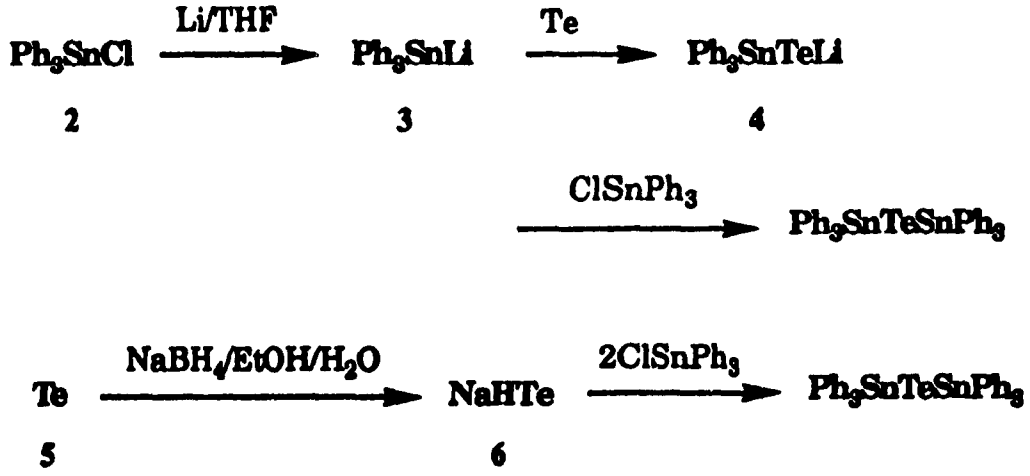
1

Bis(triphenylstannyl)telluride was first synthesized in 1964 by Schumann *via* a multi-step synthesis involving the preparation of $Ph_3Sn^-Li^+$. Its reaction with tellurium gave $Ph_3SnTeLi$ and finally the reaction of $Ph_3SnTeLi$ with Ph_3SnCl in ether gave the telluride reagent 1.[2,3] Later the preparation was improved by Mathiasch[4] in 1981 and Einstein[5] in 1983 *via* the reaction of a benzene solution of the triphenyltin chloride with an aqueous phase containing an excess amount of Na_2Te, which was prepared *in situ* from the reaction of tellurium powder with an aqueous ethanol solution of sodium borohydride.[6]

The ^{13}C, ^{119}Sn, ^{125}Te NMR spectra as well as its ^{119}Sn and ^{125}Te Mossbauer spectra have been determined.[4,5,7] This compound forms white needles and its crystal structure has been determined.[5] The molecule

exhibits a "bent" geometry in which the Sn-Te-Sn angle =103.68(2)^0 and the Te-Sn bond length = 2.7266(6)Å. The Te atom lies on a crystallographic two-fold axis (Fig. 1).

Scheme 2. Preparation of bis(triphenylstannyl)telluride (1)



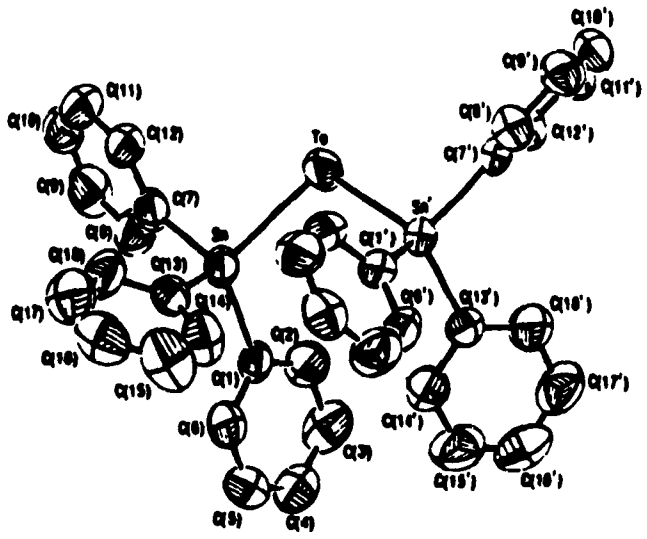


Fig. 1. ORTEP diagram of $(Ph_3Sn)_2Te$ molecule. (Hydrogen atoms are not included.)[5]

Bis(triphenylstannyl)telluride (1) is different from other alkyl tin tellurides in that this aromatic derivative is a fairly stable solid which can be prepared, purified and handled very easily. The compound can be stored in a refrigerator for long periods without obvious decomposition taking place (e.g. 1 year). These characteristics suggest that this molecule could be a useful reagent for organic synthesis. Its chemical properties or applications have not been examined before. However, t-butyldimethylsilyl and trimethylsilyl telluride (8), are much less stable and hence more difficult to work with. Silyl telluride 8 on the other hand, has been examined once. The compound was found to be a good reducing agent for the group 6A oxides (Eq. 1)[8] to give the corresponding chalcogenide.

$$\underset{7}{RM(\rightarrow O)R'} + \underset{8}{R''_3SiTeSiR''_3} \dashrightarrow \underset{9}{RMR'} + \underset{10}{R''_3SiOSiR''_3} + Te^0 \qquad \text{(Eq. 1)}$$

R, R' = alkyl and aryl

R" = trimethyl and t-butyldimethyl

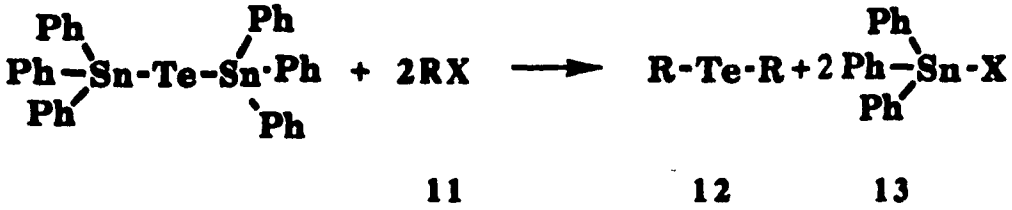
M = S, Se, Te

2.2 Bis(triphenylstannyl)telluride as a New Telluration Reagent

Telluration of different organic compounds to give diorganic tellurides is the most fundamentally studied area of organic tellurium chemistry. However, the currently employed methods generally use sodium hydrogen telluride or disodium telluride as the telluration reagent.[9,10] The reaction conditions are usually basic and without selectivity. The reaction also suffers from the formation of ditelluride, which has to be thermolyzed to remove one tellurium. Other by-products

are formed due to the existence of excess sodium borohydride. Alternatives to this reagent are generally only applicable for a specific reaction and can not be widely used. Thus, our first study of this new reagent was the telluration procedure.

Bis(triphenylstannyl)telluride (1) was prepared according to the reported procedure[5] with a modification of the solvent of crystallization and recrystallization from ethanol/hexane to ethanol/chloroform. When different organic halides 11 are treated with telluride 1, the corresponding diorganotellurides 12 were obtained (Eq. 2). Unlike procedures using NaHTe or Na_2Te, the telluride thus formed is pure and free from ditelluride.



(Eq. 2)

11 12 13

The choice of solvent has a strong influence on the reaction. A variety of solvents, e.g. THF, chloroform, acetonitrile, can be used. However, the reaction is faster when the more polar acetonitrile is used as the solvent; the rate of the reaction was found to be increased as the polarity of the solvent increased.

The reaction was also sensitive to different types of halides, showing the following reactivity: benzylic (allylic) > alkyl > aryl; iodide > bromide > chloride. The most active kind of halide (benzylic) reacts smoothly with telluride 1 to give dibenzyl telluride. Alkyl halides need to be activated with cesium fluoride.

