Some Aspects of the Chemistry of Acylation Reactions

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Submitted by

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These courses include:

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CH 603	Supramolecules: Concept and Applications
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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "Some Aspects of the Chemistry of Acylation Reactions" is the outcome of investigations carried out by me under the supervision of Dr. Anil K Saikia, at the Department of Chemistry, Indian Institute of Technology Guwahati, India.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made whenever the work described here is based on the findings of other investigators.

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CERTIFICATE

It is certified that the work described in this thesis entitled "Some Aspects of the Chemistry of Acylation Reactions" by Mr. J. William John Bosco for the award of degree of Doctor of Philosophy is an authentic record of the results obtained from the research work carried out under my supervision in the Department of Chemistry, Indian Institute of Technology Guwahati, India and this work has not been submitted elsewhere for a degree.

(Anil K. Saikia)
Supervisor

List of publications

- Palladium (II) chloride catalyzed selective acetylation of alcohols with vinyl acetate, *Chem. Comm.* **2004**, *9*, 1116.
  J. W. John Bosco and Anil K. Saikia

- Potassium fluoride assisted selective acetylation of alcohols with acetic acid, *Synth. Commun.* **2004**, *34*, 2849.
  J. W. John Bosco, B. Rama Raju and Anil K. Saikia

- Lithium chloride assisted chemoselective conversion of aldehydes into geminal diacetates under solvent-free conditions, *Synth. Commun*. **2005**, *35*,1301.
  J. W. John Bosco, N. Purkayastha, B. Rama Raju and Anil K. Saikia

- Molecular iodine catalyzed selective acetylation of alcohols with vinyl acetate, *Tetrahedron Lett*. **2006**, *47*, 4065.
  J. W. J. Bosco, Aditya Agrahari and Anil K. Saikia

- Samarium (III) chloride catalyzed selective monoacetylation of symmetric diols, **2006** (Communicated).
  J. W. John Bosco and Anil K. Saikia

- Cerium triflate catalyzed gem diacetylation of aldehydes, **2006** (Communicated).
  J. W. John Bosco and Anil K. Saikia

To

My teachers

There are many devices in a man's heart; nevertheless the counsel of the Lord, that shall stand. ***PROVERBS 19: 21***

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J. W. J. Bosco

Standard List of Abbreviations

$A_{AC}1$	acid catalyzed acyl transfer unimolecular
$A_{AC}2$	acid catalyzed acyl transfer bimolecular
Ac	acetyl
Ar	aryl
ATP	Adenosine triphosphate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Br	broad
Bu	butyl
Bz	benzoyl
^{o}C	degrees Celsius
CAN	cerium(IV) ammonium nitrate
CBz	benzyloxycarbonyl
CGA	carboxyl group activation
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DMAP	4-*N*, *N*-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
FT	fourier transform
g	grams(s)
GC	gas chromatography
h	hour(s)
HGA	Hydroxy Group Activation
HLCE	hog liver carboxylate esterase
HMPA	hexamethylphosphoric triamide
Hz	hertz
^{i}Pr	isopropyl
IR	infrared
L	liter(s)
LA	lewis acid
m	multiplet (spectral), milli
Me	methyl
MHz	megahertz
mol	moles(s)
MS	molecular sieves
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance	TBATB	tetrabutylammonium tribromide
Ph	phenyl	^{t}Bu	tertiarybutyl
PPL	porcine pancreatic lipase	TBS	*tert*-butyldimethylsilyl
ppm	parts per million (in NMR)	Tf	trifluoromethanesulfonyl
		THF	tetrahydrofuran
Pr	propyl	THP	tetrahydropyran; tetrahydropyranyl
Py	pyridine		
q	quartet (spectral)	TLC	thin layer chromatography
rt	room temperature		
s	singlet (spectral)	TMATB	tetramethylammonium tribromide
S_N1	substitution nucleophile unimolecular	TMS	trimethylsilyl
		TMSCl	trimethylsilyl chloride
S_N2	substitution nucleophilic bimolecular	t-RNA	transfer ribonucleic acid
S_Ni	substitution nucleophilic Intra molecular	Ts	tosyl (*p*-toluenesulfonyl)
		UV	ultraviolet
t	triplet (spectral)	YL	yeast lipase

Contents

Part I

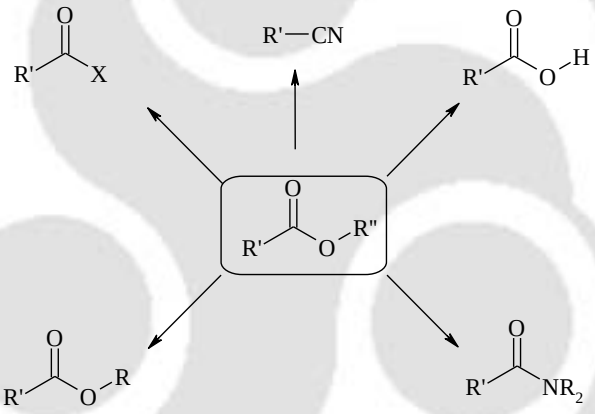
Acetylation of Alcohols

Chapter I

Introduction

1.1 General introduction

Synthesis of esters has played a most important role in organic synthesis from its infancy. This importance stemmed from its utility in diverse fields both in the laboratory and in industry. Ester moieties, irrespective of weather acyclic or cyclic, constitute major backbones, as well as functional groups of chemical significance, in numerous natural products and fine chemicals. The essential feature of esterification that particularly distinguishes it from other reactions lies in its broad utilization in industry. Within the realm of synthetic environment, organic esters represent an important family of intermediates widely employed in the synthesis of fine chemicals, drugs, perfumes, food preservatives, cosmetics, pharmaceuticals, and chiral auxiliaries. Esters can be transformed to several other functionalities as shown in (Scheme 1.1).



Scheme 1.1

Esters play a very significant role in organic chemistry because of their versatile applications.[1] The formation and further transformation of esters belongs to the fundamentals of organic chemistry. Moreover, some esters have enormous importance for example (Figure 1.1) triglycerides **1**, in the form of fats and oils are produced in million ton quantities for a number of applications. Other esters, like **2** and **3**, are olfactory components. Aspartame **5** is an important artificial sweetener, and pyrethrin **6** is the prototype of the pyrethroids, an unusually potent class of insecticides, which is chemically modified to **7** to prevent its degradation against sunlight[2]. The monomer, methyl methacrylate **8**, is the building block of vinyl polymer, poly (methyl methacrylate). The monomer, methyl α-cyanoacrylate **9**, is used in the adhesive, marketed under the trademark of "Superglue". The general class of cyanoacrylates **10** with varying alkyl group is sold as contact adhesive. The addictive alkaloid cocaine **11** is

an ester. Scopolamine **12** is used for protection against motion sickness. Aspirin **13** is the remedy for fever and pain. Due to the wide varieties of applications of esters in various fields there is a great demand for the synthesis of esters.

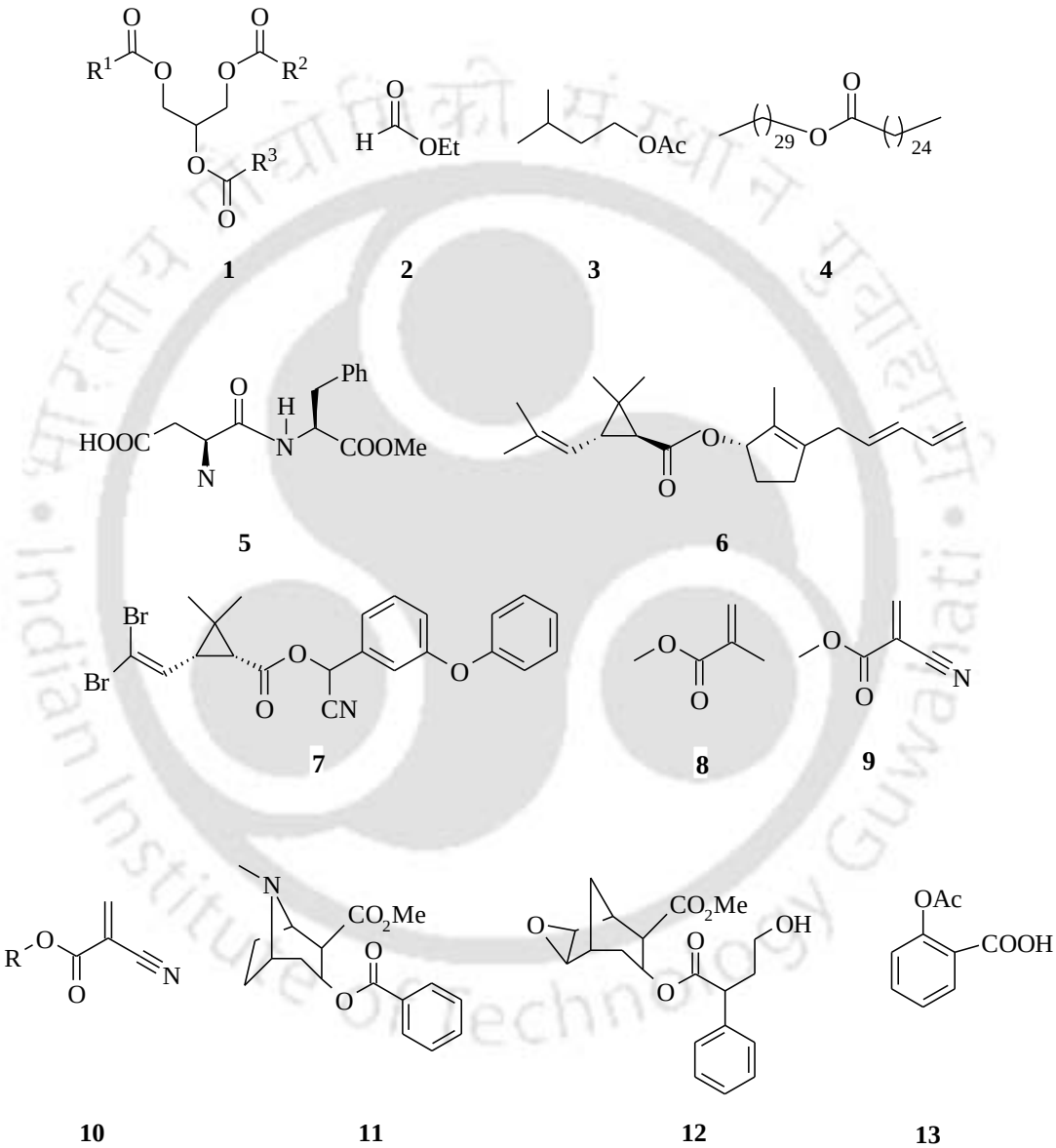
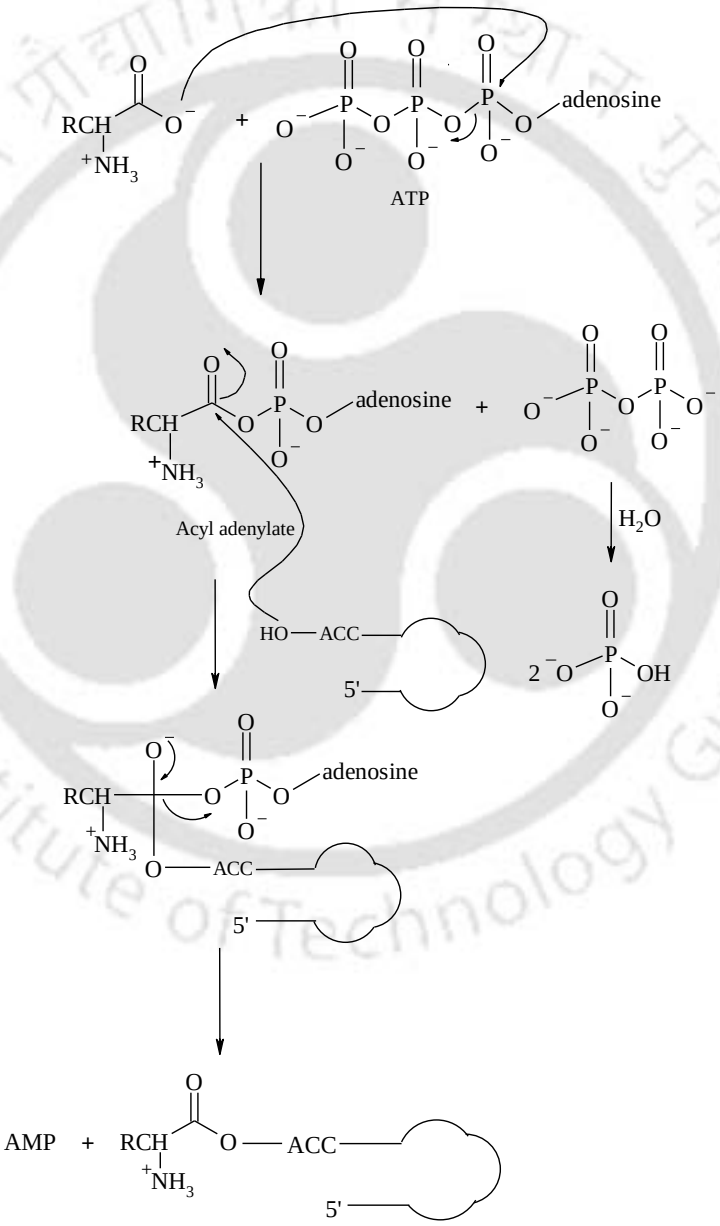


Figure 1.1

Many biological processes take place through esterification. Each *t*-RNA can carry an amino acid bound as an ester to its terminal 3′-OH group. The amino acid will be inserted into a protein during protein biosynthesis. Each *t*-RNA can carry only one particular amino acid. The attachment of *t*-RNA molecule to the amino acid is catalyzed by an enzyme called

aminoacyl-*t*-RNA synthetase. In the first step of the enzyme-catalyzed reaction, the carboxyl group of the amino acid attacks the α-phosphorus of ATP, activating the carboxyl group by forming an acyl adenylate. The pyrophosphate that is expelled is subsequently hydrolyzed, ensuring the irreversibility of the phosphoryl transfer reaction (Scheme 1.2). Then a nucleophilic acyl substitution reaction occurs i.e. the 3′-OH group of *t*-RNA attacks the



Scheme 1.2

carbonyl carbon of the amino acid, forming a tetrahedral intermediate. The aminoacyl t-RNA is formed when the adinosine monophoshate is expelled from the tetrahedral intermediate. All the steps take place at the active site of the enzyme.

Application in natural product synthesis

There are numerous reports of natural products synthesis involving esterification. The literature survey hits more than 300 studies in which esterification plays a key role in natural products synthesis[1]. As a representative example the synthesis of taxol and (-)-colletol are discussed below.

The synthesis of taxol, **14** and its analogues exemplifies how profoundly esterification contributes to this field. Although several total synthesis of taxol have been reported, the semi-synthesis starting from 10-deacetyl baccatin III, **15** is practical.

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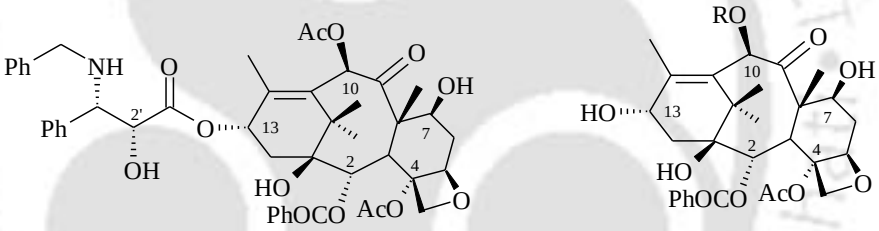
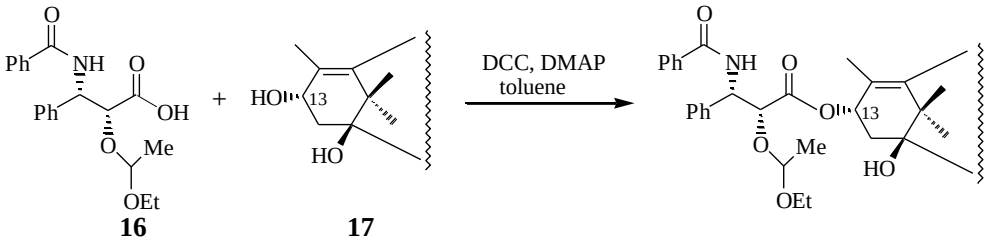


14 **15**

Figure 1.2

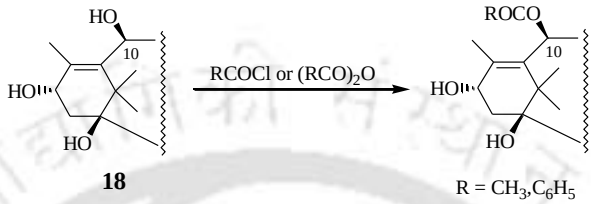
A key step in this strategy is the incorporation of the (2R, 3S)-N-benzoyl-3 phenylisoserine side chain onto the highly sterically hindered 13-position, and it is achieved by direct coupling between 10-deacetyl baccatin III, **17** and (2R, 3S)-N-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine[2] **16** (Scheme 1.3).



16 **17**

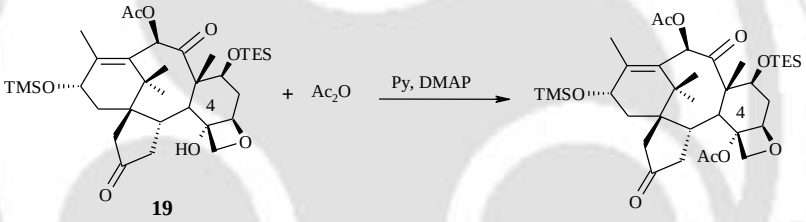
Scheme 1.3

When 10-deacetyl baccatin III is utilized, it is necessary to discriminate the C-13 OH from the other hydroxyl groups. The selective acetylation of C-10 of **18** is achieved by the following method; with acid chloride[3] or with acetic anhydride (Scheme 1.4)[4].



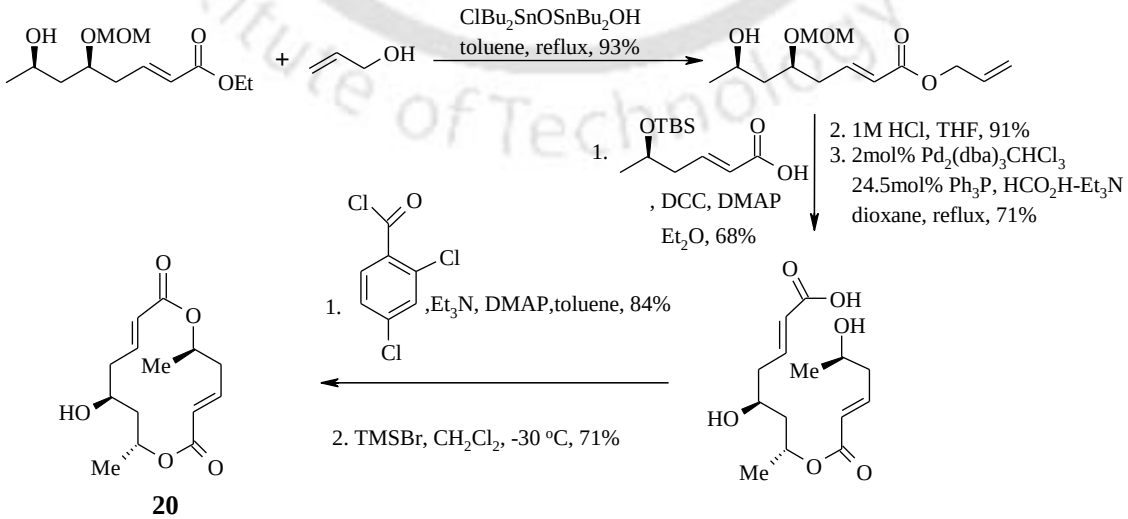
Scheme 1.4

The tertiary alcohol at the C-4 position of **19** is acetylated with acetic anhydride in pyridine (Scheme 1.5).[5]



Scheme 1.5

The next important application is seen in the synthesis of macrolides, because this is heavily

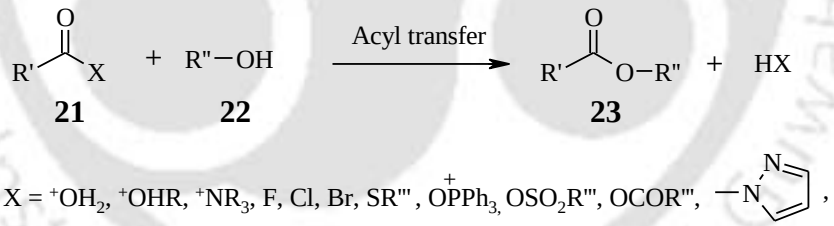


Scheme 1.6

dependent on esterification technology. The Yamaguchi technique serves quite well to this end. The various esterification technologies involve in the total synthesis of (-)-colletol, **20** is shown below (Scheme 1.6).[6] (i) Distannoxane-catalyzed transesterification, (ii) DCC / DMAP condensation and (iii) the Yamaguchi technique with 2,6-dichlorobenzoyl chloride / Et_3N / DMAP. The final lactonization proceeds in 84 % yield.

1.2 Synthesis of esters by carbonyl group activation (CGA)

This method for the synthesis of esters is the most common method (scheme 1.7). The carboxylic acid or an activated derivative there of **21** is treated with the alcohol **22**, generally in presence of a base, so that eventually the activating group X is replaced by the OR'' moiety to form the ester **23**. In effect this reaction is an S_N process at a trigonal carbon center and may proceed *via* an addition-elimination (S_N2) or an elimination-addition (S_N1) sequence. In either case, the configuration with respect to the R''-O bonds retained and no ^{18}O exchange of this oxygen is observed[7]. X must be a good leaving group on one hand as in the aliphatic S_N reactions and, additionally, its electron donation to the carbonyl function must be minimized.

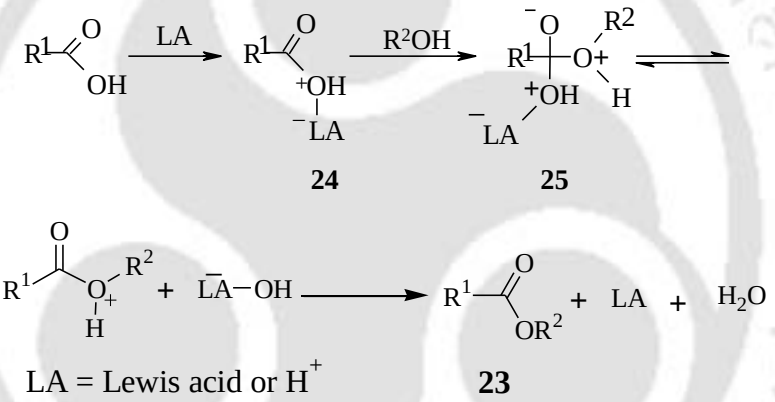


Scheme 1.7

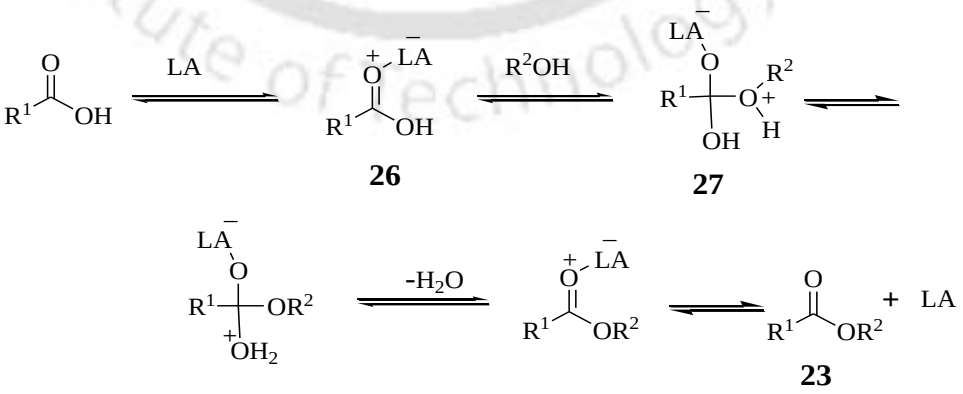
1.2.1 Direct condensation of carboxylic acid with alcohol

This method is basically atom economical and is by far the most general and the cheapest. Carboxylic acid and alcohol are mixed in a suitable solvent (toluene, dichloromethane, etc.) and treated with a Bronsted or Lewis acid. An equilibrium is formed between the starting materials, ester and water. To shift this equilibrium in favor of the products, the water can be removed by the water scavengers such as molecular sieves[8], $CaCl_2$[9] or $CaSO_4$[10] or by azeotropic distillation using Dean-Stark apparatus and soxlet thimble. If an inexpensive acid or alcohol is used, this component can be applied in excess. Acid-sensitive functional groups

in the reactants like acetals are not tolerated. Mechanistically this so-called 'Fischer-Spei esterification' proceeds via an $A_{AC}2$-type mechanism (A = acid catalysis, AC = acyl transfer, 2 = bimolecular). As shown in Schemes 1.8 and 1.9 the rate-determining step is the reversible attack of the alcohol at the carbonyl function of the activated species **24** and **26**. Two modes of proton (or Lewis acid) activation may be distinguished: either protonation of the OH function (Scheme 1.8) leading to **24** and **25**, or protonation of carbonyl oxygen (Scheme 1.9), leading to **26** and **27**. Although the first mechanism is generally formulated in the literature, the second mechanism appears for more plausible regarding the site of the initial protonation,[11] as well as the lesser degree of charge separation in the crucial intermediates **25** versus **27.**



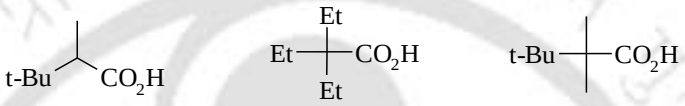
Scheme 1.8



Scheme 1.9

(i) Scope and limitations of the $A_{AC}2$ esterifications

The greatest advantage of the method lies in its simplicity; however, the rather severe conditions (extended heating in presence of mineral acid) make it questionable for sensitive substrates. Additionally, α- and β-branching in the carboxylic acid strongly retards the reaction, so that for example, acids **28**-**30** are too hindered to react. On the other hand, α- and β-branching in the alcohol induces dehydration.

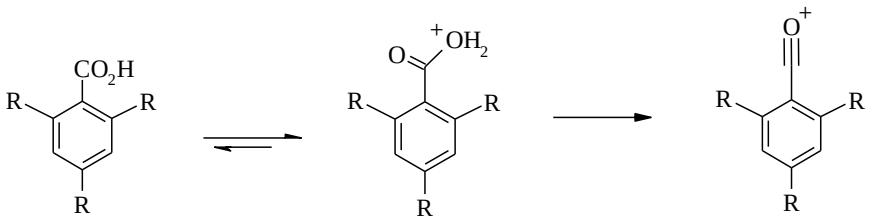


28 **29** **30**

Figure 1.3

(ii) The $A_{AC}1$ mechanism

This mechanism (A = acid catalyzed, AC = acyl transfer, 1 = unimolecular) is observed in the esterification of 2,4,6-trisubstituted benzoic acids with R groups of moderate +M effect. The $A_{AC}2$ mechanism is blocked by the steric interference of the ortho substituents. Therefore, the acylium cation **31** is generated with anhydrous sulfuric acid and then treated with the alcohol (scheme 1.10)[12]. R groups with strong +M effects, like methoxy, are not tolerable, as the aromatic nucleus undergoes sulfonation under these conditions. A variation of the $A_{AC}1$ mechanism for aliphatic acids is achieved by using the fluorides and antimony pentafluoride to generate the acylium ion **32**,[13] that reacts even with strongly hindered alcohols to form the esters (Scheme 1.11).



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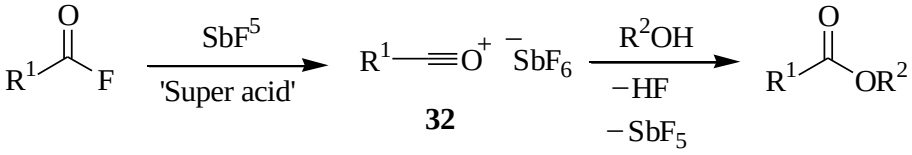
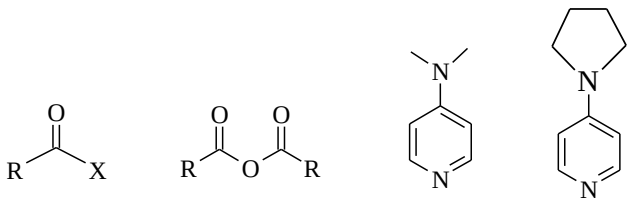
Scheme 1.10



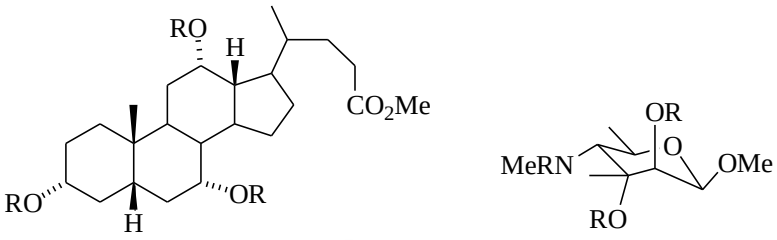
Scheme 1.11

1.2.2 Acyl transfer via anhydrides and acid chloride

In contrast to the A_{AC} esterifications this method makes use of preformed CGA species **33** and **34** to which the alcohol is added. The formation of acid chloride requires strong Lewis acids like thionyl or oxalyl chloride, which may react with acid sensitive functions in the molecule and also cause epimerization of chiral α-centers in the substrate molecule. On the other hand, using anhydrides **34** for esterification means to lose 1 mol equiv. of the acid. Thus both **33** and **34** should preferentially be used for inexpensive carboxylic acids with a low degree of functionalization. Typical and frequently encountered examples in multistep synthesis are benzoylation and acetylation of primary and secondary alcohols, whereas tertiary alcohols are generally too hindered to react, unless a strong base catalyst (*e.g.* calcium hydride)[14] is added. The acetylations are normally performed in pyridine at 1-2 ^{o}C. Acid catalysis is less common. Acid chlorides can be used in pyridine or in dichloromethane with triethylamine as the base. In any case, the anhydride should be preferred, as the reaction mixture remains almost neutral throughout the reaction and the yields are higher, particularly if the acylation is catalyzed with N, N-dimethyl aminopyridine (DMAP) **35** or, even better, 4-pyrrolidinopyridine (PPY) **36**.[15] Regular conditions are 0.05-0.2 mol equiv. of the catalyst in aprotic solvents (hexane, dichloromethane, THF, Pyridine) at room temperature. Rate enhancements compared to the uncatalyzed reactions are several powers of ten, so that even hindered hydroxyl functions **37** or **38** are smoothly acylated.



33 **34** **35** **36**



37 **38**

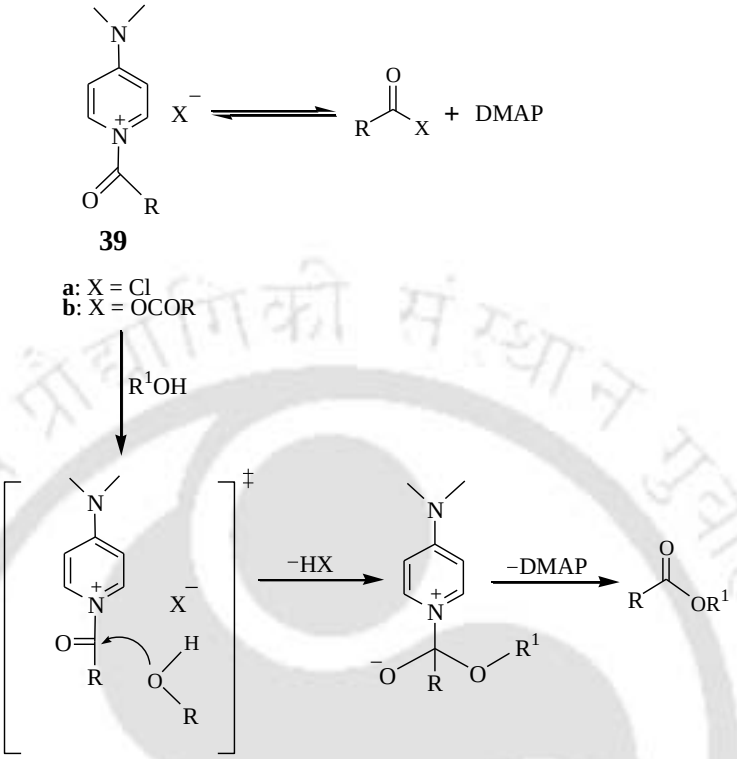
a: R = H
b: R = COMe

a: R = H;
b: R = COMe

Figure 1.4

1.2.2.1 Mechanistic aspects

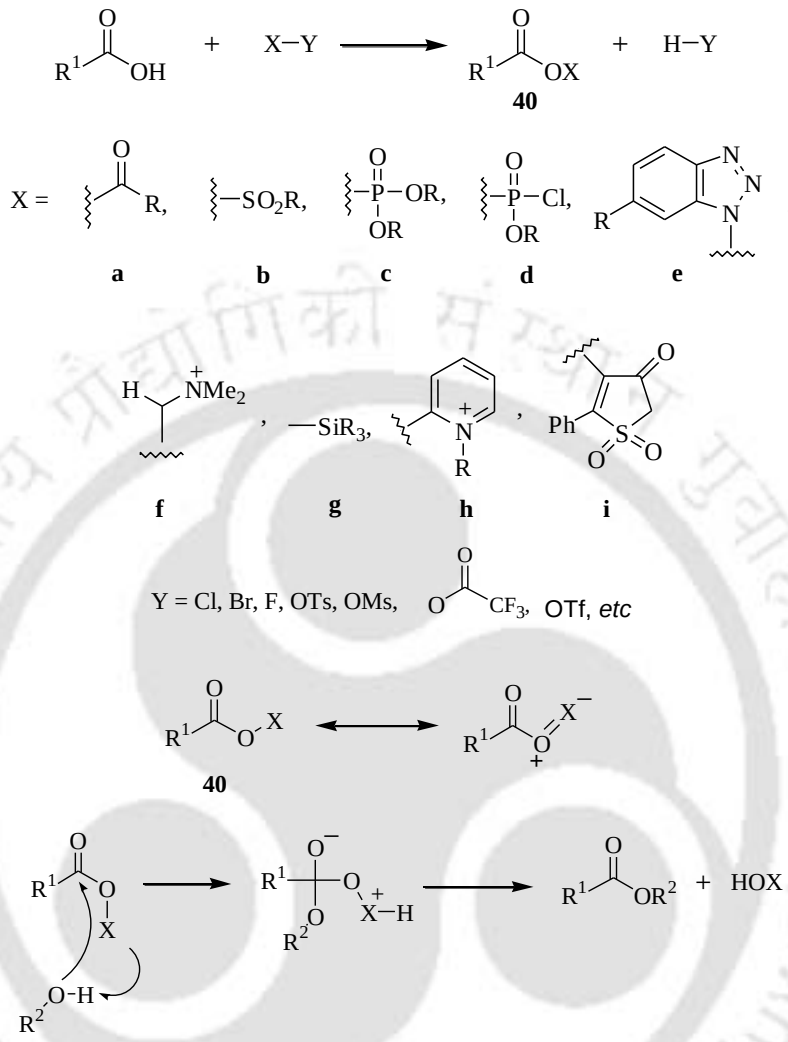
Mechanistically, the alcoholysis of acid chloride may proceed *via* a one step S_N2-like mechanism or more frequently, *via* the usual tetrahedral intermediate.[16] The reaction is accelerated by electron withdrawing substituents in the chloride and hardly affected by steric hindrance, on the other hand, benzoyl chlorides with electron-releasing substituents in the aromatic nucleus undoubtedly react via an S_N1-like mechanism, especially in protic solvents.[17] Anhydrides prefer the normal addition-elimination pathway, the rate-determining step being the formation of the tetrahedral intermediate. The drastic effect of the catalysts **35** and **36** may be attributed to the initial formation of the acyl pyridinium salt **39**, in which X^- serves as the base for the deprotonation of alcohol during it's nucleophilic attack on the carbonyl group (Scheme 1.12). This explains why acid chlorides show much smaller rate enhancements with **35** and **36** than anhydrides, although the equilibrium concentration of **39a** is much higher than that of **39b**. However, chloride is a much weaker base than the carboxylate and cannot remove the proton from the alcohol with similar efficiency. Additionally, x^- must be close to the reaction site, which means that **39** is more efficient an acylating agent as a contact than as a solvent-separated ion pair. In fact, the rates are much higher in nonpolar than in polar solvents.