Table 1. Reaction of Bis(triphenylstannyl)telluride with Organic Halides

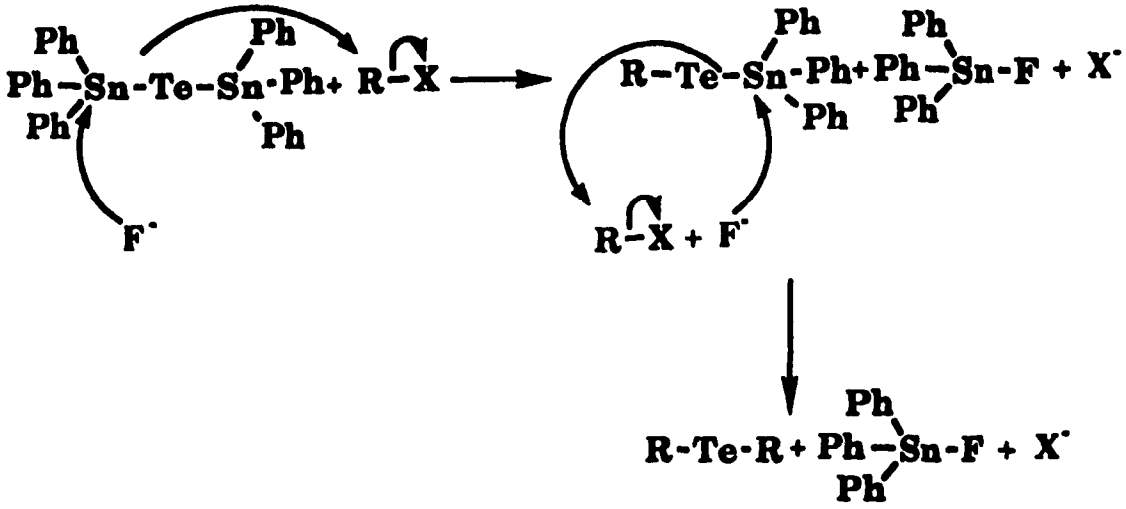
Entry	Halides	Product(12)		Yield(%)	Solvent	Time(h)
1a	$PhCH_2Br$	12a	$(PhCH_2)_2Te$	quant.[c]	CD_3CN[f]	24
1b	$PhCH_2Br$	12a	$(PhCH_2)_2Te$	33[c]	$CDCl_3$	48
1c	$PhCH_2Br$			NRx.	$CDCl_3$[f]	24
2a[b]	$CH_3(CH_2)_9I$	12b	$(CH_3(CH_2)_9)_2Te$	quant.[c]	MeCN/THF[d]	1
2b	$CH_3(CH_2)_9I$			NRx.	MeCN/THF[d]	5
3[b]	$CH_3(CH_2)_9Br$	12b	$(CH_3(CH_2)_9)_2Te$	40	MeCN/THF[d]	1
4[b]	$CH_3(CH_2)_9Cl$			NRx.	MeCN/THF[d]	5
5[b]	$o\text{-}C_6H_4(CH_2Br)_2$	12c	$o\text{-}C_6H_4(CH_2)_2Te$	50	MeCN/THF[d]	1
6[b]	C_6H_5I			NRx.	MeCN/THF[d]	5
7[b]	$(CH_3)_2CHI$	12d	$((CH_2)_2CH)_2Te$	80[c]	MeCN/THF[d]	1
8a[b]	$BrCH_2COPh$	12e	$(PhCOCH_2)_2Te$	64[e]	MeCN	5
		12e'	$+PhCOCH_3$	15[e]		
8b	$BrCH_2COPh$	12e'	$PhCOCH_3$	15[e]	MeCN	5

[a] Isolated yield unless otherwise mentioned; [b] 4 equivalents of CsF was added; [c] ^1H NMR Yield; [d] 3/1 ratio; [e] compared to an authentic sample by GLC and ^1H NMR; [f] 45°C; The others were carried out at room temperature.

The activation process is suggested to proceed as shown in Scheme 3. Attack of the fluoride on tin *in situ* delivered Ph_3SnTe^-. The highly nucleophilic anion then likely attacks the halide immediately to produce triphenylstannyl organo telluride through a S_N2 nucleophilic substitution reaction. Repetition of the fluorodestannylation and S_N2 substitution gives the final diorgano telluride. A summary of the telluration reactions

performed are collected in Table 1.[11]

Scheme 3. Activation Diagram of bis(Triphenylstannyl)telluride (1) by Fluoride Ion



Rate Determining Steps

Thus, the F^- activated telluration process can be separated into two flurodestannylations and two tellurations. A likely sequence of steps is shown as follows.

i). $Ph_3SnTeSnPh_3 + [Cs^+F^-] \xrightarrow{\text{slow}} Ph_3SnTe^-Cs^+ + FSnPh_3$

ii). $Ph_3SnTe^-Cs^+ + RX \xrightarrow{\text{fast}} Ph_3SnTeR + [Cs^+X^-]$

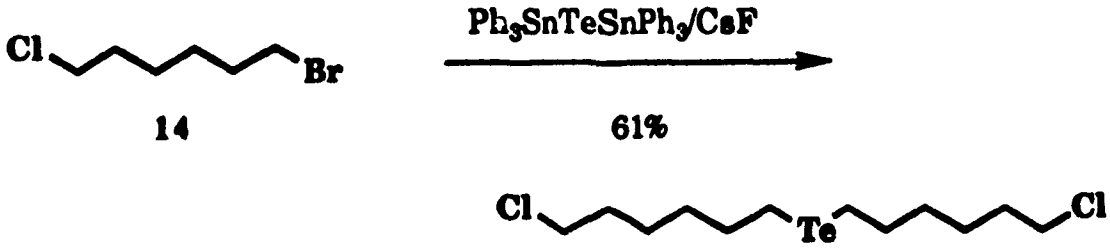
iii) $Ph_3SnTeR + [Cs^+X^-] \xrightarrow{\text{slow}} RTe^-Cs^+ + FSnPh_3$

iV) $RTe^-Cs^+ + RX \xrightarrow{\text{fast}} R\text{-}Te\text{-}R + [Cs^+X^-]$

In these steps, the two fluorodestannylations involve charge

separation, because that inorganic salt is less soluble in the organic solvent than the organic telluride salt; the two tellurations involve charge cancellation. Reactions involving charge separation normally will be accelerated by the use of more polar solvents, otherwise the reaction will not be appreciably affected. Since bis(triphenylstannyl)telluride(1)-based telluration is strongly dependent on the polarity of the solvent and more polar solvent favors the reaction, the steps that control the formation of the product in the whole telluration process are the charge separation ones involving fluorodestannylations.

Alkyl halides (alkyl iodides, or bromides) can react easily through the fluoroactivation process. Aryl halides and alkyl chlorides however are still completely inactive even when they were further activated by adding a crown ether.[12] Because of this sensitivity of the reagent, selective transformation of the bromo group (in the presence of a displaceable chlorine atom) to tellurium is possible (Scheme 4). The reaction provides the first example for the preparation of this type of compound.



Scheme 4.

When reagent 1 combined with cesium fluoride was allowed to react with α-halo carboxylic esters, high yields of symmetric telluro esters were obtained. This type of compound has not appeared before in the literature.

The only compound of this type, menthyl tellurodiacetate,[13] was obtained as a by-product from the thermal decomposition of the menthyl ester of di-n-butyl telluretine bromide. The bactericidal power of diethyl tellurodiacetate[14] has been investigated before, but the preparation was not reported. The difficulty with the preparation of this compound might come from the facile cleavage of the ester with the general telluration reagent.[15] The preparation of a variety of this class was achieved and is summarized as follows.[16]

$$Ph_3SnTeSnPh_3 + X(CH_2)_nCOOR \xrightarrow[R.\ T.]{CsF/MeCN} Te((CH_2)_nCOOR)_2 \qquad \text{(Eq. 3)}$$

16 17

X= Br, Cl	17a	R= Me	n= 1
	17b	R= Et	n= 1
	17c	R= nPr	n= 1
	17d	R= t-Bu	n= 1
	17e	R= Et	n= 3

The properties of these compounds were investigated. Surprisingly, unlike the allyl telluride[17] or α-telluroketones,[18] which decompose easily, these compounds are stable. Under the protection of nitrogen, after refluxing with AIBN in benzene for 10 h, there is no change in the compound. These compounds seem also very stable both to light and air. Under nitrogen, UV irradiation for 24 h caused no detectable decomposition. These properties seem to be the same as normal dialkyl tellurides.

Without protection by an inert gas, the sample can be kept at room temperature for several months without decomposition. Thus these

compounds appear to have potential as stable precursors for other synthetic procedures.

The reaction can also be used to prepare other symmetrical telluro esters. Thus γ-telluroester **17e** was prepared similarly. In the preparation of β-telluroesters, rapid decomposition occurred after its initial formation.

Secondary α-telluroesters, such as dimethyl 2-tellurodipropionate can also be prepared. However, rapid decomposition during the process of purification makes full characterization difficult. The decomposition product involving the formation of an α,β-unsaturated compound, methyl acrylate, was detected by ^{1}H NMR spectroscopy. The decomposition likely proceeded by a radical process.

$$\underset{\textbf{18}}{CH_3CHBrCOOMe} \xrightarrow[CsF/MeCN]{Ph_3SnTeSnPh_3} \underset{\textbf{19}}{Te(CH(CH_3)COOMe)_2} \qquad \text{(Eq. 4)}$$

$$\underset{\textbf{20}}{Te(CH(CH_3)COOMe)_2} \longrightarrow [\underset{\textbf{21}}{CH_3\dot{C}HCOOMe}] \longrightarrow \underset{\textbf{22}}{CH_2{=}CHCOOMe} \qquad \text{(Eq. 5)}$$

The decomposition reaction suggests a novel olefination methodology from organic halides, instead of carbonyl compounds as in the conventional Wittig and Peterson Olefination, in the following way.

$$Te(CH_2COOR)_2 + R'X \xrightarrow{Base} Te(CHR'COOR)_2 \longrightarrow R'CH{=}CHCOOR$$

When we reacted ethyl telluroacetate with benzaldehyde and K_2CO_3 in THF for 24 h at room temperature, we obtained *ca.* 10% of the

corresponding olefination product by ^1H NMR. Trying to improve the yield of olefination with different conditions and different bases was not successful.

In the case of bromoacetophenone as the halide, interestingly enough, more than 30 percent of the reduced product acetophenone was obtained, together with the telluride. The reduced product most likely came from the decomposition of the telluration product or its intermediate. When the reaction was carried out without adding CsF, only 15 % of the acetophenone was formed. This unexpected result suggested a useful methodology for the reduction of α-halo carbonyl compounds.

In general, the high selectivity, good yields and mild reaction conditions make this telluration reaction a more convenient and efficient route than the currently existing methods.

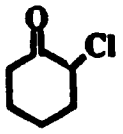
2.3 Bis(triphenylstannyl)telluride (1) as a Dehalogenation Reagent of α-Halo Carbonyl Compounds

During the study of telluration by bis(triphenylstannyl)telluride (1), we observed the formation of a dehalogenation product when it reacted with α-halo carbonyl compounds. However, this product is only the minor one. When we used $KF{\cdot}2H_2O$ as the fluride source instead of cesium fluoride, quantitative dehalogenation took place (Table 2).[19] The reaction was free from the telluration product.

An alternative possibility to this process could be *via* tellurol intermediate **29**, i.e. during the reaction, the semitelluration first takes place; a subsequent rearrangement detelluration process would then give the enolate, which rearranges to give the reduced product. A similar detelluration rearrangement has been suggested in the reaction of allyl

halides with sodium telluride.[17] The two possible paths are shown in Scheme 7.

Table 2. Dehalogenation of α-Halo Ketones by Bis(triphenylstannyl)telluride(1)

Entry	α–Halo ketone	Solvent	Time(h)	Product	Yield[a]
1	$PhCOCH_2Br$	CH_3CN	5	$PhCOCH_3$	79(quant)
2	$PhCOCH_2Br$	CD_3CN[b]	5	$PhCOCH_3$	(35)
3	$PhCOCH_2Br$	CD_3CN[c]	5	$PhCOCH_3$	(15)
4	$PhCOCH_2Br$	CH_3CN[d]	0.2	$PhCOCH_3$	(quant)
5	$PhCOCHBrCH_3$	CH_3CN	5	$PhCOCH_2CH_3$	87(quant)
6	$PhCOCHBrCH_3$	CH_3CN[d]	0.2	$PhCOCH_2CH_3$	(97)
7	$PhCOCBr(CH_3)_2$	CH_3CN	10	$PhCOCH(CH_3)_2$	69(78)
8	$PhCOCH_2Cl$	CH_3CN	10	$PhCOCH_3$	77(quant)
9		CD_3CN	5		(63)
10	CH_3COCH_2Cl	CD_3CN	4	CH_3COCH_3	(92)
11	$CH_3CH_2COCH_2Br$	CD_3CN	5	$CH_3CH_2COCH_3$	(quant)

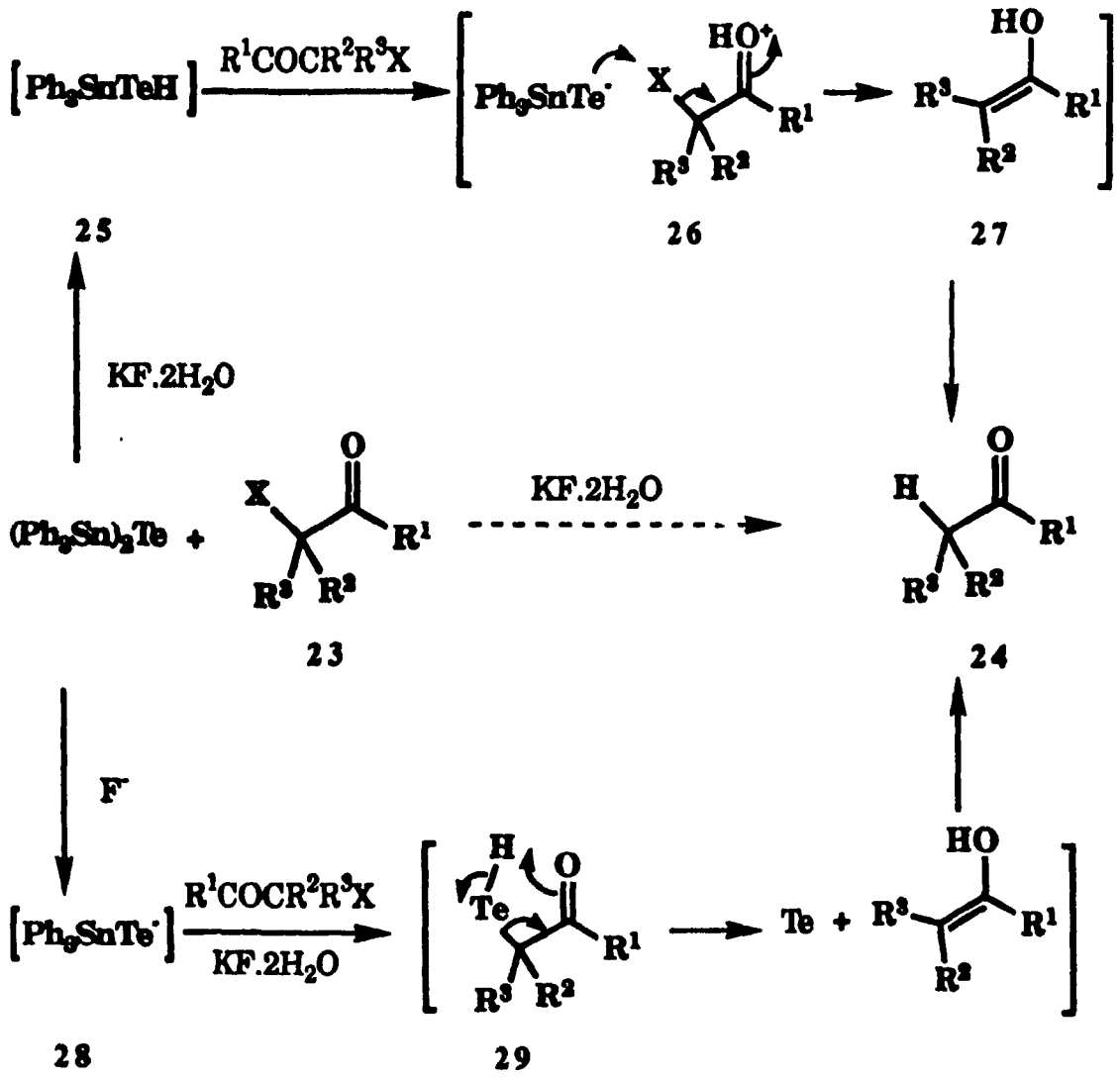
All the reactions were carried out at room temperature with the haloketone : telluride : $KF.2H_2O$ = 1 : 1 : 3 (mole ratio); [a] isolated yields; [1] Hnmr yields in parentheses; [b] with CsF as catalyst; [c] without $KF.2H_2O$; [d] refluxing.