Scheme 1.12

1.2.3 Acylation with mixed anhydrides and activated esters

This acylation process is of the utmost importance. In the first step, the carboxylic acid is treated with an activating agent X-Y to form the CGA species **40**, which acylates the alcohol in the second step. X is a substituent with a strongly electron withdrawing –I or –M effect and Y is a good leaving group. If X contains an acyl function, as in cases **a-d**, **40** is a mixed anhydride; otherwise, for instance in cases **e-i**, **40** is classified as an activated ester. In both types, the activating effect of X is two-fold ('double activation')[18] in facilitating the nucleophilic attack of the alcohol. The only difference between mixed anhydrides and activated esters lies in the fact that HOX corresponds to a carboxylic or inorganic proton acid in the case of the mixed anhydrides and to an (acidified) alcohol in the case of activated esters. As shown in Scheme 1.13, the electron-withdrawing character of X enhances the electropositive nature of the carbonyl carbon in **40**. The second, and equally important, effect



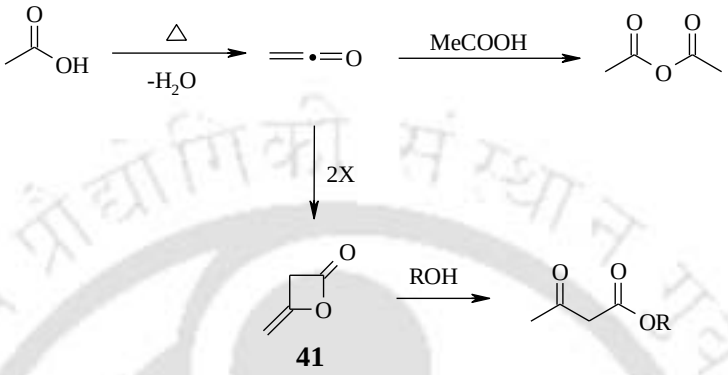
Scheme 1.13

is the ability of X to accept the proton from the alcohol. In this manner the effective nucleophilicity of the alcohol is drastically increased in the immediate proximity to the reactive center. Thus, **40** behaves very similarly to **39**, with the only difference that **40** is neutral and **39** is an ion pair. As an additional benefit of the proton transfer, the leaving group quality of the OX fragment is also greatly improved.

1.2.4 Acylation with ketenes

Ketenes are highly reactive acylating agents. However, they have found only limited application, as they are not as readily available as the other acylating agents described so far. The only exception is ketene itself, which is produced on a large scale industrially and is used

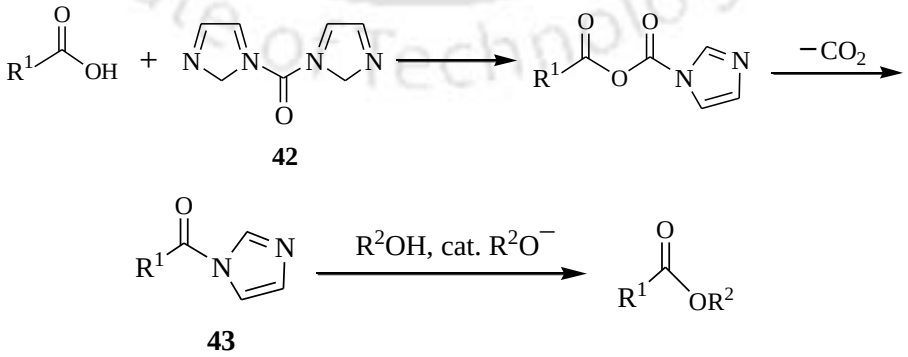
for the acylation of acetic acid to acetic anhydride.[19] A minor amount[19] of ketene is dimerized to diketene **41**, which is used to acylate alcohols to various esters of acetoacetic acid (Scheme 1.14).



Scheme 1.14

1.2.5Acylation with N-acylimidazoles

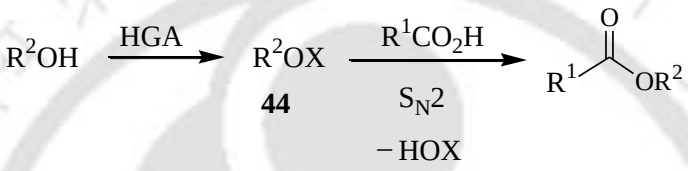
This method was introduced by Staab [20] and is suitable for the acylation of primary, secondary and tertiary alcohols. First the carboxylic acid is converted into the imidazolide **43** with carbonyldiimidazole **42**, and then the alcohol is added together with a catalytic amount of strong base (alkoxide). The ester is formed at room temperature within a few hours. If functional groups in the acid or alcohol prevent the use of base, the imidazole and the alcohol have to be heated to 70 ^{o}C for 1- 2 h.



Scheme 1.15

1.3 Esters from Carboxylic Acids and Alcohols *via* Hydroxyl Group Activation (HGA)

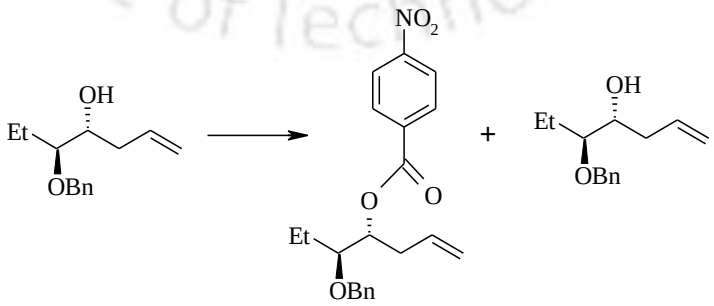
This type is a one-pot reaction with all components present from the beginning. The alcohol is first converted into an SN-activated (HGA) species **44**, which undergoes an OX displacement with the carboxylic acid to form the ester. Two methods are known to fit into this general scheme: the Mitsunobu reaction.[21]



Scheme 1.16

1.3.1 Mitsunobu reaction

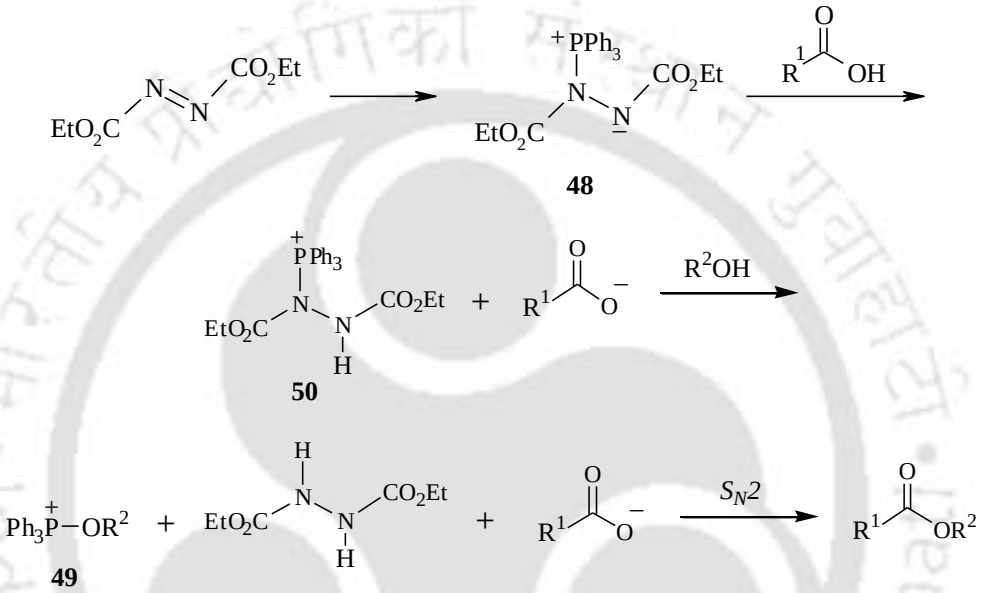
This method is unusually mild, using neutral conditions and low temperatures (20 ^{o}C and less). It tolerates a number of functional groups in the components (e.g. acetals, esters, alkenes, *etc*.). The alcohol, the carboxylic acid and triphenylphosphine are treated dropwise in an inert solvent (dichloromethane, THF, ether) with diethyl azodicarboxylate (DEAD). The ester is formed rapidly. However, tedious chromatography is frequently required to remove the by-products, triphenylphosphine oxide and hydrazo ester. The main value of the reaction



45 **46** **47**

Scheme 1.17

lies in the clean inversion of configuration at a secondary carbinol center and in its selectivity towards primary hydroxyl groups. Inversions are usually performed with benzoic or p-nitro-benzoic acid. The benzoates are purified and saponified with aqueous base to furnish the inverted alcohols in overall yields of *ca*. 50%. Elimination is the main side reaction. Thus,



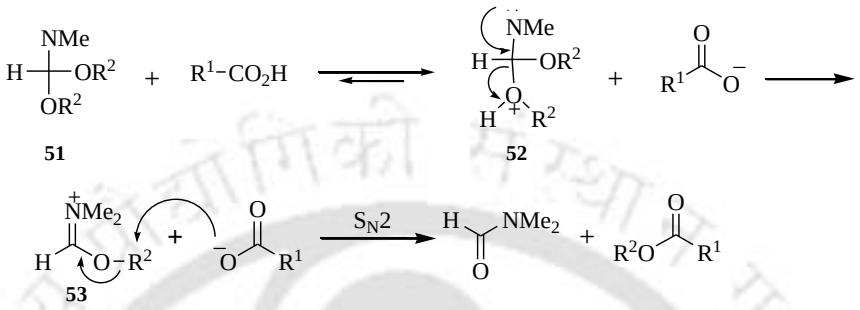
Scheme 1.18

from **45,** 75% of the desired S_N2 product **46** is formed, along with 25% of the elimination product **47 (**Scheme 1.17).[22] The mechanism of the reaction has been clarified to the point that betain **48** is the primary intermediate from which the triphenylphosphonium moiety is transferred to the alcohol from **50** to form the HGA species **49**. The rate-determining step is the final S_N2 reaction with the carboxylate (Scheme 1.18).[23]

1.3.2 Eschenmoser-Vorbrüggen reaction

In this reaction the carboxylic acid is heated together with formamidacetals **51** in an inert solvent (benzene). The products are the ester, DMF and alcohol R^2OH. Only S_N2 active R^2 groups like methyl, ethyl and benzyl can be transferred. Mechanistic studies have shown that the HGA species **53** is generated from **51** *via* elimination of R^2OH under proton donation

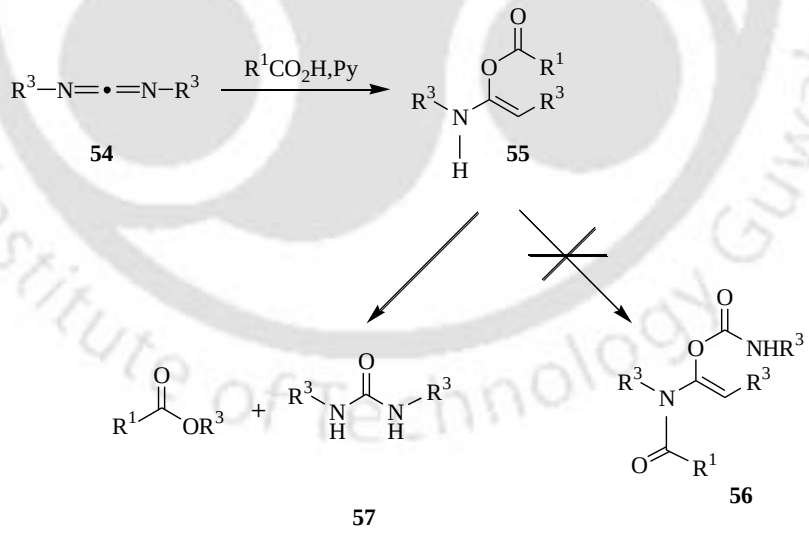
from the carboxylic acid. The carboxylate in turn undergoes an S_N2 displacement with **53** to form the ester and DMF.



Scheme 1.19

1.4 Carboxyl group activation method: the DCC Method

A reagent, which allows both CGA and HGA esterifications, is DCC (dicyclohexyl carbodiimide; **54**; R^3 = cyclohexyl). CGA esterifications can be accomplished by treating a

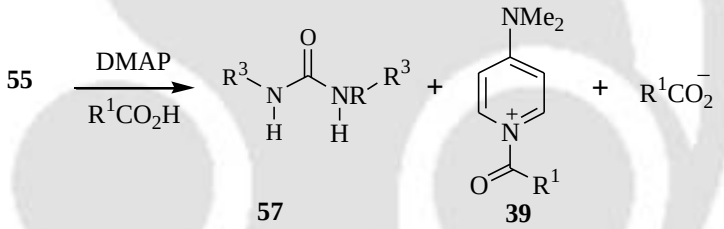


Scheme 1.20

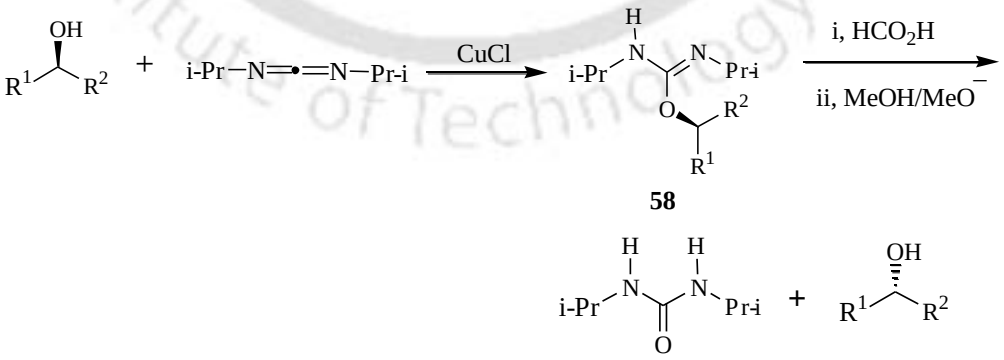
mixture of the carboxylic acid and the alcohol with DCC in hexane or pyridine with a catalytic amount of p-TsOH. The *O*-acylisourea **55** is postulated as intermediate, which reacts with the alcohol under elimination of the urea **57** and the formation of the desired ester. The urea is removed by filtration (Scheme 1.20).[24] This method is highly applicable if both the

carboxylic acid and the alcohol are valuable and bear sensitive functional groups. Numerous applications in natural products synthesis have been reported.[25]

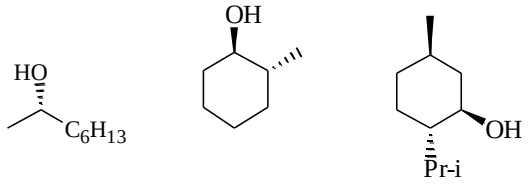
DMAP catalyzes the reaction most efficiently.[26] From **55** and excess carboxylic acid the ion pair **39** is formed, which then acts as the acylating species. However, the carboxylate is not wasted in this case, as it reacts immediately with **54** and is thus recycled.[27] Thus, the DCC method can also be used for acylations with symmetrical anhydrides and now both acyl moieties are used in esterification (Scheme 1.21).[27] The HGA variant is less common. To this end, the alcohol is first added to DCC under copper(I) catalysis to form the O-alkylisourea derivative **58**, which is isolated and treated with the acid to form the ester *via* S_N2 displacement.[28] In effect, this reaction constitutes an alternative to the Mitsunobu reaction. The carboxylic acid used for the inversion of secondary carbinols is formic acid: the formats are saponified with methoxide (Scheme 1.22). The inversion of carbinols **59-61** proceeds with high overall yields.[29]



Scheme 1.21



Scheme 1.22

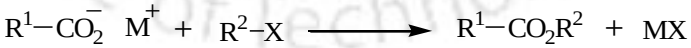


59 **60** **61**

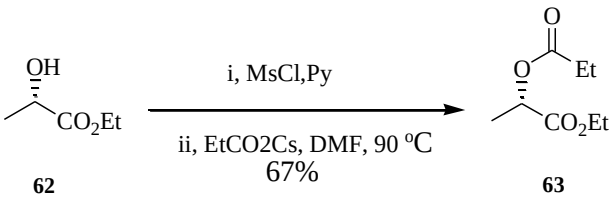
Figure 1.5

1.5 Alkylative Esterification

In this method the carboxylates are used in the form of sodium, potassium or cesium salts and are treated with alkyl bromides or iodides in DMF, hexamethylphosphoramide (HMPA), acetonitrile and/or water (Scheme 1.23). The alkylating agent must show high S_N2 reactivity. The advantage of the alkylative esterification lies in the neutral conditions under which acid sensitive functional groups can survive. Like the Mitsunobu reaction and CuCl-catalyzed DCC activation the alkylative esterification may be used for the inversion of configuration at secondary carbinol centers. For instance, lactic ester **62** is mesylated and then heated with cesium propionate in DMF[30]to give **63**; (Scheme1.24). Diazoalkanes **64** react with carboxylic acids under proton transfer to give the diazonium carboxylate **65,**[31] which collapses into the ester and nitrogen (Scheme 1.25). This method is the best for methylating sensitive carboxylic acids like **66**.[32] The extension to diazoalkanes other than diazomethane, however, has been prohibited by their poor availability and the potential danger in handling these compounds. An established procedure for preparing *t*-butyl esters is the treatment of carboxylic acids with isobutene and strong acid in aprotic solvents (Scheme 1.26).[33, 34]

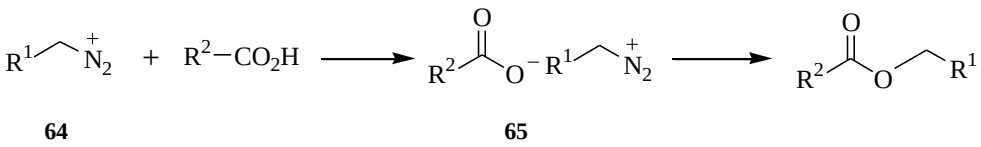


Scheme 1.23



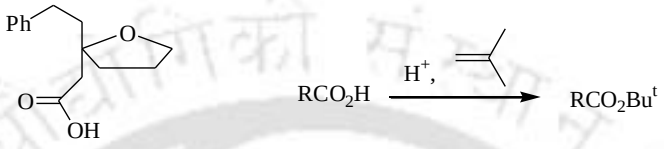
62 **63**

Scheme 1.24



64 **65**

Scheme 1.25



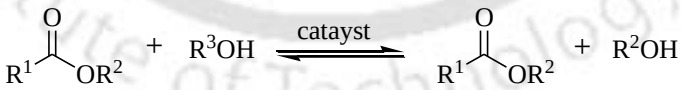
66

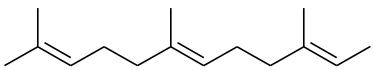
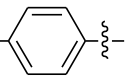
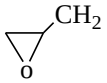
Scheme 1.26

1.6 Transesterification

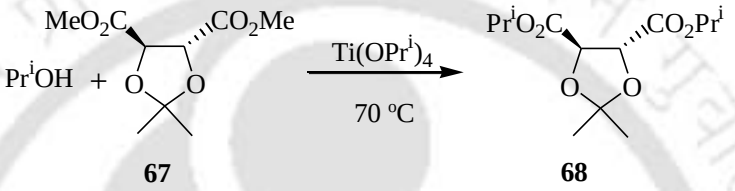
Transesterifications can, in principle, be performed by reaction of esters with alcohols, carboxylic acids and other esters. All three types are reversible, so that the equilibrium has to be shifted to the desired side either by applying an excess of the reagent or by removing a volatile product *via* distillation. In all cases acid or base catalysis is required. In laboratory practice the most common transesterification method is the reaction of valuable esters with an excess of a cheap alcohol under the catalysis of a mild base. Examples are given in Table 1.1.

Table 1.1: Transesterification of alcohols and esters



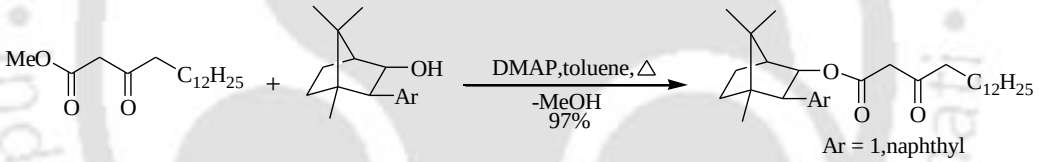
R^1	R^2	R^3	Catalyst	Yield(%)	Ref.
	Me	Et	KCN	85	37
C_6H_{13}	Me	Bu^t	Molecular sieves	83	38
MeO_2C– 	Me		TiCl	94	39

$Ti(OPr^i)_4$ has been recommended as an exceptionally mild and efficient transesterification catalyst.[35] Thus, the dimethyl ester **67** is cleanly converted into **68** without affecting the acetonide ring (Scheme 1.27). The alcohol need not necessarily be identical with the OR group in the titanate, as this exchange is slow compared to the transestefication itself. Transesterifications of β-keto esters are most efficiently catalyzed with DMAP, as illustrated by Scheme 1.28.[36]



67 **68**

Scheme 1.27

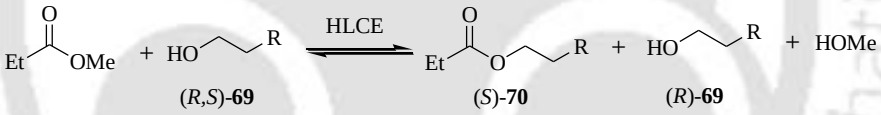


Scheme 1.28

1.7 Enzymatic Acylations and Deacylations

Enzymatic transacylations have received enormous attention in recent years.[40] The enzymes generally employed are lipases from microorganisms like Candida cylindracea, Rhizopus arrhizus or Chromo bacterium viscosum, or from mammalian liver, like porcine pancreatic lipase (PPL). Ester hydrolysis is normally performed in water, sometimes with organic solvents (acetone or acetonitrile) as additives, whereas the acylations are run as transesterifications or the alcohol with esters with the enzyme in organic solvents (ether, benzene). The enzyme may be used as a crude extract or in purified form, sometimes entrapped in sepharose or in chromosorb as a solid support. The great advantage of the enzymatic process lies in its high chemo- and stereo-selectivity. For example selective monoacetylations of the primary OH function in methyl furanosides of D-ribose, D-arabinose, D-Xylose and 2-deoxy-D-ribose with crude PPL in THF, using 2,2,2-trifluoroethyl acetate as

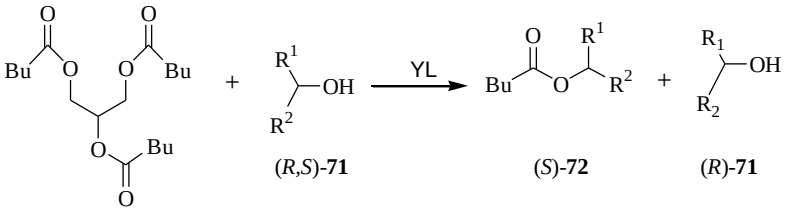
the acyl donor, have been reported.[41] Optical resolution of racemic mixtures of alcohols can be efficiently achieved by enzymatic acylations or transesterification. In the ideal case, only one enantiomer is reactive, the other remains unchanged. In this way a variety of γ-branched alcohols **69** have been resolved with high ee values in both the ester and the remaining alcohol (Scheme 1.29 and Table 1.2).[42] α-Branched alcohols have been resolved with similar efficiency (Scheme 1.30 and Table 1.3).[42] The enzymes used were HLCE (Hog Liver Carboxylate Esterase) and yeast lipase or sepharose or chromosorb in water and the acyl-donating ester as solvent. On the other hand, resolution of racemic α-halo carboxylic acids **73** with butanol can be effected with lipase (Scheme 1.31 and Table 1.4).[43] Applications of enzyme-catalyzed acyl transfer reactions, among many others, are the synthesis of the pheromone (S)-sulcatol **75** (Scheme 1.32)[44] and of (*R*)-glycidylbutyrate **76**, which serves as the starting material for the β-blocker propanolol **77**. Enzymatic esterification of racemic menthol **78** with hexanoic acid leads to optically pure ester (Scheme 1.33).[45]



Scheme 1.29

Table 1.2 Enzymatic Resolution of Alcohols by Transesterification with(HLCE)

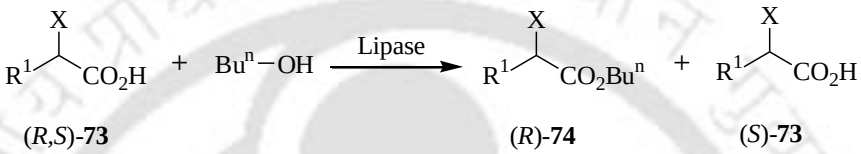
R	*% ee* (*S*)-**70**	(*R*)-**69**
CH(OMe)Me	98	—
CH(Me)Et	94	94
$CH(Me)(CH_2)_3CHMe_2$	95	97
$HC(Me)H_2CH_2CHC{=}CMe_2$	96	97



Scheme 1.30

Table 1.3 Enzymatic Resolution of Alcohols by Transesterification with YL

R^1	R^2	*% ee* (*S*)-(**72**)	(*R*)-(**71**)
Me	Et	98	97
Me	C_6H_{13}	98	89
H	$CHClCH_2Cl$	93	88

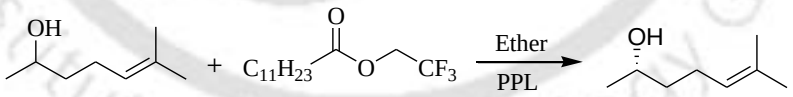


(*R*,*S*)-**73** (*R*)-**74** (*S*)-**73**

Scheme 1.31

Table 1.4 Enzymatic Resolution of Halocarboxylic Acids

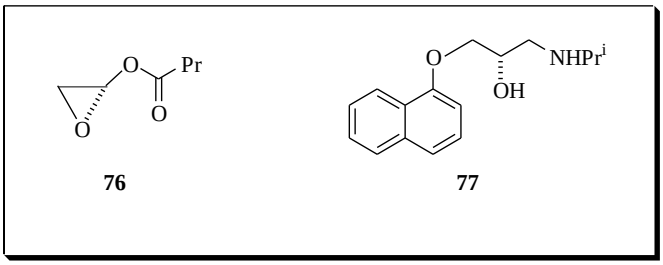
R^1	X	*% ee* (*R*)-**74**	(*R*)-**73**
Me	Br	96	99.6
Me	Cl	95	95
Bu	Br	99	62/73
Ph	Cl	99	—



(*R*,*S*)-**75** (*S*)-**75**

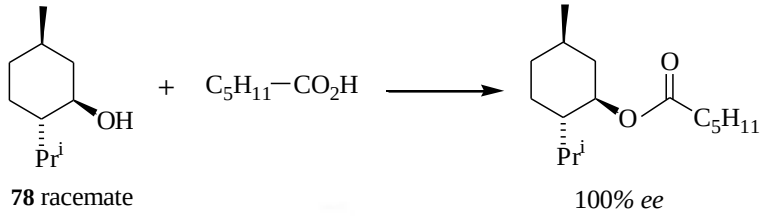
>97% *ee*

Scheme 1.32



76 **77**

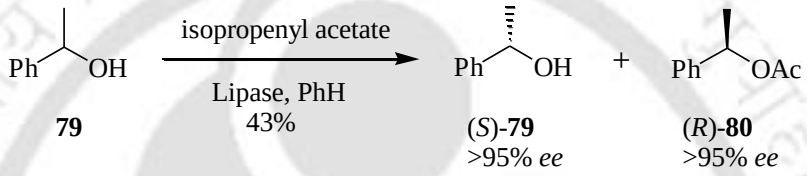
Figure 1.6



78 racemate

100% *ee*

Scheme 1.33

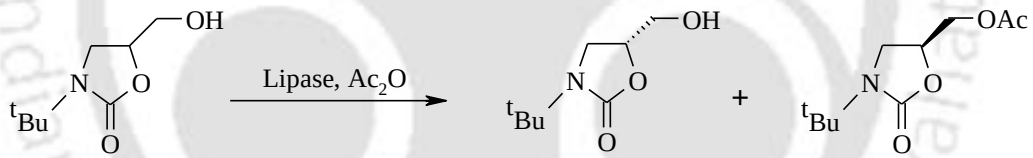


79

(*S*)-**79**
>95% *ee*

(*R*)-**80**
>95% *ee*

Scheme 1.34



81

(*R*)-**81**
>95% *ee*

(*S*)-(**82**)
>95% *ee*

Scheme 1.35

In contrast to the procedures described so far which all have to use a large excess of one component direct enzymatic acylation with isopropenyl acetate or acetic anhydride[46] requires only stoichiometric amounts of the reagents. Both acetate, **80** and **82**, and alcohol, **79** and **81** are obtained with high enantioselectivity.

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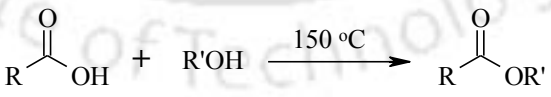
CHAPTER II

Potassium Fluoride Assisted Selective Acetylation of Alcohols with Acetic Acid

2.1 Introduction:

In general the acylation of alcohols can be achieved by treating alcohols with acid anhydrides or acid chlorides in the presence of stoichiometric amounts of amine bases such as tertiary amines,[1] 4-(dimethylamino)pyridine (DMAP) or 4-(1-pyrrolidino) pyridine (PPY)[2] and Bu_3P.[3] Acylation of alcohols can also be achieved under an acid catalyzed condition by treating alcohols with acid anhydrides in presence of protic acids[4] and Lewis acids.[5] Acylations using acid anhydrides work well, but the conversion is inherently wasteful since half of every acid anhydride molecule is lost as carboxylic acid utilizing only one acyl group for acylation. On the other hand acyl chlorides are equally efficient acylating agents but their use is restricted owing to their moisture sensitive, corrosive and lacrymating properties. The use of large amount of acylating reagents and activators should be avoided in order to promote Green chemistry and atom efficiency. To fulfill these requirements direct condensation of alcohols with carboxylic acids is the ultimate choice. But the direct condensation of carboxylic acids with alcohols is generally avoided because the equilibrium between the substrates and the products require the elimination of water from the reaction mixture using dehydrant or azeotropically to shift the equilibrium in favor of product. This has been achieved conventionally by condensing carboxylic acid and alcohol with one being in large excess to drive the reaction in forward direction.

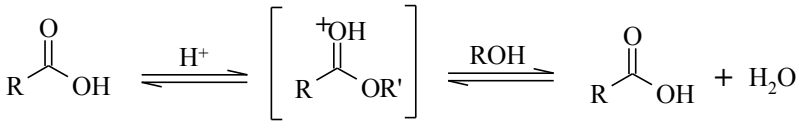
Maagerramov *et al.* have reported that this transformation can be effected by heating the alcohols and the acid in an autoclave without activatior [6] (Scheme 2.1).



R = alkyl, R' = propyl,hexyl

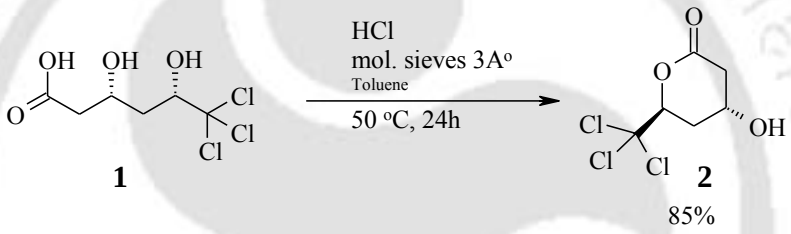
Scheme 2.1

When the substrates are acid resistant, the reaction is usually carried out in the presence of Bronsted acids[7] like HCl, HBr, H_2SO_4, $NaHSO_4$, $ClSO_4H$, NH_2SO_3, H_3PO_4, $ClSO_3H$, H_3PO_4, HBF_4, and camphorsulfonic acid (Scheme 2.2).



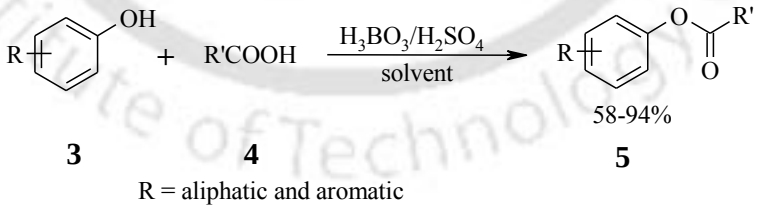
Scheme 2.2

In cases in which the acidity is not high enough to trigger the desired reaction, the acid is combined with an activator. For example, Shimizu *et al.*[8] have reported that the lactonization (Scheme 2.3) proceeds sluggishly with HCl only, but the reaction is effected smoothly in the presence of and 3A^{o} molecular sieves.



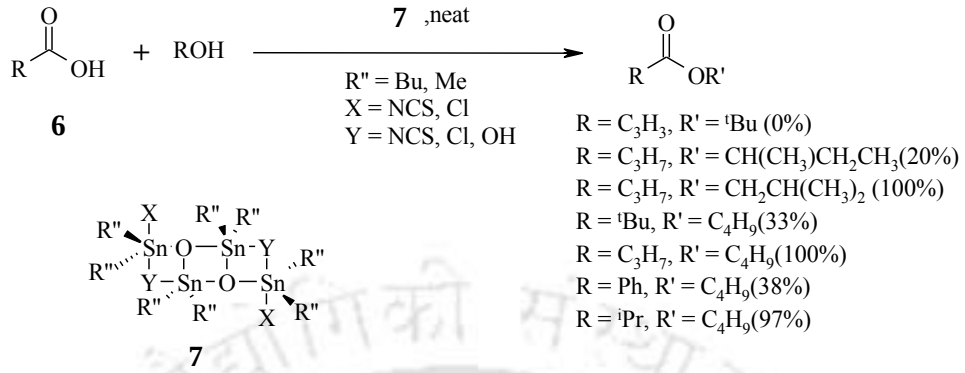
Scheme 2.3

The esterification of phenols **3** with both aliphatic and aromatic carboxylic acids **4** difficult to achieve under normal conditions can be catalyzed by a combination of H_3BO_3 and H_2SO_4 (Scheme 2.4)[9].



Scheme 2.4

The other methods to activate the acid catalysts are provided by the use of ultrasound[10] and microwaves.[11] Apart from Bronsted acid, a vast number of lewis acid have also been reported in the literature for this same transformation. Otera and coworkers[12] have reported that good yields of esters were obtained when carboxylic acids **6** are treated with 1,3-disubstituted tetraalkyldistannoxanes **7** in alcohol solvent (Scheme 2.5).

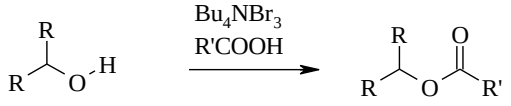


Scheme 2.5

Punniyamurthy and coworkers have reported that Cobalt(II)chloride hexahydrate ($CoCl_2.6H_2O$) efficiently catalyzed the acetylation of alcohol with AcOH in high yields. This protocol was also effective with other carboxylic acids, trifluoroacetic acid, propanoic acid, phenylacetic acid, and benzoic acid, affording the corresponding esters.[13] Kumar *et al.* have reported a simple and efficient method for the acylation of alcohols, amines and thiols using yttria-zirconia-based Lewis acid as catalyst and carboxylic acids as acylating agent. The reaction was found to be chemoselective for the amino alcohols, 2-mercaptoethanol, and 1,2-diol.[14]

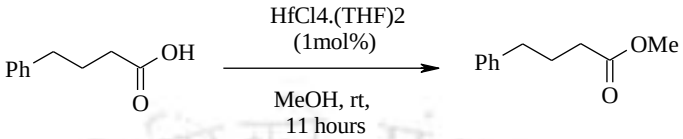
Choudary and coworkers have reported the acylation of alcohols and amines with anhydrides or acetic acid under novel heterogeneous media using Mn(III) salen complex.[15] Sharma *et al.* have reported a simple and efficient protocol for the conversion of alcohols, ethers, and ketals to acetates using catalytic amount of $FeCl_3$ (5 mol%) in AcOH or AcOH (3 equivalents) in CH_2Cl_2. A variety of other acids such as trifluoroacetic acid, formic acid, acrylic acid, propanoic acid and butanoic acids were utilized for this transformation.[16]

Patel and coworkers have reported the direct condensation of various carboxylic acids and alcohols at reflux temperature under solvent-free condition using a catalytic amount of tetrabutylammonium tribromide (TBATB) (Scheme 2.6).[17]



Scheme 2.6

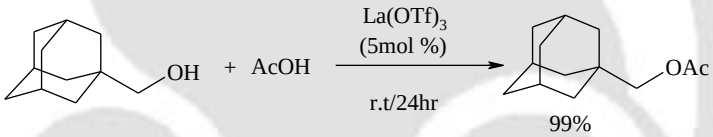
Yamamato and coworkers have reported that the water formed during the condensation of [18] carboxylic acid **8** with alcohol catalyzed by Hf(IV) and Zr(IV) salts can be removed azeo-



8 **9**

Scheme 2.7

tropically using Soxhlet thimble and calcium hydride or 4Å molecular sieves(Scheme 2.7). Barrett and coworkers have reported that the catalytic amount of $La(OTf)_3$, was sufficient for the the acylation of alcohols with acetic acid at room temperature.(Scheme 2.8).[19]



10 **11**

Scheme 2.8

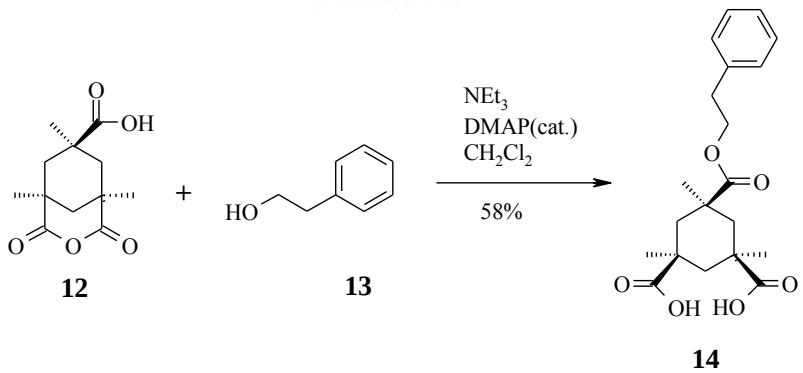
Besides these, several other reagents lewis acids accounting for this transformation includes $B(OH)_3$ [20], R_2SnO[21], diorgano tin chloride,[22] $Ce(OTf)_3$,[23] diphenylammoniumtriflate (DPAT),[24] triaryl bismuthanes,[25] $TiCl(OTf)_3$,[26] $TiCl_2(ClO4)_2$[27] and $Sc(OTf)_3$[28] CAN,[29] and $ZrOCl_2.8H_2O$[30], molecular iodine[31], $NiCl_2.6H_2O$,[32] and $Cu(OTf)_3$.[33]

Apart from Bronsted and Lewis acids, various solid acids are utilized for esterification, although the substrates that can be employed suffer from considerable limitations due to the strong acidity. Nevertheless, solid acids have a great advantage in that they can be removed from the reaction mixture by filtration and thus applied to large-scale production.

Mohan *et al.* have reported the zeolite Hβ is an efficient catalyst for the acylation of alcohols and amines with acetic acid under microwave irradiation. The process is environmentally safe and heterogeneous with excellent yields.[34]

Srivastava *et al.* have reported the application of ZSM-35, a medium pore zeolite, for the acylation of different amines, alcohols and bifunctional compds. This material is more

reactive for smaller organic compounds because of its pore dimension. Incase of bifunctional compounds like amino alcohols, amines are selectively acylated at a lower temperature.[35] Chakraborti *et al.* have reported that the fluoroboric acid supported on silica gel efficiently catalyzes acylation of structurally diverse phenols, alcohols, thiols, and amines under solvent free conditions. Acid-sensitive alcohols are smoothly acylated without competitive side reactions.[36] Sreedhar *et al.* have reported an efficient and selective acylation of alcohols and amines employing carboxylic acids as acylating agents. It was realized through the metal oxide containing activated carbon catalyst achieved by carbonization of organic ion-exchangers after incorporation of Fe^{3+}-ions with exchangeable cations present in resin.[37] Ikeda *et al.* have reported the esterification of *n*-butyric acid with *n*-butyl alcohol and transesterification of (R, S)-phenylethanol by lipase immobilized on cellulose acetate -TiO_2 gel fibre. Compared with native lipase, the activity of the immobilized lipase was stable and relatively unaffected by the water content of the solvent and the substrate concentration.[38] Other Solid acids include $K_5CoW_{12}O_{40}.3H_2O$,[39] montmorillonites clay,[40]and pillared clays,[41] amberlyst[42] nafion-H,[43] wolfatit KSP200,[44] Nb_2O_5. nH_2O, $NaHSO_4/SiO_2$,[46] and Ph_3SbO/P_4S_{10}.[47] Graphite bisulfate[48] have been reported to effect this transformation. Apart from acid-mediated reactions, base-mediated reactions to produce esters have also been reported. Generally the basic catalysts are not suitable for exstefication because esters are hydrolyzed when the reaction mixture is subjected to aqueous workup. Nonetheless, a few non-aqueous methods are available for highly functionalized substrates. ω-Hydroxy acids undergo lactonization upon exposure to KOH/KOMe/glycerin.[49] Another technique is provided by the use of DMAP. A Kemp's triacid derivative **12** is transformed into a monoester **14** by treatment with Et_3N / DMAP (cat.) (Scheme 2.9)[50]

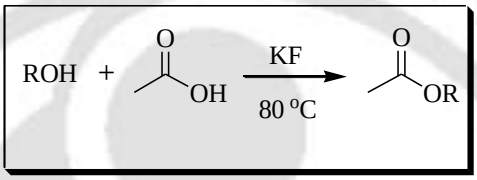


12 **13** **14**

Scheme 2.9

2.2 Results and Discussion:

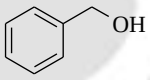
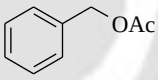
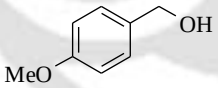
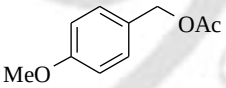
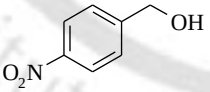
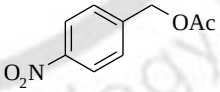
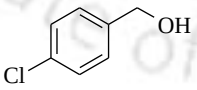
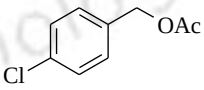
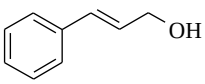
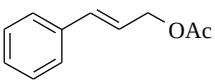
Potassium fluoride has long been used as a useful reagent in organic synthesis[51] for elimination of hydrogen halides, Michael addition, Knoevenagel condensation, fluorination on the organic substrates, decarboxylation, deprotecticon and cross coupling reactions. In this chapter[52] some of the results obtained from the acetylation of alcohols using easily available and cheap reagents such as KF and AcOH has been disclosed (Scheme 2.10).



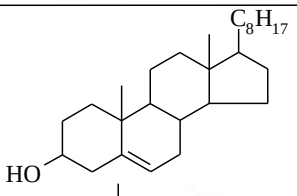
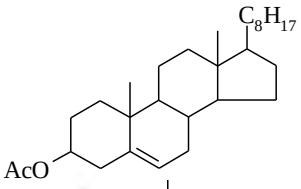
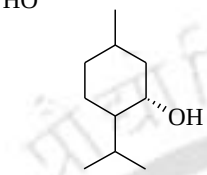
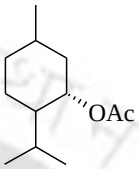
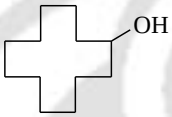
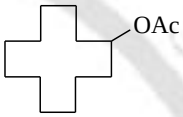
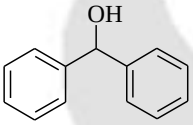
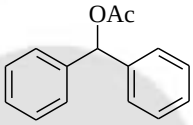
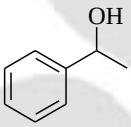
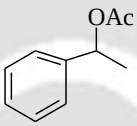
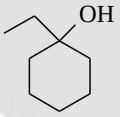
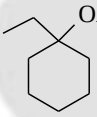
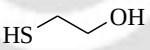
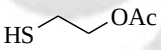
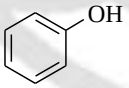
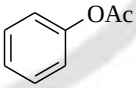
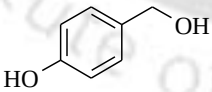
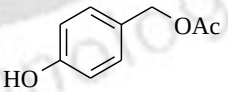
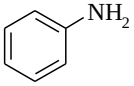
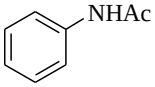
Where R = alkyl, aryl

Scheme 2.10

Table 2.1: Potasium fluoride assisted acdetylation of alcohols with acetic acid

Entry	Substrate	Time/h	Product	Yield[a](%)
1		1.5		98
2		1.5		97
3		3		94
4		2.5		96
5	$CH_3(CH_2)_8CH_2OH$	3	$CH_3(CH_2)_8CH_2OAc$	97
6	$CH_3(CH_2)_{14}CH_2OH$	3.5	$CH_3(CH_2)_{14}CH_2OAc$	92
7		2.5		97
8	$PhCH_2O(CH_2)_6OH$	3.5	$PhCH_2O(CH_2)_6OAc$	99

(a) The yields are isolated yields; The compounds are characterized by GC, ^{1}NMR, ^{13}CNMR and IR spectroscopy and by comparisons with the literature.

Entry	Substrate	Time/h	Product	Yield[a] (%)
9		5		97
10		7		95
11		6		93
12		7		94
13		5		98
14		9		41[b]
15		3		89
16		9		0
17		7		92
18		9		0

(a) The yields are isolated yields; The compounds are characterized by GC,^{1}NMR,^{13}CNMR and IR spectroscopy and by comparisons with the literature.
(b) Olefins are the byproducts

Under the reaction condition neither elimination nor fluorinated products were observed. The use of acetic acid rather than acetic anhydride or acetyl chloride is both economically and environmentally advantageous. The reaction is generalized through entries 1-18 (Table 2.1). It

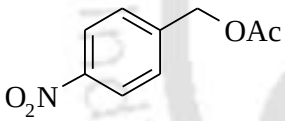
was observed that primary and secondary alcohols can be acetylated readily with a very high yield. It was observed that the protocol doesn't furnish either fluorinated products or elimination products as byproducts. This is attributed to the fact that the hydrogen bonding between fluoride ion and hydroxyl group of acetic acid reduces nucleophilicity and basicity of the fluoride ion. In the case of tertiary alcohol the reaction becomes sluggish and takes longer time with the formation of elimination products and the reaction ends up with a low yield (entry 14). This method display an extreme selectivity over alcohols which is evident from the result obtained in case of 4-Hydroxy benzyl alcohol where benzylic hydroxyl group alone gets acylatated while phenolic hydroxyl group remains unaffected. Similar result was obtained when 2-mercapto ethanol was subjected to this reaction condition. Sterically hidered secondary alcohols such as cholesterol, cyclododecanol, 1,1-diphenyl methanol also get acetylated smoothly. More importantly, the hydroxyl group residing in chiral center could be acetylated with retention of configuration, which was confirmed by comparison of the optical rotation of the acylated product with that of the literature value (entry10). The groups like double bond, chloro, nitro, methoxy, benzyloxy and thiol remain unaffected. Moreover, the reaction does not require any dry glassware and inert atmosphere. The operation is quite simple, because the dehydrating systems like Dean–Stark apparatus or agent like molecular sieve is not necessary. The purification process is very simple, as both potassium fluoride and acetic acid are water-soluble and final product does not require any tedious purification procedures. In conclusion we have developed a new, high yielding and selective methodology for the direct acetylation of primary and secondary alcohols with acetic acid and potassium fluoride. The ease of use of potassium fluoride, and low cost of both acetic acid and KF; and clean, easy work up of the product mixture makes this protocol important for both industrial and general purposes.

2.3 Experimental Section:

General: Melting points were uncorrected and recorded on a Buchi melting point apparatus. Substrates are prepared as per literature procedure. Solvents and reagents were dried and distilled before use. ^{1}H NMR spectra were recorded in $CDCl_3$ on 90 MHz (Varian EM 390), Bruker DRX-300 (300 MHz) and Varian AS 400 (400 MHz) spectrometer using TMS as internal standard. IR spectra were recorded on Nicolet Impact 410 FT-IR spectrometer as thin

films and KBr plate. GC analysis was done on HP 6890 Series GC System. Elemental analysis were performed on Perkin Elmer 2400 Series II CHNS analyzer.

Typical Experimental Procedure: In a typical reaction benzyl alcohol (0.35 g, 3.1 mmol), KF (0.22 g, 3.8 mmol) and acetic acid (5 mL) were heated at 80 ^{o}C in a round bottom flask. The reaction was monitored by TLC and GC. After completion (1.5 h) of the reaction, the reaction mixture was diluted with water (20 mL), and extracted with ethyl acetate (2x50 mL). The organic layer was washed with aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to dryness and finally purified by passing through a silica gel column to give benzyl acetate as an oil (0.45 g, 98%). Finally the compound is characterized by spectroscopic methods. **^{1}H NMR** (60 MHz, $CDCl_3$): δ 2.0 (s, 3 H, -O-CO-CH_3), 4.9 (s, 2 H, -CH_2-O-), 7.19 (m, 5 H, Ar H); **^{13}C NMR**: (100 MHz, $CDCl_3$): δ 170.8, 130.6, 128.9, 129.4, 126.7, 68.2, 21.3; **IR** (neat) : 3026, 1741, 1228, 1029 cm^{-1}.

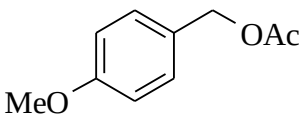


4-Nitrobenzyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3 H, -O-CO-CH_3), 5.20 (s, 2 H, O-CH_2-), 7.52 (d, *J*= 5.50 Hz, 2 H, ArH), 8.22 (d, *J*=5.62 Hz, 2 H, ArH).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 20.84, 64.68, 123.55, 128.14, 143.00, 147.40, 170.20.

IR (neat): 3098, 1741, 1516, 1347, 1244, 1055 cm^{-1}.

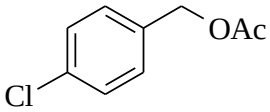


4-Methoxybenzyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3 H, -O-CO-CH_3), 3.80 (s, 3 H, O-CH_3), 5.04 (s, 2 H, -CH_2-O-), 6.88 (d, *J*=8.4 Hz, 2 H, -ArH), 7.30 (d, *J*=8.4 Hz, 2 H, -ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.96, 55.10, 65.94, 113.80, 127.80, 129.80, 159.28, 170.52.

IR (neat): 2950, 1736, 1516, 1245, 1173, 1040 cm^{-1}.

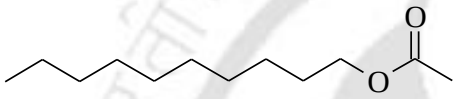


4-Chlorobenzyl acetate

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.95 (s, 3 H, -O-CO-CH_3), 4.8 (s, 2 H, -CH_2-O-), 7.0 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): □ δ 20.9, 65.4, 128.7, 129.6, 134.1, 134.4, 170.7.

IR (neat): 2960, 1746, 1495, 1383, 1234, 1096, 1014 cm^{-1}.



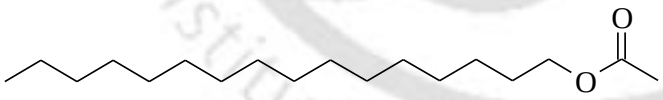
Decyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.6-1.5 (brs, 19 H, 8-CH_2-, -CH_3), 1.95 (s, 3 H, O-$COCH_3$), 3.85 (t, *J*= 6.40 Hz, 2 H, -OCH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 20.96, 22.74, 26.00, 28.72, 29.33, 29.60, 31.95, 64.58, 170.76.

IR (neat): 2927, 2859, 1742, 1243, 1098, 1039 cm^{-1}.

Anal. Calculated for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.78; H, 12.26.

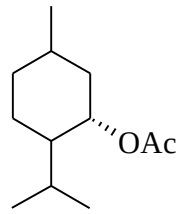


Hexadecyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.3 Hz, 3 H, -CH_3), 1.26 (m, 26 H, 13-CH_2-), 1.62 (m, 2 H, -CH_2-), 2.05 (s, 3 H, O-$COCH_3$), 4.05 (t, *J*= 6.90 Hz, 2 H, -OCH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.17, 20.73, 22.28, 25.70, 28.40, 29.10, 29.13, 29.30, 29.44, 31.69, 64.33, 170.64.

IR (neat)**:** 2924, 2853, 1747, 1465, 1373, 1240, 1040 cm^{-1}.



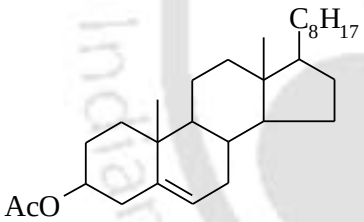
(1S)-2-isopropyl-5-methylcyclohexyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (d, *J*=6.9 Hz, 3 H, -CH_3), 0.90 (d, *J*=7.2 Hz, 6 H, 2-CH_3), 1.00-1.90 (m, 9 H, 3-CH-, 3-CH_2-), 2.09 (s, 3 H, -$OCOCH_3$), 4.67 (dt, *J*=10.8 and 4.5 Hz, 1 H, O-CH-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.42, 20.73, 21.26, 22.00, 23.55, 26.34, 31.37, 34.28, 40.93, 46.98, 73.98, 170.20.

IR (neat): 2955, 1741, 1244, 1029 cm^{-1}.

$[\alpha]_D^{25}$ –79.45 ^{o} (c 1.6g/100mL, $CHCl_3$)[lit.[53] $[\alpha]_D^{20}$ –80.5 ^{o} (c 2g/100mL, $CHCl_3$)].



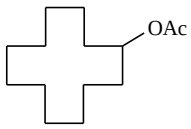
Cholesteryl acetate

M.p = 112-114 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3 H, -CH_3), 0.86 (d, *J*=4.4 Hz, 6 H, 2-CH_3), 0.91 (d, *J*=4.6 Hz, 3 H, -CH_3), 1.00 (s, 3 H, -CH_3), 1.20-1.80 (m, 26 H, -CH_2-, -CH-), 2.03 (s, 3 H, O-$COCH_3$), 2.30 (d, *J*= 5.06 Hz, 2 H, -CH_2-), 4.60 (m, *J*=4, 1 H, -O-CH-), 5.37 (m, 1 H, -CH=C-).

^{13}C NMR (400MHz, $CDCl_3$): 12.21, 19.1, 19.64, 21.42, 21.42, 21.6, 22.96, 23.2, 24.3, 24.65, 28.13, 28.3, 28.63, 32.21, 32.25, 36.23, 36.6, 36.9, 37.4, 38.5, 39.91, 40.12, 42.6, 50.4, 56.9, 57.04, 122.9, 139.9, 170.3.

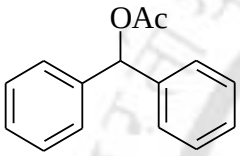
IR (KBr) : 2955, 1741, 1470, 1372, 1255, 1045 cm^{-1}.



Cyclododecyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-1.54 (m, 18 H, 9-CH_2-), 1.71(m, 4 H, 2-CH_2-), 2.04 (s, 3 H, -$OCOCH_3$), 5.0 (m,1 H, -O-CH-).

IR (neat) : 2934, 1741, 1475, 1239, 1024 cm^{-1}.



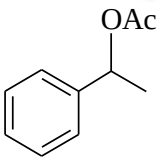
1-Acetoxy-1, 1-diphenyl-methane :

M.p = 42 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3 H, O-CO-CH_3), 6.88 (s,1 H, O-CH-), 7.31 (m, 10 H, 2 ArH).

^{13}C NMR (100MHz, $CDCl_3$): δ □21.2, 68.3, 127.0, 127.8, 128.4, 140.1, 169.9.

IR (KBr) : 3042, 1741, 1377, 1239, 1025 cm^{-1}.

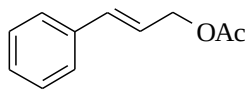


1-Phenylethyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (d, *J*=6.30 Hz, 3 H, -CH_3), 2.07 (s, 3 H, O-CO-CH_3), 5.9 (q, J= 6.6 Hz, 1 H, O-CH-), 7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): □ δ 21.3, 22.2, 72.3, 126.0, 127.8, 128.4, 141.6, 170.3.

IR (neat): 2986, 1747, 1378, 1240, 1066 cm^{-1}.

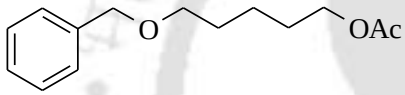


Cinnamyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 3 H, -O-$COCH_3$), 4.72 (d, *J*=6.30Hz, 2 H, O-CH_2-), 4.05 (dt, *J*=12.90 and 6.60 Hz, 1 H, -CH-), 6.64 (d, *J*=15.90 Hz, 1 H, -CH-); 7.31 (s, 5 H, -ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.00, 65.00, 122.98, 126.41, 127.86, 128.40, 133.98, 135.98, 170.53.

IR (neat): 3032, 2996, 2940, 2873, 1736, 1454, 1352, 1244, 1029 cm^{-1}.

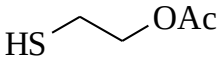


5-(benzyloxy)pentyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (m, 2 H, -CH_2-), 1.62 (m, 4 H, 2-CH_2-), 2.04 (s, 3 H, -O-$COCH_3$), 3.47 (t, *J*=6.30Hz, 2 H, O-CH_2-), 4.05 (t, *J*=6.6Hz, 2 H, O-CH_2-); 4.50 (s, 2 H, -CH_2Ph), 7.30 (s, 5 H, -ArH).

^{13}C NMR (300 MHz, $CDCl_3$): 171.2, 138.5, 128.3, 127.6, 127.5, 72.9, 70.1, 64.5, 29.12, 28.41, 22.67, 20.98.

IR (neat) : 2930, 2853, 1737, 1240, 1096, 1061, 1030 cm^{-1}.

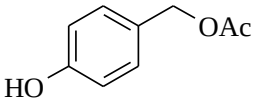


2-Acetoxy ethane thiol:

Oil

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, O-CO-CH_3), 2.75 (dt, *J*=9.00 and 6.00 Hz, 2 H, S-CH_2-), 4.19 (t, *J*=6.6 Hz, 2 H, -CH_2-).

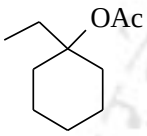
IR (neat) **:** 2542, 1741, 1377, 1239, 1025 cm^{-1}.



4-Hydroxybenzyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3 H, -O-CO-CH_3), 5.03 (s, 2 H, -CH_2-O-), 5.43 (br, 1 H, OH), 6.82 (d, *J*=8.80 Hz, 2 H, ArH), 7.25 (d, *J*=8.80 Hz, 2 H, ArH).

IR (neat): 3406, 2955, 1716, 1516, 1235, 1030 cm^{-1}.



1-Ethylcyclohexyl acetate

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 6 H, 2-CH_3), 1.25-1.41(m, 11 H, 1-CH-, 5-CH_2-), 2.16 (s, 3 H, -OCOCH_3).

IR (KBr) **:** 2929, 1736, 1459, 1275, 1131, 1070 cm^{-1}.

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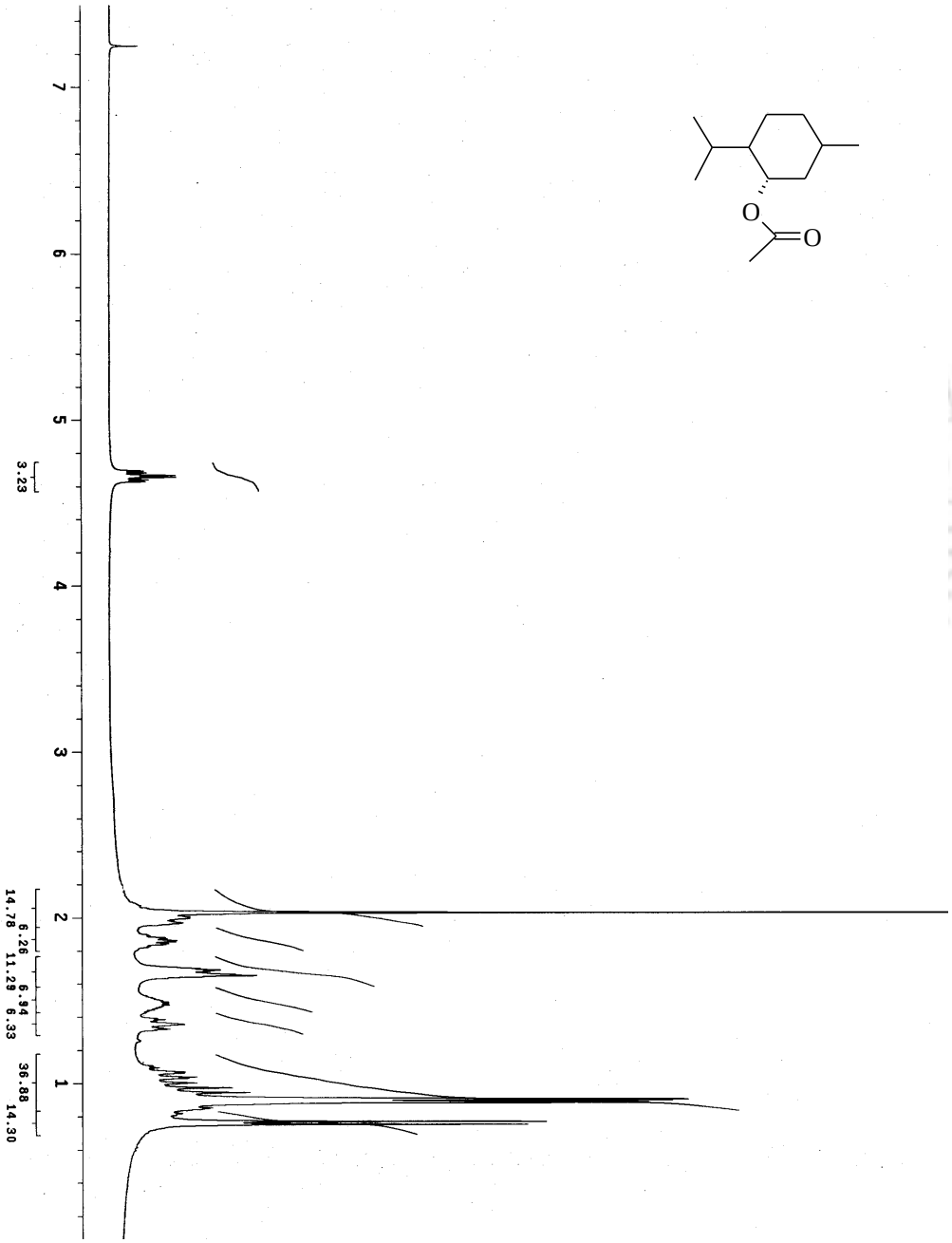
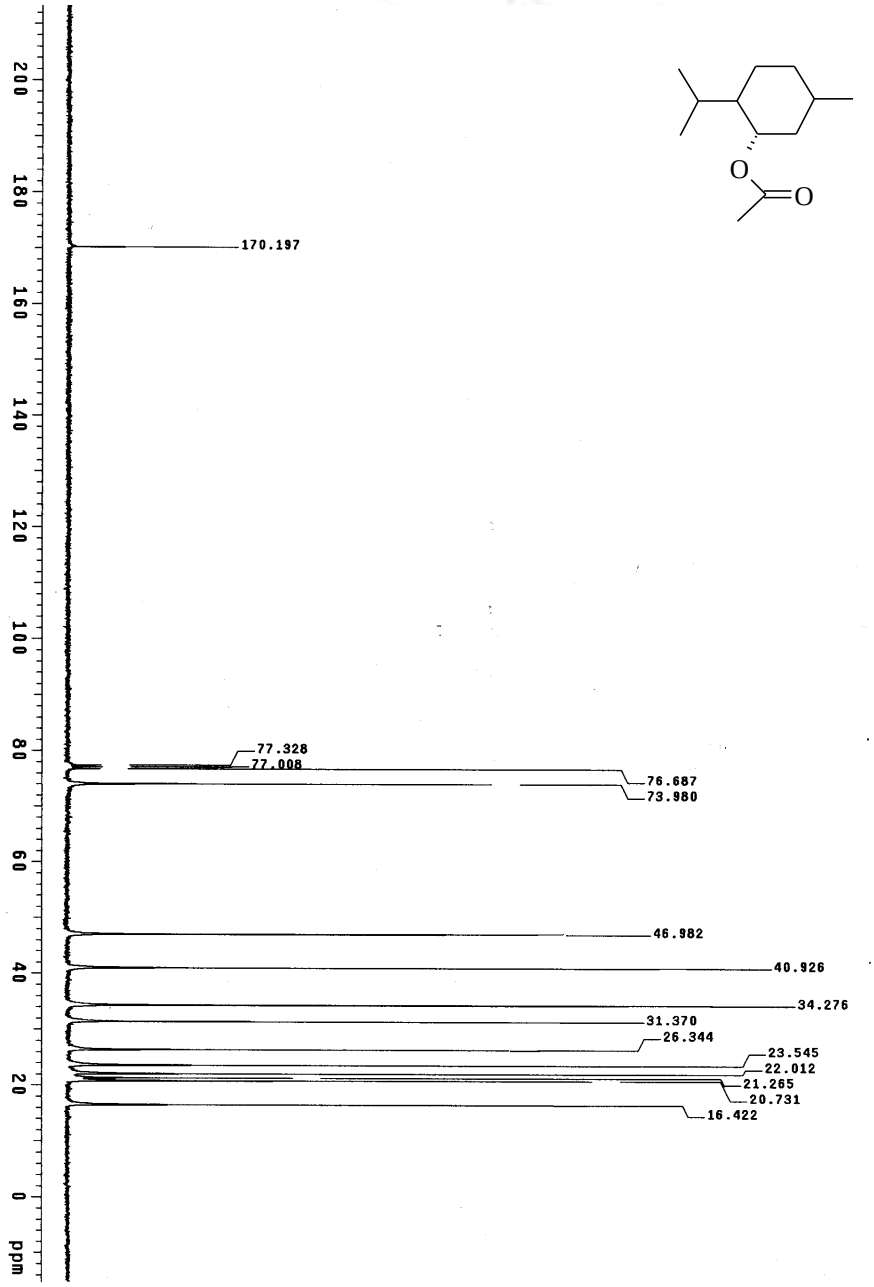
^{1}H NMR (400 MHz, $CDCl_3$): Menthyl acetate





^{13}C NMR (400 MHz, $CDCl_3$): Menthyl acetate

2.4 References

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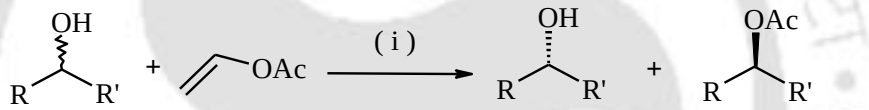
Chapter III

Transesterification with vinyl Acetate

3.1 Introduction:

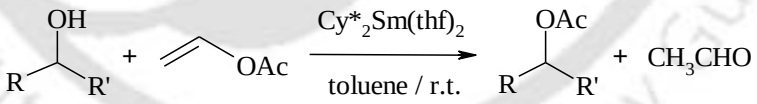
Transesterification with esters is an alternative method for the acetylation of alcohols under mild conditions, but due to the reversibility high yields cannot be achieved. In this connection vinyl acetate is a reagent of choice, since the resultant enolate is converted to acetaldehyde, which is unable to participate in the reverse reaction. Several approaches towards the transformation of alcohols to acetates using vinyl acetate **2** are known. Among these the use of Enzymes (Scheme 3.1),[1] $Cy^*_2Sm(thf)_2$ (Scheme 3.2)[2] distanoxanes,[3] iminophosphoranes,[4] *N*-heterocyclic carbenes,[5] TsOH or conc. H_2SO_4[6] and Et_2Zn[7] have been reported. However, the use of expensive and toxic metal precursors is a serious concern in the aspect of green chemistry. *N*-Heterocyclic carbenes are quite effective, but they are difficult to prepare. Hence, there is a need to develop for more efficient methods and reagents as catalysts.