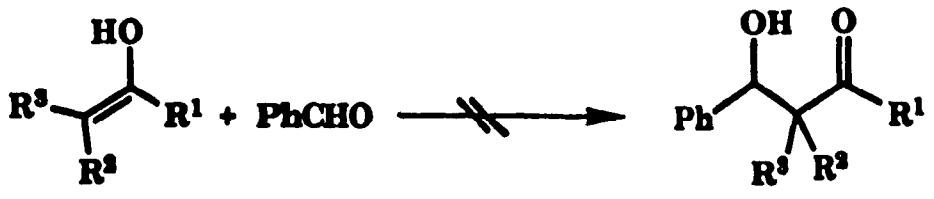
The process suggests that during the reaction with $KF.2H_2O$ a triphenylstannyl hydrogen telluride intermediate **25** was formed *in situ*;

this would reduce the halogen to hydrogen through protonation of the carbonyl, reductive enolization by the Te anion, and rearrangement of the enolate.

In both suggested mechanisms, the enolate species should be present. However, trying to trap the enolate with benzaldehyde, we were unable to obtain the aldol condensation product. Thus, there is still no direct evidence for the proposed mechanism.

Scheme 7. Possible Mechanism of the Dehalogenation Reaction





(Eq. 6)

30 31

Attempts to dehalogenate α-halo esters by this method only gave a mixture of telluration and dehalogenation products. General alkyl halides still give the telluration products by this method.

2.4 Bis(triphenylstannyl)telluride (1) as a Debromination Reagent of *vic*-Dibromides

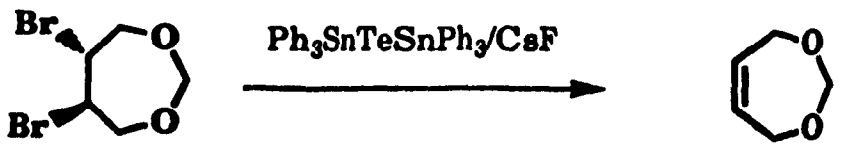
Dehalogenation of 1,2-dihalides is a common process which is encountered in organic synthesis. That sodium hydrogen telluride[20] and selenium anions[21-23] in ethanol have been used to debrominate dihalides to form olefins suggested that the combination of reagent 1/F⁻ might be useful for this important reaction. When a variety of 1,2-dibromides were treated with 1.5 equivalents of 1 in the presence of fluoride ion, excellent yields of debrominated olefins were produced (Table 3).[11]

(Eq. 7)

32 33

The reaction is carried out in acetonitrile under very mild conditions. The presence of some labile functional groups, *e. g.* sulfones (entry 3) and α-acetals (Eq. 8), do not interfere with the reaction. Other solvents can also be used as. This novel debromination method appears to be an excellent

procedure to deliver cleanly a very high yield of olefin; it is particularly effective for small quantities of substrate (0.05 mmol).



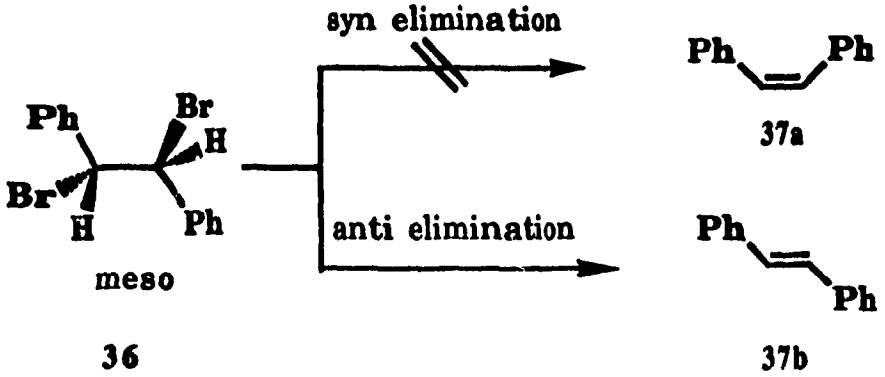
34 quantitatively 35 (Eq. 8)

Table 3. Debromination of *vic*-dibromides

Entry	Dibromide	Product	Yield(%)	Time(h)
1a[a]	$PhCHBrCH_2Br$	$PhCH=CH_2$	28[b,e]	3
1b	$PhCHBrCH_2Br$	$PhCH=CH_2$	quant[b,e]	3
2a	$CH_3(CH_2)_7CHBrCH_2Br$	$CH_3(CH_2)_7CH=CH_2$	38[c]	1.5
2b	$CH_3(CH_2)_7CHBrCH_2Br$	$CH_3(CH_2)_7CH=CH_2$	quant[c]	4
3	$PhSO_2CH_2CHBrCH_2Br$	$PhSO_2CH_2CH=CH_2$	97[d]	3
4	PhCHBrCHBrPh(meso)	PhCH=CHPh(trans)	94[d]	5

All the reactions were carried out at room temperature in acetonitrile; all of the products were compared on GC to authentic samples; [a]Telluride/dibromide=0.5, others 1.5/1; [b] Hnmr yield; [c]GLC yield; [d]isolated yield; [e]in deuterium acetonitrile.

Scheme 5. Determination of the Elimination Stereochemistry

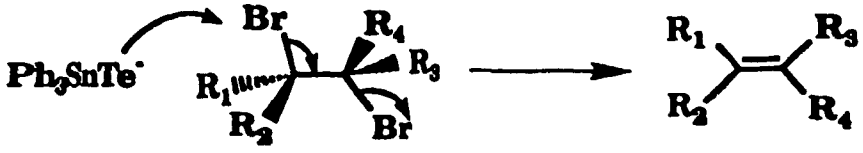


36 37a 37b

The stereochemisty of the reaction was examined through the relationship between starting dibromide 36 and the formed olefin 37b. The result shows that the reaction is a clean anti-elimination process free from the syn elimination product.