1 **2** **3:** 45%, 91% ee **4:** 47%, >98%

conditions : (i) Pseudomonas fluorescens Lipase, vinyl acetate, r.t, 24 h

Scheme 3.1



Where R=R'=H, alkyl, aryl

Scheme 3.2

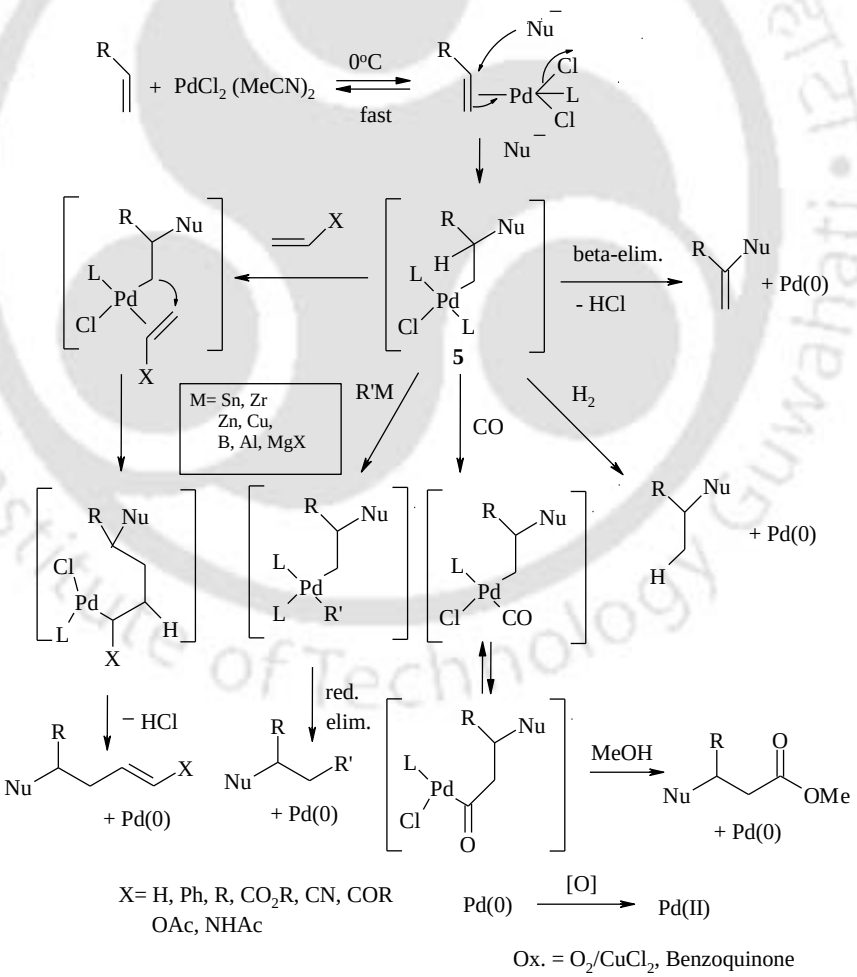
3.2. Palladium(II)Chloride catalyzed selective acetylation of alcohols with vinyl acetate

3.2.1 Palladium (II) in organic synthesis

Since palladium(II) species is electrophilic, electron rich olefins reversibly complex with Pd(II) species and give π-olefin Pd(II) intermediate (I) which activates the olefin and makes it susceptible for the nucleophilic attack. The nucleophilic attack on the olefin produces a new

carbon-nucleophile bond and a new palladium-carbon σ-bond. This unstable (usually) σ-alkyl palladium(II)intermediate **5**, furnishes different products when it is exposed to different reaction conditions (scheme 3.4). All these reaction of σ-alkylpalladium(II)complexes produce Pd(0) in the final step, while Pd(II) is required to activate the olefin for the first step (nucleophilic attack). Thus, for catalysis, Pd(0) must be reoxidized to Pd(II) in the presence of substrate, nucleophile and product. A wide array of oxidants, including O_2-$CuCl_2$, $K_2S_2O_8$, H_2O_2, benzoquinone and $FeCl_3$ are available.

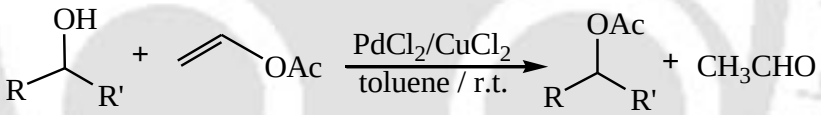
Palladium chloride has long been used as a useful reagent for various organic reactions such as oxidation of olefins,[8] Cope rearrangement,[9] cyclization reaction,[10] and deprotection of allyl ethers.[11]



Scheme 3.4

3.2.2 Results and discussion:

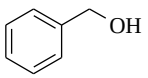
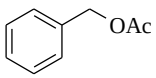
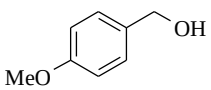
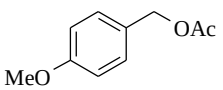
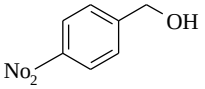
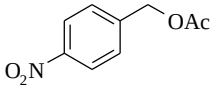
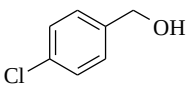
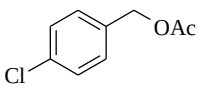
In this chapter[12], for the first time, the palladium(II) chloride catalyzed acetylation of alcohols with vinyl acetate is described. It was reported that vinyl acetate reacts with lower aliphatic alcohols in the presence of palladium(II) catalyst to give vinyl ethers.[13-15] To our surprise, when a mixture of vinyl acetate, alcohol and catalytic amounts of $PdCl_2$ and $CuCl_2$ was allowed to stir in dry toluene at room temperature, acetate was obtained in high yields (Scheme 3.5). The reaction was generalized as through entries 1–18 (Table 3.1). It was observed from Table 3.1 that reaction proceeds more rapidly with primary alcohols than secondary. Sterically hindered secondary alcohols like menthol need 2 mol% of the catalyst. Tertiary alcohols, phenols, thiols, aliphatic and aromatic amines are unaffected under these reaction conditions. With amines a palladium complex is formed. When acetic anhydride was used instead of vinyl acetate only a trace amount of the substrate **2** was converted to acetate after 3 hours. On the other hand, there were no reactions of ethyl acetate and acetic acid with

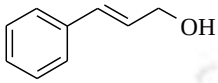
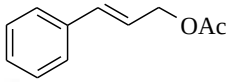
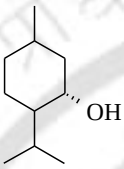
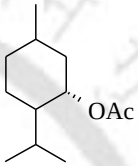
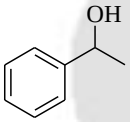
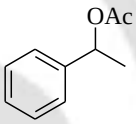
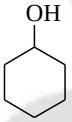
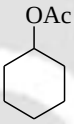
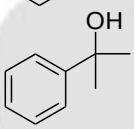
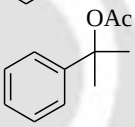
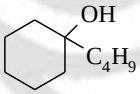
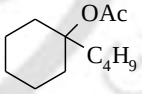
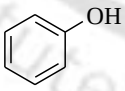
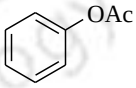
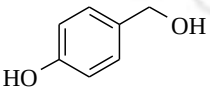
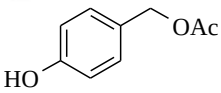
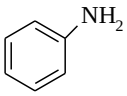
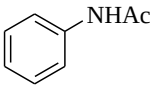


Where R=R'=H, alkyl, aryl

Scheme 3.5

Table 3.1: Palladium(II) chloride catalyzed selective acetylation of alcohols with vinyl acetate

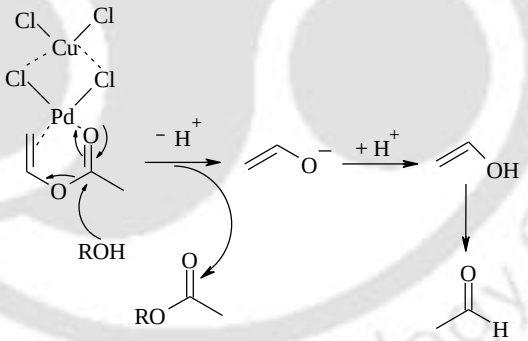
Entry	Substrate	Time(h)	Product	Yield(%)[a]
1		3.5		96
2		3		93
3		3		0
4		4		94

Entry	Substrate	Time(h)	Product	Yield(%)[a]
5	$CH_3(CH_2)_8CH_2OH$	3.5	$CH_3(CH_2)_8CH_2OAc$	84
6	$CH_3(CH_2)_{14}CH_2OH$	3.5	$CH_3(CH_2)_{14}CH_2OAc$	0
7		2.5		97
8	$PhCH_2O(CH_2)_6OH$	6	$PhCH_2O(CH_2)_6OAc$	82
10		7		95
11		5		98
12		3.5		89
13		9		0
14		9		0
15		9		0
16		4		86
17	$HSCH_2CH_2OH$	3	$HSCH_2CH_2OAc$	95
18		9		0

a.Yields refer to isolated yields.

2 under the same reaction conditions. It was observed that $PdCl_2$ alone is not a good catalyst and the reaction is accelerated by the addition of $CuCl_2$. When $CuCl_2$ was used as a catalyst only a trace amount of acetate was formed after 12 h.

This reaction proceeds through transesterification in which the metal activates the vinyl acetate by interacting with the olefinic moiety and the carbonyl group of the vinyl acetate and makes the carbonyl group more susceptible for the nucleophilic attack (Scheme 3.6). The role of copper chloride still remains unclear. But an obvious change in the reaction progress in the presence of $CuCl_2$ and in the absence of $CuCl_2$ was observed. Moreover, the brown color of the anhydrous $CuCl_2$, persists throughout the reaction progress and persists even during water work up. But when the reaction mixture is exposed to sodium bicarbonate solution, the characteristic blue color of hydrated copper chloride is retained. These observations suggest that copper chloride might have combined with palladium chloride and furnished a species which is stable to water but sensitive to base. With reference to the structure of the active species (Figure 30) proposed by Takahiro *et al.*[16] the species shown in Scheme 3.6 is assumed.



Scheme 3.6

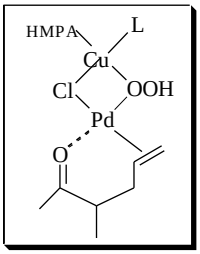
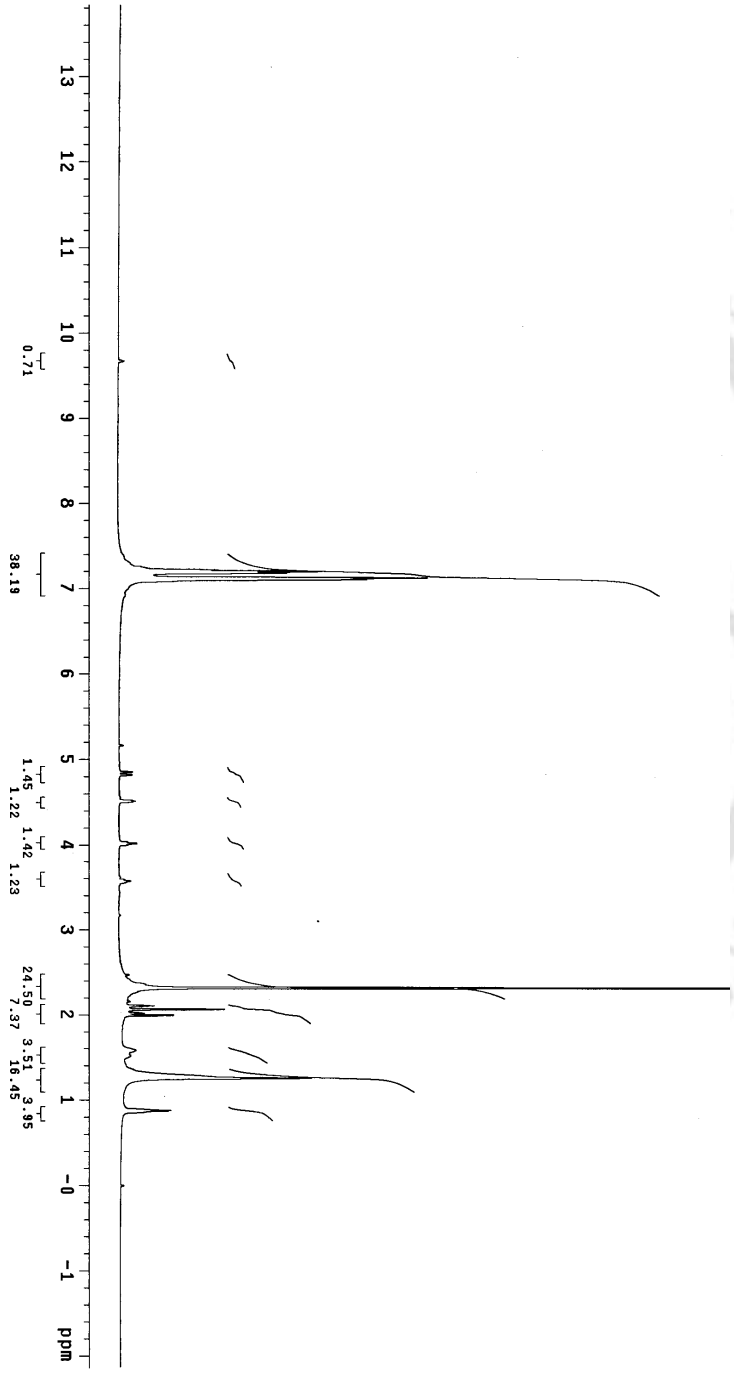


Figure 3.0

The formatuion of acetaldehyde that is detected by ^{1}H NMR (400 MHz) in the crude reaction mixture (Figure 3.1) supports the reaction mechanism.



^{1}H NMR (400 MHz, $CDCl_3$): Crude reaction mixture (decanol + vinyl acetate + $PdCl_2$ + $CuCl_2$ + toluene)

Figure 3.1

This type of catalytic transesterification seems to be of interest; since acetylation of alcohols with acetyl chloride or acetic anhydride in the presence of base resulted in side products. It is important to note that even 0.3 mol% palladium catalyst is enough for this transformation. Moreover further extention of this method can be applicable in non-enzymatic kinetic resolution of alcohols. In conclusion, an efficient catalytic acetylation method using vinyl acetate as the acetylating agent under mild conditions has been developed. A variety of primary and secondary alcohols were acetylated in good yields under mild conditions. Groups such as methoxy, benzyloxy, thioether, thiol, chloro, and phenolic hydroxyl are unaffected under these reaction conditions. As the catalyst is heterogeneous, the work up process is very simple. The catalyst can be recovered by filtering the reaction mixture. The only byproduct acetaldehyde can be removed by evaporation along with the solvent. This catalytic acetylation of alcohols offers an additional method by use of vinyl acetate, instead of acetic anhydride or acetyl chloride, as acetylating agent under mild conditions.

3.2.3 Experimental Section:

General experimental procedures: A mixture of p-methoxybenzyl alcohol, **2** (300 mg, 2.17 mmol), vinyl acetate (373 mg, 4.35 mmol), $PdCl_2$ (0.3 mol %, 1.1 mg, 0.0065 mmol) and $CuCl_2$ (23 mg, 0.17 mmol) in dry toluene (1.0 mL) was stirred at room temperature for 3 h. The reaction was monitored by TLC using ethyl acetate and hexane (9:1) as eluent. After completion of the reaction the catalyst was removed by fitration and the filtrate evaporated to dryness. Finally the product was purified by column chromatography (Silica gel; EtOAc: Hexane; 1: 9) to give 364 mg (93%) of the pure product. The compound was characterized by spectroscopic methods. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3 H, -O-CO-CH_3), 3.80 (s, 3 H, O-CH_3), 5.04 (s, 2 H, -CH_2-O-), 6.88 (d, *J*=8.4 Hz, 2 H, -ArH), 7.30 (d, *J*=8.4 Hz, 2 H, -ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.96, 55.10, 65.94, 113.80, 127.80, 129.80, 159.28, 170.52; IR (neat): 2950, 1736, 1516, 1245, 1173, 1040 cm^{-1}.

3.2.4 References:

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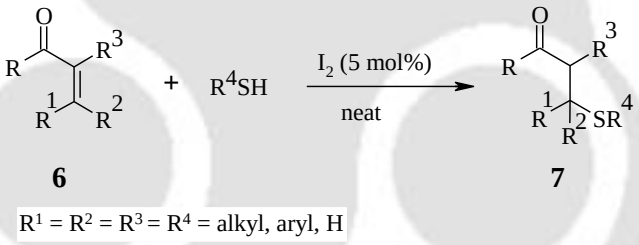
3.3 Molecular iodine catalyzed selective acetylation of alcohols with venyl acetate

3.3.1 Molecular Iodine in Organic Synthesis

In recent years molecular iodine has drawn considerable attention as an inexpensive, non-toxic, non-metallic and readily available catalyst for various organic transformations under mild and convenient conditions in excellent yields and with high selectivity.[1-36]

Das *et al.* have reported the Cross-Aldol condensation of aromatic aldehydes with cyclic ketones in the presence of catalytic amount of iodine at room temperature which afforded α,α'-bis(substituted-benzylidene) cycloalkanones in high yields.[37]

Chu *et al.* have described a simple and efficient method for the Michael reaction between various mercaptans and α,β-unsaturated Ketones **6** using a catalytic amount of iodine to generate the 1,4-adduct **7** (Scheme 3.8)[38].

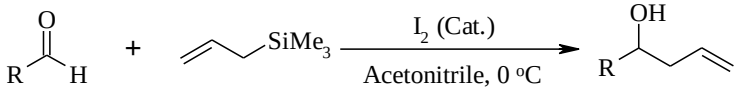


6 **7**

$R^1 = R^2 = R^3 = R^4$ = alkyl, aryl, H

Scheme 3.8

Karade *et al.* have reported the roll of molecular iodine as efficient co-catalyst for the facile oxidation of alcohols with hypervalent(III)iodine.[39] Yadav and coworkers have reported that the molecular iodine efficiently catalyzes the allylation of both aromatic and aliphatic aldehydes **8** with allyltrimethylsilane **9** in MeCN at 0 ^oC to afford the corresponding homoallyl alcohols **10** in high yields in a short reaction time (Scheme 3.9).[40]

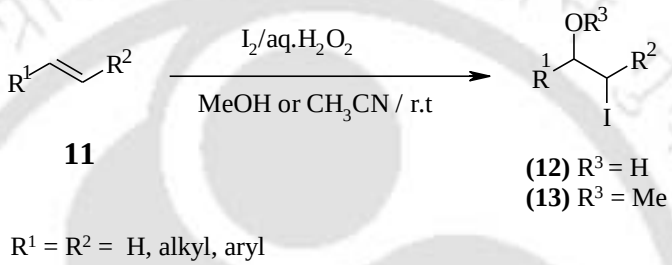


8 **9** **10**

Scheme 3.9

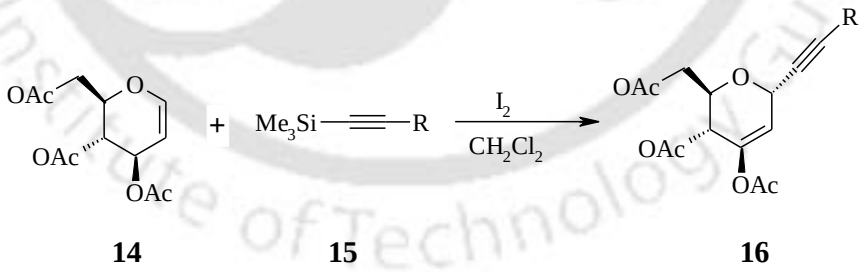
Karimi *et al* have described the deoxygenation of a variety of alkyl and aryl sulfoxides using

3- mercaptopropionic acid as a reducing agent and a catalytic amount of either I_2 (5-10 mol%) in MeCN at ambient temperature.[41] Saikia and coworkers have reported the regioselective 1,2-hydroxy and methoxy iodination of alkenes **11** by molecular iodine and aqueous hydrogen peroxide(30%). When acetonitrile is used as the solvent, hydroxyiodoalkane was obtained. On the other hand, when methanol was used as the solvent, methoxyiodoalkane was observed (Scheme 3.10).[42]



Scheme 3.10

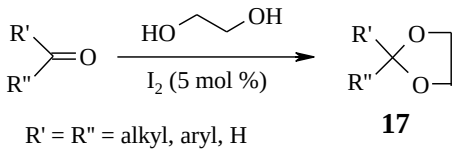
Rungnapha *et al.* have reported a convenient method for *C*-glycosidation (alkynylation) with various silylacetylenes **15** to D-glucal **14** by iodine molecule via iodo–oxonium intermediates provided exclusively the α-acetylene glycoside products **16** (Scheme 3.11).[43]



Scheme 3.11

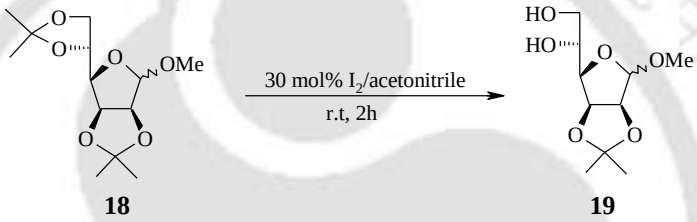
Takasu *et al.* have reported the synthesis of medium-sized cyclic γ-haloketones by radical mediated ring-opening reaction of molecular iodine catalyzed (2+2)- cloaddition products.[44] Banik *et al.*a remarkably simple molecular iodine-catalyzed protection method for various carbonyl compdounds as ketals **17** (Scheme 3.12).[45]

Deka *et al.* have reported the microwave-assisted selective monotetrahydropyranylation of



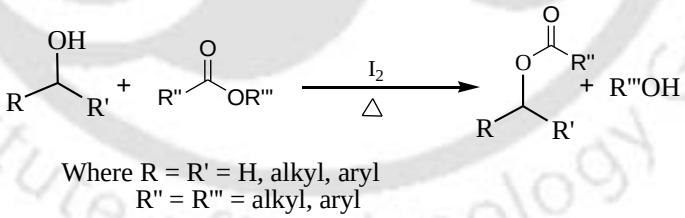
Scheme 3.12

symmetrical diols catalyzed by iodine.[46] Yadav and coworkers have reported the chemoselective hydrolysis of terminal isopropylidene acetals **18** in acetonitrile using molecular iodine as a mild and efficient catalyst (Scheme 3.13)[47]



Scheme 3.13

Kaimal and his group have reported that transesterification of alcohols can be performed with esters in the presence of molecular iodine at reflux (Scheme 3.14).[48]

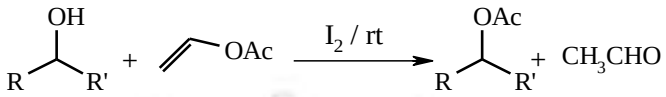


Scheme 3.14

3.3.2 Results and discussion:

Molecular iodine is found to catalyze the acetylation of alcohols with vinyl acetate effectively. We argued that if the carbonyl group and double bond of vinyl acetate was activated by iodonium ions and simultaneously reacted with a nucleophile, acetylated products would be obtained in shorter times under this reaction conditions. This proved to be the case when benzyl alcohol and the vinyl acetate were stirred at room temperature with a

catalytic amount of molecular iodine (10 mol%) yields the corresponding acetate in good yield (Scheme 3.15).[49]

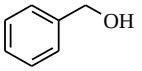
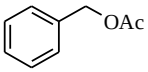
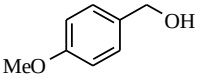
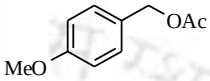
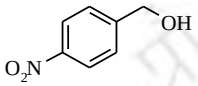
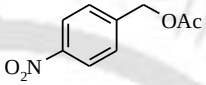
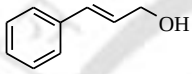
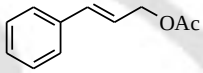
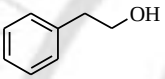
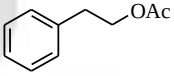
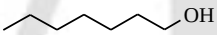
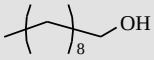
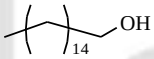
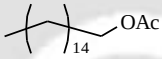
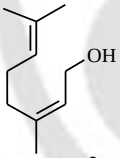
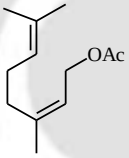
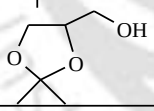
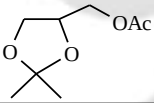


R = R' = alkyl,aryl,H

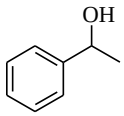
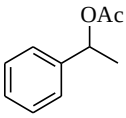
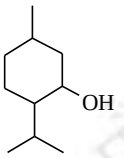
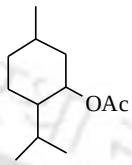
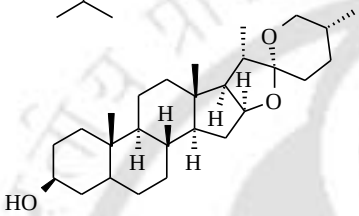
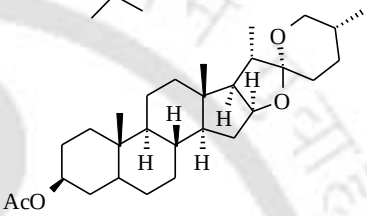
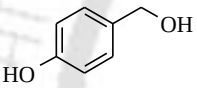
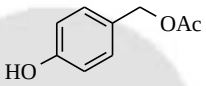
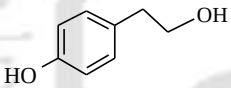
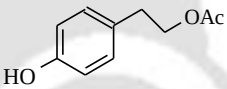
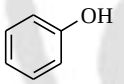
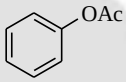
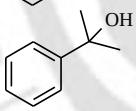
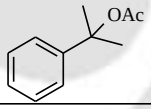
Scheme 3.15

In order to evaluate the efficiency of iodine, the generality of the reaction studied using various aliphatic, benzylic and allylic alcohols (Table 3.4). Both primary and secondary alcohols can be converted to the corresponding acetates in good yields. Electron donating groups accelerate the reaction of benzylic alcohols. Sterically hindered secondary alcohols (entries 11, 12 & 13) can also be acetylated in good yields. Entries 10 and 13 witness the mildness of this method towards acid sensitive groups. Phenols give only trace amounts of acetylated products and therefore alcohols can be chemo selectively acetylated (entries 14 and 15). Tertiary alcohols were found to react slowly under these reaction conditions. Tertiary butyl alcohol gave only an 18% yield after a prolonged reaction time (24 h) while the tertiary benzylic alcohol (entry 17**)** remained unreacted. The reaction completed quickly when carried out neat. It also worked well in solvents such as toluene and THF, but takes longer times. Thus, reaction of menthol completed within 4.5 h with 94% yield when carried out in 4 equivalents of vinyl acetate. On the other hand the same reaction took 13 h to complete when carried out in THF giving 92% yield. Interestingly, no iodo product was observed in the case of olefinic substrates (entries 4 and 9). The advantage of this reaction is that like acetic anhydride or acetyl chloride it does not generate any acidic waste, as a result the reaction medium is neutral. The only by-product, acetaldehyde can be removed by evaporation.

Table 3.4: Acetylation of alcohols with vinyl acetate using molecular iodine

Entry	Substrate	Time / h	Product	Yield(%)
1		4		97
2		1.5		98
3		6		93
4		4		91
5		4.5		96
6		4		89
7		4		91
8		4		93
9		4.5		89
10		7		87

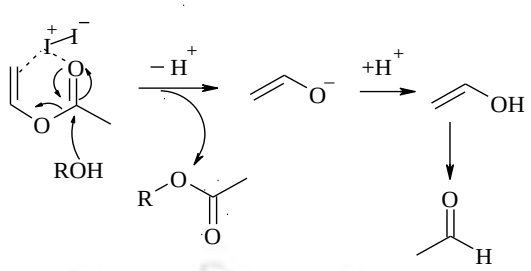
aYield refers to isolated yield. The compounds are characterized by ^{1}H NMR,^{13}C and IR spectroscopy and comparison with the literature.

Entry	Substrate	Time(h)	Product	Yield (%)[a]
11		5		93
12		4.5		94
13		4		78
14		2		95
15		3		92
16		14		Trace
17		12		0

[a]Yield refers to isolated yield. The compounds are characterized by ^{1}H NMR,^{13}C and IR spectroscopy and comparison with the literature.

Mechanistic Aspects

The reaction is a transesterification reaction as is evident from the formation of acetaldehyde, which was confirmed by ^{1}H NMR of the crude reaction mixture. The following mechanism can be proposed for the reaction. Both the carbonyl and double bond of the vinyl acetate is activated by iodine making the carbonyl group more susceptible to nucleophilic attack (Scheme 3.16). The inertness of the tertiary alcohol towards this reagent may be attributed to steric repulsion between the reagent and hindered alcohol.

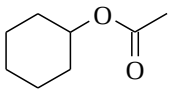


Scheme 3.16

In conclusion, an efficient catalytic acetylation reaction using vinyl acetate as the acetylating agent under mild, neat and neutral conditions have been developed. A variety of primary and secondary alcohols were acetylated in good yields. Under these reaction conditions functional groups such as methoxy, olefinic, spiroketal, ketal and phenolic groups remain unaffected. Thus the catalytic acetylation of alcohols with iodine offers an additional method using vinyl acetate instead of acetic anhydride or acetyl chloride as the acetylating agent.

3.3.3 Experimental Section:

Typical procedure for the molecular iodine catalyzed acetylation of alcohols (entry 2): Molecular iodine (0.1 mmol, 25.4 mg) was added to a mixture of *p*-methoxybenzyl alcohol (1 mmol, 138.16 mg) and vinyl acetate (3 mmol, 258 mg) and stirred at room temperature under a nitrogen atmosphere. The reaction was monitored by TLC (silica gel) using ethyl acetate and hexane (9:1) as eluent. When the reaction was comple, it was extracted with ethyl acetate (10 ml) and washed with saturated sodium thiosulphate solution (4 ml). The organic layer was dried over sodium sulphate and purified by column chromatography (silica gel; EtOAc : Hexane; 1:9). The products were characterized by spectroscopic methods. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.07 (s, 3 H, -O-CO-CH_3), 3.80 (s, 3 H, O-CH_3), 5.04 (s, 2 H, -CH_2-O-), 6.88 (d, *J*=8.4 Hz, 2 H, -ArH), 7.30 (d, *J*=8.4 Hz, 2 H, -ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.96, 55.10, 65.94, 113.80, 127.80, 129.80, 159.28, 170.52. **IR** (neat): 2950, 1736, 1516, 1245, 1173, 1040 cm^{-1}.

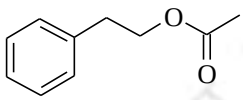


Cyclohexyl acetate

^{1}H NMR (300MHz, $CDCl_3$): δ 1.22-1.42 (m, 6 H), 1.55 (m, 1 H), 1.72-1.96 (m, 4 H), 2.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 23.8, 25.3, 31.6, 72.7, 170.7.

IR (neat): 2939, 2873, 1741, 1454, 1367, 1250, 1050, 1024 cm^{-1}.

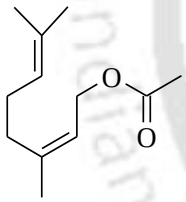


1-Acetoxy-2-phenylethan

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3 H, -O-CO-CH_3), 2.92 (t, *J* = 6.8 Hz, 2 H, -CH_2-), 4.26 (t, *J* = 7.2 Hz, 2 H, -CH_2-), 7.18-7.28 (m, 5 H, -ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.04, 35.10, 64.90, 126.37, 128.30, 128.68, 137.58, 170.75.

IR (neat): 3068, 3028, 2988, 2870, 1735, 1602, 1443, 1250, 1132, 1065, 932 cm^{-1}.

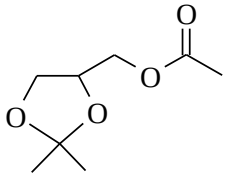


Geranyl acetate

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 3 H, -CH_3), 1.66 (s, 3 H, -CH_3), 1.70 (s, 3 H, -CH_3), 1.88-12.12 (m, 4 H, 2-CH_2-), 2.04 (s, 3 H, -$COCH_3$), 4.57(d, *J*= 7.2 Hz, 2 H, O-CH_2-), 5.07(t, *J*= 5.8 1 H, -CH-), 5.33 (t, *J*= 7.2 Hz, 1 H, -CH-);

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.45, 17.64, 21.00, 25.69, 26.30, 39.50, 61.28, 118.10, 123.52, 131.50, 141.88, 170.50;

IR (neat): 2965, 2922, 2864, 1740, 1448, 1374, 1237, 1027 cm^{-1}.

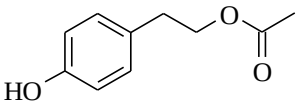


2,2-Dimethyl-1,3-dioxolane-4-methylacetate:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3 H, -CH_3), 1.42 (s, 3 H, -CH_3), 2.08 (s, 3 H, -$COCH_3$), 3.73 (m, 2 H, -CH_2-O-), 4.07 (m, 1 H), 4.15 (m, 1 H), 4.31 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.85, 25.40, 26.70, 64.76, 66.21, 73.51, 109.67, 170.43.

IR (neat): 2988, 2893, 1744, 1376, 1236, 1051, 842 cm^{-1}.



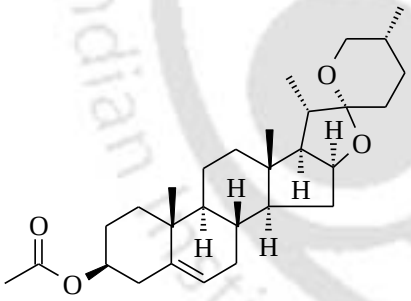
1-Acetoxy-2-(4-hydroxyphenyl)-ethane

M.p = 57 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3 H, -O-$COCH_3$), 2.86 (t, *J*=6.80 Hz, 2 H, -CH_2-), 4.23 (t, *J*=6.80Hz, 2 H, -CH_2-OAc), 5.14 (s, br, 1H, -OH), 6.76 (d, *J*=8.00Hz, 2H, -ArH), 7.07 (d, *J*=8.80Hz, 2H, -ArH).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 21.00, 34.11, 65.50, 115.26, 129.06, 129.73, 154.42, 171.75.

IR(KBr): 3421, 3021, 2960, 1721, 1516, 1449, 1372, 1254, 1034 cm^{-1}.



Dosgenin acetate

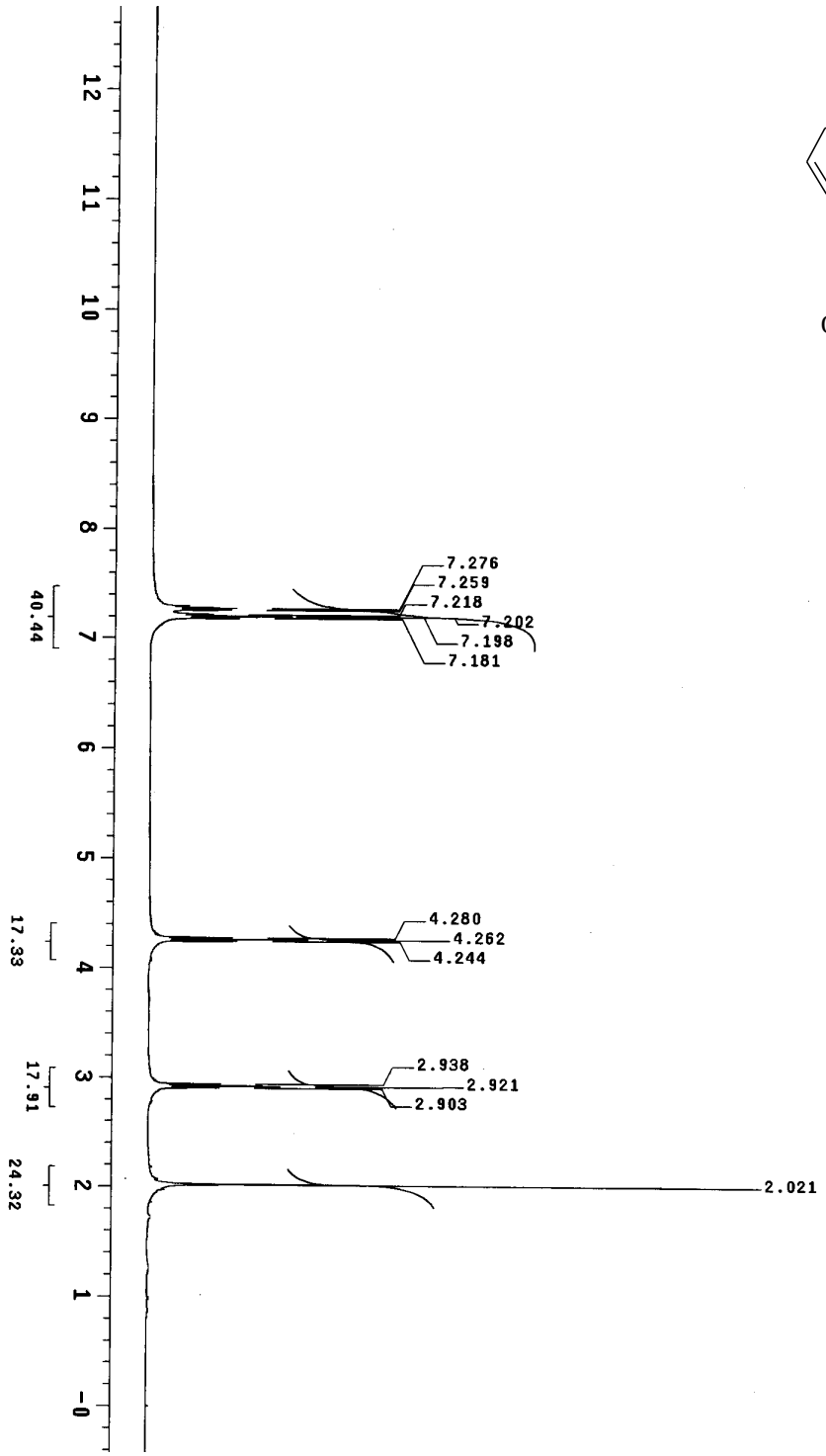
M. p.: 188 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (d, *J*=5.2 Hz, 1 H), 4.58 (m, 1 H), 3.47 (m, 1H), 3.36 (t, *J*=10.8 Hz, 1 H), 2.31 (m, 2 H), 2.02 (s, 3 H), 1.96 (m, 4 H), 1.4-1.8 (m, 22 H), 1.0 (s, 3 H), 0.95 (d, *J*=6.8 Hz, 3 H), 0.78 (s, 3 H).

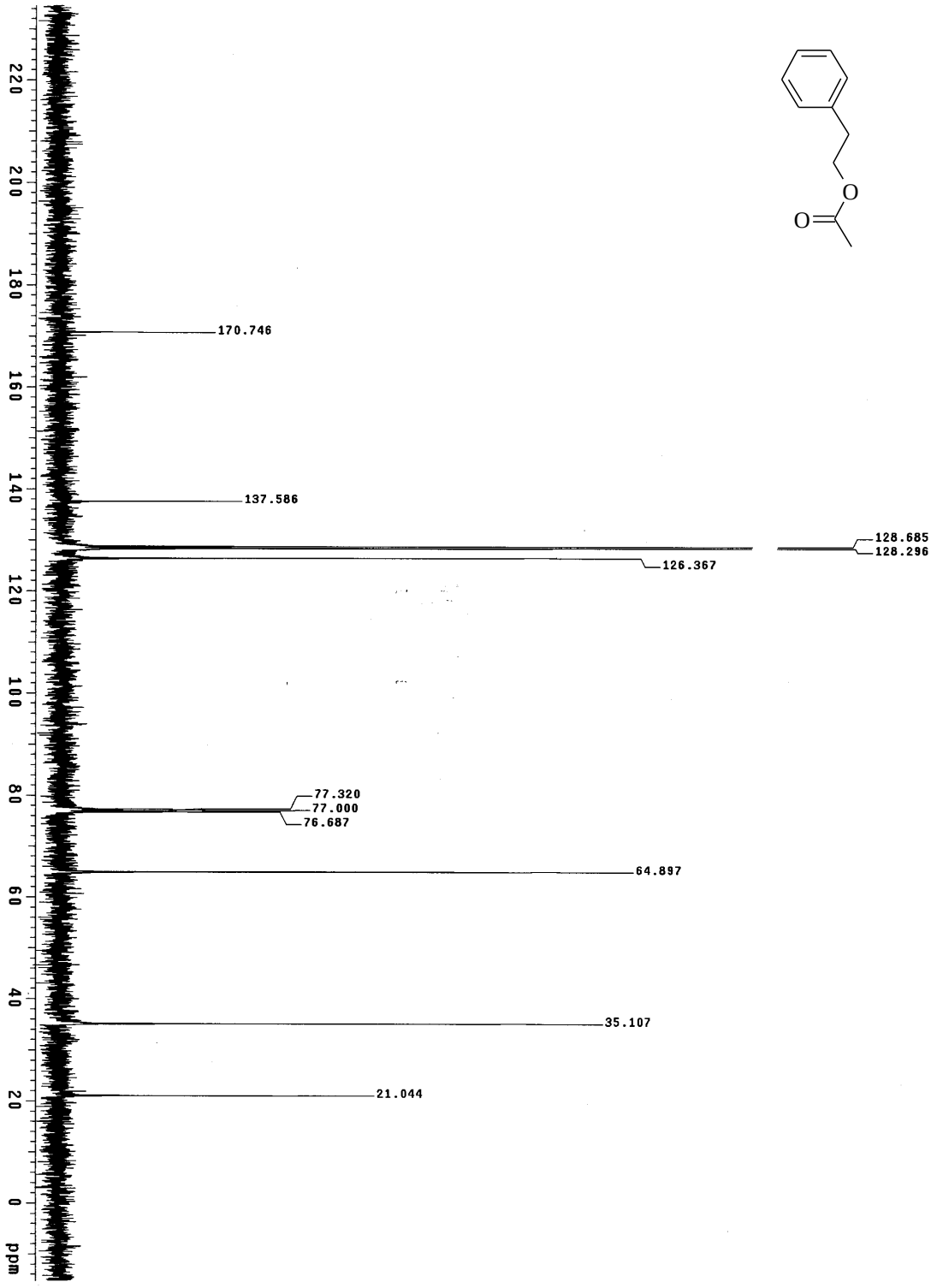
^{13}C NMR: (100 MHz, $CDCl_3$): δ 14.65, 16.40, 17.26, 19.45, 20.95, 21.53, 27.86, 28.92, 30.41, 31.52, 31.94, 32.14, 36.83, 37.05, 38.18, 39.81, 40.35, 41.70, 50.03, 56.48, 60.26, 66.86, 73.91, 80.80, 109.20, 122.24, 135.98, 139.55, 170.31.

IR(KBr): 2949, 2898, 1723, 1240, 1044 cm^{-1}.

The spectral data of the other compounds in this chapter are available in sec.2.3

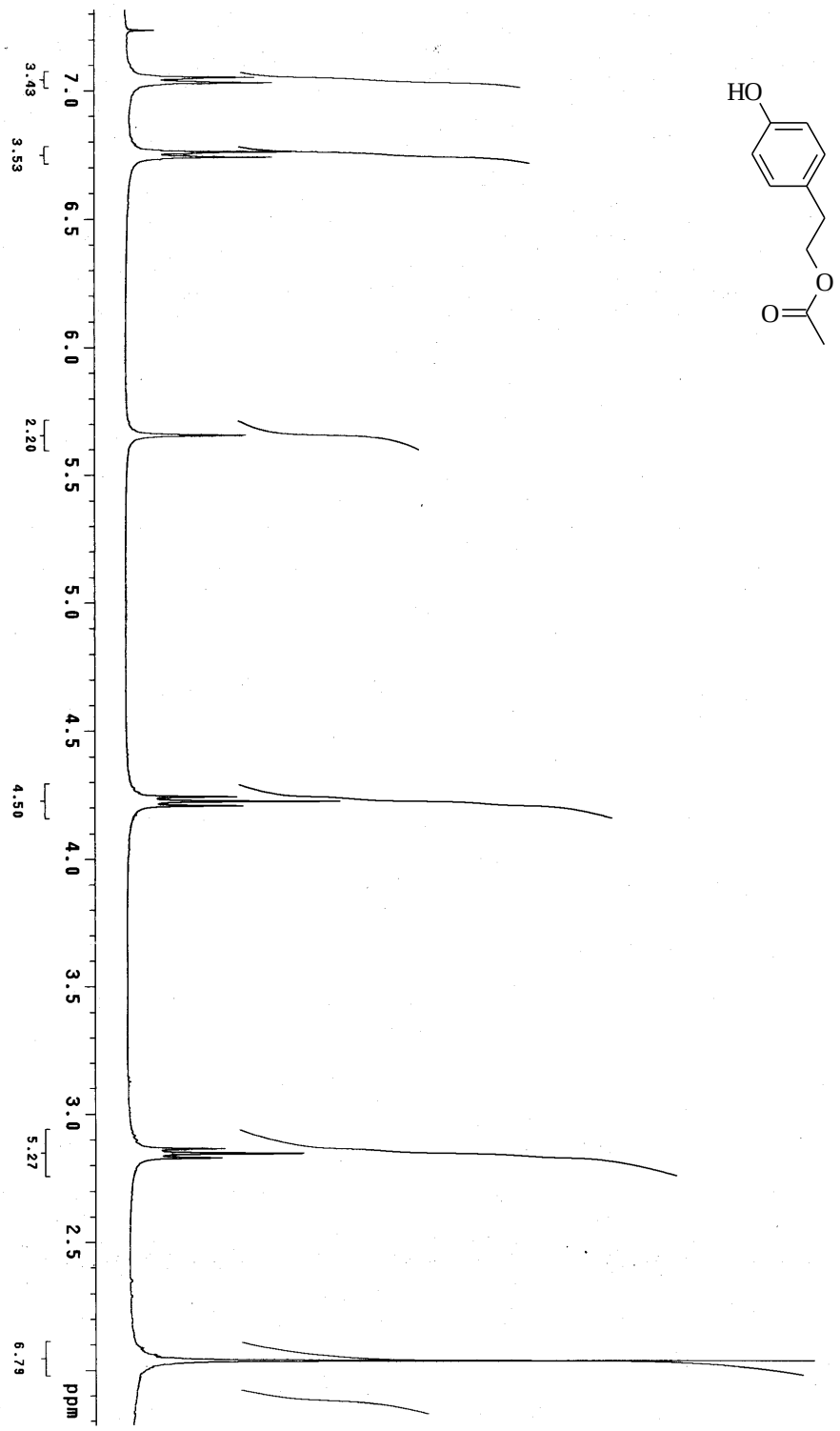


^{1}H NMR (400 MHz, $CDCl_3$): 1-Acetoxy-2-phenylethane

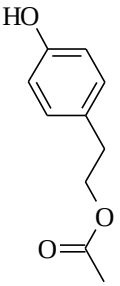


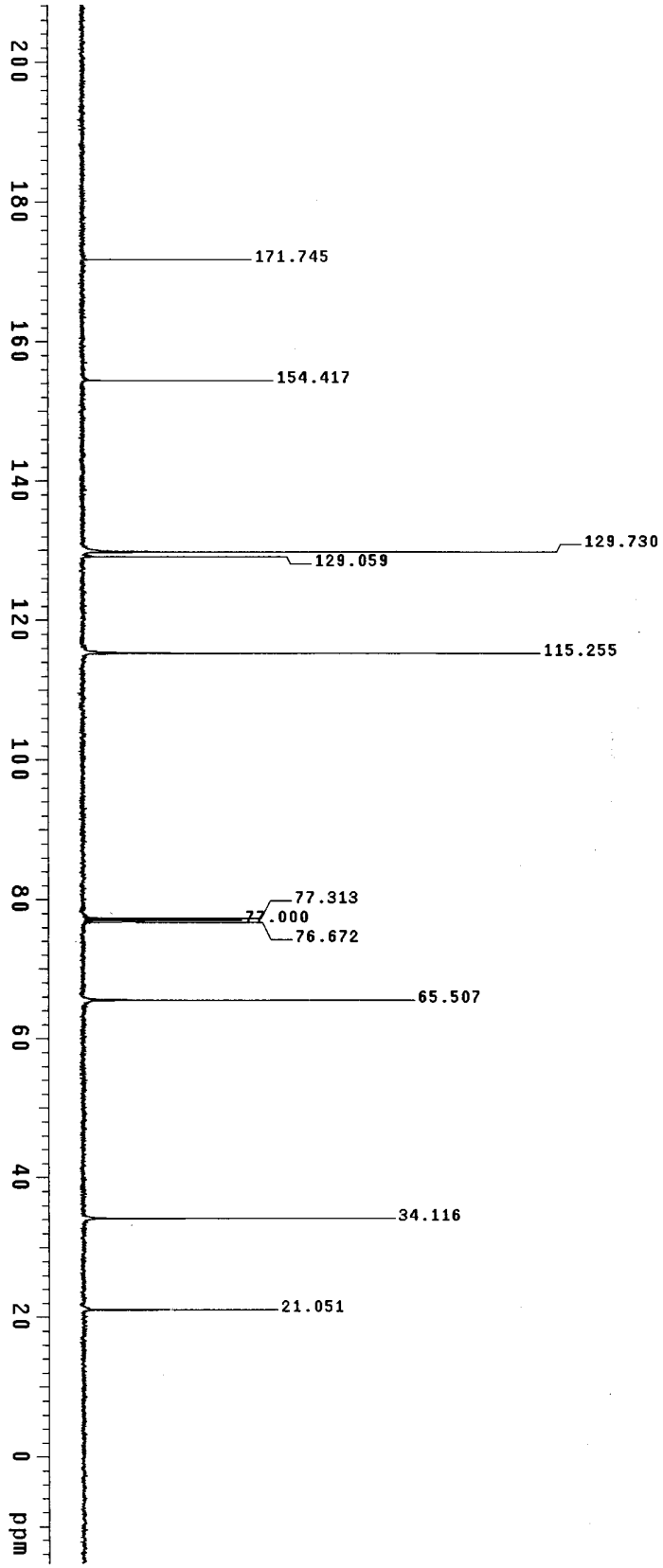
^{13}C NMR (400 MHz, $CDCl_3$): 1-Acetoxy-2-phenylethane

^{1}H NMR (400 MHz, $CDCl_3$): 1-Acetoxy-2-(4-hydroxyphenyl)-ethane



^{13}C NMR (400 MHz, $CDCl_3$): 1-Acetoxy-2-(4-hydroxyphenyl)-ethane





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Chapter IV

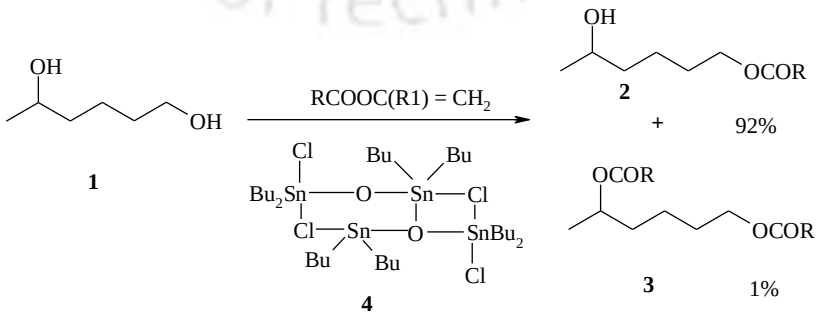
Selective monoacetylation of symmetric diols by samarium(III)chloride

4.1 Introduction

4.1.1 Selective acylation of hydroxy groups in non-symmetric diols

Selective monoacylation of non-symmetric diols or polyols is one of the most common synthetic problems. Different steric requirements in primary, secondary, and tertiary alcohols in most cases produce a substantial difference in acylation rates that can be further enhanced using special acylation methodologies. In general, tertiary alcohols are about two orders of magnitude less reactive than secondary ones and more than 10^3 less reactive than primary alcohols. Consequently, the acylation of primary and secondary hydroxy groups in the presence of tertiary hydroxyls is trivial in most cases.[1,2] Moreover, the acylation of tertiary hydroxy groups in complex substrates is often a profound synthetic problem that can be tackled using new reagents.[1] In contrast, achieving highly selective monoacylation of primary hydroxy groups in the presence of secondary ones is complicated. The difference in acylation rates between primary and secondary alcohols is about one order of magnitude and the acylation of diols containing both types of hydroxyls provides substantial amounts of a corresponding secondary ester and/or diester. Low selectivity of the acylation was also observed in reactions of acetic anhydride with both Cu(OTf)$_2$ and DMAP catalysis.[3] Low selectivity in the acylation of unsymmetric diols was obtained by solid state acetylation using acetylimidazole.[4]

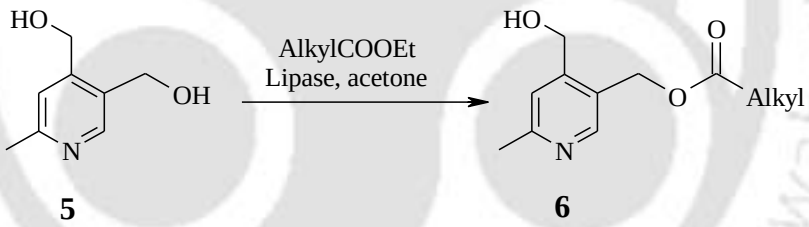
Distannoxane catalyzed transesterification of alkenyl esters was also found to possess a very high sensitivity towards steric differences in alcohols (Scheme 4.1). Reported examples



Scheme 4.1

showed almost complete absence of acylation of secondary hydroxy groups in diols.[5] The observed high sensitivity of the reaction towards the steric bulk of alcohols is probably related to the reaction mechanism that involves the formation of the highly sterically crowded transition state. This method requires the use of a large excess of alkenyl ester.

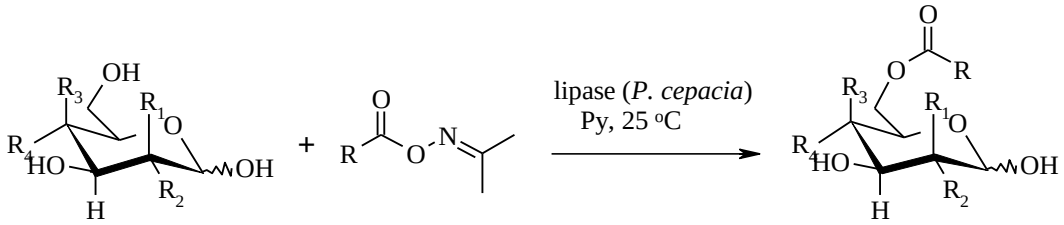
The difference in steric environment for secondary hydroxy groups can be substantial enough to ensure selective acylation in the case where one of them is attached to a cyclic scaffold. Numerous examples of high chemoselectivity in acylations of this type of substrates are known in the chemistry of natural products, especially carbohydrates[6] and steroids.[7] Selective acylation of sterically and electronically similar hydroxy groups in non-symmetric diols and polyols can be efficiently achieved using enzymatic methods. Despite the remarkable selectivity achieved in selected cases like monoacylation of rather similar primary hydroxy groups, as shown in Scheme 4.2,[8] the prediction of chemoselectivity is somewhat complicated. A number of enzymatic reactions have been reviewed.[9]



5 **6**

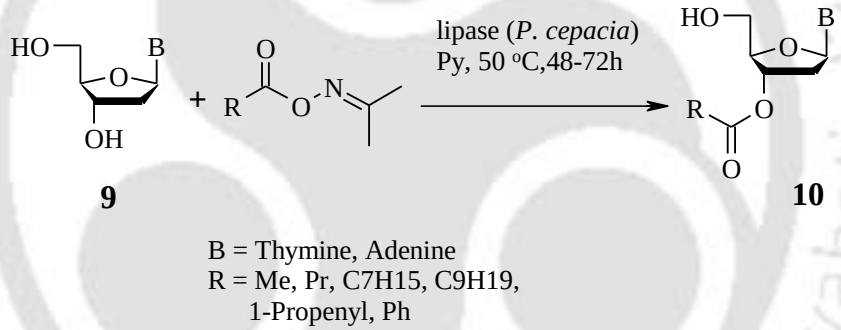
Scheme 4.2

Selective acylation of carbohydrates is a highly important application of chemoselective esterification. A number of methods targeting both the selective acylation of primary vs. secondary as well as different secondary hydroxyls in partially protected and non-protected carbohydrates have been developed.[10] The use of oxime esters **8** as acyl donors in lipase-catalyzed acylation of sugars **7** effects selective acylation (Scheme 4.3).[11] The regioselectivity is dependent on the substrates, high regioselectivity on the primary alcohol being attained for hexoses such as D-galactose and D-manose with lipase from *Pseudomonas cepacia*.



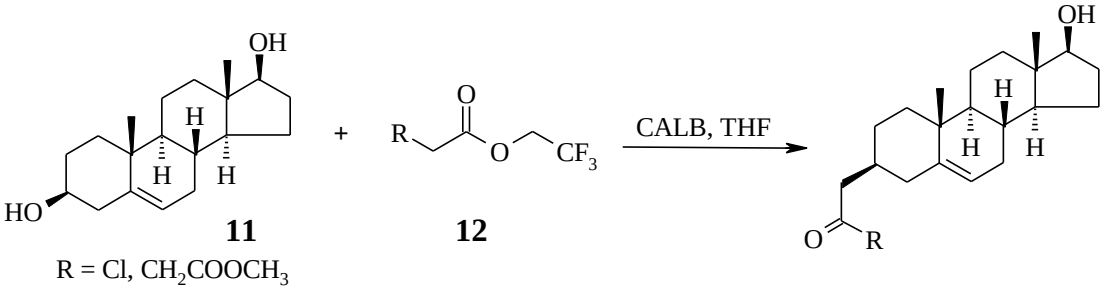
Scheme 4.3

Subjection of nucleosides to the same reaction conditions also results in preference for the primary alcohol.[12] Some 2'-deoxynucleosides **9**, however, undergo selective acylation on the 3'-position (Scheme 4.4).[13]



Scheme 4.4

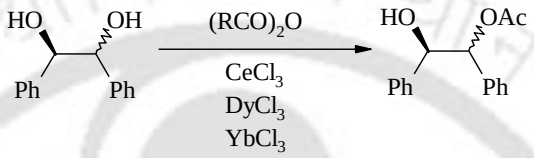
Steroids **11** are another class of compounds that frequently require selective acylation. *Candida Antartica* lipase B and 2,2,2-trifluoroethyl esters **12**, for example, showed a marked preference for the alcoholic moiety on the A ring of the sreroid skeleton (Scheme 4.5).[14]



Scheme 4.5

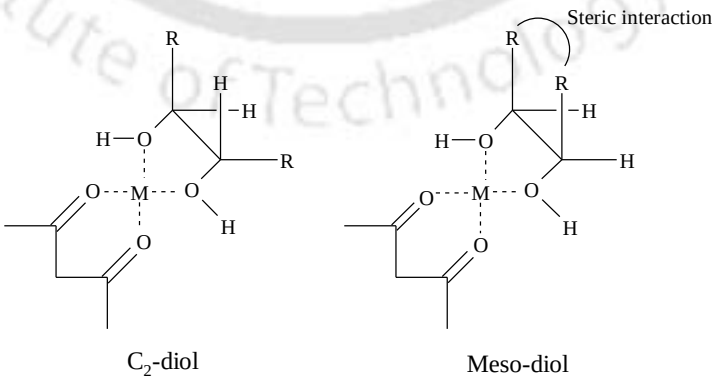
4.1.2 Monoacylation of symmetric diols

Selective monoacylation of symmetric diols is substantially more complicated because of the identical chemical environment around the hydroxy groups and the formation of a mixture of mono- and diacylated products. Paul and coworkers have reported the selective mono acylation of primary and secondary 1,2- and 1,3-diols with symmetric anhydrides. (Scheme 4.6).[15]



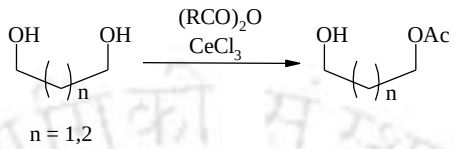
Scheme 4.6

The reaction proceeds through the formation of chelate metal complexes with Lewis acid catalysts. Cerium, dysprosium, and ytterbium chlorides were checked with the latter generally providing better results. The use of an excess of the symmetric anhydride is essential for the reaction. The proposed mechanism of the acylation involves the coordination of both diol and symmetric anhydride with a lanthanide cation followed by the intramolecular transfer of the acyl group. The high chemoselectivity of monoacylation is due to the higher stability of bidentate complexes of lanthanide catalysts with diols vs. monodentate complexes of monoesters. This mechanism (Scheme 4.7)[16] is also supported by substantially higher acylation rates of C2 symmetric diols vs. analogous meso diols. Similarly high chemo-



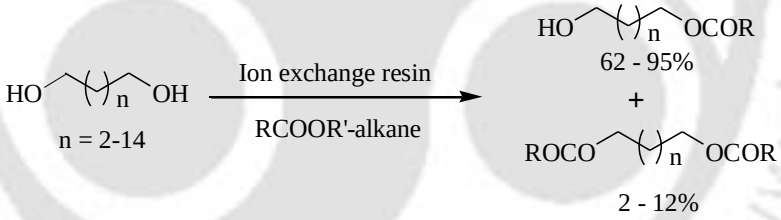
Scheme 4.7

selectivity was obtained in the acylation of symmetric 1,3 and 1,4-diols with cerium(III) chloride (Scheme 4.8).[17]



Scheme 4.8

Monoesterification of diols possessing a larger distance between hydroxy groups requires a different approach. Nishiguchi *et al*. have reported monoacylation of 1,n-diols, ranging from 1,2-ethanediol to 1,16-hexadecanediol by transesterification in ester/alkane mixtures catalyzed by strongly acidic ion-exchange resins (Schme 4.9). At 70–80% conversions a

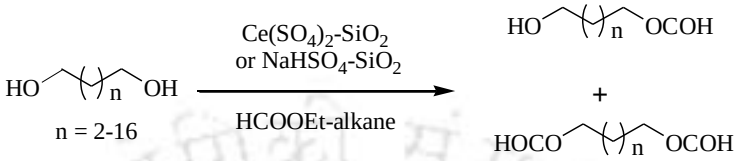


Scheme 4.9

good selectivity 20 : 1 to 15 : 1 was achieved after the optimization of ester alkane ratio. The selectivity decreases at higher conversions and different from the optimal ester–alkane ratio. The suggested mechanism of the selectivity toward monoacylation is based on the formation of a strongly acidic aqueous layer on the surface of ion-exchange resin beads. The preferential acylation of 1,n-diols is explained by their higher solubility in the water layer where the transesterification proceeds.[18]

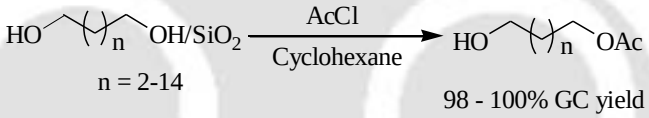
A similar mechanism of selectivity was also proposed for the selective monoesterification of different 1,n-diols with an ester–alkane mixture catalyzed by silica supported $Ce(SO_4)_2$ and $NaHSO_4$ (Scheme 4.10).The selectivity is in the 20 : 1 to 10 : 1 range for C_2 to C_{16} diols at 75–90% conversions, and was particularly high when isopropyl acetate was used as an acyl

donor. Secondary diols can also be monoformylated by the reaction with ethyl formate. Similar but lower selectivity was observed for the catalysis with unsupported $NaHSO_4$.[19]



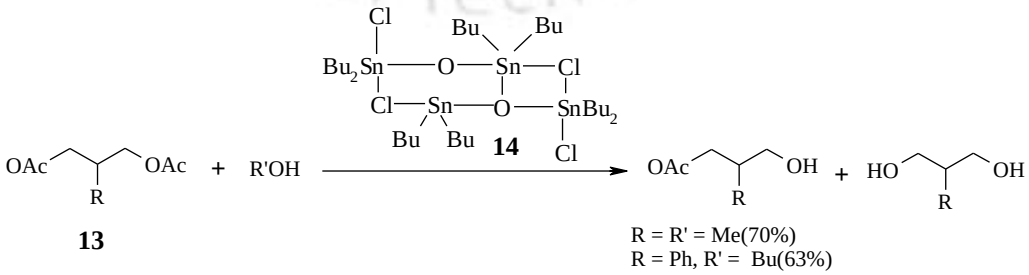
Scheme 4.10

Ogawa *et al.*[20] have reported another, but probably related, approach to monoesters of α,ω-diols involves the acylation of preadsorbed diols on silica gel with acetyl chloride in refluxing cyclohexane (Scheme 4.11). This method is remarkable because of the practically quantitative chemoselectivity for primary diols up to 1,16- hexadecanediol. Secondary and benzylic diols produced much lower selectivity.



Scheme 4.11

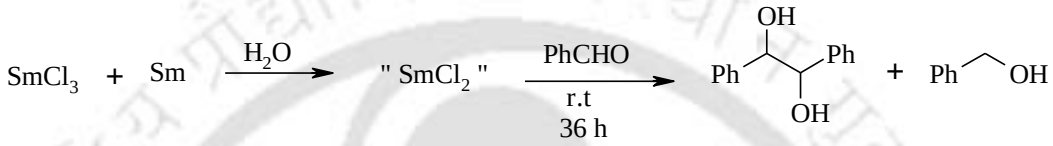
Under distannnoxane **14** catalysis conditions, α,ω-diesters **13** with fewer than four carbons are transformed into the correspnding monoesters on treatment with alcohol (Scheme 4.12).[21] 2-Substituted propylene glycols also exhibit a considerable level of selectivity.