The reaction mechanism appears to be the same as other Te anion promoted reductive elimination reaction of *vic*-dibromides.[20]

Scheme 6. Possible Mechanism of the Elimination[20]



2.5 Selective Monodesulfurization of Organic Trisulfides by Bis(triphenylstannyl)telluride (1)

The disulfide and trisulfide linkage is found in a large number of natural products[24] and bioactive antitumor compounds such as calicheamicins.[25] Cleavage of the sulfur-sulfur bond is of major importance in the chemistry and biochemistry of these compounds. Desulfurization of disulfides and trisulfides are normally carried out with phosphines,[26] phosphites[27] and aminophosphines.[28] They sometimes require long reaction times at reflux to effect the desulfurization. When we applied our tellurium reagent to different organic trisulfides, selective monodesulfurization of organic trisulfides was accomplished in a novel manner. Other bis(triphenylstannyl)chalcogenides (1, 1b, 1c) were found to reduce various trisulfide similarly (Eq. 9).

$$R\text{-}S\text{-}S\text{-}S\text{-}R \xrightarrow[1]{Ph_3Sn\text{-}X\text{-}SnPh_3} R\text{-}S\text{-}S\text{-}R \qquad \text{(Eq. 9)}$$

38 39

R= alkyl, aryl, benzyl

X= Te, Se, S

1, 1b, 1c

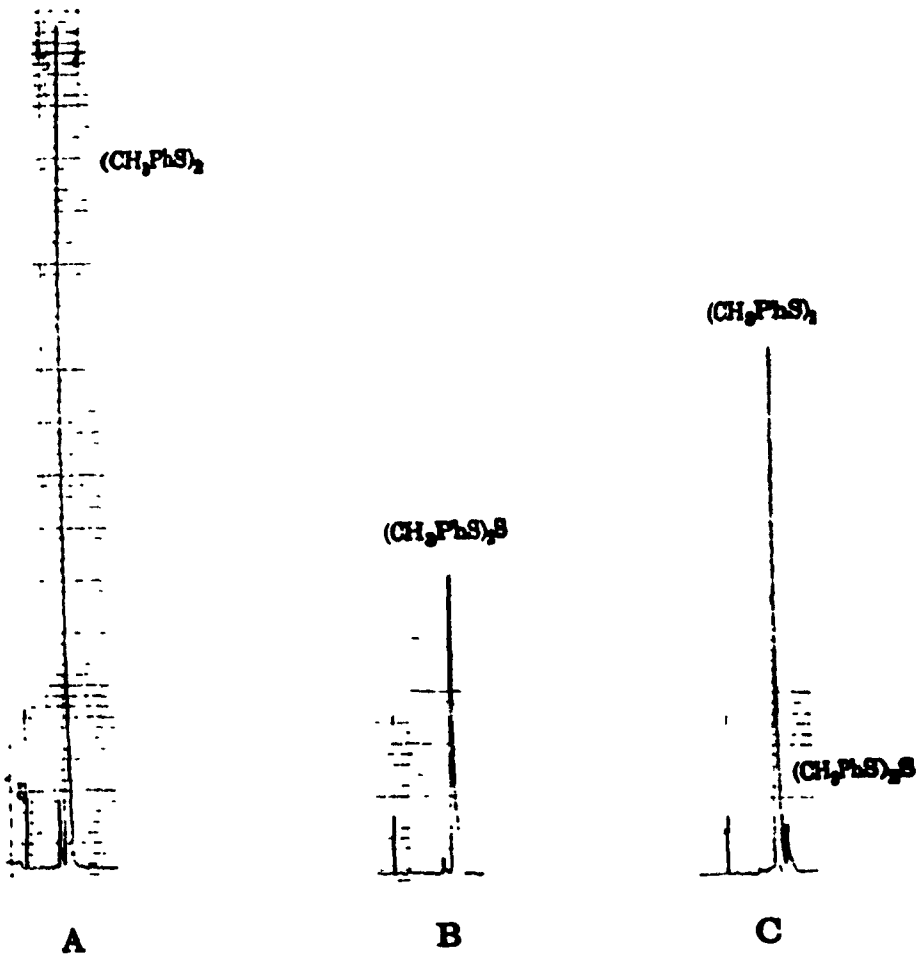


Fig. 2. HPLC Spectra of Selective Monodesulfurization of Tolyl Trisulfide. Condition: CD coated column: A. tolyl disulfide standard; B. tolyl trisulfide standard; C. desulfurization mixture.

Bis(triphenylstannyl)telluride (1) was found to be the most reactive chalcogenide; it smoothly monodesulfurizes aryl and aliphatic trisulfides.

Bis(triphenylstannyl)selenide (1b) monodesulfurizes aryl and benzyl trisulfides. In these two cases, a black powdered elemental deposit was formed which can be easily separated from the desulfurization product through filtration and be recycled. The most unreactive chalcogenide is bis(triphenylstannyl)sulfide (1c), which requires refluxing to effect desulfurization. This trend is consistent with the nucleophilicities and reducing abilities of chalcogenides. The reaction with sulfide (1c) can not be pushed to completion even after 3 days of refluxing in acetonitrile. Elemental sulfur was also not observed as a reaction product. This observation suggests that an equilibrium might be reached.

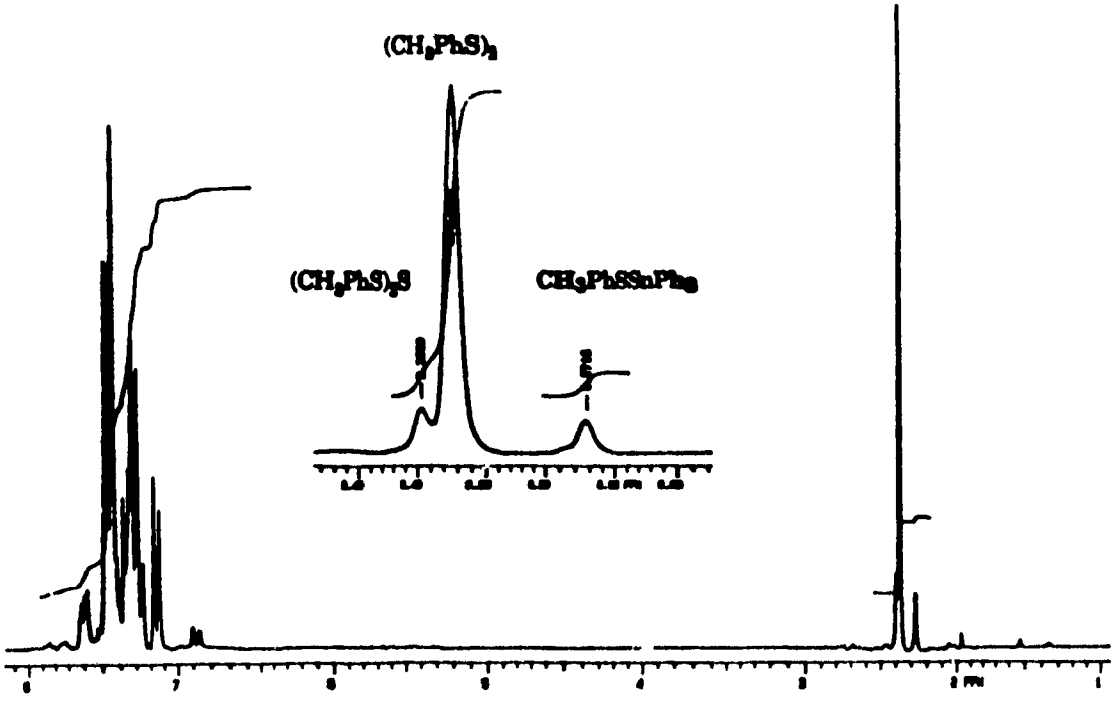


Fig. 3. ^{1}H NMR Spectra of Selective Monodesulfurization of Tolyl Trisulfide.