Scheme 4.12

4.1.3 Samarium(III)Chloride in Orgnaic Synthesis

For the past two decades, Samarium(III) Chloride has widely been used in many organic transformations. Matsukawa *et al.* have reported the samarium(II)-mediated pinacol coupling in water. Mechanistic studies of one-electron reduction in water using samarium were carried out. Unexpected disproportionation in water was observed via UV-visible spectroscopic



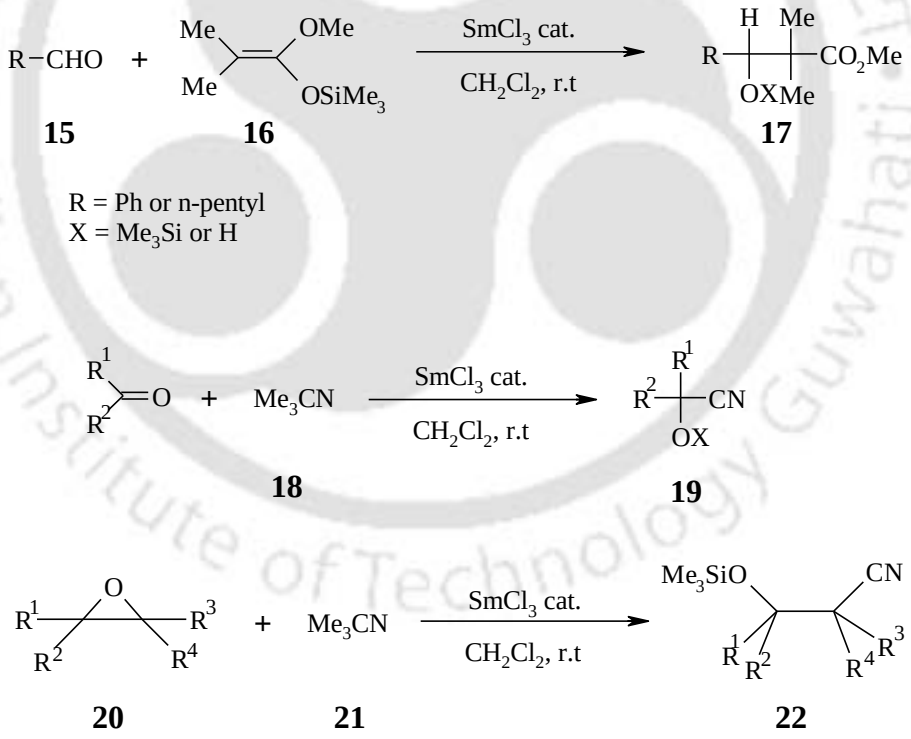
Scheme 4.13

analysis. This fact indicates that low-valent samarium species can exist in water. Furthermore, the $SmCl_3$-Mg systems were found to act as good one-electron reducing agents in water (Scheme 4.13).[22]

Yang *et al.* have reported the asymmetric addition of trimethylsilyl cyanide to benzaldehydes catalyzed by Samarium(III)Chloride and chiral Phosphorus(V) reagents.[23] Yokoyama *et al.* have reported that $Et_3GeNa/SmCl_3$ complex is a useful strong base for the stereoselective aldol condensation of various ketones and amides. As for example the reaction of 3-pentanone with benzaldehyde in THF-HMPA in the presence of $SmCl_3$ and Et_3GeNa gave 98% the corresponding aldol (syn/anti = 96/4).[24] Yamanaka *et al.*[25] have reported the partial oxidation of cyclohexane to cyclohexanol and cyclohexanone with O_2 by using $SmCl_3$ dissolved in $MeCO_2H$, CH_2Cl_2, and H_2O in the presence of Zn powder. The yield was influenced by the amount of H_2O, CH_2Cl_2 required as a solvent, and the Sm catalytic species is thought to be Sm^{3+}. Hebri *et al.* have reported the samarium trichloride-catalyzed electrosynthesis of γ-butyrolactones from the direct reductive coupling of 3-chloro esters and carbonyl compounds[26] and electrochemical reduction of a series of organic halides including chloro and fluoro derivatives bearing various functional groups.[27] A series of β-oxo nitriles were obtained in good yields through the electrochemical coupling of nitriles with aromatic or aliphatic esters catalyzed by samarium(III)chloride using *t*-Butyl aclcohol as a probase. Electrolyses were run under mild conditions in an undivided cell with a magnesium anode.[28]

$SmCl_3$-catalyzed electrochemical coupling reaction of benzoates yielding 1,2-diphenyl-1,2-ethanediones also have been reported. The coupling of methyl benzoate in the presence of 10% anhydrous $SmCl_3$ gave 1,2-diphenyl-1,2-ethanedione in 68% yield and benzoin as byproduct. In the absence of catalyst the reaction gave 23% 1,2-diphenyl-1,2-ethanedione and 5% benzoin. Coupling of methyl benzoate with methyl pivalate did not yield a dissymetric diketone[29] Ukaji *et al.* have reported the cleavage of acetals or ketals in the presence of a stoichiometric or catalytic amount of $SmCl_3$ and Me_3SiCl to give the corresponding carbonyl compounds in the absence of a proton source.[30]

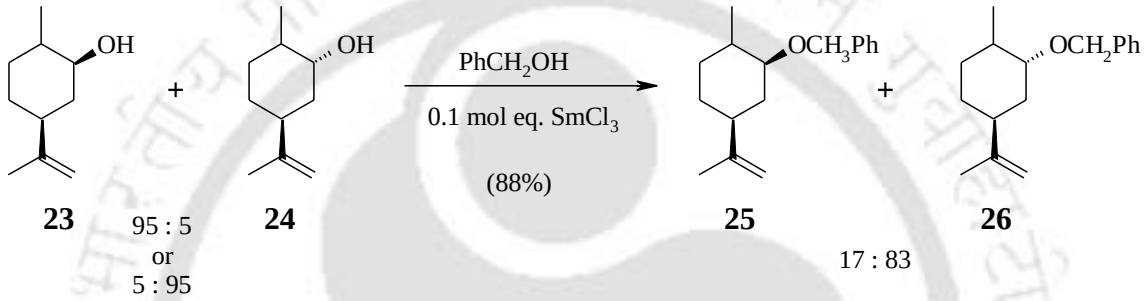
Kagan and coworkers have reported the Samarium(III) Chloride catalyze the aldol addition of silyl enol ethers **16** to aldehydes **15**, the addition of trimethylsilyl cyanide **21** to aldehydes and ketones, as well as the synthesis of β-cyanosilyl ethers **22** (Scheme 4.14).[31]



$R^1 = R^2 = R^3 = R^4$ = H, alkyl or aryl

Schme 4.14

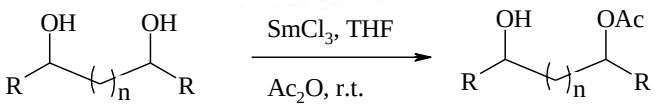
Ouertani *et al.* have studied the behavior of various allylic alcohols in the presence of catalytic amounts of $SmCl_3$ (Schme 4.15). Diallyl ethers were obtained in many cases in good yields. Mixed allyl alkyl ethers **25** and **26** were prepared if 2-5 equivalents of an aliphatic alcohol was present. The reactions were interpreted as proceeding through a pseudo-allylic carbonium intermediate initiated by a preliminary complexation of the allyl hydroxyl to the samarium ion.[32]



Scheme 4.15

4.2 Results and discussion:

Although there are several methods of selective monoacylation of 1,2-, 1,3-, and 1,4-symmetric diols,[15-17,21,33] there are a few for the monoacylation of higher homologues of the symmetric diols.[18-20] In this chapter samarium catalyzed monoacetylation of symmetric diols having 1-8 carbons is disclosed. Thus when 1,5-pentane diol was strirred at room temperature with catalytic amount of $SmCl_3$ and acetic anhydride yielded monoacetate in good yield (Scheme 4.18).

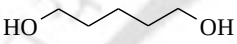
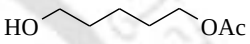
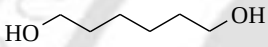
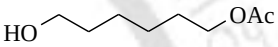
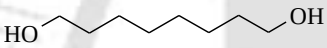
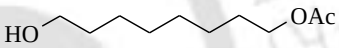
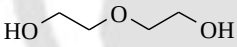
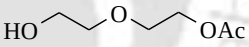
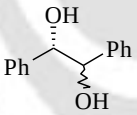
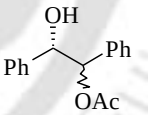
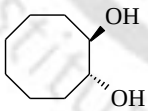
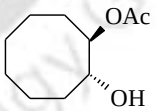
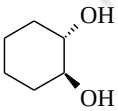
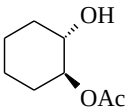
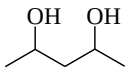
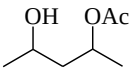


Where R=H, alkyl, aryl; n = 0-6

Scheme 4.18

The reaction is generalyzed through entry 1-10 (Table 4.1). It was observed that the reaction could be extended from symmetric 1,2- to 1-8 diols. Symmetric olefinic diols also gave monoacetylated product. The formation of acetate from the vicinal and 1,3-diols can be explained from the mechanism as suggested by Clarke where a cyclic transition state intermediate is formed. But, this mechanism cannot be applied to diols longer than 1,3 diols.

Table 4.1: Samarium(III)chloride catalyzed selective monoacetylation of symmetric diols

S.No	Substrate	Time/h	Tem./ °C	Product	Yield(%)
1		3	25		92
2		4	25		90
3		18	25		82
4		7	50		76
5		7	50		79
6		9	50		81
7		7	25		88
8		22	25		79
9		24	25		81
10		20	50		51

Selectivity in this case is different from the previous one. When sterically hindered vicinal diols like hydrobenzoin are subjected to this reaction condition, excusively mono acylated product was observed as white powder which after crystallization in hexane. Cyclic vicinal

diols like cycloocatane 1,2-diol and cyclohexane 1,2-diol cosume subsequently long time but no diacetates were observed. In case of 1,3 diol like pentane-2,4-diol, longer time and poor reaction progress are the limitations. It was observed that the catalyst gets precipitated at the bottom of the round bottom flask. When the mixture is heated the reaction progresses with poor conversion. Continuing in this same condition holds no control over the selectivity. It was observed that the acid sensitive diol like diethylene glycol does progress withought any cleavage. It is remarkable that the olefinic diols like cis-butene-1,4-diol gets monoacylated smoothly.

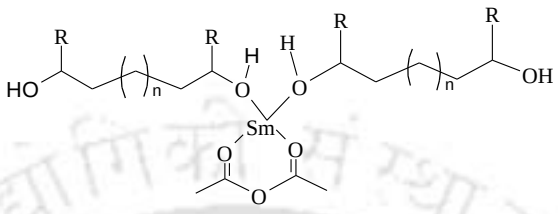
It is evident from the Table 4.2 that the reaction preceeds efficiently with good selectivity when toluene or THF are used as solvents. In DCM and DMF the reaction doesn't progress. The conversion is quicker under solvent free condition but poor selectivity was observed. It is remarkable that the amount of acetic anhydride also has crucial effect on this method. When the amount of anhydride is increased, the reaction preceeds faster with poor selectivity.

Table 4.2: Optimisation of the reaction with 1,5-pentanediol

Ac_2o (eq)	Solvent	Time(h)	Yield(%)	
			Mono	Di
2	THF	3	89	2
2	DCM	3.5	–	–
2	–	2	48	37
2	Toluene	3	84	4
2	DMF	4	–	–
5	THF	2.5	72	18

The exact mechanism is not yet established. Yet a plausible mechanism is represented as shown in scheme 4.20. We believe that initially one of the hydroxyl groups of diols and acetic anhydride coordinated to samarium (III) chloride similar to mechanism proposed by Clarke and remain on the surface of the catalyst. The other hydroxyl group of the diol attacks the

activated carbonyl group of the anhydride, as these types of long chain diols are flexible. After acetylation the product goes to the solvent and new cycle starts.



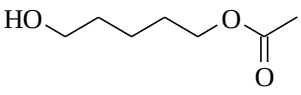
Scheme 4.20

In summary a convenient method for the monoacetylation of symmetric diols with catalytic amount of $SmCl_3$ has been disclosed. Both short as well long chain symmetric diols can be acetylated with the formation of minimum amount of diacetate.

4.3 Experimetal section:

Typical experimental procedure:

Acetic anhydride (204 mg, 2 mmol) is added to the mixture of 1,6-hexanediol (118 mg, 1 mmol) and $SmCl_3$ (12.8 mg, 0.05 mmol) in 3 ML of dry THF. The mixture is stirred in nitrogen atmosphere and the reaction progress is monitored by thin layer chromatography (silica gel; EtOAc:Hexane; 1:3). When the reaction completes, the solvent is evaporated in rotary evaporator and the crude reaction mixture is purified by preparatory thin layer chromatography (silica gel; EtOAc:Hexane; 1:3). The products were confirmed by IR, ^{1}NMR and ^{13}C NMR spectroscopic techniques.

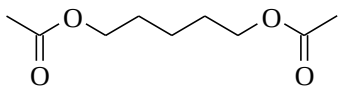


5-Hydroxypentyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 2 H, -CH_2-), 1.62 (m, 4 H, 2 –CH_2), 2.05 (s, 3 H, CH_3CO-), 2.74 (bs, 1 H, -OH), 3.63 (t, *J* = 6.8 Hz, 2 H, -CH_2OH), 4.06 (t, *J* = 6.8 Hz, 2 H, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.40, 22.61, 28.77, 32.57, 62.78, 64.80, 171.48.

IR (neat): 3417, 2941, 2868, 1734, 1461, 1374, 1244, 1042 cm^{-1}.

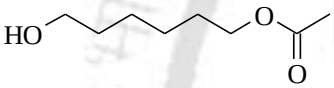


1,5-Diacetoxypentane

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 2 H, -CH_2-), 1.64 (m, 4 H, 2 –CH_2), 2.03 (s, 6 H, CH_3CO-), 4.04 (s, *J* = 6.4 Hz, 4 H, 2-CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21, 22.30, 28.30, 64.20, 170.82.

IR (neat): 2948, 1739, 1460, 1372, 1241, 1042 cm^{-1}.

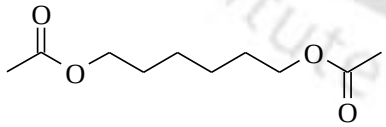


6-Hydroxyhexyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 4 H, 2-CH_2-), 1.55 (m, 2 H, –CH_2-), 1.64 (m, 2 H, -CH_2CO-), 2.04 (s, 3 H, -CH_3CO-), 3.14 (bs, 1 H, -OH), 3.61 (t, *J* = 6.8 Hz, 2 H, -CH_2OH-), 4.05 (t, *J* = 6.8 Hz, 2 H, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.95, 25.34, 25.65, 28.47, 32.38, 62.33, 64.41, 171.07.

IR (neat): 3406, 2938, 2864, 1733, 1462, 1375, 1246, 1045 cm^{-1}.

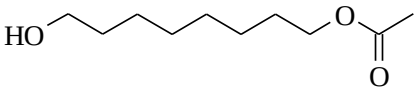


1,6-Diacetoxyhexane

^{1}H NMR (400 MHz, $CDCl_3$): δ 1. 38 (m, 4 H, 2-CH_2-), 1.64 (m, 4 H, 2 –CH_2), 2.05 (s, 6 H, CH_3CO-), 4.05 (t, *J* = 6.8 Hz, 4 H, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.41, 25.67, 28.54, 64.37, 170.94.

IR (neat): 2946, 2862, 1738, 1463, 1374, 1243, 1039 cm^{-1}.

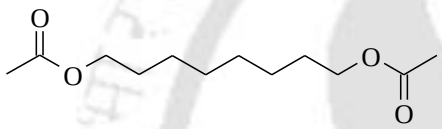


8-Hydroxyoctyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 8 H, 4-CH_2-), 1.56 (m, 2 H, –CH_2-), 1.60 (m, 2 H, -CH_2-), 2.04 (s, 3 H, -CH_3CO-), 3.35 (bs, 1 H, -OH), 3.62 (t, *J* = 6.8 Hz, 2 H, -CH_2OH-), 4.04 (t, *J* = 6.8 Hz, 2 H, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.05, 25.70, 25.87, 28.60, 29.22, 29.31, 32.70, 62.81, 64.60, 171.13.

IR (neat): 3450, 2930, 2859, 1733, 1462, 1372, 1244, 1043 cm^{-1}.

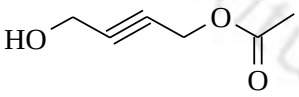


1,8-Diacetoxyoctane

^{1}H NMR (100 MHz, $CDCl_3$): δ 1. 38 (m, 8 H, 4-CH_2-), 1.63 (m, 4 H, 2 –CH_2), 2.04 (s, 6 H, 2CH_3CO-), 4.05 (t, 4 H, *J* = 6.8 Hz, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.10, 25.67, 28.54, 64.37, 170.95.

IR (neat): 2946, 2862, 1738, 1463, 1374, 1243, 1039 cm^{-1}.

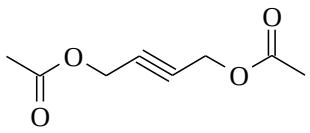


4-Hydroxybut-2-ynyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3 H, CH_3CO-), 2.97 (bs, 1 H, -OH), 4.29 (s, 2 H, -CH_2OH), 4.70 (s, 2 H -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ δ 20.9, 58.2, 60.1, 125.3, 133.3, 171.2.

IR (neat): 3437, 2940, 2873, 1742, 1445, 1380, 1250, 1030 cm^{-1}

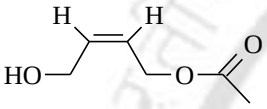


1,4-Diacetoxybut-2yne

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 6 H, 2 CH_3CO-), 4.7 (m, 4 H, 2 –CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 51.92, 80.55, 169.7.

IR (neat): 3305, 2940, 2873, 2202,1742, 1445, 1380, 1250, 1032 cm^{-1}

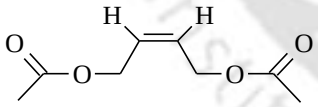


(Z)-4-Hydroxybut-2-enyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3 H, CH_3CO-), 3.7 (bs, 1 H, -OH), 4.3 (d, *J* = 6.4Hz, 2 H, -C<u>H</u>$_2$OH,), 4.70 (d, *J* = 6.8 Hz, 2 H, -CH_2OCO-), 5.6 (m, 1 H, -C<u>H</u>-CH_2-OH), 5.8 (m, 1 H, -C<u>H</u>-CH_2-OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.04, 58.4, 60.15, 125.4, 133.2, 170.9.

IR (neat): 3436, 3043, 2960, 1748, 1442, 1372, 1239, 1040, 983 cm^{-1}

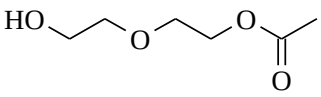


(Z)-1,4-Diacetoxybut-2-ene

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 6 H, 2 CH_3CO-), 4.6 (m, 4 H, 2 –CH_2OCO-), 5.7 (m, 2 H, 2CH-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 59.88, 127.77, 170.355.

IR (neat): 3047, 2950, 1751, 1444, 1372, 1239, 1040, 983 cm^{-1}.

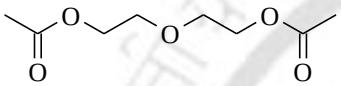


2-(2-Hydroxyethoxy)ethyl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3 H, CH_3CO-), 2.84 (bs, 1 H, -OH), 3.6 (t, *J* = 4 Hz, 2 H, -C$\underline{H}_2$OH,), 3.7 (m, 4 H, -C$\underline{H}_2$-O-C$\underline{H}_2$-), 4.2 (t, *J* = 4.8 Hz, 2 H, -CH_2-OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.89, 61.44, 63.39, 68.90, 72.31, 170.8.

IR (neat): 3439, 2942, 2879, 1735, 1448, 1377, 1247, 1130, 1055cm^{-1}.

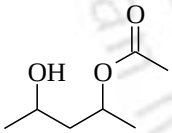


Di(ethyleneglycol)diacetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6 H, 2CH_3CO-), 3.7 (t, 4 H, 2 –C$\underline{H}_2$-O-C$\underline{H}_2$-), 4.2 (t, 4 H, 2CH2OCO-).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 20.98, 63.41, 69.03, 170.69.

IR (neat): 2957, 2883, 1742, 1444, 1374, 1231, 1136, 1054cm^{-1}.

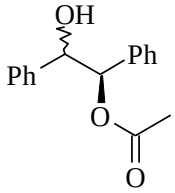


4-Hydroxypentan-2-yl acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.2 (d, *J*=6.4 Hz, 3 H, -CH_3), 1.26 (d, *J*=6.4 Hz, 3 H, -CH_3), 1.55-166 (m, 2 H, -CH_2-), 2.00 (s, 0.46 H, CH_3CO-), 2.10 (s, 0.54 H, CH_3CO-), 2.93 (bs, 1 H, -OH), 3.73 (m, 0.54 H, -CHOH), 3.87 (m, 0.46 H, -CHOH-), 5.00 (m, 0.46 H, -CHOAc), 5.15 (m, 0.54 H, -CHOAc).

^{13}C NMR (100 MHz, CDCl3): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.479, 20.80, 21.5, 21.50, 23.13, 23.9, 45.30, 46.11, 63.68, 65.74, 68.33, 69.55, 174.20.

IR (neat): 3464, 2974, 1729,1455, 1375, 1252, 1111, 1035 cm^{-1}



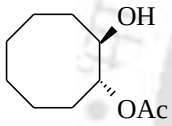
Hydrobenzoin monoacetate

M. p = 79 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3 H, CH_3CO-), 2.4 (bs, 1 H, -OH), 4.97 (d, 1 H, -CHOH, *J* = 6Hz), 5.89 (d, 1 H, -CHOCO-, *J* = 5.6Hz), 7.28 (m, 10 H, 2ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.06, 76.1, 78.8, 126.72, 127.5, 127.81, 127.86, 128, 128.17, 136.18, 139.3, 169.5.

IR (KBr): 3443, 3058, 2934, 1728, 1660, 1598, 1441, 1375, 1239, 1040.



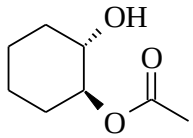
M.p = 37 ^{o}C

***Trans*-Cyclooctanediol monoacetate**

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.5 (m, 4 H, 2-CH_2-), 1.8 (m, 8 H, 4-CH_2), 2.0 (s, 3 H, -CH_3CO-), 2.05 (bs, 1 H, -OH), 3.82 (m, 1 H, -CHOH), 4.87 (m, 1 H, CHOAc).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.59, 21.95, 22.90, 27.34, 30.03, 30.48, 33.51, 71.40, 74.34, 170.24.

IR (CH_2Cl_2): 3418, 2927, 2857, 1732, 1447, 1371, 1249, 1050 cm^{-1}.

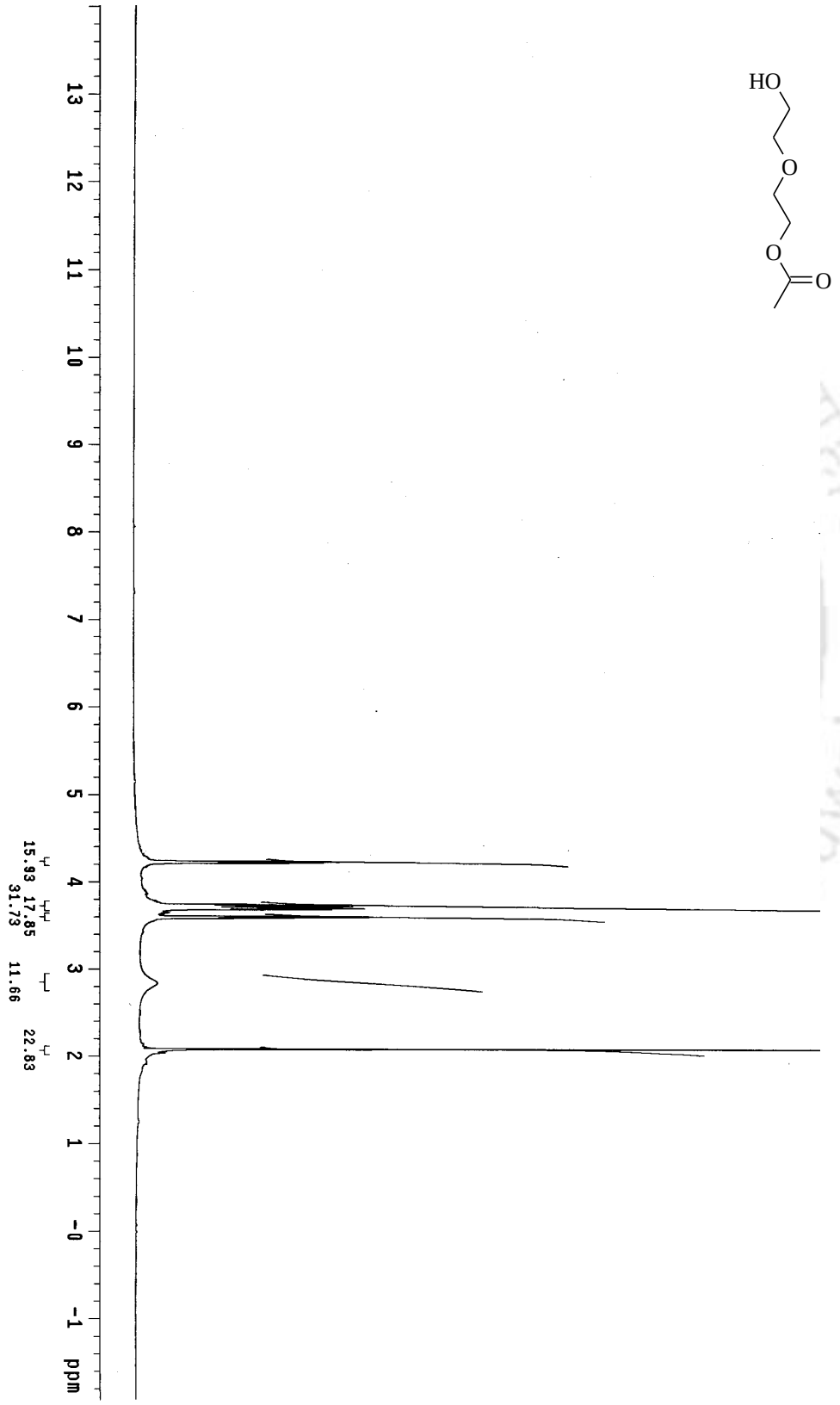


***Tras*-Cyclohexanediol monoacetate**

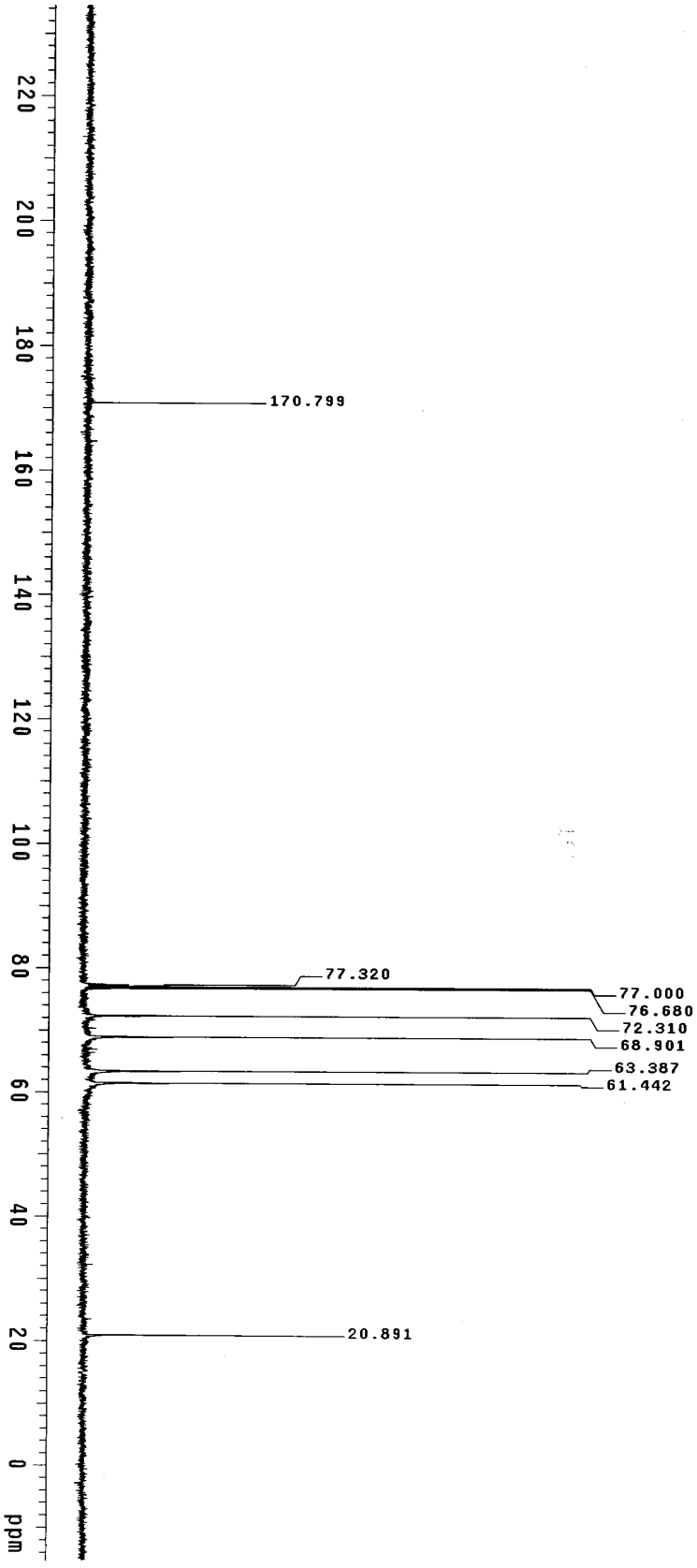
^{1}NMR (400 MHz): δ 1.18-1.31 (m, 4 H, -CH_2-), 1.64 (m, 2 H, -CH_2-), 1.96 (m, 2 H, -CH_2-), 2.00 (s, 3 H, -$OCOCH_3$), 3.46-3.51 (m, 2 H, -CHOH, -OH), 4.52 (m, 1H, -CHOAc).

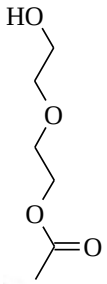
^{13}C NMR (100Hz, $CDCl_3$): δ 20.94, 21.11, 21.83, 26.80, 30.13, 68.92, 74.04,170.72.

IR (neat): 3410, 2927, 2857, 1734, 1447, 1371, 1241, 1050 cm^{-1}.



^{1}HNMR (400MHz, $CDCl_3$): Diethyleneglycol monoacetate





^{13}HNMR (400MHz, $CDCl_3$): Diethyleneglycol monoacetate

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Part II

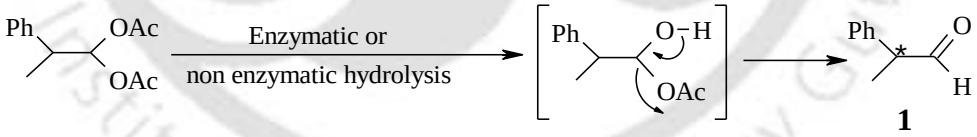
Synthesis of Geminaldiacetates

Chapter I

Introduction

1.1 Significance and applications

Geminal diacetates are gaining importance in organic synthesis as an alternative to acetals, oxathioacetals and thioacetals for the protection of aldehydes as they are stable in neutral and basic media.[1] They are superior to acetals because, during acetalization of acetals, the water formed in the reaction medium must be removed either by physical or by chemical means. This procedure is not necessitated during gem-diacylation of aldehydes. The acylals of α β-unsaturated aldehydes are important starting materials for the synthesis of acetoxy dienes and vinyl acetate.[2] They are also useful reagent for cross linking reagents for cellulose in cotton and serve as activators in the composition of the bleaching mixture used for the treatment of wine-strained fabrics.[3] In addition, *gem*-diacetates are useful intermediates for nucleophilic substitution reactions.[4] Since the C-O bond of acylals are enantiotopic, they can be used for the optical resolution of aldehydes. The nucleophilic hydrolysis of acylals lead to a "hemiacylas" which looses a carboxylate group to liberate the starting aldehyde. If the deprotection step is accomplished enzymatically the liberated aldehyde **1** is expected to be enatiomerically enriched (Scheme 1.1)

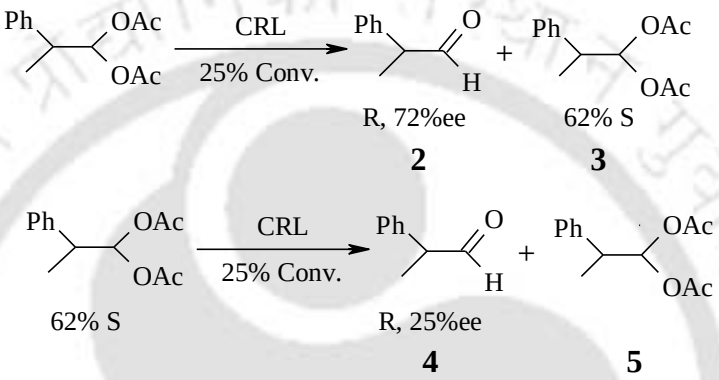


Scheme 1.1

Smonou *et al*.[5] have reported a new and convenient method for the optical resolution of aldehydes through lipase-catalyzed resolution of the corresponding acylals (Scheme 1.2). It was observed the Candida Rugosa Lipase (CRL) showed the best stereoselectivity than other hydrolytic enzymes like Pig Liver Esterase (PLE), Pig Pancreatic Lipase (PPL), P. Fluorescens Lipase (PFL).

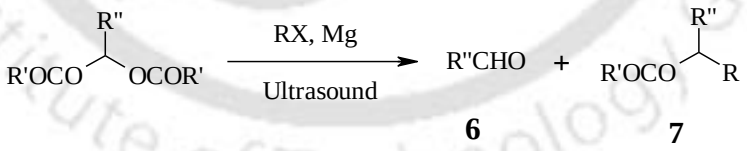
Acylas have remarkable reactivity towards the nucleophiles and yield the esters of secondary alcohols, which carry potential interest in the synthetic organic chemistry. Their reactivity towards nitrogen, [6] oxygen[7] and carbon[8] nucleophiles has been reported.

Sydnes *et al* [9] have prepared the aldehyde acylals and reacted with Grignard and alkyllithium reagents. Acylals from formaldehyde furnished complex reaction mixtures when reacted with both reagents. Acylals of other aldehydes gave reaction mixtures that consisted mainly of an ester **7**, generated by replacing one of the carboxy groups with the organic part of the organometallic reagent, and regenerated aldehyde **6**. The esters were formed in the highest



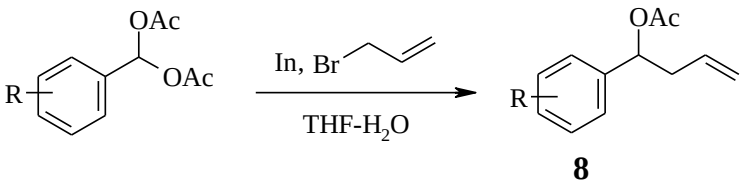
Scheme 1.2

yields. Yields more than 90% were experienced when the acylals were reacted with Grignard reagents under Barbier conditions (Scheme 1.3).



Scheme 1.3

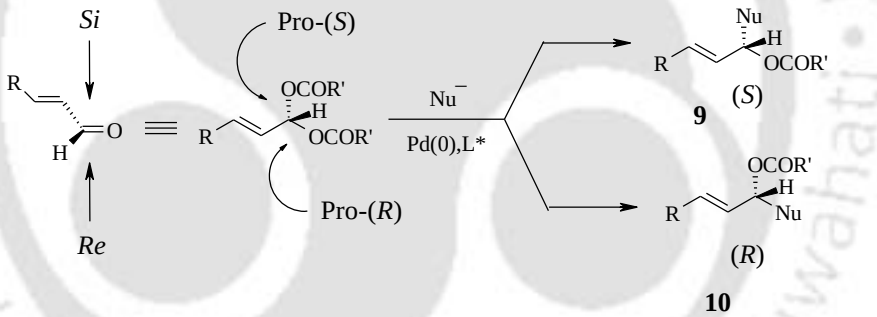
Yadav and coworkers have reported Indium-mediated allylation of *gem*-diacetates to the corresponding homoallylic acetates in aqueous media (Scheme 1.4).[10] The reaction of aromatic diacetates with an equimolar ratio of allyl bromide and indium metal in THF:H_2O (4:1), resulted in the formation of the mono-allylated products in good yields while aliphatic and allylic diacetates gave homoallylic acetates **8** in moderate yields.



8

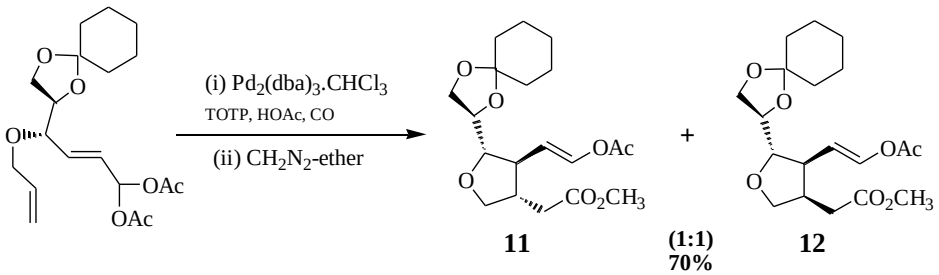
Scheme 1.4

Acylals of α, β-unsaturated aldehydes can serve as synthons for allylic esters which is a versitile synthetic building block in organic chemistry.[11] This feature originates from the steric and electronic properties of the allylic setting which allows for easy introduction of a new bond and provides strong diastereofacial guidance to the addition reactions of the adjacent alkene. The π-face of the carbonyl group can be discriminated in a catalytic fashion by the asymmetric allylic alkylation (AAA) of *gem*-dicarboxylates (Scheme 1.5) [12]



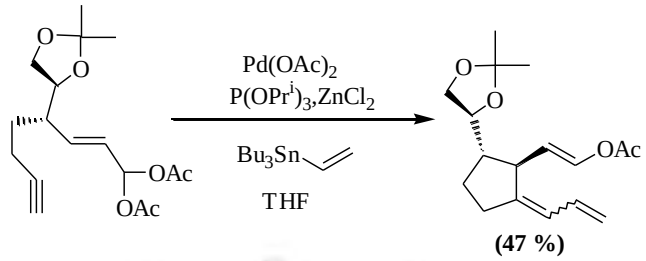
Scheme 1.5

Cedric and coworkers[13] have reported that Pd(0) and Pd(II)-catalysed cyclisation reactions of acyclic carbohydrate-derived 1,l-diacetoxy-2,7-diene and l,l-diacetoxy-2-en-7-yne compounds proceed in a specific fashion to furnish chiral multi-functionalised furanoids **11, 12** and **14** and cyclopontanoid **13** products. (Scheme 1.6 – Scheme 1.8).