Table 4. Selective Monodesulfurization of Trisulfides

Entry	RSSSR	$(Ph_3Sn)_2X$ (equ.)	Solvent	Temp.	Time(h)	RSSR (Yield)[1]	RSSSR (Recov.)[1]
1	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Te$(1)	B	Reflux	8	65	37
2	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Te$(1.2)	A	R. T.	3	80	0
3	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Te$(1)	A	0°C	4	84	9
4	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Te$(1)	C	R. T	15	20	40
5	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Te$(1)	A	-35°C	15	85	9
6	$(CH_3PhS)_2S$	$(Ph_3Sn)_2Se$(1)	A	R. T.	6	86	7
7	$(CH_3PhS)_2S$	$(Ph_3Sn)_2S$(1)	A	R. T.	4	0	100
8	$(CH_3PhS)_2S$	$(Ph_3Sn)_2S$(1)	A	Reflux	15	58	42
9	$(CH_3PhS)_2S$	$(Ph_3Sn)_2S$(1)	A	Reflux	72	60	39
10	$(FPhS)_2S$	$(Ph_3Sn)_2Te$(1)	A	R. T.	3	85[2]	10[2]
11	$(PhCH_2S)_2S$	$(Ph_3Sn)_2Te$(1)	B	Reflux	10	5	5
12	$(PhCH_2S)_2S$	$(Ph_3Sn)_2Te$(1.1)	A	R. T.	4	72	9
13	$(PhCH_2S)_2S$	$(Ph_3Sn)_2Se$(1)	A	R. T.	12	19	7
14	$(PhCH_2S)_2S$	$(Ph_3Sn)_2Se$(1)	A	Reflux	4	39	28
15	$(PhCH_2S)_2S$	$(Ph_3Sn)_2S$(1)	A	Reflux	12	26	52
16	$(PhCH(CH_3)S)_2S$	$(Ph_3Sn)_2Te$(1)	A	R. T.	10	5	95
17	$(CH_3CH_2CH_2S)_2S$	$(Ph_3Sn)_2Te$(1)	A	R. T.	4	10[3]	90[3]
18	$(CH_3CH_2CH_2S)_2S$	$(Ph_3Sn)_2Te$(1)	A	R. T.	72	70[3]	28[3]
19	$(CH_3CH_2CH_2S)_2S$	$(Ph_3Sn)_2Se$(1)	A	R. T.	24	12[3]	86[3]
20	$(CH_3CH_2CH_2S)_2S$	$(Ph_3Sn)_2S$(1)	A	Reflux	24	3[3]	94[3]

A: Acetonitrile; B: Toluene; C: THF; [1]The product distribution were determined by ^{1}HNMR and confirmed by HPLC with internal standard, the difference is further reacted product, otherwise mentioned; [2]determined by ^{19}FNMR; [3]determined by GC with an internal standard, further reaction products were not determined.

To demonstrate this, ditolyl disulfide and bis(triphenylstannyl)disulfide (40) were mixed and refluxed under the same conditions

as the desulfurization reaction. As a result, ditolyl trisulfide was formed and the ratio of trisulfide/disulfide was found to be the same. Thus the following equilibrium has been established (Eq. 10).

$$Ph_3Sn\text{-}SS\text{-}SnPh_3 + R\text{-}SS\text{-}R \rightleftharpoons Ph_3Sn\text{-}S\text{-}SnPh_3 + R\text{-}SSS\text{-}R \quad \text{(Eq. 10)}$$

40

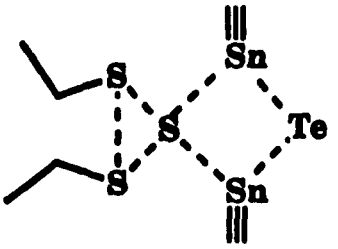
This desulfurization reaction is generally more selective than previous phosphine reactions. A large reactivity difference between different types of trisulfides was observed. Desulfurization of aromatic trisulfides by this method took place most easily. It is likely that the reactivity difference is due to the better leaving ability of ArS^- vs RS^-. Thus, telluride reagent **1** can differentiate aromatic and benzylic from alkyl trisulfides, and the selenide reagent **1b** can differentiate aromatic from benzylic trisulfides.

The reaction is also strongly dependent on the use of solvent. For instance, 10 h refluxing of ditolyl trisulfide with the telluride in toluene is inferior to that of 3 h room temperature stirring in acetonitrile. It is also different from the previous methods in that the reaction with aromatic trisulfides smoothly takes place even at -35°C. It seems that polar solvents favor the reaction. Solvent was also found to be important to the selectivity. The use of a more polar solvent THF (compared to toluene) can increase the rate of the reaction, even though very low selectivity was found.

The possible mechanism for the desulfurization may either be a concerted one through transition state **41** or a stepwise one involving ionic species **42-47**.

Scheme 8. Possible Mechanism of Desulfurization Reaction

Path 1



41

Path 2

$$Ph_3SnTeSnPh_3 \xrightarrow{\text{Solvent}} Ph_3SnTe^{\cdot} \xrightarrow{RSSSR} Ph_3SnTeSSR + RS^{\cdot}$$

42 43

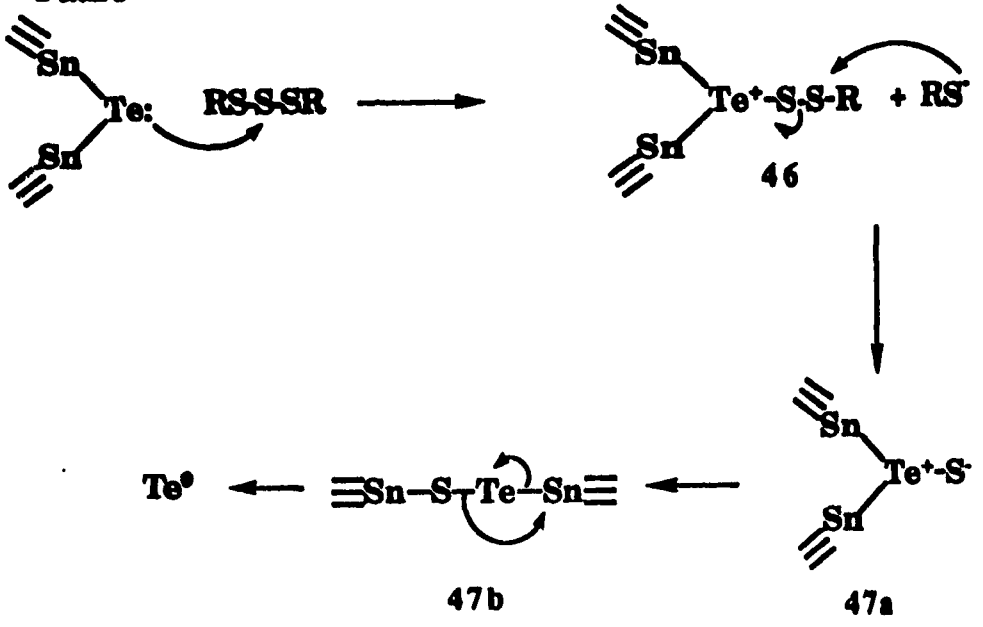
$$\xrightarrow{} RSSR + Ph_3SnS^{\cdot} + Te^{0}$$

44

$$Ph_3SnS^{\cdot} + Ph_3Sn^{+}\ \text{"Solvent"} \xrightarrow{} Ph_3SnSSnPh_3$$

45

Path 3



This process was examined by a intermolecular crossed reaction (Eq. 11).

$$\underset{48}{PhCH_2SSSCH_2Ph} + \underset{49}{CH_3C_6H_4SSSC_6H_4CH_3} \xrightarrow[MeCN/r.t./\ 4h]{Ph_3SnTeSnPh_3} \underset{50\ (70\%)}{PhCH_2SSC_6H_4CH_3} + \underset{51\ (8\%)}{CH_3C_6H_4SSC_6H_4CH_3} + \underset{52\ (14\%)}{PhCH_2SSCH_2Ph} \qquad \text{(Eq. 11)}$$

This large portion of crossed product rules out a concerted mechanism and suggests that the reaction occurs in a stepwise manner. The result is also consistent with the observation that polar solvents facilitate the reaction.

The chalcogenide desulfurization exposes a novel alternative to the conventional phosphorous method. The large reactivity difference of bis(triphenylstannyl)chalcogenides with different trisulfides makes this method unique. Furthermore, the reactivity and selectivity of this reagent can also possibly be controlled and modified by changing the triphenyl group to trialkyl and the tin atom silicon.

2.6 Cleavage of Organic Disulfides by Bis(triphenylstannyl)telluride (1)

When bis(triphenylstannyl)telluride (1) and selenide (1b) was added in excess or when they reacted with ditolyl disulfide 53, further reaction takes place to give a new compound with a small chemical shift of the methyl substituent. Initially, we suspected that the compound may be further desulfurized to give monosulfide 54 (Eq. 12)

$$\underset{53}{TolSSTol} + Ph_3SnXSnPh_3 \xrightarrow{\quad X \quad} TolSTol + \underset{54}{Ph_3SnSSnPh_3} + X^{\circ} \qquad \text{(Eq. 12)}$$

However, when we tried to isolate the product by flash column chromatography, we obtained 89% of tolyl thiol (**55**). Furthermore, the chemical shift of the methyl group of the unknown compound is at higher field than it should be for monosulfide, even higher than the methyl of tolyl thiol. This chemical shift suggests that the sulfur may be connected to a metal, which could be the triphenylstannyl group.

$$\underset{\textbf{55}}{CH_3PhSH} + \underset{\textbf{56}}{ClSnPh_3} \xrightarrow{NaOH/H_2O/CCl_4} \underset{\textbf{57}}{CH_3PhSSnPh_3} \qquad \textbf{(Eq. 13)}$$

In order to prove this assumption, we prepared tolyl triphenylstannyl sulfide (**57**) according to a standard procedure (Eq. 13).[29] Both the melting point and spectroscopic data were consistent with the unknown compound. Therefore, the thiol was due to the hydrolysis of the triphenylstannyl sulfide on silica gel during the separation. Thus, reaction of bis(triphenylstannyl)telluride and selenide with organic disulfides gave triphenylstannyl organo sulfide **58** quantitatively. The reaction, however, was only successful with aromatic disulfides. Benzylic and alkyl disulfides failed to react under the same conditions.

$$RSSR + Ph_3SnXSnPh_3 \longrightarrow \underset{\textbf{58}}{2RSSnPh_3} + X^0 \qquad \textbf{(Eq. 14)}$$

R= aryl X= Te, Se

This might be a preferable method for the preparation of triorganylstannyl organic sulfides (a class of potential synthetic useful

precursors), which is usually prepared from odorous thiols and a trialkylstannyl halogenide.[29]

2.7 Conclusion

In conclusion, we have developed a new tellurium reagent, bis(triphenylstannyl)telluride (1), which is a synthetic equivalent of Te^{-2} or TeH^- depending on the fluorodestannylation method. The reagent is stable and crystalline, and can be prepared, stored and used very easily. It also displays other capabilities such as desulfurization in addition to being as an equivalent of Barton's reagent. All the reactions with this reagent proceeded under very mild conditions.

2.8 Experimental

Melting points are uncorrected. Infrared spectra were obtained from films on NaCl plates for liquids and as a KBr pellet for solids on an Analect FTIR AQS-18 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on Varian XL-200, XL-300, and Gemini-200 instruments. Low Resolution Mass Spectra were determined on a DuPont 21-492B spectrometer, High Resolution Mass Spectra were performed at the Biomedical Mass Spectrometry Unit, McGill University. Column chromatography was performed on silica gel 60 (Merck and EM Science). Acetonitrile was dried by refluxing over CaH_2.

Preparation of bis(triphenylstannyl)telluride (1):[7]

A mixture of tellurium powder (3.54 g, 0.0279 mol), $NaBH_4$ (2.46 g, 0.065 mol), ethanol (40 mL) and water (10 mL) was placed under nitrogen in a 250 mL flask, which was equipped with a water condenser. The

mixture was stirred and refluxed until the Te almost disappeared to form a purple solution. To the reaction mixture, a solution of triphenyltin chloride (21.51 g, 0.0558 mmol) in benzene was added over 40 min through a dropping funnel, and stirred at room temperature for 2 h. The whole reaction mixture was filtered through celite. The aqueous phase in the filtrate was removed and the benzene solution evaporated to dryness to give a solid mixture. The solid was dissolved in a small amount of chloroform. To the solution, absolute ethanol was added to form a large amount of colorless needle-like crystals. Recrystallization from chloroform and alcohol gave 12.65 g (55%) of pure bis(triphenylstannyl)telluride (1), m.p. 146-148°C (lit.[7] 148°C). ^{1}H NMR($CDCl_3$): δ=7.3 (m)ppm; ^{119}Sn NMR($CDCl_3$): δ= -142.3 (s)ppm.

General Procedure of Telluration Reaction:

The corresponding halide in the appropriate solvent was protected under nitrogen. To the solution, bis(triphenylstannyl)telluride (0.5 eq.) was added in one portion, followed by the addition of an excess amount of CsF (or without CsF). The reaction mixture was stirred and followed by TLC or ^{1}H NMR.

Dibenzyl telluride (12a):

The compound was prepared by the general procedure from benzyl bromide at 45°C in acetonitrile for 24 h without the activation of CsF, and isolated by column chromatography. ^{1}H NMR($CDCl_3$): δ= 4.05(s, 4H), 7.3(m, 10H), J(Te-H)=; MS(EI): 312(M, 0.8%), 310(0.6), 298(9.7), 296(9.6), 207(2.8), 205(3.5), 196(9.3), 154(15), 92(25), 91(100), 78(17), 77(19.3). The data agree with literature.[30]

Didecyl telluride (12b):

The compound was prepared by the general procedure from decyl iodide and bromide in a mixture of acetonitrile/THF (3/1) at room temperature with the activation of CsF, and isolated by column chromatography. ^{1}H NMR($CDCl_3$): δ= 0.87(t, 6H), 1.25(br, 14H), 1.70(m, 4H), 2.61(t, 4H)ppm; ^{13}C NMR($CDCl_3$): δ= 6.1, 15.5, 24.0, 30.2, 30.6, 30.9, 30.95, 33.4, 33.6, 33.8ppm, J(^{125}Te-^{13}C)= ; MS(EI): 413(M+1, 15%), 412(M, 63%), 411(16), 410(59), 409(9), 408(40), 407(18), 271(30), 269(28), 267(32), 159(19), 157(18), 86(41), 71(50), 57(100); HRMS: $C_{20}H_{42}Te+H^+$, calcd. 413.2427, found 413.2428.