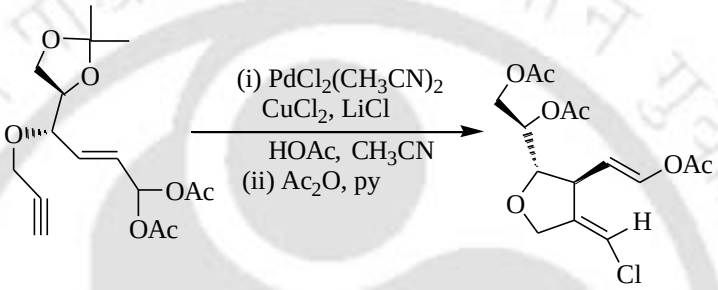
11 **(1:1) 70%** **12**

Scheme 1.6



13

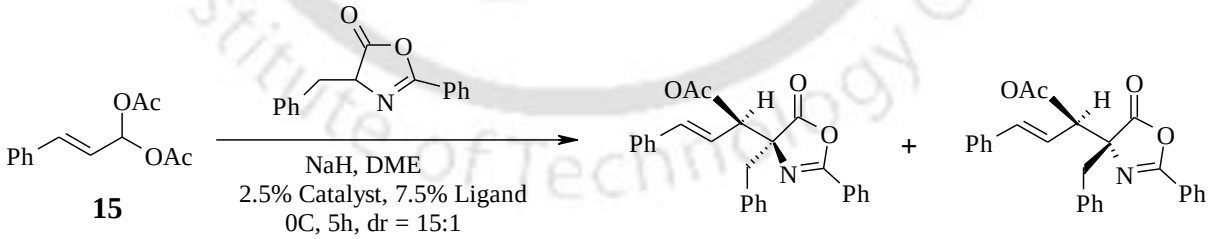
Scheme 1.7



14

Scheme 1.8

Since the C-O single bonds in the acylals are enantiotopic they can be used as the carbonyl surrogates in asymmetric synthesis. The nucleophilic substitution on the acylal of cinnamaldehyde **15** leads to the formation of **16** which is the key intermediate in the synthesis of **18** and **19**, which are antifungal agents (Scheme 1.9).[14]



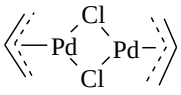
15

(75%, 99% ee)

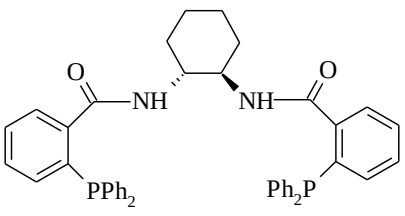
16

(5%, 98% ee)

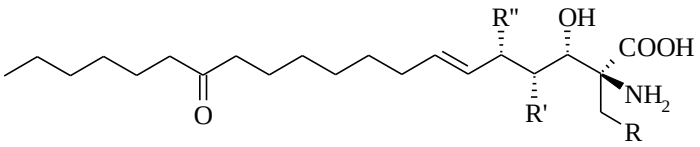
17



Catalyst



Ligand

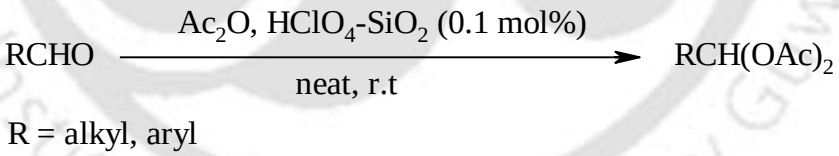


Sphingofungin E **(18)**: R = CH_2OH, R' = OH, R" = OH
Sphingofungin F **(19)**: R = CH_3, R' = OH, R" = OH

Scheme 1.9

1.2 Preparation

Numerous methods are available in the literature for the conversion of an aldehydic carbonyl group to the corresponding *gem*-diacetates using acid anhydrides. Rahman *et al.* have reported the synthesis of aldehydes into the corresponding acylas under catalyst free conditions.[15] Traditionally the acylals were prepared in the presence of protic acids such as H_3PO_4, [16] H_2SO_3,[17] $HClO_4$,[18] $MeSO_3H$.[19] or in the presence of Lewis acid catalysts. Kamble *et al.* have reported the synthesis of acylals from structurally diverse aldehydes in excellent yields under solvent-free conditions using $HClO_4$-SiO_2 as a mild, convenient, reusable, and heterogeneous catalyst (Scheme 1.10).[20]



Scheme 1.10

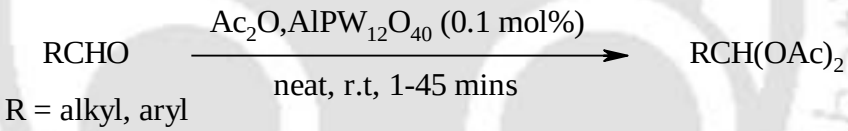
Desai *et al.* have developed an efficient method for the chemoselective synthesis of acylals from aldehydes and acetic anhydride in the presence of silica sulfuric acid as a reusable solid acid catalyst under solvent-free conditions. Ketones are found to remain unaffected under the reaction conditions. The deprotection of acylals has also been achieved using silica sulfuric acid in methanol medium.[21] Heravi *et al.* have reported synthesis of a variety of aromatic aldehydes with acetic anhydride in the presence of catalytic amount of 12-molybdophosphoric acid, $H_3PMo_{12}O_{40}$, in excellent yields. Ketones are not affected under the reaction conditions.

The catalyst in dry acetone has also been successfully applied for deprotection of the resulting acylals.[22]

Mirjalili *et al.* have used the combination of P_2O_5 and SiO_2 as an efficient catalyst for the conversion of aldehydes to their corresponding acylals with excellent yields at room temperature under mild conditions.[23]

Eshghi *et al.* have reported a facile and efficient method for the preperation of 1,1-diacetates of aldehydes catalyzed by P_2O_5/montmorillonite K-10 in dry media. Both aromatic and aliphatic aldehydes gave high yields (70-95%) of the corresponding 1,1-diacetates. Advantages of this method are the use of an inexpensive and selective catalyst, with high yields in simple operation and short reaction time under solvent-free conditions.[24]

Firouzabadi *et al.* have described an efficient and chemoselective preperation of acylals from structurally different aldehydes in the presence of $AlPW_{12}O_{40}$ and acetic anhydride in high yields at room temperature under solvent-free conditions (Scheme 1.11). [25]



Scheme 1.11

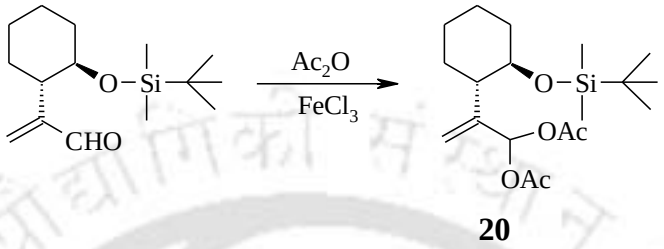
Roy *et al.* have reported a mild and efficient method for the chemoselective synthesis of geminal diacetates from aldehydes using acetic anhydride in the presence of a catalytic amount of ceric ammonium nitrate in excellent yield.[26]

Karmakar *et al.* have described the selective and easy synthesis of acylals in dry media using montmorillonite K-10 clay in an Erlenmeyer flask under microwave activation.[27]

Curini *et al.* have reorted that the layered zirconium sulfophenyl phosphonate was found to be an efficient heterogeneous catalyst for the preperation and deprotection of 1,1-diacetates.[28]

Carrigan *et al.* have reported that the aromatic aldehydes are smoothly converted into the corresponding acylals in good yields in the presence of 0.10 mol% $Bi(OTf)_3.xH_2O$. Ketones are not affected under the reaction conditions. The highly catalytic nature of Bismuth triflate and the fact that it is relatively nontoxic, easy to handle and insensitive to small amounts of air and moisture makes this procedure especially attractive for large-scale synthesis.[29] During

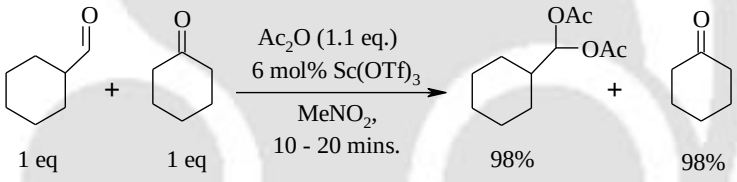
a study aimed at the synthesis of α-methylene lactones, a new preparation of geminal diacetate **20** was discovered (Scheme 1.12). [30]



20

Scheme 1.12

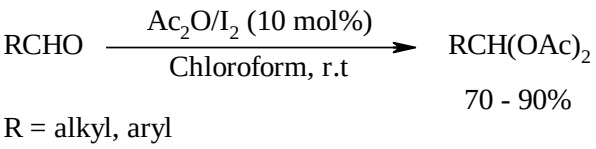
Aggarwal and coworkers have reported an efficient method for the formation and deprotection of geminal diacetates **21** using $Sc(OTf)_3$ (Scheme 1.13). [31]



21 **22**

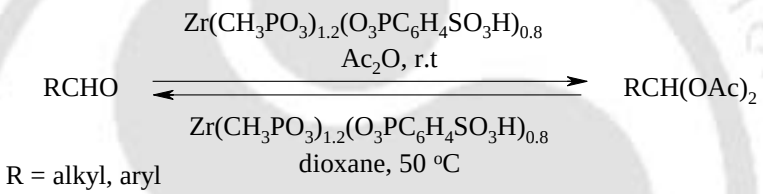
Scheme 1.13

Smitha *et al.* have developed a novel, mild and efficient method for the preparation of geminal-diacetates and dipivalates in high yields through a reaction of aldehydes with acetic anhydride or pivalic anhydride using zirconium(IV)chloride as a catalyst under solvent free conditions.[32] Deka *et al.* have reported the molecular Iodine catalyzed synthesis of acylals from aldehydes and acetic anhydride in short time with excellet yields.[33] (Scheme 1.14)



Scheme 1.14

Chakraborti *et al.* have reported an efficient procedure for the synthesis of aldehyde 1,1-diacetates from aldehydes and acetic anhydride, under solvent-free conditions, in the presence of a catalytic amount of copper II) tetrafluoroborate hydrate in excellent yields.[34] Ranu and coworkers have reported zinc tetrafluoroborate catalyzed conversion of an aldehyde to its 1,1-diacetate with acetic anhydride under solvent-free condition. A similar reaction of an aldehyde with a mixture of potassium cyanide and acetic anhydride in methylene chloride was also catalyzed by the same catalyst to provide the corresponding geminal cyanoacetate.[35]
Layered zirconium sulfophenyl phosphonate was found to be an efficient heterogeneous catalyst for the preparation and deprotection of 1,1-diacetates (Scheme 1.15). [36]

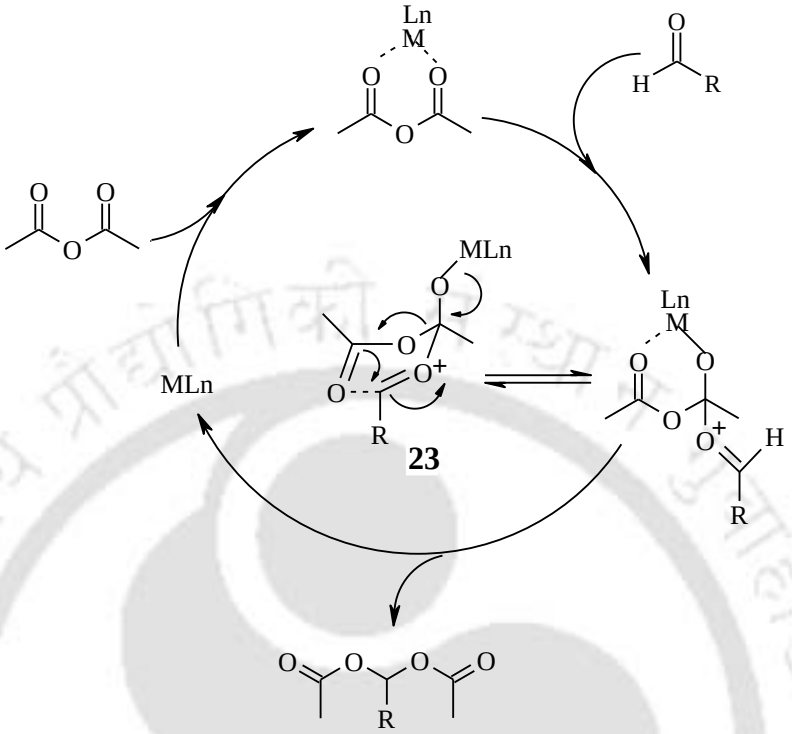


Scheme 1.15

Kavala *et al.* have reported an efficient method of preparing giminal dicarboxylates with various aldehydes and anhydrides catalyzed by tetrabutyl ammonium tribromide with detailed mechanistic study.[37] Other catalysts such as $ZnCl_2$[38], PCl_3,[39] Nafion-H,[40] $CoCl_2$,[41] Zeolite,[42] clay,[43] Cu $(OTf)_2$,[44] NBS,[45] $LiBF_4$,[46] $InCl_3$,[47] $FeCl_3$-SiO_2,[48] $H_6P_2W_{18}O_{62}\cdot 24H_2O$,[49] Zinc(II) perchlorate,[50] also have been reported to effect this transformation.

1.3 Mechanistic Aspects

Mechanism of this reaction has been a subject of controversy.[51-53] The role of a metal derived catalyst was to activate the anhydride, through coordination with the carbonyl oxygen atoms of the anhydride, to make it susceptible to nucleophilic attack by the carbonyl oxygen atom of the aldehyde to form the transition state **23** that subsequently undergoes rearrangement to form the 1,1-diacetate and liberates the catalyst (Scheme 1.16) [50].



23

Scheme 1.16

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CHAPTER II

Lithium Chloride Assisted Chemoselective Conversion of Aldehydes into Geminal Diacetates under Solvent-free Conditions

Introduction:

2.1 Orgnaic reactions in solvent free conditions

Solvent free reactions have attracted considerable attention in chemical processes due to their safety, economy, easy work up, high yield and fast reaction rate.[1] A general assumption with regard to organic reactions is that they are performed in a solvent medium. The rationale behind this concept is simple. That is, the reactants can interact effectively if they are in a homogeneous solution, which facilitates the stirring, shaking or other ways of agitation, whereby the reactant molecules come together rapidly and continuously. Moreover, uniform heating or cooling of the mixture, if needed, can be carried out in a solution relatively easily. However, the role of a solvent in the context of an organic reaction is much more complex than merely providing a homogeneous setting for a large number of collisions of the reactants to take place. A solvent has the power to enhance or reduce the speed of a reaction, at times enormously. Changing of solvent of a reaction can influence the rate of that reaction, and it can be powerful enough to change the reaction course itself. This may manifest in altered yields and ratios of the products. Thus a solvent could be deeply and inseparably associated with the process of an organic reaction through the solvation of the reactants, products, transition-state or other intervening species. Such intimate interactions between the solvent and the reaction partners are due to many factors that include electrostatic, steric and conformational effects, among others. In spite of such a strong involvement, the solvent does not normally become part of the product, except in the case of solvolysis reactions, and is recovered unchanged after the reaction is over. Even then, one may not envisage or plan to perform a reaction in the absence of a solvent.

In principle, any liquid can be used as a solvent. However, the number of commonly used solvents is severely restricted. They include a few hydrocarbons, chlorinated hydrocarbons, a few ethers, esters, alcohols, amide derivatives, sulphoxides, etc. Liquid ammonia, CS_2, and of course water, are also frequently used as medium to carry out synthesis. The suitability of a solvent for a reaction depends on many factors. At times the liquid reactant itself would serve

as solvent. In any case, a solvent is usually considered to be an inevitable component of a reaction. A reaction under solvent free condition or in solid state was generally thought to be not quite feasible, or at least not quite efficient, though several solid-state organic reactions have been known for a long time. However, the chemists' concern for developing environmentally[2,3] benign synthetic procedures has made them turn their attention to minimize or circumvent the use of solvents that are a major cause of pollution. This has led, in recent times, to vigorous research activity and reinvestigation of known reactions to achieve organic synthesis under solvent-free condition. A solvent-free or solid-state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices. Thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction. Solvent-free reactions obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour. These would be especially important during industrial production.

2.2 Lithium Chloride in Organic Synthesis

Lithium Chloride is a very week Lewis acid and dissolved in many solvents. Sabitha *et al*. have reported the Lithium chloride catalyzed acetylation of alcohols, thiols, phenols and amines with acetic anhydride.[4] Rajaram *et al.* have reported the application of LiCl / $NaBH_4$ for the reductive cleavage of organic disulfides to mercaptans under mild conditions, in excellent yields.[5]

Mogilaiah *et el.*[6] have reported an efficient, practical and eco-friendly method of preparation of 1,8-naphthyridines by Friedlander condensation between 2-aminonicotinaldehyde and active methylene compounds in the presence of LiCl in combination with microwave irradiation and also with a pestle and mortar.

Tulba *et al.*[7] have reported the preparation of a series of amides of 2,4-dichloro-5-pentadecylphenoxyacetic acid by direct amidation reaction of the acid with different aromatic amines. Reaction was carried out in N-methyl pyrrolidone, with pyridine as solvent, and tri-phenyl phosphite and LiCl as catalysts. Various substituted acetamides were synthesized in good yields.

Shailaja et al. have reported a one-pot synthesis of the 3,4-dihydropyrimidin-2(1H)-ones catalyzed by $SnCl_2$-LiCl involving three-component cyclization of aldehydes with ethyl acetoacetate and urea or thiourea.[8] Mogilaia et al have reported a simple and efficient procedure for the synthesis of trans-cinnamic acids by the condensation of aromatic aldehydes with malonic acid using LiCl as catalyst under solvent-free conditions using microwave irradiation. The products are obtained in excellent yields and in a state of high purity.[9] Kurono *et al.*[10] have reported LiCl catalyzed cyanosilylation of various hetero-substituted ketones. α,α-Dialkoxy ketones are completely converted to silylated cyanohydrins with a substrate-to-catalyst molar ratio of 100,000 at room temperature. Acetophenones substituted by an electron-attracting group at the ortho or para position show higher reactivity than substrates with an electron-donating function.

Lee *et al.*[11] have reported the preparations of block copolymers of α-methylstyrene with cyclohexyl methacrylate or methyl methacrylate by the subsequent monomer addition technique via anionic living polymerisation using s-BuLi as initiator in the presence of LiCl in THF. Addition of LiCl to the polymerisation system results in narrowing the molecular weight distribution of the block copolymers.

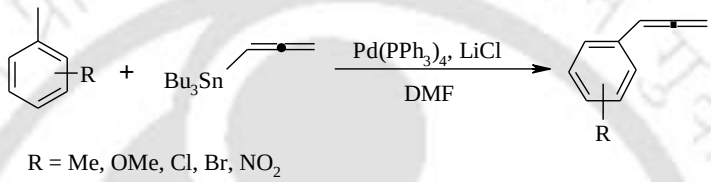
Yum *et al.*[12] have reported the preparation of heteroaryl ketones and aldehydes, such as pyridinylbutanone **1** and pyridinylpropanal **2** in 45-75% yields by LiCl-mediated Heck reaction of heteroaryl halides in the presence of palladium diacetate.

1 **2**

Figure 2.1

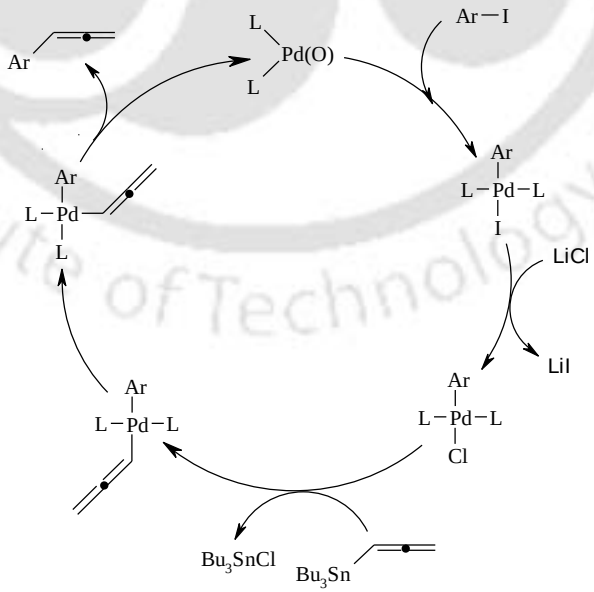
Dai *et al.* have reported the oxidative coupling of methane to C_2-hydrocarbons using LiCl/MnO_2-H_3BO_3 as catalyst.[13] Mogilaiah *et al.*[14] have reported microwave assisted Claisen-Schmidt condensation of 2-(4 acetylphenyl-amino)-3-(4-methoxyphenyl)-1,8-naphthyridine with various aromatic aldehydes under solvent-free conditions to prepare α,β-unsaturated ketones using LiCl as catalyst. The products are obtained in good yields and excellent purities.

A selective synthesis of conjugated enynes from α-arylalkynols using LiCl-acidic Al_2O_3 under solvent-free conditions has been reported by Pourjavadi and coworkers.[15] LiCl is used as additive in a variety of reactions catalyzed by palladium compounds.[16] Chien-Hong Cheng and coworkers[16] have reported an efficient method for the preparation of various monosubstituted arylallenes, disubstituted allenes and alkenylallenes via palladium-catalyzed coupling of allenylstannanes with aryl iodides or alkenyl iodides. The coupling reaction was carried out in the presence of $Pd(PPh_3)_4$ and LiCl using DMF as solvent (Scheme 2.1).



Scheme 2.1

It is likely that the chloride ion undergoes halide exchange with the coordinated iodide in the oxidative addition product to give organopalladium chloride prior to the transmetalation step. The chloro complex facilitates the transmetalation with allenylstannane by the formation of stable Bu_3SnCl (Scheme 2.2).

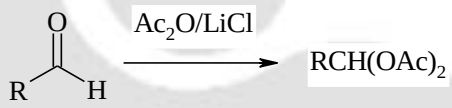


Scheme 2.2

Lithium chloride is also known to effect various transformations such as chlorination[17,18] dehydrohalogenation[19] deprotection of THP[20] and epoxide ring opening.[21]

2.3 Results and discussion:

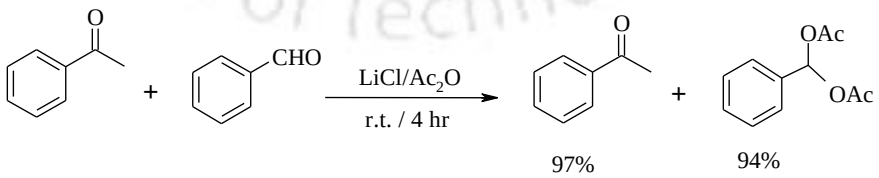
In this chapter[22] we report a simple and efficient method for the conversion of aldehydes into *gem*-diacetates using lithium chloride and acetic anhydride under neutral and solvent free conditions (Scheme 2.3). Thus, the treatment of benzaldehyde with acetic anhydride in the presence of lithium chloride at ambient temperature gave benzal diacetate in 95% yield. The reaction is generalized through entry 1-13 as shown in Table 2.1.



Where R= alkyl, aryl

Scheme 2.3

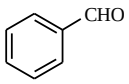
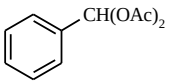
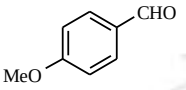
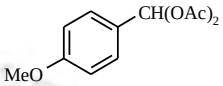
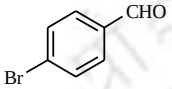
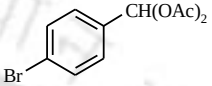
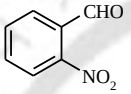
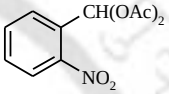
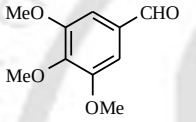
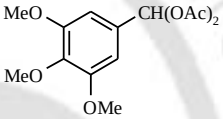
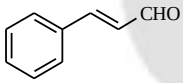
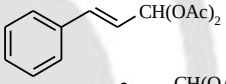
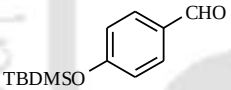
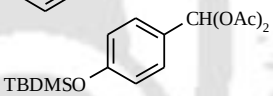
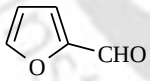
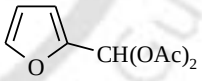
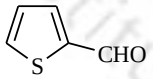
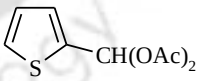
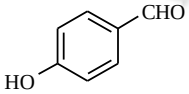
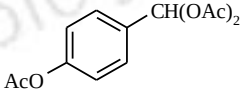
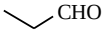
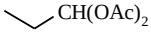
It was also observed that when a mixture of aldehyde and ketone was treated with the same reagent only aldehyde was selectively protected (with 94% yield) leaving behind the ketone (97% recovered) unaffected (Scheme 2.4). Therefore, aldehydes can be chemo-selectively protected as acylals in the presence of ketones. Both aromatic and aliphatic aldehydes could be converted to their corresponding gem diacetates in high yields.



Scheme 2.4

However, the aliphatic aldehydes and aromatic aldehydes having electron-withdrawing groups react sluggishly. The groups like methoxy, bromide, nitro, TBDMS, THP, double bond remain unaffected under the reaction conditions. The mildness of the protocol enables

Table 2.1: Lithium chloride assisted conversion of aldehydes into geminal diacetates

Entry	Substrate	Time/h	Temp./^{o}C	Product	% Yield[a]
1		6	25		95
2		5	25		96
3		4	80		89
4		8	80		95
5		4	25		98
6		12	80		75
7		7	25		91
8	$CH_3(CH_2)_8CHO$	4	80	$CH_3(CH_2)_8CH(OAc)_2$	97
9	$CH_3(CH_2)_{14}CHO$	6	80	$CH_3(CH_2)_{14}CH(OAc)_2$	92
10		5	25		87
11		5	25		84
12		10	25		85[b]
13		5	80		89

[a]Yields refer to isolated yield. Compounds are characterized by GC, 1H, 13C NMR and IR spectra

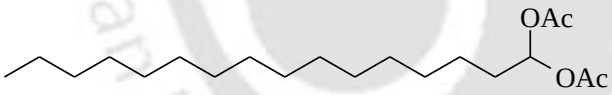
the acid sensitive compounds like 2-furaldehyde, 2-thiophenecarboxaldehyde to be converted to their corresponding diacetates without any difficulties.

In conclusion, the present work describes a mild, chemo-selective, high yielding and solvent free method for the protection of aldehydes as *gem*-diacetates using LiCl under neutral conditions thereby leaving acid and base sensitive groups intact.

2.4 Experimental Section:

Typical experimental section: A mixture of aldehyde (1 eq.), acetic anhydride (2.0 eq.), and LiCl (1.1 eq.) was stirred at room temperature or gently heated with stirring at 80 ^{o}C (oil bath) without any solvent under nitrogen for a certain time as required for a complete reaction which is monitored by thin layer chromatography (silica gel; EtOAc: Hexane; 1:9). The resulting diacetate was extracted with 10 Ml of ethyl acetate, washed with of dilute $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography over silica gel (EtOAc: Hexane; 1:9).

Spectral data



1,1-Diacetoxy-hexadecane

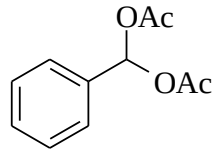
M.p.= 50 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J*= 7.2 Hz, 3 H, CH_3), 1.25 (brm, 24 H, 12 x CH_2), 1.62 (m, 2 H, CH_2), 1.74 (m, 2 H, -CH_2-), 2.07 (s, 6 H, 2 -$OCOCH_3$), 6.76 (t, *J*= 6.00 Hz, 1 H, -$CH(OAc)_2$)

^{13}C NMR (100 MHz, $CDCl_3$): 169.18, 90.85, 33.60, 32.34, 30.11, 29.93, 29.85, 29.78, 29.60, 23.83, 23.14, 21.31, 14.59.

IR (KBr**):** 2930, 2853, 1767, 1245, 1015 cm^{-1}.

Anal. Calculated for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.42; H, 11.05.

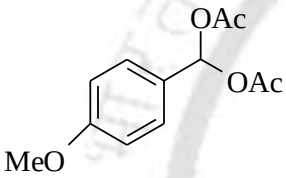


1,1-Diacetoxy-1-phenyl methane

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 6 H, 2 -$OCOCH_3$), 7.38-7.40 (m, 3 H, Ar-H), 7.50-7.54 (m, 2 H, ArH), 7.68 (s, 1 H, $CH(OAc)_2$).

^{13}CNMR (100 MHz, $CDCl_3$): δ 21.2, 89.9, 126.8, 128.7, 129.9, 135.6, 168.8.

IR (neat**)** : 2976, 2848, 1757, 1598, 1373, 1250, 1122 cm^{-1}.



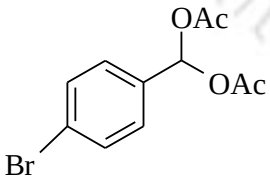
1,1-Diacetoxy-1- (4-methoxy-phenyl) methane

M.p.= 66 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 6 H, 2 -$OCOCH_3$), 3.80 (s, 3 H, –OMe), 6.74 (d, *J*= 9Hz, 2 H, ArH), 7.35 (d, *J*= 9Hz, 2 H, ArH), 7.40 (s, 1 H, -$CH(OAc)_2$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 160.72, 128.34, 127.92, 114.15, 90.04, 55.68, 21.35.

IR (KBr**)**: 2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.



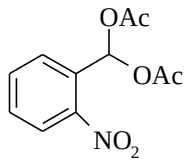
1,1-Diacetoxy-1-(4-bromo-phenyl) methane

M.p.= 83 ^{o}C

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.10 (s, 6 H, 2 -$OCOCH_3$), 7.40 (m, 4 H, ArH, -$CH(OAc)_2$).

^{13}CNMR (100 MHz, $CDCl_3$): δ. 21.1, 88.6, 124.0, 128.0, 142.0, 142.8, 168.6.

IR (KBr**)**: 2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.

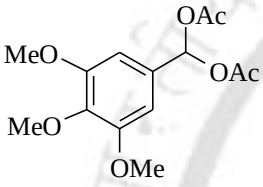


1,1-Diacetoxy-1-(2-nitro-phenyl) methane

M.p.= 85-86 ^{o}C

^{1}H NMR: (60 MHz, $CDCl_3$): δ 2.10 (s, 6 H, 2 -$OCOCH_3$), 7.35-7.90 (m, 4 H, ArH, -$CH(OAc)_2$), 7.40 (s, 1 H, -$CH(OAc)_2$).

IR (KBr**)**: 2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.



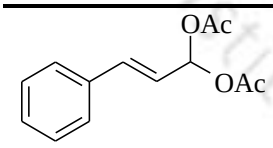
1,1-Diacetoxy-1-(3,4,5-Trimethoxy-phenyl) methane

M.p.= 114-116 ^{o}C

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.15 (s, 6 H, 2 -$OCOCH_3$), 3.80 (s, 3 H, –OMe), 3.90 (s, 6 H, 3 –OMe), 6.60 (s, 2 H, ArH), 7.40 (s, 1 H, -$CH(OAc)_2$).

^{13}C NMR (400 MHz, $CDCl_3$): 168.83, 153.51, 139.21, 131.03, 104.05, 90.08, 61.17, 56.56, 21.37.

IR (KBr**)**: 2976, 2848, 1757, 1598, 1373, 1250, 1122 cm^{-1}.



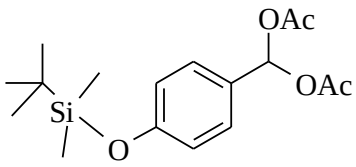
1,1-Diacetoxy-3phenyl-prop-2-ene

M.p.= 84 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 6 H, 2 -$OCOCH_3$), 6.21 (dd, *J*=15.9 and 6.3 Hz, 1 H, =CH-), 6.86 (d, *J*=15.9 Hz, 1 H, Ph-CH=), 7.33 (m, 6 H, C_6H_5-, -$CH(OAc)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.79, 135.78, 135.31, 129.03, 128.87, 127.21, 121.92, 90.02, 21.34.

IR (KBr): : 3062, 3032, 1767, 1454, 1380, 1244, 1208, 1145, 1064, 1008, 963, 760, 699 cm^{-1}



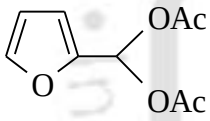
1,1-Diacetoxy-1-(4-tert-butyl dimethylsilyloxyphenyl) methane

M.p.= 57-59 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 3 H, -CH_3), 0.16 (s, 3 H, -CH_3), 0.24 (s, 9 H, -$C(CH_3)_3$), 2.12 (s, 6 H, 2 -$OCOCH_3$), 7.79 (d, *J*=8.4 Hz, 2 H, ArH), 7.99 (d, *J*=8.4 Hz , 2 H, ArH), 8.05 (s, 1 H, -$CH(OAc)_2$).

^{13}CNMR (100 MHz, $CDCl_3$): δ -3.91, 18.6, 21.3, 26.0, 89.9, 120.2, 128.2, 128.4, 133.8, 157.0, 168.9.

IR (KBr): 2962, 2852, 1756, 1652, 1240, 11600, 1060 cm^{-1}.

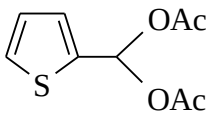


2-(Diacetoxymethyl)furan

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 6 H, 2 -$OCOCH_3$), 6.38 (dd, *J*=3.6 and 1.6 Hz, 1 H), 6.52 (dd, *J*= 3.6 and 2.0 Hz, 1 H), 7.45 (d, *J*= 1.6 Hz, 1 H), 7.71 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.50, 148.24, 143.78, 110.58, 109.94, 83.78, 21.12.

IR (neat) : 2940, 1767, 1240, 1066, 1009 cm^{-1}.

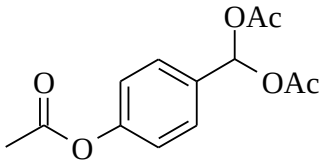


2-(Diacetoxymethyl)thiophene

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 6 H, 2 -$OCOCH_3$), 6.38 (dd, *J*=3.6 and 1.6 Hz, 1 H), 6.52 (dd, *J*= 3.6 and 2.0 Hz, 1 H), 7.45 (d, *J*= 1.6 Hz, 1 H), 7.71 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.50, 148.24, 143.77, 110.58, 109.93, 83.72, 21.10.

IR (neat) : 2940, 1762, 1680, 1245, 1020, 753 cm^{-1}.



1,1-Diacetoxy-1-(4-acetoxy-phenyl) methane

M.p.= 57 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 6 H, 2 -$OCOCH_3$), 2.30 (s, 3 H, -$OCOCH_3$); 7.12 (d, *J*=8.8 Hz, 2 H, ArH), 7.53 (d, *J*= 8.8 Hz, 2 H, ArH), 7.67 (s, 1 H, -$CH(OAc)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.29, 168.77, 151.71, 133.24, 128.25, 122.02, 89.41, 21.54, 21.28.

IR (KBr) : 2940, 1762, 1680, 1373, 1204, 1015, 840 cm^{-1}.

2.5. References

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CHAPTER III

Cerium (IV) triflate catalyzed selective *gem*-diacetylation of aldehydes with acetic anhydride

3.1 Lanthanide triflates in organic synthesis

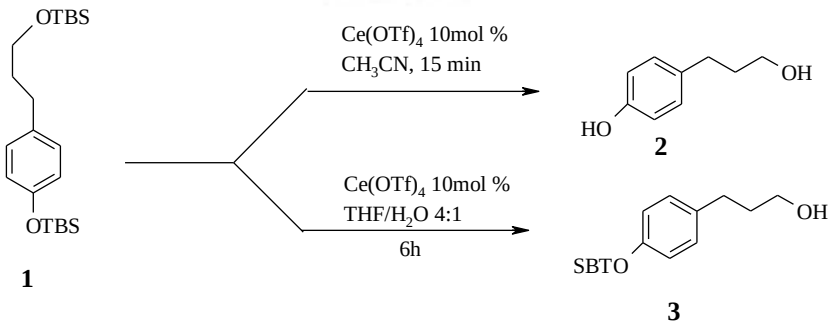
Environmental concerns about today's chemical research and industry are ever increasing. The challenge for a sustainable environment calls for clean reaction processes that avoid the use of hazardous and harmful organic solvents.[1] Water, the most abundant and renewable resource on the planet, is no doubt the most desirable solvent in this respect. After being ignored for decades, water has recently been recognized again as a solvent for organic reactions [2-4] Lanthanide trifluoromethanesulfonates (triflates) are unique Lewis acids that are currently of great research interest. Unlike common Lewis acids that decompose readily in the presence of water, lanthanide triflates are stable in water and function well in aqueous media[5]. They effect numerous reactions such as Diels-Alder reaction[6], aldol reaction,[7-12] Michael addition[13] allylation of carbonyl and imine groups.[14, 15] in aqueous solutions or simply in water

3.2 Cerium (IV) triflates in orgnic synthesis

Cerium is the less rare "rare earth"; its salts are commercially available and inexpensive.[16] $Ce(OTf)_4.xH_2O$ is commercially available, orange coloured,highly reactive, cheap, non-toxic, stable and water tolerant Lewis acid.

Iranpoor *et al.*[17] have reported the esterification reactions of alcohols with acetic, chloroacetic, trifluoroacetic, propionic, stearic, and benzoic acids with $Ce(OTf)_4$ in a solvent or under solvent-free conditions with high yields. The formylation and acetylation of primary and secondary alcohols were also easily achieved in ethyl formate and ethyl acetate.

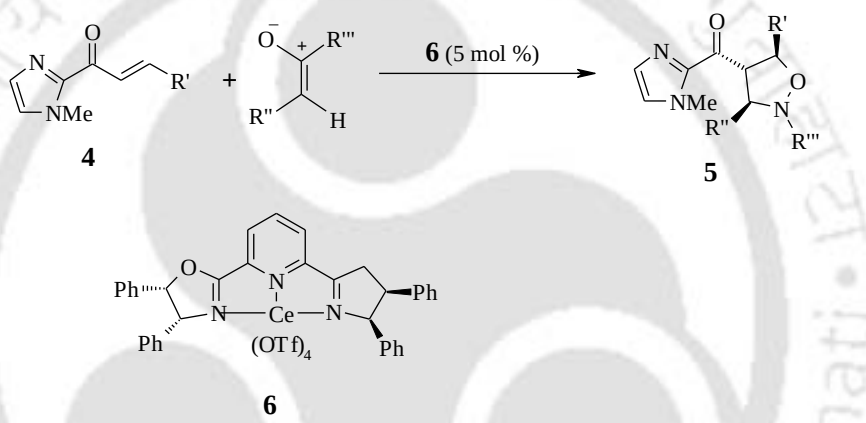
Bartoli and coworkers have reported the deprotection of **1** promoted by catlayltic amount of cerium(IV) triflate under mild condition (Scheme 3.1).[18] Laali and co-workers[19] have reported



Scheme 3.1

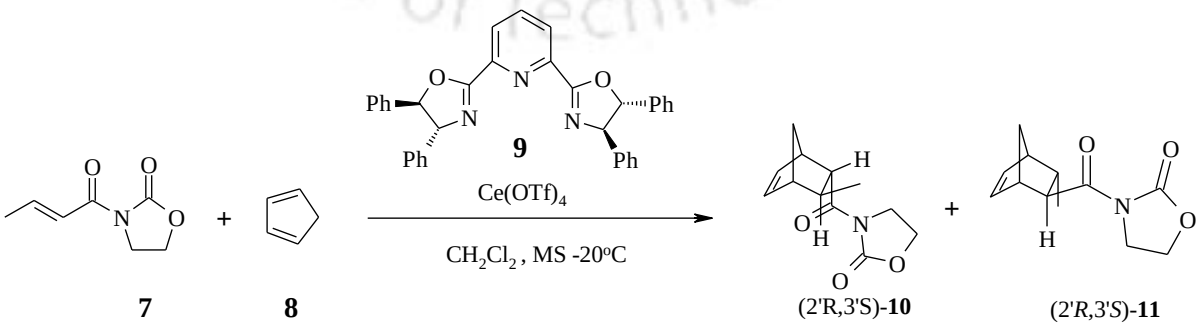
the benzylic oxidation of aromatics with cerium(IV) triflate. It was shown that the mode of preperation of $Ce(OTf)_4$ and the percentage of H_2O present in the sample have a remarkable influence on oxidation ability. A variety of mono and dialkylbenzenes, haloalkylbenzenes, bicyclic and tricyclic ring systems, and alkoxybenzenes surveyed.

Evans[20] and coworkers have reported the preparation of isoxazolidine derivatives **5** by enantioselective nitrone cycloadditions of α,β-unsaturated 2-Acyl imidazoles **4** catalyzed by bis(oxazolinyl)pyridine-cerium(IV) triflate complexes **6** (Scheme 3.2).



Scheme 3.2

A simple and general one-pot three-component synthesis of β-aminophosphonates from aromatic aldehydes, amines, and di-ethyl phosphite catalyzed by metal triflates at solvent free condition is described by Iranpoor and coworkers.[21] Several β -substituted alcohols were prepared by $Ce(OTf)_4$ catalyzed nucleophilic ring opening of epoxides with sodium salts of



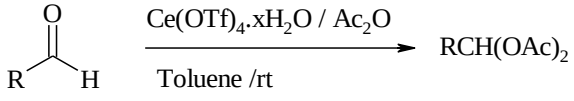
Scheme 3.3

nucleophiles such as CN^-, N_3^-, NO_3^-, NO_2^-, SCN^-, Br^- and Cl^- in micellar media.[22] Desimoni and coworkers[23] have reported an efficient catalyst for highly enantioselective exo-Diels-Alder reaction between alkenoyl-1,3-oxazolidin-2-ones **7** and cyclopentadiene **8** catalyzed by $Ce(OTf)_4$ (Scheme 3.3).

Although commercial cerium (IV) triflates have already been used as Lewis acid catalyst in various transformations, its applications in organic synthesis has not been extensively sorted out.

3.3 Results and discussion:

In the previous chapter, we have discussed the synthetic protocol for the synthesis acylals promoted by LiCl. Although it is mild and efficient towards aromatic aldehyde bearing electron-donating groups, the reaction goes sluggishly with aliphatic aldehydes and aromatic aldehydes carrying electron-withdrawing groups. The non-catalytic nature of that method prevents it from being economically viable. Moreover the excess of acetic anhydride and heating conditions are the other limitations of that method. Hence in continuation of our interest in acylal synthesis we were in search of a catalytic, rapid and high yielding protocol for the acylal synthesis. As $Ce(OTf)_4.xH_2O$ is known as a cheap, easily available and nontoxic Lewis acid, it is envisaged that this might be a suitable catalyst for the acylal synthesis. In this chapter the efficacy of $Ce(OTf)_4.xH_2O$ towards the selective *gem*-diacetylation of aldehydes in very good yields under mild conditions is reported. Thus when a mixture of benzaldehyde, acetic anhydride and $Ce(OTf)_4.xH_2O$ (0.1 mol%) in toluene was stirred at room temperature, benzal diacetate was obtained in 95% yield within 5 minutes (Scheme 3.3). Interestingly no dry conditions were maintained during the reaction.

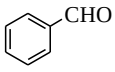
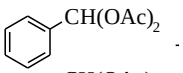
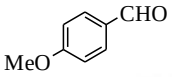
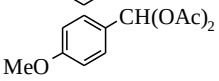
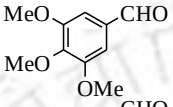
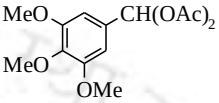
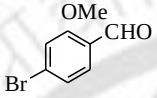
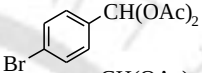
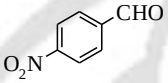
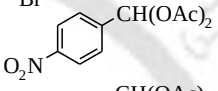
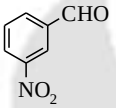
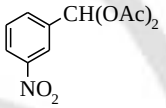
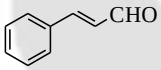
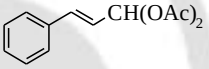
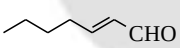
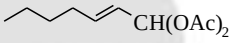
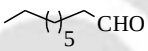
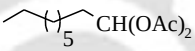
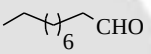
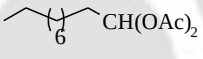
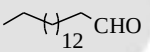
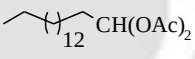
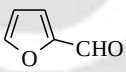
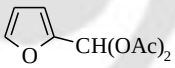
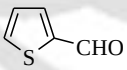
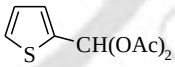
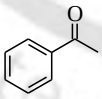
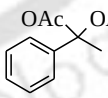
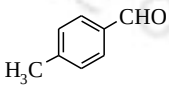
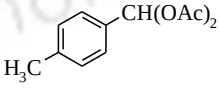
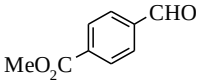
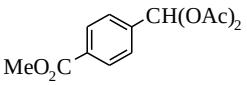
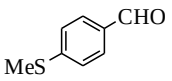
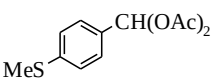
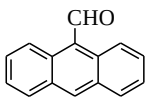
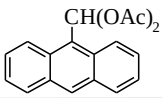


where R= alkyl, aryl

Scheme 3.3

In order to probe the efficiency of $Ce(OTf)_4.xH_2O$ as catalyst, the generality of the reaction was studied using a wide range of aromatic, unsaturated and aliphatic aldehydes (Table 3.1).

Table 3.1: Conversion of aldehydes to geminal diacetates catalyzed by $Ce(OTf)_4.xH_2O$

Entry	Substrate **(a)**	Time/min	Product **(b)**	% Yield [a]
1		5		95
2		5		96
3		10		98
4		15		92
5		25		95
6		40		96
7		5		89
8		10		90
9		10		89
10		10		92
11		10		93
12		5		97
13		10		95
14		30		0
15		5		97
16		15		90
17		30		92[b]
18		30		95[b]

aYields refer to isolated yield. Compounds were characterized by GC, 1H, 13C NMR and IR spectra.

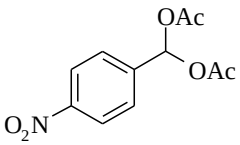
[b]Two equivalent of acetic anhydride and 1 mol% of catalyst were used

It was observed from the Table 3.1 that both activated and deactivated aromatic aldehydes gave the corresponding acylals in very good yield. More importantantly aliphatic aldehydes, which are somehow sluggish for this transformation, can be converted to their corresponding diacetates in good yields within a few minutes. Ketones remain unreacted under these reaction conditions. Therefore, aldehydes can be chemoselectively protected in the presence of ketones. Acid sensitive compounds like 2-furylaldehyde, 2-thiophenecarboxaldehyde and cinnamaldehyde are also protected as *gem*-diacetates in high yields without any side products, which are normally observed under strongly acidic conditions. Sterially hindered aldehyde (entries 3 and 18) also gave good yield. Under these reaction conditions many functional groups like methyl ether, thioether, ester, bromo, nitro and olefins are unaffected. As far as the catalyst is concern, it is a commercially available, stable to air and moisture and very low catalyst loading (0.1 mol%) is required for this transformation.

In conclusion, an efficient catalytic method for *gem*-diacetylation of aldehydes has been developed. A variety of aldehydes were acetylated in good yields under mild and neutral conditions. The catalytic, high yield, rapid, selective, functional group tolerance, mild reaction conditions, and easy work up of this reaction make this method an attractive alternative to the existing methods. Therefore, this protocol will find a wider use in protection of aldehyde as diacetate in organic synthesis.

3.4 Experimental Section:

In a typical experiment a mixture of 4-methoxybenzaldehyde (4.2 mmol), acetic anhydride (5.0 mmol), $Ce(OTf)_4.xH_2O$ (0.0042 mmol) in toluene (4 ml) was stirred at room temperature for 5 minutes. After completion of the reaction the reaction mixture was diluted with ethyl acetate (10 ml) and washed with water (10 ml). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel (silica gel; EtOAc:Hexane; 1:9) to give 96% of the product. Finally the product was characterized by spectroscopic methods.



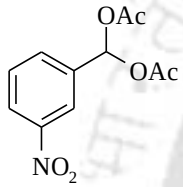
1,1-Diacetoxy-1-(4-Nitro-phenyl) methane

M.p. = 130°C

IR(KBr) : 2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.10 (s, 6 H, 2 -$OCOCH_3$), 7.35-7.90 (m, 4 H, ArH), 7.40 (s, 1 H, -$CH(OAc)_2$).

^{13}CNMR (100 MHz, $CDCl_3$): δ 21.1, 88.6, 124.0, 128.0, 142.0, 148.7, 168.6.



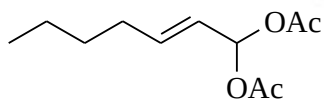
1,1-Diacetoxy-1-(3-Nitro-phenyl) methane

M.p. = 66-67°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 6 H, 2-$OCOCH_3$), 7.60 (t, *J*=8.0 Hz, 1 H, ArH), 7.72 (s, 1 H, ArH), 7.84 (d, *J*=7.6 Hz, 1 H, ArH), 8.25 (d, J=7.6 Hz, 1 H, ArH), 8.37 (s, 1 H, -$CH(OAc)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.00, 88.48, 121.90, 124.58, 129.80, 132.94, 137.58, 148.34, 168.50.

IR(KBr) : 2940, 1764, 1619, 1238, 1202, 1091, 1010 cm^{-1}.

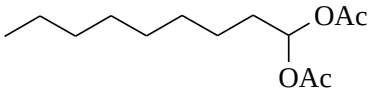


1,1-Diacetoxy-hept-2-ene

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J*= 7.2 Hz, 3 H, -CH_3), 1.26-1.42 (brm, 4 H, 2-CH_2-), 2.06 (m, 2H, -CH_2-), 2.10 (s, 6 H, 2-$OCOCH_3$), 5.50 (m, 1 H, -CH-), 6.00 (m, 1 H, -CH-), 7.07 (d, *J*= 6.4 Hz, 1 H, -$CH(OAc)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.16, 21.18, 22.46, 30.82, 31.91, 89.97, 123.17, 138.30, 168.65.

IR (neat) : 2961, 2932, 2874, 1763, 1372, 1242, 1206,1008 cm^{-1}.

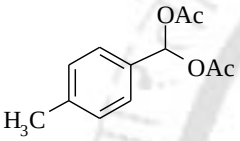


1,1-Diacetoxy-nonane

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J*= 6.8 Hz, 3 H, -CH_3), 1.26-1.40 (brm, 12 H, 6-CH_2),1.74 (m, 2H, -CH_2-), 2.07 (s, 6 H, 2-OCOCH_3), 6.75 (t, *J*= 5.6 Hz, 1 H, - CH(OAc)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 21.01, 22.9 23.7, 24.16, 29.43, 29.63, 32.07, 33.4, 90.7, 168.9.

IR (neat) : 2927, 2859, 1760, 1245, 1114, 1009 cm^{-1}.



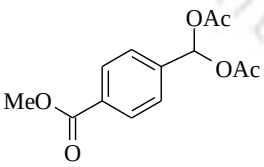
1,1-Diacetoxy-1-(4-Methyl-phenyl) methane

M.p. = 79-81^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 6 H, 2 -OCOCH_3), 2.36 (s, 3 H, –CH_3), 7.21 (d, *J*= 9 Hz, 2 H, ArH), 7.35 (d, *J*= 9 Hz, 2 H, ArH), 7.64 (s, 1 H, -CH(OAc)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.35, 21.76, 90.10, 126.81, 129.97, 132.77, 139.97, 168.91.

IR (KBr) :2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.



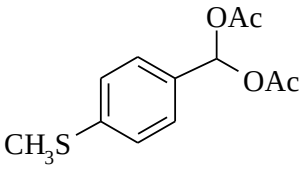
Benzoic acid, 4-[bis (acetyloxy)methyl]-, methyl ester

M.p = 67-69 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 6 H, 2 -OCOCH_3), 3.91 (s, 3 H, – CO_2CH_3), 7.57 (d, *J* = 9Hz, 2 H, ArH), 7.69 (s, 1 H, -CH(OAc)$_2$), 8.06 (d, *J*= 9Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.28, 52.68, 89.28, 126.93, 130.10, 131.53, 140.10, 166.54, 168.80.

IR (KBr) : 2976, 1763, 1519, 1612, 1373, 1250 cm^{-1}.



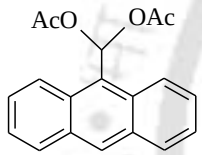
Methanediol, [4-(methylthio) phenyl]-, diacetate

M.p. = 50 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6 H, 2 -$OCOCH_3$), 2.47 (s, 3 H, - SCH_3), 7.23 (d, *J*=8.4 Hz, 2 H, ArH), 7.40 (d, *J*=8.4 Hz, 2 H, ArH), 7.60 (s, 1 H, - $CH(OAc)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.74, 21.15, 89.71, 126.20, 127.18, 132.10, 140.87, 168.70.

IR (neat) : 2997, 2931, 1759, 1597, 1224, 1068 cm^{-1}.



1, 1-Diacetoxy-9-methylanthracene

M.p. = 197-198 ^{o}C.

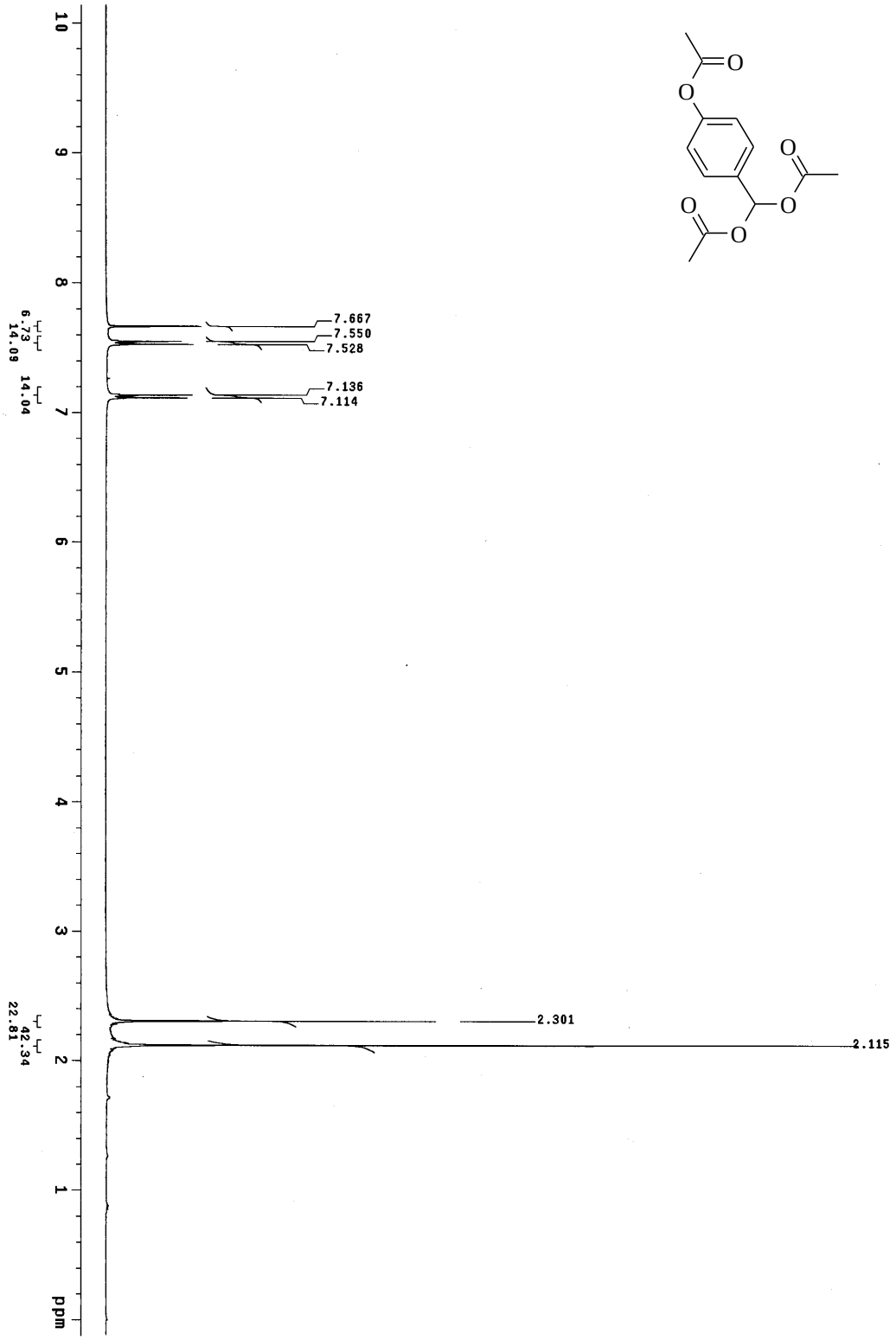
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 6 H, 2 -$OCOCH_3$), 7.46 (m, 2 H, ArH), 7.56 (m, 2 H, ArH), 7.98 (d, *J*=8.4 Hz, 2 H, ArH), 8.50 (s, 1 H, ArH), 8.67 (d, *J*=9.2 Hz, 2 H, ArH), 9.20 (s, 1 H, -$CH(OAc)_2$).

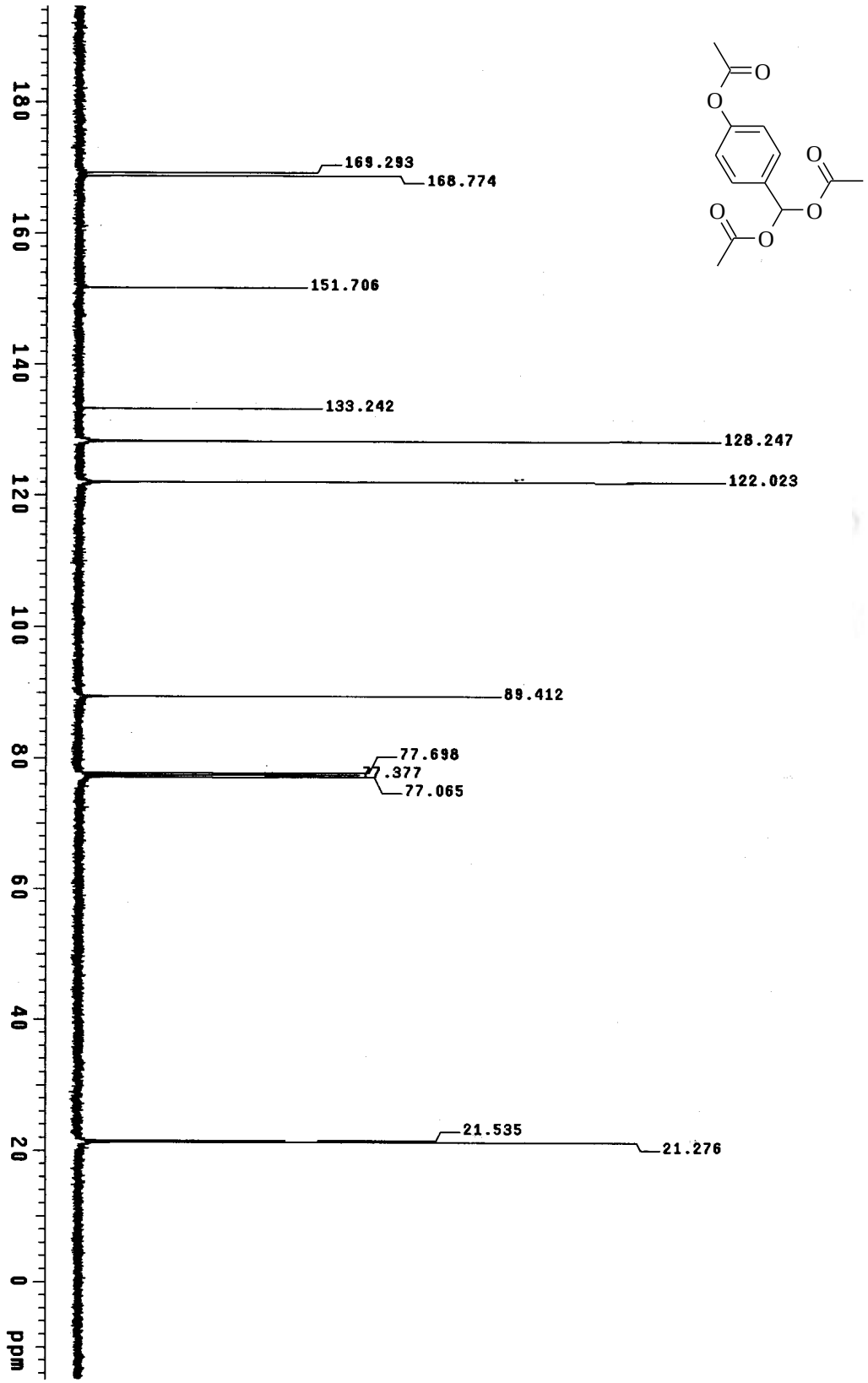
^{13}C NMR (100 MHz, $CDCl_3$): δ 21.24, 87.61, 124.78, 125.18, 126.81, 129.11, 130.00, 130.63, 131.44, 169.00.

IR (KBr) : 2924, 2858, 1756, 1623, 1234, 1085 cm^{-1}.

The spectral data of other compounds in Table 3.1 are given in the previous chapter.

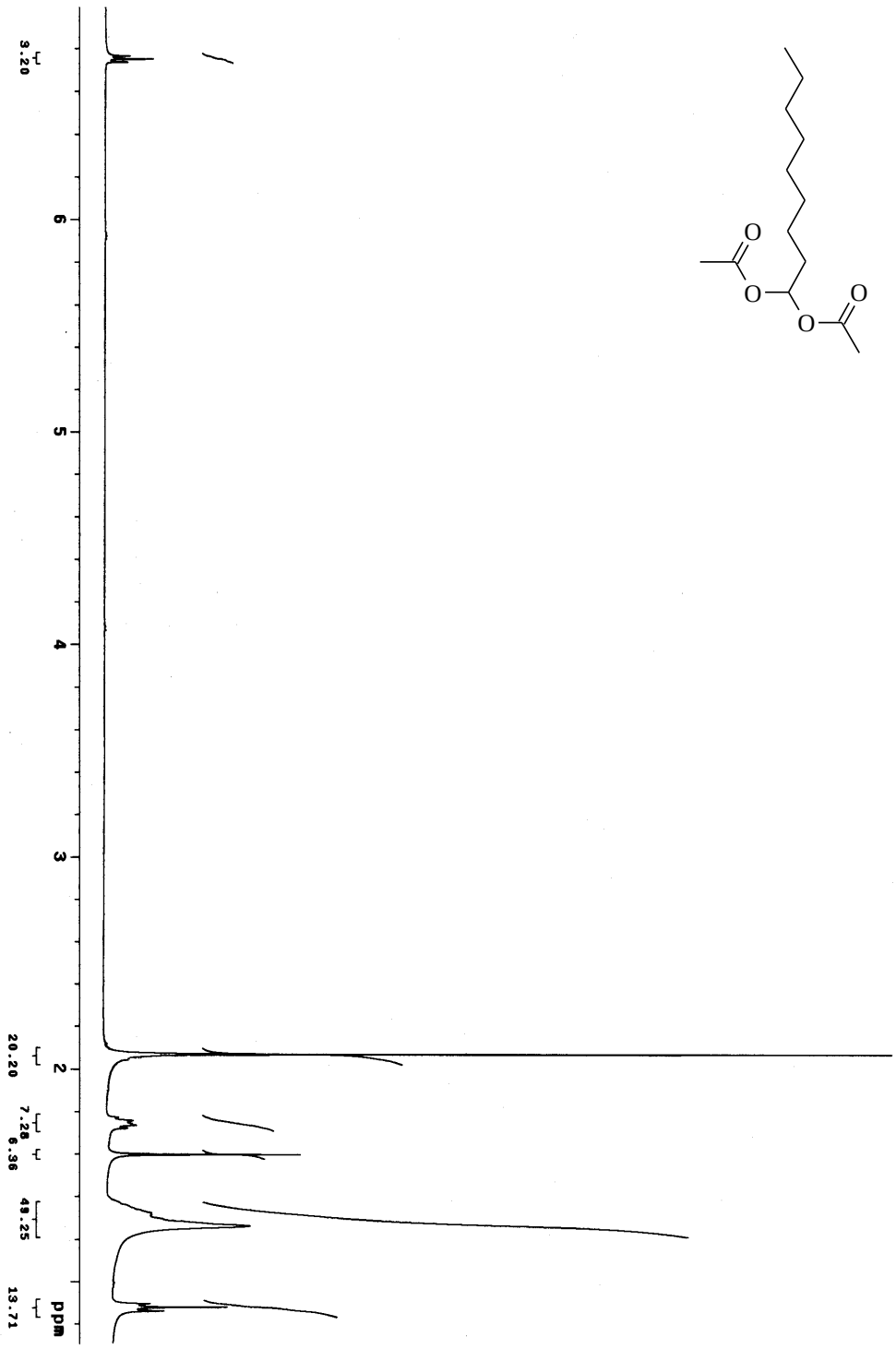
^{1}HNMR (400MHz, CDCl3): 1,1-Diacetoxy-1-(4-acetoxy-phenyl) methane

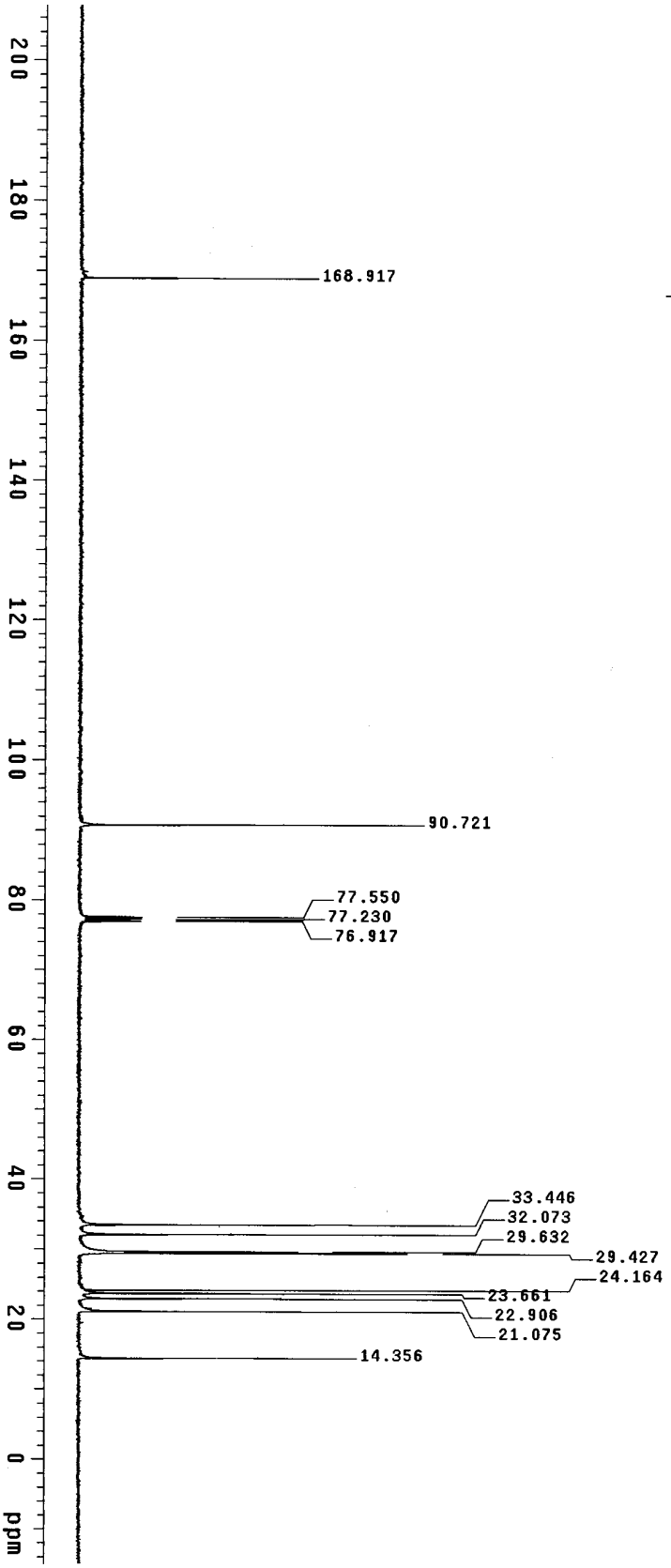


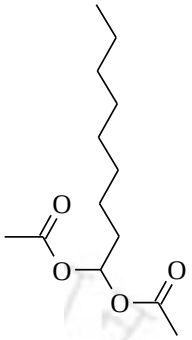


^{13}CNMR (400MHz, CDCl3): 1,1-Diacetoxy-1-(4-acetoxy-phenyl) methane

^{1}HNMR (400MHz, CDCl3): 1,1-Diacetoxy-nonane







^{13}CNMR (400MHz, CDCl3): 1,1-Diacetoxy-nonane

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