Di-1-(6-chlorohexyl) telluride (15):

^{1}H NMR($CDCl_3$): δ= 1.3-1.5(br, 8H), 1.65-1.9(br, 8H), 2.6(t, 4H), 3.55(t, 4H)ppm. MS(EI): 372(M+4, 3%), 370(M+2, 20), 368(M, 48), 333(18), 249(79), 247(65), 193(19), 83(59), 55(100).

Dimethyl tellurodiacetate (17a):

A mixture of methyl α-bromoacetate (71 mg, 0.42 mmol), bis(triphenylstannyl)telluride (1) (182 mg, 0.22 mmol), and CsF (152 mg, 1.0 mmol) in 10 mL of acetonitrile was stirred at room temperature under nitrogen for 3 h. The reaction mixture was filtered through celite. Evaporation of the solvent gave a crude material, which was extracted by chloroform leaving a white solid. The chloroform extract was concentrated under vacuum and further purified by a short flash column to give 65 mg (88%) of pure 17a as a yellowish oil. ^{1}H NMR($CDCl_3$): δ= 3.70 (s, 6H), 3.52(s, 4H)ppm, J(Te^{125}-H^{1}) = 34Hz. ^{13}C NMR($CDCl_3$): δ= 173.85, 52.48, 1.84ppm, J(Te^{125}-C^{13})= 170.4Hz; IR($CDCl_3$): υ= 2950, 1723, 1265cm^{-1}. HRMS: $C_6H_{10}O_4Te$, calc 275.9646; found, 275.9641.

Diethyl tellurodiacetate (17b):

The procedure was the same as in **17a**, yield 90% as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ= 4.16(q, 4H), 3.52(s, 4H), 1.26(t, 6H)ppm, $J(Te^{125}\text{-}H^{1})$ = 34Hz. ^{13}C NMR ($CDCl_3$): δ= 173.67, 61.29, 10.03, 2.31ppm, $J(Te^{125}\text{-}C^{13})$= 171.3Hz; IR($CDCl_3$): υ= 2985, 1722, 1263$cm^{-1}$. HRMS: $C_8H_{14}O_4Te$, calc 303.9959; found, 303.9954.

Dipropyl tellurodiacetate (17c):

The reaction was carried out in the same way as in **17a**, stirring for 5 h. The final extraction was performed with hexane. Evaporation of hexane without further purification gave pure **17c** in 99% yield as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ= 4.05(t, 4H), 3.50(s, 4H), 1.06(m, 4H), 0.93(t, 6H)ppm, $J(Te^{125}\text{-}H^{1})$ = 34Hz. ^{13}C NMR($CDCl_3$): δ= 173.50, 66.83, 21.83, 10.30, 2.21ppm, $J(Te^{125}\text{-}C^{13})$= 168.9Hz; IR($CDCl_3$): υ= 2970, 1717, 1268$cm^{-1}$. HRMS: $C_{10}H_{18}O_4Te$, calc. 332.0272; found, 332.0269.

Di-t-butyl tellurodiacetate (17d):

The reaction was carried out in the same way as for **17c**, using t-butyl α-bromoacetate or chloroacetate (stirred for 5 h and 12 h respectively) to give **17d** in 99% yield as a yellowish oil. ^{1}H NMR($CDCl_3$): δ= 4.05(q, 4H), 3.42(s, 4H), 1.44(s, 18H)ppm, $J(Te^{125}\text{-}H^{1})$ = 32.4Hz. ^{13}C NMR($CDCl_3$): δ= 172.61, 81.02, 27.78, 4.13ppm, $J(Te^{125}\text{-}C^{13})$= 167.3Hz; IR($CDCl_3$): υ= 2961, 1706, 1285$cm^{-1}$. HRMS: $C_{12}H_{22}O_4Te$, calc. 360.0585; found, 360.0579.

Diethyl tellurodibutyrate (17e):

The reaction was carried out in the same way as for **17a** with stirring for 6 h. The final extraction was done with methylene chloride. Evaporation of the methylene chloride and flash column purification gave

17e in 75% yield as a yellowish oil. ^{1}H NMR($CDCl_3$): δ= 4.1(q, 4H), 2.65(t, 4H), 2.4(t, 4H), 2.1(m, 4H), 1.25(t, 6H)ppm. ^{13}C NMR($CDCl_3$): δ= 172.80, 60.35, 36.25, 27.33, 14.20, 1.69ppm, J(Te^{125}-C^{13})= 158.4Hz; IR($CDCl_3$): υ= 2983, 1728, 1376cm^{-1}. HRMS: $C_{12}H_{22}O_4Te$, calc. 360.0585; found, 360.0580.

General Procedure for Debromination of *vic*-Dibromides

A solution of the *vic*-dibromide (0.5 mmol) in 15 mL of acetonitrile was deoxygenated for 5 min with a flow of nitrogen. To the solution, bis(triphenylstannyl)telluride (1) (620 mg, 0.75 mmol) was added in one portion followed by CsF (456 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for the corresponding time under nitrogen. Work-up of the reaction mixture gave the olefins which were identical to authentic samples.

General Procedure for Dehalogenation of α-Halo Carbonyl Compounds

A solution of α-carbonyl compound (0.5 mmol) in 15 mL of acetonitrile was deoxygenated for 5 min with a flow of nitrogen. To the solution, bis(triphenylstannyl)telluride (1) (414 mg, 0.5 mmol) was added in one portion followed by $KF.2H_2O$ (228 mg, 1.5 mmol). The reaction mixture was stirred at the appropriate temperature for the corresponding time under nitrogen. Workup of the reaction mixture gave the corresponding carbonyl compound.

General Procedure for Desulfurization of Trisulfides

A solution of the trisulfide (0.1 mmol) in 5 mL of acetonitrile was deoxygenated for 5 min with a flow of nitrogen. To the solution, bis(triphenylstannyl)chalcogenide (1) (0.1 mmol) was added in one portion

followed by stirring under nitrogen at the corresponding temperature. The reaction mixture was filtered through celite. The final product was checked by ^1H NMR, GLC or HPLC spectra.

Cleavage of Ditolyl Disulfide by Bis(triphenylstannyl)telluride (1):

A solution of the ditolyl disulfide (246 mg, 1 mmol) in 20 mL of acetonitrile was deoxygenated for 5 min with a flow of nitrogen. To the solution, bis(triphenylstannyl)telluride (1) (827 mg, 1 mmol) was added in one portion followed by stirring under nitrogen at room temperature for 3 h. The black reaction mixture was filtered through celite. Evaporation of the solvent left a yellowish oil. Addition of 2 mL ethanol to the oil produced white crystals which was further purified by recrystalization (CCl_4/ethanol), 94% m.p. 102-104°C the same as the following tolyl triphenylstannyl sulfide standard. (Lit.[29] 102-104°C).

Preparation of Tolyl Triphenylstannyl Sulfide (57):[29]

A solution of triphenylstannyl chloride (3.85 g, 10 mmol) and p-tolylthiol (1.24 g, 10 mmol) in 30 mL of CCl_4 was mixed with 30 mL aqueous solution of NaOH (0.4 g, 10 mmol) at room temperature. The reaction mixture was stirred vigorously for 3 h. The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave the title compound which was purified by recrystalization CCl_4/ethanol; yield 4.54 g (96%) m.p. 102-104.[29]

Preparation of Benzyl Tolyl Disulfide (50):[31]

A solution of N-(p-tolylthio)phthalimide (3.8 g, 0.014 mol) and α-toluenethiol (1.74 g, 0.014 mol) in 70 mL of dry benzene was refluxed under nitrogen for 3 days. The solution was filtered to remove crystalline

phthalimide and the benzene solvent was removed under reduced pressure. The residue of crude benzyl p-tolyl disulfide was recrystallized from ligroin to give the title compound 3.27 g (95%), m.p. 33-34°C (lit.[32] 34-35°C).

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